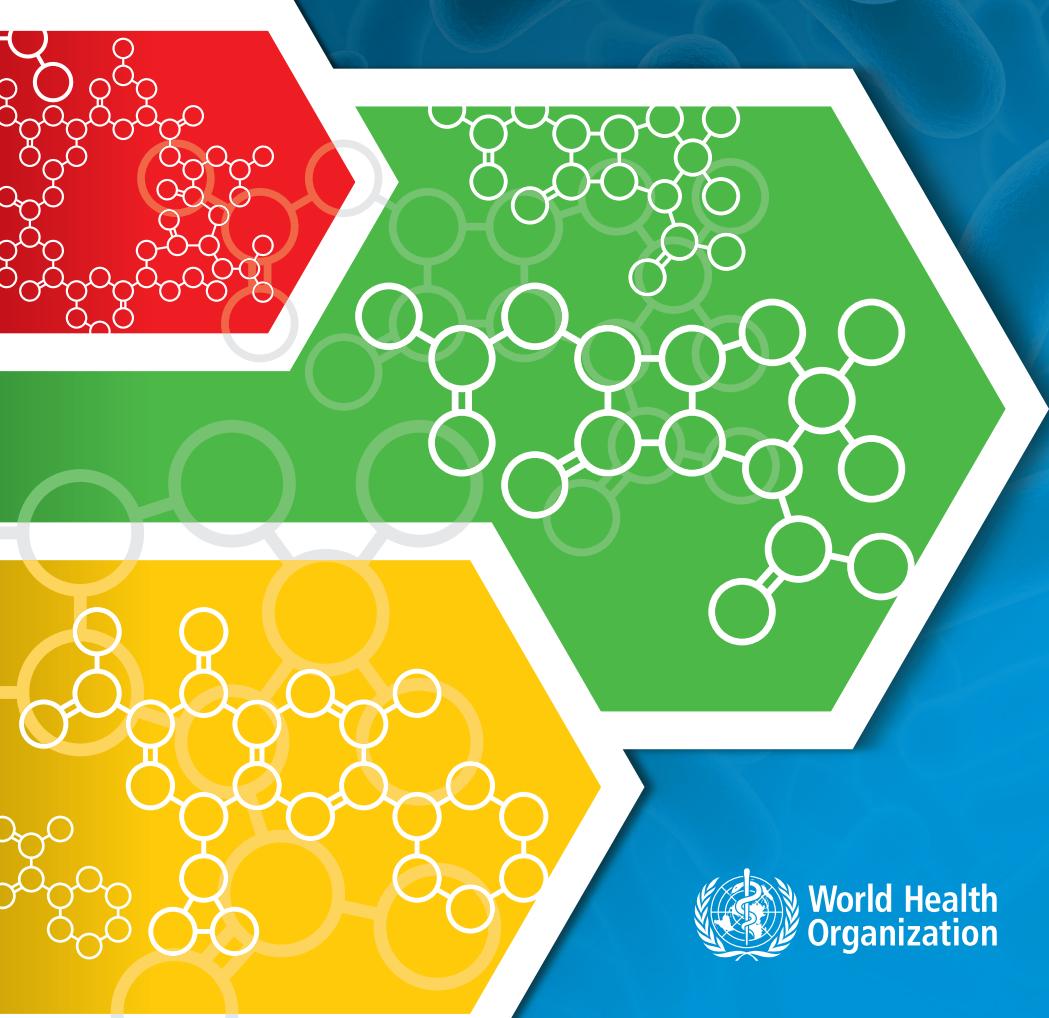


The WHO AWaRe (Access, Watch, Reserve) antibiotic book



World Health
Organization

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Foreword

Antimicrobial resistance (AMR) is a threat to global health and development and is estimated to contribute to more than five million deaths globally each year. We need urgent global action, using a One Health approach, to keep our precious medicines working. One of the critical health targets of the 2030 Sustainable Development Goals is for access to safe, effective and affordable medicines for all. In the case of antibiotics and other antimicrobials, using them carefully is vital to maintaining their effectiveness.

The inappropriate use and overuse of antibiotics are driving a global increase in AMR and have a pernicious impact on the effectiveness of these critical medicines. It threatens to send us back to the pre-antibiotic era, when a routine infection could mean death. Through the Global Action Plan on AMR, WHO is working to improve the surveillance of antimicrobial resistance and reduce inappropriate antibiotic consumption.

The new AWaRe antibiotic book, produced as an adjunct to WHO's Essential Medicines List (EML), provides concise, evidence-based guidance for more than 30 of the most common clinical infections in children and adults in both primary health care and hospital settings. The EML has been a key strategic component of WHO's goal to improve the use of medicines since 1977. The latest version of the EML, published in 2021, includes 39 antibiotics out of 479 medicines, reflecting the vital role these medicines play in health care.

Given the urgency of the threat to human health from AMR, and the many clinical infections for which antibiotics play a lifesaving role, WHO took a pragmatic approach to developing simple, practical guidance on how they should be used. The AWaRe system groups the hundreds of different antibiotics used globally into three simple categories – Access, Watch and Reserve – based on their clinical importance and the risk of their use promoting resistance. The AWaRe antibiotic book provides clear guidance on the choice of antibiotic, formulation, dose and duration for essential antibiotics for hospital and primary health care settings, including guidance on when not to use antibiotics.

There is an urgent need to develop and implement clear, globally accepted indicators, building on the AWaRe system, to promote the appropriate use of antibiotics and reduce their inappropriate use. Many challenges remain, including how data should inform local policies, and how to change patterns of medicine use formed over decades, particularly in low- and middle-income countries.

The 2022 AWaRe book is an important step along the road towards the improved use of antibiotics in humans, the development of stronger AMR policy and better clinical care.



A handwritten signature in blue ink, appearing to read "Tedros Adhanom Ghebreyesus".

Dr Tedros Adhanom Ghebreyesus
WHO Director-General

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WHO Essential Medicines Team

The development and writing was led by Veronica Zanichelli, Benedikt Huttner, Bernadette Cappello and Lorenzo Moja, WHO Essential Medicines Team, with support from members of the Essential Medicines List (EML) Antimicrobial Working Group; under the coordination of Clive Ondari, Director Health Products Policy and Standards Department; and Mariangela Simão, Assistant Director-General Access to Medicines and Health Products Division.

WHO is especially grateful to Professor Mike Sharland, who generously contributed his time and expertise in supporting the Essential Medicines Team in this project, and as Chair of the EML Antimicrobial Working Group.

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Acronyms and abbreviations

AMR	antimicrobial resistance
AmpC	ampicillinase C
AWaRe	Access, Watch and Reserve classification of antibiotics
CAP	community-acquired pneumonia
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CT	computed tomography
DALYs	disability-adjusted life years
EDL	WHO Model List of Essential In Vitro Diagnostics
EML	WHO Model List of Essential Medicines
EMLc	WHO Model List of Essential Medicines for Children
ESBL	extended-spectrum beta-lactamase
GLASS	Global Antimicrobial Resistance and Use Surveillance System
HAP	hospital-acquired pneumonia
HIV	human immunodeficiency virus
MRI	magnetic resonance imaging
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
OXA-48	oxacillinase-48
SAGE-IVD	Strategic Advisory Group of Experts on In Vitro Diagnostics
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
STI	sexually transmitted infection
TB	tuberculosis
UTI	urinary tract infection
VAP	ventilator-associated pneumonia
WHO	World Health Organization

Glossary

Antibiotic resistance

Antibiotic resistance is a subset of antimicrobial resistance that specifically refers to bacteria becoming resistant to antibiotics (medicines that act against bacteria).

Antimicrobial resistance (AMR)

AMR is the ability of bacteria, viruses, fungi and parasites to resist the effects of antimicrobial medicines that kill susceptible organisms or keep them from growing.

Antimicrobial resistance predates the use of antimicrobials in human medicine and many bacteria, viruses, fungi and parasites are intrinsically resistant to some antimicrobials. Microorganisms can also acquire resistance by being exposed to antimicrobials.

Infection with antimicrobial-resistant pathogens makes infections harder to treat and increases the risk of disease spread, severe illness and death.

Antiseptics

Antiseptics are antimicrobial products used to slow or stop the growth of microorganisms. They are usually used on the skin or mucous membranes, for example, the mouth. These include, for example, chlorhexidine. These products can be used as hand rubs, hand or mouth washes and skin preparations.

Access, Watch and Reserve (AWaRE) classification

AWaRe is the WHO classification of antibiotics introduced by WHO as part of the 2017 Model List of Essential Medicines.

In the AWaRe classification, there are three categories of antibiotics:

- Access antibiotics that have a narrow spectrum of activity and a good safety profile in terms of side-effects.
- Watch antibiotics that are broader-spectrum antibiotics and are recommended as first-choice options for patients with more severe clinical presentations or for infections where the causative pathogens are more likely to be resistant to Access antibiotics.
- Reserve antibiotics that are last-choice antibiotics used to treat multidrug-resistant infections.

This classification can be used to give an indirect indication of the appropriateness of antibiotic use. The World Health Organization (WHO) has defined a target that at least 60% of global antibiotic consumption at the national level should be from the Access group.

Carbapenemases

Carbapenemases are beta-lactamases, enzymes that can break the beta-lactam ring (an essential component of beta-lactam antibiotics) and make penicillins, cephalosporins, monobactams and carbapenems ineffective.

Coronavirus disease 2019 (COVID-19)

COVID-19 is an infectious disease caused by the severe acute respiratory syndrome coronavirus 1 (SARS-CoV-2). The first human cases of COVID-19 were reported in December 2019.

C-reactive protein

C-reactive protein is a laboratory test used to detect inflammation as an indicator of various conditions, including bacterial infection, and to monitor response to treatment.

Disability-adjusted life years (DALYs)

DALYs are an indicator used to assess the overall burden of disease. It is a time-based measure that combines years of life lost due to premature mortality and years of healthy life lost due to disability. One DALY represents the loss of the equivalent of one year of full health.

Model List of Essential In Vitro Diagnostics

The WHO Model List of Essential In Vitro Diagnostics (or Essential Diagnostics List (EDL)) is a list of in vitro diagnostics that are recommended by WHO and that was first published in 2018. The EDL can be used as a reference for programme and laboratory managers, and procurement and reimbursement officers who are developing or updating their own national lists of essential diagnostics. The list is updated every one to two years based on proposed additions and changes submitted to WHO by stakeholders and reviewed by the WHO Strategic Advisory Group of Experts on In Vitro Diagnostics (SAGE-IVD).

Enzyme immunoassay

An enzyme immunoassay is a laboratory test that uses enzyme-labelled antibodies and antigens to detect biologic molecules.

WHO Model List of Essential Medicines

The WHO Model List of Essential Medicines (or Essential Medicines List (EML)) is a list of those medicines that satisfy the priority health care needs of the population. The first EML was published in 1977. The EML includes the most efficacious, safe and cost-effective medicines for priority conditions, selected on the basis of current and estimated future public health relevance, evidence of effectiveness and safety, and cost-effectiveness. The EML is updated every 2 years based on proposed additions and changes submitted to WHO by stakeholders and reviewed by the WHO Expert Committee on the Selection and Use of Essential Medicines.

WHO Model List of Essential Medicines for Children

The WHO Model List of Essential Medicines for Children (or Essential Medicines List for Children (EMLc)) is a list of those medicines that satisfy the priority health care needs for children up to 12 years of age. The first EMLc was published in 2007. The EML includes the most efficacious, safe and cost-effective medicines for priority conditions in children, selected on the basis of current and estimated future public health relevance, evidence of effectiveness and safety, and cost-effectiveness. The EMLc is updated every 2 years based on proposed additions and changes submitted to WHO by stakeholders and reviewed by the WHO Expert Committee on the Selection and Use of Essential Medicines.

Extended-spectrum beta-lactamases (ESBLs)

ESBLs are a group of beta-lactamases, enzymes that can break the beta-lactam ring, which is an essential component of beta-lactam antibiotics, thus making penicillins, cephalosporins and monobactams (but not carbapenems) ineffective.

Genotypic resistance

Genotypic resistance is a type of resistance of an organism to an antibiotic or antibiotics due to genetic mutation and expression of resistance genes. It is determined by methods of antimicrobial susceptibility testing that detect resistance genes. This information may be important for choosing the correct antibiotic and for epidemiological and surveillance reasons.

Glutamate dehydrogenase

Glutamate dehydrogenase is a constitutive enzyme produced by all strains of *Clostridioides difficile* and it is easily detected in stool samples.

Global Antimicrobial Resistance and Use Surveillance System (GLASS)

The GLASS is the WHO surveillance system for antimicrobial resistance and use launched in 2015 to collect official national data in selected bacterial pathogens causing common infections in humans

Intramuscular

Route of administration of an injection to deliver a medication deep into the muscles.

Intravenous

Route of administration of an injection or infusion to deliver a medication into a vein.

Methicillin-resistant *Staphylococcus aureus* (MRSA)

MRSA are strains of *Staphylococcus aureus* that are resistant to methicillin and other beta-lactam antibiotics due to the presence of the *mecA* (or sometimes *mecC*) gene which produces a different penicillin-binding protein with lower affinity for beta-lactam antibiotics.

Microbiota

Microbiota is a collective term for the microorganisms that live in or on the human body.

Nucleic acid amplification test

Nucleic acid amplification is a laboratory test used to detect a particular nucleic acid sequence to identify virus or bacteria in different biological samples. There are several ways of amplification, one of the most commonly used is the polymerase chain reaction.

Non-fermenters

Non-fermenters are bacteria that cannot catabolize glucose and thus are unable to ferment. The most relevant in this context are *Acinetobacter baumannii* and *Pseudomonas aeruginosa*.

Phenotypic resistance

Phenotypic resistance is a type of resistance determined by methods of antimicrobial susceptibility testing such as disk diffusion, broth microdilution and agar dilution and considered the reference standard for detection of antibiotic resistance. Susceptibility/resistance is determined based on the ability of defined concentrations of antibiotics to inhibit growth. It can generally not determine the cause of the resistance (e.g. beta-lactamases versus efflux pumps), information that may be relevant for choosing the correct antibiotic.

Pharmacodynamics

Pharmacodynamics are the molecular, biochemical and physiological effects of medicines and their mechanisms of action – what the medicine does to the body.

Pharmacokinetics

Pharmacokinetics is the dynamics of absorption, distribution, metabolism and elimination of medicines by the body – what the body does to the medicine.

Rapid diagnostic tests

Rapid diagnostic tests are diagnostic assays designed for use at the point of care.

1. Introduction

There is a clear need for simple resources to improve the quality of antibiotic prescribing globally. The AWaRe book was designed as a tool to make the antibiotics section of the World Health Organization (WHO) Model List of Essential Medicines (EML) and Model List of Essential Medicines for Children (EMLc) more helpful to prescribers and to update the 2001 *WHO model prescribing information* (1).

Aim and scope

The aim of the AWaRe book is to provide short, clinical guidance on the management of common infections, including recommendations for empiric antibiotic treatment at the first clinical presentation and when a “no antibiotic” approach is appropriate. Guidance is given on the choice of antibiotics that should be used to treat the most likely bacterial pathogens causing each infection in adults and children, the dosage and the treatment duration.

The AWaRe book is intended for all health care workers who prescribe and dispense antibiotics in high-, middle- and low-income settings in both the primary health care and the facility/hospital setting. It aims to complement the *WHO policy guidance on integrated antimicrobial stewardship activities* and the toolkit for health care facilities in low- and middle-income countries (2,3). The AWaRe book is not intended to replace existing local and national antibiotic prescribing guidelines and clinical judgment, but to provide simple guidance where currently none is available.

Methods

The antibiotic treatment recommendations outlined in the AWaRe book are based on reviews of the evidence undertaken for the 2017, 2019 and 2021 updates of the EML and EMLc. The EML and EMLc provide a list of safe and effective antibiotics that should be available and affordable for patients globally. The AWaRe book provides guidance on how to best use these antibiotics based on the principles of the Access, Watch and Reserve (AWaRe) framework (Box 1.1).

Box 1.1 – Principles of the AWaRe framework

- Maximizing clinical effectiveness
- Minimizing toxicity
- Minimizing unnecessary costs to patients and health care systems
- Reducing the emergence and spread of antibiotic resistance (i.e. prioritizing antibiotics that are less likely to lead to antibiotic resistance in an individual patient and the community)
- Parsimony (i.e. avoiding the inclusion of many similar antibiotics)
- Simplification (i.e. same Access antibiotic recommended for multiple indications)
- Alignment with existing WHO guidelines

The detailed reviews on the optimal choice of antibiotics to be used for each specific clinical infection were based on a standardized analysis of systematic reviews, meta-analyses and clinical practice guidelines by experts in evidence-based medicines from McMaster University (Hamilton, Canada).

Details of the evidence underlying the recommendations and the methodology can be found in the following publications:

- *The selection and use of essential medicines: report of the WHO Expert Committee, 2017.* WHO technical report series; 1006 (4).
- *The selection and use of essential medicines: report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2019.* WHO technical report series; 1021 (5).
- *The selection and use of essential medicines: report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2021.* WHO technical report series; 1035 (443).

The choice of antibiotics to use for each specific infection are formal recommendations based on the evaluation made by the EML Expert Committee on the evidence presented for the EML updates or derived from existing WHO guidelines where available. The AWaRe book also provides guidance on diagnosis, symptomatic treatment and treatment duration based on non-systematic reviews of the literature and expert opinion. Some factors to be considered when using the AWaRe book are outlined in Box 1.2.

Box 1.2 – General considerations about the use of the AWaRe book

As with any general guidance document, the individual circumstances of the patients need to be considered. Comorbidities (e.g. immunosuppression which changes the pathogens that need to be considered, or renal or hepatic insufficiency which may require dose adaption of antibiotics), concomitant medications (risk of interactions), pregnancy and breastfeeding status (some antibiotics may be contraindicated), allergies (see the chapter on allergies to antibiotics) and national regulations all may require an adaption of the guidance and **it is the responsibility of each prescriber to make sure that all these considerations are taken into account when prescribing an antibiotic.**

Patients should be informed about the most common side-effects of the antibiotic, how it should be stored and taken, how long to take it for and what to do if symptoms worsen or fail to improve and how leftover antibiotics should be properly disposed of.

Structure

There are separate chapters for 35 infections, divided for ease of use into primary health care and hospital facility sections fully acknowledging that there is overlap between these groups.

Each chapter on a clinical infection includes:

- **Background information.** The pathophysiology, epidemiology, global burden, most common pathogens and how to make the clinical diagnosis, including assessing disease severity.
- **Diagnostic tools.** As the availability of diagnostic tools varies considerably in different settings, the empiric antibiotic recommendations are based on clinical signs and symptoms. Relevant diagnostic tests (including imaging and laboratory tests) are suggested based on *WHO Model List of Essential In Vitro Diagnostics* (EDL) (6). The list of tests provided for each infection is not based on a formal assessment of their predictive value, but as a general guide of tests that could be clinically helpful, where available.
- **Treatment.** Guidance is given where appropriate for “no antibiotic care” including symptomatic management for low-risk patients with minor infections that do not need antibiotic treatment. First- and second-choice antibiotic options are then given where relevant based on the EML, EMLc and AWaRe system as well as other WHO guidance documents.

- Guidance on which infections may benefit most from **targeted clinical microbiology surveillance** to help inform both local and national empiric antibiotic guidance.

Each chapter is complemented by an infographic containing a short summary of the most important information (e.g. clinical presentation, diagnostic tests, treatment) separately for children and adults that can be rapidly and easily consulted when needed.

General antibiotic stewardship principles have been included throughout all the AWaRe book. These include guidance on a risk-based prescribing approach with the no antibiotic care option, short standard durations across infections, rapid oral step down from intravenous antibiotics and standardized dosing to improve medicine purchasing and programme delivery.

The AWaRe book also includes chapters on the Reserve antibiotics listed in the 2021 EML and EMLc, the principles behind their selection and how these last-resort medicines should be used to preserve their effectiveness.

The AWaRe book is available both in print and electronic formats. Downloadable infographics with the key information for end-users are also provided for each infection (see Web Annex).

2. Improving the use of antibiotics with the AWaRe book

Background

About 90% of all antibiotics are taken by patients in the primary health care setting. It is estimated that around half of all antibiotic use is inappropriate in some way, such as: the use of an antibiotic when none is indicated; the choice of an antibiotic with unnecessarily broad spectrum (e.g. Watch instead of Access antibiotics; see the following section); and the wrong dose, duration of treatment, and delivery or formulation of the antibiotic (7).

Note

The term antibiotic stewardship is preferred to antimicrobial stewardship and is used throughout the AWaRe book to acknowledge the fact that the book only provides guidance on antibiotic treatment.

AWaRe

The AWaRe book gives guidance on first- and second-choice antibiotics for common infections in line with the recommendations in the EML and EMLc (8,9). WHO has classified antibiotics into four groups, Access, Watch, Reserve (AWaRe) and a fourth – Not Recommended – group. As well as the antibiotics in the EML and EMLc, more than 200 other antibiotics have now been classified into AWaRe groups to help inform local and national policy development and implementation (10).

Access antibiotics have a narrow spectrum of activity, lower cost, a good safety profile and generally low resistance potential. They are often recommended as empiric first- or second-choice treatment options for common infections (see Box 2.1 for WHO's target for their use).

Watch antibiotics are broader-spectrum antibiotics, generally with higher costs and are recommended only as first-choice options for patients with more severe clinical presentations or for infections where the causative pathogens are more likely to be resistant to Access antibiotics, such as upper urinary tract infections (UTIs).

Reserve antibiotics are last-choice antibiotics used to treat multidrug-resistant infections (see chapter on Reserve antibiotics).

The AWaRe system is also represented as a traffic-light approach: Access = green, Watch = orange and Reserve = red. Simple graphics using the traffic light approach can be used to show the proportions of Access and Watch antibiotics used in settings such as a community clinic or pharmacy or as part of central monitoring of antibiotic consumption.

Countries, regions and districts are encouraged to use the AWaRe book as a basis for developing their own quality indicators and targets for safely reducing total levels of inappropriate antibiotic prescribing to improve patient safety and care, while reducing resistant infections and costs for patients and health systems (see Box 2.2 for goals of the AWaRe book).

Box 2.1 – WHO target for the use of Access antibiotics

To promote responsible use of antibiotics and slow the spread of antibiotic resistance, the WHO Global Programme of Work includes a target that at least “**60% of total antibiotic prescribing at the country level should be Access antibiotics by 2023**” (11,12)

Box 2.2 – Improving the use of antibiotics with the AWaRe book

- No antibiotic care – safely reducing antibiotic use
- Improving Access antibiotic use and reducing inappropriate use of oral and IV Watch antibiotics
- Reducing the use of Not Recommended antibiotics
- Improving AWaRe-ness!
- Improving appropriate antibiotic dosing and duration

No antibiotic care – safely reducing antibiotic use

Key messages

- Most otherwise healthy patients with mild common infections **can be treated without antibiotics** as these infections are frequently self-limiting and the potential medicine-related adverse events outweigh the clinical benefits.
- The risks of taking antibiotics when they are not needed should always be considered, such as side-effects, allergic reactions, *Clostridioides difficile* infection and selection of resistant bacteria.
- Patients treated with symptomatic care only (no antibiotic care) should be clearly informed of what danger signs to monitor and what to do if they occur.

Management of low risk (mild) infections in primary health care

Most infections encountered in primary health care are not caused by bacteria (e.g. most respiratory tract infections have a viral cause) and therefore the patient will not benefit from antibiotic treatment (Table 2.1). Even when the cause of the infection is bacterial, many infections are frequently self-limiting, with a low risk of severe complications and the benefit of antibiotics is limited, shortening of the duration of symptoms by usually only around 1 or 2 days. Most otherwise healthy patients with mild infections may safely receive symptomatic treatment alone, such as anti-inflammatory medicines, pain killers or complementary medicines. Whenever appropriate, guidance on diagnosing mild infections that can be treated with *No Antibiotic Care* is given in the AWaRe book.

Table 2.1 – Common infections in primary health care where mild cases can be safely treated with No Antibiotic Care (i.e. symptomatic management only) – see individual chapters for more details

Infection (in alphabetical order)	Can it be safely treated without antibiotics?	Comment
Acute diarrhoea	Yes, in the great majority of cases (unless there is significant bloody diarrhoea)	Most cases do not require antibiotic treatment because the infection is of viral origin and the illness is usually self-limiting regardless of the causative pathogen. The cornerstone of treatment is rehydration and electrolyte replacement.
Bronchitis	Yes	Nearly all cases have a viral origin and there is no evidence that antibiotics are needed.
COPD exacerbations	Yes, in most mild cases	Most exacerbations of COPD are not triggered by bacterial infections; only certain cases will benefit from antibiotic treatment.
Dental infections	Yes, in most mild cases	Dental treatment rather than prescribing antibiotics is generally more appropriate in the management of dental infections.
Otitis media	Yes, in most mild cases	Most mild cases of acute otitis media can be managed symptomatically and do not require antibiotic treatment.
Pharyngitis	Yes, in most mild cases	Most cases do not require antibiotics because the infection is viral. ^a

continues

Table 2.1 continued

Infection (in alphabetical order)	Can it be safely treated without antibiotics?	Comment
Sinusitis	Yes, in most mild cases	Most cases do not require antibiotics as the infection is viral.
Skin and soft tissue infections (mild)	Only for certain conditions and in certain patients	In cases of wounds at low risk of becoming infected, antibiotic treatment is not needed. In cases of animal bites, only wounds in high-risk anatomical locations and patients with severe immunosuppression benefit from antibiotic treatment.
Urinary tract infection (lower)	Only in very select patients with no risk factors for complicated infections	In young women who are not pregnant, with mild symptoms and who may wish to avoid or delay antibiotic treatment, symptomatic treatment alone can be considered.

COPD: chronic obstructive pulmonary disease.

^a Refer to the pharyngitis chapter for situations that require antibiotic treatment, for example, pharyngitis in settings where rheumatic fever is endemic.

Are antibiotics needed?

In 2006, WHO proposed that the percentage of patients attending a primary health care facility receiving an antibiotic should be less than 30% (13). However, on average, around half of patients presenting with any infection in primary care still receive an antibiotic, thus contributing to the emergence and spread of antimicrobial resistance (AMR) (14). It is therefore important that both health care professionals and patients consider the risks of taking antibiotics when they are not needed. These risks include the immediate risk of side-effects of the medicine, most commonly diarrhoea or allergic reactions (such as a rash; see chapter on allergy to antibiotics) and rarely more serious side-effects. Bacteria in patients prescribed an antibiotic for a respiratory infection or a UTI – as examples of infections for which antibiotics are often prescribed – commonly develop antibiotic resistance to the prescribed (and other) antibiotics. These patients are also more likely to transmit resistant bacteria to other people (14). Patients with infections caused by antibiotic-resistant bacteria are more likely to have a delayed clinical recovery (15). Furthermore, antibiotic treatment alters the patient's microbiota (i.e. all microorganisms that live in or on the human body), with potential long-term consequences and an increased risk of infection by *Clostridioides difficile*, a bacterium that can cause severe diarrhoea.

Think D8 – before prescribing!

Before prescribing antibiotics to patients, prescribers should consider the eight Ds (Box 2.3).

Box 2.3 – Points to always consider when prescribing

Diagnose – what is the clinical diagnosis? Is there evidence of a significant bacterial infection?

Decide – are antibiotics really needed? Do I need to take any cultures or other tests?

Drug (medicine) – which antibiotic to prescribe? Is it an Access or Watch or Reserve antibiotic? Are there any allergies, interactions or other contraindications?

Dose – what dose, how many times a day? Are any dose adjustments needed, for example, because of renal impairment?

Delivery – what formulation to use? Is this a good quality product? If intravenous treatment is needed, when is step down to oral delivery possible?

Duration – for how long? What is the stop date?

Discuss – inform the patient of the diagnosis, likely duration of symptoms, any likely medicine toxicity and what to do if not recovering.

Document – write down all decisions and the management plan.

Improving Access antibiotic use and reducing inappropriate use of oral Watch antibiotics

Key messages

- The great majority of common infections in primary health care can be treated without any antibiotics or with Access antibiotics.
- Reducing the inappropriate use of Watch antibiotics is key to control antibiotic resistance.

The Sixty-eighth World Health Assembly in May 2015 endorsed a global action plan to tackle AMR (Box 2.4) (16).

Box 2.4 – The five objectives of the global action plan

1. Improve awareness and understanding of antimicrobial resistance.
2. Strengthen surveillance and research.
3. Reduce the incidence of infection.
4. **Optimize the use of antimicrobial medicines.**
5. Ensure sustainable investment in countering antimicrobial resistance

The AWaRe book therefore aims to address one of the objectives of the WHO global action plan “Optimize the use of antimicrobial medicines” with a focus on antibacterial medicines or antibiotics (antimicrobials also include antifungal, antiviral and antiprotozoal medicines). The AWaRe book provides guidance on when not to prescribe antibiotics and, if indicated, which antibiotics to prescribe for the most common infections. The AWaRe book focusses on the optimal use of Access antibiotics as they remain the first-choice options for most infections.

The AWaRe book recommends that nine of the 10 most common infections seen in primary health care can be treated safely with either no antibiotics or Access antibiotics (Table 2.2). Only one infection, acute bloody diarrhoea (dysentery), requires the empiric treatment with antibiotics in the Watch category, such as ciprofloxacin or azithromycin.

The use of oral Watch antibiotics globally is increasing. They are now very commonly taken by patients in primary health care for minor infections (fever/cough/diarrhoea) in both high-income countries and low- and middle-income countries. Reducing the inappropriate use of both oral and intravenous Watch antibiotics is a critical strategy for the global control of antibiotic resistance, while ensuring vulnerable populations have continued or, where appropriate, improved access to Access antibiotics.

Table 2.2 – Common infections seen in primary health care settings and the antibiotic options recommended in the AWaRe book

! Important		
Infection	ACCESS / WATCH	First-choice antibiotic option (when an antibiotic is indicated^a)
Bronchitis	No antibiotic	No antibiotic
Community-acquired pneumonia (mild cases)	ACCESS	Amoxicillin OR Phenoxycephalpenicillin
Chronic obstructive pulmonary disease exacerbations	ACCESS	Amoxicillin (for most mild cases the first choice is symptomatic treatment and antibiotics are not necessary)
Dental infections	ACCESS	Amoxicillin OR Phenoxycephalpenicillin (for most cases the first choice is a dental procedure and antibiotics are not necessary)
Infectious diarrhoea ^b	No antibiotic or WATCH	Most mild non-bloody diarrhoea is caused by viral infections and antibiotics are not necessary For acute severe bloody diarrhoea/dysentery - Ciprofloxacin
Otitis media	ACCESS	Amoxicillin (for most mild cases the first choice is symptomatic treatment and antibiotics are not necessary)

continues

Table 2.2 continued

Infection	ACCESS / WATCH	First-choice antibiotic option (when an antibiotic is indicated ^a)
Pharyngitis	ACCESS	Amoxicillin OR Phenoxytmethylpenicillin (for most mild cases the first choice is symptomatic treatment and antibiotics are not necessary)
Sinusitis	ACCESS	Amoxicillin OR Amoxicillin+clavulanic acid (for most mild cases the first choice is symptomatic treatment and antibiotics are not necessary)
Skin and soft tissue infection (mild cases) ^c	ACCESS	Amoxicillin+clavulanic acid OR Cefalexin OR Clloxacillin
Urinary tract infection, lower	ACCESS	Amoxicillin+clavulanic acid OR Nitrofurantoin OR Sulfamethoxazole+trimethoprim OR Trimethoprim

^a The decision to treat is based on assessment of the patient and on a minimum set of criteria to start antibiotics described in the chapters for each infection.

^b Only oral antibiotic options are reported here.

^c Cloxacillin and cefalexin have a narrower spectrum of antibacterial activity compared to amoxicillin+clavulanic acid with good efficacy in mild skin and soft tissue infections. Therefore, from an antibiotic stewardship perspective, these two antibiotics are the preferred options whenever possible (except for bite wounds). Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Reducing the use of Not Recommended antibiotics

Key messages

- The wide use of fixed-dose combinations of antibiotics that are not compatible with the EML and not approved by the major regulatory agencies is of concern. Their use should be reduced as these combinations may result in increased toxicity and selection of resistance.
- WHO has developed a list of fixed-dose combinations of antibiotics whose use is strongly discouraged (10).

In some countries, there is substantial use of fixed-dose combinations of antibiotics, which contain two or more agents in a single formulation. Recent data suggest that these combinations represent up to 20% of global antibiotic prescribing, especially in middle-income countries (17). Some fixed-dose combinations of antibiotics are well established (e.g. sulfamethoxazole+trimethoprim) but other combinations often consisting of two or more broad-spectrum antibiotics, combined with antifungal and probiotic agents are of concern because they may contribute to the emergence and spread of AMR.

Improving AWaRe-ness!

Key messages

- All prescribers and dispensers have a responsibility to improve the use of antibiotics.
- Patients also have responsibilities and efforts should be made to ensure they know basic principles of appropriate antibiotic use (e.g. taking antibiotics as prescribed and not using leftover antibiotics for a later illness) and symptomatic care.

All prescribers, dispensers and users of antibiotics, including both private and public providers, have a clear responsibility to ensure the best use of the medicines they give or take. Table 2.3 outlines some of the responsibilities of these various stakeholders. The aim is to provide a general framework of responsibility with broad examples that could lead into a programme of interventions.

Table 2.3 – Responsibilities of different stakeholders for improving the use of antibiotics

Group	Responsibility	Examples of practical actions
Health care policy-makers and relevant programme managers	<ul style="list-style-type: none"> • Discourage the unnecessary use of antibiotics. • Focus on promoting the use of Access antibiotics where appropriate. • Ensure local access to and availability of antibiotics in the national EML at the appropriate cost, quality and in the correct formulation^a. • Make sure that the national EML is regularly updated and aligned with the WHO Model Lists where appropriate. • Undertake regular surveillance of antibiotic use at all levels, including by AWaRe group (e.g. Access/Watch ratio). 	<ul style="list-style-type: none"> • Review national and local guidance documents and compare them with the AWaRe book. • Disseminate new guidance to all levels of the health care services. • Review provision of Access antibiotics, cost, quality^b, sustainability and barriers to use. • Develop a monitoring programme for antibiotic use across all levels of health care provision, including the Access/Watch antibiotics ratio. • Regularly review the national EML and align to the WHO Model Lists where synergies exist. • Disseminate data to providers on antibiotic use appropriately and regularly.
Physicians	<ul style="list-style-type: none"> • Be AWaRe of the AWaRe book and focus clinical care on D8! <ul style="list-style-type: none"> - Diagnosis – which infection - Decide – are antibiotics needed - Drug (medicine) – which antibiotic - Dose – at what dose - Delivery – what formulation - Duration – for how long - Discuss – with patient - Document – in the notes. • Know which infections could be managed with antibiotics in your setting. • Know which signs and symptoms would require hospital referral. 	<ul style="list-style-type: none"> • Review national and local guidance documents and compare them with the AWaRe book. • Adapt or adopt EML guidance. • Assist with developing and implementing educational programmes. • Develop local tools for monitoring local patterns of antibiotic use and disseminate data appropriately and regularly to relevant stakeholders. • Act as local champions of the AWaRe book.

continues

Table 2.3 *continued*

Group	Responsibility	Examples of practical actions
Pharmacists	<ul style="list-style-type: none"> • Be AWaRe of the AWaRe book. • Do not provide antibiotics without a prescription. • Discourage self-medication with antibiotics. • Monitor relative use of Access and Watch antibiotics. 	<ul style="list-style-type: none"> • Review, adapt or adopt the AWaRe book in line with local guidance documents. • Ensure in-pharmacy availability of the most common infection chapters of the AWaRe book and summaries of Access and Watch lists. • Monitor local patterns of antibiotic use such as Access/Watch ratios and disseminate data appropriately and regularly to relevant stakeholders.
Professional societies	<ul style="list-style-type: none"> • Be aware of AWaRe and the AWaRe book. • Contribute to awareness campaigns. • Educate health care workers about AWaRe. 	<ul style="list-style-type: none"> • Disseminate new guidance to all levels of the health care services.
Nurses	<ul style="list-style-type: none"> • Be AWaRe of the AWaRe book and advise or prescribe accordingly. 	<ul style="list-style-type: none"> • Review, adapt or adopt the AWaRe book in line with local guidance documents.
Community health workers	<ul style="list-style-type: none"> • Know which infections could be managed with antibiotics or with symptomatic treatment alone in your setting. • Know which signs and symptoms would require medical referral. • Be AWaRe of the AWaRe book. 	<ul style="list-style-type: none"> • Review local availability of antibiotics. • Review practices and procedures that are non-compliant with the AWaRe book. • Monitor patterns of antibiotic use.

continues

Table 2.3 continued

Group	Responsibility	Examples of practical actions
Patients	<ul style="list-style-type: none"> • Be aware of AWaRe. • Avoid using leftover antibiotics. • Avoid asking for antibiotics over the counter in pharmacies and asking physicians to prescribe them. • Avoid stockpiling leftover antibiotics • Contribute to awareness campaigns (e.g. with family members and the community). • Return any expired, unwanted or unused antibiotic to a pharmacy or health centre for safe disposal. 	<ul style="list-style-type: none"> • Act as champions for the better use of antibiotics. • Promote antibiotic-related educational activities for patients.

AWaRe: Access Watch and Reserve; EML: WHO Model Lists of Essential Medicines (8).

^a This includes discouraging the excessive use of fixed-dose combinations of antibiotics.

^b This includes preventing and detecting the production and use of substandard and falsified medicinal antibiotics.

Substandard and falsified medicinal antibiotics

As antibiotics are the most common medicines used globally, the production and use of substandard and falsified medicinal antibiotics is a major problem. WHO estimates that up to one in 10 medical products in low- and middle-income country settings are substandard or falsified with antibiotics amongst the most commonly reported (18). These products are typically found in informal market settings, which are a major source of antibiotics for patients globally, but also in less well-regulated pharmacies. All those involved in giving antibiotics to patients should take all reasonable steps to ensure that good quality medicinal products are provided, which are registered and licensed by the relevant national medicines regulatory authorities. Guidance on how to identify a possible problem of substandard and falsified medicinal antibiotics is provided in the WHO publication: *Substandard and falsified medical products* (18).

Community health care workers

Community health care workers include informal health care providers, that is providers with no or limited formal training. In rural areas in low- and middle-income country settings,

they are often the first medical contact for many people in the community. Antibiotics are commonly prescribed by these informal providers, including the inappropriate prescription of broad-spectrum antibiotics or frequent prescription of antibiotics to treat upper respiratory tract infections that are often of viral origin (19).

Improved antibiotic use could be helped by further education of this sector with a focus on the optimal use of Access antibiotics. Educational activities and training on how to manage common infections using the AWaRe book could be considered, for example, to decrease the use of oral Watch antibiotics and limit the use of antibiotics for severe infections only.

Appropriate antibiotic dosing and duration

Key messages

- Prescribers should always consult local and national dosing guidelines, where available.
- The dosing guidance provided in the AWaRe book is for the most common clinical infections in patients with normal kidney and liver function but the need for dose adjustments should always be considered.
- The guidance on duration of treatment is generally the shortest suggested duration for specific infections. More severe infections or patients with underlying conditions or immunosuppression may require longer courses of treatment than suggested in the AWaRe book.



Other relevant WHO resources (please check regularly for updates)

- WHO report on consensus guidance on paediatric dosing regimens for access antibiotics on the essential medicines list for children (20).

For each infection discussed in the AWaRe book, guidance is given for both children and adults on the dose of antibiotic to be prescribed, how often the dose should be taken, the route of administration of the antibiotic and the duration of antibiotic treatment.

The guidance is based on: (i) existing WHO guidelines, (ii) a review of recent literature, (iii) a review of recent guidelines from different WHO regions and (iv) expert opinion (the EML Antimicrobial Working Group).

Users of the AWaRe book should be aware of the limited evidence underlying many antibiotic prescribing strategies, particularly the very poor evidence for dosing guidance for older antibiotics (when approval processes were less stringent and methods to determine

pharmacokinetic/pharmacodynamic target attainment less developed), which may explain some of the variation in international recommendations. The AWaRe book therefore does not provide formal recommendations for dosage, frequency of use, route of administration and duration, but rather provides general guidance on what would be considered appropriate dosing strategies and duration in most clinical cases.

Dosing

Wherever appropriate the same dose is given for each antibiotic for all infections to help local procurement and prescribing. In the hospital facility section, guidance is also given on when to consider **step down** from intravenous to oral antibiotics, encouraging the early discharge of patients from hospital when clinically appropriate.

Guidance on dose adjustments for abnormal kidney and liver function is not covered, and the summary of product characteristics should be consulted. In addition, detailed information on antibiotic administration, for example, the use of continuous or prolonged infusion times of beta-lactams in multidrug-resistant infections, is not covered as this is beyond the scope of the AWaRe book (21,22).

Even though this dosing is not covered in the AWaRe book, higher doses or more frequent administration may be required in certain situations such as: patients with very severe infections (including sepsis / septic shock) or infections of certain body sites such as infections of the central nervous system; patients with significant underlying disease (e.g. severe immunosuppression); and overweight patients.

Dosing in children

For children, weight-based dosing was generally used for oral treatments based on WHO ranges. For children weighing more than 30 kg, adult dosing should be considered. The 2019 EML report on consensus guidance on paediatric dosing regimens was used as a reference but adapted by infection and severity of disease (20).

Treatment duration

For treatment duration, where there was an acceptable range for the duration of therapy, the lowest number of days supported by the review of guidelines and expert opinion is used.

Strong evidence-based guidance on the most appropriate duration of treatment for many infections is limited. Therefore, duration is often individualized based on clinical response, on the success of surgical source control and, if available, changes in laboratory markers of infection. When an alternative diagnosis is established which does not require antibiotics, antibiotic treatment should be stopped. Shorter treatment where clinically appropriate is generally associated with less toxicity and a lower risk of selection and transmission of antibiotic resistance, with equivalent clinical outcomes.



Intravenous or oral antibiotics

Most non-severe infections can be safely treated with oral antibiotics and this approach is encouraged as it has several advantages, for example, less risk of line-associated infections and avoidance of hospitalizations. However, this is provided that there is no risk of poor enteral absorption (e.g. no vomiting) or need to treat pathogens for which effective oral options are not available, for example in the case of infections caused by certain multidrug-resistant pathogens.

When intravenous treatment is started (e.g. for severe infections), rapid oral step down should be considered as soon as this can be safely done.

3. Allergy to antibiotics

Key messages

- True severe allergy to antibiotics is rare and allergies are often over-reported
- Beta-lactam antibiotics (penicillins and cephalosporins) of the Access group are among the most effective and safe medicines for many infections, and they should only be avoided when there is a high suspicion of true allergy.
- Cephalosporins and carbapenems can be safely used in most cases of non-severe penicillin allergy.
- All patients who are labelled as allergic should be carefully evaluated and their antibiotic allergy risk level should be determined.
- Routine skin testing before prescribing a beta-lactam antibiotic (e.g. penicillin or amoxicillin) is not needed, and direct oral challenge can be performed in carefully selected low-risk phenotypes.

The AWaRe book does not include alternative antibiotic options in cases of allergy to first-choice antibiotics. The reason for this is that a true allergy to antibiotics (true meaning an allergic reaction that is immune-mediated) is rare and the AWaRe book focuses on the empiric treatment options for most patients. Beta-lactam antibiotics of the Access group are among the most effective and safe medicines for many infections. Avoiding the use of this class, unless clearly justified because of severe allergy, exposes the patient to the risk of receiving suboptimal treatment for their infection.

This chapter on allergy describes general principles of the mechanisms of allergies to antibiotics and the implications for treatment. From the perspective of antibiotic stewardship, it is important to avoid over-diagnosing antibiotic allergies. Such over-diagnosis often occurs with antibiotics in the Access category (e.g. with penicillins) and can lead to the subsequent prescription of antibiotics in the Watch category, for example, macrolides that may be less effective and less safe. The detailed management of allergic reactions is beyond the scope of this chapter.

Definitions

- An **allergy** is a reaction of the immune system to a “non-self” substance.
- An **adverse reaction** is a response to a medicine which is harmful and unintended, and which occurs at the doses normally used (23). Most adverse

reactions can be classified as type A or type B reactions (Table 3.1) depending on whether or not their effects are related to the primary mechanism of action of the medicine (type A, i.e. if they are predictable based on the mechanism of action or not) and also whether the immune system is involved (type B, i.e. hypersensitivity reactions) (24). Most patients with type A adverse reactions (e.g. nausea, vomiting, headache and injection site reactions) should not be labelled as having a beta-lactam allergy, to prevent avoidance of beta-lactam antibiotics.

- A **hypersensitivity reaction** is any adverse reaction that is immunologically mediated. Hypersensitivity reactions are type B reactions and can be classified based on the timing of onset of symptoms after taking the antibiotic as well as on the underlying mechanism, that is, immediate reactions (potentially IgE-mediated) or delayed reactions (potentially T cell-mediated). Immediate reactions usually occur within 1–2 hours of taking the antibiotic and delayed reactions usually after more than 6–24 hours. Reactions occurring within 2–6 hours are often called accelerated.

Table 3.1 – Characteristics of adverse reactions to medicines

Type A (or on-target) adverse reaction ^a : characteristics	Type B (or off-target) adverse reaction ^a : characteristics
<ul style="list-style-type: none"> • Pharmacologically predictable • Dose/level dependent • Non-immune mediated • Less influenced by genetic factors <p>Examples: antibiotic-associated diarrhoea and acute tubular necrosis due to aminoglycosides</p>	<ul style="list-style-type: none"> • Pharmacologically unpredictable • Non-dose dependent • Often immunologically mediated hypersensitivity reactions^b (IgE or T-cell mediated) <p>Examples: skin exanthema, angioedema or anaphylaxis (immune-mediated)</p>

^a On-target (or augmented) means the effects are related to the primary mechanism of action of the medicine. Off-target means the effects are not related to the primary mechanism of action of the medicine.

^b These reactions are immunologically mediated. They can be immediate (< 2 hours), accelerated (2–6 hours) or delayed (> 6 hours) reactions based on when symptoms appear after the administration of the antibiotic.

Epidemiology

Allergies to medicines are frequently self-reported, especially for antibiotics (25) with 5–15% of patients in high-income countries reporting a penicillin allergy (24). However, in most cases (> 95%), these patients do not have a true immunologically mediated allergy and it is very likely that they can tolerate the antibiotic if re-exposed or challenged (26).

Severe allergies to antibiotics (e.g. anaphylactic shock) are rare; nonetheless, antibiotics are the most common cause of life-threatening immunologically mediated reactions (24).

Allergy to antibiotics is often over-diagnosed and patients are frequently labelled in health records as allergic to certain antibiotics (particularly to beta-lactams and sulfonamides) based on an unverified, vague, unknown or old (e.g. > 10 years) history of allergy reported by the patient, most often rashes. In most cases, these patients are unlikely to have a true allergy to the antibiotic and they will be able to safely tolerate it. Alternative explanations may exist for what the patients experienced previously, such as: (i) the antibiotic may have interacted with a concomitant infection, for example, antibiotic–infection interactions can occur in case of viral infections (e.g. the rash observed in patients with infectious mononucleosis caused by Epstein–Barr virus exposed to amoxicillin); or (ii) there may have been an “intolerance”/type A adverse reaction of the antibiotic manifested as, for example, nausea, vomiting, diarrhoea or headache; or (iii) a viral rash may have been confused with an allergic reaction. In addition, it is important to bear in mind that even true allergies are not always long-lasting and may decrease or disappear over time (> 10 years) (26).

This over-diagnosis of allergy has important consequences because incorrectly labelling a patient as allergic to an antibiotic often results in the unnecessary use of alternative antibiotics. These alternatives may be less effective for the infection being treated and may expose the patient to other (sometimes more toxic) side-effects.

Unfortunately, most patients with a history of allergy to antibiotics are not evaluated to confirm the existence (or persistence) of the allergy.

Cross-reactivity

Antibiotic cross-reactivity refers to the development of an allergic reaction to different substances that have a closely related structure, for example, cross-reactivity can occur between penicillin and other beta-lactams (Table 3.2) (26–28), which may be due to an immunological reaction to the beta-lactam ring shared by these antibiotics.

In patients with true allergy, cross-reactivity may occur and is generally predictable based on shared beta-lactam structures (e.g. R1 side chains), with the most frequently encountered example being aminopenicillins (e.g. amoxicillin, ampicillin) and aminocephalosporins such as cephalexin.

Table 3.2 – Cross-reactivity to antibiotics

Penicillins with other beta-lactams	% of cross-reactivity ^a	Safety of use
Penicillins and cephalosporins	< 2	Cephalosporins can be safely used in most cases of penicillin allergy and vice versa ^b .

continues

Table 3.2 continued

Penicillins with other beta-lactams	% of cross-reactivity^a	Safety of use
Penicillins and carbapenems	< 1	Carbapenems can be safely used in most cases of penicillin allergy and vice versa ^b .
Penicillins and monobactams	0	Monobactams can be safely used in case of penicillin, cephalosporins (except ceftazidime) or carbapenem allergy ^c .

^a Percentage of patients allergic to penicillins that can develop an allergic reaction if exposed to a different beta-lactam (cephalosporins, carbapenems or monobactams).

^b In cases of previous life-threatening reactions caused by the exposure to penicillins or other beta-lactams, any use of beta-lactams should be avoided, or an allergy specialist should be consulted.

^c Monobactams can be safely used in cases of beta-lactam allergies except when there is an allergy to ceftazidime, a third-generation cephalosporin, because of similarities in the side chains of aztreonam and ceftazidime.

Clinical presentation

Signs and symptoms of antibiotic allergy can vary in severity, ranging from mild reactions that can be safely managed in an outpatient setting with or without need for symptomatic treatment (e.g. antihistamines) to severe reactions that require hospitalization and even admission to intensive care. Immediate and delayed reactions can be severe or non-severe.

Gastrointestinal symptoms and headache are not usually due to an allergic reaction but rather to an intolerance of the antibiotic that can vary in intensity from person to person or to *Clostridioides difficile* infection in case of diarrhoea.

Most cases of allergic reactions to antibiotics are not severe and often present as mild skin reactions (most commonly mild rash, hives and itching) with no systemic symptoms.

Severe reactions are rare but can become life-threatening. They can be immediate or delayed after administration of the antibiotic.

- Immediate severe reactions should be suspected if there is airway involvement, bronchospasm, wheezing, angioedema (swelling of the tissue under the skin with or without hives) or anaphylaxis. Usually, these reactions develop fewer than 4 hours after taking the antibiotic.
- Delayed severe reactions should be suspected in patients who have taken an antibiotic and present with severe skin symptoms (e.g. a painful blistering rash) and fever, joint pain or signs of organ involvement (e.g. hepatitis). Thrombocytopenia

(low platelet count), haemolytic anaemia (destruction of red blood cells) and signs and symptoms of hepatitis or nephritis in severe cases are suggestive of organ involvement. Usually, these reactions develop more than 24 hours after taking the antibiotic.

Allergy evaluation

All patients who are labelled as allergic should be carefully evaluated and their antibiotic allergy risk level should be determined. When evaluating a patient, a full history of their allergy should be taken from the patient with details of past reactions, including timing relative to antibiotic administration (immediate, intermediate, delayed or unknown) and treatment received (if any). Patients can be classified into three risk categories for allergy to antibiotics: low, moderate, and high risk; see Table 3.3 for examples but other assessment tools are also available (29,30). Detailed documentation of all elements of the allergy is crucial. The patient should be educated about what types of antibiotics to avoid, if any, and should be provided, if possible, with written information such as a so-called allergy passport.

Table 3.3 – Antibiotic allergy risk levels based on the patient’s allergy history

Allergy risk category	Examples
Low	<ul style="list-style-type: none"> Patients with a history of isolated symptoms consistent with intolerance of an antibiotic, such as nausea, vomiting, diarrhoea or headache Patients with a history of mild skin reactions especially if > 5 years before assessment Patients with local injection site reactions Patients with a history of unknown reactions a long time ago without features of immediate IgE-mediated reactions Patients with a family history of antibiotic allergy
Moderate	<ul style="list-style-type: none"> Patients with a history of acute onset urticaria Patients with a history of reactions that look like IgE-mediated reactions but with no history of anaphylaxis
High	<ul style="list-style-type: none"> Patients with a history of severe or life-threatening reaction (immediate or delayed) to an antibiotic (e.g. anaphylaxis, Stevens–Johnson syndrome or blistering or mucosal involvement rash) Patients with a positive skin test Patients with recurrent reactions or reactions to multiple antibiotics

Source: Shenoy ES, et al (26).

Testing techniques for patients at low and moderate risk of antibiotic allergy include skin tests (this applies only to IgE-mediated reactions) and direct oral challenge tests. In direct oral challenge tests, a single therapeutic dose of the antibiotic is given orally to the patient under medical supervision with the ability to treat acute allergic responses. The patient should be kept under observation (usually at least 1-2 hours) to check for objective signs of an allergic reaction. A detailed description of different types of tests available is beyond the scope of this chapter. Routine skin testing before prescribing a beta-lactam antibiotic (e.g. penicillin and amoxicillin) is not needed in children or adults and should not be recommended in guidelines as this is an unnecessary barrier to the use of Access antibiotics.

In settings where allergy testing, specialist advice or treatment for anaphylaxis are not available, then pragmatic decisions should be based on a detailed history of any reported possible penicillin allergy. A rapid risk assessment needs to be done, including the medical importance of the infection the patient is presenting with (i.e. benefit–risk assessment in that patient and whether an antibiotic is really needed) and the availability of alternative antibiotics with similar effectiveness. Please see the relevant infection chapters and symptomatic non-antibiotic treatment of minor infections within chapters.

Patients with a definite history of immediate collapse, breathing difficulties or severe facial swelling within a few minutes to 1–2 hours of taking a penicillin class of antibiotic are likely to have had a true anaphylactic reaction. If any alternative antibiotics are available, they are preferred. Patients who have only had gastrointestinal symptoms or a rash appearing a few days after receiving an antibiotic of the penicillin group and who have shown no signs of becoming seriously unwell are generally less likely to develop severe anaphylaxis if they receive such antibiotics again in the future. Therefore, if one of these antibiotics is the most appropriate and available treatment option, they can be given and the patient advised to stop it if they develop a new skin rash, especially if the onset is rapid, the rash is raised and itchy and/or accompanying symptoms are present such as shortness of breath.



PRIMARY HEALTH CARE

4. Bronchitis

Key messages

- **Antibiotics are not needed** for most cases.
- Acute bronchitis usually presents as a persistent cough, with or without mild fever.
- Almost all cases are viral and self-limiting; patients should be informed that cough can last several weeks.
- Yellow/green colour of the sputum **does not** indicate bacterial infection and the need for antibiotics.
- Clinical presentation can differentiate bronchitis from pneumonia.

Other relevant WHO resources (please check regularly for updates)

- Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, 2013 (31).
- Coronavirus disease (COVID-19) pandemic (32).
- Living guidance for clinical management of COVID-19: living guidance, 23 November 2021 (33).
- Therapeutics and COVID-19: living guideline, 16 September 2022 (34).
- Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper –February 2019 (35).
- *Haemophilus influenzae* type b (Hib) vaccination position paper – July 2013: Introduction (36).
- Vaccines against influenza: WHO position paper – May 2022 (37).

Definition

Acute bronchitis is a self-limiting inflammation of the trachea and bronchi characterized by persistent cough, with or without fever, usually caused by a viral infection (38).

Bronchitis

Definition

A self-limiting inflammation of the trachea and bronchi characterized by persistent cough +/- fever ($\geq 38.0^{\circ}\text{C}$) usually caused by a viral infection

Diagnosis

Clinical Presentation

- Acute onset (<2 weeks) of cough lasting > 5 days +/- sputum production and shortness of breath (colour of the sputum does not indicate bacterial infection) +/- fever ($\geq 38.0^{\circ}\text{C}$)
- Generally a mild condition; cough usually lasts 10-20 days (can last longer)

Important: Symptoms can overlap with pneumonia and this can lead to inappropriate treatment with antibiotics. This should be avoided with a careful patient assessment

• **Bronchitis:** Less severe presentation, usually self-limiting (but cough may take weeks to resolve)

• **Pneumonia (see "Community-acquired pneumonia" infographic):** More severe presentation with shortness of breath and systemic signs of infection (e.g. increased heart and respiratory rate)

Microbiology Tests

Usually not needed; consider testing for Influenza virus or SARS-CoV-2 (e.g. during influenza season or outbreaks based on local epidemiological risk/situation/protocols)

Other Laboratory Tests

Usually not needed

Imaging

Usually not needed



Most Likely Pathogens

Respiratory viruses:

- Rhinovirus
- Influenza virus (A and B)
- Parainfluenza virus
- Coronavirus (including SARS-CoV-2)
- Respiratory syncytial virus (RSV)
- Metapneumovirus
- Adenovirus
- Other respiratory viruses

Treatment



No Antibiotic Care

- Symptomatic treatment
 - Bronchodilators (in case of wheezing), mucolytic or antitussive agents, can be considered based on local practices and patient preferences
- Patients should be informed that:
- Great majority of cases are self-limiting and of viral origin
 - Cough can persist for several weeks

Symptomatic Treatment

Medicines are listed in alphabetical order and should be considered equal treatment options

 Ibuprofen 200-400 mg q6-8h (Max 2.4 g/day)

OR

 Paracetamol (acetaminophen) 500 mg-1 g q4-6h (max 4 g/day)

• **Hepatic impairment/cirrhosis:** Max 2 g/day

Antibiotic Treatment

Antibiotic treatment is **not recommended and should be avoided** as there is no evidence of a significant clinical benefit and there is a risk of side effects of antibiotics

Bronchitis

Definition

A self-limiting inflammation of the trachea and bronchi characterized by persistent cough +/- fever ($\geq 38.0^{\circ}\text{C}$) usually caused by a viral infection

Diagnosis

Clinical Presentation

- Acute onset of cough lasting > 5 days, usually with runny nose and mild fever, with no clinical signs of pneumonia
- Generally a mild condition, cough usually lasts 1-3 weeks

Important: Symptoms can overlap with pneumonia and this can lead to inappropriate treatment with antibiotics. This should be avoided with a careful patient assessment

- **Bronchitis:** Less severe presentation, usually self-limiting (but cough may take weeks to resolve)
- **Pneumonia (see "Community-acquired pneumonia" infographic):** More severe presentation with shortness of breath and systemic signs of infection (e.g. increased heart and respiratory rate)

Microbiology Tests

Usually not needed; consider testing for Influenza virus or SARS-CoV-2 (e.g. during influenza season or outbreaks based on local epidemiological risk/situation/protocols)

Other Laboratory Tests

Usually not needed

Imaging

Usually not needed

Most Likely Pathogens

Respiratory viruses:

- Rhinovirus
- Influenza virus (A and B)
- Parainfluenza virus
- Coronavirus (including SARS-CoV-2)
- Respiratory syncytial virus (RSV)
- Metapneumovirus
- Adenovirus
- Other respiratory viruses

Treatment

No Antibiotic Care

- Symptomatic treatment
 - Bronchodilators (in case of wheezing), mucolytic or antitussive agents, can be considered based on local practices and patient preferences
- Patients/parents should be informed that:
- Great majority of cases are self-limiting and of viral origin
 - Cough can persist for several weeks

Symptomatic Treatment

Medicines are listed in alphabetical order and should be considered equal treatment options

- Ibuprofen (do not use if <3 months of age)
- **Pain control/antipyretic:** 5-10 mg/kg q6-8h
 - **Oral weight bands:**

6-<10 kg	50 mg q8h
10-<15 kg	100 mg q8h
15-<20 kg	150 mg q8h
20-<30 kg	200 mg q8h
≥30 kg	200-400 mg q6-8h (Max 2.4 g/day)

OR

- Paracetamol (acetaminophen)
- **Pain control/antipyretic:** 10-15 mg/kg q6h
 - **Oral weight bands:**

3-<6 kg	60 mg q6h
6-<10 kg	100 mg q6h
10-<15 kg	150 mg q6h
15-<20 kg	200 mg q6h
20-<30 kg	300 mg q6h
≥30 kg	500 mg-1 g q4-6h (Max 4 g/day or 2 g/day if hepatic impairment/cirrhosis)

Antibiotic Treatment

Antibiotic treatment is **not recommended and should be avoided** as there is no evidence of a significant clinical benefit and there is a risk of side effects of antibiotics

Pathophysiology

Acute bronchitis is caused by tissue damage of the bronchial wall and inflammatory response triggered by the proliferation of microorganisms in the affected bronchi.

Epidemiology

Acute bronchitis is a very common condition that can affect people of all ages, mostly during the seasons when respiratory viruses are common. Smoking and exposure to air pollution are risk factors. Acute bronchitis is one of the most common reasons for consultations in the primary health care setting and it is associated with frequent unnecessary use of antibiotics both in children and adults (39–41).

Most likely pathogens

A causative pathogen is not identified in most cases of acute bronchitis. Most cases of acute bronchitis are of viral origin (Table 4.1).

Table 4.1 – Pathogens most frequently associated with acute bronchitis (in descending order of frequency)

Respiratory viruses
Rhinovirus
Influenza virus (A and B)
Parainfluenza virus
Coronavirus (including SARS-CoV-2)
Respiratory syncytial virus
Metapneumovirus
Adenovirus
Other respiratory viruses

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

Note. Nearly all cases of acute bronchitis have a viral origin. Only in a very small proportion of cases, are atypical pathogens (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*) involved. Atypical bacteria are intracellular and are colourless with Gram staining. They also have intrinsic resistance to beta-lactams either because they lack a cell wall (*Mycoplasma*) and / or are intracellular pathogens (*Chlamydia*).

Clinical presentation

Well-established clinical features of acute bronchitis include acute onset (less than 2 weeks) of cough lasting > 5 days with or without sputum production (of note yellow/green sputum

does not indicate a bacterial infection). Bronchitis is generally a mild condition with no tachycardia (i.e. no increased heart rate) or tachypnoea (i.e. no increased respiratory rate) and in most cases of acute bronchitis there is no fever. Cough usually persists for 10-20 days (around 1–3 weeks) but it can last longer.

Because the predominant symptoms are cough with or without fever, these symptoms can overlap with the clinical picture of pneumonia. As a result, patients can be incorrectly diagnosed as having pneumonia in the initial assessment and are often therefore inappropriately treated with antibiotics. This misdiagnosis can be avoided with careful patient assessment to clearly differentiate the two infections.

Usually, patients with pneumonia:

- are clinically unwell and with systemic signs of infection (e.g. fever, increased heart rate, increased respiratory rate or focal chest signs),
- are short of breath,
- have cough with sputum production.

Please refer to the chapter on community-acquired pneumonia (CAP) for the typical clinical presentation of patients with pneumonia.

In patients with pre-existing chronic obstructive pulmonary diseases (COPD), please refer to the chapter on this condition.

Laboratory tests

Patient microbiology tests

No microbiology test is usually required.

During the influenza season or in case of outbreaks, a nasopharyngeal swab to test for influenza could be considered. Local policies should be followed as to whether during the coronavirus disease 2019 (COVID-19) pandemic a nasopharyngeal swab or other sample (e.g. pharyngeal swab or saliva) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing (nucleic acid amplification test or rapid antigen test) should be obtained. Refer to the latest WHO guidelines for the management of patients with suspected SARS-CoV-2 infection.

Other tests

In the great majority of cases of bronchitis, laboratory tests are not needed.

In uncertain cases some experts advocate the use of biomarkers of infection (C-reactive protein, procalcitonin) to differentiate viral bronchitis from bacterial pneumonia, but these add costs and can also result in inappropriate prescribing due to the limited sensitivity and specificity of these tests.

Using microbiology surveillance data

As antibiotics are not recommended no routine microbiology surveillance is required.

Surveillance of circulating respiratory viruses can be useful to predict and follow epidemics and outbreaks, for example, SARS-CoV-2, influenza virus and respiratory syncytial virus.

Imaging

Imaging is usually not needed.

No antibiotic care

Patients or parents should be informed about the natural course of acute bronchitis. It should be explained that the cough can persist for several weeks, often at night, the great majority of cases are self-limiting (and of viral origin) and there is no benefit from a course of antibiotic treatment. For symptomatic care for cold or mild influenza symptoms refer to Table 4.2. There is no clear evidence to support the usefulness of bronchodilators (in case of wheezing), or mucolytic or antitussive agents, but their use could be considered based on local practices and patient preferences.

Table 4.2 – Medicines to consider for symptomatic treatment of acute bronchitis

Medicine	Formulation	Dose and frequency
Ibuprofen ^a	Oral liquid: 200 mg/5 mL Tablet: 200 mg; 400 mg; 600 mg	Adults: 200–400 mg given every 6 to 8 hours (maximum dose of 2.4 g a day) Children: <ul style="list-style-type: none">• Pain control/antipyretic treatment: 5–10 mg/kg given every 6 to 8 hours6–< 10 kg: 50 mg given every 8 hours10–< 15 kg: 100 mg given every 8 hours15–< 20 kg: 150 mg given every 8 hours20–< 30 kg: 200 mg given every 8 hours≥ 30 kg: use adult dose
Paracetamol (acetaminophen) ^b	Oral liquid: 120 mg/5 mL; 125 mg/5 mL Suppository: 100 mg Tablet: 100 mg to 500 mg	Adults: 500 mg–1 g given every 4 to 6 hours (maximum dose of 4 g a day) ^c Children: <ul style="list-style-type: none">• Pain control/antipyretic treatment: 10–15 mg/kg given every 6 hours3–< 6 kg: 60 mg given every 6 hours6–< 10 kg: 100 mg given every 6 hours10–< 15 kg: 150 mg given every 6 hours15–< 20 kg: 200 mg given every 6 hours20–< 30 kg: 300 mg given every 6 hours≥ 30 kg: use adult dose

^a Not for children < 3 months.^b Not recommended for use as an anti-inflammatory as it has not been proven to have such an effect.^c In patients with hepatic impairment or cirrhosis, maximum daily dose should be 2 g.

Antibiotic treatment

Antibiotic treatment is **not recommended** for acute bronchitis and should be avoided. There is no evidence of a meaningful clinical benefit of antibiotics and their use is not supported by the available clinical evidence (42).

5. Acute otitis media

Key messages

- **Antibiotics are not needed** for most cases.
- Symptomatic treatment alone (pain and fever control with close follow up) is appropriate in mild cases especially in children > 2 years.
- Antibiotic treatment could be considered in selected cases (e.g. severe symptoms, immunosuppression or bilateral otitis in children < 2 years).
- Amoxicillin has good activity against *Streptococcus pneumoniae*, the most common bacterial pathogen in acute otitis media.
- Higher doses of amoxicillin are effective against most resistant strains of *Streptococcus pneumoniae*.

Other relevant WHO resources (please check regularly for updates)

- Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, 2013 (31).
- Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper – February 2019 (35).
- *Haemophilus influenzae* type b (Hib) vaccination position paper – July 2013 (36).
- Vaccines against influenza WHO position paper – May 2022 (37).

Definition

Acute otitis media is an infection of the middle ear that occurs mostly in infants and children younger than 5 years, typically as a complication of a viral upper respiratory tract infection.

Acute otitis media

Definition

Infection of the middle ear that is rare in adults, often as a complication of a viral upper respiratory tract infection

Diagnosis

Clinical Presentation

Acute onset of ear pain (unilateral or bilateral), fever ($\geq 38.0^{\circ}\text{C}$), +/- ear discharge

Microbiology Tests

- Not needed unless a complication is suspected
- Cultures of pus from perforated ear drums should not be used to guide treatment

Other Laboratory Tests

Not needed unless a complication is suspected

Imaging

Not needed unless a complication (e.g. mastoiditis, brain abscess) is suspected

Otoscopy

Required for definitive diagnosis if available:
Bulging, inflamed/congested tympanic membrane (may be opaque/show decreased mobility)

Most Likely Pathogens

Respiratory viruses (most cases):

- Respiratory syncytial virus (RSV)
- Rhinovirus
- Coronavirus (including SARS-CoV-2)
- Influenza virus (A and B)
- Other respiratory viruses

Bacteria (rarely bacterial superinfections can occur):

- Streptococcus pneumoniae*
- Haemophilus influenzae*
- Moraxella catarrhalis*
- Streptococcus pyogenes* (group A *Streptococcus*)

Prevention

Overlaps with prevention of upper respiratory tract infections; hand hygiene, vaccination against *S. pneumoniae*, influenza and SARS-CoV-2 viruses can be useful

Treatment

Clinical Considerations

Important: Most non-severe cases can be managed

symptomatically with **no antibiotic treatment**

- Instruct patients to monitor symptoms and report back in case they worsen/persist after few days

Antibiotics should be considered if:

- Severe symptoms (e.g. systemically very unwell, ear pain despite analgesics, fever $\geq 39.0^{\circ}\text{C}$)

Symptomatic Treatment

Medicines are listed in alphabetical order and should be considered equal treatment options

 Ibuprofen 200-400 mg q6-8h (Max 2.4 g/day)

OR

 Paracetamol (acetaminophen) 500 mg-1 g q4-6h (max 4 g/day)

Hepatic impairment/cirrhosis: Max 2 g/day

Antibiotic Treatment Duration

5 days

Antibiotic Treatment

Antibiotic treatment is not required in the great majority of cases (see "Clinical Considerations" when antibiotics may be indicated)

All dosages are for normal renal function

First Choice

 Amoxicillin 500 mg q8h **ORAL**

Second Choice

 Amoxicillin+clavulanic acid 500 mg+125 mg q8h **ORAL**

Acute otitis media

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Definition

Infection of the middle ear that occurs mostly in children under 5 years of age, often as a complication of a viral upper respiratory tract infection

Most Likely Pathogens

Respiratory viruses:

- Respiratory syncytial virus (RSV)
- Rhinovirus
- Coronavirus (including SARS-CoV-2)
- Influenza virus (A and B)
- Other respiratory viruses

Bacteria (rarely bacterial superinfections can occur):

- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Moraxella catarrhalis*
- *Streptococcus pyogenes* (group A *Streptococcus*)

Prevention

Overlaps with prevention of upper respiratory tract infections; hand hygiene, vaccination against *S. pneumoniae*, *H. influenzae* and influenza viruses can be useful

Diagnosis

Clinical Presentation

Acute onset of ear pain (unilateral or bilateral), fever (38.0°C) +/- ear discharge

Microbiology Tests

- Not needed unless a complication is suspected
- Cultures of pus from perforated ear drums should not be used to guide treatment

Other Laboratory Tests

Not needed unless a complication is suspected

Imaging

Not needed unless a complication (e.g. mastoiditis, brain abscess) is suspected

Otoscopy

Required for definitive diagnosis if available:
Bulging, inflamed/congested tympanic membrane (may be opaque/show decreased mobility)

Acute otitis media

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Rx Treatment

Clinical Considerations

Important: Most non-severe cases can be managed symptomatically with no antibiotic treatment, especially in children >2 years of age

- Instruct caregivers to monitor symptoms and report back in case they worsen/persist after few days

Antibiotics should be considered if:

- Severe symptoms (e.g. systemically very unwell, ear pain despite analgesics, fever ≥39.0 °C)
- Immunocompromised children
- Bilateral acute otitis media in children <2 years

Rx Symptomatic Treatment

Medicines are listed in alphabetical order and should be considered equal treatment options

- Ibuprofen (do not use if <3 months of age)
- Pain control/antipyretic: 5-10 mg/kg q6-8h
 - Oral weight bands:

6-<10 kg	50 mg q8h
10-<15 kg	100 mg q8h
15-<20 kg	150 mg q8h
20-<30 kg	200 mg q8h
≥30 kg	200-400 mg q6-8h (Max 2.4 g/day)

OR

- Paracetamol (acetaminophen)
- Pain control/antipyretic: 10-15 mg/kg q6h
 - Oral weight bands:

3-<6 kg	60 mg q6h
6-<10 kg	100 mg q6h
10-<15 kg	150 mg q6h
15-<20 kg	200 mg q6h
20-<30 kg	300 mg q6h
≥30 kg	500 mg-1 g q4-6h (Max 4 g/day or 2 g/day if hepatic impairment/cirrhosis)

Antibiotic Treatment Duration

5 days

Rx Antibiotic Treatment

Antibiotic treatment is not required in the great majority of cases (see "Clinical Considerations" when antibiotics may be indicated)

All dosages are for normal renal function

First Choice

-  Amoxicillin 80-90 mg/kg/day **ORAL**
- Oral weight bands:

3-<6 kg	250 mg q12h
6-<10 kg	375 mg q12h
10-<15 kg	500 mg q12h
15-<20 kg	750 mg q12h
≥20 kg	500 mg q8h or 1 g q12h

Second Choice

-  Amoxicillin+clavulanic acid 80-90 mg/kg/day of amoxicillin component **ORAL**

- Oral weight bands:

3-<6 kg	250 mg of amox/dose q12h
6-<10 kg	375 mg of amox/dose q12h
10-<15 kg	500 mg of amox/dose q12h
15-<20 kg	750 mg of amox/dose q12h
≥20 kg	500 mg of amox/dose q8h or 1 g of amox/dose q12h

Amox = amoxicillin

Oral liquid must be refrigerated after reconstitution

Pathophysiology

Pathogens that infect the middle ear come from the nasopharynx through the Eustachian tube usually following a viral infection of the upper respiratory tract. Inflammation and oedema cause narrowing of the tube and accumulation of mucosal secretions which favours growth of pathogens in the middle ear. This sequence of events triggers the typical signs and symptoms of otitis media.

Epidemiology

Acute otitis media is very common in young children under 5 years of age with most experiencing at least one episode before the age of 3 years. Acute otitis media can complicate upper respiratory tract infections in up to a third of cases, especially in the first year of life (43). The estimated global incidence of acute otitis media in 2017 was 317 million cases, for all ages and both sexes combined (44). Children are more at risk of acute otitis media because their Eustachian tubes are narrower than those of an adult, which results in impaired drainage of fluids away from the middle ear. The incidence declines with age and adults are rarely affected. In countries where vaccination programmes against pneumococcal infection have been implemented, the incidence of acute otitis media among children has declined substantially (45,46). In low- and middle-income countries, acute otitis media is still an important cause of hearing loss in children due to its progression into chronic suppurative otitis media when untreated (47).

Most likely pathogens

Several bacterial and/or viral respiratory pathogens are associated with acute otitis media (Table 5.1) (48). Most cases of otitis media are triggered by infections with respiratory viruses (respiratory syncytial virus, rhinovirus and coronavirus), which can be complicated by superinfection with bacteria.

Table 5.1 – Pathogens most frequently associated with acute otitis media (in descending order of frequency)

Respiratory viruses (most cases)	Bacteria (rarely)
Respiratory syncytial virus	<i>Streptococcus pneumoniae</i>
Rhinovirus	<i>Haemophilus influenzae</i>
Coronavirus (including SARS-CoV-2)	<i>Moraxella catarrhalis</i>
Influenza virus (A and B)	<i>Streptococcus pyogenes</i> (group A <i>Streptococcus</i>)
Other respiratory viruses	

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

Otitis media caused by possible antibiotic-resistant pathogens

Amoxicillin has good activity against most isolates of *Streptococcus pneumoniae*. Local patterns of susceptibility and individual risk factors should be considered when evaluating the possibility of an infection caused by isolates likely to be resistant to amoxicillin. Resistance is more likely in the case of recent exposure to amoxicillin (less than 3 months) or recurrent episodes (more than four episodes a year) of acute otitis media. Higher doses of amoxicillin are still active against most resistant strains of *Streptococcus pneumoniae* and this antibiotic remains the treatment of choice.

Clinical presentation

Typical signs and symptoms of acute otitis media include recent onset of ear pain (unilateral or bilateral), fever ($\geq 38.0^{\circ}\text{C}$) and at times, ear discharge.

Laboratory tests

Patient microbiology tests

In uncomplicated cases, microbiological tests are usually not needed and cultures of pus from perforated ear drums should not be used to guide treatment.

Other tests

When acute otitis media is suspected clinically, blood tests are usually not needed (except in situations where complications such as mastoiditis are suspected).

Using microbiology surveillance data

There is no role for routine surveillance for resistant pathogens.

Otoscopy

Otoscopy is required for a definitive diagnosis of acute otitis media. However, otoscopy or health care personnel with otoscopy skills may not be available in all settings.

In settings where otoscopy is available, classic findings include bulging, inflamed/congested tympanic membrane that may be opaque and show decreased mobility (Figure 5.1).

Figure 5.1 – Image of inflamed/congested tympanic membrane in otitis media



Source: © B. Welleschik, CC BY-SA 3.0, via Wikimedia Commons.

Imaging

In uncomplicated cases, no imaging study is needed. If available, imaging (e.g. computed tomography (CT) scan) may be indicated only in situations where complications such as mastoiditis are suspected.

No antibiotic care

Most non-severe cases of acute otitis media can be managed symptomatically and do not require antibiotic treatment, especially in children older than 2 years.

Non-severe cases usually have mild symptoms, often pain in one ear, and mild fever (< 39.0 °C), which improves with antipyretics. A watchful waiting approach with symptomatic management (i.e. analgesics and antipyretics) is appropriate (Table 5.2). Watchful waiting involves careful monitoring of the child by caregivers, with instructions to seek care in case of worsening of fever, pain or persistence of the symptoms.

The great majority of cases usually resolve spontaneously over a few days with no need for antibiotic treatment and the risk of complications (e.g. acute mastoiditis) is very low. Reassessment could be considered if symptoms do not improve over 3 days.

Table 5.2 – Medicines to consider for pain control of acute otitis media

Important		
Medicines are listed in alphabetical order and they should all be considered equal treatment options.		
Medicine	Formulation	Dose and frequency
Ibuprofen ^a	Oral liquid: 200 mg/5 mL Tablet: 200 mg; 400 mg; 600 mg	Adults: 200–400 mg given every 6 to 8 hours (maximum dose of 2.4 g a day) Children: <ul style="list-style-type: none">• Pain control/antipyretic treatment: 5–10 mg/kg given every 6 to 8 hours6–< 10 kg: 50 mg given every 8 hours10–< 15 kg: 100 mg given every 8 hours15–< 20 kg: 150 mg given every 8 hours20–< 30 kg: 200 mg given every 8 hours≥ 30 kg: use adult dose
Paracetamol (acetaminophen) ^b	Oral liquid: 120 mg/5 mL; 125 mg/5 mL Suppository: 100 mg Tablet: 100 mg to 500 mg	Adults: 500 mg–1 g given every 4 to 6 hours (maximum dose of 4 g a day) ^c Children: <ul style="list-style-type: none">• Pain control/antipyretic treatment: 10–15 mg/kg given every 6 hours3–< 6 kg: 60 mg given every 6 hours6–< 10 kg: 100 mg given every 6 hours10–< 15 kg: 150 mg given every 6 hours15–< 20 kg: 200 mg given every 6 hours20–< 30 kg: 300 mg given every 6 hours≥ 30 kg: use adult dose

^a Not for children < 3 months.^b Not recommended for use as an anti-inflammatory as it has not been proven to have such an effect.^c In patients with hepatic impairment or cirrhosis, maximum daily dose should be 2 g.

Antibiotic treatment

Antibiotic treatment should be considered in specific cases (see Table 5.3 for choice of antibiotics):

- in cases with severe symptoms, for example, systemically very unwell, ear pain despite analgesics, fever $\geq 39.0^{\circ}\text{C}$,
- in immunocompromised children because of the higher risk of complications, and
- in cases with bilateral acute otitis media in children under 2 years.

There is no clear consensus on offering antibiotic treatment in non-severe cases of recurrent acute otitis media (i.e. three or more episodes in the previous 6 months or four or more episodes in the previous year), in non-severe cases presenting with otorrhoea and in non-severe cases in neonates.

Table 5.3 – Empiric antibiotic treatment for acute bacterial otitis media

! Important			
	Adults	Children	Total treatment duration (49–51)
First choice	Amoxicillin (oral): 500 mg given every 8 hours	Amoxicillin (oral): 80–90 mg/kg/day Oral weight bands: 3–6 kg: 250 mg given every 12 hours 6–< 10 kg: 375 mg given every 12 hours 10–< 15 kg: 500 mg given every 12 hours 15–< 20 kg: 750 mg given every 12 hours ≥ 20 kg: 500 mg given every 8 hours or 1 g given every 12 hours	5 days

continues

Table 5.3 continued

	Adults	Children	Total treatment duration (49–51)
Second choice	Amoxicillin+clavulanic acid (oral): 500 mg + 125 mg given every 8 hours	Amoxicillin+clavulanic acid ^a (oral): 80–90 mg/kg/day of amoxicillin component Oral weight bands: 3–< 6 kg: 250 mg of amoxicillin/dose given every 12 hours 6–< 10 kg: 375 mg of amoxicillin/dose given every 12 hours 10–< 15 kg: 500 mg of amoxicillin/dose given every 12 hours 15–< 20 kg: 750 mg of amoxicillin/dose given every 12 hours ≥ 20 kg: 500 mg of amoxicillin/dose given every 8 hours or 1 g of amoxicillin/dose given every 12 hours	5 days

Note. All dosages are for normal renal and hepatic function.

^a Oral liquid formulations must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Prevention

Prevention of acute otitis media is the same as prevention of upper respiratory tract infections. All strategies (e.g. hand hygiene) that help prevent upper respiratory tract infections can be useful in preventing otitis media, including vaccination against *Streptococcus pneumoniae* and *Haemophilus influenzae* type b for all children (35,36). For countries considering vaccination programmes for influenza, vaccination of high-risk groups could also be considered (e.g. young children) (37).

6. Pharyngitis

Key messages

- **Antibiotics are not needed** for most cases since most cases are self-limiting and of viral origin.
- Pharyngitis (sore throat) is a very common condition and one of the main causes of antibiotic overuse in primary health care.
- In bacterial pharyngitis, antibiotic treatment only reduces sore throat pain for around 1 day.
- Cases caused by *Streptococcus pyogenes* (group A *Streptococcus*) can very rarely be complicated by, for example, rheumatic fever, rheumatic heart disease and acute glomerulonephritis.
- The only clear indication for antibiotic treatment of pharyngitis is to reduce the probability of developing rheumatic fever in endemic settings.

Other relevant WHO resources (please check regularly for updates)

- Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, 2013 (31).
- Rheumatic heart disease – fact sheet (52).
- Rheumatic fever and rheumatic heart disease: report of a WHO expert consultation, Geneva, 20 October–1 November 2001 (53).
- Diphtheria vaccine: WHO position paper – August 2017 (54).

Definition

Pharyngitis is commonly defined as an inflammation of the pharynx characterized by sore throat and painful swallowing.



Pharyngitis

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Definition

Inflammation of the pharynx characterized by sore throat and painful swallowing



Most Likely Pathogens

Viruses (> 80% of cases):

- Respiratory viruses (most cases)
- Epstein Barr virus (rarely)

Bacteria:

- Group A Streptococcus (5-10% in adults)
- Streptococci (group C and G)

Other infectious causes:

- Acute HIV-infection and other sexually transmitted diseases (syphilis, gonorrhoea)
- Acute toxoplasmosis
- Diphtheria

Non infectious (rare):

- Pollution
- Allergens
- Smoking



Diagnosis



Clinical Presentation

Sore throat and painful swallowing

- **Viral:** Symptoms are often the same as those of a viral upper respiratory tract infection (URTI) with cough, headache and myalgia

- **Bacterial:** More severe presentation, fever ($\geq 38.0^{\circ}\text{C}$), tender cervical lymph nodes and pharyngeal exudates (see "Centor Clinical Scoring System")



Microbiology Tests

**Low likelihood of Group A Streptococcus (GAS)
(Centor score 0-2):**

- Tests usually not needed

Higher likelihood of GAS (Centor score 3-4):

- Rapid antigen test or throat culture could be considered, especially in countries where rheumatic fever (RF) and rheumatic heart disease are frequent
- Tests should only be performed if antibiotic treatment is considered following a positive test result



Other Laboratory Tests

Blood tests usually not needed



Imaging

Usually not needed unless a complication is suspected

Pharyngitis

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Centor Clinical Scoring System

- This system can help indicate infection origin (bacterial or viral) and whether antibiotics are necessary
- However even with a score of 4, the probability of GAS infection is only 50% and this score has only been validated in high-income settings

Signs & Symptoms (1 point each)

- Fever > 38.0 °C
- No cough
- Tender anterior cervical lymphadenitis
- Tonsillar exudates

Score 0-2

- GAS pharyngitis unlikely

- **Symptomatic treatment only**

Score 3-4 - In case of low risk of RF (e.g. countries with **low** prevalence of RF)

- **Antibiotic treatment can be withheld** even in cases of likely GAS pharyngitis

Score 3-4 - In case of high risk of RF (e.g. countries with **med/high** prevalence of RF)

- Antibiotic treatment recommended

Rx Treatment

Rx Symptomatic Treatment

Medicines are listed in alphabetical order and should be considered equal treatment options

-  Ibuprofen 200-400 mg q6-8h (Max 2.4 g/day)

OR

-  Paracetamol (acetaminophen) 500 mg-1 g q4-6h (max 4 g/day)
- **Hepatic impairment/cirrhosis:** Max 2 g/day



Antibiotic Treatment Duration

Depending on the local prevalence or previous history of rheumatic fever:

- Low Risk of RF: **5 days**
- High Risk of RF: **10 days**

Note: when clarithromycin or cefalexin are used treatment duration is always 5 days

Rx Antibiotic Treatment

The only clear indication for antibiotic treatment is to reduce the probability of developing rheumatic fever in endemic settings (however, after 21 years of age the risk of RF is lower)

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice

-  Amoxicillin 500 mg q8h **ORAL**
ACCESS

OR

-  Phenoxymethylpenicillin (as potassium) 500 mg (800 000 IU) q6h **ORAL**
ACCESS

Second Choice

-  Cefalexin 500 mg q8h **ORAL**
ACCESS

OR

-  Clarithromycin 500 mg q12h **ORAL**
WATCH

GAS remains universally susceptible to penicillin. However, resistance to macrolides is common in some communities

Pharyngitis

Page 1 of 2

Definition

Inflammation of the pharynx characterized by sore throat and painful swallowing

Most Likely Pathogens

Viruses (> 80% of cases):

- Respiratory viruses (most cases)
- Epstein Barr virus

Bacteria:

- Group A Streptococcus (20-30% in children)
- Streptococci (group C and G)

Other infectious causes:

- Acute toxoplasmosis
- Diphtheria

Non infectious (rare):

- Pollution
- Allergens
- Smoking

Diagnosis

Clinical Presentation

Sore throat and painful swallowing

- **Viral:** Symptoms are often the same as those of a viral upper respiratory tract infection (URTI) with cough, headache and myalgia

- **Bacterial:** More severe presentation, fever ($\geq 38.0^{\circ}\text{C}$), tender cervical lymph nodes and pharyngeal exudates

Microbiology Tests

Lower likelihood to be caused by Group A Streptococcus (GAS) (Centor score 0-2):

- Tests usually not needed

Higher likelihood to be caused by GAS (Centor score 3-4):

- Rapid antigen test or throat culture could be considered, especially in countries where rheumatic fever (RF) and rheumatic heart disease are frequent
- Negative rapid antigen test could be confirmed with a throat culture if available

Other Laboratory Tests

Blood tests usually not needed

Imaging

Usually not needed unless a complication is suspected

Pharyngitis

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Centor Clinical Scoring System

- This system can help indicate infection origin (bacterial or viral) and whether antibiotics are necessary
- However even with a score of 4, the probability of GAS infection is only 50% and this score has only been validated in high-income settings

Signs & Symptoms (1 point each)

- Fever > 38.0 °C
- No cough
- Tender anterior cervical lymphadenitis
- Tonsillar exudates

Score 0-2

- GAS pharyngitis unlikely
- **Symptomatic treatment only**

Score 3-4 - In case of low risk of RF (e.g. countries with **low** prevalence of RF)

- **Antibiotic treatment can be withheld** even in cases of likely GAS pharyngitis

Score 3-4 - In case of high risk of RF (e.g. countries with **med/high** prevalence of RF)

- Antibiotic treatment recommended

Rx Treatment

Rx Symptomatic Treatment

Medicines are listed in alphabetical order and should be considered equal treatment options

-  Ibuprofen (do not use if <3 months of age)
 - Pain control/antipyretic: 5-10 mg/kg q6-8h
 - Oral weight bands:

6-<10 kg	50 mg q8h
10-<15 kg	100 mg q8h
15-<20 kg	150 mg q8h
20-<30 kg	200 mg q8h
≥30 kg	200-400 mg q6-8h (Max 2.4 g/day)

OR

-  Paracetamol (acetaminophen)
 - Pain control/antipyretic: 10-15 mg/kg q6h
 - Oral weight bands:

3-<6 kg	60 mg q6h
6-<10 kg	100 mg q6h
10-<15 kg	150 mg q6h
15-<20 kg	200 mg q6h
20-<30 kg	300 mg q6h
≥30 kg	500 mg-1 g q6h (Max 4 g/day or 2 g/day if hepatic impairment/cirrhosis)

Rx Antibiotic Treatment

The only clear indication for antibiotic treatment is to reduce the probability of developing rheumatic fever in endemic settings

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice

-  Amoxicillin 80-90 mg/kg/day **ORAL**
 - Oral weight bands:

3-<6 kg	250 mg q12h
6-<10 kg	375 mg q12h
10-<15 kg	500 mg q12h
15-<20 kg	750 mg q12h
≥20 kg	500 mg q8h or 1 g q12h

OR

-  Phenoxymethylpenicillin (as potassium):
 - 10-15 mg/kg/dose (16 000-24 000 IU/kg/dose)
q6-8h **ORAL**

Second Choice

-  Cefalexin 25 mg/kg/dose q12h **ORAL**
 - Oral weight bands:

3-<6 kg	125 mg q12h
6-<10 kg	250 mg q12h
10-<15 kg	375 mg q12h
15-<20 kg	500 mg q12h
20-<30 kg	625 mg q12h
≥30 kg	500 mg q8h

OR

-  Clarithromycin 7.5 mg/kg/dose q12h **ORAL**

GAS remains universally susceptible to penicillin. However, resistance to macrolides is common in some communities

Antibiotic Treatment Duration

Depending on the local prevalence or previous history of rheumatic fever:

- Low Risk of RF: **5 days**
- High Risk of RF: **10 days**

Note: when clarithromycin or cefalexin are used treatment duration is always 5 days

Pathophysiology

Viruses and bacteria responsible for pharyngitis gain access to the mucosal cells of the pharynx through different mechanisms and start replicating in these cells. Damage is caused to the cells where pathogens are replicating.

Epidemiology

Sore throat is one of the most common conditions in patients presenting to primary health care and remains a very frequent cause of inappropriate antibiotic prescribing. Up to 60% of patients with sore throat are given antibiotics in many high-income outpatient settings (55,56).

Incidence and prevalence data on sore throat are unavailable for most low- and middle-income country settings. Most cases of pharyngitis are self-limiting and of viral origin. Cases of sore throat caused by bacteria (mostly *Streptococcus pyogenes*) are rare and were responsible for about 10% of cases among patients with sore throat of all ages in a meta-analysis, but severe complications can occur (57). These complications are either due to invasion of the organism in the pharynx (e.g. suppurative complications such as quinsy) or to an abnormal immunological response (e.g. acute rheumatic fever) (58,59). Suppurative complications occur in a very small number of cases, are difficult to predict and most can be readily treated (60,61). For this reason, the prevention of suppurative complications should not be considered an indication for antibiotic treatment in sore throat.

Rheumatic fever is also a rare complication due to an autoimmune inflammatory reaction to untreated streptococcal pharyngitis; usually less than 3% of untreated cases of pharyngitis caused by *Streptococcus pyogenes* trigger rheumatic fever in settings where this condition is endemic (53,62). The incidence of rheumatic fever peaks between 5 and 15 years of age and is rare in people older than 30 years.

When rheumatic fever develops, it usually presents (70–75% of cases) as an acute febrile illness with joint manifestations (e.g. pain or tenderness) and carditis. Less frequently, rheumatic fever can present as a predominantly neurological and/or behavioural disorder. Symptoms usually develop 2–3 weeks after the initial symptoms of pharyngitis are evident. Ultimately, rheumatic fever can result in damage to the heart valves (rheumatic heart disease). About 60% of people with rheumatic fever will develop rheumatic heart disease and the risk is two times higher for females than males.

Despite the lack of data from many countries, 30 million people worldwide are thought to be affected by rheumatic heart disease, with an estimated 320 000 deaths in 2015 (63).

Cases of rheumatic fever are concentrated in the WHO African, South-East Asian and Western Pacific regions; these regions account for about 84% of cases. With 27% of all cases of rheumatic fever in 2015 India has the highest burden worldwide (53).

Most likely pathogens

Most (> 80%) cases of pharyngitis are caused by a viral infection (respiratory viruses have been identified in 25–45% of cases; less frequently, the Epstein–Barr virus or other viruses of the herpesvirus family or SARS-CoV-2 are the cause). A minority of cases of pharyngitis are caused by bacteria, mainly *Streptococcus pyogenes* (group A *Streptococcus*). Other streptococci (group C and G) have also been implicated as causes of pharyngitis (Table 6.1). Other infectious causes that need to be considered are acute human immunodeficiency virus (HIV) infection and other sexually transmitted infections (STIs) such as syphilis and gonorrhoea, acute toxoplasmosis and diphtheria – consider diphtheria if fever and greyish-white membranes covering the tonsil(s) are present in a child not vaccinated against diphtheria. Rarely, the cause of pharyngitis is non-infectious, for example, exposure to pollution, allergens and smoking.

Table 6.1 – Pathogens most frequently associated with pharyngitis (in descending order of frequency)

Viruses (most cases)	Bacteria (rarely)
Respiratory syncytial virus	<i>Streptococcus pyogenes</i> (group A <i>Streptococcus</i>)
Rhinovirus	Group C <i>Streptococcus</i>
Coronavirus (including SARS-CoV-2)	Group G <i>Streptococcus</i>
Influenza virus (A and B)	<i>Treponema pallidum</i>
Other respiratory viruses	<i>Neisseria gonorrhoeae</i>
Other viruses (rarely)	
Epstein–Barr virus	
HIV	

HIV: human immunodeficiency virus; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

Pharyngitis caused by antibiotic-resistant pathogens

Streptococcus pyogenes is still universally very susceptible to penicillin. Resistance to penicillin has never been reported and there is no evidence of increasing minimal inhibitory concentrations. However, resistance to macrolides is common in some settings.

Clinical presentation

Pharyngitis is characterized by sore throat and painful swallowing. Typical accompanying signs and symptoms can vary depending on the etiology. If the cause is viral, symptoms

match those of a viral upper respiratory tract infection, and cough, headache and myalgia are likely to be present. If the cause is bacterial, a more severe presentation is usually seen, with fever ($\geq 38.0^{\circ}\text{C}$), tender cervical lymph nodes and pharyngeal exudates. Several clinical scoring systems have been developed to identify patients with higher likelihood of pharyngitis being caused by *Streptococcus pyogenes* (see the next section).

Scoring symptoms of pharyngitis

The specific cause of pharyngitis may be difficult to recognize based on symptoms alone. Scoring systems can help differentiate a viral infection from one of bacterial origin. The rationale is to help health care workers standardize the therapeutic approach and decide whether antibiotic treatment could be given based on the most likely etiology. However, scoring systems have a low specificity (i.e. high risk of incorrectly identifying patients with viral pharyngitis as having a *Streptococcus pyogenes* infection) and can lead to unnecessary antibiotic treatment. Moreover, most systems have only been validated in high-income settings.

One of the most widely used systems in the adult population is the Centor clinical scoring system (Table 6.2). However, even with the highest score of 4, the probability of an infection caused by *Streptococcus pyogenes* is only 50% (64).

In low- and middle-income countries, other scores could be considered that have been specifically validated in these settings (65).

Table 6.2 – Centor score for the clinical assessment of pharyngitis

Relevant signs and symptoms	Points
Fever $> 38.0^{\circ}\text{C}$	1
No cough	1
Tender anterior cervical lymphadenitis	1
Tonsillar exudates	1
Total score	Likelihood of <i>Streptococcus pyogenes</i> infection (%)
0	1–2.5
1	5–10
2	11–17
3	28–35

continues

Table 6.2 *continued*

4	51–53
Centor score 0 – 1 – 2	<ul style="list-style-type: none"> • <i>Streptococcus pyogenes</i> pharyngitis unlikely • Give symptomatic treatment only
Centor score 3 – 4	<ul style="list-style-type: none"> • Score suggestive of <i>Streptococcus pyogenes</i> pharyngitis • In countries with a low prevalence of rheumatic fever, antibiotic treatment can be withheld even in cases of likely <i>Streptococcus pyogenes</i> pharyngitis • In countries with medium to high prevalence of rheumatic fever, antibiotic treatment is recommended as it reduces the likelihood of developing rheumatic fever by around two thirds.

Laboratory tests

Patient microbiology tests

The choice of whether microbiological tests are helpful and which to consider is based on the likelihood of *Streptococcus pyogenes* infection. In many settings no tests are routinely available. The rationale for identifying cases caused by *Streptococcus pyogenes* is that those are the cases that may benefit the most from antibiotic treatment in certain settings (mostly to prevent rheumatic fever). In general, most guidelines prefer rapid antigen tests to cultures because they give results more quickly. Table 6.3 summarizes the microbiology tests that could be considered to diagnose pharyngitis.

Table 6.3 – Microbiology tests that could be considered if available for the diagnosis of pharyngitis as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
Group A <i>Streptococcus</i> antigen ^a (RDT)	To aid in the diagnosis of Group A streptococcal pharyngitis	Community settings and health facilities without laboratories ^b

continues

Table 6.3 continued

Diagnostic test	Purpose of the test	Settings where the test should be available
Throat culture	First step in detection and identification of bacterial species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics; RDT: rapid diagnostic test.

^a Possible specimens include: throat swabs.

^b Community and health settings without laboratories are settings such as health posts and centres, doctors' offices, outreach clinics, ambulatory care. These tests are also assumed to be available at health care facilities with laboratories.

In the case of a low likelihood of *Streptococcus pyogenes* as the causative pathogen (i.e. a Centor score of 0 to 2; see Table 6.2), rapid antigen test or throat culture are not usually needed.

In the case of a higher likelihood of *Streptococcus pyogenes* as the causative pathogen (i.e. Centor score 3–4), rapid antigen test or throat culture could be considered, especially in countries where rheumatic fever and rheumatic heart disease are important problems. (Note: WHO recommends the use of a rapid antigen test as part of the strategy for primary prevention of rheumatic fever through the effective treatment of streptococcal pharyngitis (53)).

In children and adolescents with a Centor score of 3 or 4, a negative rapid antigen test could be confirmed with a throat culture if available.

Other tests

When pharyngitis is suspected, blood tests are not usually needed unless a complication is thought to be present.

Using microbiology surveillance data

As amoxicillin or penicillin are the recommended first line treatment and *Streptococcus pyogenes* is still universally very susceptible to these antibiotics, there is no role for routine surveillance to inform empiric guidance.

Imaging

When pharyngitis is thought to be the cause of clinical symptoms, imaging is usually not required unless a complication is suspected.

No antibiotic care

Most cases of pharyngitis are of viral origin and do not benefit from antibiotics. In most cases, including those of bacterial origin, symptoms resolve within a week. Symptomatic treatment with oral analgesics and/or antipyretics, such as paracetamol and/or ibuprofen (Table 6.4) may be helpful.

Table 6.4 – Medicines to consider for pain control of pharyngitis

! Important		
Medicine	Formulation	Dose and frequency
Ibuprofen ^a	Oral liquid: 200 mg/5 mL Tablet: 200 mg; 400 mg; 600 mg	Adults: 200–400 mg given every 6 to 8 hours (maximum dose of 2.4 g a day) Children: <ul style="list-style-type: none">Pain control/antipyretic treatment: 5–10 mg/kg given every 6 to 8 hours6–< 10 kg: 50 mg given every 8 hours10–< 15 kg: 100 mg given every 8 hours15–< 20 kg: 150 mg given every 8 hours20–< 30 kg: 200 mg given every 8 hours≥ 30 kg: use adult dose
Paracetamol (acetaminophen) ^b	Oral liquid: 120 mg/5 mL; 125 mg/5 mL Suppository: 100 mg Tablet: 100 mg to 500 mg	Adults: 500 mg–1 g given every 4 to 6 hours (maximum dose of 4 g a day) ^c Children: <ul style="list-style-type: none">Pain control/antipyretic treatment: 10–15 mg/kg given every 6 hours3–< 6 kg: 60 mg given every 6 hours6–< 10 kg: 100 mg given every 6 hours10–< 15 kg: 150 mg given every 6 hours15–< 20 kg: 200 mg given every 6 hours20–< 30 kg: 300 mg given every 6 hours≥ 30 kg: use adult dose

^a Not for children < 3 months.

^b Not recommended for use as an anti-inflammatory as it has not been proven to have such an effect.

^c In patients with hepatic impairment or cirrhosis, maximum daily dose should be 2 g.

Antibiotic treatment

Most cases of pharyngitis are of viral origin and do not benefit from antibiotics.

When bacterial pharyngitis is suspected or proven, the decision to give antibiotic treatment is usually based on the likelihood of *Streptococcus pyogenes* infection and on the local prevalence or patient history of rheumatic fever. Options to consider are given in Table 6.5. Second choice options reported in Table 6.5 should only be considered in patients allergic to first-choice options. In the case of clarithromycin, the prevalence of macrolide resistance in the setting where the patient acquired the infection should be considered since macrolide resistance among *Streptococcus pyogenes* is high in certain countries.

In general, patients will fall into one of the following two categories.

- Patients treated in settings with a low prevalence of rheumatic fever. **Antibiotic treatment is not needed in most cases.** Antibiotics could be considered in some patients who have a high likelihood of pharyngitis caused by *Streptococcus pyogenes* (i.e. Centor score 3–4). However, even with a Centor score of 3 or 4, antibiotic treatment is not necessary in most cases. Antibiotic treatment reduces sore throat pain only by around 1 day and the pain can alternatively be managed by regular analgesia.

Antibiotic treatment could be discussed with patients or their caregivers on a case-by-case basis, weighing the benefits (e.g. reduced transmission and slight reduction in duration of symptoms) and risks (e.g. side-effects of antibiotics, effect on the intestinal microbiota) (66). Relief of symptoms or prevention of suppurative complications is not considered an indication for antibiotic treatment. The rationale is that most suppurative complications are not severe and can be readily recognized and treated.

- Patients treated in settings with a medium to high prevalence of rheumatic fever and rheumatic heart disease or patients with a history of rheumatic fever or rheumatic heart disease. Antibiotic treatment is usually given if the likelihood of *Streptococcus pyogenes* pharyngitis is high (i.e. Centor score 3–4). The rationale is to prevent rheumatic fever or its recurrence. However, after 21 years of age, the risk of rheumatic fever is usually lower.

Table 6.5 – Empiric antibiotic treatment in patients with a high likelihood of *Streptococcus pyogenes* pharyngitis

 **Note**

The only clear indication for antibiotic treatment is to reduce the probability of developing rheumatic fever in endemic settings; however, after 21 years of age, the risk of rheumatic fever is lower.

 **Important**

Where more than one antibiotic is recommended for an infection, they are listed in alphabetical order and they should be considered equal treatment options, unless otherwise indicated.

	Adults	Children	Total treatment duration (67,68)
First choice	Amoxicillin (oral): 500 mg given every 8 hours OR Phenoxycephalothin (oral): 500 mg (800 000 IU ^a) given every 6 hours	Amoxicillin (oral): 80–90 mg/kg/day Oral weight bands: 3–6 kg: 250 mg given every 12 hours 6–< 10 kg: 375 mg given every 12 hours 10–< 15 kg: 500 mg given every 12 hours 15–< 20 kg: 750 mg given every 12 hours ≥ 20 kg: 500 mg given every 8 hours or 1 g given every 12 hours OR Phenoxycephalothin (oral): 10–15 mg/kg/dose (16 000–24 000 IU/kg/dose ^a) given every 6 to 8 hours	5 ^b or 10 ^c days depending on the local prevalence or previous history of rheumatic fever

continues

Table 6.5 continued

	Adults	Children	Total treatment duration (67,68)
Second choice	<p>Cefalexin (oral): 500 mg given every 8 hours</p> <p>OR</p> <p>Clarithromycin^d (oral): 500 mg given every 12 hours</p>	<p>Cefalexin (oral): 25 mg/kg/dose given every 12 hours</p> <p>Oral weight bands:</p> <p>3–< 6 kg: 125 mg given every 12 hours</p> <p>6–< 10 kg: 250 mg given every 12 hours</p> <p>10–< 15 kg: 375 mg given every 12 hours</p> <p>15–< 20 kg: 500 mg given every 12 hours</p> <p>20–< 30 kg: 625 mg given every 12 hours</p> <p>≥ 30 kg: use adult dose</p> <p>OR</p> <p>Clarithromycin^d (oral): 7.5 mg/kg/dose given every 12 hours</p>	5 days

IU: international units.

Note. All dosages are for normal renal and hepatic function.

^a Units of the potassium salt.

^b In settings with a low prevalence of rheumatic fever or in patients with no history of rheumatic fever or rheumatic heart disease.

^c In settings with a high prevalence of rheumatic fever or in patients with a history of rheumatic fever or rheumatic heart disease and who are aged between 3 and 21 years.

^d In settings with a high prevalence of macrolide resistance among *Streptococcus pyogenes*, clarithromycin should not be recommended for the empiric treatment of *Streptococcus pyogenes* pharyngitis. Azithromycin could be used as an alternative (e.g. when clarithromycin is not available) but there are increasing concerns about its potential for the emergence and spread of antibiotic resistance because of its long half-life.

ACCESS antibiotics are highlighted in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Prevention

Streptococcus pyogenes pharyngitis, rheumatic fever and rheumatic heart disease

Currently, there is no licensed vaccine to prevent pharyngitis caused by *Streptococcus pyogenes*. Hand and respiratory hygiene are the best methods to limit transmission to

others. In countries where rheumatic fever is endemic, primary prevention of rheumatic fever relies on effective treatment of *Streptococcus pyogenes* pharyngitis.

In patients with a previous episode of rheumatic fever, long-term antibiotic prophylaxis with benzathine benzylpenicillin every 3–4 weeks is recommended in order to prevent subsequent episodes of *Streptococcus pyogenes* pharyngitis, which would carry a higher risk of a new episode of rheumatic fever and ultimately rheumatic heart disease (53). The duration of prophylaxis should be decided on a case-by-case basis.

Of note, WHO is currently developing guidelines for the prevention and management of rheumatic fever and rheumatic heart disease (52).

Other causes of bacterial pharyngitis: diphtheria

WHO recommends that all children worldwide be immunized against diphtheria and that people of any age who are unvaccinated or not fully vaccinated against diphtheria receive the doses necessary to complete their vaccination (54).

7. Acute sinusitis

Key messages

- **Antibiotics are not needed** in the great majority of cases.
- Most cases of sinusitis occur as a complication of a viral upper respiratory tract infection and are self-limited.
- Symptoms can last for a long time (up to 4 weeks).
- Yellow/green coloured nasal discharge alone is not a sign of bacterial infection and not an indication for antibiotic treatment.
- If antibiotic treatment is required, amoxicillin has good activity against *Streptococcus pneumoniae*, the most common bacterial cause of acute bacterial sinusitis.

Other relevant WHO resources (please check regularly for updates)

- Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper –February 2019 (35).
- *Haemophilus influenzae* type b (Hib) vaccination position paper – July 2013: Introduction (36).
- Vaccines against influenza WHO position paper – May 2022 (37).

Definition

Acute sinusitis is a symptomatic inflammation of the paranasal sinuses and nasal cavity. Most cases occur as a complication of a viral upper respiratory tract infection (e.g. a common cold caused by respiratory viruses such as rhinovirus) and symptoms can last up to 4 weeks. Acute sinusitis can also be associated with asthma, allergic rhinitis, smoking or exposure to smoke. This guidance applies mainly to maxillary sinusitis as this is the most common clinical condition.

Acute sinusitis

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Definition

A symptomatic inflammation of the paranasal sinuses and nasal cavity

Most Likely Pathogens

Respiratory viruses:

- Influenza virus (A and B)
- Rhinovirus
- Coronavirus (including SARS-CoV-2)
- Respiratory syncytial virus (RSV)
- Other respiratory viruses

Bacteria (rarely):

- *Streptococcus pneumoniae*
- *Haemophilus influenzae*

Diagnosis

Clinical Presentation

- Diagnosis is made clinically; symptoms of bacterial and viral sinusitis overlap considerably
- Symptoms usually last 10-14 days and are self-limiting
- Main symptoms are nasal drainage, nasal obstruction or congestion, unilateral dental or facial pain, facial fullness or pressure, and sometimes cough
- Location of pain depends on involved sinuses
- Acute bacterial sinusitis suspected when:
 - Signs/symptoms persist ≥10 days without improvement OR
 - Significant worsening of symptoms after initial mild phase

Microbiology Tests

Usually not needed

Other Laboratory Tests

Usually not needed

Imaging

Usually not needed unless a complication or an alternative diagnosis is suspected

Acute sinusitis

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Rx Treatment



No Antibiotic Care

- Treatment is to improve symptoms, but **antibiotics have minimal impact on symptom duration in most cases**
- Symptomatic treatment includes antipyretic and analgesic medications, nasal irrigation with a saline solution and topical intranasal glucocorticoids or decongestants
- Most guidelines recommend using disease severity (duration and intensity of symptoms) to direct treatment



Mild to Moderate Presentation (<10 days duration and improving):

- Watchful waiting approach with symptom relief and **no antibiotic treatment**



Clinical Considerations

Antibiotics should be considered if:

- Severe onset of symptoms
- Fever $\geq 39.0^{\circ}\text{C}$ & purulent nasal discharge or facial pain for at least 3-4 consecutive days
- Patients at increased risk of complications e.g. those with chronic underlying comorbid diseases (deciding on a case-by-case basis)
- "Red flag" signs/symptoms suggestive of complicated infection such as systemic toxicity, persistent fever $\geq 39.0^{\circ}\text{C}$, periorbital redness and swelling, severe headache, or altered mental status



Symptomatic Treatment

Medicines are listed in alphabetical order and should be considered equal treatment options



Ibuprofen 200-400 mg q6-8h (Max 2.4 g/day)

OR



Paracetamol (acetaminophen) 500 mg-1 g q4-6h (max 4 g/day)

• **Hepatic impairment/cirrhosis:** Max 2 g/day



Antibiotic Treatment Duration

5 days



Antibiotic Treatment

Antibiotic treatment is not required in the great majority of cases (see "Clinical Considerations" when antibiotics may be indicated)

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated



Amoxicillin 1 g q8h **ORAL**

OR



Amoxicillin+clavulanic acid 500 mg+125 mg q8h **ORAL**

Acute sinusitis

Page 1 of 2

Definition

A symptomatic inflammation of the paranasal sinuses and nasal cavity. Much less common than in adults because sinuses are not fully developed.



Most Likely Pathogens

Respiratory viruses:

- Influenza virus (A and B)
- Rhinovirus
- Coronavirus (including SARS-CoV-2)
- Respiratory syncytial virus (RSV)
- Other respiratory viruses

Bacteria (rarely):

- *Streptococcus pneumoniae*
- *Haemophilus influenzae*



Diagnosis



Clinical Presentation

- Diagnosis is made clinically; symptoms of bacterial and viral sinusitis overlap considerably
- Symptoms usually last 10-14 days and are self-limiting
- Main symptoms are nasal drainage, nasal obstruction or congestion, unilateral dental or facial pain, facial fullness or pressure, and cough
- Location of pain depends on involved sinuses
- Acute bacterial sinusitis suspected when:
 - Signs/symptoms persist ≥10 days without improvement OR
 - Significant worsening of symptoms after initial mild phase



Microbiology Tests

Usually not needed



Other Laboratory Tests

Usually not needed



Imaging

Usually not needed unless a complication or an alternative diagnosis is suspected

Acute sinusitis

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Rx Treatment



No Antibiotic Care

- Treatment is to improve symptoms, but **antibiotics have minimal impact on symptom duration in most cases**
- Symptomatic treatment includes antipyretic and analgesic medications, nasal irrigation with a saline solution and topical intranasal glucocorticoids or decongestants
- Most guidelines recommend using disease severity (duration and intensity of symptoms) to direct treatment

Mild to Moderate Presentation (<10 days duration and improving trend of symptoms):
 • Watchful waiting approach with symptom relief and **no antibiotic treatment**



Clinical Considerations

Antibiotics should be considered if:

- Severe onset of symptoms
- Fever ≥39.0 °C and purulent nasal discharge or facial pain for at least 3-4 consecutive days
- Patients at increased risk of complications e.g. those with chronic underlying comorbid diseases (deciding on a case-by-case basis)
- "Red flag" signs/symptoms suggestive of complicated infection such as systemic toxicity, persistent fever ≥39.0°C, periorbital redness and swelling, severe headache, or altered mental status



Symptomatic Treatment

Medicines are listed in alphabetical order and should be considered equal treatment options



- Ibuprofen (do not use if <3 months of age)
- Pain control/antipyretic:** 5-10 mg/kg q6-8h
- Oral weight bands:**

6-<10 kg	50 mg q8h
10-<15 kg	100 mg q8h
15-<20 kg	150 mg q8h
20-<30 kg	200 mg q8h
≥30 kg	200-400 mg q6-8h (Max 2.4 g/day)

OR



- Paracetamol (acetaminophen)
- Pain control/antipyretic:** 10-15 mg/kg q6h
- Oral weight bands:**

3-<6 kg	60 mg q6h
6-<10 kg	100 mg q6h
10-<15 kg	150 mg q6h
15-<20 kg	200 mg q6h
20-<30 kg	300 mg q6h
≥30 kg	500 mg-1 g q4-6h (Max 4 g/day or 2 g/day if hepatic impairment/cirrhosis)



Antibiotic Treatment Duration

5 days



Antibiotic Treatment

Antibiotic treatment is not required in the great majority of cases (see "Clinical Considerations" when antibiotics may be indicated)

All dosages are for normal renal function
 Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated



- Amoxicillin 80-90 mg/kg/day **ORAL**
- Oral weight bands:**

3-<6 kg	250 mg q12h
6-<10 kg	375 mg q12h
10-<15 kg	500 mg q12h
15-<20 kg	750 mg q12h
≥20 kg	500 mg q8h or 1 g q12h

OR



- Amoxicillin+clavulanate acid 80-90 mg/kg/day of amoxicillin component **ORAL**
- Oral weight bands:**

3-<6 kg	250 mg of amox/dose q12h
6-<10 kg	375 mg of amox/dose q12h
10-<15 kg	500 mg of amox/dose q12h
15-<20 kg	750 mg of amox/dose q12h
≥20 kg	500 mg of amox/dose q8h or 1 g of amox/dose q12h

Amox = amoxicillin

Oral liquid must be refrigerated after reconstitution

Pathophysiology

Nasal congestion, usually triggered by an infection of the upper respiratory tract, can lead to obstruction of the sinus ostia with consequent hypoxia of the sinuses and mucus retention. Mostly the maxillary and the anterior ethmoid sinuses are involved. The inflammatory response that develops produces the signs and symptoms of acute sinusitis.

Epidemiology

Upper respiratory tract infections are a common reason for consultations in an outpatient setting, both for children and adults. According to the 2017 Global Burden of Disease study, upper respiratory tract infections are one of the top three causes of new disease globally for all ages and both sexes combined – an estimated 17.1 billion cases are recorded a year (44). Acute sinusitis accounts for 0.5% of all upper respiratory tract infections and is much more common in adults than in children whose sinuses are not fully developed.

Most available data are from high-income settings and show that antibiotics are frequently prescribed in cases of acute viral sinusitis (7,41).

Most likely pathogens

Acute sinusitis is usually caused by respiratory viruses; only a small percentage (usually less than 2%) of cases are complicated by bacterial infection (Table 7.1).

Table 7.1 – Pathogens most frequently associated with acute sinusitis (in descending order of frequency)

Respiratory viruses (most cases) ^a	Bacteria
Influenza virus (A and B)	Rarely
Respiratory syncytial virus	<i>Streptococcus pneumoniae</i>
Parainfluenza virus	<i>Haemophilus influenzae</i>
Rhinovirus	Very rarely
Coronavirus (including SARS-CoV-2)	<i>Moraxella catarrhalis</i>
Other respiratory viruses	<i>Streptococcus pyogenes</i> (group A <i>Streptococcus</i>) <i>Staphylococcus aureus</i>

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

^a About 98% of cases are caused by respiratory viruses.

Sinusitis caused by antibiotic-resistant pathogens

Amoxicillin has good clinical activity against the great majority of isolates of *Streptococcus pneumoniae*. However, since the introduction of anti-pneumococcal vaccines, there is concern about increasing incidence of acute sinusitis caused by *Haemophilus influenzae* and *Moraxella catarrhalis* and an increased incidence of beta-lactamase production among these strains that may result in amoxicillin resistance. Higher doses of amoxicillin are still active against most resistant strains of *Streptococcus pneumoniae* and this antibiotic remains the treatment of choice.

Local patterns of susceptibility and individual risk factors should be considered when evaluating the possibility of an infection caused by isolates likely to be resistant to amoxicillin.

Clinical presentation

The diagnosis of sinusitis is made based on clinical criteria and the time pattern; it is important to consider that symptoms of acute bacterial sinusitis and acute viral sinusitis overlap considerably. Symptoms usually last for 10–14 days and are self-limiting.

The main symptoms of acute sinusitis are purulent nasal drainage, nasal obstruction or congestion, unilateral dental or facial pain, and facial fullness or pressure. Cough may also be present.

The location of pain in sinusitis depends on which sinuses are affected. For example, pain can be localized on the forehead (frontal sinuses), over cheekbones/teeth/upper jaw (maxillary sinuses) or behind the nose (ethmoid and sphenoid sinuses).

Acute bacterial sinusitis should be suspected in two situations:

- signs and symptoms persist without improvement for more than 10 days
- symptoms become significantly worse after an initial mild phase.

Yellow/green colour of nasal discharge alone is not a sign of bacterial infection and is not an indication for antibiotic treatment.

Laboratory tests

Patient microbiology tests

When sinusitis is suspected clinically, nasal cultures or nucleic acid tests for respiratory viruses are not usually needed.

Other tests

When sinusitis is suspected clinically, blood tests are usually not needed.

Using microbiology surveillance data

As the great majority of cases have no positive bacterial cultures, there is no role for routine surveillance to inform empiric guidance.

Imaging

When sinusitis is suspected clinically, imaging is not usually needed unless a complication or an alternative diagnosis is suspected.

No antibiotic care

The goal of treatment is to improve symptoms. Antibiotics have only minimal effect on the duration of symptoms in most cases and current evidence suggests that even without antibiotic treatment, most cases in healthy patients resolve within 1–2 weeks (69).

Most guidelines recommend using disease severity (i.e. duration and intensity of symptoms) to direct treatment.

In case of mild to moderate presentation (less than 10 days duration and improving symptoms), a watchful waiting approach with symptom relief and no antibiotic treatment is usually adequate. Symptoms should be managed with antipyretic and analgesic medications (Table 7.2). Nasal irrigation with a saline solution and topical intranasal glucocorticoids or decongestants may also be used to relieve symptoms, even though their effectiveness in relieving symptom is still uncertain (70).

The rationale of a watchful waiting approach is that in uncomplicated cases in adults, antibiotics (compared to no treatment) can shorten the duration of symptoms and improve the course of infection (e.g. resolution of purulent nasal discharge) only in a small percentage of patients. However, these potential benefits must be balanced against the risk of adverse events from antibiotics (e.g. gastrointestinal side-effects, allergic reaction and rash) and of increasing bacterial resistance (69).

Table 7.2 – Medicines to consider for symptomatic treatment of acute sinusitis

Medicine	Formulation	Dose and frequency
Ibuprofen ^a	Oral liquid: 200 mg/5 mL Tablet: 200 mg; 400 mg; 600 mg	Adults: 200–400 mg given every 6 to 8 hours (maximum dose of 2.4 g a day) Children: <ul style="list-style-type: none">• Pain control/antipyretic treatment: 5–10 mg/kg given every 6 to 8 hours 6–< 10 kg: 50 mg given every 8 hours 10–< 15 kg: 100 mg given every 8 hours 15–< 20 kg: 150 mg given every 8 hours 20–< 30 kg: 200 mg given every 8 hours ≥ 30 kg: use adult dose
Paracetamol (acetaminophen) ^b	Oral liquid: 120 mg/5 mL; 125 mg/5 mL Suppository: 100 mg Tablet: 100 mg to 500 mg	Adults: 500 mg–1 g given every 4 to 6 hours (maximum dose of 4 g a day) ^c Children: <ul style="list-style-type: none">• Pain control/antipyretic treatment: 10–15 mg/kg given every 6 hours 3–< 6 kg: 60 mg given every 6 hours 6–< 10 kg: 100 mg given every 6 hours 10–< 15 kg: 150 mg given every 6 hours 15–< 20 kg: 200 mg given every 6 hours 20–< 30 kg: 300 mg given every 6 hours ≥ 30 kg: use adult dose

^a Not for children < 3 months.^b Not recommended for use as an anti-inflammatory as it has not been proven to have such an effect.^c In patients with hepatic impairment or cirrhosis, maximum daily dose should be 2 g.

Antibiotic treatment

Antibiotic treatment is not required in the great majority of cases of sinusitis.

Antibiotic treatment could be considered in certain cases, such as severe onset of symptoms, patients with underlying comorbid diseases or in those at increased risk of

complications (see antibiotic options in Table 7.3). Severe onset is defined as fever $\geq 39.0\text{ }^{\circ}\text{C}$ and purulent nasal discharge or facial pain for at least 3–4 consecutive days (71). The decision to treat with antibiotics in patients with chronic comorbid diseases should always be made on a case-by-case basis. Relevant comorbid conditions to consider include chronic malignancies and immunodeficiency.

Antibiotic treatment could also be considered in cases with “red flag” signs and symptoms suggestive of a complicated infection, such as systemic toxicity, persistent fever $\geq 39.0\text{ }^{\circ}\text{C}$, periorbital redness and swelling, severe headache and altered mental status.

Prevention

Prevention of sinusitis is based on the prevention of upper respiratory tract infections. All strategies (e.g. hand and respiratory hygiene, influenza, pneumococcal and COVID-19 vaccines) that help prevent upper respiratory tract infections could be useful in preventing sinusitis, including vaccination against *Streptococcus pneumoniae* and *Haemophilus influenzae* type b for all children worldwide (35,36). For countries considering vaccination programmes for influenza, vaccination of high-risk groups could be considered, for example, children aged 6 months to 5 years (37).

Table 7.3 – Empiric antibiotic treatment for bacterial sinusitis

Note		
Antibiotic treatment is not required in the great majority of cases: see Antibiotic treatment section.		
Adults	Children	Total treatment duration (72)
Amoxicillin (oral): 1 g given every 8 hours OR Amoxicillin+clavulanic acid (oral): 500 mg + 125 mg given every 8 hours	Amoxicillin (oral): 80–90 mg/kg/day Oral weight bands: 3–< 6 kg: 250 mg given every 12 hours 6–< 10 kg: 375 mg given every 12 hours 10–< 15 kg: 500 mg given every 12 hours 15–< 20 kg: 750 mg given every 12 hours ≥ 20 kg: 500 mg given every 8 hours or 1 g given every 12 hours OR Amoxicillin+clavulanic acid ^a (oral): 80–90 mg/kg/day of amoxicillin component Oral weight bands: 3–< 6 kg: 250 mg of amoxicillin/dose given every 12 hours 6–< 10 kg: 375 mg of amoxicillin/dose given every 12 hours 10–< 15 kg: 500 mg of amoxicillin/dose given every 12 hours 15–< 20 kg: 750 mg of amoxicillin/dose given every 12 hours ≥ 20 kg: 500 mg of amoxicillin/dose given every 8 hours or 1 g of amoxicillin/dose given every 12 hours	5 days

Note. All dosages are for normal renal and hepatic function.

^a Oral liquid formulations must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

8. Oral and dental infections

Note

Antibiotic prophylaxis before dental procedures is not addressed in this chapter. Local/national guidance documents should be consulted for this purpose.

Key messages

- Untreated tooth decay is the most common global health condition. Dental caries and periodontal disease are largely preventable.
- Key to prevention of dental infection is to maintain good oral health; this includes reducing sugar consumption, regular toothbrushing and interdental cleaning and stopping tobacco smoking.
- **Antibiotics are not needed for dental pain**, which can be treated with analgesics or a dental procedure if appropriate.
- Antibiotics should not be used before a dental procedure to decrease inflammation or to cure toothache.
- Antibiotics are not needed before most dental procedures to prevent surgical site infections.
- For people with a severe spreading dental infection, effective antibiotics and surgical management are vital. Sepsis and the spread of infection may block the upper airway or move to the brain and are life-threatening so should be managed promptly.

Other relevant WHO resources (please check regularly for updates)

- Guideline: sugars intake for adults and children, 2015 (73).
- Oral health – fact sheet (74).
- Ending childhood dental caries: WHO implementation manual, 2019 (75).
- WHO monograph on tobacco cessation and oral health integration, 2017 (76).
- Information brochure for early detection and management of noma, 2016 (77).

Definition

Various dental conditions and terms are defined below. The anatomy of a healthy tooth is illustrated in Figure 8.1.

Abscess: localized collection of pus caused by a bacterial infection in the tooth, gingivae (gums) or alveolar bone supporting the tooth. Abscesses can be categorized as:

- apical abscess, when the infection at the apex of the dental root originates from within the dental pulp. This is the most common form of dental abscess and usually results from untreated dental caries.
- periodontal abscess, where there is a collection of pus between the root and alveolar bone usually resulting from serious gum diseases.

Alveolar bone: part of the jawbones which surrounds and supports the teeth.

Apical periodontitis: inflammation (associated with pain) within the alveolar bone around the apex of a tooth, often occurring as a consequence of a necrotic pulp following pulpitis, tooth fracture or trauma.

Dental caries: tooth decay.

Dental pulp: blood vessels and nerves within the inner part of the tooth.

Dry socket (alveolar osteitis): a recognized inflammatory complication of tooth extraction which may develop a few days after extraction, last for more than a week and is extremely painful.

Gingivae (gums): soft tissue covering the alveolar bone.

Necrotic pulp: An irreversible condition that occurs when the pulp within the tooth becomes non-vital (dies) and is often associated with apical periodontitis.

Noma (cancrum oris/gangrenous stomatitis): an acute necrotizing disease that destroys the soft tissues and bones of the mouth and face as it progresses from necrotizing periodontal disease (previously known as necrotizing ulcerative gingivitis), mostly in malnourished children living in extreme poverty and with weakened immune systems.

Pericoronitis: inflammation of the gingiva (gum) surrounding a partially erupted tooth, often a lower wisdom tooth, which may be associated with an infection.

Periodontal disease: a group of inflammatory diseases affecting the tissues that surround and support the teeth. This includes:

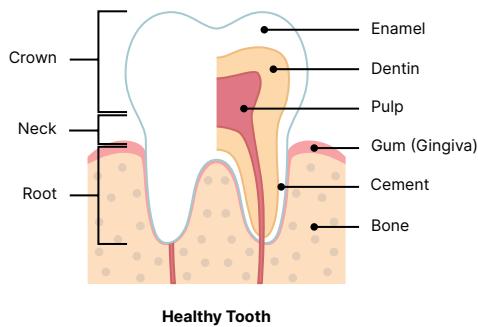
- **Gingivitis:** inflammation of the gingivae (gums).
- **Periodontitis:** chronic inflammatory disease of bacterial etiology that affects the soft and hard tissues which support the tooth, including alveolar bone.
- **Necrotizing periodontal disease (previously known as necrotizing ulcerative gingivitis):** a severe gum infection characterized by necrosis and ulcerations caused by a bacterial infection and often accompanied by severe pain and a strongly unpleasant smell.

Plaque: biofilm of microbes, mainly bacteria, which grows on surfaces within the mouth and contributes to oral diseases such as caries and periodontal disease.

Pulpitis: inflammation of the dental pulp causing pain. This condition often occurs as a result of the progression of dental caries and can lead to apical periodontitis which can then evolve into a dental abscess.

Spreading infection: development of sepsis or the spread of infection through the fascial spaces to vital structures of the head and neck (such as cellulitis) which can occur rapidly and become life-threatening.

Figure 8.1 – Anatomy of a healthy tooth



Oral and dental infections

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Definitions of Conditions That May Require Antibiotic Treatment

- **Abscess:** Localized collection of pus caused by a bacterial infection in the tooth, gums or alveolar bone supporting the tooth. Abscesses can be categorized as:
 - **Apical Abscess (more common):** Infection at the apex of the dental root that originates from within the dental pulp usually resulting from untreated dental caries
 - **Periodontal abscess:** Collection of pus between the root and alveolar bone usually resulting from serious gum diseases
- **Pericoronitis:** Inflammation of the gingiva (gum) surrounding a partially erupted tooth, often a lower wisdom tooth, which may be associated with an infection
- **Necrotizing periodontal disease:** A severe gum infection characterized by necrosis and ulcerations caused by a bacterial infection. Previously known as necrotizing ulcerative gingivitis
- **Noma:** An acute necrotizing disease that destroys the soft tissues and bones of the mouth and face as it progresses from necrotizing periodontal disease (previously known as necrotizing ulcerative gingivitis), rare in adults

Only oral and dental infections where antibiotic treatment is usually required are reported

Common dental procedures are beyond the scope of this guidance



Most Likely Pathogens

Important: most dental infections are caused by conditions that favour the growth of pathogens in the mouth, including an abundance of sugars (e.g. sucrose) and reduced saliva flow (dry mouth)

Bacteria associated with caries:

- Acidogenic bacteria such as:
 - *Streptococcus* spp. (e.g. *S. mutans*)
 - *Lactobacillus* spp.
 - *Actinomyces* spp.

Bacteria associated with periodontal disease:

- Mostly anaerobes such as:
 - *Capnocytophaga* spp.
 - *Prevotella* spp.
 - *Aggregatibacter* spp.
 - *Porphyromonas* spp.



Dental Terminology Definitions

- **Alveolar bone:** Part of the jawbones that surrounds and supports the teeth
- **Dental pulp:** Blood vessels and nerves within the inner part of the tooth
- **Gingivae (gums):** Soft tissue covering the alveolar bone
- **Plaque:** Biofilm of microbes, mainly bacteria, which grows on surfaces within the mouth and contributes to oral diseases such as caries and periodontal disease



Prevention

- Minimize sugar consumption
- Prevent the accumulation of dental plaque with regular dental cleaning and good oral hygiene; fluoride is important because it strengthens the tooth enamel making it more resistant to caries
- Smoking cessation

Oral and dental infections

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Diagnosis

Clinical Presentation

Dental abscess:

- Acute severe and persistent localized toothache that can radiate to the ear, jaw and neck
- Tooth tenderness (e.g. with chewing) and swelling of the cheek above the affected tooth are often present
- If left untreated, the infection can spread and present with signs of cellulitis around the eye or throat; fever ($\geq 38.0^{\circ}\text{C}$), tachycardia and lymphadenopathy

Pericoronitis:

- Inflamed, swollen gum tissue surrounding a partially erupted tooth
- Antibiotics are not normally required, although if infection is present, it should be carefully monitored as it can spread rapidly causing difficulty opening the mouth, swallowing or breathing
- Cellulitis of the neck (e.g. Ludwig angina) can be present and is a medical emergency

Necrotizing periodontal disease:

- Severe pain and inflamed ulcerated gums that bleed easily, necrosis of the interdental papillae, foul breath and a bad taste in the mouth
- It may also be accompanied by systemic symptoms, such as fever $\geq 38.0^{\circ}\text{C}$, malaise and lymphadenopathy

Noma:

- It begins as necrotizing periodontal disease, it progresses rapidly destroying the soft tissues and bones of the mouth and further progressing to perforate the hard tissues and skin of the face
- If detected early, its progression can be rapidly halted, through basic oral hygiene rules, diet supplementation with proteins and nutrients and with antibiotics



Microbiology Tests

Mild cases:

Usually not needed

Severe cases requiring hospitalization:

Consider doing blood and/or pus aspirates cultures



Other Laboratory Tests

Mild cases:

Usually not needed

Severe cases requiring hospitalization:

White blood cell count, C-reactive protein and/or procalcitonin



Point-of-Care Tests and Investigations to Assist Diagnosis

Point-of-care tests can be done to establish the source of the dental pain/infection and make appropriate treatment decisions, for example:

• Tapping the tooth to evaluate response to percussion:

- Tenderness indicates that the pain originates in the supporting bone and may be due to an abscess

• Periodontal probing:

- Can identify a periodontal abscess if pus exudes from a pocket greater than 3mm or necrotizing ulcerative disease if there is extremely tender gingival tissue and grey sloughing

• Checking response to a cold stimulus:

- No response to cold may indicate a non-vital/necrotic pulp



Imaging

Dental radiographs should be undertaken wherever possible as part of the diagnosis to differentiate between the various causes of dental pain

Oral and dental infections

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Rx Treatment

Clinical Considerations

Important:

- Most dental infections and dental pain can be treated without antibiotic treatment by removal of the cause and drainage of the infection using a dental procedure (e.g. extraction of the tooth)
- Antibiotics do not prevent severe complications and cannot replace local surgical treatment
- Antibiotics should not be used before a dental procedure to "decrease inflammation" or to cure toothache. Antibiotics should not be used prior to most dental procedures to prevent surgical site infections

- Regular use of mouthwashes with an antiseptic product (e.g. chlorhexidine) is not necessary for the control of dental infections; rinsing with salty water is usually adequate

Antibiotic treatment is not needed in most cases but can be considered (always complementary to dental procedures):

- In patients with severe, spreading infections with systemic signs (e.g. facial swelling, inability to open the mouth, fever $\geq 38.0^{\circ}\text{C}$, tachycardia)
- In severely immunocompromised patients and patients with uncontrolled diabetes (higher risk of complications)



Antibiotic Treatment Duration

If adequate source control achieved: **3 days**

If adequate source control **not** achieved: **5 days**

Note: patients should be reassessed before the end of treatment to check the resolution of the infection

Rx Symptomatic Treatment

Medicines are listed in alphabetical order and should be considered equal treatment options

- Ibuprofen 200-400 mg q6-8h (Max 2.4 g/day)

OR

- Paracetamol (acetaminophen) 500 mg-1 g q4-6h (max 4 g/day)

• **Hepatic impairment/cirrhosis:** Max 2 g/day

Rx Antibiotic Treatment

Antibiotic treatment is not required in the great majority of cases (see "Clinical Considerations" when antibiotics may be indicated)

For the treatment of infections of dental soft tissues (e.g. pericoronitis or necrotizing periodontal disease), metronidazole is an option

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

- Amoxicillin 500 mg q8h **ORAL**
ACCESS

OR

- Phenoxymethylpenicillin (as potassium) 500 mg (800 000 IU) q6h **ORAL**

Oral and dental infections

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Definitions of Conditions That May Require Antibiotic Treatment

- **Abscess:** Localized collection of pus caused by a bacterial infection in the tooth, gums or alveolar bone supporting the tooth. Abscesses can be categorized as:
 - *Apical Abscess* (*more common*): Infection at the apex of the dental root that originates from within the dental pulp usually resulting from untreated dental caries
 - *Periodontal abscess*: Collection of pus between the root and alveolar bone usually resulting from serious gum diseases
- **Pericoronitis:** Inflammation of the gingiva (gum) surrounding a partially erupted tooth, often a lower wisdom tooth, which may be associated with an infection
- **Necrotizing periodontal disease:** A severe gum infection characterized by necrosis and ulcerations caused by a bacterial infection. Previously known as necrotizing ulcerative gingivitis
- **Noma:** An acute necrotizing disease that destroys the soft tissues and bones of the mouth and face as it progresses from necrotizing periodontal disease (previously known as necrotizing ulcerative gingivitis), mostly in malnourished children living in extreme poverty and with weakened immune systems

Only oral and dental infections where antibiotic treatment is usually required are reported

Common dental procedures are beyond the scope of this guidance



Most Likely Pathogens

Important: most dental infections are caused by conditions that favour the growth of pathogens in the mouth, including an abundance of sugars (e.g. sucrose) and reduced saliva flow (dry mouth)

Bacteria associated with caries:

- Acidogenic bacteria such as:
 - *Streptococcus* spp. (e.g. *S. mutans*)
 - *Lactobacillus* spp.
 - *Actinomyces* spp.

Bacteria associated with periodontal disease:

- Mostly anaerobes such as:
 - *Capnocytophaga* spp.
 - *Prevotella* spp.
 - *Aggregatibacter* spp.
 - *Porphyromonas* spp.



Dental Terminology Definitions

- **Alveolar bone:** Part of the jawbones that surrounds and supports the teeth
- **Dental pulp:** Blood vessels and nerves within the inner part of the tooth
- **Gingivae (gums):** Soft tissue covering the alveolar bone
- **Plaque:** Biofilm of microbes, mainly bacteria, which grows on surfaces within the mouth and contributes to oral diseases such as caries and periodontal disease



Prevention

- Minimize sugar consumption
- Prevent the accumulation of dental plaque with regular dental cleaning and good oral hygiene; fluoride is important because it strengthens the tooth enamel making it more resistant to caries
- Promote smoking cessation

Oral and dental infections

Page 2 of 3



Diagnosis

Clinical Presentation

Dental abscess:

- Acute severe and persistent localized toothache that can radiate to the ear, jaw and neck
- Tooth tenderness (e.g. with chewing) and swelling of the cheek above the affected tooth are often present
- If left untreated, the infection can spread and present with signs of cellulitis around the eye or throat; fever ($\geq 38.0^{\circ}\text{C}$), tachycardia and lymphadenopathy

Pericoronitis:

- Inflamed, swollen gum tissue surrounding a partially erupted tooth
- Antibiotics are not normally required, although if infection is present, it should be carefully monitored as it can spread rapidly causing difficulty opening the mouth, swallowing or breathing
- Cellulitis of the neck (e.g. Ludwig angina) can be present and is a medical emergency

Necrotizing periodontal disease:

- Characterized by severe pain and inflamed ulcerated gums that bleed easily, necrosis of the interdental papillae, foul breath and a bad taste in the mouth
- It may also be accompanied by systemic symptoms, such as fever $\geq 38.0^{\circ}\text{C}$, malaise and lymphadenopathy

Noma:

- It begins as necrotizing periodontal disease, it progresses rapidly destroying the soft tissues and bones of the mouth and further progressing to perforate the hard tissues and skin of the face
- If detected early, its progression can be rapidly halted, through basic oral hygiene rules, diet supplementation with proteins and nutrients and with antibiotics



Microbiology Tests

Mild cases:

Usually not needed
Severe cases requiring hospitalization: Consider doing blood and/or pus aspirates cultures



Other Laboratory Tests

Mild cases:

Usually not needed
Severe cases requiring hospitalization: White blood cell count, C-reactive protein and/or procalcitonin



Point-of-Care Tests and Investigations to Assist Diagnosis

Point-of-care tests can be done to establish the source of the dental pain/infection and make appropriate treatment decisions, for example:

• Tapping the tooth to evaluate response to percussion:

- Tenderness indicates that the pain originates in the supporting bone and may be due to an abscess

• Periodontal probing:

- Can identify a periodontal abscess if pus exudes from a pocket greater than 3mm or necrotizing ulcerative disease if there is extremely tender gingival tissue and grey sloughing

• Checking response to a cold stimulus:

- No response to cold may indicate a non-vital/necrotic pulp



Imaging

Dental radiographs should be undertaken wherever possible as part of the diagnosis to differentiate between the various causes of dental pain

Oral and dental infections

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Rx Treatment

Clinical Considerations

Important:

- Most dental infections and dental pain can be treated without antibiotic treatment by removal of the cause and drainage of the infection using a dental procedure (e.g. extraction of the tooth)
- Antibiotics do not prevent severe complications and cannot replace local surgical treatment
- Antibiotics should not be used before a dental procedure to "decrease inflammation" or to cure toothache. Antibiotics should not be used prior to most dental procedures to prevent surgical site infections

- Regular use of mouthwashes with an antiseptic product (e.g. chlorhexidine) is not necessary for the control of dental infections; rinsing with salty water is usually adequate

Antibiotic treatment is not needed in most cases but can be considered (always complementary to dental procedures):

- In patients with severe, spreading infections with systemic signs (e.g. facial swelling, inability to open the mouth, fever ≥ 38.0 °C, tachycardia)
- In severely immunocompromised patients and patients with uncontrolled diabetes (higher risk of complications)



Antibiotic Treatment Duration

If adequate source control achieved: **3 days**

If adequate source control **not** achieved: **5 days**

Note: patients should be reassessed before the end of treatment to check the resolution of the infection

Rx Symptomatic Treatment

Medicines are listed in alphabetical order and should be considered equal treatment options



Ibuprofen (do not use if <3 months of age)

- Pain control/antipyretic: 5-10 mg/kg q6-8h
- Oral weight bands:

6-<10 kg	50 mg q8h
10-<15 kg	100 mg q8h
15-<20 kg	150 mg q8h
20-<30 kg	200 mg q8h
≥30 kg	200-400 mg q6-8h (Max 2.4 g/day)

OR



Paracetamol (acetaminophen)

- Pain control/antipyretic: 10-15 mg/kg q6h
- Oral weight bands:

3-<6 kg	60 mg q6h
6-<10 kg	100 mg q6h
10-<15 kg	150 mg q6h
15-<20 kg	200 mg q6h
20-<30 kg	300 mg q6h
≥30 kg	500 mg-1 g q4-6h (Max 4 g/day or 2 g/day if hepatic impairment/cirrhosis)

Rx Antibiotic Treatment

Antibiotic treatment is not required in the great majority of cases (see "Clinical Considerations" when antibiotics may be indicated)

For the treatment of infections of dental soft tissues (e.g. pericoronitis or necrotizing periodontal disease), metronidazole is an option

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated



Amoxicillin 80-90 mg/kg/day ORAL

- Oral weight bands:

3-<6 kg	250 mg q12h
6-<10 kg	375 mg q12h
10-<15 kg	500 mg q12h
15-<20 kg	750 mg q12h
≥20 kg	500 mg q8h or 1 g q12h

OR



Phenoxymethylpenicillin (as potassium):
10-15 mg/kg/dose (16 000-24 000 IU/kg/dose)
q6-8h ORAL

Pathophysiology

Most dental conditions relate to the oral microbiota in dental plaque and do not require antibiotic treatment. Dental plaque is a microbe rich biofilm that sticks to surfaces within the mouth, including teeth, dentures and orthodontic appliances. In the presence of free sugars, especially sucrose from the diet, plaque bacteria can create an environment that favours tooth decay (dental caries). Acid produced by plaque bacteria in the presence of sugar causes this destruction, which is reversible only when confined to the outer enamel layer. Unless it is removed, the progression of caries is hard to stop once it enters the deeper parts of the tooth.

If dental caries progresses to reach the pulp, inflammatory pain (pulpitis) occurs which can eventually lead to pulpal necrosis and the tooth becoming non-vital. When this occurs, a tooth may initially be pain free or become tender to touch (apical periodontitis). If left to progress further, a localized accumulation of pus (periapical abscess) may form or an infection of the tooth, gums or alveolar bone supporting the tooth may spread to adjacent vital structures in the head and neck (e.g. cellulitis) or through the bloodstream (e.g. sepsis).

Accumulation of dental plaque around the gingival margin of teeth (at the gumline) and in periodontal pockets (below the gumline) can stimulate an inflammatory response. In some people this can lead to immune-mediated destruction of the periodontal structures (e.g. gums or alveolar bone) which support the teeth. Progressive destruction of these periodontal tissues may lead to teeth becoming mobile and eventually to tooth loss.

Some protective mechanisms to reduce plaque accumulation include saliva and the cleansing action of the tongue. Regular removal of plaque through oral hygiene practices, such as toothbrushing and interdental cleaning, is essential to prevent and manage dental caries and periodontal disease.

Epidemiology

Despite being largely preventable, oral disease (including dental caries and periodontal disease) is common and an important public health problem (78).

Untreated dental caries affect almost half of the world's population (42% in 2015) making it the most prevalent of the oral conditions reported in the Global Burden of Disease Study (78).

The prevalence of untreated caries in permanent teeth was highest in young people aged 15–19 years. Periodontal disease is less common than dental caries, with an overall yearly prevalence of around 7%. As periodontal disease may progress through life, it is highest in older people aged 55–59 years (78).

Common risk factors for dental infections include diets high in free sugars and poor oral hygiene leading to dental caries. Poor oral hygiene, smoking or chewing tobacco, stress, malnutrition and being immunocompromised are risk factors for periodontal diseases,

including necrotizing periodontal disease (previously known as necrotizing ulcerative gingivitis). Poor oral hygiene and severe malnutrition are also risk factors for noma, a necrotizing disease most commonly seen in children living in low-income countries and with a 90% fatality rate if left untreated.

Most likely pathogens

The normal oral microbiota is richly diverse, including both aerobic and anaerobic bacteria, together with fungi, especially *Candida* spp.. Most dental infections are caused by conditions in the oral environment which favour the growth of pathogens. For example, an abundance of free sugars, such as sucrose, favours cariogenic bacteria (e.g. *Streptococcus mutans*) resulting in tooth decay. Reduced saliva flow makes patients with a dry mouth at increased risk of dental caries as there is less natural protection from the saliva. Furthermore, a recent course of antibiotics is a common cause for oral candidiasis (thrush). While the precise composition of an individual's oral microbiota will differ between parts of the mouth and will change over time and between individuals, Table 8.1 shows a typical mix of the bacteria that are part of the oral microbiota in health and disease. The oral microbiota and associated disease can be significantly different depending on the precise location. For example, enamel caries is more often associated with *Streptococcus mutans* whereas *Actinomyces* spp. predominate in root caries.

Table 8.1 – Normal resident oral microbiota and pathogens most frequently associated with dental infections (in descending order of frequency)

Normal resident oral microbiota ^a	Bacteria associated with caries ^b	Bacteria associated with periodontal disease
<i>Streptococcus</i> spp.	<i>Streptococcus</i> spp. (e.g. <i>Streptococcus mutans</i>)	Anaerobes (most cases), e.g.: <i>Prevotella</i> spp.
<i>Actinomyces</i> spp.		
<i>Prevotella</i> spp.	<i>Lactobacillus</i> spp.	<i>Capnocytophaga</i> spp.
<i>Veillonella</i> spp.	<i>Actinomyces</i> spp.	<i>Aggregatibacter</i> spp. <i>Porphyromonas</i> spp.

^a A richly diverse group of pathogens, including both aerobic bacteria and anaerobes.

^b Mostly acidogenic bacteria

Clinical presentation

Typical signs and symptoms of selected oral conditions are described in the following two sections. Dental pain is often due to inflammation rather than infection and careful diagnosis is required to ensure optimal treatment is provided and antibiotic use minimized.

The severity of signs and symptoms may range from mild diseases (most cases) that can be safely managed in an outpatient setting to severe infections of dental origin (including sepsis) that require hospitalization and intravenous antibiotic treatment. Oral and dental infections commonly involve the lymph nodes and can also spread through the fascial spaces of the head and neck to block the airway, move into the brain through the periorbital area and can present as osteomyelitis. Please refer to the chapters on sepsis, lymphadenitis and osteomyelitis if these sequelae are suspected.

Conditions that may require antibiotic treatment

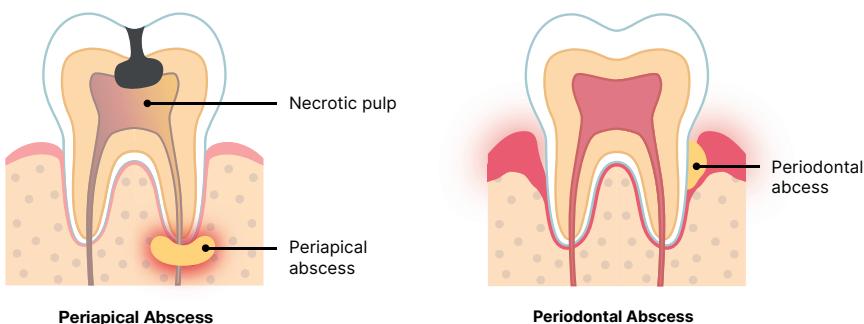
Abscess

An apical abscess (Figure 8.2) is the most common type of dental abscess. It is often, but not always, painful and characterized by persistent localized pain that can radiate to the ear, jaw and neck. Tooth tenderness (stimulated by chewing or food trapping) is common as well as swelling of the soft tissues adjacent to the affected tooth.

If an apical abscess is left untreated, there is a high risk of spread to vital structures of the head and neck or systemic spread of the infection that can then lead to sepsis. Signs that the infection has spread include cellulitis around the eye or throat (causing difficulties swallowing or breathing, e.g. Ludwig angina), fever ($\geq 38.0^{\circ}\text{C}$), malaise, tachycardia (increased heart rate) and lymphadenopathy. This must be treated as a medical emergency.

A periodontal abscess (Figure 8.2) is less common than an apical abscess. It is usually a localized accumulation of pus in the periodontal tissues (gums and alveolar bone supporting the tooth) which can be readily drained by professional cleaning of the periodontal pocket or by extraction of the tooth without the need for antibiotics.

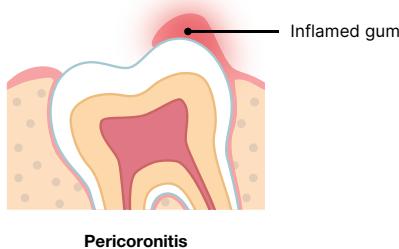
Figure 8.2 – Periapical and periodontal abscess



Pericoronitis

Pericoronitis is inflammation and sometimes infection of the gum around a partially erupted tooth, often a lower wisdom tooth (Figure 8.3). It usually occurs in late adolescence and early adult life and can be treated by professional cleaning, saline (hot salty water) mouthwash and, if necessary, by draining the infection. Antibiotics are not normally required, although if infection is present, it should be carefully monitored as it can spread rapidly causing difficulty opening the mouth, swallowing or breathing. Cellulitis of the neck (e.g. Ludwig angina) is a medical emergency as it can quickly become life-threatening.

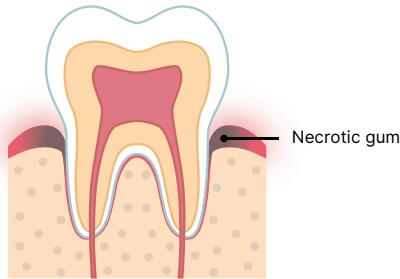
Figure 8.3 – Pericoronitis



Necrotizing periodontal disease

Necrotizing periodontal disease (Figure 8.4), which was previously known as necrotizing ulcerative gingivitis, is characterized by the following: severe pain and inflamed ulcerated gums that bleed easily; necrosis of the interdental papillae; foul breath; and a bad taste in the mouth. It may also be accompanied by systemic symptoms, such as fever $\geq 38.0\text{ }^{\circ}\text{C}$, malaise and lymphadenopathy.

Figure 8.4 – Necrotizing periodontal disease



Noma

Noma is a necrotizing disease that destroys the mouth and face. It begins as necrotizing periodontal disease that progresses rapidly, destroying the soft tissues and bones of the mouth and further progressing to perforate the hard tissues and skin of the face. It mostly affects young children between the ages of 2 and 6 years suffering from severe malnutrition, living in extreme poverty and with weakened immune systems. Its prevalence is highest in sub-Saharan Africa. Noma is fatal for 90% of the children affected. If detected early, its progression can be rapidly halted, through basic oral hygiene rules, diet supplementation with proteins and nutrients and with antibiotics. Early detection helps to prevent suffering, disability and death. Please also refer to the WHO information brochure for early detection and management of noma for more information about this topic (77).

Conditions that do not require antibiotic treatment

Dental caries progression to pulpal disease

Dental caries is the localized destruction of dental hard tissue (enamel or dentine) by acid-producing plaque bacteria in the presence of dietary sugar. This process can be reversible in early lesions. Caries can sometimes lead to the formation of cavities (i.e. holes in the tooth) which are often hidden in the space between the teeth. Diagnosis is based on response of the tooth to cold/hot stimulus and radiographic imaging. Cavities and devitalized teeth may appear dark in colour compared to other teeth.

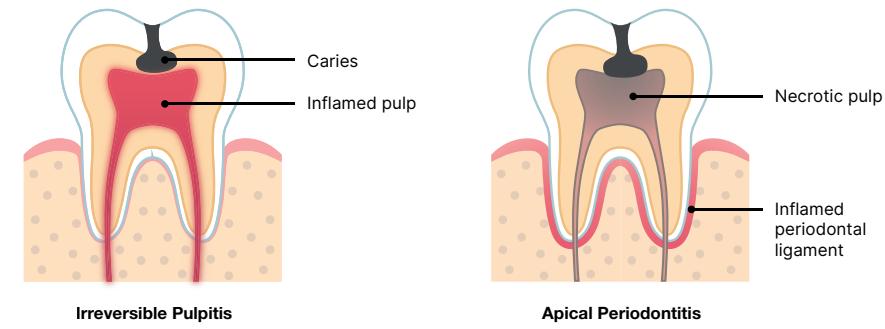
Caries develops slowly and can be pain free in the initial phase. However, if left untreated, the lesion can extend to the dental pulp causing pulpitis to begin with, then pulpal necrosis and ultimately dental abscess. Severe disease or necrosis of the dental pulp as a consequence of dental caries can be associated with systemic infections.

Reversible pulpitis is characterized by acute pain or discomfort initially caused by drinking hot or cold beverages. It is possible to treat the problem at this stage with a simple restoration.

If caries progresses, irreversible pulpitis (Figure 8.5) develops causing constant severe pain which characteristically keeps the patient awake at night. This pain may stop suddenly when progression of the disease leads to necrosis of the dental pulp.

If left untreated, apical periodontitis (Figure 8.5) often develops, characterized by dull throbbing in the surrounding area (mouth and jaw) and soreness while biting. The pain may be eased by cold and made worse by heat (e.g. hot and cold beverages). Progression of the condition may lead to an apical abscess, and this is the most common cause of dental abscess.

Figure 8.5 – Irreversible pulpitis and apical periodontitis



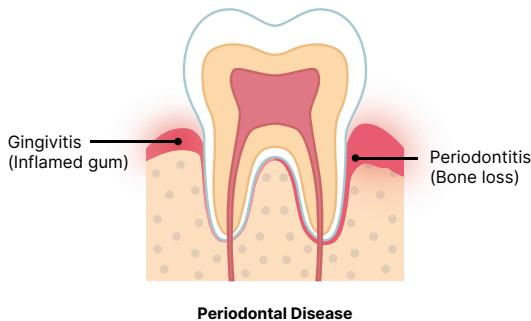
Dry socket / alveolar osteitis

Dry socket (alveolar osteitis) is a recognized inflammatory complication of tooth extraction. It occurs 2–3 days after extraction and can last for up to 10 days. Severe pain develops a few days after the dental procedure, associated with slow healing of the socket; it may be accompanied by an unpleasant taste. Appropriate pain control is necessary as pain may last for many days. Antibiotics are not appropriate for the prophylaxis or treatment of dry socket unless osteomyelitis is suspected; please refer to the chapter on osteomyelitis if this is suspected.

Periodontal disease

Periodontal disease (Figure 8.6) is the term used to describe a range of conditions affecting the tissues that surround and support the teeth, including gingivitis and periodontitis. As these are generally immune-mediated diseases, it is usually inappropriate to use antibiotics for their treatment.

Figure 8.6 – Periodontal disease



Gingivitis

Gingivitis is characterized by redness and swelling of the gums due to the build up of food debris and microbial biofilm. It is usually painless, but bleeding when toothbrushing is common. Halitosis may be present. In its early stages, gingivitis is reversible with good oral hygiene. Severe forms of gingivitis are known but are rare.

Periodontitis

Periodontitis is an inflammatory disease characterized by the progressive destruction of the alveolar bone which supports the teeth. It is often a hidden disease as it is generally painless and progresses below the gums. Halitosis may be present. In case of periapical periodontitis, soreness, while biting can occur due to a devitalized (dead) tooth.

The disease process of periodontitis occurs over time (usually years) and people often only become aware of it when their teeth start to move or fall out; a more aggressive destruction of the bone may sometimes be seen. Oral health professionals use special probes when carrying out periodontal screening to enable early diagnosis and treatment of periodontitis. Addressing risk factors, including effective cleaning of the periodontal tissues (under the gums), smoking cessation and good diabetes control are essential. Antibiotics are only appropriate for the treatment of aggressively destructive conditions; antibiotics are not appropriate for chronic periodontitis.

Laboratory tests

Patient microbiology tests

Routine microbiology tests are not required in most cases of dental infection but can be considered in severe cases requiring hospitalization, when culture and sensitivity testing (e.g. blood and/or pus aspirates for culture) can help in the selection of an appropriate antibiotic, for example, if cellulitis (e.g. Ludwig angina) is spreading to vital structures or if sepsis is suspected. Please also refer to the chapter on sepsis, if suspected.

Other tests

Most dental infections are bacterial, except for oral thrush (a fungal infection usually caused by *Candida* spp.) and cold sores (a viral infection) which are easily recognizable clinically.

Acute dental conditions are routinely diagnosed using point-of-care tests and investigations (see point-of-care tests and investigations in the following section).

Routine laboratory tests are not required in most cases of dental infections but may be considered in severe cases requiring hospitalization.

Using microbiology surveillance data

Routine microbiology surveillance of oral microbiota does not generally take place, so such data are unavailable for clinical guidance.

Point-of-care tests and investigations to assist diagnosis

Establishing the source of the dental pain/infection is an important element of accurate diagnosis and is essential to make appropriate treatment decisions. Sensitivity of the tooth to a cold stimulus indicates a vital pulp; depending on the intensity and duration of the stimulated pain, this may indicate pulpitis.

No response to cold may indicate a non-vital/necrotic pulp and tenderness to percussion (tapping the tooth) indicates that the pain originates in the supporting bone and may be due to an abscess. Periodontal probing can identify a periodontal abscess if pus exudes from a pocket greater than 3 mm or necrotizing ulcerative disease if there is extremely tender gingival tissue and grey sloughing.

Imaging

If a dental infection is suspected, imaging using dental radiographs (X-rays) should be done wherever possible as part of the diagnosis. Radiographs are important for differentiating between the various causes of dental pain, including how far caries (decay) has progressed and where tenderness to percussion is associated with a radiolucency (i.e. black area on radiographic image) in the alveolar bone suggesting an abscess. Location of the radiolucency relative to the tooth helps differentiate between an apical or periodontal abscess.

Treatment

Dental bacterial infections are rarely self-limiting and may rapidly become life-threatening if left untreated. Most dental infection and pain are amenable to treatment by removal of the cause and drainage of the infection using a dental procedure, such as extraction of the tooth. Removal of the cause of the infection using a dental procedure is usually the quickest and safest way of resolving the problem, and is essential to avoid the risk of rapidly spreading and potentially life-threatening infection. Antibiotics are normally only required for the treatment of spreading infections.

No antibiotic care

Most dental infections are characterized by some level of dental pain and, while adequate pain control should always be offered, the prescription of medications alone is not usually appropriate.

Caries, pulpal disease and dental abscesses are best treated with a dental procedure to remove the source of the problem; using painkillers alone is suboptimal as the condition can progress to a life-threatening spreading infection.

Dry socket (alveolar osteitis) is an extremely painful and common occurrence following dental extraction. It occurs 2–3 days after extraction and can last for up to 10 days. This condition requires optimum pain management but no antibiotics are needed unless osteomyelitis is suspected; please refer to the chapter on osteomyelitis if this is suspected.

Ibuprofen and paracetamol are first choice painkillers for dental pain (Table 8.2). In the case of severe pain, ibuprofen and paracetamol may work better when taken in combination.

Caution should be exercised as the incidence of paracetamol (acetaminophen) overdose in relation to dental pain is relatively high. Opioid painkillers should be avoided as they offer no benefit for this sort of pain and are associated with the risk of substance misuse.

Table 8.2 – Medicines to control acute dental pain

Important		
Medicines are listed in alphabetical order and they should all be considered equal treatment options.		
Medicine	Formulation	Dose and frequency
Ibuprofen ^a	Oral liquid: 200 mg/5 mL Tablet: 200 mg; 400 mg; 600 mg	Adults: 200–400 mg given every 6 to 8 hours (maximum dose of 2.4 g a day) Children: <ul style="list-style-type: none"> Pain control/antipyretic treatment: 5–10 mg/kg given every 6 to 8 hours 6–< 10 kg: 50 mg given every 8 hours 10–< 15 kg: 100 mg given every 8 hours 15–< 20 kg: 150 mg given every 8 hours 20–< 30 kg: 200 mg given every 8 hours ≥ 30 kg: use adult dose

continues

Table 8.2 *continued*

Medicine	Formulation	Dose and frequency
Paracetamol (acetaminophen) ^b	Oral liquid: 120 mg/5 mL; 125 mg/5 mL Suppository: 100 mg Tablet: 100 mg to 500 mg	Adults: 500 mg–1 g given every 4 to 6 hours (maximum dose of 4 g a day) ^c Children: <ul style="list-style-type: none">• Pain control/antipyretic treatment: 10–15 mg/kg given every 6 hours3–< 6 kg: 60 mg given every 6 hours6–< 10 kg: 100 mg given every 6 hours10–< 15 kg: 150 mg given every 6 hours15–< 20 kg: 200 mg given every 6 hours20–< 30 kg: 300 mg given every 6 hours≥ 30 kg: use adult dose

^a Not for children < 3 months, or for people with hypersensitivity to aspirin or any other NSAID (non-steroidal anti-inflammatory drug), or for people with a history of gastrointestinal bleeding or ulceration.

^b Not recommended for use as an anti-inflammatory as it has not been proven to have such an effect. Warning: overdose is relatively common among people with severe dental pain.

^c In patients with hepatic impairment or cirrhosis, maximum daily dose should be 2 g.

Oral antiseptics

Regular use of mouthwashes with an antiseptic product (e.g. chlorhexidine) is not required for the control of dental infections. Such products could be considered in case of acute exacerbations of periodontal disease. Of note, no formulation of oral antiseptics is currently included in the EML and EMLc and rinsing with saline (salty water) is usually adequate as well as being cheaper and more readily available. Caution should be exercised with the use of chlorhexidine mouthwash in patients following extractions or treatment of alveolar osteitis (dry socket following dental extraction) as it has been associated with anaphylaxis.

Dental procedures

Dental procedures are usually the quickest and safest solutions for dental pain and infection.

Commonly performed dental procedures are briefly described in Table 8.3. Detailed information on these procedures is beyond the scope of this chapter.

Table 8.3 – Commonly performed procedures for certain dental diseases

Dental disease	Procedure
Abscess	<p>1. Apical abscess</p> <p>Source control through:</p> <ul style="list-style-type: none"> • Tooth extraction • Pulp extirpation (drainage of pus and removal of necrotic pulp tissue by drilling through the tooth into the pulp) followed by root canal treatment <p>OR</p> <ul style="list-style-type: none"> • Soft tissue incision and drainage followed by tooth extraction or root canal treatment. <p>2. Periodontal abscess</p> <p>Source control through:</p> <ul style="list-style-type: none"> • Tooth extraction <p>OR</p> <ul style="list-style-type: none"> • Drainage of any pus collection by professional cleaning of the periodontal tissues.
Apical periodontitis/ pulpal necrosis	<p>Source control through:</p> <ul style="list-style-type: none"> • Tooth extraction <p>OR</p> <ul style="list-style-type: none"> • Pulp extirpation (drainage of pus and removal of necrotic pulp tissue by drilling through the tooth into the pulp) followed by root canal treatment
Dental caries (decay)/reversible pulpitis	<p>Removal of caries and restorative filling</p> <p>Where access to dental care is not readily available or for people who are unable to accept a dental procedure (e.g. due to dental phobia), silver diamine fluoride may be appropriate to stop progression of the caries.</p>
Dry socket (alveolar osteitis)	<p>Reassurance that this is a common yet painful outcome</p> <p>Irrigation of the socket with saline</p>
Pericoronitis	<p>Source control through:</p> <ul style="list-style-type: none"> • Tooth extraction <p>OR</p> <ul style="list-style-type: none"> • Drainage of any pus collection by irrigation under the operculum (flap of gum over the erupting tooth) with saline

continues

Table 8.3 *continued*

Dental disease	Procedure
Pulpitis (when irreversible)	Source control through: <ul style="list-style-type: none">• Tooth extraction OR <ul style="list-style-type: none">• Pulp extirpation (removal of the inflamed pulp and treatment of the root canal)
Necrotizing periodontal disease (previously known as necrotizing ulcerative gingivitis)^a	<ul style="list-style-type: none">• Regular toothbrushing with a fluoride-containing toothpaste and use of an interdental brush or dental floss to remove plaque• Professional cleaning around the teeth and periodontal tissues to remove the mineralized material known as scale, tartar or calculus• Smoking cessation advice
Noma	<ul style="list-style-type: none">• Please refer to the WHO guidance for early detection and management of noma (77)

^a Necrotizing periodontal disease can often be resolved by procedures alone – antibiotics are often not required.

Antibiotic treatment

Up to 10% of antibiotic prescribing in the outpatient setting can be by dentists for the treatment of oral and dental infections or prophylaxis of surgical procedures, of which a large proportion have been shown to be unnecessary or inappropriate (79). Efforts should be made to restrict the use of antibiotics only to situations when their use is strictly necessary (79,80).

Antibiotic treatment is required only for few dental conditions.

Antibiotics are not appropriate for inflammatory conditions (including periodontitis, irreversible pulpitis and dry socket treatment) because they do not prevent the development of severe complications and cannot replace local surgical or non-surgical treatment.

Antibiotics should not be used before a dental procedure to: calm an infection; decrease inflammation; cure toothache (pain relief is best achieved by a dental procedure not a dental prescription); or prevent surgical site infections.

Effective antibiotic treatment (along with a procedure for source control) is essential in patients with severe, spreading dental infections. Severe cases include those with systemic signs of infection, for example, facial swelling, inability to open the mouth, fever $\geq 38.0^{\circ}\text{C}$ and tachycardia. Even when necessary, antibiotics should only be used to complement surgical source control, for example, drainage of the abscess or tooth extraction. Antibiotic use could

also be considered in severely immunocompromised patients (including patients with uncontrolled diabetes) because they have a higher risk of complications. When antibiotic treatment is considered necessary, empiric use of amoxicillin or phenoxycephalosporin as indicated in Table 8.4 is considered appropriate. Using two antibiotics (e.g. amoxicillin and metronidazole) as adjunctive treatment is not necessary in the vast majority of cases and noma is usually the only indication for dual antibiotic therapy (using two antibiotics such as amoxicillin and metronidazole).

The AWaRe book does not include alternative antibiotic options in cases of allergy to first-choice antibiotics. For dental infections, only penicillin options are recommended by the AWaRe book, which may be considered problematic by some prescribers. However, even though allergies to antibiotics (particularly to beta-lactams) are frequently self-reported or indicated in health records, in most cases (> 95%), these patients do not have a true immunologically mediated allergy and it is very likely that they can safely tolerate the medicine if re-exposed to it. Please refer to the chapter on allergies to antibiotics for more information about this aspect.

Prevention

Dental caries does not occur without sugar, thus minimizing dietary free sugars is key to avoiding dental pain and infections caused by dental caries. Further information on dietary sugar can be found in the WHO guidance document on sugar intake for adults and children (73).

As the progression of dental caries and periodontal disease may continue slowly from childhood to adulthood, the negative health effects of oral disease are cumulative. Even a small reduction in the risk factors early in life confers significant benefit in later life.

Stopping tobacco use, whether smoked or smokeless, should also be promoted for the prevention of periodontal disease and oral cancer.

Preventing the accumulation of dental plaque is important for preventing dental diseases such as dental caries or periodontal disease.

Where people are unable to perform adequate oral hygiene themselves, regular professional dental cleaning may be necessary to maintain oral health.

Fluoride plays an important role in improving oral health by strengthening the tooth enamel and making it more resistant to dental caries. Further information on fluoride and oral health can be found on the WHO website (74). For prevention of dental caries in children, refer to the WHO guidance document (75).

Table 8.4 – Empiric antibiotic treatment for selected cases of severe dental infections

Note		
Important		
Adults	Children	Total treatment duration
Amoxicillin ^a (oral): 500 mg given every 8 hours OR Phenoxycephalothin ^a (oral): 500 mg (800 000 IU ^b) given every 6 hours	Amoxicillin ^a (oral): 80–90 mg/kg/day Oral weight bands: 3–< 6 kg: 250 mg given every 12 hours 6–< 10 kg: 375 mg given every 12 hours 10–< 15 kg: 500 mg given every 12 hours 15–< 20 kg: 750 mg given every 12 hours ≥ 20 kg: 500 mg given every 8 hours or 1 g given every 12 hours OR Phenoxycephalothin ^a (oral): 10–15 mg/kg/dose (16 000–24 000 IU/kg/dose ^b) given every 6 to 8 hours ≥ 30 kg: use adult dose	3 days, if adequate source control is achieved; otherwise 5 days ^c Patients should be reassessed before the end of treatment to check the resolution of the infection.

IU: international units.

Note. All dosages are for normal renal and hepatic function.

^a For the treatment of infections of the dental soft tissues (e.g. pericoronitis or necrotizing periodontal disease), metronidazole is an option.

^b Units of the potassium salt.

^c If source control is not achieved or in cases where operative dental treatment is not available, often because of the unavailability of dentists in many low resource settings.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

9. Localized acute bacterial lymphadenitis

This chapter does not include severe or generalized infections or infections caused by viral, fungal or parasitic pathogens.

Key messages

- **Antibiotics are not needed** for the great majority of cases of enlarged lymph nodes as they are caused by viral infections.
- A watchful waiting approach is reasonable when the patient is not severely ill and bacterial lymphadenitis or a malignancy is not suspected, because the condition is usually self-limiting.
- Human immunodeficiency virus (HIV) infection, tuberculosis and spreading dental infection should always be considered in the differential diagnosis.
- If bacterial lymphadenitis is suspected, empiric antibiotic treatment should cover *Staphylococcus aureus* and *Streptococcus pyogenes* with Access group antibiotics.

Definition

Lymphadenitis is the inflammation and enlargement ($> 1\text{--}2 \text{ cm}$) of one or several lymph nodes. It can be classified as localized (most cases) where only one lymph node region is affected or generalized when multiple lymph node regions are affected. Lymphadenitis can also be classified based on the anatomical site of the lymph node region affected (e.g. cervical or axillary) and on the depth of the lymph node affected, either superficial or deep lymph nodes. Lymphadenitis has several infectious and non-infectious causes, including skin infections, dental infections, cancer or lymphoproliferative disorders. The term lymphadenitis (i.e. enlargement of a lymph node with inflammatory signs) and lymphadenopathy (i.e. disease of a lymph node in which they are abnormal in size and/or consistency) are often used interchangeably, although in lymphadenitis the inflammatory component (redness, warmth and pain) is more pronounced. Infection in the lymph nodes can be caused by bacteria, viruses, fungi or parasites. This chapter focuses on localized acute bacterial lymphadenitis, although most enlarged lymph nodes are caused by viral infections.

Localized acute bacterial lymphadenitis

Page 1 of 2

This guidance excludes management of severe or generalized infections or those caused by viral, fungal or parasitic pathogens

Definition

Lymphadenitis refers to the inflammation and acute enlargement (>1-2 cm) of one or several lymph nodes

Classification based on:

- Number of lymph node regions affected:
 - *Localized* (most cases): 1 lymph node region affected
 - *Generalized*: >1 lymph node region affected
- Location of the affected lymph node (e.g. cervical, axillary)
- Depth of the affected lymph node (superficial or deep)

Most Likely Pathogens

Viruses (most cases):

- Epstein-Barr virus, Cytomegalovirus (both viruses can cause infectious mononucleosis)
- Respiratory viruses

Bacteria (more rarely):

- *Staphylococcus aureus* (including MRSA)
- *Streptococcus pyogenes* (group A *Streptococcus*)

Consider in specific situations (based on history and physical examination):

- Sexually transmitted infections (e.g. HIV)
- Zoonoses (e.g. brucellosis, tularemia, bartonellosis - the latter mostly following cat bites or scratches)
- Mycobacterial infections (including nontuberculous)

Diagnosis

Clinical Presentation

- Acute onset of a palpable, painful red and inflamed enlarged lymph node (>1-2 cm) +/- fever ($\geq 38.0^{\circ}\text{C}$), and other signs/symptoms of systemic disease & cellulitis
- Bacterial cause more probable if unilateral involvement, fluctuance and skin drainage of the lymph node

Microbiology Tests

Usually not needed; consider testing for HIV and tuberculosis if these are suspected

Other Laboratory Tests

Usually not needed but may be considered in selected cases

Biopsy

Consider when a malignancy is suspected

Imaging

- Usually not needed
- Ultrasound can be considered to confirm lymph node involvement, to quantify the enlargement and to detect the presence of an abscess; it is not reliable to rule out malignancies (biopsy should be performed)

Localized acute bacterial lymphadenitis

Page 2 of 2

R_X Treatment

Clinical Considerations

Important:

- The great majority of cases of enlarged lymph nodes are caused by viral infections and antibiotics are **not needed**
- A watchful waiting approach with follow up is appropriate (except if malignancy is suspected)

If symptoms are consistent with a bacterial infection, empiric treatment against *S. aureus* and *Streptococcus pyogenes* (group A *Streptococcus*) is indicated



Antibiotic Treatment Duration

5 days

R_X Antibiotic Treatment

Note: history is key in order to adapt treatment if necessary

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

Amoxicillin+clavulanic acid 500 mg+125 mg q8h **ORAL** OR 1 g+200 mg q8h **IV**

OR

Cefalexin 500 mg q8h **ORAL**

OR

Cloxacillin 500 mg q6h **ORAL** OR 2 g q6h **IV**

Cloxacillin and cefalexin have a narrower spectrum of antibacterial activity compared to amoxicillin+clavulanic acid with good efficacy in mild skin and soft tissue infections. From an antibiotic stewardship perspective, these would be the preferred options whenever possible

If cloxacillin is unavailable, any other IV antistaphylococcal penicillin could be used. For oral administration, dicloxacillin and flucloxacillin are preferred options within the class as they have better oral bioavailability

Localized acute bacterial lymphadenitis

Page 1 of 2

This guidance excludes management of severe or generalized infections or those caused by viral, fungal or parasitic pathogens

Definition

- Lymphadenitis refers to the inflammation and enlargement ($>1\text{-}2\text{ cm}$) of one or several lymph nodes
- Lymphadenopathy is another term often used

Classification based on:

- Number of lymph node regions affected:
 - *Localized* (most cases): 1 lymph node region affected
 - *Generalized*: >1 lymph node region affected
- Location of the affected lymph node (e.g. cervical, axillary)
- Depth of the affected lymph node (superficial or deep)

Most Likely Pathogens

Viruses (most cases):

- Epstein-Barr virus (can cause infectious mononucleosis)
- Cytomegalovirus (can cause infectious mononucleosis)
- Respiratory viruses

Bacteria (more rarely):

- *Staphylococcus aureus* (including MRSA)
- *Streptococcus pyogenes* (group A *Streptococcus*)

Consider in specific situations (based on history and physical examination):

- Sexually transmitted infections (e.g. HIV)
- Zoonoses (e.g. brucellosis, tularemia, bartonellosis - the latter mostly following cat bites or scratches)
- Mycobacterial infections (including nontuberculous)

Diagnosis

Clinical Presentation

- Acute onset of a palpable, painful red and inflamed enlarged lymph node ($>1\text{-}2\text{ cm}$) +/- fever ($\geq 38.0^{\circ}\text{C}$), and other signs/symptoms of systemic disease & cellulitis
- Bacterial cause more probable if unilateral involvement, fluctuance and skin drainage of the lymph node

Microbiology Tests

Usually not needed; consider testing for HIV and tuberculosis if these are suspected

Other Laboratory Tests

Usually not needed but may be considered in selected cases

Biopsy

Consider when a malignancy is suspected

Imaging

- Usually not needed
- Ultrasound can be considered to confirm lymph node involvement, to quantify the enlargement and to detect the presence of an abscess; it is not reliable to rule out malignancies (biopsy should be performed)

Localized acute bacterial lymphadenitis

Page 2 of 2

Rx Treatment

Clinical Considerations

Important:

- The great majority of cases of enlarged lymph nodes are caused by viral infections and antibiotics are **not needed**
- A watchful waiting approach with follow up is appropriate (except if malignancy is suspected)

If symptoms are consistent with a bacterial infection, empiric treatment against *S. aureus* and *Streptococcus pyogenes* (group A *Streptococcus*) is indicated

Antibiotic Treatment Duration

5 days

Rx Antibiotic Treatment

Note: history is key in order to adapt treatment if necessary

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

 Amoxicillin+clavulanic acid

ACCESS

IV:

- 1st week of life: 50 mg/kg/dose of amoxicillin component q12h
- > 1st week of life: 50 mg/kg/dose of amoxicillin component q8h
- ORAL:** 80-90 mg/kg/day of amoxicillin component

• Oral weight bands:

3-<6 kg	250 mg of amox/dose q12h
6-<10 kg	375 mg of amox/dose q12h
10-<15 kg	500 mg of amox/dose q12h
15-<20 kg	750 mg of amox/dose q12h
≥20 kg	500 mg of amox/dose q8h or 1 g of amox/dose q12h

Amox = amoxicillin

Oral liquid must be refrigerated after reconstitution

OR

 Cefalexin 25 mg/kg/dose q12h **ORAL**

ACCESS

• Oral weight bands:

3-<6 kg	125 mg q12h
6-<10 kg	250 mg q12h
10-<15 kg	375 mg q12h
15-<20 kg	500 mg q12h
20-<30 kg	625 mg q12h
≥30 kg	500 mg q8h

OR

 Cloxacillin **IV**

ACCESS

- Neonates: 25-50 mg/kg/dose q12h
- Children: 25 mg/kg/dose q6h
- ORAL:** 15 mg/kg/dose q6h
- Oral weight bands:**

3-<6 kg	62.5 mg q6h
6-<10 kg	125 mg q6h
10-<15 kg	250 mg q6h
15-<20 kg	375 mg q6h
≥20 kg	500 mg q6h

Cloxacillin and cefalexin have a narrower spectrum of antibacterial activity compared to amoxicillin+clavulanic acid with good efficacy in mild skin and soft tissue infections. From an antibiotic stewardship perspective, these would be the preferred options whenever possible

If cloxacillin is unavailable, any other IV antistaphylococcal penicillin could be used. For oral administration, dicloxacillin and flucloxacillin are preferred options within the class as they have better oral bioavailability

Pathophysiology

Lymph nodes are an important part of the immune system which act as filters of lymph fluid. Lymphadenitis from an infectious cause is due to the immune system's response to localized or generalized inflammation and to the pathogen spreading to one or more lymph node regions.

Epidemiology

Lymphadenitis is a common condition worldwide and can occur at all ages; for example, cervical lymphadenitis occurs very frequently in healthy children. Lymphadenitis is usually associated with benign conditions (e.g. most infectious causes); however, it can also be a sign of malignancy (e.g. lymphoma).

Since lymphadenitis has many different causes, the epidemiology of the disease will reflect the specific etiology. For example, in Africa, tuberculous lymphadenitis (the most frequent cause of extrapulmonary tuberculosis (TB)) is still an important cause of persistent lymphadenitis, and chronic lymphadenopathy may be a sign of HIV infection (81).

Most likely pathogens

Pathogens that can cause lymphadenitis are listed in Table 9.1.

Table 9.1 – Pathogens most frequently associated with acute lymphadenitis (in descending order of frequency)

Viruses	Bacteria
Most cases	Most cases
Epstein–Barr virus	<i>Staphylococcus aureus</i> (including MRSA)
Cytomegalovirus	<i>Streptococcus pyogenes</i> (group A <i>Streptococcus</i>)
Respiratory viruses	
More rarely	More rarely^a
HIV	Anaerobes
	<i>Bartonella henselae</i> (mostly following cat bites or scratches)
	<i>Chlamydia trachomatis</i> (serovars L ₁ , L ₂ and L ₃ which cause lymphogranuloma venereum)
	<i>Corynebacterium diphtheriae</i>
	<i>Francisella tularensis</i>
	<i>Haemophilus ducreyi</i>
	<i>Neisseria gonorrhoeae</i>
	<i>Rickettsia</i> spp.
	<i>Yersinia pestis</i>

MRSA: methicillin-resistant *Staphylococcus aureus*.

Note. Pathogens associated with chronic lymphadenitis such as mycobacteria (including non-tuberculous) are not included in the table.

^a This is not a full list but aims to show the variety of bacteria associated with localized lymphadenitis. The bacteria are listed in alphabetical order. Sexually transmitted infections and zoonoses need to be considered in the differential diagnosis.

Clinical presentation

Lymphadenitis is a noticeable enlargement (> 1–2 cm) of a lymph node. Acute onset, unilateral involvement, fluctuance and fluid that drains from the lymph node to the skin suggest a bacterial cause. Tenderness and inflammation are frequently associated with infectious causes. Fever ($\geq 38.0^{\circ}\text{C}$) and other signs and symptoms of systemic disease may be present, accompanied by cellulitis. Viral respiratory infections, infectious mononucleosis (caused by Epstein–Barr virus or cytomegalovirus), (acute) HIV infection and mycobacterial infections (mostly TB) always need to be considered when diagnosing the cause of acute lymphadenitis based on clinical history and findings. As the first step, it is important to identify the cause of the enlargement. Location of the enlarged lymph node and accompanying signs and symptoms of infection (e.g. symptoms of a dental infection, skin lesions, pharyngitis and signs and symptoms of an STI) can help establish the diagnosis. History and physical examination (including palpation of lymph nodes) usually help in the diagnosis and guide the investigation and treatment.

Laboratory tests

Patient microbiology tests

Routine microbiology testing is usually not needed because in most cases with an infectious cause, identifying the etiologic agent will not change the initial management. However, HIV infection and tuberculosis should be considered in the differential diagnosis and adequate testing should be done when these diseases are suspected.

Other tests

Routine laboratory testing is usually not needed. However, it may be considered in certain cases, for example, persistent lymph node enlargement for more than 4 weeks or the presence of warning signs such as important weight loss.

Using microbiology surveillance data

Routine surveillance is not helpful to inform empiric guidance.

Biopsy

An excisional biopsy of the lymph node could be considered if a malignancy is suspected. An alternative technique that can be used is fine needle aspiration, another type of biopsy technique where a very thin needle is inserted into the mass under examination for sampling of cells/tissue.

Imaging

Routine imaging is usually not needed to begin with. An ultrasound can be considered to confirm lymph node involvement, to measure the size of the enlargement and to detect the presence of an abscess. However, ultrasound cannot reliably rule out malignancies; in suspected cases an excisional biopsy should be performed.

Antibiotic treatment

In certain cases, a watchful waiting approach without antibiotics is indicated when follow-up is feasible and the patient is not severely ill or a malignancy is not suspected. This approach is reasonable because the condition is frequently self-limiting – for example, mild cervical lymphadenitis is usually caused by a viral infection of the upper respiratory tract, especially in children but could also be associated with a dental infection.

If symptoms are consistent with a bacterial infection (e.g. fever, and painful, tender and inflamed lymph node), empiric treatment against *Staphylococcus aureus* and *Streptococcus pyogenes* is indicated. Antibiotic options are given in Table 9.2.

Table 9.2 – Empiric antibiotic treatment for bacterial lymphadenitis^a

Where more than one antibiotic is recommended for an infection, they are listed in alphabetical order and they should be considered equal treatment options, unless otherwise indicated.		
Important		
Adults	Children	Total treatment duration
<p>Amoxicillin+clavulanic acid</p> <p>IV: 1 g + 200 mg given every 8 hours</p> <p>Oral: 500 mg + 125 mg given every 8 hours</p> <p>OR</p> <p>Cefalexin (oral): 500 mg given every 8 hours</p> <p>OR</p> <p>Cloxacillin^b IV: 2 g given every 6 hours</p> <p>Oral: 500 mg given every 6 hours</p>	<p>Amoxicillin+clavulanic acid^c (IV/oral): 80–90 mg/kg/day of amoxicillin component</p> <p>Oral weight bands:</p> <ul style="list-style-type: none"> 3-< 6 kg: 250 mg of amoxicillin/dose given every 12 hours 6-< 10 kg: 375 mg of amoxicillin/dose given every 12 hours 10-< 15 kg: 500 mg of amoxicillin/dose given every 12 hours 15-< 20 kg: 750 mg of amoxicillin/dose given every 12 hours ≥ 20 kg: 500 mg of amoxicillin/dose given every 8 hours or 1 g of amoxicillin/dose given every 12 hours <p>OR</p>	5 days

continues

Table 9.2 continued

Adults	Children	Total treatment duration
	<p>Cefalexin (oral): 25 mg/kg/dose given every 12 hours</p> <p>Oral weight bands:</p> <ul style="list-style-type: none"> 3-< 6 kg: 125 mg given every 12 hours 6-< 10 kg: 250 mg given every 12 hours 10-< 15 kg: 375 mg given every 12 hours 15-< 20 kg: 500 mg given every 12 hours 20-< 30 kg: 625 mg given every 12 hours ≥ 30 kg: use adult dose <p>OR</p> <p>Cloxacillin^b</p> <p>IV:</p> <ul style="list-style-type: none"> • Neonates: 25–50 mg/kg/dose given every 12 hours • Children: 25 mg/kg/dose given every 6 hours <p>Oral: 15 mg/kg/dose given every 6 hours</p> <p>Oral weight bands:</p> <ul style="list-style-type: none"> 3-< 6 kg: 62.5 mg given every 6 hours 6-< 10 kg: 125 mg given every 6 hours 10-< 15 kg: 250 mg given every 6 hours 15-< 20 kg: 375 mg given every 6 hours ≥ 20 kg: 500 mg given every 6 hours 	

IV: intravenous.

Note. All dosages are for normal renal and hepatic function.

^a Patient history is key in order to adapt treatment if necessary; for example, lymphadenitis in the context of cat scratch fever caused by *Bartonella henselae* would require a different antibiotic treatment.

^b If cloxacillin is unavailable, any other IV antistaphylococcal penicillin could be used. For oral administration, dicloxacillin and flucloxacillin are preferred options within the class as they have better oral bioavailability.

^c Oral liquid formulations must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

10. Bacterial eye infections (excluding trachoma)

Note

See separate chapter on trachoma.

Key messages

- **Conjunctivitis** is mostly self-limiting and of viral origin. Allergies and toxic irritants should be included in the differential diagnosis. Topical antibiotics can be considered if a bacterial infection is suspected. Sexually transmitted infections should be included in the differential diagnosis in sexually active people and in newborns of infected mothers.
- **Keratitis** is mostly caused by bacteria and viruses in high-income countries and fungi predominate in low- and middle-income countries. Risk factors include eye trauma and prolonged contact lens use; in the latter case, *Acanthamoeba*, a parasite, or *Pseudomonas aeruginosa* should be considered as potential causes of the infection. Topical antibiotics are indicated as infectious keratitis is a potentially blinding condition.
- **Endophthalmitis** mostly occurs after a penetrating eye trauma (including eye surgery) or dissemination to the eye of a distant infection (e.g. endocarditis). It can be caused by bacteria or fungi. Treatment ideally requires both intravitreal and intravenous antibiotics as it is a potentially blinding condition.
- **Periorbital (or preseptal) cellulitis** is usually a mild condition more common in children. It can be treated with oral antibiotics active against Gram-positive pathogens from the skin (e.g. *Staphylococcus aureus*). It is very important to distinguish periorbital (or preseptal) from orbital cellulitis (deeper more severe infection) because the management is different.

Other relevant WHO resources (please check regularly for updates)

- Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, 2013 (31).

Definition

Pathogens can infect most ocular structures and present with many combinations of signs and symptoms. It is important to determine which anatomical part is infected (Figure 10.1)

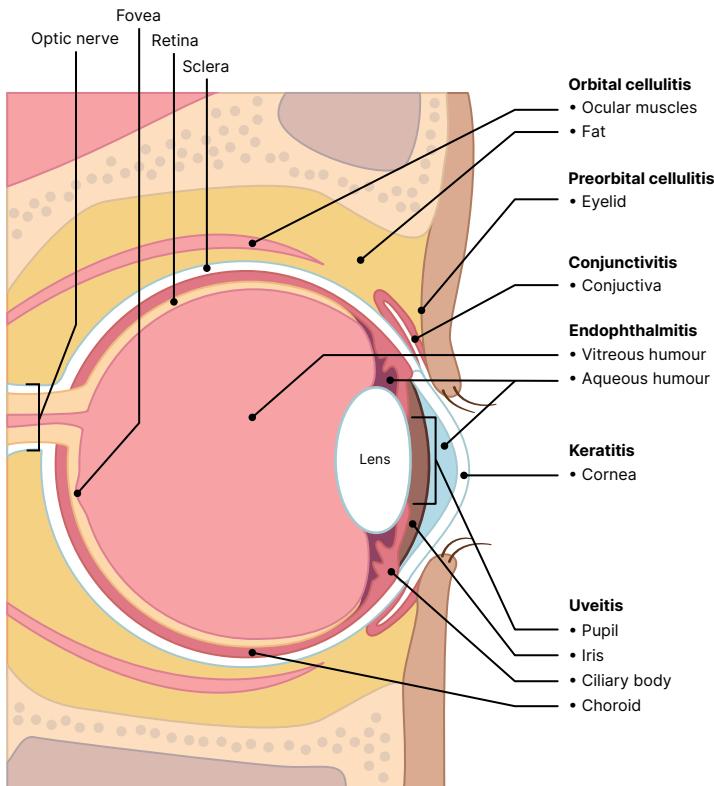
because the most probable causative pathogens may differ, with implications for treatment. In addition, eye infections can be acquired in different ways (e.g. exogenous or endogenous, see the pathophysiology section for more information on transmission) and this also has implications for treatment and helps determine the most likely causative pathogens.

It should be noted that many conditions presented in this chapter could also be of non-infectious origin (e.g. systemic inflammatory diseases affecting other parts of the body or, in the case of conjunctivitis, allergies or toxic irritants), but non-infectious eye conditions are beyond the scope of this chapter.

This chapter focuses on eye infections of bacterial origin presented in alphabetical order.

Infections not addressed in the AWaRe book (because they are rare) include: canaliculitis (infection of the lacrimal canaliculi) and dacryocystitis (infection of the lacrimal sac).

Figure 10.1 – Eye anatomy and locations of common eye infections



Conjunctivitis

Bacterial eye infection

Definition

Infection of the conjunctiva (i.e. the mucosa that covers the inside part of the eyelids and the sclera, which is the white part of the eye)

Diagnosis

Clinical Presentation

- **Most cases are mild and self-limiting**

- Usually the eye is red, watery and itchy and patients have a feeling of "sand in the eye"
- Vision is normal and there is no pain (if pain is present consider corneal involvement)
- Thick purulent eye discharge can be present in bacterial infection

Hyperacute Bacterial Conjunctivitis:

- Severe infection that presents with decreased vision, purulent eye discharge, eyelid swelling, pain on palpation and preauricular adenopathy
- Consider urgent referral to an ophthalmologist due to risk for rapid progression to corneal perforation

Microbiology Tests

Usually not needed unless *Neisseria gonorrhoeae* or *Chlamydia trachomatis* are suspected

Other Laboratory Tests

Usually not needed

Imaging

Usually not needed

Most Likely Pathogens

- Most cases are of viral origin
- Bacterial cases are less common than viruses
- Consider *Chlamydia trachomatis* (serovars D to K) and *Neisseria gonorrhoeae* in the context of sexually transmitted infections (STI) see "STI – Chlamydia urogenital infections and gonococcal infection"
- Hyperacute bacterial conjunctivitis is mostly caused by *Neisseria gonorrhoeae*

Important: non-infectious causes (mostly allergies) should always be considered

Treatment

Clinical Considerations

- Most cases resolve without treatment in 7-10 days
- Antibiotics can be considered in case of suspected bacterial conjunctivitis or conjunctivitis in the context of a sexually transmitted infection

Antibiotic Treatment Duration

Since treatment duration varies, please refer to the corresponding treatment section

Bacterial Conjunctivitis

 **Gentamicin 0.3% EYE DROPS**
1 drop in the affected eye q6h
Treatment duration: 5 days

OR

 **Oflloxacin 0.3% EYE DROPS**
1 drop in the affected eye q6h
Treatment duration: 5 days

OR

 **Tetracycline 1% EYE OINTMENT**
1 cm in the affected eye q6h
Treatment duration: 5 days

Gonococcal Conjunctivitis

All dosages are for normal renal function

 **Ceftriaxone 250 mg IM**
Treatment duration: Single dose

COMBINED WITH

 **Azithromycin 1 g ORAL**
Treatment duration: Single dose

Conjunctivitis

Bacterial eye infection • Page 1 of 2

Definition

Infection of the conjunctiva (i.e. the mucosa that covers the inside part of the eyelids and the sclera, which is the white part of the eye)

Most Likely Pathogens

- Most cases are of viral origin
- Bacterial cases can occur in children more frequently than in adults (although less common than viruses)
- Consider *Chlamydia trachomatis* (serovars D-K) and *Neisseria gonorrhoeae* in neonates after vaginal delivery from infected mothers

Important: non-infectious causes (mostly allergies) should always be considered

Diagnosis

Clinical Presentation

- **Most cases are mild and self-limiting**
- Usually the eye is red, watery and itchy and patients have a feeling of "sand in the eye"
- Vision is normal and there is no pain (if pain is present consider corneal involvement)
- Thick purulent eye discharge can be present in bacterial infection

Hyperacute Bacterial Conjunctivitis:

- Severe infection that presents with decreased vision, purulent eye discharge, eyelid swelling, pain on palpation and preauricular adenopathy
- Consider urgent referral to an ophthalmologist due to risk for rapid progression to corneal perforation

Microbiology Tests

Usually not needed unless *Neisseria gonorrhoeae* or *Chlamydia trachomatis* are suspected

Other Laboratory Tests

Usually not needed

Imaging

Usually not needed

Conjunctivitis

Bacterial eye infection • Page 2 of 2

Rx Treatment

Clinical Considerations

- Most cases resolve without treatment in 7-10 days
- Antibiotics can be considered in case of suspected bacterial conjunctivitis

Antibiotic Treatment Duration

Since treatment duration varies, please refer to the corresponding treatment section

Rx Bacterial Conjunctivitis



Gentamicin 0.3% EYE DROPS

- 1 drop in the affected eye q6h

Treatment duration: 5 days

OR



Ofloxacin 0.3% EYE DROPS

- 1 drop in the affected eye q6h

Treatment duration: 5 days

OR



Tetracycline 1% EYE OINTMENT

- 1 cm in the affected eye q6h

Treatment duration: 5 days

Rx Gonococcal Ophthalmia Neonatorum

All dosages are for normal renal function



Ceftriaxone 50 mg/kg IM

Treatment duration: Single dose

Rx Chlamydial Ophthalmia Neonatorum

Topical therapy alone is not effective

All dosages are for normal renal function



Azithromycin 20 mg/kg q24h ORAL

Treatment duration: 3 days

Rx Prevention of both Chlamydial and Gonococcal Ophthalmia Neonatorum



Erythromycin 0.5% EYE OINTMENT

- To be applied to both eyes soon after birth

OR



Tetracycline 1% EYE OINTMENT

- To be applied to both eyes soon after birth

Endophthalmitis

Bacterial eye infection

Definition

- Infection of the intraocular fluids (vitreous and aqueous humor) and the retina
- Most cases occur as a result of penetrating eye trauma, after eye surgery or as a complication of keratitis
- Rare cases are due to bacteremia or fungemia from distant sites of infection (e.g. endocarditis, liver abscess)



Diagnosis

Clinical Presentation

- Usually painful red eye, blurred vision and trouble looking at bright light
- In cases where pathogens reach the eye through the bloodstream from other sites of infection, signs and symptoms of bacteremia/fungemia can be present although usually ocular symptoms occur first



Microbiology Tests

- Consider microscopy and culture of a sample of aqueous or vitreous humour aspirate
- Consider blood cultures if a distant source of infection is suspected (i.e. endogenous endophthalmitis)



Other Laboratory Tests

Consider tests to detect organ dysfunction



Imaging

Usually not needed



Most Likely Pathogens

Exogenous (Most Cases):

- Bacteria:**
 - Mostly coagulase-negative Staphylococci, less frequently *Staphylococcus aureus*
 - Streptococcus* spp.
 - Klebsiella* spp. (more frequent in Asia)
 - Bacillus cereus* (mostly in case of penetrating trauma)
- Fungi:**
 - Fusarium* spp.
 - Aspergillus* spp.

Endogenous (Rare):

- Bacteria:**
 - Mostly coagulase-negative Staphylococci, less frequently *Staphylococcus aureus*
 - Streptococcus* spp.
 - Klebsiella* spp. (more frequent in Asia)
 - Bacillus cereus* (mostly in case of penetrating trauma)
- Fungi:**
 - Mostly *Candida albicans*

Treatment



Clinical Considerations

- Endophthalmitis is an ocular emergency because it is a potentially blinding condition
- Systemic antibiotics (in combination with intravitreal antibiotics) should be considered given the severity of this condition, especially when referral to an ophthalmologist is not rapidly available

The cornerstone of treatment is intravitreal injection of antibiotics. Two common approaches to administer intravitreal antibiotics:

1. "Tap and inject": first a sample of vitreous humour is collected for culture (through vitreous aspiration), then antibiotics are injected into the vitreous

2. Vitrectomy is performed (i.e. eye surgery to remove some or all the inflamed vitreous from the eye as a form of source control) and during the procedure, the antibiotic is injected into the vitreous



Antibiotic Treatment Duration

Intravitreal: Single dose

If no clinical improvement after 48 hours, the injection can be repeated

Systemic: Depends on underlying source of bacteremia



Bacterial Endophthalmitis

All dosages are for normal renal function



Vancomycin 1 mg INTRAVITREAL INJECTION

----- COMBINED WITH -----



Ceftazidime 2.25 mg INTRAVITREAL INJECTION

IF ENDOGENOUS INFECTION,
ADD



Ceftriaxone 2 g q24h IV

----- COMBINED WITH -----



Vancomycin 15-20 mg/kg q12h IV

Endophthalmitis

Bacterial eye infection

Definition

- Infection of the intraocular fluids (vitreous and aqueous humor) and the retina
- Most cases occur as a result of penetrating eye trauma, after eye surgery or as a complication of keratitis
- Rare cases are due to bacteremia or fungemia from distant sites of infection (e.g. endocarditis, liver abscess)



Diagnosis



Clinical Presentation

- Usually painful red eye, blurred vision and trouble looking at bright light
- In cases where pathogens reach the eye through the bloodstream from other sites of infection, signs and symptoms of bacteremia/fungemia can be present although usually ocular symptoms occur first



Microbiology Tests

- Consider microscopy and culture of a sample of aqueous or vitreous humour aspirate
- Consider blood cultures if a distant source of infection is suspected (i.e. endogenous endophthalmitis)



Other Laboratory Tests

Consider tests to detect organ dysfunction



Imaging

Usually not needed



Most Likely Pathogens

Exogenous (Most Cases):

- Bacteria:**
 - Mostly coagulase-negative Staphylococci, less frequently *Staphylococcus aureus*
 - Streptococcus* spp.
 - Klebsiella* spp. (more frequent in Asia)
 - Bacillus cereus* (mostly in case of penetrating trauma)
- Fungi:**
 - Fusarium* spp.
 - Aspergillus* spp.

Endogenous (Rare):

- Bacteria:**
 - Mostly coagulase-negative Staphylococci, less frequently *Staphylococcus aureus*
 - Streptococcus* spp.
 - Klebsiella* spp. (more frequent in Asia)
 - Bacillus cereus* (mostly in case of penetrating trauma)
- Fungi:**
 - Mostly *Candida albicans*

Treatment



Clinical Considerations

- Endophthalmitis is an ocular emergency because it is a potentially blinding condition
- Systemic antibiotics (in combination with intravitreal antibiotics) should be considered given the severity of this condition, especially when referral to an ophthalmologist is not rapidly available

The cornerstone of treatment is intravitreal injection of antibiotics. Two common approaches to administer intravitreal antibiotics:

1. "Tap and inject": first a sample of vitreous humour is collected for culture (through vitreous aspiration), then antibiotics are injected into the vitreous

2. Vitrectomy is performed (i.e. eye surgery to remove some or all the inflamed vitreous from the eye as a form of source control) and during the procedure, the antibiotic is injected into the vitreous



Antibiotic Treatment Duration

Intravitreal: Single dose

- If no clinical improvement after 48 hours, the injection can be repeated

Systemic: Depends on underlying source of bacteremia



Bacterial Endophthalmitis

All dosages are for normal renal function



Vancomycin 1 mg **INTRAVITREAL INJECTION**

----- COMBINED WITH -----



Ceftazidime 2.25 mg **INTRAVITREAL INJECTION**

----- IF ENDOGENOUS INFECTION, ADD -----



Ceftriaxone 80 mg/kg/dose q24h **IV**

----- COMBINED WITH -----



Vancomycin **IV**

- Neonates: 15 mg/kg/dose q12h
- Children: 15 mg/kg/dose q8h

Keratitis

Bacterial eye infection

Definition

Infection of the cornea (i.e. transparent covering of the eye)



Most Likely Pathogens

High Income Countries:

- Bacteria and viruses are the most common causes

Low and Middle Income Countries:

- Fungi predominate (especially in rural settings where eye trauma from plants is a common risk factor)

Bacteria:

- *Pseudomonas* spp. (mostly in individuals who wear contact lenses)
- *Staphylococcus epidermidis*
- *Staphylococcus aureus*
- *Streptococcus pneumoniae*

Fungi:

- Mostly *Fusarium* spp.
- *Aspergillus* spp.

Viruses:

- Reactivation of herpes simplex virus (especially in patients who are immunocompromised)

Parasites:

- Acanthamoeba (contact lenses)



Diagnosis



Clinical Presentation

Usually painful eye, decreased vision, more tears and corneal oedema with a feeling of "having something in the eye" and difficulty in keeping the eye open +/- eye discharge



Microbiology Tests

- Consider microscopy and culture of a corneal sample (e.g. corneal scrapings or corneal biopsy)
- Consider nucleic acid amplification testing for herpes simplex virus in patients who are immunocompromised



Other Laboratory Tests

Usually not needed



Imaging

Usually not needed; specialist eye examination may be considered

Rx Treatment



Clinical Considerations

- Infectious keratitis is an ocular emergency because it is a potentially blinding condition with poor prospects of visual restoration
- Patients with keratitis should stop wearing contact lenses until the infection is healed
- Consider giving cycloplegic eye drops (cyclopentolate 1% or atropine 1%) to reduce photophobia and to reduce the formation of pupillary adhesions to the lens



Antibiotic Treatment Duration

2 weeks

Duration is often personalized to the individual based on clinical improvement



Bacterial Keratitis



Ofloxacin 0.3% EYE DROPS

- 1 drop in the affected eye q1h for 48 hours, then q4h until healed

Drops are preferred over ointments because they have a better corneal penetration

Keratitis

Bacterial eye infection



Definition

Infection of the cornea (i.e. transparent covering of the eye)



Most Likely Pathogens

High Income Countries:

- Bacteria and viruses are the most common causes

Low and Middle Income Countries:

- Fungi predominate (especially in rural settings where eye trauma from plants is a common risk factor)

Bacteria:

- Pseudomonas* spp. (mostly in individuals who wear contact lenses)
- Staphylococcus epidermidis*
- Staphylococcus aureus*
- Streptococcus pneumoniae*

Fungi:

- Mostly *Fusarium* spp.
- Aspergillus* spp.

Viruses:

- Reactivation of herpes simplex virus (especially in patients who are immunocompromised)



Diagnosis



Clinical Presentation

- Usually painful eye, decreased vision, more tears and corneal oedema with a feeling of "having something in the eye" and difficulty in keeping the eye open +/- eye discharge
- Keratitis is rare in children



Microbiology Tests

- Consider microscopy and culture of a corneal sample (e.g. corneal scrapings or corneal biopsy)
- Consider nucleic acid amplification testing for herpes simplex virus in patients who are immunocompromised



Other Laboratory Tests

Usually not needed



Imaging

Usually not needed; specialist eye examination may be considered



Treatment



Clinical Considerations

- Infectious keratitis is an ocular emergency because it is a potentially blinding condition with poor prospects of visual restoration
- Consider giving cycloplegic eye drops (cyclopentolate 1% or atropine 1%) to reduce photophobia and to reduce the formation of pupillary adhesions to the lens



Antibiotic Treatment Duration

2 weeks

Duration is often personalized to the individual based on clinical improvement



Bacterial Keratitis



Ofloxacin 0.3% EYE DROPS

- 1 drop in the affected eye q1h for 48 hours, then q4h until healed

Drops are preferred over ointments because they have a better corneal penetration

Periorbital cellulitis

Bacterial eye infection

Definition

Infection of subcutaneous eyelid tissues anterior to the orbital septum (the globe and the tissues within the bony orbit are not involved)

Important: most cases result from adjacent infections (e.g. infection of the eyelid, lacrimal sac, periorbital sinuses, dental infections) or follow bites or trauma of the eyelid

Diagnosis

Clinical Presentation

- Usually unilateral signs of inflammation around the affected eye (e.g. red, swollen, warm and tender eyelid) with no restricted or painful eye movement +/- fever ($\geq 38.0^{\circ}\text{C}$)
- Vision is normal

Important:

- This is usually a mild condition that is rare in adults; complications are rare
- It is important to differentiate with orbital cellulitis (where there is usually restricted eye movements, protrusion of the eye and loss of vision)

Microbiology Tests

- Usually not needed
- Cultures are difficult to obtain and blood cultures when performed are usually negative

Other Laboratory Tests

Usually not needed

Imaging

Consider a CT scan of the orbits and sinuses to assess the presence of orbital involvement and possible complications (e.g. abscess)



Most Likely Pathogens

Bacteria:

- Staphylococcus aureus* (including MRSA strains)
- Streptococcus pneumoniae*
- Haemophilus influenzae*
- Moraxella catarrhalis*
- Anaerobes should be suspected if there is a history of animal or human bite or if necrosis is present

Viruses:

- Consider a virus (e.g. herpes simplex virus or varicella-zoster virus) if there is a vesicular skin rash

Treatment



Clinical Considerations

Most cases can be managed in the outpatient setting with oral antibiotics especially in adults with no signs of severe infection



Antibiotic Treatment Duration

10-14 days (depending on the severity)



Antibiotic Treatment

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

 Amoxicillin+clavulanic acid 500 mg+125 mg q8h **ORAL** OR 1 g+200 mg q8h **IV**

-----OR-----

 Cefalexin 500 mg q8h **ORAL**

-----OR-----

 Cloxacillin 500 mg q6h **ORAL** OR 2 g q6h **IV**

Cloxacillin has a narrower spectrum of antibacterial activity compared to amoxicillin+clavulanic acid and cefalexin with limited coverage of Gram-negative bacteria from the upper respiratory tract that may cause periorbital cellulitis. Therefore, when this infection is suspected, amoxicillin+clavulanic acid or cefalexin would be the preferred options

Periorbital cellulitis

Bacterial eye infection • Page 1 of 2

Definition

Infection of subcutaneous eyelid tissues anterior to the orbital septum (the globe and the tissues within the bony orbit are not involved)

Important: most cases result from adjacent infections (e.g. infection of the eyelid, lacrimal sac, periorbital sinuses) or follow bites or trauma of the eyelid

Most Likely Pathogens

Bacteria:

- *Staphylococcus aureus* (including MRSA strains)
- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Moraxella catarrhalis*
- Anaerobes should be suspected if there is a history of animal or human bite or if necrosis is present

Viruses:

- Consider a virus (e.g. herpes simplex virus or varicella zoster virus) if there is a vesicular skin rash

Diagnosis

Clinical Presentation

- Usually unilateral signs of inflammation around the affected eye (e.g. red, swollen, warm and tender eyelid) with no restricted or painful eye movement +/- fever ($\geq 38.0^{\circ}\text{C}$)
- Vision is normal

Important:

- This is usually a mild condition, complications are rare
- It is important to differentiate with **orbital cellulitis** (where there is usually restricted eye movements, protrusion of the eye and loss of vision)

Microbiology Tests

- Usually not needed
- Cultures are difficult to obtain and blood cultures when performed are usually negative

Other Laboratory Tests

Usually not needed

Imaging

Consider a CT scan of the orbits and sinuses to assess the presence of orbital involvement and possible complications (e.g. abscess)

Periorbital cellulitis

Bacterial eye infection • Page 2 of 2

R_X Treatment

Clinical Considerations

Most cases can be managed in the outpatient setting with oral antibiotics especially in children >1 year with no signs of severe infection



Antibiotic Treatment Duration

10-14 days (depending on the severity)

R_X Antibiotic Treatment

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated



Amoxicillin+clavulanic acid

ACCESS

- IV:
• 1st week of life: 50 mg/kg/dose of amoxicillin component q12h
• > 1st week of life: 50 mg/kg/dose of amoxicillin component q8h
ORAL: 80-90 mg/kg/day of amoxicillin component

• Oral weight bands:

3-<6 kg	250 mg of amox/dose q12h
6-<10 kg	375 mg of amox/dose q12h
10-<15 kg	500 mg of amox/dose q12h
15-<20 kg	750 mg of amox/dose q12h
≥20 kg	500 mg of amox/dose q8h or 1 g of amox/dose q12h

Amox = amoxicillin

Oral liquid must be refrigerated after reconstitution

OR



Cefalexin 25 mg/kg/dose q12h ORAL

ACCESS

• Oral weight bands:

3-<6 kg	125 mg q12h
6-<10 kg	250 mg q12h
10-<15 kg	375 mg q12h
15-<20 kg	500 mg q12h
20-<30 kg	625 mg q12h
≥30 kg	500 mg q8h

OR



Cloxacillin

ACCESS

IV

- Neonates: 25-50 mg/kg/dose q12h
• Children: 25 mg/kg/dose q6h
ORAL: 15 mg/kg/dose q6h
• Oral weight bands:

3-<6 kg	62.5 mg q6h
6-<10 kg	125 mg q6h
10-<15 kg	250 mg q6h
15-<20 kg	375 mg q6h
≥20 kg	500 mg q6h

Cloxacillin has a narrower spectrum of antibacterial activity compared to amoxicillin+clavulanic acid and cefalexin with limited coverage of Gram-negative bacteria from the upper respiratory tract that may cause periorbital cellulitis. Therefore, when this infection is suspected, amoxicillin+clavulanic acid or cefalexin would be the preferred options



Pathophysiology

Eye infections can result either from external contamination through direct inoculation of the pathogen into the eye/s (exogenous transmission) or from dissemination of the pathogen through the bloodstream from a distant site of infection (endogenous transmission). Exogenous transmission can occur by contact with infected secretions (mostly by rubbing the eye/s with contaminated hands), or as a result of a penetrating eye injury, which includes eye surgery where bacteria from the flora could be introduced. The use of contact lenses and eye contact with water (e.g. during swimming) are also risk factors for exogenous transmission. In addition, certain STIs (e.g. gonococcal and chlamydial infections) can be transmitted from infected mothers to their child during vaginal delivery. Endogenous transmission occurs when pathogens are spread through the bloodstream from other sites of infection (e.g. in the case of endocarditis, UTIs, abdominal abscesses, meningitis and indwelling catheters), mainly in high-risk patients, such as immunocompromised patients and people who inject drugs.

Blepharitis

Definition

Blepharitis is an infection of the eyelid margin. It can be anterior (less common than posterior blepharitis and characterized by inflammation at the base of the eyelashes) or posterior (more common, characterized by inflammation of the inner portion of the eyelid at the level of the meibomian glands).

Hordeolum (sty) is a common acute bacterial infection of one or more eyelid glands.

Epidemiology

Blepharitis is a chronic condition and most cases are not due to infections but to a dysfunction of oil glands in the eyelids. In posterior blepharitis (the most common form), chronic infections may also play a role. The bacteria that comprise the flora in posterior blepharitis are the same as those found on the skin but are present in greater numbers (82).

Most likely pathogens

The most common causative pathogens of blepharitis are shown in Table 10.1.

Table 10.1 – Pathogens most frequently associated with blepharitis (in descending order of frequency)

Type of organism	Pathogen
Bacteria	<i>Staphylococcus aureus</i>
	Coagulase-negative <i>Staphylococcus</i>
Mites	<i>Demodex folliculorum</i> ^a
	<i>Demodex brevis</i> ^b

Note. Blepharitis does not usually have an infectious origin.

^a *Demodex folliculorum* has been identified in 30% of patients with chronic anterior blepharitis but is also found with about the same prevalence in asymptomatic people. However, this organism is clearly a contributing factor in some patients as evidenced by the improvement seen in response to eradication therapy.

^b *Demodex brevis* has been associated with posterior blepharitis.

Clinical presentation

Patients with blepharitis typically present with inflamed eyelids that are red, swollen and itchy with crusts at the base of the eyelid and on the eyelashes mostly in the morning. Usually both eyes are affected and most cases are chronic.

Blepharitis is more common in adults than in children, but children can have severe episodes of anterior and/or posterior blepharitis, often characterized by more conjunctival and corneal findings (83,84).

Blepharitis related to *Demodex* infestation characteristically presents with cylindrical dandruff or “sleeves” on the eyelashes (85). Patients with hordeolum usually present with a tender swelling of the eyelid/s with a lash at its apex.

Laboratory tests

Patient microbiology tests

Microbiology tests are not usually needed.

Other tests

Laboratory tests (other than microbiology) are not usually helpful.

Using microbiology surveillance data

Routine surveillance is not helpful to inform empiric guidance.

Imaging

Imaging is usually not needed.

Antibiotic treatment

Antibiotic treatment is not usually needed. Good eyelid hygiene is the most important treatment and cases usually resolve without further measures. Warm compresses 5 to 10 minutes two to four times per day, lid massage and washing, and use of preservative-free artificial tears four to eight times per day can also help.

Patients with severe or refractory symptoms may require additional therapies but this is beyond the scope of this chapter.

Conjunctivitis

Definition

Conjunctivitis is an infection of the conjunctiva, the mucosa that covers the inside part of the eyelids and the outer surface of the eye – the sclera.

Epidemiology

Conjunctivitis is the most frequent eye infection and most cases are of viral origin in both children and adults. Bacterial cases, although less common, can occur, especially in children. Non-infectious causes (mostly allergies but sometimes also toxic irritants) should always be considered in the differential diagnosis (86). Most cases of conjunctivitis are exogenous and infection is mostly acquired by touching the eye with contaminated hands.

Most likely pathogens

Pathogens most frequently associated with conjunctivitis (86) are shown in Table 10.2.

Table 10.2 – Pathogens most frequently associated with conjunctivitis (in descending order of frequency)

Type of organism	Pathogen
Viruses	Most infectious cases are of viral origin Adenovirus (usually) Herpes simplex virus (rarely) Varicella-zoster virus (rarely)
Bacteria (87)	In children <i>Staphylococcus aureus</i> <i>Streptococcus pneumoniae</i> <i>Haemophilus influenzae</i> <i>Moraxella catarrhalis</i> In adults <i>Staphylococcus aureus</i> Consider <i>Chlamydia trachomatis</i> (serovars D–K) and <i>Neisseria gonorrhoeae</i> in the context of sexually transmitted infections or in neonates after vaginal delivery from infected mothers. <i>Chlamydia trachomatis</i> (serovars A–C) can cause trachoma. Trachoma is covered in a separate chapter.

Clinical presentation

Patients with conjunctivitis (including cases of viral origin) usually present with a red, watery and itchy eye. They often describe a feeling of “sand in the eye” with no pain (if there is pain, this usually indicates corneal involvement) and they have normal vision. In cases of bacterial infection, a thick purulent discharge from the eye is usually present. Patients may refer to all discharge as pus; however, in bacterial conjunctivitis, the complaint of discharge predominates, while in viral and allergic conjunctivitis, patients report a burning and gritty feeling or itching and the eye usually presents with a watery discharge. In most cases, conjunctivitis is a mild self-limiting condition.

A severe form of conjunctivitis is hyperacute bacterial conjunctivitis which is mostly caused by *Neisseria gonorrhoeae*. It is characterized by severe purulent discharge and decreased vision. Usually, eyelid swelling, pain on palpation and preauricular adenopathy are present (86).

In neonates, conjunctivitis can be caused by a range of pathogens. In general, gonococcal or staphylococcal infection is more likely to present early with symptoms in the first 5 days of life, with chlamydial infection generally presenting later (> 5 days after birth).

Laboratory tests

Patient microbiology tests

Usually no test is required unless *Neisseria gonorrhoeae* or *Chlamydia trachomatis* are suspected.

Other tests

Laboratory tests (other than microbiology) are usually not helpful.

Using microbiology surveillance data

Routine surveillance is not helpful to inform empiric guidance.

Imaging

Imaging is usually not needed.

Antibiotic treatment

Most cases of infectious conjunctivitis are self-limiting, of viral origin and resolve without treatment in 7–10 days. In patients with typical presentation of bacterial conjunctivitis (i.e. red eye with purulent discharge and normal vision), antibiotic treatment could be considered to shorten the duration of symptoms (88) based on the patient's preferences. In these cases, antibiotic treatment is usually topical (eye drops or eye ointment) and prescribed empirically (Table 10.3) based on local availability. Systemic antibiotic treatment is only required in cases of systemic infections, for example, conjunctivitis in the context of an STI (Table 10.3). Steroid eye drops (alone or in combination with antibiotic drops) are not usually needed for the treatment of conjunctivitis; in fact, steroids might even make the condition worse if it is caused by herpes virus infection or the cornea is affected.

Urgent referral of the patient to an ophthalmologist, if available, should be considered when hyperacute bacterial conjunctivitis (mostly caused by *Neisseria gonorrhoeae*) is suspected because of the risk of rapid progression to corneal perforation.

Table 10.3 – Empiric antibiotic treatment for bacterial conjunctivitis

Type of eye infection	Antibiotic treatment	Total treatment duration
Bacterial conjunctivitis (children and adults)	Gentamicin (eye drops): 0.3%, 1 drop in the affected eye every 6 hours OR Ofloxacin (eye drops): 0.3%, 1 drop in the affected eye every 6 hours OR Tetracycline (eye ointment): 1%, 1 cm in the affected eye every 6 hours	5 days
Gonococcal conjunctivitis (adults, adolescents)	Ceftriaxone (IM) ^a : 250 mg AND Azithromycin (oral): 1 g	Single dose
Gonococcal ophthalmia neonatorum (i.e. gonococcal conjunctivitis of the newborn) Symptoms usually appear within 5 days of birth	Ceftriaxone (IM) ^b : 50 mg/kg	Single dose
Chlamydial ophthalmia neonatorum (i.e. chlamydial conjunctivitis of the newborn) Symptoms usually appear > 5 days after birth	Azithromycin (oral) ^c : 20 mg/kg given once a day Topical therapy alone is not effective.	3 days
Ocular prophylaxis (topical treatment for the prevention of both gonococcal and chlamydial ophthalmia neonatorum) ^d	Erythromycin (eye ointment): 0.5% OR Tetracycline (eye ointment): 1%	Antibiotic needs to be applied to both eyes soon after birth (single dose)

continues



Table 10.3 *continued*

IM: intramuscular.

Note. All dosages are for normal renal and hepatic function.

^a Concurrent treatment with azithromycin for chlamydial infection is usually recommended.

^b Ceftriaxone should not be administered in neonates receiving calcium-containing IV fluids and it should be avoided in infants with hyperbilirubinaemia. Cefotaxime can be used as an alternative. Alternatives to ceftriaxone indicated in the 2016 WHO guidelines but not included the EMLc for this indication are kanamycin (IM) 25 mg/kg or spectinomycin (IM) 25 mg/kg (89).

^c An alternative indicated in the 2016 WHO guidelines but not included in the EML for this indication is erythromycin (oral) 50 mg/kg per day divided in four doses for 14 days (89).

^d Alternatives indicated in the 2016 WHO guidelines but not included in the EML for this indication are: povidone–iodine (water-based solution; do not use alcohol-based solutions) 2.5%; silver nitrate (solution) 1%; chloramphenicol (eye ointment) 1% (89).

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Endophthalmitis

Definition

Endophthalmitis is an infection of the inner part of the eye globe, in particular, the intraocular fluids: vitreous and aqueous humour, and the retina.

Epidemiology

Endophthalmitis mostly has an exogenous cause and occurs as a result of penetrating eye trauma, after eye surgery or as a complication of keratitis. Endogenous cases of endophthalmitis are rare but can occur because of bacteraemia or fungaemia from distant sites of infection, most often endocarditis and liver abscess depending on the setting (90,91). Injection of drugs is a common risk factor in patients with endogenous infections. Endophthalmitis refers to bacterial or fungal infection within the eye, including involvement of the vitreous and/or aqueous humours. Endophthalmitis is not caused by viruses or parasites; infections due to these organisms are included in the term uveitis (92).

Most likely pathogens

Table 10.4 shows the most common causative pathogens associated with endophthalmitis.

Table 10.4 – Pathogens most frequently associated with endophthalmitis

Type of endophthalmitis	Most common causative pathogens (in descending order of frequency)
Exogenous – most cases	<p>Bacteria</p> <p>Most cases</p> <ul style="list-style-type: none"> Coagulase-negative staphylococci <p>Less frequently</p> <ul style="list-style-type: none"> <i>Staphylococcus aureus</i> (93) <i>Streptococcus</i> spp.^a <i>Klebsiella</i> spp. (more frequent in Asia ; often in conjunction with liver abscess) <i>Bacillus cereus</i> (mostly in cases of penetrating trauma) <p>Fungi^b</p> <ul style="list-style-type: none"> <i>Fusarium</i> spp. <i>Aspergillus</i> spp.
Endogenous – rare	<p>Bacteria: same as above</p> <p>Fungi^c</p> <ul style="list-style-type: none"> Mostly <i>Candida albicans</i>

^a *Streptococcus viridans* is more frequently encountered in case of post-intravitreal injection endophthalmitis compared to post-cataract endophthalmitis (94).

^b In tropical regions, fungal endophthalmitis is often due to molds and is usually exogenous in origin.

^c In temperate climates, fungal endophthalmitis is usually endogenous and caused by *Candida* spp.

Clinical presentation

Endophthalmitis is usually an acute condition and patients present with a painful red eye, blurred vision and trouble looking at bright light (i.e. photophobia). Most cases are exogenous and typically occur after eye surgery (usually within days or a few weeks) or trauma. In rare cases, endophthalmitis can result from the haematogenous spread of pathogens from distant sites of infection, such as endocarditis and liver abscess. In these cases, signs and symptoms of bacteraemia can be present although in most cases ocular symptoms occur first.

Laboratory tests

Patient microbiology tests

Microbiology tests to consider when endophthalmitis is suspected are shown in Table 10.5.

A positive culture of aqueous or vitreous humour in the presence of compatible signs and symptoms could confirm the diagnosis.

**Table 10.5 – Microbiology tests to consider when endophthalmitis is suspected as indicated in the WHO EDL (6)**

Diagnostic test	Purpose of the test	Settings where the test should be available
Microscopy (Gram stain) and culture of aqueous or vitreous humour aspirate	Microbial morphology and detection and identification of bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories
Blood cultures and antimicrobial susceptibility testing	To detect bacterial and fungal bloodstream infections in patients with suspected endogenous endophthalmitis	Health care facilities with clinical laboratories

EDL: WHO Model List of Essential In Vitro Diagnostics.

Other tests

Laboratory tests (other than microbiology) are usually not needed.

Using microbiology surveillance data

Routine surveillance is not helpful to inform empiric guidance.

Imaging

Imaging is usually not needed.

Antibiotic treatment

This condition should be treated by an ophthalmologist where available. Urgent referral of the patient to an ophthalmologist, if available, should be considered when endophthalmitis is suspected because this condition could potentially threaten the patient's sight.

With bacterial endophthalmitis, the cornerstone of treatment is intravitreal injection of antibiotics. There are two common approaches:

- “tap and inject”: first a sample of vitreous humour is collected for culture (through vitreous aspiration) and then antibiotics are injected into the vitreous
- vitrectomy is performed – that is, eye surgery to remove some or all the inflamed vitreous from the eye as a form of source control – and during the procedure, the antibiotic is injected into the vitreous.

■ PRIMARY HEALTH CARE

10. Bacterial eye infections (excluding trachoma)

Systemic antibiotics (in combination with intravitreal antibiotics) should also be considered given the severity of this condition, especially when referral to an ophthalmologist is not readily available (Table 10.6). In cases of endogenous infections, systemic antibiotics should always be given. However, evidence of their added benefit (e.g. on visual acuity) compared to intravitreal treatment alone is still controversial. The ability to rapidly reach adequate concentrations of antibiotics in the eye varies by antibiotic (95).

There is limited evidence of the benefit of additive treatment with intravitreal steroid therapy compared to antibiotics alone (96).

Table 10.6 – Empiric antibiotic treatment for bacterial endophthalmitis

Type of bacterial endophthalmitis	Antibiotic treatment	Total treatment duration
Exogenous	Intravitreal injection Vancomycin 1 mg AND Ceftazidime 2.25 mg Systemic antibiotics alone are not effective in treating bacterial exogenous endophthalmitis. Whether systemic antibiotics provide any benefit in these cases as adjunctive therapy to intravitreal antibiotics is still debatable.	Intravitreal antibiotics: single dose. If no clinical improvement after 48 hours, the intravitreal injection can be repeated.
Endogenous	ADD Systemic treatment <i>Adults</i> Ceftriaxone (IV): 2g given once a day AND Vancomycin (IV): 15–20 mg/kg given every 12 hours <i>Neonates and children</i> Ceftriaxone (IV): 80 mg/kg/dose given once a day AND Vancomycin (IV): <ul style="list-style-type: none">• Neonates: 15 mg/kg/ dose given every 12 hours• Children: 15 mg/kg/dose given every 8 hours	Duration of systemic antibiotics should be determined by the need to treat the underlying source of bacteraemia (e.g. 6 weeks in many cases of endocarditis).

IV: intravenous.

Note. All dosages are for normal renal and hepatic function.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.



Keratitis

Definition

Keratitis is an infection of the cornea, the transparent covering of the eye.

Epidemiology

Keratitis is common and the estimated number of cases is more than 2 million per year (97). The highest (epidemic) burden is in South, South-East and East Asia (97), especially in rural settings among male workers in high-risk professions as eye trauma is the predominant risk factor (98). In high-income countries, the number of cases of keratitis has increased over time, probably because of the increased use of contact lenses; their use is currently the most common risk factor in this setting. The disease is rare in children, but it is also harder to diagnose, mostly because it is more difficult to obtain a clinical history and to collect a sample for microbiology tests.

Most likely pathogens

The most common pathogens causing keratitis (97,98) are shown in Table 10.7.

Table 10.7 – Pathogens most frequently associated with keratitis^a (in descending order of frequency)

Type of organism	Pathogen
Fungi	Mostly <i>Fusarium</i> spp. <i>Aspergillus</i> spp.
Bacteria	<i>Pseudomonas</i> spp. (contact lenses) <i>Staphylococcus epidermidis</i> <i>Staphylococcus aureus</i> <i>Streptococcus pneumoniae</i>
Viruses	Mostly Herpes simplex virus (usually type 1) Varicella zoster virus
Parasites	<i>Acanthamoeba</i> (contact lenses)

^a Bacteria and viruses are the most common causes of keratitis in high-income countries, while fungi predominate in low- and middle-income countries. Global variations in etiology largely reflect patient-based risk factors such as population demographic, occupation, contact lens use, concomitant ocular and systemic illness, as well as environmental factors such as geographical location, climate and virulence of causative organisms. For example, *Pseudomonas* spp. and *Acanthamoeba* spp. are often associated with the use of contact lenses and fungal keratitis must be considered after any traumatic corneal injury, notably from vegetable matter. In the paediatric population, there appears to be a higher incidence of atypical infections, for example, due to *Acanthamoeba* (97).

Clinical presentation

Patients with keratitis generally present with a painful eye, decreased vision, more tears and corneal oedema. They often describe a feeling of "having something in the eye" and have difficulty keeping the affected eye open. A discharge from the eye may be seen depending on the causative pathogen. Most infectious cases are of bacterial origin, although in low- and middle-income countries, fungal infections are common, for example, as a result of trauma from plants or sand or mud in rural settings (97). Reactivation of herpes simplex virus could also cause keratitis, especially in patients with HIV infection or in patients with other forms of immunosuppression. Ophthalmologic examination with a slit lamp is usually needed to visualize the cornea and confirm the diagnosis: focal white infiltrates in the corneal stroma with an epithelial defect and underlying tissue loss are the critical sign of keratitis.

Laboratory tests

Patient microbiology tests

A positive culture in the presence of compatible signs and symptoms could confirm the diagnosis (Table 10.8).

Table 10.8 – Microbiology tests to consider when keratitis is suspected as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
Microscopy (Gram stain) and culture of corneal scrapings or corneal biopsy material	Microbial morphology and detection and identification of bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories

EDL: WHO Model List of Essential In Vitro Diagnostics.

Note. Nucleic acid amplification testing (i.e. polymerase chain reaction) for viral etiology (e.g. herpes simplex virus) could be considered based on clinical presentation and individual risk factors.

Other tests

Laboratory tests (other than microbiology) are usually not helpful.

Using microbiology surveillance data

Routine surveillance is not helpful to inform empiric guidance.



Imaging

Imaging is usually not needed. Specialist eye examination may be considered.

Antibiotic treatment

Patients should stop wearing contact lenses. Topical antibiotic treatment is indicated even though consensus on the most effective treatment is lacking (Table 10.9) (99). Cycloplegic eye drops (cyclopentolate 1% or atropine 1%) can be used for comfort, to reduce photophobia from ciliary spasm and to reduce the formation of pupillary adhesions to the lens.

Oral antibiotics can be considered in selected cases (e.g. scleral extension or impending perforation) or in case of gonococcal infection. With viral keratitis, topical and oral antiviral treatment is usually indicated (but management of viral infections is beyond the scope of this chapter).

Note

Infectious keratitis is an ocular emergency as it is a potentially blinding condition for which the prospect of visual restoration is often poor.

Table 10.9 – Empiric antibiotic treatment for bacterial keratitis

Antibiotic treatment	Total treatment duration
Children and adults Ofloxacin ^a (eye drops): 0.3%, 1 drop in the affected eye every hour for 48 hours then every 4 hours until healed	2 weeks but duration is often personalized to the individual based on clinical improvement.

^a A fluoroquinolone is usually given to patients who wear contact lenses because *Pseudomonas aeruginosa* is often the causative pathogen. For most patients, hourly treatment is indicated for the first 24 to 48 hours. Drops are preferred because ointments have poor corneal penetration. However, ointments may be used at bedtime to allow the patient to sleep through the night, but only after a positive response has been demonstrated to the initial intensive eyedrop treatment.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Orbital cellulitis

Definition

Orbital cellulitis is an infection affecting eye tissues behind the orbital septum within the bony orbit (i.e. fat and ocular muscles within the orbit).

Due to the complexity of this infection, treatment of this condition is not addressed in the AWaRe book, but some general information is presented in the following section.

Epidemiology

Orbital cellulitis is more common in young children and in most cases it is a complication of bacterial sinusitis.

Most likely pathogens

The most common causative pathogens of orbital cellulitis are shown in Table 10.10.

Table 10.10 – Pathogens most frequently associated with orbital cellulitis (in descending order of frequency)

Type of organism	Pathogen
Bacteria	In adults <i>Staphylococcus aureus</i> <i>Streptococcus</i> spp. <i>Bacteroides</i> spp.
	In children <i>Haemophilus influenzae</i> (rare in vaccinated children (100))
	Following eye trauma <i>Pseudomonas aeruginosa</i> <i>Escherichia coli</i>
	Following a dental abscess Polymicrobial infection (including anaerobes)
Fungi ^a	Mostly in immunocompromised patients, such as those with diabetes, receiving chemotherapy and with HIV infection <i>Zygomycetes</i> (e.g. <i>Mucor</i>) <i>Aspergillus</i> spp.

^a Fungal infections are rare but they should be considered in immunocompromised patients including patients with poorly controlled diabetes.



Clinical presentation

Patients with orbital cellulitis typically have unilateral local signs of inflammation around the affected eye. The eyelids are usually swollen, red, warm and tender. Sometimes fever is present ($\geq 38.0^{\circ}\text{C}$). These findings are also present in cases of periorbital (or preseptal) cellulitis (see next section); however, in addition to these symptoms, patients with orbital cellulitis present with restricted extraocular motility with pain on attempted eye movement, conjunctival chemosis (i.e. swelling) and hyperaemia (i.e. redness) as critical signs. Usually this condition is accompanied by protrusion of the eye (i.e. proptosis) and loss of vision may be present (101). Signs of optic neuropathy (e.g. afferent pupillary defect and dyschromatopsia) may be present in severe cases. In neglected cases, orbital cellulitis may lead to cavernous sinus thrombosis, brain abscess or even death.

Laboratory tests

Patient microbiology tests

Blood cultures and cultures of samples collected can be considered (Table 10.11).

Table 10.11 – Microbiology tests to consider when orbital cellulitis is suspected as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
Microscopy (Gram stain), culture and antimicrobial susceptibility testing of abscess material	Microbial morphology and detection and identification of bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories
Blood cultures and antimicrobial susceptibility testing	To detect bacterial and fungal bloodstream infections	Health care facilities with clinical laboratories

EDL: WHO Model List of Essential In Vitro Diagnostics.

Other tests

Laboratory tests (other than microbiology) are usually not helpful.

Using microbiology surveillance data

Routine surveillance is not helpful to inform empiric guidance.

Imaging

A CT scan of the orbits and sinuses (axial, coronal and parasagittal views, with contrast if possible) should be obtained if available. The reason for doing a CT scan is to assess the presence or absence of orbital involvement when the diagnosis is uncertain and the presence of possible complications, for example, subperiosteal or orbital abscess, cavernous sinus thrombosis and intracranial extension.

Antibiotic treatment

Note

General information is presented but treatment is not addressed in the AWaRe book.

Patients with orbital cellulitis should be admitted to the hospital and an infectious disease physician and otorhinolaryngology/ophthalmology specialists should be consulted. Most patients with uncomplicated orbital cellulitis can be treated with antibiotics alone (102,103).

Surgery for source control (e.g. drainage of purulent collections) may be needed in severe and complicated cases (e.g. in cases of abscess) in combination with systemic antibiotic treatment (104,105). Surgery is almost always indicated in patients with intracranial extension of the infection.

Periorbital (or preseptal) cellulitis

Definition

Periorbital (or preseptal) cellulitis is an infection of subcutaneous eyelid tissues anterior to the orbital septum; in this case, the globe and the tissues within the bony orbit are not involved.

Epidemiology

This is usually a mild condition that most commonly affects children. Most cases are exogenous and result from adjacent infection (hordeolum, dacryocystitis, infection of the periorbital sinuses, severe dental infection) or follow animal and insect bites or trauma of the eyelid. Periorbital (or preseptal) cellulitis is much more common than orbital cellulitis (106).

The most common pathogens associated with periorbital (or preseptal) cellulitis are shown in Table 10.12.

Table 10.12 – Pathogens most frequently associated with periorbital (or preseptal) cellulitis (in descending order of frequency)

Type of organism	Pathogen
Bacteria	<i>Staphylococcus aureus</i> (including MRSA) <i>Streptococcus pneumoniae</i> <i>Haemophilus influenzae</i> (rare in vaccinated children (100)) <i>Moraxella catarrhalis</i> Anaerobes (suspect if there is a history of animal or human bite or if necrosis is present)
Viruses	If the infection is associated with a vesicular skin rash, suspect: <i>Herpes simplex virus</i> <i>Varicella-zoster virus</i>

MRSA: methicillin-resistant *Staphylococcus aureus*.

Clinical presentation

It is very important to distinguish periorbital (or preseptal) from orbital cellulitis. Patients with periorbital (or preseptal) cellulitis typically present with unilateral local signs of inflammation around the affected eye but do not have restricted or painful eye movements, as occurs in case of orbital cellulitis. The eyelid/s is generally swollen, red, warm and tender and sometimes fever is present ($\geq 38.0^{\circ}\text{C}$). In severe cases, conjunctival chemosis (i.e. swelling) may also occur. Vision is normal, while in case of orbital cellulitis loss of vision may be present (101). In periorbital (or preseptal) cellulitis, serious complications are rare (107).

Laboratory tests

Patient microbiology tests

Usually no test is required. Cultures are difficult to obtain and blood cultures when performed are usually negative.

Other tests

Laboratory tests (other than microbiology) are usually not helpful.

Using microbiology surveillance data

Routine surveillance is not helpful to inform empiric guidance.

Imaging

A CT scan of the orbits and sinuses (axial, coronal, and parasagittal views, with contrast if possible) could be considered. The reason for doing a CT scan is to assess the presence or absence of orbital involvement when the diagnosis is uncertain and the presence of possible complications is suspected, for example, subperiosteal or orbital abscess, cavernous sinus thrombosis, or intracranial extension.

Antibiotic treatment

Systemic antibiotic treatment is indicated and is usually given empirically based on the most likely causative pathogens because cultures are difficult to obtain and blood cultures when performed are usually negative (Table 10.13). Empiric treatment of MRSA may be considered in certain cases based on individual risk factors (e.g. known MRSA colonization) and on the local prevalence of community-acquired MRSA. In these cases, the literature suggests using clindamycin or sulfamethoxazole+trimethoprim; however, no formal recommendation can be made in the AWaRe book as these options are not currently listed in the EML and EMLc for this indication.

Most cases of periorbital (or preseptal) cellulitis can be managed with oral antibiotic treatment; however, in severely ill patients or very young children, intravenous treatment may be considered (105).

Adults and children older than 1 year with mild periorbital (or preseptal) cellulitis and no signs of systemic toxicity can generally be treated as outpatients with oral antibiotics, provided close follow-up can be ensured.

Children younger than 1 year, patients who cannot cooperate fully for an examination, who are severely ill or in case of no noticeable improvement or worsening after 24 to 48 hours of oral antibiotics should generally be admitted to the hospital and managed according to the recommendations for orbital cellulitis.

Table 10.13 – Empiric antibiotic treatment for periorbital (or preseptal) cellulitis^a

Where more than one antibiotic is recommended for an infection, they are listed in alphabetical order and they should be considered equal treatment options, unless otherwise indicated.		
Note		
Adults	Children	Total treatment duration
<p>Amoxicillin+clavulanic acid IV: 1 g + 200 mg given every 8 hours Oral: 500 mg + 125 mg given every 8 hours</p> <p>OR</p> <p>Cefalexin (oral): 500 mg given every 8 hours</p> <p>OR</p> <p>Cloxacillin^b IV: 2 g given every 6 hours Oral: 500 mg given every 6 hours</p>	<p>Amoxicillin+clavulanic acid^c</p> <p>IV: First week of life: 50 mg/kg of amoxicillin/dose given every 12 hours Beyond first week of life: 50 mg/kg of amoxicillin/dose given every 8 hours</p> <p>Oral: 80–90 mg/kg/day of amoxicillin component</p> <p>Oral weight bands:</p> <p>3–< 6 kg: 250 mg of amoxicillin/dose given every 12 hours</p> <p>6–< 10 kg: 375 mg of amoxicillin/dose given every 12 hours</p> <p>10–< 15 kg: 500 mg of amoxicillin/dose given every 12 hours</p> <p>15–< 20 kg: 750 mg of amoxicillin/dose given every 12 hours</p> <p>≥ 20 kg: 500 mg of amoxicillin/dose given every 8 hours or 1 g of amoxicillin/dose given every 12 hours</p> <p>OR</p>	10–14 days (depending on the severity)

continues

Table 10.13 *continued*

Adults	Children	Total treatment duration
	<p>Cefalexin (oral): 25 mg/kg/dose given every 12 hours</p> <p>Oral weight bands:</p> <ul style="list-style-type: none"> 3-< 6 kg: 125 mg given every 12 hours 6-< 10 kg: 250 mg given every 12 hours 10-< 15 kg: 375 mg given every 12 hours 15-< 20 kg: 500 mg given every 12 hours 20-< 30 kg: 625 mg given every 12 hours ≥ 30 kg: use adult dose <p>OR</p> <p>Cloxacillin^b</p> <p>IV:</p> <ul style="list-style-type: none"> • Neonates: 25–50 mg/kg/dose given every 12 hours • Children: 25 mg/kg/dose given every 6 hours <p>Oral: 15 mg/kg/dose given every 6 hours</p> <p>Oral weight bands:</p> <ul style="list-style-type: none"> 3-< 6 kg: 62.5 mg given every 6 hours 6-< 10 kg: 125 mg given every 6 hours 10-< 15 kg: 250 mg given every 6 hours 15-< 20 kg: 375 mg given every 6 hours ≥ 20 kg: 500 mg given every 6 hours 	

IV: intravenous.

Note. All dosages are for normal renal and hepatic function.

^a It should be noted that these specific recommendations are not included in the EML and EMLc (8,9). The options presented are based on what is recommended for mild skin and soft tissues infections.

^b If cloxacillin is unavailable, any other IV antistaphylococcal penicillin could be used. For oral administration; dicloxacillin and flucloxacillin are preferred options within the class as they have better oral bioavailability.

^c Oral liquid formulations must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.



Infectious uveitis

Definition

Uveitis is an infection of the uvea, which is composed of:

- iris – the coloured ring-shaped part of the eye behind the cornea
- ciliary body – the part that extends around the iris, has a muscular component and produces the aqueous humour that keeps the eye in a pressurized state
- choroid – a vascular layer.

Epidemiology

Infectious uveitis can be caused by a large number of pathogens and most cases are associated with systemic infections, but it may also occur as an isolated condition. Therefore, the epidemiology depends on the underlying infection. In general, certain factors can increase the risk of specific infections, for example, cytomegalovirus is mostly associated with uveitis in immunocompromised patients.

Most likely pathogens

Table 10.14 shows the most common causative pathogens of uveitis.

Table 10.14 – Pathogens most frequently associated with uveitis^a (in alphabetical order)

Type of organism	Pathogen
Bacteria	<i>Bartonella henselae</i> (with cat-scratch disease) <i>Mycobacterium tuberculosis</i> ^b <i>Treponema pallidum</i> (with neurosyphilis)
Parasites	<i>Toxoplasma gondii</i>
Viruses	Cytomegalovirus Herpes simplex virus Varicella-zoster virus

^a Usually in the context of infectious or autoimmune or inflammatory systemic conditions. Therefore consider individual risk factors and presentation to identify the most likely causative pathogen.

^b Ocular tuberculosis usually results from haematogenous dissemination of the infection from pulmonary or extra-pulmonary sites.

Clinical presentation

The symptoms of uveitis are non-specific and depend on the portion of the uveal tract that is involved. Findings also differ depending upon the location of the involvement, and visual loss may occur with anterior, intermediate or posterior involvement. Anterior uveitis is about four times more common than posterior uveitis (108). Patients with uveitis usually have a painful red eye and decreased vision. Infectious forms of uveitis are mostly of viral origin (e.g. herpes simplex virus, cytomegalovirus) or they may occur as a reactivation of toxoplasmosis.

When uveitis is suspected, patients should be seen by an ophthalmologist, if available, because the list of potential conditions associated with uveitis is large and, in some cases, uveitis is a potentially sight-threatening condition.

Laboratory tests

Patient microbiology tests

The need for microbiology tests should be guided by the type of eye infection suspected (see Table 10.15 for tests to consider).

Table 10.15 – Microbiology tests to consider when uveitis is suspected as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
Microscopy (Gram stain) and culture ^a	Microbial morphology and detection and identification of bacterial species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics.

Note. Nucleic acid amplification testing (i.e. polymerase chain reaction) for viral etiology (e.g. herpes simplex virus) could be considered based on clinical presentation and individual risk factors.

^a Depending on the type of infection, consider conjunctival swabs, corneal scrapings or corneal biopsy, aqueous or vitreous humour aspirate.

Other tests

Laboratory tests (other than microbiology) are usually not helpful.

Using microbiology surveillance data

Routine surveillance is not helpful to inform empiric guidance.

Imaging

Specialist eye examination may be considered depending on the type of infection.

Antibiotic treatment

Note

General information is presented but treatment is not addressed in the AWaRe book.

Treatment for uveitis depends on the etiology (including non-infectious causes), location and clinical severity. Because of the large variety of conditions associated with uveitis, a review of treatment options is beyond the scope of this chapter.

11. Trachoma

Key messages

- Trachoma is an eye disease caused by specific serovars (A through C) of the bacterium *Chlamydia trachomatis*.
- Repeated infections over the years can lead to permanent corneal damage and blindness.
- Treatment depends on the stage of the disease. It may require eye surgery to prevent blindness if corneal damage has already occurred.
- Mass antibiotic administration programmes in endemic areas aim to reduce the reservoir of *Chlamydia trachomatis*.



Other relevant WHO resources (please check regularly for updates)

- Trachoma – fact sheet (109).
- Resolution WHA51.11. Global elimination of blinding trachoma, 1998 (110).
- The simplified trachoma grading system, amended, 2020 (111).
- Trachoma control: a guide for programme managers, 2006 (112).

Definition

Trachoma is an eye disease caused by specific serovars (A through C) of the bacterium *Chlamydia trachomatis* (other serovars cause urogenital diseases, please see the chapter on sexually transmitted infections – Chlamydia urogenital infections). Trichiasis is the advanced clinical consequence of trachoma characterized by the eyelashes turning inwards which leads over time to permanent corneal damage. Trichiasis is a sight-threatening condition that requires surgical treatment.

Trachoma

Definition

Eye disease caused by specific serovars (A, B and C) of the bacterium *Chlamydia trachomatis* (other serovars cause urogenital diseases, see "Sexually transmitted infections – Chlamydial urogenital infections")

Pathogen

- *Chlamydia trachomatis* is a Gram-negative obligate intracellular bacterium
- Strains associated with trachoma are serovars A, B, Ba, and C

Diagnosis

Clinical Presentation

Acute:

- Usually signs and symptoms of conjunctivitis with redness of the eye, eye discomfort, mucopurulent discharge and light sensitivity
- Rare in adults

Advanced:

- Conjunctival scarring, signs of chronic conjunctival inflammation and eyelashes turned inward
- Mostly seen in adults due to repeated infections over time

WHO has a trachoma grading system used in field assessments to evaluate the extent of disease during examination (Reference: Solomon AW et al. The simplified trachoma grading system, amended. Bull World Health Organ. 2020;98(10):698-705)

Microbiology Tests

- Usually not needed
- Consider testing a conjunctival sample (culture or nucleic acid amplification tests for *Chlamydia trachomatis*) in a selected subgroup of people to decide whether to stop or continue antibiotic treatment at the population level

Other Laboratory Tests

Usually not needed

Imaging

Usually not needed

Rx Treatment

Clinical Considerations

- Antibiotic treatment is often given as part of mass drug administration programmes in endemic areas to reduce the reservoir of *Chlamydia trachomatis*
- If corneal damage has already occurred due to the inversion of the eyelashes, surgery is needed to correct the eyelid rotation and prevent blindness
- Repeated infections over the years can lead to permanent corneal damage and blindness

Important: Reinforce education on personal and community hygiene measures

- Infection spreads via the hands through direct contact with contaminated people or objects
- Flies can contribute by transporting contaminated eye/nose secretions to non-infected people
- Risk factors include living in overcrowded conditions and poor sanitation; most transmission occurs within families

Antibiotic Treatment Duration

Since treatment duration varies according to the antibiotic used, please refer to the corresponding antibiotic section for treatment duration

Rx Antibiotic Treatment

All dosages are for normal renal function

 Azithromycin 20 mg/kg (max 1 g) **ORAL**
Treatment duration: Single dose

Administered once a year for 3 years as part of mass drug administration programmes

Topical Treatment

 Azithromycin 1.5% **EYE DROPS**
• 1 drop in both eyes q12h
Treatment duration: 3 days

————— OR —————

 Tetracycline 1% **EYE OINTMENT**
• 1 cm in both eyes q12h
Treatment duration: 6 weeks

Topical treatment is used in areas where oral azithromycin is not readily available. Topical azithromycin may be as effective as oral azithromycin

Trachoma

Definition

Eye disease caused by specific serovars A, B and C of the bacterium *Chlamydia trachomatis*

Pathogen

- *Chlamydia trachomatis* is a Gram-negative obligate intracellular bacterium
- Strains associated with trachoma are serovars A, B, Ba, and C

Diagnosis

Clinical Presentation

Acute:

- Usually signs and symptoms of conjunctivitis with redness of the eye, eye discomfort, mucopurulent discharge and light sensitivity
- More common in children living in endemic areas

Advanced:

- Conjunctival scarring, signs of chronic conjunctival inflammation and eyelashes turned inward
 - Mostly seen in adults due to repeated infections over time
- WHO has a trachoma grading system used in field assessments to evaluate the extent of disease during examination (Reference: Solomon AW et al. The simplified trachoma grading system, amended. Bull World Health Organ. 2010;98(10):698-705)*

Microbiology Tests

- Usually not needed
- Consider testing a conjunctival sample (culture or nucleic acid amplification tests for *Chlamydia trachomatis*) in a selected subgroup of people to decide whether to stop or continue antibiotic treatment at the population level

Other Laboratory Tests

Usually not needed

Imaging

Usually not needed

Treatment

Clinical Considerations

- Antibiotic treatment is often given as part of mass administration programmes in endemic areas to reduce the reservoir of *Chlamydia trachomatis*
- If corneal damage has already occurred due to the inversion of the eyelashes, surgery is needed to correct the eyelid rotation and prevent blindness
- Repeated infections over the years can lead to permanent corneal damage and blindness

Important: Reinforce education on personal and community hygiene measures

- Infection spreads via the hands through direct contact with contaminated people or objects
- Flies can contribute by transporting contaminated eye/nose secretions to non-infected people
- Risk factors include living in overcrowded conditions and poor sanitation; most transmission occurs within families

Antibiotic Treatment Duration

Since treatment duration varies according to the antibiotic used, please refer to the corresponding antibiotic section for treatment duration

Antibiotic Treatment

All dosages are for normal renal function

 Azithromycin 20 mg/kg (max 500 mg) **ORAL**
Treatment duration: Single dose

Administered once a year for 3 years as part of mass drug administration programmes

Topical Treatment

 Azithromycin 1.5% **EYE DROPS**
• 1 drop in both eyes q12h
Treatment duration: 3 days

OR

 Tetracycline 1% **EYE OINTMENT**
• 1 cm in both eyes q12h
Treatment duration: 6 weeks

Topical treatment is used in areas where oral azithromycin is not readily available. Topical azithromycin may be as effective as oral azithromycin

Pathogen

Trachoma is caused by *Chlamydia trachomatis*, a Gram-negative obligate intracellular bacterium. There are several strains of *Chlamydia trachomatis*, some associated with trachoma and some associated with sexually transmitted urogenital diseases. Strains associated with trachoma are serovars A, B, Ba and C.

Pathophysiology

Chlamydia trachomatis infection spreads via the hands through direct contact with contaminated people or objects. Flies can also spread the infection by transporting contaminated eye and/or nose secretions from infected to non-infected people. Chronic inflammation of the conjunctiva caused by repeated infections over the years can cause inversion of the eyelashes that can lead to permanent corneal damage through formation of scars on the cornea (the transparent front part of the eye). This can eventually lead to vision impairment and blindness (113).

Epidemiology

Trachoma is the leading cause of infectious blindness in the world and is responsible for about 1% of cases of blindness. According to the most recent WHO estimates, more than 137 million people worldwide live with trachoma (109). The infection is a public health problem in over 40 countries, most of which are in Africa (109).

Risk factors of trachoma include living in overcrowded conditions and poor sanitation, and most transmission occurs within families. Active disease (i.e. conjunctivitis) is more common in young children living in endemic areas. Children younger than 10 years and those with intense inflammatory trachoma probably represent the main source of ocular *Chlamydia trachomatis* infection in endemic communities (114). Corneal scars are mostly seen in adults because repeated infections over time need to occur before permanent corneal damage is established. Individuals with corneal scars are at increased risk of blindness.

In 1993, WHO adopted the SAFE strategy for the elimination of trachoma:

- **Surgery** to treat advanced diseases,
- **Antibiotics** to clear infection,
- **Facial cleanliness** and
- **Environmental improvement** to reduce transmission.

In 1996, WHO established the alliance for the global elimination of trachoma, whose goal was to eliminate trachoma as a public health problem by 2020 (Box 11.1). In addition, in

1998, the World Health Assembly adopted a resolution on trachoma to urge WHO Member States to implement measures to target the elimination of trachoma (110). As of July 2020, 13 out of 30 countries that are implementing the SAFE strategy have achieved the WHO elimination targets. As part of the elimination strategy, data reported to WHO for 2019 indicate that about 92 000 people had corrective surgery for trichiasis and 95 million people received antibiotic treatment, that is, 57% of people needing antibiotics for trachoma received them (109).

Box 11.1 – World Health Organization definitions related to trachoma

WHO defines trachoma as a public health problem when:

- the prevalence of follicular trachoma in children aged 1–9 years is $\geq 10\%$ (see the section on clinical presentation for the classification of trachoma), or
- the prevalence of trachomatous trichiasis in people aged ≥ 15 years is at least 1%.

WHO criteria for defining elimination of trachoma as a public health problem are (115):

- the prevalence of follicular trachoma in children aged 1–9 years is $< 5\%$ or
- the prevalence of trachomatous trichiasis in people aged ≥ 15 years is $< 0.2\%$ and
- there is evidence that the health system can identify and manage cases of trachomatous trichiasis.

Clinical presentation

Trachoma diagnosis is based on clinical signs. Trachoma presents as an active disease (i.e. conjunctivitis) with symptoms such as redness of the eye, eye discomfort, mucopurulent discharge and light sensitivity.

The other presentation is the advanced disease where there is conjunctival scarring, signs of chronic conjunctival inflammation and eyelashes turned inwards.

The WHO trachoma grading system is used in field assessments to evaluate the extent of disease during examination (111).

The grading system includes:

- Trachomatous inflammation, follicular – five or more follicles of > 0.5 mm on a specific area of the upper tarsal conjunctiva
- Trachomatous inflammation, intense – papillary hypertrophy and inflammatory thickening of the upper tarsal conjunctiva obscuring more than half the deep tarsal vessels

- Trachomatous conjunctival scarring – grossly visible scars on the tarsal conjunctiva
- Trachomatous trichiasis – at least one ingrown eyelash touching the globe of the eye or evidence of epilation (eyelash removal)
- Corneal opacity – corneal opacity blurring part of the pupil margin.

Laboratory tests

Patient microbiology tests

The diagnosis of trachoma is mostly clinical and microbiology tests are not routinely done. However, such tests may be considered (Table 11.1) to decide whether to stop or continue antibiotic treatment at the population level, for example, on a selected subgroup of people (113).

Table 11.1 – Microbiology tests to consider if trachoma is suspected as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
Qualitative test for <i>Chlamydia trachomatis</i> (i.e. nucleic acid amplification test) ^a	To diagnose chlamydial infection	Health care facilities with clinical laboratories
Microscopy (Gram stain) and culture ^a	Initial step to detect and identify bacterial species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics.

^a Possible specimens: conjunctival swabs.

Other tests

When trachoma is suspected based on clinical signs and epidemiology of the community, laboratory tests are not usually needed.

Using microbiology surveillance data

Routine surveillance is not helpful to inform empiric guidance.

Imaging

When trachoma is suspected, imaging is not usually needed.

Antibiotic treatment

The appropriate treatment of trachoma depends on the stage of disease.

If trichiasis has already developed, surgery is needed to prevent blindness by stopping the eyelashes continuing to erode the cornea (112,116).

Antibiotic treatment is generally given to treat *Chlamydia trachomatis* infection in association with reinforced education on personal and community hygiene measures. Usually, antibiotic treatment is given once a year for at least 3 years as part of a mass antibiotic administration programme in endemic areas to reduce the reservoir of *Chlamydia trachomatis* (Table 11.2) (112).

Table 11.2 – Empiric antibiotic treatment for trachoma

Adults and children	Total treatment duration
Azithromycin (oral): 20 mg/kg (maximum 1 g (adults); 500 mg (children))	Single dose (azithromycin)
OR	
Azithromycin (eye drops) ^a : 1.5%, 1 drop administered to both eyes every 12 hours	3 days (topical treatment with azithromycin)
OR	
Tetracycline (eye ointment): 1% 1 cm administered to both eyes every 12 hours	6 weeks (topical treatment with tetracycline)
Topical treatment is used in areas where oral azithromycin is not readily available.	

Note. Antibiotic treatment is mostly given once a year for at least 3 years as part of mass administration programmes in endemic areas.

^a Azithromycin eye drops may be as effective as oral azithromycin (117).

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Prevention

For prevention of trachoma, please refer to the epidemiology section where the WHO SAFE strategy is described.

12. Community-acquired pneumonia – mild

Key messages

- Rapidly decide if the patient has mild community-acquired pneumonia (CAP), which can be managed in primary care with oral antibiotic treatment, or severe CAP, which has a higher short-term mortality risk and requires hospital admission. Scores can be helpful to make this distinction.
- Clinically relevant high-level beta-lactam resistance in *Streptococcus pneumoniae* (the main bacterial cause of CAP) is rare in most countries and oral Access group penicillins (amoxicillin, phenoxymethylpenicillin) remain first choice for mild and moderate cases of CAP.
- Laboratory tests are usually not needed in mild cases.
- Treatment duration can be limited to 5 days in most cases (3 days in children in areas of low prevalence of human immunodeficiency virus (HIV)).

Other relevant WHO resources (please check regularly for updates)

- Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, 2013 (31).
- Revised WHO classification and treatment of pneumonia in children at health facilities: evidence summaries (118).
- Coronavirus disease (COVID-19) pandemic (32).
- Living guidance for clinical management of COVID-19: living guidance, 23 November 2021 (33).
- Therapeutics and COVID-19: living guideline, 16 September 2022 (34).
- Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper –February 2019 (35).
- *Haemophilus influenzae* type b (Hib) vaccination position paper – July 2013: Introduction (36).
- Vaccines against influenza WHO position paper – May 2022 (37).
- WHO consolidated guidelines on tuberculosis: module 4: treatment: drug-susceptible tuberculosis treatment (119).

Definition

CAP is an acute illness affecting the lungs caused by pathogens, most often bacteria and viruses. It usually presents with fever, cough, sputum production (in adults), rapid and difficult breathing with new or worsening pulmonary infiltrate(s) on chest imaging.

Community-acquired pneumonia

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Definition

An acute illness affecting the lungs usually presenting with cough, sputum production, and rapid and difficult breathing with a new or worsening pulmonary infiltrate on a chest radiograph

Most Likely Pathogens

"Typical" bacteria:

- *Streptococcus pneumoniae* (most cases)
- *Haemophilus influenzae* (chronic lung diseases, smoking)
- *Moraxella catarrhalis* (chronic lung diseases, smoking)
- *Staphylococcus aureus* (often associated with influenza)
- *Enterobacteriaceae* (severe comorbidities, e.g. chronic lung diseases, dementia, stroke)

"Atypical" bacteria:

- *Mycoplasma pneumoniae* (more frequent in young adults)
- *Chlamydia pneumoniae* and *psittaci* (more frequent in young adults)
- *Legionella* spp. (chronic lung diseases or other underlying illness, travel, exposure to hot tubs)
- *Coxiella burnetii* (rural areas, exposure to livestock)

Respiratory viruses:

- Influenza viruses (A and B)
- Respiratory syncytial virus (RSV)
- Metapneumovirus
- Parainfluenza virus
- Coronavirus (including SARS-CoV-2)
- Adenovirus
- Rhinovirus
- Other respiratory viruses

Pathogens to consider in specific settings:

- *Burkholderia pseudomallei* (SE Asia, Australia)
- *Mycobacterium tuberculosis*
- *Pneumocystis jirovecii* (people with HIV or other immunosuppression)

Investigating for Tuberculosis (TB)

- Consider specific investigations for TB in endemic settings especially in high-risk patients (e.g. HIV)
- A rapid molecular test performed on a single sputum specimen is the preferred first line diagnostic test for pulmonary TB and to detect rifampicin resistance
- Consider a lipoarabinomannan rapid urinary antigen test in severely immunocompromised HIV patients with signs and symptoms of tuberculosis

Diagnosis

Clinical Presentation

- New onset (<2 weeks) or worsening cough with fever ($\geq 38.0^{\circ}\text{C}$), sputum production, dyspnea, tachypnea, reduced oxygen saturation, crepitations on lung auscultation, chest pain/discomfort without alternative explanation
- Extrapulmonary features (i.e. confusion, disorientation) may predominate in elderly, and immunocompromised patients and fever may be absent

Microbiology Tests

Mild cases: usually not needed

Severe cases (to guide antimicrobial treatment): blood cultures, urinary antigens for *L. pneumophila* and *S. pneumoniae*

Selected cases (depending on epidemiology and risk factors): sputum rapid molecular test for *M. tuberculosis*, nasopharyngeal swab for influenza viruses and SARS-CoV-2, HIV testing in settings with high HIV prevalence and in case of recurrent and/or severe pneumonia

Other Laboratory Tests

Determine disease severity: blood urea nitrogen (see CURB-65 Scoring System box), blood pH and gases, white blood cell count

Differentiate bacterial and viral (taking into account pre-test probability): C-reactive protein and/or procalcitonin

Note: tests depend on availability and clinical severity (e.g. blood gases will only be done in severe cases)

Imaging

- Chest X-ray not necessary in mild cases
- Infiltrate may not always be evident (e.g. dehydration) and non-infectious etiologies may mimic infiltrates (e.g. lung edema, pulmonary embolism)
- Radiologic appearance cannot be used to accurately predict pathogen

Community-acquired pneumonia

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CURB-65 Severity Scoring System

Signs & Symptoms (1 point each)

- Presence of confusion (new onset)
- Urea > 19 mg/dL (or > 7 mmol/L)*
- Respiratory rate > 30/min
- Systolic BP < 90 mmHg (<12 kPa) or Diastolic BP ≤ 60 mmHg (<8 kPa)
- Age ≥ 65 years

Other considerations such as severe comorbid illnesses or inability to maintain oral therapy should be taken into account. CURB-65 has not been extensively validated in low-income settings.

*The CRB-65 score, which does not require laboratory values for its calculation, can also be used, the score value interpretation is the same as for CURB-65

Score 0–1

- Consider outpatient treatment

Score 2

- Consider inpatient treatment
- Consider adding clarithromycin to beta-lactam for atypical coverage
- Perform microbiology tests

Score ≥3

- Inpatient treatment (consider ICU)
- Consider adding clarithromycin
- Perform microbiology tests

Rx Treatment

Antibiotic Treatment Duration

Treat for 5 days

If severe disease, consider longer treatment and look for complications such as empyema, if patient not clinically stable at day 5

Rx Severe Cases

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice

 Cefotaxime 2 g q8h IV/IM

OR

 Ceftriaxone 2 g q24h IV (1 g q24h IM*)

*A larger volume would be painful to give as intramuscular injection

IF CURB-65 ≥2,
CONSIDER ADDING

 Clarithromycin 500 mg q12h ORAL (or IV)

Clarithromycin has excellent oral bioavailability and the intravenous route should be reserved for patients with impaired gastrointestinal function

Second Choice

 Amoxicillin+clavulanic acid 1 g+200 mg q8h IV

- A higher daily dose can be considered: 1 g+200 mg q6h

IF CURB-65 ≥2,
CONSIDER ADDING

 Clarithromycin 500 mg q12h ORAL (or IV)

Clarithromycin has excellent oral bioavailability and the intravenous route should be reserved for patients with impaired gastrointestinal function

Rx Mild to Moderate Cases

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice

 Amoxicillin 1 g q8h ORAL

OR

 Phenoxymethylpenicillin (as potassium) 500 mg (800 000 IU) q6h ORAL

Second Choice

 Amoxicillin+clavulanic acid 875 mg+125 mg q8h ORAL

OR

 Doxycycline 100 mg q12h ORAL

Community-acquired pneumonia

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Definition

An acute illness affecting the lungs usually presenting with cough, and rapid and difficult breathing with a new or worsening pulmonary infiltrate on a chest radiograph



Most Likely Pathogens

"Typical" bacteria:

- *Streptococcus pneumoniae* (most common cause of CAP beyond the 1st week of life)
- *Haemophilus influenzae*
- *Moraxella catarrhalis*
- *Staphylococcus aureus*
- *Enterobacteriales*

"Atypical" pathogens (more frequent in children >5 years compared to younger children):

- *Mycoplasma pneumoniae*
- *Chlamydophila pneumoniae*

Respiratory viruses:

- Respiratory syncytial virus (RSV)
- Influenza viruses (A and B)
- Metapneumovirus
- Parainfluenza virus
- Coronavirus (including SARS-CoV-2)
- Adenovirus
- Rhinovirus
- Other respiratory viruses



Diagnosis



Clinical Presentation

- New onset (<2 weeks) or worsening cough with fever ($\geq 38.0^{\circ}\text{C}$), dyspnea, tachypnea, reduced oxygen saturation, crepitations, cyanosis, grunting, nasal flaring, pallor
- Pneumonia is diagnosed on: fast breathing for age and/or chest indrawing
 - Check for hypoxia with oxygen saturometer if available
- Children with runny nose and cough and no signs of severity usually do not have pneumonia and should not receive an antibiotic, only home care advice



Microbiology Tests

Mild cases: usually not needed

Severe cases (to guide antimicrobial treatment): blood cultures

Tests for COVID-19 and influenza can be considered if clinically indicated and available



Other Laboratory Tests

No test clearly differentiates viral or bacterial CAP

Consider: full blood count and C-reactive protein

Note: tests depend on availability and clinical severity (e.g. blood gases will only be done in severe cases)



Imaging

- Chest X-ray not necessary in mild cases
- Look for lobar consolidation or pleural effusion
- Radiologic appearance cannot be used to accurately predict pathogen



Investigating for Tuberculosis (TB)

- Consider specific investigations for TB in endemic settings especially in high-risk patients (e.g. HIV)
- A rapid molecular test performed on a single sputum specimen is the preferred first line diagnostic test for pulmonary TB and to detect rifampicin resistance

Community-acquired pneumonia

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Severity Assessment and Considerations

Children with **pneumonia**:

- Should be treated with oral amoxicillin at home with home care advice
- Pneumonia is diagnosed on either:
 1. Fast breathing (respiratory rate > 50 breaths/minute in children aged 2-11 months; resp rate > 40 breaths/min in children aged 1-5 years)
 2. Chest indrawing

Children with **severe pneumonia** (or a child with pneumonia who cannot tolerate oral antibiotics):

- **Should be admitted to hospital and treated with intravenous antibiotics**
- Severe pneumonia is characterized by signs of pneumonia:
 - Fast breathing (+/- chest indrawing)
 - PLUS
 - A general danger sign:
 - Inability to breastfeed or drink
 - Convulsions
 - Lethargy or reduced level of consciousness



Antibiotic Treatment Duration

3 days: in areas of low HIV prevalence and no chest indrawing

5 days: in areas of high HIV prevalence and the child has chest indrawing

If severe disease, consider longer treatment and look for complications such as empyema, if patient not clinically stable at day 5

Mild to Moderate Cases

All dosages are for normal renal function

Amoxicillin 80-90 mg/kg/day **ORAL**

• Oral weight bands:

3-<6 kg	250 mg q12h
6-<10 kg	375 mg q12h
10-<15 kg	500 mg q12h
15-<20 kg	750 mg q12h
≥20 kg	500 mg q8h or 1 g q12h

Treatment

Severe Cases

Please see Severity Assessment and Considerations for diagnosis of severe cases

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice

Amoxicillin 50 mg/kg/dose **IV/IM**

- ACCESS • ≤1wk of life: q12h
• >1wk of life: q8h

OR

Ampicillin 50 mg/kg/dose **IV/IM**

- ACCESS • ≤1wk of life: q12h
• >1wk of life: q8h

OR

Benzylpenicillin 30 mg/kg/dose (50 000 IU/kg/dose) q8h **IV**

- ACCESS

COMBINED WITH

Gentamicin **IV/IM**

- ACCESS • Neonates: 5 mg/kg/dose q24h
• Children: 7.5 mg/kg/dose q24h

IF HIV POSITIVE AND <1 YR OLD
To treat potential *Pneumocystis jirovecii* pneumonia, **ADD**

Sulfamethoxazole+trimethoprim 40 mg/kg SMX+8 mg/kg TMP q8h **IV/ORAL** for 3 weeks

Second Choice

If NO Clinical Response to First Choice after 48-72 hours

Cefotaxime 50 mg/kg/dose q8h **IV/IM**

OR

Ceftriaxone 80 mg/kg/dose q24h **IV/IM**

Pathophysiology

CAP occurs when microbial pathogens (usually inhaled in the upper airways) reach the lower respiratory tract and proliferate in the alveoli. Less frequently, these pathogens can also reach the alveoli via the blood or by direct spread, for example, from an infection of the pleural or intra-abdominal space. Once in the alveoli, host immune defences are activated to eliminate the pathogens. Only when these defences fail, pneumonia manifests itself because of the tissue damage and inflammatory response triggered by the proliferation of microorganisms in the affected lung(s).

Epidemiology

CAP is common worldwide and is a leading cause of morbidity and mortality, with an especially high burden in low-income countries (120). According to the Global Burden of Disease study, in 2017 there were an estimated 471 million new cases of lower respiratory tract infections globally among all ages and sexes combined. This number included CAP cases but also a majority of cases of viral bronchitis – therefore caution is needed in interpreting this number (44). The incidence of CAP varies with age and a country's income level. The most common causative pathogens worldwide are *Streptococcus pneumoniae* and viruses (see the following section); viral–bacterial coinfections may occur.

In low-income countries, lower respiratory tract infections (including CAP) were the leading cause of death in 2016, with a crude yearly attributable mortality of about 75 per 100 000 population (121). In general, the incidence of CAP is highest in children younger than 5 years in these countries. In 2015, an estimated 0.9 million children younger than 5 years died of pneumonia and of these, about 0.5 million occurred in sub-Saharan Africa (122). Undernutrition, HIV infection, exposure to smoke and air pollution are common risk factors for severe CAP in children younger than 5 years. As a result of better access to medical care, better nutrition and greater vaccination coverage, global mortality rates in children have declined by more than 30% since 2000. In high-income countries, CAP mainly affects adults 65 years and older and, in general, the incidence of CAP and risk of death increase with age (123).

Most likely pathogens

In **neonates and young infants aged up to 2 months**, pneumonia is mainly caused by *Streptococcus pneumoniae*, group B *Streptococcus*, Enterobacteriales or *Staphylococcus aureus*.

In **children aged 2 months to 5 years**, pneumonia is more likely to be of viral origin, for example, respiratory syncytial virus, influenza and parainfluenza virus. The most important bacterial pathogen in children younger than 5 years is *Streptococcus pneumoniae*.

In **older children** *Streptococcus pneumoniae* is still common but atypical bacteria such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* may be the cause. So-called atypical bacteria have intrinsic resistance to beta-lactam antibiotics and cannot be visualized by Gram staining. *Haemophilus influenzae*, *Moraxella catarrhalis* and *Staphylococcus aureus* also cause CAP in some children (Table 12.1).

In **adults**, viruses are common causes of CAP, either by directly causing pneumonia or by favouring superinfection with bacteria. Among bacteria, the most common causative agents are *Streptococcus pneumoniae*, followed by atypical bacteria (see definition in the paragraph above) such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella pneumophila*. *Haemophilus influenzae*, *Moraxella catarrhalis* and *Staphylococcus aureus* are also quite common (Table 12.1).

However, determining the cause of bacterial pneumonia is difficult in all age groups and no causative pathogen is identified in most cases, even if extensive microbiological tests are performed, which is usually not the case for mild cases. Furthermore, there may be important geographic differences in the cause of pneumonia; for example, *Burkholderia pseudomallei* is a cause of CAP in South-East Asia, while *Coxiella burnetii* is more common in regions where exposure to livestock is common.

Table 12.1 – Pathogens most frequently associated with community-acquired pneumonia (in descending order of frequency)

Typical bacteria	Atypical bacteria ^b	Respiratory viruses	Other pathogens to consider in specific settings
<i>Streptococcus pneumoniae</i> ^a	<i>Mycoplasma pneumoniae</i> ^b	Influenza virus (A and B)	<i>Burkholderia pseudomallei</i> (South-East Asia, Australia)
<i>Haemophilus influenzae</i>	<i>Chlamydia pneumoniae</i> ^b	Respiratory syncytial virus ^c	
<i>Moraxella catarrhalis</i>	and <i>Chlamydia psittaci</i> ^b	Metapneumovirus	
<i>Staphylococcus aureus</i>	<i>Legionella</i> spp.	Parainfluenza virus	<i>Mycobacterium tuberculosis</i>
Enterobacteriales (e.g. <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i>)	<i>Coxiella burnetii</i>	Coronavirus (including SARS-CoV-2)	<i>Pneumocystis jirovecii</i> (in people with HIV or other types of cellular immunosuppression)
		Adenovirus	
		Rhinovirus	
		Other respiratory viruses	

HIV: human immunodeficiency virus; SARS-CoV-2: severe acute respiratory syndrome coronavirus-2.

^a The most common bacterial cause of community acquired pneumonia in all age groups (beyond the first week of life) is *Streptococcus pneumoniae*.

^b Atypical bacteria remain colourless with Gram staining. They also have intrinsic resistance to beta-lactams. *Mycoplasma pneumoniae* and *Chlamydia* spp. are more frequent in children > 5 years (compared with younger children) and in young adults. Risk factors for *Chlamydia psittaci* include exposure to birds.

^c Up to 50% of cases of pneumonia in children < 5 years are caused by a virus, most commonly respiratory syncytial virus.

Community-acquired pneumonia caused by antibiotic-resistant pathogens

AMR is a potential problem with all pathogens associated with CAP. However, clinically relevant high-level beta-lactam resistance in *Streptococcus pneumoniae* is still rare globally. Resistance to macrolides in *Streptococcus pneumoniae* and *Mycoplasma pneumoniae* is highly prevalent in some settings (124,125).

Note

CAP caused by low-level and intermediate-level pneumococcal penicillin resistance can be successfully treated with higher oral doses of the Access antibiotics amoxicillin or penicillin in children and adults.

There is no evidence of improved clinical outcomes in patients with pneumococcal pneumonia in the primary health care setting treated with oral cephalosporins, amoxicillin+clavulanic acid or macrolides compared to amoxicillin and penicillin, and these antibiotics are associated with higher rates of toxicity.

Clinical presentation

Nearly all respiratory diseases can mimic the symptoms of CAP. Based on clinical features alone it is often impossible to distinguish bacterial from viral pneumonia or from other non-infectious causes. Local epidemiology and laboratory tests may help.

Well established clinical features of CAP include a combination of new onset (less than 2 weeks) of symptoms, worsening cough with or without sputum production, dyspnoea (difficulty in breathing), tachypnoea (abnormal respiratory rates to diagnose rapid breathing vary with age), reduced oxygen saturation, crepitations on lung auscultation, or chest pain or discomfort without an alternative explanation. Fever $\geq 38.0^{\circ}\text{C}$ for 3–4 days is usually present but may be absent, especially in elderly people. Extrapulmonary features such as confusion or disorientation may be the main symptoms in elderly people, immunocompromised patients and malnourished children. The severity of signs and symptoms may range from a mild disease that can be safely managed in an outpatient setting with oral antibiotic treatment to severe pneumonia with respiratory distress, sepsis requiring intensive care and intravenous antibiotic treatment, and a high associated mortality.

In children, WHO defines fast breathing pneumonia as a child with a high respiratory rate for their age (> 50 breaths/minute in children 2–11 months of age; > 40 breaths/minute in children aged 1–5 years). They may or may not have chest indrawing.

Laboratory tests

Patient microbiology tests

In mild cases that can be managed in the outpatient setting, microbiology tests are usually not needed. Tests for COVID-19 and influenza can be considered if clinically indicated and available. The TB lipoarabinomannan rapid antigen urinary test should be considered in patients living with HIV who are severely immunocompromised and who present with signs and symptoms of TB.

For more information on this topic, the interested reader can refer to the 2019 WHO policy update: *Lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis of active tuberculosis in people living with HIV: policy update 2019* (126).

Other tests

In mild cases, laboratory tests are usually not needed. If available, point-of-care testing for C-reactive protein could be considered in adult patients if there is diagnostic uncertainty.

In general, C-reactive protein has good negative predictive value, and a negative test can be used to help rule out bacterial pneumonia, unless the pre-test probability is high or the clinical presentation is severe.

Using microbiology surveillance data

The great majority of episodes of CAP in the primary care setting are caused by pneumococcal isolates that clinically respond to oral penicillins. Therefore, routine clinical microbiology surveillance of CAP does not help to inform local empiric guidance.

Imaging

When mild CAP is suspected clinically, a chest X-ray is usually not necessary.

Scores to determine disease severity and guide treatment decisions

WHO recommends that children who meet the criteria of severe pneumonia should be admitted to hospital (see the hospital facility section for the management of severe cases).

As a general rule for children, hospitalization is indicated in cases of severe illness (e.g. cough and severe respiratory distress, marked tachypnoea and tachycardia) and/or if the child is unable to take oral therapy.



In children, severe pneumonia is characterized by signs of pneumonia (fast breathing with or without chest indrawing) plus a general danger sign, such as inability to breastfeed or drink, convulsions, lethargy or a reduced level of consciousness (118).

In adults, several scores exist that measure severity and help predict 30-day mortality. These scores, in addition to clinical judgement, can be used to determine the need for hospitalization in immunocompetent adults diagnosed with CAP. In view of its simplicity, one of the more frequently used scores is the CURB-65 (127), or its modification, CRB-65, which does not require laboratory values for its calculation (Table 12.2). However, it should be noted that these scores have not been extensively validated in low-income settings and for this reason there is no clear consensus about their use in these settings (128). As well as severity scores, other factors, such as severe comorbid illnesses (e.g. HIV infection) or inability to maintain oral therapy, should always be taken into account in determining the need for hospital admission.

Table 12.2 – CURB-65 criteria and scoring, and treatment decisions for community-acquired pneumonia

Criterion	Points
Presence of confusion (new onset)	1
Urea > 19 mg/dL (or > 7 mmol/L) ^a	1
Respiratory rate > 30 breaths/min	1
Systolic blood pressure < 90 mmHg (< 12 kPa) or diastolic blood pressure ≤ 60 mmHg (≤ 8 kPa)	1
Age ≥ 65 years	1
CURB-65 score/CRB-65 score	Where to treat
0–1	Candidate for outpatient treatment Low 30-day mortality risk (< 1.5%)
2	Consider inpatient treatment 30-day mortality risk ≈ 10% Consider adding clarithromycin (see Community-acquired pneumonia – severe) If tests are available, consider testing for atypical pathogens (e.g. <i>Legionella</i> spp., <i>Mycoplasma</i> spp.)

continues

Table 12.2 *continued*

CURB-65 score/CRB-65 score	Where to treat
≥ 3	Inpatient treatment (consider admission to intensive care) High 30-day mortality risk ($\approx 20\%$) Consider adding clarithromycin (see Community-acquired pneumonia – severe) Consider testing for atypical pathogens (e.g. <i>Legionella</i> spp., <i>Mycoplasma</i> spp.)

Note. The CURB-65 score is not validated in low-and middle-income countries.

^a Urea is not required for the calculation of the CRB-65 score, a modification of the CURB-65 score that does not require laboratory tests.

Ruling out tuberculosis

TB is a cause of subacute lower respiratory tract infection and should be considered in settings endemic for TB, especially in high-risk patients (e.g. children or adults with HIV), with a slow onset of symptoms and persistent cough, or those who do not respond to the initial antibiotic treatment. In such cases, specific investigations for TB should be done. A rapid molecular test (GeneXpert® MTB/RIF assay) performed on a single sputum specimen is currently the preferred first-line diagnostic test for pulmonary TB and to detect rifampicin resistance in both children and adults. When this rapid test is not available, microscopy examination of sputum smears could be considered for the detection of acid-fast bacilli (129). For TB management and treatment, refer to the *WHO consolidated guidelines on tuberculosis* (119).

Symptomatic care

Patients and/or their caregivers in the primary health care setting should be informed about the natural course of CAP, including the possibility of a viral etiology that would not benefit from antibiotic treatment and that cough and other symptoms often take 2–3 weeks to fully recover from. Patients should also receive clear advice on seeking medical care with any worsening of symptoms and recommended symptomatic treatment (e.g. antipyretics) (Table 12.3).

Table 12.3 – Medicines to consider for symptomatic treatment of community-acquired pneumonia

Medicine	Formulation	Dose and frequency
Ibuprofen ^a	Oral liquid: 200 mg/5 mL Tablet: 200 mg; 400 mg; 600 mg	Adults: 200–400 mg given every 6 to 8 hours (maximum dose of 2.4 g a day) Children: <ul style="list-style-type: none">• Pain control/antipyretic treatment: 5–10 mg/kg given every 6 to 8 hours6–< 10 kg: 50 mg given every 8 hours10–< 15 kg: 100 mg given every 8 hours15–< 20 kg: 150 mg given every 8 hours20–< 30 kg: 200 mg given every 8 hours≥ 30 kg: use adult dose
Paracetamol (acetaminophen) ^b	Oral liquid: 120 mg/5 mL; 125 mg/5 mL Suppository: 100 mg Tablet: 100 mg to 500 mg	Adults: 500 mg–1 g given every 4 to 6 hours (maximum dose of 4 g a day) ^c Children: <ul style="list-style-type: none">• Pain control/antipyretic treatment: 10–15 mg/kg given every 6 hours3–< 6 kg: 60 mg given every 6 hours6–< 10 kg: 100 mg given every 6 hours10–< 15 kg: 150 mg given every 6 hours15–< 20 kg: 200 mg given every 6 hours20–< 30 kg: 300 mg given every 6 hours≥ 30 kg: use adult dose

^a Not for children < 3 months.^b Not recommended for use as an anti-inflammatory as it has not been proven to have such an effect.^c In patients with hepatic impairment or cirrhosis, maximum daily dose should be 2 g.

Antibiotic treatment

The primary goal of empiric antibiotic treatment in CAP is to provide effective and timely treatment for *Streptococcus pneumoniae* infection because this is the predominant bacterial

pathogen and untreated pneumococcal pneumonia is associated with high mortality (see Table 12.4 for adults and Table 12.5 for children for treatment recommendations). Amoxicillin or phenoxymethylpenicillin (sometimes also called penicillin V) are the recommended first choice options for mild-to-moderate CAP.

Empiric treatment should be guided by the age of the patient, severity of symptoms, presence of comorbidities and previous antibiotic treatment. Clinical improvement should be evident within 48–72 hours of starting antibiotic therapy. If there is no response to treatment, a complication (such as empyema) should be considered. Duration of treatment should be guided by measures of clinical improvement (e.g. resolution of fever); usually 5 days of treatment are adequate for adults and 3–5 days for children.

Table 12.4 – Empiric antibiotic treatment for mild cases of community-acquired pneumonia in adults

! Important		
	Adults	Total treatment duration (130,131)
First choice	Amoxicillin (oral): 1 g given every 8 hours OR Phenoxymethylpenicillin (oral): 500 mg (800 000 IU ^a) given every 6 hours	5 days
Second choice	Amoxicillin+clavulanic acid (oral): 875 mg + 125 mg given every 8 hours OR Doxycycline (oral): 100 mg given every 12 hours	5 days

IU: international units.

Note. All dosages are for normal renal and hepatic function.

^a Units of the potassium salt.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Table 12.5 – Empiric antibiotic treatment for mild cases of community-acquired pneumonia in children

Children	Total treatment duration
Pneumonia (fast breathing and/or chest indrawing) – treat at home with oral antibiotic	<p>Amoxicillin (oral): 80–90 mg/kg/day</p> <p>Oral weight bands:</p> <ul style="list-style-type: none"> 3–< 6 kg: 250 mg given every 12 hours 6–< 10 kg: 375 mg given every 12 hours 10–< 15 kg: 500 mg given every 12 hours 15–< 20 kg: 750 mg given every 12 hours ≥ 20 kg: 500 mg given every 8 hours or 1 g given every 12 hours <p>Children with fast-breathing pneumonia who fail to respond to first-line treatment with amoxicillin should have the option of referral to a facility where there is appropriate second-line treatment.</p>

HIV: human immunodeficiency virus.

Note: All dosages are for normal renal and hepatic function.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Prevention

Vaccination can prevent many cases of CAP. Available vaccines are active against pneumococcal infection, *Haemophilus influenzae* type b disease and influenza, and several vaccines against SARS-CoV-2 are available. Vaccines are never 100% effective and because they are serogroup-specific, they do not protect against all strains of bacteria or viruses. Duration of protection is also variable. As a result, even vaccinated people can develop CAP. *Haemophilus influenzae* type b conjugate vaccines and pneumococcal conjugate vaccines should be included in all routine infant immunization programmes as they have been very successful in reducing invasive disease and in many countries, in reducing rates of pneumococcal resistance. Countries should consider the inclusion of yearly seasonal influenza vaccination for high-risk populations (pregnant women, elderly people, patients with chronic medical conditions and health care workers) in their vaccination plan.

13. Exacerbation of chronic obstructive pulmonary disease

Key messages

- **Antibiotics are not needed** for most mild cases.
- Avoid routine sputum culture in mild cases as patients may be colonized by multiple bacteria, making results difficult to interpret.
- Supplementary oxygen and short-acting inhaled beta-2-agonists are the mainstay of treatment. Steroids are also recommended in many guidelines as they can improve lung function and shorten time to recovery.
- Consider antibiotics only in severe cases requiring hospital admission. Most exacerbations are not due to acute bacterial infection.

Other relevant WHO resources (please check regularly for updates)

- Chronic obstructive pulmonary disease (COPD) – fact sheet (132).
- Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach (133).
- Coronavirus disease (COVID-19) pandemic (32).
- Living guidance for clinical management of COVID-19: living guidance, 23 November 2021 (33).
- Therapeutics and COVID-19: living guideline, 16 September 2022 (34).
- Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper –February 2019 (35).
- Vaccines against influenza WHO position paper – May 2022 (37).

Definition

An exacerbation of COPD is an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication in patients with underlying COPD (134).

Exacerbation of chronic obstructive pulmonary disease

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Definition

Acute worsening of patient's respiratory symptoms beyond normal day-to-day variations that results in additional therapy in patients with underlying chronic obstructive pulmonary disease (COPD). COPD refers to a group of diseases that block air flow and impair breathing and includes emphysema and chronic bronchitis

Most Likely Pathogens

Respiratory viruses (most cases):

- Influenza virus (A and B)
- Respiratory syncytial virus (RSV)
- Parainfluenza virus
- Rhinovirus
- Coronavirus (including SARS-CoV-2)
- Other respiratory viruses

Bacteria (more rarely):

- *Haemophilus influenzae*
- *Moraxella catarrhalis*
- *Streptococcus pneumoniae*
- Gram-negative bacteria including *Pseudomonas aeruginosa* (including multidrug-resistant strains)

Prevention

Recommend smoking cessation, reduced indoor air pollution, use of long-acting inhaled β_2 -agonists (\pm anticholinergics) and vaccination (e.g. against influenza, *S. pneumoniae* and SARS-CoV-2)

Diagnosis

Clinical Presentation

Recent and sustained worsening of dyspnea and cough with increased sputum production compared to the baseline in a patient with COPD

Important: symptoms can overlap with pneumonia (pneumonia more likely if tachycardia, tachypnea at rest and crepitations that persist after coughing are present)

Microbiology Tests

Usually not needed but can be considered in severe cases; the respiratory tract of people with COPD may be colonized with bacteria (e.g. *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *P. aeruginosa*, *S. maltophilia*) and a positive culture may indicate colonization rather than acute infection

Other Laboratory Tests

Consider C-reactive protein and/or procalcitonin, complete blood count, and blood pH and gases

Imaging

Consider a chest radiograph in patients requiring hospitalization to exclude other diagnoses and in outpatients if pneumonia suspected

Exacerbation of chronic obstructive pulmonary disease

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Rx Treatment



No Antibiotic Care

- Details of COPD exacerbations management are not discussed here, refer to specific guidelines
- Supplementary oxygen and short-acting inhaled β_2 -agonists (\pm anticholinergics)
- Systemic steroids are usually recommended (improve lung function and favour faster recovery)



Clinical Considerations

Antibiotics are not needed for most cases

- Their use could be considered in patients with dyspnea and an increased volume of purulent sputum
- In case of frequent exacerbations consider risk of infections caused by multidrug-resistant pathogens and previous colonization of the respiratory tract



Antibiotic Treatment Duration

5 days



Mild to Moderate Cases

Antibiotic treatment is not required in the great majority of cases (see "Clinical Considerations" when antibiotics may be indicated)

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice



Amoxicillin 500 mg q8h ORAL

ACCESS

Second Choice



Cefalexin 500 mg q8h ORAL

ACCESS

OR-----



Doxycycline 100 mg q12h ORAL

ACCESS



Severe Cases

All dosages are for normal renal function



Amoxicillin+clavulanic acid 500 mg+125 mg q8h ORAL

ACCESS



Pathophysiology

Exacerbations of COPD are a worsening of the existing underlying chronic inflammation of the respiratory tract and are caused in most cases by irritants (e.g. pollution, smoking, dusts and chemicals) or respiratory tract infections. Exacerbations can accelerate a decline in lung function (i.e. disease progression). The frequency of exacerbations of COPD is variable among individuals with COPD but they occur more often in cases of severe COPD (135).

Epidemiology

According to the Global Burden of Diseases study, in 2017, there were 299 million prevalent cases of COPD and 3.19 million deaths caused by COPD (44,136). In 2014, more than 90% of deaths occurred in low- and middle-income countries (137).

COPD includes emphysema and chronic bronchitis. The most prevalent risk factor is exposure to tobacco smoke and indoor household air pollution (138). The incidence of exacerbations increases with age, especially in smokers, and mortality is higher in severe episodes.

Most likely pathogens

Exacerbations of COPD are triggered by viral infections in most cases when a pathogen is identified (Table 13.1). However, in most cases of exacerbation of COPD, no pathogen is identified (139,140).

Table 13.1 – Pathogens most frequently associated with exacerbations of chronic obstructive pulmonary disease (in descending order of frequency)

Respiratory viruses (most cases)	Bacteria (less frequently)
Influenza virus (A and B)	<i>Haemophilus influenzae</i>
Respiratory syncytial virus	<i>Moraxella catarrhalis</i>
Parainfluenza virus	<i>Streptococcus pneumoniae</i>
Rhinovirus	Gram-negative bacteria, including <i>Pseudomonas aeruginosa</i> (including multidrug-resistant strains such as those producing ESBL and carbapenemases)
Coronavirus (including SARS-CoV-2)	
Other respiratory viruses	

ESBL: extended-spectrum beta-lactamases; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

Clinical presentation

An exacerbation of COPD should be suspected in cases of recent and sustained worsening of dyspnoea and cough with increased sputum production compared with the baseline of patients with COPD, that is, chronic bronchitis and emphysema. Symptoms can overlap with those of pneumonia; however, tachycardia, tachypnoea at rest and crepitations that persist (i.e. that do not clear) after coughing suggest pneumonia.

The decision to hospitalize a person with an exacerbation of COPD should be guided by the severity of symptoms, assessment of comorbidities and availability of home support.

Laboratory tests

Patient microbiology tests

When an exacerbation of COPD is suspected clinically, sputum Gram stain and culture are not recommended routinely. In people with COPD, the respiratory tract may for example be colonized with *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* and *Pseudomonas aeruginosa*, and a positive culture may indicate colonization rather than acute infection.

Other tests

When exacerbations of COPD are suspected clinically, certain laboratory tests could be considered, in particular tests that can help identify patients with bacterial infections and that can help assess the severity of the exacerbation. The rationale is that these patients would benefit the most from antibiotic treatment. For example, C-reactive protein (141,142), procalcitonin, and complete blood count and blood gas analysis may be useful. However, there is no clear consensus across guidelines about which tests should be performed routinely in the hospital setting and such tests may not be available in many settings.

Using microbiology surveillance data

Routine surveillance of clinical isolates from patients presenting with exacerbations of COPD is not helpful to inform local or national prescribing guidance.

Imaging

A chest X-ray could be considered in patients requiring hospitalization in order to exclude other diagnoses (e.g. pneumonia, pulmonary oedema) or in outpatients if pneumonia is suspected and chest radiography is available.



No antibiotic care

The core treatment of an exacerbation episode consists of supplementary oxygen and short-acting inhaled beta-2-agonists (with or without anticholinergics). Most guidelines currently recommend using systemic steroids because they help improve lung function and shorten time to recovery.

A detailed discussion of non-antibiotic management of COPD is beyond the scope of this chapter. Additional information can be found on the WHO website (132).

Antibiotic treatment

Most exacerbations of COPD are not triggered by bacterial infections, therefore only certain cases will benefit from antibiotic treatment.

Note

Antibiotic treatment is not required in the great majority of cases of acute exacerbations of chronic obstructive pulmonary disease.

Antibiotics are not needed for most cases. Their use could be considered in severe exacerbations of COPD. Most guidelines suggest antibiotic treatment for patients hospitalized because of an acute exacerbation of COPD, especially if an increased volume and purulence of sputum is present, because these cases are more likely to be caused by a bacterial infection. Severe exacerbations benefit more from antibiotic treatment (see Table 13.2 for antibiotic options). Current evidence suggests that the benefit in terms of reduced short-term mortality and reduced treatment failure is limited to hospitalized patients in intensive care units (143). Previous colonization of the respiratory tract (e.g. with *Pseudomonas aeruginosa*) needs to be taken into account when choosing empiric treatment. Patients with frequent episodes of COPD exacerbations may have received multiple courses of antibiotic treatment during the year and have a higher risk of infections caused by multidrug-resistant pathogens.

■ PRIMARY HEALTH CARE

13. Exacerbation of chronic obstructive pulmonary disease

Table 13.2 – Empiric antibiotic treatment for exacerbation of chronic obstructive pulmonary disease

Severity	First choice	Second choice	Total treatment duration
Mild to moderate cases	Amoxicillin (oral): 500 mg given every 8 hours OR Doxycycline (oral): 100 mg given every 12 hours	Cefalexin (oral): 500 mg given every 8 hours	5 days
Severe cases	Amoxicillin+clavulanic acid (oral): 500 mg + 125 mg given every 8 hours	–	5 days

Note. All dosages are for normal renal and hepatic function.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Prevention

Appropriate measures to prevent further exacerbations include smoking cessation, reduced indoor air pollution, use of long-acting inhaled beta-2-agonists (with or without anticholinergics) and vaccination against influenza, *Streptococcus pneumoniae* infection and COVID-19 (35,37). Currently, there is no clear consensus on the prophylactic use of antibiotics (e.g. macrolides) in patients with severe COPD and frequent episodes of exacerbation (144). For specific preventive measures for chronic respiratory diseases, refer to the WHO publication on global surveillance, prevention and control of chronic respiratory diseases (133).

14. Acute infectious diarrhoea/ gastroenteritis

Note

This chapter does not include enteric fever and *Clostridioides difficile* infection; please refer to the respective chapters when these infections are suspected.

Key messages

- **Antibiotics are not needed** in the great majority of cases of watery diarrhoea with or without a fever.
- Most cases of infectious diarrhoea are self-limiting and are caused by viruses.
- Antibiotics should only be used in patients with severe bloody diarrhoea (dysentery) or in immunocompromised patients.
- When an antibiotic is needed, ciprofloxacin is the first choice, but azithromycin is preferred in areas with a high prevalence of ciprofloxacin resistance among specific bacteria causing infectious diarrhoea (e.g. intestinal/non-invasive/diarrhoeal *Salmonella*, *Shigella* spp.).
- Cholera should be treated with antibiotics only in the context of outbreaks to prevent transmission but the most important intervention is rehydration.

Other relevant WHO resources (please check regularly for updates)

- Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, 2013 (31).
- The treatment of diarrhoea: a manual for physicians and other senior health workers, fourth revision. (145).
- Diarrhoeal disease – fact sheet (146).
- Cholera vaccines: WHO position paper – August 2017 (147).
- Global Taskforce on Cholera Control. Use of antibiotics for the treatment and control of cholera (148).
- Rotavirus vaccines: WHO position paper – July 2021 (149).
- Schistosomiasis – health topic (150).

Definition

Acute diarrhoeal disease (also known as gastroenteritis) is a disease characterized by acute onset (usually defined as a duration of < 14 days) of diarrhoea. Diarrhoea is defined as the passage of unusually loose or watery stools occurring at least three times a day (or more frequently than is normal for the individual). Consistency (how liquid/runny) rather than frequency (how often) is the most important factor to consider and frequent passing of formed stool is not diarrhoea. In breastfed babies, frequent loose pale-coloured stools are not considered diarrhoea (145). Most cases of acute diarrhoea have an infectious origin, but non-infectious causes are also possible, for example: adverse effects of medicines, including antibiotics and cytotoxic chemotherapy; endocrine diseases; inflammatory bowel diseases; and irritable bowel syndrome. Acute diarrhoea can be further subclassified as **watery** diarrhoea or **bloody** diarrhoea (i.e. presence of visible blood in the stool).

Acute infectious diarrhoea/gastroenteritis

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This guidance excludes Clostridioides difficile infection or enteric fever (see separate chapters)

Definition

New (<14 days) onset of diarrhoea (≥ 3 unformed/liquid stools in 24 hrs or more than normal for individual). Diarrhoea can be watery or bloody (dysentery)

Important: Non-infectious causes are also possible and must be considered (e.g. adverse effects of medicines including antibiotics, bowel and endocrine diseases)

Most Likely Pathogens

Most cases have a viral origin

Always consider these risk factors as they may influence the most likely etiologic agents:

- History of recent travel
- Recent consumption of potentially unsafe food
- Recent antibiotic exposure (risk of *C. difficile*)
- Immunosuppression
- Severe malnutrition

Watery diarrhoea:

- Most likely cause is viral (mostly norovirus and rotavirus)
- Consider cholera in endemic settings or in the context of outbreaks

Bloody diarrhoea (dysentery):

- Most likely cause are bacteria, mostly:
 - *Shigella* spp.
 - *Campylobacter* spp.
 - Diarrhoeal non-typhoidal *Salmonella*
 - Enterotoxigenic *Escherichia coli*

Consider parasites if symptoms do not resolve:

- Usually parasites are responsible for persistent (14–29 days duration) or chronic (>30 days duration) rather than acute diarrhoea
 - *Entamoeba histolytica*
 - *Giardia intestinalis*
 - Other protozoal parasites and very rarely *Schistosoma* (intestinal species)

Prevention

- Access to safe drinking-water, use of improved sanitation, hand washing with soap, good food hygiene, health education about how these infections spread
- Vaccination against cholera in endemic areas and during outbreaks

Diagnosis

Clinical Presentation

- Diarrhoea, nausea, vomiting, bloating, abdominal pain and cramping; fever may be absent
- Most cases are self-limiting in a few days
- Patients may present with varying degrees of dehydration and can present with severe malnutrition (both a risk factor and a consequence of diarrhoea)

Important:

- Rapidly evaluate the degree of dehydration (especially in the elderly)
- Signs of severe dehydration (two or more must be present):
 - Lethargy and/or unconsciousness
 - Sunken eyes
 - Inability to drink
 - Skin pinch goes back very slowly (≥ 2 seconds)

Microbiology Tests

Usually not needed

Consider testing if:

- Bloody diarrhoea
- Immunocompromised patients (to exclude parasitic infections)
- Recent antibiotic use (to exclude *C. difficile*)
- Suspected cholera outbreak

Tests to consider:

- Stool culture
- Stool microscopy (for parasites)
- *Vibrio cholerae* antigen (e.g. in outbreaks)
- Test for *C. difficile* (if recent antibiotic exposure)

Other Laboratory Tests

Usually not needed but consider in severe cases (e.g. check electrolytes)

Imaging

Usually not needed

Acute infectious diarrhoea/gastroenteritis

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Rx Treatment



No Antibiotic Care

Important: Rehydration and electrolyte replacement is the main treatment for acute infectious diarrhoea. Fluid losses can be compensated by drinking adequate fluids.

Antidiarrhoeal and antiemetic drugs are not routinely needed (they do not prevent dehydration or improve nutritional status)



Antibiotic Treatment Duration

Since treatment duration varies according to the antibiotic used, please refer to the corresponding antibiotic section for treatment duration

Rx Cholera Antibiotic Treatment

Treat with antibiotics only in:

- Patients hospitalized with severe dehydration OR
- Regardless of degree of dehydration:
 - High purging or failure of first 4 hour course of rehydration therapy OR
 - Co-existing conditions (e.g. pregnancy) OR
 - Co-morbidities (e.g. severe acute malnutrition, HIV)

All dosages are for normal renal function

First Choice



Azithromycin 1 g **ORAL**

Treatment duration: single dose

Azithromycin preferred because of the decreasing susceptibility of cholera to tetracyclines and fluoroquinolones

OR



Doxycycline 300 mg single dose **ORAL**

Treatment duration: 3 days

• If single dose is not tolerated: 100 mg q12h

Second Choice



Ciprofloxacin 1 g **ORAL**

Treatment duration: single dose



Clinical Considerations

- **Antibiotics usually not needed**, including in cases with severe dehydration
- Consider antibiotic treatment ONLY if:
 - Significant acute bloody diarrhoea
 - Severely immunocompromised patients

Rx Antibiotic Treatment

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

If symptoms do not resolve within 24-48 hours of treatment, consider giving metronidazole for treatment of *Entamoeba histolytica* and *Giardia intestinalis*

First Choice



Ciprofloxacin 500 mg q12h **ORAL**

Treatment duration: 3 days

Second Choice



Azithromycin **ORAL**

• Day 1: 500 mg q24h

• Day 2-4: 250 mg q24h

Treatment duration: 4 days

Azithromycin is preferred in case of high prevalence of ciprofloxacin resistance among bacteria frequently associated with acute infectious diarrhoea (e.g. *Salmonella* spp., *Shigella* spp.)

OR



Cefixime 400 mg q24h **ORAL**

Treatment duration: 3 days

OR



Sulfamethoxazole+trimethoprim 800 mg +

160 mg q12h **ORAL**

Treatment duration: 5 days

Use only if local data suggest susceptibility

In patients taking sulfamethoxazole-trimethoprim for prophylaxis, treat with a different antibiotic unless susceptibility is confirmed

OR



Ceftriaxone 1 g q24h **IV/IM**

Treatment duration: 3 days

Acute infectious diarrhoea/gastroenteritis

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Definition

New (<14 days) onset of diarrhoea (≥ 3 unformed/liquid stools in 24 hrs or more than normal for individual).
Diarrhoea can be watery or bloody (dysentery)

Important: Non-infectious causes are also possible and must be considered (e.g. adverse effects of medicines including antibiotics, bowel and endocrine diseases)

Most Likely Pathogens

Most cases have a viral origin

Always consider these risk factors as they may influence the most likely etiologic agents:

- History of recent travel
- Recent consumption of potentially unsafe food
- Immunosuppression
- Severe malnutrition

Watery diarrhoea:

- Most likely cause is viral, mostly:
 - Rotavirus
 - Norovirus
 - Adenovirus
- Consider cholera in endemic settings or in the context of outbreaks

Bloody diarrhoea (dysentery):

- Most likely cause are bacteria, mostly:
 - *Shigella* spp.
 - *Campylobacter* spp.
 - Diarrhoeal non-typhoidal *Salmonella*
 - Enterotoxigenic *Escherichia coli*

Consider parasites if symptoms do not resolve:

- Usually parasites are responsible for persistent (14–29 days duration) or chronic (>30 days duration) rather than acute diarrhoea
 - *Entamoeba histolytica*
 - *Giardia intestinalis*
 - Other protozoal parasites and very rarely *Schistosoma* (intestinal species)

Prevention

- Access to safe drinking-water, use of improved sanitation, hand washing with soap, good food hygiene, health education about how these infections spread
- Exclusive breastfeeding for the first 6 months of life
- Vaccination against rotavirus and against cholera (in endemic areas and during outbreaks)

This guidance excludes enteric fever (see separate chapter)

Diagnosis

Clinical Presentation

- Diarrhoea, nausea, vomiting, bloating, abdominal pain and cramping; fever may be absent
- Most cases are self-limiting in a few days
- Patients may present with varying degrees of dehydration and can present with severe malnutrition (both a risk factor and a consequence of diarrhoea)

Important:

- Rapidly evaluate the degree of dehydration
- Signs of severe dehydration (two or more must be present):
 - Lethargy and/or unconsciousness
 - Sunken eyes
 - Inability to drink
 - Skin pinch goes back very slowly (≥ 2 seconds)

Microbiology Tests

Usually not needed

Consider testing if:

- Bloody diarrhoea
- Immunocompromised patients (to exclude parasitic infections)
- Suspected cholera outbreak

Tests to consider:

- Stool culture
- Stool microscopy (for parasites)

Other Laboratory Tests

Usually not needed but consider in severe cases (e.g. check electrolytes)

Imaging

Usually not needed

Acute infectious diarrhoea/gastroenteritis

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Rx Treatment

No Antibiotic Care

- Important:** Rehydration and electrolyte replacement is the main treatment for acute infectious diarrhoea
- Low-osmolarity oral rehydration solution (ORS) is recommended
 - In addition to ORS, zinc tablets (10-20 mg/day) for 10-14 days can shorten duration and severity of symptoms

Antidiarrhoeal and antiemetic drugs are not routinely needed (they do not prevent dehydration or improve nutritional status)

Antibiotic Treatment Duration

Since treatment duration varies according to the antibiotic used, please refer to the corresponding antibiotic section for treatment duration

Rx Cholera Antibiotic Treatment

Treat with antibiotics only in:

- Patients hospitalized with severe dehydration OR
 - Regardless of degree of dehydration:
 - High purging or failure of first 4 hour course of rehydration therapy OR
 - Co-morbidities (e.g. severe acute malnutrition, HIV)
- All dosages are for normal renal function

First Choice

- Azithromycin 20 mg/kg **ORAL**
Treatment duration: single dose

Azithromycin preferred because of the decreasing susceptibility of cholera to tetracyclines and fluoroquinolones

Second Choice

- Ciprofloxacin 15 mg/kg **ORAL**
Treatment duration: single dose

OR

- Doxycycline **ORAL**
 - <45 kg (<12 yrs): 2-4 mg/kg
 - >45 kg (>12 yrs): 300 mg**Treatment duration:** single dose

Clinical Considerations

- Antibiotics usually not needed**, including in cases with fever and/or severe dehydration
- Consider antibiotic treatment ONLY if:
 - Significant bloody diarrhoea
 - Severely immunocompromised patients

Rx Antibiotic Treatment

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

If symptoms do not resolve within 24-48 hours of treatment, consider giving metronidazole for treatment of *Entamoeba histolytica* and *Giardia intestinalis*

First Choice

- Ciprofloxacin 15 mg/kg/dose q12h **ORAL**
• **Oral weight bands:**

3-<6 kg	50 mg q12h
6-<10 kg	100 mg q12h
10-<15 kg	150 mg q12h
15-<20 kg	200 mg q12h
20-<30 kg	300 mg q12h
≥30 kg	500 mg q12h

Treatment duration: 3 days

Second Choice

- Azithromycin 10 mg/kg/dose q24h **ORAL**
Treatment duration: 4 days

For children with bloody diarrhoea/dysentery ONLY azithromycin is preferred if suspected ciprofloxacin resistance

OR

- Cefixime 10 mg/kg/dose q24h **ORAL**
Treatment duration: 5 days

OR

- Sulphamethoxazole+trimethoprim 20 mg/kg + 4 mg/kg q12h **ORAL**
• **Oral weight bands:**

3-<6 kg	100 mg+20 mg q12h
6-<10 kg	200 mg+40 mg q12h
10-<30 kg	400 mg+80 mg q12h
≥30 kg	800 mg+160 mg q12h

Treatment duration: 5 days

Use only if local data suggest susceptibility

In patients taking sulphonamethoxazole-trimethoprim for prophylaxis, treat with a different antibiotic unless susceptibility is confirmed

OR

- Ceftriaxone 80 mg/kg/dose q24h **IV/IM**
Treatment duration: 3 days

Pathophysiology

Acute diarrhoeal diseases can be acquired through ingestion of food or water contaminated with viral or bacterial pathogens (rarely protozoal or fungal pathogens) or through direct contact with someone carrying the pathogen. Establishment of an enteric infection depends on the capacity of the pathogen to invade the mucosa and overcome the host defences. It is dependent on several factors, including the inoculum, the virulence of the organism and the status of host defences. Production of enterotoxins (i.e. bacterial proteins that act on the host's intestinal cells) is a frequently encountered mechanism of disease.

Epidemiology

In 2017, 6.2 billion episodes of diarrhoeal disease were estimated to have occurred worldwide, including 500 000 incident cases of intestinal/non-invasive/diarrhoeal non-typhoidal *Salmonella* disease (44).

Children younger than 5 years are often affected. About 1.7 billion cases of acute diarrhoeal disease occur each year in this age group where it is an important cause of death (about 450 000 deaths in 2016). Acute malnutrition, living in or travelling to areas with limited access to safe drinking-water and adequate sanitation are the leading risk factors for acute diarrhoeal diseases (146,151).

Most likely pathogens

Most cases of community-acquired acute watery diarrhoeal disease have a viral origin. However, bacteria and parasites can also be causes (152). For returning travellers, it is important to consider travel-associated diarrhoea. Table 14.1 and Table 14.2 give the pathogens most frequently associated with acute diarrhoeal disease (in children and adults respectively), and Table 14.3 the pathogens associated with chronic or persistent diarrhoea.

Table 14.1 – Pathogens most frequently associated with acute infectious diarrhoea in children (in descending order of frequency)

Setting	Viruses (most cases)	Bacteria	Parasites
Low income	Rotavirus	<i>Escherichia coli</i>	<i>Cryptosporidium</i> spp.
	Measles virus ^a	<i>Shigella</i> spp.	
High income	Norovirus	Intestinal/non-invasive/ diarrhoeal non-typhoidal	–
	Rotavirus	<i>Salmonella</i>	
	Adenovirus	<i>Campylobacter</i> spp.	
	Measles virus ^a		

^a Diarrhoea is the most common complication in measles.

Table 14.2 – Pathogens most frequently associated with acute infectious diarrhoea in adults (in descending order of frequency)

Setting	Viruses (most cases)	Bacteria
Low income	Norovirus	<i>Campylobacter</i> spp.
		Intestinal/non-invasive/diarrhoeal non-typhoidal <i>Salmonella</i>
		<i>Shigella</i> spp.
		<i>Escherichia coli</i>
High income	Norovirus	Intestinal/non-invasive/diarrhoeal non-typhoidal <i>Salmonella</i>
		<i>Campylobacter</i> spp.
		<i>Escherichia coli</i>
		<i>Shigella</i> spp.
		<i>Listeria monocytogenes</i>

Table 14.3 – Pathogens most frequently associated with persistent (14–29 days) or chronic (> 30 days) infectious diarrhoea in people living with HIV^a (in descending order of frequency)

Parasites	Viruses	Fungi (rarely) ^b
<i>Cryptosporidium</i> spp.	<i>Cytomegalovirus</i>	<i>Histoplasma capsulatum</i>
<i>Microsporidium</i> spp.		<i>Coccidioides</i> spp.
<i>Cystoisospora belli</i>		<i>Penicillium</i> spp.

HIV: human immunodeficiency virus.

^a It should be noted that in these cases, patients often receive unnecessary antibiotic treatment.

^b Rarely in the context of disseminated infections in patients with low CD4 count.

Clinical presentation

In acute diarrhoea, the main symptom is new onset (< 14 days) of three or more unformed stools a day, with or without fever. Nausea, vomiting, bloating, abdominal pain and cramping may also be present. In most cases, the disease is self-limiting. Since some causative pathogens can be endemic in certain settings and absent in others, it is always important to consider where the patient became infected (including history of recent travel) and recent consumption of potentially unsafe food (e.g. raw meat or unpasteurized milk products). Recent antibiotic use (past 3 months), cytotoxic chemotherapy or the presence of immunosuppression (e.g. HIV infection) also need to be investigated.

Five common clinical presentations can help identify cases that require specific treatment and management (145).

1. Patients with **watery diarrhoea**. In these patients, the most likely cause is viral, mostly rotavirus and norovirus. A mild fever and vomiting may also occur. The main risk is severe dehydration and management is symptomatic (e.g. fluid replacement).
2. Patients with **bloody diarrhoea** (dysentery or invasive diarrhoea with damage to the intestinal mucosa). In these patients, the most likely cause are bacteria, mostly *Shigella* spp., *Campylobacter* spp., intestinal/non-invasive/diarrheal non-typhoidal *Salmonella* or enterotoxigenic *Escherichia coli*. These cases may benefit from antibiotic treatment. In addition to dehydration, these infections can be complicated by sepsis and malnutrition. *Entamoeba histolytica* can rarely also cause bloody diarrhoea weeks or months after the infection; often these infections are responsible for chronic rather than acute bloody diarrhoea. Other protozoal parasites and very rarely *Schistosoma* can also cause bloody diarrhoea; only *Schistosoma mansoni* and *Schistosoma japonicum*, the intestinal species.

3. Patients with **persistent diarrhoea** (symptoms lasting > 14 days). In these patients, a parasite is often implicated (e.g. *Giardia intestinalis*, *Entamoeba histolytica*) and the main risks are malnutrition and dehydration.
4. **Diarrhoea with severe malnutrition.** In these patients, malnutrition is both a cause and consequence of diarrhoea.
5. **Diarrhoea with recent antibiotic exposure** (*Clostridioides difficile*). This condition is mostly hospital-acquired; please refer to the chapter on *Clostridioides difficile* infection if this is suspected.

Patients may present with varying degrees of dehydration and this should be promptly assessed, especially in children and elderly people. In children, the degree of dehydration can be rated on a scale of three as indicated in Table 14.4 (146).

Table 14.4 – Classification of dehydration

Severity of dehydration	Signs
Severe dehydration: at least two signs from the list on the right must be present	<ul style="list-style-type: none">• Lethargy and/or unconsciousness• Sunken eyes• Inability to drink• Skin pinch goes back very slowly (≥ 2 seconds)
Some dehydration: at least two signs from the list on the right must be present	<ul style="list-style-type: none">• Restlessness, irritability• Sunken eyes• Drinks eagerly, is thirsty
No dehydration	Too few signs to classify as some or severe dehydration

Source: WHO Pocket book of hospital care for children (31).

Laboratory tests

Patient microbiology tests

Routine stool testing is not needed since most cases are self-limiting and knowing the causative agent would not alter management. Testing may be done for infection control purposes, if there is a high risk of spreading the disease in specific settings.

However, in certain cases and based on local availability, a stool test (e.g. stool microscopy, stool culture, antigen testing and nucleic acid amplification tests) could be considered (Table 14.5), but only when identifying the causative pathogen may benefit the



patient, for example, because specific treatment can be provided or a multidrug-resistant pathogen may be detected.

Selected cases that could benefit from stool testing include:

- patients with bloody diarrhoea
- patients with suspected cholera in the context of outbreaks
- immunocompromised patients with acute diarrhoea
- history of diarrhoea following antibiotic use (suspicion of *Clostridioides difficile* infection). Please refer to the chapter on *Clostridioides difficile* infection if this infection is suspected.

Table 14.5 – Microbiology tests to consider in certain cases of diarrhoeal disease as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Setting where the test should be available
Stool culture and antimicrobial susceptibility testing	To detect and identify bacterial species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories
Stool microscopy	To detect and identify parasites and their ova (eggs) or cysts	Health care facilities with clinical laboratories
<i>Vibrio cholerae</i> antigen ^a (RDT)	To detect or exclude a cholera outbreak (not for use in case management)	Community settings and health facilities without laboratories

EDL: Model List of Essential In Vitro Diagnostics; RDT: rapid diagnostic test.

^a Possible specimens include stool and rectal swab.

Other tests

Routine laboratory tests are usually not needed. However, for severe cases, electrolytes should be checked if available.

Using microbiology surveillance data

Targeted clinical microbiological surveys of cases of acute bloody diarrhoea in the primary care setting in children and adults, specifically focusing on quinolone and macrolide resistance rates in *Shigella* and intestinal/non-invasive/diarrhoeal non-typhoidal *Salmonella*, may be helpful to inform local empiric antibiotic guidance.

Imaging

Routine imaging is not needed for acute diarrhoeal disease.

No antibiotic care

Rehydration is the main treatment for acute diarrhoeal disease (oral or intravenous). In children, treating any diarrhoea with oral rehydration therapy using a low-osmolarity oral rehydration solution to prevent dehydration is recommended (145). In addition, zinc tablets (10–20 mg/day) for 10–14 days are usually recommended to shorten the duration and severity of symptoms (31,145).

In adults, an oral rehydration solution is not usually needed, and fluid losses can be compensated by drinking adequate fluids. However, in severely dehydrated adult patients, an oral rehydration solution can be given. Antidiarrhoeal and antiemetic medicines are not routinely needed because they do not prevent dehydration and do not improve nutritional status (145).

Antibiotic treatment

Antibiotics are not needed in most cases of acute diarrhoeal disease because they are of viral origin and the illness is usually self-limiting regardless of the causative pathogen. Rehydration is the main treatment for acute diarrhoeal disease (145). Even in cases with severe dehydration, antibiotic treatment is not routinely needed.

However, in patients with significant acute bloody diarrhoea and in severely immunocompromised patients, antibiotics may be given (see Table 14.6 for empiric options based on the risk of fluoroquinolone resistance). Bloody diarrhoea could be caused by certain strains of *Escherichia coli* (Shiga toxin-producing *Escherichia coli* also known as enterohaemorrhagic *Escherichia coli*). In these cases (mostly in children), the use of antibiotics is controversial because there is a theoretical concern that it could worsen symptoms of haemolytic uraemic syndrome, characterized by haemolytic anaemia, renal injury and low platelets. However as there is clear evidence of benefit in shigellosis, empiric treatment with antibiotics should not be withheld because of a concern of causing haemolytic uraemic syndrome.

If symptoms do not resolve after 24–48 hours of antibiotic treatment, adding a treatment course of metronidazole for possible *Entamoeba histolytica* infection could be considered.

In addition, antibiotic treatment should be considered in the context of cholera in the following cases (see Table 14.7 for antibiotic options):

- suspected cholera in patients hospitalized with severe dehydration
- regardless of degree of dehydration:
 - high purging or failure of first 4-hour course of rehydration therapy or
 - coexisting conditions (e.g. pregnancy) or
 - comorbidities (e.g. severe acute malnutrition, HIV infection) that pose elevated risk in cholera illness.

 **Note**

Only certain cases of diarrhoeal disease benefit from antibiotic treatment, namely patients with significant acute bloody diarrhoea and/or who are severely immunocompromised.

Table 14.6 – Empiric antibiotic treatment for selected cases of infectious acute diarrhoea

 **Important**

Where more than one antibiotic is recommended for an infection, they are listed in alphabetical order and they should be considered equal treatment options, unless otherwise indicated.

	Adults	Children	Total treatment duration
First choice	Ciprofloxacin^{a,b} (oral): 500 mg given every 12 hours	Ciprofloxacin^a (oral): 15 mg/kg/dose given every 12 hours Oral weight bands: 3–< 6 kg: 50 mg given every 12 hours 6–< 10 kg: 100 mg given every 12 hours 10–< 15 kg: 150 mg given every 12 hours 15–< 20 kg: 200 mg given every 12 hours 20–< 30 kg: 300 mg given every 12 hours ≥ 30 kg: use adult dose	3 days

continues

Table 14.6 *continued*

	Adults	Children	Total treatment duration
Second choice	<p>Oral options</p> <p>Azithromycin^c (oral): 500 mg given once a day (on day 1) followed by 250 mg given once a day for 3 days</p> <p>OR</p> <p>Cefixime^d (oral): 400 mg given once a day</p> <p>OR</p> <p>Sulfamethoxazole+trimethoprim^{d,e} (oral): 800 mg + 160 mg given every 12 hours</p> <p>Parenteral option</p> <p>Ceftriaxone^d (IV/IM): 1 g given once a day</p>	<p>Oral options</p> <p>Azithromycin^c (oral): 10 mg/kg/dose given once a day</p> <p>OR</p> <p>Cefixime^d (oral): 10 mg/kg/dose given once a day</p> <p>OR</p> <p>Sulfamethoxazole+trimethoprim^{d,e} (oral): 20 mg/kg + 4 mg/kg given every 12 hours</p> <p>Oral weight bands (mg of the sulfamethoxazole/trimethoprim component): 3–< 6 kg: 100 mg/20 mg given every 12 hours 6–< 10 kg: 200 mg/40 mg given every 12 hours 10–< 15 kg: 400 mg/80 mg given every 12 hours 15–< 20 kg: 400 mg/80 mg given every 12 hours 20–< 30 kg: 400 mg/80 mg given every 12 hours ≥ 30 kg: use adult dose</p> <p>Parenteral option</p> <p>Ceftriaxone^d (IV/IM): 80 mg/kg/dose given once a day</p>	<p>Azithromycin: 4 days</p> <p>Cefixime: 3 days (adults) 5 days (children)</p> <p>Sulfamethoxazole+trimethoprim: 5 days</p> <p>Ceftriaxone: 3 days</p>

IM: intramuscular; IV: intravenous.

Note. All dosages are for normal renal and hepatic function.

^a If symptoms do not resolve within 24–48 hours of treatment, consider *Entamoeba histolytica* or *Giardia intestinalis* as possible causes and provide appropriate treatment.

^b The use of fluoroquinolones (such as ciprofloxacin) can be associated with important side-effects including: (i) mental health disturbances such as disorientation, agitation, nervousness, memory impairment and delirium; (ii) serious blood sugar disturbances such as hypoglycaemic coma; (iii) increased risk of tendinitis and tendon rupture; (iv) worsening symptoms in those with myasthenia gravis; and (v) potential irreversible neuropathy (serious nerve damage).

continues

Table 14.6 continued

^c Azithromycin is preferred in cases of high prevalence of ciprofloxacin resistance among bacteria frequently associated with acute infectious diarrhoea (e.g. Intestinal/non-invasive/diarrhoeal non-typhoidal *Salmonella*, *Shigella* spp.). Of note azithromycin can cause abnormal changes in the electrical activity of the heart leading to a potentially fatal irregular heart rhythm, especially in patients with known risk factors such as long QT interval or arrhythmias.

^d Cefixime, ceftriaxone and sulfamethoxazole+trimethoprim are not active against *Campylobacter* spp.

^e Ideally, sulfamethoxazole+trimethoprim should only be used if local data suggest susceptibility or if the isolated strain is susceptible. As per WHO 2005 guidelines, this antibiotic should not be used empirically when shigellosis is suspected (145). In patients taking sulfamethoxazole+trimethoprim for prophylaxis, a different antibiotic should be used for treatment unless susceptibility is confirmed.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Table 14.7 – Empiric antibiotic treatment for cholera

Note

For indications for antibiotic use, please refer to the technical note on the use of antibiotics for the treatment and control of cholera from the Global Task Force on Cholera Control (148).

Important

Where more than one antibiotic is recommended for an infection, they are listed in alphabetical order and they should be considered equal treatment options, unless otherwise indicated.

Adults	Children
First choice	First choice
Azithromycin ^a (oral): 1 g, single dose	Azithromycin ^a (oral): 20 mg/kg, single dose
OR	
Doxycycline (oral): 300 mg, single dose (or 100 mg given every 12 hours for 3 days if single dose is not tolerated)	
Second choice	Second choice
Ciprofloxacin (oral): 1 g, single dose	Ciprofloxacin (oral): 15 mg/kg, single dose
OR	
	Doxycycline (oral)
	<ul style="list-style-type: none"> • < 45 kg (< 12 years): 2 to 4 mg/kg, single dose • > 45 kg (> 12 years): 300 mg, single dose

Note. All dosages are for normal renal and hepatic function.

^a Azithromycin is preferred because of the decreasing susceptibility of cholera to tetracyclines and fluoroquinolones. Because of the long half-life of azithromycin, it should only be recommended for outbreak situations, where single-dose treatment is especially useful.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Prevention

Key measures to prevent acute diarrhoeal diseases include access to safe drinking-water, use of improved sanitation, handwashing with soap, exclusive breastfeeding for the first 6 months of life, good personal and food hygiene, health education about how infections spread and vaccination against rotavirus, particularly in countries with a high rate of death associated with rotavirus (146). Vaccination against cholera should also be considered, especially in endemic areas, in humanitarian crises (high risk of cholera) and during outbreaks. Vaccination against cholera should always be accompanied with other prevention and control strategies. Vaccination against measles could also substantially reduce the incidence and severity of diarrhoeal diseases and therefore every infant should be immunized against measles at the recommended age. For updated information on vaccination against rotavirus, cholera and measles, refer to the most recent WHO position papers (147,149,153).

15. Enteric fever

Key messages

- Most cases of enteric fever are caused by *Salmonella* Typhi (70–80% of cases).
- Access to safe water and appropriate hygiene among food handlers is key to prevent the infection. Vaccination should also be offered in endemic areas and during outbreaks.
- Symptoms are often difficult to distinguish from other febrile illnesses.
- Blood cultures should be taken in all cases requiring hospitalization.
- Choice of empiric antibiotic treatment depends on the risk of fluoroquinolone resistance of *Salmonella* Typhi.



Other relevant WHO resources (please check regularly for updates)

- Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, 2013 (31).
- Typhoid vaccines: WHO position paper – March 2018 (154).

Definition

Enteric fever is a severe systemic illness characterized by fever and abdominal pain caused by the bacterium *Salmonella enterica*, serotypes Typhi or Paratyphi.

Enteric fever

Definition

- A severe systemic illness characterized by fever and abdominal pain caused by infection with *Salmonella enterica*
- Acquired through ingestion of contaminated food/water

Severity:

- **Mild:** Not critically ill with no signs of intestinal perforation, peritonitis, sepsis or septic shock
- **Severe:** Critically ill with confirmed/suspected intestinal perforation, peritonitis, sepsis or septic shock

Pathogen

Enteric fever is caused by *Salmonella enterica* serotypes Typhi or Paratyphi A, B or C

Diagnosis

Clinical Presentation

- It can be difficult to distinguish enteric fever from other febrile illnesses
- Symptoms include protracted fever ($\geq 38.0^{\circ}\text{C}$ for >3 days) +/ headache, loss of appetite and nausea; gastrointestinal symptoms may also be present (diarrhoea more frequent in people living with HIV)
- Consider peritonitis if there is severe pain, diffuse rebound tenderness upon sudden release of pressure on the abdomen and abdominal muscular tensing; peritonitis occurs as a result of intestinal bleeding and perforation
- Encephalopathy can also occur in severe cases

Microbiology Tests

- **Mild Cases:** Usually not needed
- **Severe Cases:** Blood cultures (ideally before starting antibiotics)
- Bone marrow culture is the reference standard test but is often not feasible
- Note: the Widal serology is not a reliable method to diagnose acute illness (a positive result may be due to previous infection)

Other Laboratory Tests

- **Mild Cases:** Usually not needed
- **Severe Cases:** Complete blood count, creatinine, electrolytes, glucose, C-reactive protein and / or procalcitonin

Imaging

Usually not needed

Prevention

Access to safe water and adequate sanitation, health education, appropriate hygiene among food handlers, and typhoid vaccination

Treatment

Clinical Considerations

- Antibiotic treatment should be started as soon as the diagnosis is suspected; delays are associated with higher risk of complications and severe disease
- **Empiric treatment should be chosen based on:**
 - Severity of presentation
 - Local prevalence of fluoroquinolone resistance among *Salmonella enterica* serotypes Typhi or Paratyphi
- Fever usually decreases slowly after 3-5 days of treatment
- If initially treated IV, step down from IV to oral antibiotics is suggested when the patient has clinically improved, is afebrile and is able to tolerate oral treatment

Antibiotic Treatment Duration

Mild Cases: **7 days***

Severe Cases: **10 days***

*if clinical improvement and the patient is afebrile for 48 hours

Low Risk of Fluoroquinolone Resistance

All dosages are for normal renal function

Mild and Severe Cases

 Ciprofloxacin 500 mg q12h **ORAL**

High Risk of Fluoroquinolone Resistance

All dosages are for normal renal function

Mild Cases

 Azithromycin 1 g once on day 1, then 500 mg q24h **ORAL**

Severe Cases

 Ceftriaxone 2 g q24h **IV**

Enteric fever

Definition

- A severe systemic illness characterized by fever and abdominal pain caused by infection with *Salmonella enterica*
- Acquired through ingestion of contaminated food/water

Severity:

- *Mild*: Not critically ill with no signs of intestinal perforation, peritonitis, sepsis or septic shock
- *Severe*: Critically ill with confirmed/suspected intestinal perforation, peritonitis, sepsis or septic shock

Pathogen

Enteric fever is caused by *Salmonella enterica* serotypes Typhi or Paratyphi A, B or C

Diagnosis

Clinical Presentation

- It can be difficult to distinguish enteric fever from other febrile illnesses
- Symptoms include protracted fever ($\geq 38.0^{\circ}\text{C}$ for >3 days)
- +/- headache, loss of appetite and nausea; gastrointestinal symptoms may also be present
- Diarrhoea is common
- Consider peritonitis if there is severe pain, diffuse rebound tenderness upon sudden release of pressure on the abdomen and abdominal guarding; peritonitis occurs as a result of intestinal bleeding and perforation
- Encephalopathy can also occur in severe cases

Microbiology Tests

- *Mild Cases*: Usually not needed
- *Severe Cases*: Blood cultures (ideally before starting antibiotics)
- Note: the Widal serology is not a reliable method to diagnose acute illness (a positive result may be due to previous infection)

Other Laboratory Tests

- *Mild Cases*: Usually not needed
- *Severe Cases*: Complete blood count, creatinine, electrolytes, glucose, C-reactive protein

Imaging

Routine imaging is not needed

Prevention

Access to safe water and adequate sanitation, health education, appropriate hygiene among food handlers, and typhoid vaccination

Treatment

Clinical Considerations

- Antibiotic treatment should be started as soon as the diagnosis is suspected; delays are associated with higher risk of complications and severe disease
- **Empiric treatment should be chosen based on:**
 - Severity of presentation
 - Local prevalence of fluoroquinolone resistance among *Salmonella enterica* serotypes Typhi or Paratyphi
- Fever usually decreases slowly after 3-5 days of treatment
- If initially treated IV, step down from IV to oral antibiotics is suggested when the patient has clinically improved, is afebrile and is able to tolerate oral treatment

Antibiotic Treatment Duration

Mild Cases: 7 days*

Severe Cases: 10 days*

*If clinical improvement and the patient is afebrile for 48 hours

Low Risk of Fluoroquinolone Resistance

All dosages are for normal renal function

Mild and Severe Cases

	Ciprofloxacin 15 mg/kg/dose q12h ORAL
Oral weight bands:	
3-<6 kg	50 mg q12h
6-<10 kg	100 mg q12h
10-<15 kg	150 mg q12h
15-<20 kg	200 mg q12h
20-<30 kg	300 mg q12h
≥30 kg	500 mg q12h

High Risk of Fluoroquinolone Resistance

All dosages are for normal renal function

Mild Cases

	Azithromycin 20 mg/kg/dose q24h ORAL
---	---

Severe Cases

	Ceftriaxone 80 mg/kg/dose q24h IV
---	--

Pathogen

Enteric fever is caused by *Salmonella enterica* serotypes Typhi or Paratyphi A, B or C, a Gram-negative bacterium. Non-typhoidal *Salmonella* is not a cause of enteric fever but may cause infectious gastroenteritis, bloodstream infections, meningitis or bone and joint infections. Please refer to the relevant chapters if these infections are suspected.

Pathophysiology

Enteric fever is acquired through ingestion of food or water contaminated with *Salmonella* Typhi or Paratyphi or through direct contact with someone carrying the pathogen. Humans are the only source of these bacteria. Once the pathogen is ingested, it invades the intestinal mucosa primarily through the distal ileum. Once there, host immune defences are activated to eliminate the pathogen. However, these white cells can also act as carriers of the infection through the lymphatic system to the liver, spleen, bone marrow and lymph nodes, and ultimately to the bloodstream. Natural infection does not provide complete protection so recurrent illness is possible (155).

Epidemiology

Most cases of enteric fever are caused by *Salmonella* Typhi (70–80% of cases). Even though the absolute number of new cases of enteric fever has declined by 45% and the number of deaths by 41% since the 1990s, the disease is still endemic, mostly in sub-Saharan Africa and in South Asia. Based on available data, India, Pakistan and Bangladesh are the countries with the highest incidence of enteric fever with > 500 cases per 100 000 population in 2017. In 2017, about 14.3 million cases of enteric fever occurred worldwide. In endemic countries, children are affected the most with almost 60% of cases occurring in children younger than 15 years. Based on the data available, when appropriately treated with antibiotics, the case fatality rate for enteric fever is about 1% (156). Complications (e.g. intestinal perforation) in hospitalized cases are estimated to occur in 20–30% of cases, with a higher risk in people presenting for care after having had symptoms for more than 10 days (157).

Clinical presentation

Symptoms of enteric fever are often non-specific, making it difficult to distinguish enteric fever from other febrile illnesses. As a result, misdiagnosis of cases can occur. In patients with enteric fever, protracted fever ($\geq 38.0^{\circ}\text{C}$ for more than 3 days) is the main symptom. Headache is often present as well as loss of appetite and nausea. Gastrointestinal symptoms may not be present, and diarrhoea is seen more frequently in children and in people with HIV. The clinical presentation can vary from mild illness with a low-grade fever and malaise to severe disease presenting with septic shock and peritonitis because of intestinal bleeding

and perforation. Encephalopathy can also occur in severe cases. Of note, clinical features are also not useful to distinguish infections caused by *Salmonella enterica* serotype Typhi from those caused by *Salmonella enterica* serotype Paratyphi.

Laboratory tests

Patient microbiology tests

In patients with suspected enteric fever, the diagnosis is largely dependent on the clinical presentation and detection of the pathogen in blood cultures, even though the sensitivity is low, especially when antibiotic treatment has already been started. **A blood culture should be taken in all possible cases with fever requiring hospitalization, ideally before starting antibiotic treatment.** Bone marrow cultures is the most sensitive diagnostic method, but these cultures are very rarely done because they are more difficult to perform and invasive. Stool cultures are usually negative in the early phases of the infection and therefore they are of limited diagnostic use (Table 15.1). Widal serology is still widely used in low- and middle-income countries; however, it is not a reliable method to diagnose acute illness because a positive result may represent a previous infection, and in returning travellers, vaccination prior to travel affects the results. Ideally the Widal serology requires two samples taken 10 days apart to demonstrate a four-fold rise of anti-*Salmonella* Typhi antibodies and this is not practical in many low-resource settings.

Table 15.1 – Microbiology tests to consider when enteric fever is suspected as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Setting where the test should be available
Blood cultures ^a and antimicrobial susceptibility testing	To detect bacterial and fungal bloodstream infections (sepsis)	Health care facilities with clinical laboratories
Bone marrow culture ^b and antimicrobial susceptibility testing	Initial step in detection and identification of bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories
Stool culture ^c and antimicrobial susceptibility testing	Initial step in detection and identification of bacterial species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics.

^a Often the mainstay of diagnosis. Without antibiotic treatment, blood cultures are often positive (5–7 out of 10 patients) however sensitivity is low, if antibiotics have already been started.

^b The gold standard for diagnosis but it is often not feasible to do.

^c Low sensitivity and not useful in the early phase (first week) of disease when the test is often negative.

Other tests

Routine laboratory testing is not always needed but could be considered in severe cases (i.e. routine haematology and biochemistry).

Using microbiology surveillance data

Targeted clinical microbiological surveys of enteric fever-related bloodstream infection focusing on *Salmonella enterica* serotype Typhi and Paratyphi resistance rates may help inform local and national empiric antibiotic guidance.

Imaging

Routine imaging is not needed.

Antibiotic treatment

Antibiotic treatment options are shown in Table 15.2. In cases of enteric fever, antibiotic treatment should be started promptly because delays are associated with higher risk of complications and severe disease. In general, antibiotic treatment is given to shorten the duration of symptoms and to reduce the risk of complications, such as intestinal perforation and chronic carriage. Chronic carriers are asymptomatic people who continue to harbour the pathogen for months or even years after their initial infection and can transmit the infection. Fever usually decreases slowly, after around 3–5 days of effective treatment. Mild cases can be treated as outpatients with oral treatment, while severe cases should be treated as inpatients with systemic intravenous treatment.

The choice of oral antibiotic, if possible, should be based on the sensitivity of the isolated pathogen. When choosing empiric treatment, the local prevalence of fluoroquinolone resistance should be considered because of the increasing number of resistant isolates, mostly in Asia (158). In these settings, a third-generation cephalosporin or azithromycin are appropriate options because resistance to these antibiotics is still low in most settings; < 5% for ceftriaxone and only sporadic cases with resistance to azithromycin. Of note, antibiotics that were widely used in the 1980s and 1990s but fell into disuse because of resistance or toxicity concerns (e.g. ampicillin, chloramphenicol and sulfamethoxazole+trimethoprim) are again effective in some settings, mostly in Asia. However, the empiric use of these older options for treatment is discouraged because it could prompt a rebound of multidrug-resistant organisms.

In recent years, outbreaks of enteric fever caused by extensively antibiotic-resistant *Salmonella* Typhi have been reported, for example, in Pakistan since 2016 (159). These extensively antibiotic-resistant isolates are resistant to ampicillin, sulfamethoxazole+trimethoprim, chloramphenicol, fluoroquinolones and third-generation cephalosporins and represent a public health threat including the risk of travel/migration-related spread to other countries and regions.

Step-down to oral treatment is based on improvement of symptoms and signs of infection and the ability to take oral antibiotics which allows discharge of the patient home when clinically appropriate.

Table 15.2 – Empiric antibiotic treatment for enteric fever

Risk of fluoroquinolone resistance ^a	Adults	Children	Total treatment duration
Low	Ciprofloxacin ^b (oral): 500 mg given every 12 hours	Ciprofloxacin (oral): 15 mg/kg/dose given every 12 hours Oral weight bands: 3–< 6 kg: 50 mg given every 12 hours 6–< 10 kg: 100 mg given every 12 hours 10–< 15 kg: 150 mg given every 12 hours 15–< 20 kg: 200 mg given every 12 hours 20–< 30 kg: 300 mg given every 12 hours ≥ 30 kg: use adult dose	Mild cases: 7 days Severe cases: 10 days if the patient is clinically improving and without a fever for 48 hours
High	Mild cases Azithromycin ^c (oral): 1 g given once a day (on day one) followed by 500 mg given once a day Severe cases Ceftriaxone ^d (IV): 2 g given once a day	Mild cases Azithromycin (oral): 20 mg/kg/dose given once a day Severe cases Ceftriaxone (IV): 80 mg/kg/dose given once a day	

IV: intravenous.

Note. All dosages are for normal renal and hepatic function.

^a It should be noted that there is no clearly defined prevalence of resistance in a certain setting that defines low versus high risk of fluoroquinolone resistance.

^b The use of fluoroquinolones (such as ciprofloxacin) can be associated with important side-effects including: (i) mental health disturbances such as disorientation, agitation, nervousness, memory impairment and delirium; (ii) serious blood sugar disturbances such as hypoglycaemic coma; (iii) increased risk of tendinitis and tendon rupture; (iv) worsening symptoms in those with myasthenia gravis; and (v) potential irreversible neuropathy (serious nerve damage).

^c Azithromycin can cause abnormal changes in the electrical activity of the heart leading to a potentially fatal irregular heart rhythm especially in patients with known risk factors such as long QT interval or arrhythmias.

continues

Table 15.2 *continued*

^dIn settings where ceftriaxone-resistance is increasing, azithromycin should be prioritized. Outbreaks of enteric fever caused by extensively antibiotic-resistant *Salmonella* Typhi have been reported, for example, in Pakistan since 2016 (159) and in travel-related cases across the world (162–164). In general, when ceftriaxone is used, changing to oral treatment could be considered when there is symptomatic improvement. If available, the choice of oral options to use could be guided by results of susceptibility testing, including the possibility of using certain first-choice options that were used in the past.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Combination treatment

Currently, a single antibiotic regimen is recommended. However, the combination of a third-generation cephalosporin (ceftriaxone) and azithromycin has been reported to reduce the duration of symptoms. This approach is suggested in some guidelines for severe cases (160,161).

Prevention

Access to safe water and adequate sanitation, health education, appropriate hygiene among food handlers and typhoid vaccination are all effective strategies for prevention and control of enteric fever. For updated information on vaccines to prevent enteric fever, please refer to the 2018 WHO position paper on typhoid vaccines (154). Vaccination should be prioritized in countries with the highest burden of enteric fever (especially where antibiotic resistance is high) and in response to confirmed outbreaks. Single-dose typhoid conjugated vaccines are also available that can be used in younger children (from the age of 6 months onwards) and confer prolonged duration of protection. Recommendations on these newer vaccines can also be found in the 2018 WHO position paper (154).

16. Skin and soft tissue infections – mild bacterial impetigo, erysipelas and cellulitis

This chapter does not cover severe skin infections or skin infections caused by viral, fungal or parasitic pathogens, or management of diabetic foot infections. Please refer to the specific chapters about other skin and soft tissue infections – traumatic wounds (including bite wounds), burn wounds, necrotizing fasciitis, pyomyositis, if these infections are suspected.

Key messages

- Topical treatment can be used for mild impetigo.
- Diagnostic tests are usually not needed in mild cases (avoid swabs of intact skin).
- The most likely causative pathogens are *Staphylococcus aureus* and *Streptococcus* spp.
- Oral antibiotics of the Access group are adequate for most cases.
- There is no need to empirically treat for MRSA in most cases.



Other relevant WHO resources (please check regularly for updates)

- Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, 2013 (31).

Definition

The terminology used to define skin and soft tissue infections has changed over the years. In general, the terms bacterial skin and soft tissue infections and bacterial skin and skin structures infections are often used interchangeably.

While there is no universally accepted classification of skin infections, there are numerous ways to classify skin and soft tissue infections based on certain characteristics of the infection such as anatomic location (folliculitis, fasciitis, myositis), body location (e.g. extremities, face), timing (acute, chronic, recurrent), presence of tissue necrosis (necrotizing or not necrotizing), macroscopic presence of pus (purulent or non-purulent) or involvement

of deep subcutaneous tissue and/or severity of disease (complicated or uncomplicated). Further classifications are based on the origin of the infection (bites, burns; see corresponding chapters) or host characteristics (e.g. immunosuppression, diabetes).

A more recent definition by the United States Food and Drug Administration uses the term acute bacterial skin and skin structure infections (ABSSSI) to include a subset of conditions such as cellulitis and erysipelas, wound infections and major cutaneous abscesses, provided the area of the skin surface affected is at least 75 cm². This definition was introduced "to assist sponsors developing drugs for the treatment of skin infections" and has limited clinical applicability outside trials (165).

This chapter focuses on the mild superficial forms of skin infections that do not affect deeper tissue layers: impetigo, erysipelas and cellulitis. For the more severe forms of skin and soft tissue infections, please refer to the corresponding chapters: necrotizing fasciitis, pyomyositis, burn wounds and severe infections with sepsis. The following syndromes are not covered in the current edition of the AWaRe book: acne, diabetic foot infections and surgical site infections.

Impetigo / Erysipelas / Cellulitis

Skin and soft tissue infection

Definition

Superficial bacterial skin infections, not affecting the deeper tissue layers

Diagnosis

Clinical Presentation

Impetigo: Acute onset of superficial skin lesions usually without systemic symptoms
 • Most cases: papules progressing to vesicles and pustules that break to form crusts (**non-bullous form**)
 • Minority of cases: vesicles evolve to form larger bullae (**bullous form**)

Erysipelas: Acute onset of a painful red skin lesion with well-defined indurated margins usually on face or legs
 • Bullae may be present or develop in first days
 • Fever ($\geq 38.0^{\circ}\text{C}$) and other signs of systemic infection may be present

Cellulitis: Acute onset of a skin lesion presenting with redness, swelling and induration, warmth and pain or tenderness of the affected area
 • Most commonly affected areas: legs and face
 • Fever ($\geq 38.0^{\circ}\text{C}$) and other signs of systemic infection may be present
 • Redness alone may not indicate an infection
 • A clear clinical distinction between cellulitis and erysipelas is often difficult to make

Microbiology Tests

Not needed in most mild cases
 • Tissue swab cultures are to be avoided, especially in case of intact skin

Other Laboratory Tests

Not needed in most mild cases

Imaging

Routine imaging of mild cases not necessary
 • Ultrasound may be considered if abscess or subdermal involvement suspected

Most Likely Pathogens

Bacteria (most cases):

- *Streptococcus pyogenes* (group A Streptococcus) - especially in case of erysipelas
- *Staphylococcus aureus* (including MRSA)

Additional bacteria (more rarely e.g immunocompromised and/or diabetic patients, traumatic skin lesions):

- Enterobacteriads
- *Pseudomonas* spp.
- Anaerobes

This guidance excludes skin infections caused by viral, fungal or parasitic pathogens; diabetic foot infections; necrotizing fasciitis; pyomyositis; severe infections with sepsis; and surgical site infections

Rx Treatment

Clinical Considerations

- **Empiric antibiotic options** need to have good activity against both *Streptococcus pyogenes* (group A *Streptococcus*) and MSSA
- **Empiric treatment against community-acquired MRSA:** Consider in selected cases based on individual risk factors, known colonization and local prevalence
- **Mild infections:** Oral treatment is adequate
- **Intravenous antibiotics:** May be required if infection rapidly spreading and not responding to oral antibiotics

Antibiotic Treatment Duration

Treat for 5 days

Longer durations may be required in case of no clinical improvement or if an underlying medical condition is present

Topical Treatment

Localized non-bullous impetigo: Topical treatment is preferred over an oral antibiotic, whenever possible. For example, a 5 day course with mupirocin 2% ointment

Rx Antibiotic Treatment

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

Amoxicillin+clavulanic acid 500 mg +125 mg q8h **ORAL**

Cefalexin 500 mg q8h **ORAL**

Cloxacillin 500 mg q6h **ORAL**

Cloxacillin and cefalexin have a narrower spectrum of antibacterial activity compared to amoxicillin+clavulanic acid with good efficacy in mild skin and soft tissue infections. From an antibiotic stewardship perspective, these would be the preferred options whenever possible (except for bite wounds). If cloxacillin is unavailable, dicloxacillin or flucloxacillin could be used

Impetigo / Erysipelas / Cellulitis

Skin and soft tissue infection • Page 1 of 2

This guidance excludes skin infections caused by viral, fungal or parasitic pathogens; necrotizing fasciitis; pyomyositis; severe infections with sepsis; and surgical site infections



Definition

Superficial bacterial skin infections, not affecting the deeper tissue layers



Most Likely Pathogens

Bacteria (most cases):

- *Streptococcus pyogenes* (group A Streptococcus) - especially in case of erysipelas
- *Staphylococcus aureus* (including MRSA)



Diagnosis



Clinical Presentation

Impetigo: Acute onset of superficial skin lesions usually without systemic symptoms

- Most cases: papules progressing to vesicles and pustules that break to form crusts (**non-bullous form**)
- Minority of cases: vesicles evolve to form larger bullae (**bullous form**)

Erysipelas: Acute onset of a painful red skin lesion with well-defined indurated margins usually on face or legs

- Bullae may be present or develop in first days
- Fever ($\geq 38.0^{\circ}\text{C}$) and other signs of systemic infection may be present

Cellulitis: Acute onset of a skin lesion presenting with redness, swelling and induration, warmth and pain or tenderness of the affected area

- Most commonly affected areas: legs and face
- Fever ($\geq 38.0^{\circ}\text{C}$) and other signs of systemic infection may be present
- Redness alone may not indicate an infection

A clear clinical distinction between cellulitis and erysipelas is often difficult to make



Microbiology Tests

Not needed in most mild cases

- Tissue swab cultures are to be avoided, especially in case of intact skin



Other Laboratory Tests

Not needed in most mild cases



Imaging

Routine imaging of mild cases not necessary

- Ultrasound may be considered if abscess or subdermal involvement suspected

Impetigo / Erysipelas / Cellulitis

Skin and soft tissue infection • Page 2 of 2

Rx Treatment

Clinical Considerations

- **Empiric antibiotic options** need to have good activity against both Group A *Streptococcus* and MSSA
- **Empiric treatment against community-acquired MRSA:** Consider in selected cases based on individual risk factors, known colonization and local prevalence
- **Mild infections:** Oral treatment is adequate
- **Intravenous antibiotics:** May be required if infection rapidly spreading and not responding to oral antibiotics

Antibiotic Treatment Duration

Treat for **5 days**

Longer durations may be required in case of no clinical improvement or if an underlying medical condition is present

Topical Treatment

Localized non-bullous impetigo: Topical treatment is preferred over an oral antibiotic, whenever possible. For example, a 5 day course with mupirocin 2% ointment

Rx Antibiotic Treatment

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

 Amoxicillin+clavulanic acid 80-90 mg/kg/day of amoxicillin component **ORAL**

• **Oral weight bands:**

3-<6 kg	250 mg of amox/dose q12h
6-<10 kg	375 mg of amox/dose q12h
10-<15 kg	500 mg of amox/dose q12h
15-<20 kg	750 mg of amox/dose q12h
≥20 kg	500 mg of amox/dose q8h or 1 g of amox/dose q12h

Amox = amoxicillin

Oral liquid must be refrigerated after reconstitution

OR

 Cefalexin 25 mg/kg/dose q12h **ORAL**

• **Oral weight bands:**

3-<6 kg	125 mg q12h
6-<10 kg	250 mg q12h
10-<15 kg	375 mg q12h
15-<20 kg	500 mg q12h
20-<30 kg	625 mg q12h
≥30 kg	500 mg q8h

OR

 Cloxacillin 15 mg/kg/dose q6h **ORAL**

• **Oral weight bands:**

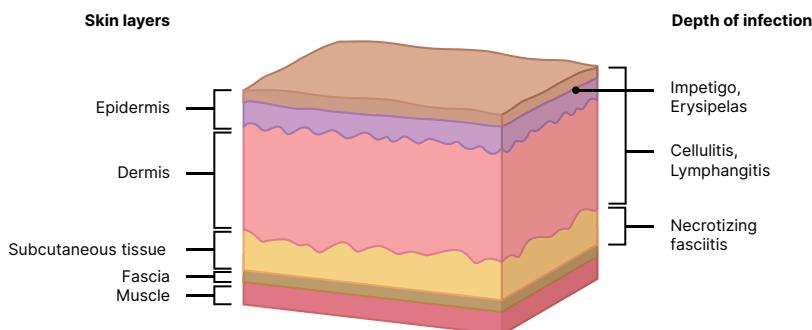
3-<6 kg	62.5 mg q6h
6-<10 kg	125 mg q6h
10-<15 kg	250 mg q6h
15-<20 kg	375 mg q6h
≥20 kg	500 mg q6h

Cloxacillin and cefalexin have a narrower spectrum of antibacterial activity compared to amoxicillin+clavulanic acid with good efficacy in mild skin and soft tissue infections. From an antibiotic stewardship perspective, these would be the preferred options whenever possible (except for bite wounds). If cloxacillin is unavailable, dicloxacillin or flucloxacillin could be used

Pathophysiology

Damage of the skin can lead to infections of the deeper layers beneath the epidermis. When such damage occurs, both endogenous pathogens (i.e. that naturally reside in the body) and exogenous pathogens (i.e. that enter the body from the environment) can penetrate the epidermis and spread to deeper structures through the lymphatic system. Depending on the depth of the infection, different clinical diseases can occur: impetigo and erysipelas (infections of the upper layer of the skin) and cellulitis (infection of the deep dermis and subcutaneous tissue) (Figure 16.1). Cellulitis of the face can also occur as a consequence of local spreading of a dental infection, for example, dental abscess spreading to the surrounding soft tissue can result in cellulitis.

Figure 16.1 – Anatomy of the skin and locations of common infections



Epidemiology

Bacterial skin infections occur worldwide and can affect all age groups; erysipelas is more frequent in children and elderly patients. In 2013, skin diseases (not limited to bacterial infections) were the fourth leading cause of non-fatal diseases (166). Cellulitis, the most common skin infection, accounted for 0.04% (4 in 10 000) of the overall burden of all diseases combined in 2013. It was the only skin condition that showed a significant decrease (~13.2%) between 2005 and 2013 in disability-adjusted life years (DALYs), a proxy for morbidity and mortality. This decrease was attributed to reduced mortality (166). In 2017, the Global Burden of Disease study reported 43 million new cases of cellulitis worldwide (44). Diabetes, peripheral arterial disease, HIV infection and other causes of immunosuppression are risk factors for severe skin infections.

Most likely pathogens

The most common pathogens causing skin infections are listed in Table 16.1.

Table 16.1 – Pathogens most frequently associated with skin infections (in descending order of frequency)

Most cases	More rarely (e.g. in immunocompromised and/or diabetic patients, traumatic skin lesions)	Cases with specific environmental exposures
<i>Streptococcus pyogenes</i> (group A <i>Streptococcus</i>), especially in the case of erysipelas	Enterobacteriales (including multidrug-resistant strains such as those producing ESBL and carbapenemases) <i>Pseudomonas aeruginosa</i> (including multidrug-resistant strains such as those producing ESBL and carbapenemases) Anaerobes	<i>Aeromonas hydrophila</i> (exposure to fresh water) <i>Erysipelothrix rhusiopathiae</i> (contact with animals colonized with the organism, mostly pigs and fish) <i>Vibrio vulnificus</i> (exposure to seawater)
<i>Staphylococcus aureus</i> (including MRSA)		

ESBL: extended-spectrum beta-lactamases; MRSA: methicillin-resistant *Staphylococcus aureus*.

Clinical presentation (only mild cases are covered)

The morphology of different skin lesions is described in Table 16.2 and illustrated in Figure 16.2.

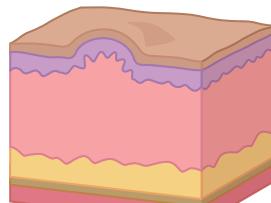
Table 16.2 – Morphology of skin lesions

Type of skin lesion	Morphology
Bulla	Larger (> 10 mm) fluid-filled blister
Papule	Small (< 10 mm), elevated lesion that can be palpated
Pustule	Small (< 10 mm) vesicle containing pus
Vesicle	Small (< 10 mm) fluid-filled blister

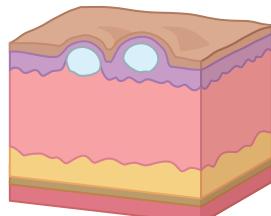
■ PRIMARY HEALTH CARE

16. Skin and soft tissue infections – mild bacterial impetigo, erysipelas and cellulitis

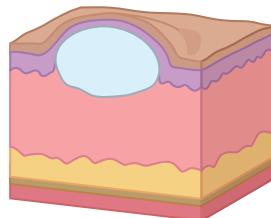
Figure 16.2 – Types and morphology of skin lesions



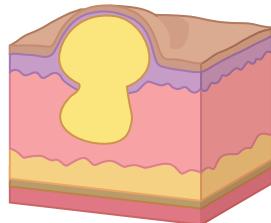
Papule



Vesicle



Bulla



Pustule

Impetigo

Impetigo is characterized by acute onset of superficial skin lesions usually without associated systemic symptoms. In most cases, impetigo presents with papules that progress to vesicles and pustules which break to finally form crusts (non-bullous form) (Figure 16.3). In a minority of cases (mostly in young children), vesicles develop to form larger bullae (bullosus form).

Figure 16.3 – Case of impetigo on the chin



Source: © James Heilman, MD, CC BY-SA 4.0, via Wikimedia Commons

Erysipelas

Erysipelas is characterized by acute onset of a red skin lesion with well defined indurated margins, usually on the face or legs (Figure 16.4). Bullae may be present or develop in the first few days. The lesion is usually painful. Fever ($\geq 38.0^{\circ}\text{C}$) and other signs of systemic infection (e.g. tachycardia, leukocytosis) may be present.

Figure 16.4 – Case of erysipelas on the cheek



Source: CDC Public Health Image Library/Dr Thomas F. Sellers, Emory University

Cellulitis

While erysipelas affects only the superficial skin layers and has clearly demarcated borders, cellulitis also affects subcutaneous tissues. Cellulitis is characterized by an acute onset of a skin lesion presenting with a combination of redness, swelling and induration, warmth and pain (or tenderness) of the affected area (see Figure 16.5). The condition can occur anywhere on the body, but predominantly affects the skin of the lower part of the legs and feet or the face.

In patients with cellulitis, fever ($\geq 38.0^{\circ}\text{C}$) and other signs of systemic infection (e.g. tachycardia, leukocytosis) may be present. Skin redness alone may not indicate an infection, for example, redness is often present in patients with chronic venous stasis – bilateral versus unilateral involvement may indicate a non-infectious etiology, although bilateral cellulitis can occasionally occur. The severity of the infection should always be carefully assessed, especially to exclude the possibility of involvement of the muscular fascia (fasciitis). Facial and neck cellulitis, commonly arising from dental infection, can lead to potentially fatal deep space infections such as Ludwig angina. Cellulitis of the face can spread to the brain

■ PRIMARY HEALTH CARE

16. Skin and soft tissue infections – mild bacterial impetigo, erysipelas and cellulitis

and lead to serious complications such as cavernous sinus thrombosis. These are medical emergencies but are overall rare.

Figure 16.5 – Case of cellulitis in the lower leg



Source: John Campbell, CC0 1.0 Universal (CC0 1.0), via Flickr

Laboratory tests

Patient microbiology tests

Most mild cases of impetigo, erysipelas and cellulitis do not require routine microbiology tests. Surface swabs of intact, unbroken skin should not be taken in cases of erysipelas or cellulitis to avoid detecting pathogens that colonize the skin leading to unnecessary antibiotic treatment.

Tissue swab cultures can be considered in certain cases (Table 16.3). For example, cultures could be done for lesions that are clearly purulent (therefore most likely due to *Staphylococcus aureus*) to diagnose or exclude the presence of methicillin-resistant *Staphylococcus aureus* (MRSA). However, in many settings doing tissue swab cultures is not standard practice outside of the operating theatre. When swabs are taken, the lesion should always be cleaned and debrided before sample collection to identify the pathogens causing the infection and not colonizing organisms. For a correct interpretation of cultures, it is very important that the origin of the culture (exact location, superficial swab or intraoperatively obtained culture) is adequately documented.

Cultures can be considered for chronic lesions such as diabetic foot infections (not covered in this chapter) to exclude the presence of multidrug-resistant organisms, for example, those producing extended-spectrum beta-lactamases (ESBLs).

Table 16.3 – Microbiology tests to consider for the diagnosis of skin infections in certain cases as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Setting where the test should be available
Tissue swab culture and antimicrobial susceptibility testing	Initial step to detect and identify bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics.

Other tests

Routine laboratory tests are not required in mild cases (167).

Using microbiology surveillance data

Routine surveillance is not helpful in informing empiric guidance.

Imaging

Routine imaging of mild cases of impetigo, erysipelas and cellulitis is not necessary. However, initial imaging (e.g. ultrasound, X-ray) may be considered if an abscess or subdermal involvement are suspected. In these cases, management often requires a surgical approach, for example, incision and drainage in case of abscess and management of the primary dental cause.

Topical treatment (only for localized non-bullous impetigo)

For localized non-bullous impetigo, topical treatment could be considered as an alternative to oral antibiotics. This treatment can be as effective as oral antibiotic treatment and has the advantage that the risk of adverse events is minimal because of less systemic absorption (168).

Of the different topical treatments available, mupirocin ointment (2%) could be considered for a short course of treatment (5 days). However, widespread use of mupirocin can rapidly increase resistance to mupirocin in *Staphylococcus aureus* and limit its usefulness for targeted preventive purposes in carriers of *Staphylococcus aureus*; mupirocin is active against both methicillin-susceptible *Staphylococcus aureus* and MRSA. Alternative treatments are available but they are not included in the EML and EMLc (8,9). These alternatives are fusidic acid and hydrogen peroxide cream (1%). Topical corticosteroids should not be used routinely in these cases.

Antibiotic treatment (for widespread impetigo, erysipelas and cellulitis)

In most cases of mild infections, oral antibiotic treatment is adequate (Table 16.4). Empiric antibiotic options need to have good activity against the most likely pathogens (*Streptococcus* spp. and *Staphylococcus aureus*). Empiric treatment against community-acquired MRSA may be considered in certain cases (e.g. clearly purulent lesions) based on individual risk factors (e.g. known MRSA colonization) and on the local prevalence of community-acquired MRSA. In these cases, the literature suggests using clindamycin or sulfamethoxazole+trimethoprim; these options are however not currently listed in the EML and EMLc for this indication.

Table 16.4 – Empiric antibiotic treatment for mild skin infections

Important		
Note		
Adults	Children	Total treatment duration
Amoxicillin+clavulanic acid (oral): 500 mg + 125 mg given every 8 hours OR Cefalexin (oral): 500 mg given every 8 hours OR Cloxicillin ^a (oral): 500 mg given every 6 hours	Amoxicillin+clavulanic acid ^b (oral): 80–90 mg/kg/day of amoxicillin component Oral weight bands: 3–< 6 kg: 250 mg of amoxicillin/dose given every 12 hours 6–< 10 kg: 375 mg of amoxicillin/dose given every 12 hours 10–< 15 kg: 500 mg of amoxicillin/dose given every 12 hours 15–< 20 kg: 750 mg of amoxicillin/dose given every 12 hours ≥ 20kg: 500 mg of amoxicillin/dose given every 8 hours or 1 g of amoxicillin/dose given every 12 hours OR	5 days ^d

continues

Table 16.4 *continued*

Adults	Children	Total treatment duration
	<p>Cefalexin (oral): 25 mg/kg/dose given every 12 hours</p> <p>Oral weight bands:</p> <ul style="list-style-type: none"> 3-< 6 kg: 125 mg given every 12 hours 6-< 10 kg: 250 mg given every 12 hours 10-< 15 kg: 375 mg given every 12 hours 15-< 20 kg: 500 mg given every 12 hours 20-< 30 kg: 625 mg given every 12 hours ≥ 30 kg: use adult dose <p>OR</p> <p>Cloxacillin^{a,c} (oral): 15 mg/kg/dose given every 6 hours</p> <p>Oral weight bands:</p> <ul style="list-style-type: none"> 3-< 6 kg: 62.5 mg given every 6 hours 6-< 10 kg: 125 mg given every 6 hours 10-< 15 kg: 250 mg given every 6 hours 15-< 20 kg: 375 mg given every 6 hours ≥ 20 kg: 500 mg given every 6 hours 	

Note. All dosages are for normal renal and hepatic function.

^a If cloxacillin is unavailable, dicloxacillin or flucloxacillin could be used.

^b Oral liquid formulations must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures.

^c The WHO *Pocket book of hospital care for children* (31) suggests amoxicillin plus cloxacillin. However, cloxacillin can be safely used as a single antibiotic option because it has good activity against both methicillin-susceptible *Staphylococcus aureus* and *Streptococcus pyogenes* (often referred to as group A *Streptococcus*). Amoxicillin alone is not suitable because it has variable activity against methicillin-susceptible *Staphylococcus aureus*.

^d The optimal duration of antibiotic treatment is not known (169); duration is often individualized based on clinical response.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

17. Burn wound-related infections

Key messages

- Burn wounds predispose to infections (damage of the skin's protective barrier, immunosuppression in severe cases) and should be monitored for signs of cellulitis (redness, pain and swelling around the wound).
- Avoid the routine use of antibiotics to prevent infections if there are no signs of systemic infection and in otherwise healthy patients.
- Mild infections should be treated with antibiotics with good activity against the most likely pathogens (Gram-positive bacteria from the skin microbiota)
- Multidrug-resistant organisms are a major concern in patients with severe burn wounds often because of prolonged hospitalization and frequent antibiotic exposure.
- Sepsis and septic shock are a frequent complication of severe burns.

Other relevant WHO resources (please check regularly for updates)

- Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, 2013 (31).
- Burns – fact sheet (170).

Definition

A burn wound is an injury to the skin or other organic tissue primarily caused by heat or due to radiation, radioactivity, electricity, friction or contact with chemicals. Burns can be classified based on the cause and depth of the burn.

Burn wound-related infections

Definition

An injury to the skin or other organic tissue primarily caused by heat or due to radiation, radioactivity, electricity, friction or contact with chemicals. Burns can be classified based on cause and depth of the burn

Diagnosis

Clinical Presentation

Diagnosis of a wound infection relies on the clinical examination

- Burn wounds should be monitored for signs of infection such as increased pain, redness or swelling of the area surrounding the wound
- Redness alone may not indicate infection
- Signs of invasive infection (e.g. change in wound colour, signs of sepsis) should be carefully monitored

Microbiology Tests

- Routine testing (including wound cultures) is not needed in mild cases with no signs of systemic infection
- Identifying the pathogen in mild cases will not benefit the patient as it will rarely change management
- In severe cases, refer to the Sepsis infographic if this is suspected

Other Laboratory Tests

- Routine testing is not needed in mild cases with no signs of systemic infection
- Because of the inflammatory response associated with the burn, biomarkers of infection are of limited use to diagnose bacterial infections

Imaging

Routine imaging not necessary

Most Likely Pathogens

Mostly polymicrobial. Hospital-acquired multidrug-resistant organisms are a major concern in burn patients often because of prolonged hospitalization and frequent antibiotic exposure

Early after the injury:

- Streptococcus* spp.
- Staphylococcus aureus* (including MRSA)
- Staphylococcus* spp. other than *S. aureus*
- Enterobacteriaceae**

During hospitalization:

- Pseudomonas aeruginosa**
- Acinetobacter baumannii**
- Fungi (e.g. *Candida* spp.)

*Including multidrug-resistant strains

This guidance excludes severe infections

Rx Treatment

Clinical Considerations

- Meticulous observation of infection control procedures to prevent transmission of multidrug-resistant organisms
- Irrigation and debridement of necrotic tissue to prevent infection of the wound
- Appropriate daily cleaning and dressing of the wound
- Only infected wounds should be treated
- Coverage against MRSA may be considered based on local prevalence and on individual risk factors

Antibiotic Treatment Duration

Treat for **5 days (mild cases)**
(Potentially longer if severe systemic infections)

Prophylactic Antibiotics

Avoid the routine use of antibiotics to prevent infections (no clear evidence of a benefit and increased risk of colonization with resistant bacteria)

Topical Treatment

Local antiseptics could be considered based on local protocols

Rx Antibiotic Treatment

Only infected wounds should be treated

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

 Amoxicillin+clavulanic acid 500 mg+125 mg q8h ORAL
ACCESS

OR

 Cefalexin 500 mg q8h ORAL
ACCESS

OR

 Cloxacillin 500 mg q6h ORAL
ACCESS

Cloxacillin and cefalexin have a narrower spectrum of antibacterial activity compared to amoxicillin+clavulanic acid with good efficacy in mild skin and soft tissue infections. From an antibiotic stewardship perspective, these would be the preferred options whenever possible

If cloxacillin is unavailable, dicloxacillin or flucloxacillin could be used

Burn wound-related infections

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This guidance excludes severe infections

Definition

- An injury to the skin or other organic tissue primarily caused by heat or due to radiation, radioactivity, electricity, friction or contact with chemicals
- Burns can be classified based on cause and depth of the burn

Most Likely Pathogens

Mostly polymicrobial. Hospital-acquired multidrug-resistant organisms are a major concern in burn patients often because of prolonged hospitalization and frequent antibiotic exposure

Early after the injury:

- *Streptococcus* spp.
- *Staphylococcus aureus* (including MRSA)
- *Staphylococcus* spp. other than *S. aureus*
- *Enterobacteriaceae**

During hospitalization:

- *Pseudomonas aeruginosa**
- *Acinetobacter baumannii**
- Fungi (e.g. *Candida* spp.)

*Including multidrug-resistant strains

Diagnosis

Clinical Presentation

- Diagnosis of a wound infection relies on the clinical examination
- Burn wounds should be monitored for signs of infection such as increased pain, redness or swelling of the area surrounding the wound
 - Redness alone may not indicate infection
 - Signs of invasive infection (e.g. change in wound colour, signs of sepsis) should be carefully monitored

Microbiology Tests

- Routine testing (including wound cultures) is not needed in mild cases with no signs of systemic infection
- Identifying the pathogen in mild cases will not benefit the patient as it will rarely change management
- In severe cases, refer to the Sepsis infographic if this is suspected

Other Laboratory Tests

- Routine testing is not needed in mild cases with no signs of systemic infection
- Because of the inflammatory response associated with the burn, biomarkers of infection are of limited use to diagnose bacterial infections

Imaging

Routine imaging not necessary

Burn wound-related infections

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Rx Treatment

Clinical Considerations

- Meticulous observation of infection control procedures to prevent transmission of multidrug-resistant organisms
- Irrigation and debridement of necrotic tissue to prevent infection of the wound
- Appropriate daily cleaning and dressing of the wound
- Only infected wounds should be treated
- Coverage against MRSA may be considered based on local prevalence and on individual risk factors

Antibiotic Treatment Duration

Treat for **5 days (mild cases)**
(Potentially longer if severe systemic infections)

Prophylactic Antibiotics

Avoid the routine use of antibiotics to prevent infections (no clear evidence of a benefit and increased risk of colonization with resistant bacteria)

Topical Treatment

Local antiseptics could be considered based on local protocols

Rx Antibiotic Treatment

Only infected wounds should be treated

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated



Amoxicillin+clavulanic acid 80-90 mg/kg/day or amoxicillin component **ORAL**

• Oral weight bands:

3-<6 kg	250 mg of amox/dose q12h
6-<10 kg	375 mg of amox/dose q12h
10-<15 kg	500 mg of amox/dose q12h
15-<20 kg	750 mg of amox/dose q12h
≥20 kg	500 mg of amox/dose q8h or 1 g of amox/dose q12h

Amox = amoxicillin

Oral liquid must be refrigerated after reconstitution

OR



Cefalexin 25 mg/kg/dose q12h **ORAL**

• Oral weight bands:

3-<6 kg	125 mg q12h
6-<10 kg	250 mg q12h
10-<15 kg	375 mg q12h
15-<20 kg	500 mg q12h
20-<30 kg	625 mg q12h
≥30 kg	500 mg q8h

OR



Clloxacillin 15 mg/kg/dose q6h **ORAL**

• Oral weight bands:

3-<6 kg	62.5 mg q6h
6-<10 kg	125 mg q6h
10-<15 kg	250 mg q6h
15-<20 kg	375 mg q6h
≥20 kg	500 mg q6h

Clloxacillin and cefalexin have a narrower spectrum of antibacterial activity compared to amoxicillin+clavulanic acid with good efficacy in mild skin and soft tissue infections. From an antibiotic stewardship perspective, these would be the preferred options whenever possible

If clloxacillin is unavailable, dicloxacillin or flucloxacillin could be used

Pathophysiology

Burns predispose to infection because they allow entry of pathogens from the patient's own skin microbiota and the environment into the wound. Burns can also cause immunosuppression that allows rapid bacterial colonization and proliferation. Sepsis and septic shock are a frequent complication of severe burns.

Epidemiology

Burn wounds are an important public health problem in low- and middle-income countries where they are among the leading causes of DALYs lost. An estimated 180 000 deaths every year are caused by burns and most occur in low- and middle-income countries (170). Infections (including but not limited to the skin) are the most frequent complications encountered in patients with burn injuries and are the leading cause of death in patients with severe wounds. Skin infections (e.g. cellulitis) are in general the first infections to occur, usually in the first week of the injury.

Most likely pathogens

Table 17.1 gives the pathogens that often infect burn wounds. In most cases, infection is caused by several pathogens. Multidrug-resistant organisms are a major concern in burn patients often because of prolonged hospitalization and frequent antibiotic exposure (171).

Table 17.1 – Pathogens most frequently associated with infected burn wounds (in descending order of frequency)

Time infection acquired	Bacteria	Fungi
Soon after the injury	<i>Streptococcus</i> spp. <i>Staphylococcus aureus</i> (including MRSA) <i>Staphylococcus</i> spp. other than <i>Staphylococcus aureus</i> Enterobacterales (including multidrug-resistant strains such as those producing ESBL and carbapenemases)	Infrequent

continues

Table 17.1 continued

Time infection acquired	Bacteria	Fungi
Additionally, during hospitalization	<i>Pseudomonas aeruginosa</i> <i>Acinetobacter baumannii</i> (including multidrug-resistant strains such as those producing ESBL and carbapenemases)	<i>Candida</i> spp.

ESBL: extended-spectrum beta-lactamases; MRSA: methicillin-resistant *Staphylococcus aureus*.

Clinical presentation

Diagnosis of a burn wound infection requires clinical examination. For this reason, burn wounds should be monitored for signs of infection, such as increased pain and redness or swelling of the area surrounding the wound. Redness alone may represent inflammation and does not necessarily indicate infection. Signs of invasive infection (e.g. change in the colour of the wound, signs of sepsis) should also be carefully monitored. Please also refer to the chapter on sepsis if suspected. Patients with burn injuries may also develop other complications dependent on their supportive care such as pneumonia, UTIs or catheter-related infections.

Laboratory tests

Patient microbiology tests

In mild cases of infection of a burn wound where there are no signs of systemic infection, routine testing (including wound cultures) is not required. These tests are not needed because identifying the causative pathogen in mild cases will not benefit the patient as it will not change management. In severe cases, blood cultures can be considered. Please also refer to the chapter on sepsis if suspected.

Other tests

Routine testing in mild cases with no signs of systemic infection is not required. In addition, because of the inflammatory response associated with the burn itself, results of laboratory tests (e.g. biomarkers of infection) may be of limited help.

In severe cases, certain laboratory tests can be considered to make an initial assessment of the patient and to help guide the duration of antibiotic treatment. Please also refer to the chapter on sepsis if suspected.

Using microbiology surveillance data

Targeted clinical surveys of bloodstream infection isolates at a local unit level may be helpful to inform empiric guidance. Empiric guidance should not usually be informed by routine surface skin swabs.

Imaging

Routine imaging is not required unless a complication is suspected.

Management

Irrigation and debridement of necrotic tissue to prevent infection of the burn wound is suggested. Appropriate daily cleaning and dressing of the wound are the cornerstone of treatment.

Infection control procedures should be meticulously observed to prevent transmission of multidrug-resistant organisms.

Topical treatment

Local antiseptics could be considered based on local protocols.

Preventive antibiotic use

Routine use of antibiotics to prevent infection in burn wounds should be avoided if there are no signs of systemic infection or in otherwise healthy patients. Use of antibiotics as a preventive treatment is controversial because there is no clear evidence that it can prevent infection (172,173). In addition, such use can lead to colonization with resistant microorganisms, so caution is needed.

Antibiotic treatment

Empiric treatment of mild infections should include antibiotics with good activity against the most likely pathogens, *Staphylococcus aureus* and *Streptococcus* spp. Antibiotic options are shown in Table 17.2. Empiric treatment against community-acquired MRSA may be considered and should be based on local prevalence of invasive isolates and individual patient risk factors (e.g. known MRSA colonization).

It is important to note that because hospital-acquired multidrug-resistant organisms are frequently found in burn units, the results of microbiology cultures should where possible guide antibiotic treatment. Empiric use of RESERVE group antibiotics should, however, generally be avoided unless there is a high suspicion of the infection being caused by multidrug-resistant organisms. Please also refer to the chapter on sepsis if suspected.

Note

Only infected wounds should be treated with antibiotics

Table 17.2 – Empiric antibiotic treatment for mild burn wound infections

Important

Where more than one antibiotic is recommended for an infection, they are listed in alphabetical order and they should be considered equal treatment options, unless otherwise indicated.

Note

Cloxacillin and cefalexin have a narrower spectrum of antibacterial activity compared to amoxicillin+clavulanic acid with good efficacy in mild skin and soft tissue infections. Therefore, from an antibiotic stewardship perspective, these two antibiotics are the preferred options whenever possible.

Adults	Children	Total treatment duration
Amoxicillin+clavulanic acid (oral): 500 mg + 125 mg given every 8 hours OR Cefalexin (oral): 500 mg given every 8 hours OR Cloxacillin ^a (oral): 500 mg given every 6 hours	Amoxicillin+clavulanic acid ^b (oral): 80–90 mg/kg/day of amoxicillin component Oral weight bands: 3–< 6 kg: 250 mg of amoxicillin/dose given every 12 hours 6–< 10 kg: 375 mg of amoxicillin/dose given every 12 hours 10–< 15 kg: 500 mg of amoxicillin/dose given every 12 hours 15–< 20 kg: 750 mg of amoxicillin/dose given every 12 hours ≥ 20 kg: 500 mg of amoxicillin/dose given every 8 hours or 1 g of amoxicillin/dose given every 12 hours OR	5 days

continues

Table 17.2 *continued*

Adults	Children	Total treatment duration
	<p>Cefalexin (oral): 25 mg/kg/dose given every 12 hours</p> <p>Oral weight bands:</p> <p>3-< 6 kg: 125 mg given every 12 hours</p> <p>6-< 10 kg: 250 mg given every 12 hours</p> <p>10-< 15 kg: 375 mg given every 12 hours</p> <p>15-< 20 kg: 500 mg given every 12 hours</p> <p>20-< 30 kg: 625 mg given every 12 hours</p> <p>≥ 30 kg: use adult dose</p> <p>OR</p> <p>Cloxacillin^{a,c} (oral): 15 mg/kg/dose given every 6 hours</p> <p>Oral weight bands:</p> <p>3-< 6 kg: 62.5 mg given every 6 hours</p> <p>6-< 10 kg: 125 mg given every 6 hours</p> <p>10-< 15 kg: 250 mg given every 6 hours</p> <p>15-< 20 kg: 375 mg given every 6 hours</p> <p>≥ 20 kg: 500 mg given every 6 hours</p>	

Note. All dosages are for normal renal and hepatic function.

^a If cloxacillin is unavailable, dicloxacillin or flucloxacillin could be used.

^b Oral liquid formulations must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures.

^c The WHO *Pocket book of hospital care for children* suggests amoxicillin plus cloxacillin; however, cloxacillin can be safely used as a single antibiotic option since it has good activity against both methicillin-susceptible *Staphylococcus aureus* and *Streptococcus pyogenes*. Amoxicillin alone is not suitable because it has variable activity against methicillin-susceptible *Staphylococcus aureus*.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

18. Wound and bite-related infections

Note

This chapter does not include severe infections, surgical wounds and management of bites from poisonous animals or arthropods (insects, ticks, mites).

Please refer to the specific chapters about other skin and soft tissue infections – burn wounds, impetigo/erysipelas/cellulitis, necrotizing fasciitis, pyomyositis, if these infections are suspected.

Key messages

- In general, uninfected wounds **do not require antibiotic treatment** except in very select cases.
- Skin wounds predispose to infection (e.g. cellulitis) but not every wound becomes infected. In fact, only a minority of wounds become infected in immunocompetent people.
- Adequate cleaning and debridement of the skin wound are the cornerstone of initial treatment.
- Need for post-exposure prophylaxis for certain infectious diseases (e.g. tetanus, rabies) should always be evaluated on a case-by-case basis.
- The presence of signs of invasive infection should always be carefully evaluated.

Other relevant WHO resources (please check regularly for updates)

- Prevention and management of wound infections, 2013 (174).
- Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, 2013 (31).
- Snakebite envenoming – health topic (175).
- Snakebite envenoming: a strategy for prevention and control, 2019 (176).
- Global status report on road safety, 2018 (177).
- Tetanus vaccines: WHO position paper – February 2017 (178).
- Rabies vaccines: WHO position paper – April 2018 (179).
- Hepatitis B vaccines: WHO position paper – July 2017 (180).
- Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, 2021 update (181).

Definition

Skin wounds include any traumatic injury characterized by damage to and exposure of deeper skin tissue. Examples of skin wounds include those caused by human or animal bites or burns, road traffic injuries, and gunshot and stab wounds. The severity of the clinical findings can vary from mild wounds with no systemic involvement to severe infections including tetanus (infection by *Clostridium tetani*) and gas gangrene (infection by gas-producing bacteria such as *Clostridium perfringens*).

Wound and bite-related infections

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This guidance excludes severe infections, surgical wounds and management of bites from arthropods and poisonous animals

Definition

Any traumatic skin injury characterized by damage and exposure of deeper skin tissue



Diagnosis

Clinical Presentation

Infection may or may not be present at time of clinical evaluation

- **Superficial infections:** Symptoms of cellulitis (redness, swelling, warmth, lymphangitis, pain around wound)
- **Invasive wound infection:** Change in wound colour, signs of sepsis (should be carefully monitored)



Laboratory Tests

Routine testing not needed in mild cases with no signs of systemic infection



Imaging

Routine imaging not necessary

- May be considered in selected cases based on extent and depth of lesion



Most Likely Pathogens

Infection commonly polymicrobial (mix of human skin and animal oral microbiota, and environmental organisms)

Wounds

Most cases:

- *Streptococcus* spp.
- *Staphylococcus aureus* (including MRSA)

More rarely:

- Anaerobes
- Enterobacteriales
- *Enterococcus* spp.
- *Clostridium tetani* (soil contaminant)

Bites

Human:

- Anaerobes
- *Streptococcus* spp.
- *Staphylococcus aureus*

Cat:

- Anaerobes
- *Pasteurella multocida*
- *Staphylococcus aureus*

Dog:

- Anaerobes
- *Capnocytophaga canimorsus*
- *Pasteurella multocida*
- *Staphylococcus aureus*

Monkey:

- Anaerobes
- *Streptococcus* spp.
- *Staphylococcus aureus*

Reptile:

- Anaerobes
- Enterobacteriales
- *Pseudomonas aeruginosa*

Rodent:

- *Pasteurella multocida*

Wound and bite-related infections

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Rx Treatment

Clinical Considerations

- **Rapidly after injury:** Thorough washing and flushing of the wound (~15 minutes), with soap or detergent and copious amounts of water followed by debridement and immobilization
- **Risk of tetanus and rabies:** Quickly evaluate need to provide adequate post-exposure prophylaxis
- **Signs/symptoms of infection:** Empiric treatment should include antibiotics with good activity against most likely pathogens (*Staphylococcus* spp. and *Streptococcus* spp. and anaerobes)
- **Animal/human bites:** Empiric treatment against both aerobic and anaerobic bacteria required; empiric treatment against community-acquired MRSA usually not required

WHO Guidance

- Rabies: <https://apps.who.int/iris/handle/10665/272372>
- Tetanus: <https://apps.who.int/iris/handle/10665/254583>



Antibiotic Treatment Duration

Treat for 5 days

Prophylactic Antibiotics

- In the absence of systemic signs of infection avoid antibiotics to prevent infections in otherwise healthy patients
- No clear evidence that antibiotics can prevent the infection
- Consider in selected cases (e.g. severely immunocompromised patients) and/or high-risk clinical areas (face, hands, near joints)
- Duration: 3 days

Rx Bite-related wounds

Only infected wounds should be treated

All dosages are for normal renal function



Amoxicillin+clavulanic acid 500 mg+125 mg
q8h ORAL

Amoxicillin+clavulanic acid is the preferred treatment option for bite wound infections because of its activity against anaerobic bacteria.

Rx Not bite-related wounds

Only infected wounds should be treated

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated



Amoxicillin+clavulanic acid 500 mg+125 mg
q8h ORAL

OR



Cefalexin 500 mg q8h ORAL

OR



Cloxacillin 500 mg q6h ORAL

Cloxacillin and cefalexin have a narrower spectrum of antibacterial activity compared to amoxicillin+clavulanic acid with good efficacy in other cases of mild skin and soft tissue infections. Therefore, from an antibiotic stewardship perspective, these would be the preferred options whenever possible (except for bite wounds)

If cloxacillin is unavailable, dicloxacillin or flucloxacillin could be used

Wound and bite-related infections

Page 1 of 2

This guidance excludes severe infections, surgical wounds and management of bites from arthropods and poisonous animals

Definition

Any traumatic skin injury characterized by damage and exposure of deeper skin tissue



Diagnosis

Clinical Presentation

Infection may or may not be present at time of clinical evaluation

- **Superficial infections:** Symptoms of cellulitis (redness, swelling, warmth, lymphangitis, pain around wound)
- **Invasive wound infection:** Change in wound colour, signs of sepsis (should be carefully monitored)



Laboratory Tests

Routine testing not needed in mild cases with no signs of systemic infection



Imaging

Routine imaging not necessary

- May be considered in selected cases based on extent and depth of lesion



Most Likely Pathogens

Infection commonly polymicrobial (mix of human skin and animal oral microbiota, and environmental organisms)

Wounds

Most cases:

- *Streptococcus* spp.
- *Staphylococcus aureus* (including MRSA strains)

More rarely:

- Anaerobes
- Enterobacteriales
- *Enterococcus* spp.
- *Clostridium tetani* (soil contaminant)

Bites

Human:

- Anaerobes
- *Streptococcus* spp.
- *Staphylococcus aureus*

Dog:

- Anaerobes
- *Capnocytophaga canimorsus*
- *Pasteurella multocida*
- *Staphylococcus aureus*

Reptile:

- Anaerobes
- Enterobacteriales
- *Pseudomonas aeruginosa*

Cat:

- Anaerobes
- *Pasteurella multocida*
- *Staphylococcus aureus*

Monkey:

- Anaerobes
- *Streptococcus* spp.
- *Staphylococcus aureus*

Rodent:

- *Pasteurella multocida*

Wound and bite-related infections

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Rx Treatment

Clinical Considerations

- Rapidly after injury:** Thorough washing and flushing of the wound (~15 minutes), with soap or detergent and copious amounts of water followed by debridement and immobilization
- Risk of tetanus and rabies:** Quickly evaluate need to provide adequate post-exposure prophylaxis
- Signs/symptoms of infection:** Empiric treatment should include antibiotics with good activity against most likely pathogens (*Staphylococcus* spp. and *Streptococcus* spp. and anaerobes)
- Animal/human bites:** Empiric treatment against both aerobic and anaerobic bacteria required; empiric treatment against community-acquired MRSA usually not required

WHO Guidance

- Rabies: <https://apps.who.int/iris/handle/10665/272372>
- Tetanus: <https://apps.who.int/iris/handle/10665/254583>

Antibiotic Treatment Duration

Treat for 5 days

Rx Not bite-related wounds

Only infected wounds should be treated

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated



Amoxicillin+clavulanic acid 80-90 mg/kg/day of amoxicillin component **ORAL**

• Oral weight bands:

3-<6 kg	250 mg of amox/dose q12h
6-<10 kg	375 mg of amox/dose q12h
10-<15 kg	500 mg of amox/dose q12h
15-<20 kg	750 mg of amox/dose q12h
≥20 kg	500 mg of amox/dose q8h or 1 g of amox/dose q12h

Amox = amoxicillin

Oral liquid must be refrigerated after reconstitution

OR



Cefalexin 25 mg/kg/dose q12h **ORAL**

• Oral weight bands:

3-<6 kg	125 mg q12h
6-<10 kg	250 mg q12h
10-<15 kg	375 mg q12h
15-<20 kg	500 mg q12h
20-<30 kg	625 mg q12h
≥30 kg	500 mg q8h

OR



Cloxacillin 15 mg/kg/dose q6h **ORAL**

• Oral weight bands:

3-<6 kg	62.5 mg q6h
6-<10 kg	125 mg q6h
10-<15 kg	250 mg q6h
15-<20 kg	375 mg q6h
≥20 kg	500 mg q6h

Cloxacillin and cefalexin have a narrower spectrum of antibacterial activity compared to amoxicillin+clavulanic acid with good efficacy in other cases of mild skin and soft tissue infections. Therefore, from an antibiotic stewardship perspective, these would be the preferred options whenever possible (except for bite wounds). If cloxacillin is unavailable, dicloxacillin or flucloxacillin could be used.

Rx Bite-related wounds

Only infected wounds should be treated

All dosages are for normal renal function



Amoxicillin+clavulanic acid 80-90 mg/kg/day of amoxicillin component **ORAL**

• Oral weight bands:

3-<6 kg	250 mg of amox/dose q12h
6-<10 kg	375 mg of amox/dose q12h
10-<15 kg	500 mg of amox/dose q12h
15-<20 kg	750 mg of amox/dose q12h
≥20 kg	500 mg of amox/dose q8h or 1 g of amox/dose q12h

Amox = amoxicillin

Oral liquid must be refrigerated after reconstitution

Amoxicillin+clavulanic acid is the preferred treatment option for bite wound infections because of its activity against anaerobic bacteria.

Pathophysiology

Skin wounds predispose to infection because they facilitate entry of pathogens from the patient's own skin microbiota and the environment into the wound. With bites, pathogens from the oral cavity of the biting animal can also penetrate the skin.

Epidemiology

Traumatic wounds

Road traffic injuries occur worldwide but the majority of deaths (> 90%) occur in low- and middle-income countries. Overall each year about 1.3 million people die as a result of road traffic incidents with many more suffering from non-fatal injuries (between 20 and 50 million people) (177,182). In people younger than 30 years, this is the leading cause of death.

In 2016, the Global Burden of Disease study reported about 251 000 deaths from firearm injuries globally (outside of war settings), the majority caused by homicides (64%), followed by suicides (27%) and unintentional firearm deaths (9%). Overall, the global age-standardized rate of firearm deaths decreased by about 0.9% a year between 1990 and 2016 with differences between countries. Most firearm injury deaths occur among people aged 20 to 24 years (183).

Bite wounds

Human and animal bites occur worldwide; most cases are caused by animals (dogs in > 90% of cases) (184). Less frequently, bites are caused by other mammals such as cats, rodents (e.g. rats, mice) and bats. In certain countries (e.g. in Africa and in South-East Asia), snake and monkey bites are also frequently reported. Children are more likely to have animal bites (185). The risk of developing a bacterial infection from a dog bite is unclear and depends on many different factors related to the patient (i.e. the person bitten), the characteristics of the bite (depth, location) and the initial management of the bite. However, available data suggest that in 10–20% of cases of dog bites, the wound will become infected (185,186). In comparison, wounds caused by cat bites have a higher risk of becoming infected (up to 50%) because of the deeper penetration of their teeth (185,186).

Animal bites are a significant risk factor for transmission of rabies, especially in settings where prophylaxis with rabies vaccine in domestic and wild animals is not routinely given. The Global Burden of Disease study estimated 13 400 new cases of rabies worldwide in 2017 (44). Deaths from rabies and dog bites are a problem mostly in low- and middle-income countries where post-exposure treatment and appropriate access to health care may be lacking (184).

Small rodents are vectors of numerous pathogens and are a reservoir for many zoonotic diseases. Rodents (mostly rats) are also responsible for an appreciable proportion of bites to humans (187). Rat bites primarily affect people (mostly children < 5 years) living in poorer conditions in rat-infested environments, including in high-income countries. Most bites occur on the face and hands and usually occur at night while sleeping. Although rare, rat bites can cause severe infections, such as rat-bite fever, caused by *Streptobacillus moniliformis* or *Spirillum minus*. Tetanus infection can also be caused by bites and it should be considered in patients who have not been immunized against the infection. In 2019, almost 15 000 cases of tetanus were reported globally (188).

Most likely pathogens

Traumatic wounds

In most cases, infections from traumatic wounds are polymicrobial with a mix of human skin microbiota and environmental organisms (Table 18.1).

Table 18.1 – Pathogens most frequently associated with traumatic skin wounds (in descending order of frequency), except bites, see Table 18.2

Most cases ^a	More rarely
<i>Streptococcus</i> spp.	Anaerobes
<i>Staphylococcus aureus</i> (including MRSA)	Enterobacteriales
	<i>Enterococcus</i> spp.
	<i>Clostridium tetani</i> (soil contaminant)

MRSA: methicillin-resistant *Staphylococcus aureus*.

^a Mostly Gram-positive pathogens from the skin microbiota.

Bite wounds

In infections from bites, causative pathogens may also be from the animal/human oral microbiota with differences among species (Table 18.2) (187).

Table 18.2 – Pathogens most frequently associated with bites

Species causing the bite	Pathogens
Human	<p>Common bacterial pathogens</p> <p>Anaerobes from the oral microbiota such as <i>Prevotella</i> and <i>Fusobacterium</i> spp. <i>Streptococcus</i> spp. <i>Staphylococcus aureus</i></p> <p>Non-bacterial pathogens</p> <p>Hepatitis B virus Hepatitis C virus HIV</p>
Cat	<p>Common bacterial pathogens</p> <p>Anaerobes such as <i>Bacteroides</i> spp., <i>Cutibacterium</i> spp., <i>Fusobacterium</i> spp., <i>Peptostreptococcus</i> spp. and <i>Prevotella</i> spp. <i>Pasteurella multocida</i> <i>Staphylococcus aureus</i></p> <p>Other bacterial pathogens</p> <p><i>Bartonella henselae</i> (agent of cat-scratch disease) <i>Francisella tularensis</i> (agent of tularaemia)</p> <p>Non-bacterial pathogens</p> <p>Rabies virus</p> <p>Soil contaminants</p> <p><i>Clostridium tetani</i> (agent of tetanus)</p>
Dog	<p>Common bacterial pathogens</p> <p>Anaerobes such as <i>Bacteroides</i> spp., <i>Cutibacterium</i> spp., <i>Fusobacterium</i> spp., <i>Peptostreptococcus</i> spp. and <i>Prevotella</i> spp. <i>Capnocytophaga canimorsus</i> <i>Pasteurella multocida</i> <i>Staphylococcus aureus</i></p> <p>Other bacterial pathogens</p> <p><i>Francisella tularensis</i> (agent of tularaemia) <i>Leptospira</i> spp. (agent of leptospirosis)</p> <p>Non-bacterial pathogens</p> <p>Rabies virus</p> <p>Soil contaminants</p> <p><i>Clostridium tetani</i> (agent of tetanus)</p>

continues

Table 18.2 *continued*

Species causing the bite	Pathogens
Monkey	<p>Bacterial pathogens</p> <p>Anaerobes such as <i>Bacteroides</i> spp., <i>Cutibacterium</i> spp., <i>Fusobacterium</i> spp., <i>Peptostreptococcus</i> spp. and <i>Prevotella</i> spp.</p> <p><i>Streptococcus</i> spp.</p> <p><i>Staphylococcus aureus</i></p> <p>Non-bacterial pathogens</p> <p>Hepatitis B virus (macaques)</p> <p>Herpes B virus</p> <p>Monkeypox virus</p> <p>Rabies virus</p> <p>Soil contaminants</p> <p><i>Clostridium tetani</i> (agent of tetanus)</p>
Rodent (e.g. mice, rats)	<p>Bacterial pathogens</p> <p><i>Francisella tularensis</i> (agent of tularaemia)</p> <p><i>Leptospira</i> spp. (agent of leptospirosis)</p> <p><i>Pasteurella multocida</i></p> <p><i>Spirillum minor</i> (agent of rat-bite fever in Asia)</p> <p><i>Streptobacillus moniliformis</i> (agent of rat-bite fever in North America)</p> <p>Non-bacterial pathogens</p> <p>Rabies virus</p> <p>Monkeypox virus</p> <p>Soil contaminants</p> <p><i>Clostridium tetani</i> (agent of tetanus)</p>
Reptile (e.g. crocodiles, lizards, snakes, turtles)	<p>Bacterial pathogens</p> <p>Anaerobes such as <i>Prevotella</i> and <i>Fusobacterium</i> spp.</p> <p>Enterobacteriales</p> <p><i>Pseudomonas aeruginosa</i></p> <p>Non-typhoidal <i>Salmonella</i> spp.</p> <p>Soil contaminants</p> <p><i>Clostridium tetani</i> (agent of tetanus)</p>

Clinical presentation (only mild cases are covered)

Wounds range in severity from minor superficial abrasions to deep wounds with involvement and destruction of the deep tissues. An infection may or may not be present at the time of clinical evaluation. Usually, signs and symptoms of infection appear > 12 hours after the injury. Superficial infections may manifest with signs and symptoms of cellulitis characterized by redness, swelling, warmth, lymphangitis and pain of the area surrounding the wound. Fever ($\geq 38.0^{\circ}\text{C}$) may be present. Patients should also be carefully monitored for signs of invasive infection, for example, change in colour of the wound due to necrosis and signs of sepsis.

Laboratory tests

Patient microbiology tests

In mild cases with no signs of systemic infection, routine testing, including wound cultures, is not required. These tests are not needed because identifying the causative pathogen in mild cases is rare even when microbiology tests are performed, most infections are polymicrobial and microbiology results will not affect management of the condition in most cases.

Other tests

Routine testing in mild cases with no signs of systemic infection is not required.

Using microbiology surveillance data

Routine surveillance is not helpful in informing empiric guidance.

Imaging

Routine imaging is not required. Imaging may be considered in certain cases based on the size and depth of the wound, particularly if a complication, such as development of an abscess or necrotizing infection, is suspected.

No antibiotic care

Initial management of wounds

It is important to provide rapid and appropriate treatment of a wound after an injury has occurred to minimize the risk of infection. For prevention and management of wound infections, please refer to the 2013 WHO guidance publication (174).

Adequate cleaning and debridement are the cornerstone of initial treatment. It is important to thoroughly wash and flush the wound for about 15 minutes with soap or detergent and a lot of clean water, followed by debridement and immobilization of the wound.

Post-exposure prophylaxis

Traumatic wounds

After any wound, the risk of tetanus needs to be promptly evaluated to provide adequate post-exposure prophylaxis by vaccination with or without passive immunization using tetanus immunoglobulin when needed according to local/international recommendations.

For tetanus post-exposure prophylaxis, please refer to the WHO tetanus vaccines position paper (178).

Bite wounds

With animal bites, in addition to the risk of tetanus, the risk of rabies needs also to be rapidly evaluated based on the exposure category to provide adequate post-exposure prophylaxis when needed (Table 18.3).

For rabies post-exposure prophylaxis, please refer to the WHO rabies vaccines position paper (179).

With human bites, the risk of hepatitis B and C virus and HIV transmission also needs to be evaluated and post-exposure prophylaxis offered when applicable (180,181).

Table 18.3 – Risk of rabies exposure according to the type of contact with the animal suspected of having rabies (179)

Category ^a	Type of contact	Risk of exposure
I	Touching or feeding animals, animal licks on intact skin	No exposure
II	Nibbling of uncovered skin, minor scratches or abrasions without bleeding	Exposure
III	Single or multiple transdermal bites or scratches, contamination of mucous membrane or broken skin with saliva from animal licks, exposures due to direct contact with bats	Severe exposure

^a The category of exposure determines the indicated post-exposure prophylaxis procedure.

Preventive antibiotic use

Routine use of antibiotics to prevent infection of the wound is not required in most cases (unless there are systemic signs of infection in which case antibiotics would be used as treatment and not as prophylaxis) and should be discouraged.

Preventive antibiotic use may be considered in very few specific cases where the potential risk of infection is judged to outweigh the risk of overusing antibiotics.

These cases include:

- Wounds in high-risk clinical areas (e.g. face, hands, areas near a joint)
- Severely immunocompromised patients.

However, there is no clear evidence that use of antibiotics can prevent infection after a wound has occurred, including bite wounds. In addition, such use exposes the patient to the negative effects of antibiotics, for example, alteration of the intestinal microbiota, and selection of resistant microorganisms.

Antibiotic treatment

If signs and symptoms of infection are present, empiric treatment should include antibiotics with good activity against the most likely pathogens, *Staphylococcus aureus* and *Streptococcus* spp. and anaerobic organisms. With animal bites, the type of animal should also be considered (see Table 18.2), but in general, empiric treatment against both aerobic and anaerobic bacteria is required, since most infections are caused by multiple pathogens (polymicrobial infections). Empiric treatment against community-acquired MRSA is usually not required. If cellulitis around the wound develops, refer to the chapter on bacterial impetigo, erysipelas and cellulitis. Antibiotic options for empiric treatment are given in Table 18.4.

Note

Only infected wounds should be treated with antibiotics.

Table 18.4 – Empiric antibiotic treatment for mild infections from traumatic wounds and bites

! Important

Where more than one antibiotic is recommended for an infection, they are listed in alphabetical order and they should be considered equal treatment options, unless otherwise indicated.

Note

Amoxicillin+clavulanic acid is the preferred treatment option for **bite wound infections** because of its activity against anaerobic bacteria.

Cloxacillin and cefalexin have a narrower spectrum of antibacterial activity compared to amoxicillin+clavulanic acid with good efficacy in **other** cases of mild skin and soft tissue infections. Therefore, from an antibiotic stewardship perspective, these would be the preferred options whenever possible, except for bite wounds.

Adults	Children	Total treatment duration
<p>Amoxicillin+clavulanic acid (oral): 500 mg + 125 mg given every 8 hours</p> <p>OR</p> <p>Cefalexin (oral): 500 mg given every 8 hours</p> <p>OR</p> <p>Cloxacillin^a (oral): 500 mg given every 6 hours</p>	<p>Amoxicillin+clavulanic acid^b (oral): 80–90 mg/kg/day of amoxicillin component</p> <p>Oral weight bands:</p> <p>3–< 6 kg: 250 mg of amoxicillin/dose given every 12 hours</p> <p>6–< 10 kg: 375 mg of amoxicillin/dose given every 12 hours</p> <p>10–< 15 kg: 500 mg of amoxicillin/dose given every 12 hours</p> <p>15–< 20 kg: 750 mg of amoxicillin/dose given every 12 hours</p> <p>≥ 20 kg: 500 mg of amoxicillin/dose given every 8 hours or 1 g of amoxicillin/dose given every 12 hours</p> <p>OR</p>	<p>3 days (preventive treatment of wounds at high risk of infection)</p> <p>5 days (treatment of infected wounds)</p>

continues

Table 18.4 *continued*

Adults	Children	Total treatment duration
	<p>Cefalexin (oral): 25 mg/kg/dose given every 12 hours</p> <p>Oral weight bands:</p> <ul style="list-style-type: none"> 3-< 6 kg: 125 mg given every 12 hours 6-< 10 kg: 250 mg given every 12 hours 10-< 15 kg: 375 mg given every 12 hours 15-< 20 kg: 500 mg given every 12 hours 20-< 30 kg: 625 mg given every 12 hours ≥ 30 kg: use adult dose <p>OR</p> <p>Cloxacillin^a (oral): 15 mg/kg/dose given every 6 hours</p> <p>Oral weight bands:</p> <ul style="list-style-type: none"> 3-< 6 kg: 62.5 mg given every 6 hours 6-< 10 kg: 125 mg given every 6 hours 10-< 15 kg: 250 mg given every 6 hours 15-< 20 kg: 375 mg given every 6 hours ≥ 20 kg: 500 mg given every 6 hours 	

Note. All dosages are for normal renal and hepatic function.

^aIf cloxacillin is unavailable, dicloxacillin or flucloxacillin could be used.

^bOral liquid formulations must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

19. Sexually transmitted infections – chlamydial urogenital infection

Note

In general this chapter applies to adults and young people older than 12 years. In children, specialist advice should be sought where possible. Consideration should be given that an STI in a child may be due to child sexual abuse.

Key messages

- *Chlamydia trachomatis* urogenital infection is a common sexually transmitted infection (STI) globally, especially among young sexually active people.
- Symptoms overlap with gonococcal infection and co-infection is frequent. Therefore, patients should be tested for both pathogens simultaneously, when available and evaluated for other STIs (e.g. human immunodeficiency virus (HIV) infection, syphilis, trichomoniasis).
- Asymptomatic people should also be treated because they can transmit the infection to others.
- Preventive services should be offered (e.g. condoms, brief sexuality education, HIV pre-exposure prophylaxis to people at high risk of HIV infection) and sexual partners should be informed and treated.
- Reporting of this infection to health authorities is encouraged according to local regulations.

Other relevant WHO resources (please check regularly for updates)

- Sexually transmitted infections (STIs) – fact sheets (189).
- WHO guidelines for the treatment of *Chlamydia trachomatis* (190).
- WHO guidelines for the management of symptomatic sexually transmitted infections (191).
- Laboratory diagnosis of sexually transmitted infections including human immunodeficiency virus (192).
- Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021 (193).

Definition

Chlamydial urogenital infection is an STI caused by certain biovars of the bacterium *Chlamydia trachomatis*.

Chlamydial urogenital infection

Sexually transmitted infection • Page 1 of 2

In general this guidance applies to adults and young people aged over 12 years. In children, specialist advice should be sought where possible. Consideration should be given that an STI in a child may be due to child sexual abuse

For Chlamydial ocular infections (Trachoma) see separate infographic

Definition

A sexually transmitted infection (STI) caused by certain strains of the bacterium *Chlamydia trachomatis*

Pathogen

Chlamydia trachomatis is an intracellular Gram-negative bacterium; strains associated with urogenital infection are mostly genital tract biovars (serovars D to K) and rarely lymphogranuloma venereum biovar (serovars L1, L2, L3)

Prevention

Important elements of prevention include:

- Sexuality education
- Promoting consistent use of condoms
- Pre- and post-test counselling
- Safe sex and risk reduction counselling
- Interventions targeting high-risk groups

Important:

- Sexual partners should be informed of the disease and treated
- Reporting of this infection to health authorities is encouraged according to local regulations

Diagnosis

Clinical Presentation

- Most persons remain asymptomatic though they can still transmit the infection
 - If symptoms occur they overlap with those of gonococcal infection (co-infection possible and common)
- Most common symptoms:**
- *In men:* acute urethritis with “clear” urethral discharge and dysuria
 - *In women:* vaginal discharge, dyspareunia (painful intercourse), and dysuria
 - *Additionally in both sexes:*
 - Symptoms of acute proctitis with pain, pruritus, anal discharge and bleeding
 - Symptoms of lymphogranuloma venereum (men>women):
 - Ulcerative lesion or a papule usually on the genitalia or rectum and inguinal or femoral lymphadenopathy (usually unilateral)
 - Often the lesion remains unnoticed in women or when located in the rectum

Imaging

Usually not needed

Microbiology Tests

- See WHO guidance “Laboratory diagnosis of sexually transmitted infections”
<https://apps.who.int/iris/handle/10665/85343>
- **Important:** all patients with suspected chlamydial urogenital infection should also be tested for gonococcal infection (as symptoms overlap) and other STIs (e.g. HIV, syphilis)

Reference standard:

- Nucleic acid amplification test (a test for both *Chlamydia* and *Neisseria gonorrhoeae* is available)
- Samples that can be used: urine (lower sensitivity and specificity in women), urethral, vulvovaginal, endocervical or anorectal samples collected with a swab
- Perform *Chlamydia* genovar testing for lymphogranuloma venereum in anorectal samples of men who have sex with men

Other tests to consider:

- Microscopy (Gram stain)
 - In a symptomatic patient, it can be used to exclude *Neisseria gonorrhoeae* (therefore suggesting non-gonococcal urethritis)
 - Leukocytes are usually present but not a specific finding for chlamydial infection
- Culture: if symptoms persist despite adequate treatment (but it is rarely performed)
- Note: urines are not good specimens for microscopy and culture

Other Laboratory Tests

Usually not needed

Chlamydial urogenital infection

Sexually transmitted infection • Page 2 of 2

Rx Treatment

Clinical Considerations

Treatment is aligned with the WHO 2016 guidelines for chlamydial urogenital infections (<https://apps.who.int/iris/handle/10665/246165>) and the WHO 2021 guidelines for the management of symptomatic sexually transmitted infections (<https://apps.who.int/iris/handle/10665/342523>) but only options listed in the 2021 EML are reported

Treatment is always indicated when infection is diagnosed, including in asymptomatic persons because they can transmit the infection to others

Antibiotic Treatment Duration

Since treatment duration varies according to the antibiotic used, please refer to the corresponding antibiotic section for treatment duration

Rx Lymphogranuloma Venereum

All dosages are for normal renal function

 Doxycycline 100 mg q12h **ORAL**
Treatment duration: 21 days

Rx Uncomplicated Urogenital Infection

All dosages are for normal renal function

 Doxycycline 100 mg q12h **ORAL**
Treatment duration: 7 days

OR

 Azithromycin 1 g **ORAL**
Treatment duration: single dose

Recent data suggest that doxycycline is more effective than azithromycin, therefore it could be given priority if adherence is not a concern (except in pregnant women where it is contraindicated)

Rx Anorectal Infection

All dosages are for normal renal function

 Doxycycline 100 mg q12h **ORAL**
Treatment duration: 7 days

Rx Infection in Pregnant Women

All dosages are for normal renal function

 Azithromycin 1 g **ORAL**
Treatment duration: single dose



Pathogen

Chlamydial urogenital infection is caused by *Chlamydia trachomatis*, an intracellular Gram-negative bacterium. There are several strains of *Chlamydia trachomatis* and not all are associated with STI (see the chapter on trachoma). Chlamydial urogenital infections associated with STI are caused mostly by genital tract biovars (serovars D to K) and, more rarely, lymphogranuloma venereum biovar (serovars L1, L2, L3). Lymphogranuloma venereum is an ulcerative disease extending to regional lymph nodes (often the inguinal and anorectal area) and is more common in men (see the paragraph on lymphogranuloma venereum later in this chapter). This disease is endemic in many tropical and sub-tropical regions; in other settings, the infection is most commonly seen among men who have sex with men.

Pathophysiology

Chlamydia trachomatis infects the mucosa of the urogenital tract during sexual contact and produces a local inflammatory response that causes vaginal, urethral or anal discharge. Invasive infections caused by more invasive serovars of *Chlamydia trachomatis* can also spread to regional lymph nodes.

Epidemiology

Chlamydial urogenital infection is one of the most common STIs worldwide, including in low-income settings where it is probably under-reported (194,195). Young sexually active adults are at particularly high risk. Undiagnosed and untreated, chlamydial urogenital infections can lead to complications such as pelvic inflammatory disease (infection of the upper female reproductive tract), ectopic pregnancy and infertility in women (196,197). Maternal infection can cause serious health problems to the child, such as preterm birth, low birth weight or conjunctivitis. The 2021 WHO global progress report on HIV, viral hepatitis and STIs reported an estimated 128 million new chlamydial infections in 2020 among adults aged 15 to 49 years (193).

Clinical presentation

Signs and symptoms of chlamydial infection mostly overlap with those of gonococcal infection. In most cases, the infection is asymptomatic, and it is therefore impossible to determine how long a person has been infected. Even in the absence of symptoms, infected individuals can transmit the infection.

When symptoms occur (usually 1–2 weeks after being infected), particularly in men, the most common clinical presentation is acute urethritis characterized by profuse usually clear urethral discharge and dysuria. Most women with chlamydial cervical infection are

asymptomatic. The ones who may be symptomatic have vaginal discharge, dyspareunia (painful intercourse) and dysuria. Some women may have lower abdominal pain or pelvic tenderness because of ascending infection, causing pelvic inflammatory disease.

In both sexes (but in males more than females), symptoms of acute proctitis with pain, pruritus, discharge and bleeding of the rectum may occur. Pharyngitis (mostly manifesting as a mild sore throat) and conjunctivitis are other conditions that usually coexist with genital infection.

Lymphogranuloma venereum is characterized by inguinal or femoral lymphadenopathy (usually unilateral) with or without an associated primary lesion. The classic lesion is a transient, ulcerative lesion or a papule usually located on the genitalia or rectum. In many cases, the lesion may remain unnoticed; for example, the infection may be completely asymptomatic in women when located on the cervix or can sometimes present with symptoms of acute urethritis in men. Rectal exposure can cause proctitis with pain, pruritus, discharge and bleeding of the rectum.

Laboratory tests

Patient microbiology tests

Molecular testing has greatly improved the detection of *Chlamydia trachomatis* (and *Neisseria gonorrhoeae*) among both symptomatic and asymptomatic men and women. Molecular testing has become the recommended reference standard technology to diagnose and screen populations for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. Table 19.1 indicates the types of specimens that can be used for this purpose.

For more comprehensive information on the diagnosis of chlamydial infection, please refer to the most recent (2013) WHO guideline for the laboratory diagnosis of STIs (192). Please check the WHO website regularly for possible updates.

Patients with chlamydial urogenital infection should be offered testing for HIV and other STIs, such as hepatitis B, hepatitis C, gonococcal infection and syphilis. Test of cure (i.e. testing after the end of treatment) could be considered in pregnant women 3–4 weeks after the end of treatment.

Tests to consider when chlamydial infection is suspected are listed in Table 19.1. Additional tests for other STIs that could be considered when chlamydial urogenital infection is confirmed or suspected are shown in Table 19.2. Surveillance, including etiologic studies of STI syndromes, will be important to inform local and national guidance.

If symptoms persist at review, partner notification and treatment history should be checked. People with recurrent or persistent infection should be referred to a centre with laboratory capacity to diagnose *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Mycoplasma genitalium* and *Trichomonas vaginalis* and to test for antibiotic-resistant *Neisseria gonorrhoeae* and *Mycoplasma genitalium*.

Table 19.1 – Microbiology tests to consider when chlamydial infection is suspected as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
<p>Qualitative test for <i>Chlamydia trachomatis</i> and <i>Neisseria gonorrhoeae</i> infections (i.e. nucleic acid amplification test)^{a,b}</p> <p>This is the recommended reference standard</p>	<p>To diagnose chlamydial and/or gonorrhoeal urogenital disease and extragenital infection</p>	<p>Health care facilities with clinical laboratories</p>
<p>Microscopy (Gram stain)^c</p> <p>Gram stain of vaginal and urethral discharge will usually show the presence of leukocytes (> 10 leukocytes/high power field for urethral discharge and > 20 leukocytes/high power field for vaginal discharge) but this finding is not specific for chlamydial infections. If carried out by an experienced person, a Gram stain negative for intracellular diplococci (<i>Neisseria gonorrhoeae</i> is an intracellular diplococcus) with the presence of > 5 leukocytes/high power field in the context of urethral discharge in a man can be presumed to suggest non-gonococcal urethritis.</p>	<p>To assess microbial morphology, and presence or absence of white blood cells</p>	<p>Health care facilities with clinical laboratories</p>
<p>Culture^{c,d} and antimicrobial susceptibility testing (rarely performed)</p>	<p>Initial step to detect and identify bacterial species for selection of appropriate antibiotic regimens</p>	<p>Health care facilities with clinical laboratories</p>

EDL: Model List of Essential In Vitro Diagnostics.

^a Usually chlamydial and gonococcal infections are tested at the same time since their clinical presentations are very similar.

^b Possible specimens among women, are a vulvovaginal specimen, which may be self-collected. An endocervical swab can also be an alternative but requires a speculum. First-catch urine is another option, but the sensitivity and specificity tend to be lower in women. Among men, possible specimens are first-catch urine or urethral swabs. Anorectal and pharyngeal samples are also adequate. For anorectal samples among men who have sex with men, *Chlamydia genovar* testing for lymphogranuloma venereum should be done to guide the appropriate treatment regimen for this condition.

^c Possible specimens are urethral swabs, endocervical swabs, vaginal swabs, rectal swabs, oropharyngeal swabs and conjunctival swabs. Note. Urine samples are not good specimens for microscopy and culture.

^d Consider culture if symptoms persist despite adequate treatment: note, urine samples are not good specimens for culture. Processing *Chlamydia trachomatis* for culture requires highly experienced laboratories and technicians and is too complex, laborious and time-consuming to be of economic value. It is rarely performed in middle- or high-income countries nowadays except for special purposes.

Table 19.2 – Additional tests for other sexually transmitted infections to consider in patients with confirmed or suspected chlamydial urogenital infection as indicated in the WHO EDL (6)

Infection	Diagnostic test	Purpose of the test	Settings where the test should be available
Gonorrhoea	<i>Neisseria gonorrhoeae</i> NAAT	To diagnose gonorrhoeal urogenital disease and extragenital infection	Health care facilities with clinical laboratories
HIV	Anti-HIV-1 and -HIV-2 antibody (RDT)	Self-testing to screen for HIV	Community settings and health facilities without laboratories ^a
HIV	Anti-HIV-1 and -HIV-2 antibody (RDT and immunoassay)	To screen for HIV infection	Community settings and health facilities without laboratories ^a (RDT) Health care facilities with clinical laboratories (immunoassay)
HIV	Combined anti-HIV-1/HIV-2 antibody and p24 antigen (RDT and immunoassay)	To screen for HIV infection	Community settings and health facilities without laboratories ^a (RDT) Health care facilities with clinical laboratories (immunoassay)
Hepatitis B	Hepatitis B virus surface antigen (RDT, immunoassay)	To screen for acute and chronic hepatitis B virus infection in people aged > 12 months	Community settings and health facilities without laboratories ^a (RDT) Health care facilities with clinical laboratories (immunoassay)

continues

Table 19.2 continued

Infection	Diagnostic test	Purpose of the test	Settings where the test should be available
Hepatitis B	IgM-specific antibodies to hepatitis B core antigen (immunoassay)	To aid in the diagnosis of acute HBV infection in the context of outbreak investigation	Health care facilities with clinical laboratories (immunoassay)
Hepatitis C	Anti-hepatitis C antibody (RDT, immunoassay)	To screen for hepatitis C virus infection in people aged > 18 months	Community settings and health facilities without laboratories ^a (RDT) Health care facilities with clinical laboratories (immunoassay)
Syphilis	Antibodies to <i>Treponema pallidum</i> ^b (RDT)	To diagnose or help to diagnose <i>Treponema pallidum</i>	Community settings and health facilities without laboratories ^a
Syphilis and HIV (combined test)	Combined antibodies to <i>Treponema pallidum</i> and to HIV-1 and HIV-2 (RDT)	To diagnose or help to diagnose HIV and/or <i>Treponema pallidum</i>	Community settings and health facilities without laboratories ^a
Trichomoniasis	Microscopy	To assess microbial morphology, and presence or absence of white blood cells	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics; HIV: human immunodeficiency virus; NAAT: nucleic acid amplification test; RDT: rapid diagnostic test.

^a Community and health settings without laboratories are facilities such as health posts and centres, doctors' offices, outreach clinics and ambulatory care. These tests are assumed to be available at health care facilities with laboratories.

^b Usually, a non-treponemal test (e.g. rapid plasma reagin, Venereal Disease Research Laboratory test) is used for screening. Please refer to the chapter on syphilis for more details on testing.

Other tests

When chlamydial urogenital infection is suspected, laboratory tests other than microbiology are not usually needed.

Using microbiology surveillance data

Targeted surveillance may be helpful to inform treatment policies.

Imaging

When chlamydial urogenital infection is suspected, imaging is not usually needed.

Antibiotic treatment

Antibiotic treatment is always indicated when the infection is diagnosed. Table 19.3 gives recommendations taken from the 2016 WHO guidelines on the treatment of chlamydial infections (190) and the 2021 WHO guidelines on the management of symptomatic STIs (191). Please check the WHO website regularly for possible updates. Recommendations in the EML overlap with the WHO guidelines (azithromycin or doxycycline are the recommended treatment options) but fewer treatment alternatives are included in the EML (8).

If symptoms persist at review:

- check partner notification and treatment history; and
- for people with recurrent or persistent urethral discharge, refer to a centre with laboratory capacity to diagnose *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Mycoplasma genitalium* and *Trichomonas vaginalis* and test for antibiotic-resistant *Neisseria gonorrhoeae* and *Mycoplasma genitalium*.

Prevention

Important elements of prevention include counselling and behavioural approaches including comprehensive sexuality education, pre- and post-test counselling, safe sex and risk reduction counselling and promoting consistent use of condoms. Interventions targeting high-risk groups (e.g. men who have sex with men, transgender people, sex workers, people who inject drugs) may be considered. Also consider offering pre-exposure prophylaxis for HIV to people at high risk of HIV infection. Sexual partners should always be informed of the infection and treated (189). Reporting of this infection to health authorities according to local regulations should also be done.

Table 19.3 – Antibiotic treatment for chlamydial urogenital infections as indicated in the most recent WHO guidelines (190,191)**Please check the WHO website regularly for possible updates**

Type of chlamydial infection	Treatment	Total treatment duration
Uncomplicated urogenital infection ^a	Doxycycline ^b (oral): 100 mg given every 12 hours OR Azithromycin (oral): 1g	7 days (doxycycline) Single dose (azithromycin)
Anorectal infection ^c	Doxycycline (oral): 100 mg given every 12 hours	7 days
Infection in pregnant women ^d	Azithromycin (oral): 1g	Single dose
Lymphogranuloma venereum ^e	Doxycycline (oral): 100 mg given every 12 hours	21 days
Ophthalmia neonatorum ^f (i.e. chlamydial conjunctivitis)	Azithromycin (oral): 20 mg/kg given once a day	3 days
Ocular prophylaxis ^g (topical treatment for the prevention of both gonococcal and chlamydial ophthalmia neonatorum)	Erythromycin (eye ointment): 0.5%	Antibiotic needs to be applied to both eyes soon after birth (single dose)

EML: Model List of Essential Medicines; EMLc: Model List of Essential Medicines for children.

Note. All dosages are for normal renal and hepatic function.

^a Alternatives indicated in the 2021 WHO guidelines but not included in the WHO EML for this indication are: erythromycin (oral): 500 mg every 6 hours; ofloxacin (oral): 200–400 mg every 12 hours. The recommended duration of treatment is 7 days for both options.

^b According to recent data, doxycycline is more effective than azithromycin and could be given priority if adherence to treatment is not a concern (198–200). The 2021 WHO guidelines for the management of symptomatic sexually transmitted infections recommend doxycycline as the first-line option and azithromycin as an effective substitute (191). Therefore, exceptionally in this case, alternative antibiotic options are not presented in alphabetical order and doxycycline is mentioned first in the Table.

^c Alternatives indicated in the 2021 WHO guidelines but not included in the EML for this indication are: erythromycin (oral): 500 mg every 6 hours. The recommended duration of treatment is 14 days.

^d Alternatives indicated in the 2021 WHO guidelines but not included in the EML for this indication are: erythromycin (oral): 500 mg every 6 hours. The recommended duration of treatment is 7 days.

continues

Table 19.3 *continued*

^e Alternatives indicated in the 2021 WHO guidelines but not included in the EML for this indication are: erythromycin (oral): 500 mg every 6 hours. The recommended duration of treatment is 21 days.

^f Alternatives indicated in the 2016 WHO guidelines but not included in the EMLc for this indication are: erythromycin (oral): 50 mg/kg per day divided in 4 doses for 14 days.

^g Alternatives indicated in the 2016 WHO guidelines but not included the EMLc for this indication are: tetracycline hydrochloride (eye ointment) 1%; povidone–iodine (water-based solution. Do not use alcohol-based solutions) 2.5%; silver nitrate (solution) 1%; chloramphenicol (eye ointment) 1%.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

20. Sexually transmitted infections – gonococcal infection

Note

In general this chapter applies to adults and young people older than 12 years. In children, specialist advice should be sought where possible. Consideration should be given that an STI in a child may be due to child sexual abuse.

Key messages

- *Neisseria gonorrhoeae* is a common curable sexually transmitted infection (STI) and resistance to antibiotics (including extensively resistant strains) is an increasing public health problem.
- Symptoms overlap with urogenital *Chlamydia trachomatis* infection and co-infection is frequent. Therefore, patients should be tested for both pathogens simultaneously, when available, and evaluated for other STIs (human immunodeficiency virus (HIV) infection, syphilis, trichomoniasis).
- Asymptomatic people should also be treated because they can transmit the infection to others.
- Preventive services should be offered (e.g. condoms, brief sexuality education, HIV pre-exposure prophylaxis for people at high risk of HIV infection) and sexual partners should be informed and treated.
- Reporting of this infection to health authorities is encouraged according to local regulations.

Other relevant WHO resources (please check regularly for updates)

- Sexually transmitted infections (STIs) – fact sheets (189).
- Global action plan to control the spread and impact of antimicrobial resistance in *Neisseria gonorrhoeae* (201).
- WHO guidelines for the treatment of *Neisseria gonorrhoeae* (89).
- WHO guidelines for the management of symptomatic sexually transmitted infections (191).
- Laboratory diagnosis of sexually transmitted infections including human immunodeficiency virus (192).
- Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021 (193).
- Global Antimicrobial Resistance and Use Surveillance System (GLASS) Report: 2021 (202).

Gonococcal infection

Sexually transmitted infection • Page 1 of 3

In general this guidance applies to adults and young people aged over 12 years. In children, specialist advice should be sought where possible. Consideration should be given that an STI in a child may be due to child sexual abuse



Definition

A sexually transmitted infection (STI) caused by the bacterium *Neisseria gonorrhoeae*



Pathogen

- *Neisseria gonorrhoeae* is a Gram-negative bacterium that can easily develop resistance to antibiotics leading to infections that are difficult to treat, which is an increasing public health problem worldwide
- Data on *Neisseria gonorrhoeae* resistance is available through GLASS (The WHO Global Antimicrobial Resistance Surveillance System) and GASP (The WHO Gonococcal AMR surveillance program)
<https://www.who.int/data/gho/data/themes/topics/who-gonococcal-amr-surveillance-programme-who-gasp>



Diagnosis



Clinical Presentation

- Some persons remain asymptomatic (women>men) though they can still transmit the infection
- If symptoms occur they overlap with those of chlamydial infection (co-infection possible and common)

Most common symptoms (usually occur a few days after infection):

- In men: acute urethritis with profuse mucopurulent urethral discharge and dysuria +/- testicular discomfort
- In women: mucopurulent vaginal discharge and dysuria +/- vaginitis with vaginal pain and inflammation and lower abdominal pain. Cervical discharge, cervical ectopy and friability and easy bleeding on contact may also occur
- Additionally in both sexes:
 - Symptoms of acute proctitis with pain, pruritus, anal discharge and bleeding
 - Pharyngitis and conjunctivitis are other possible presentations
 - Rarely infection can disseminate, typically leading to localized infection in one or more joints
- In pregnant women:
 - Infection can transmit to the child during vaginal delivery
- In newborns:
 - Acute ocular infection and pharyngitis can occur a few days after birth
 - Disseminated infection with septic arthritis (usually in multiple joints) may also occur



Microbiology Tests

- See WHO guidance "Laboratory diagnosis of sexually transmitted infections"
<https://apps.who.int/iris/handle/10665/85343>
- Important: all patients with suspected gonococcal infection should also be tested for chlamydial urogenital infection (as symptoms overlap) and other STIs (e.g. HIV, syphilis)

Reference standard:

- Nucleic acid amplification test (a test for both *N. gonorrhoeae* and *Chlamydia* is available)
- Samples that can be used: urine (lower sensitivity and specificity in women), urethral, vulvovaginal, endocervical or anorectal samples collected with a swab

Other tests to consider:

- Culture + antimicrobial susceptibility testing: If symptoms persist despite adequate treatment and for surveillance of *Neisseria gonorrhoeae* resistance
- Microscopy (Gram stain)
 - Samples that can be used: urethral, endocervical, conjunctival samples collected with a swab
- Blood cultures: If disseminated infection is suspected



Other Laboratory Tests

Usually not needed



Imaging

Usually not needed

Gonococcal infection

Sexually transmitted infection • Page 2 of 3

Prevention

Important elements of prevention include:

- Sexuality education
- Promoting consistent use of condoms
- Pre- and post-test counselling
- Safe sex and risk reduction counselling
- Interventions targeting high-risk groups

Important:

- Sexual partners should be informed of the disease and treated
- Reporting of this infection to health authorities is encouraged according to local regulations

Rx Treatment (Section 1 of 2)



Treatment Recommendations

- Treatment is aligned with the WHO 2016 guidelines for the treatment of gonococcal infection (<https://apps.who.int/iris/handle/10665/246114>) and the WHO 2021 guidelines for the management of symptomatic sexually transmitted infections (<https://apps.who.int/iris/handle/10665/34252>) but only options listed in the 2021 EML are reported
- WHO is in the process of revising current treatment recommendations and dosages, please check the WHO website regularly for possible updates



Clinical Considerations

- Treatment is always indicated when infection is diagnosed, including in asymptomatic patients because they can transmit the infection to others
- Local resistance data should determine the most appropriate therapy and if data not available, dual therapy is preferred
- If symptoms do not resolve in approximately 5 days, resistant infection or alternative diagnosis should be suspected



Antibiotic Treatment Duration

Single Dose



Genital and Anorectal Infections

All dosages are for normal renal function

Dual Therapy

First Choice



Ceftriaxone 250 mg IM
WATCH

----- COMBINED WITH -----



Azithromycin 1 g ORAL
WATCH

Second Choice



Cefixime 400 mg ORAL
WATCH

----- COMBINED WITH -----



Azithromycin 1 g ORAL
WATCH

Single Therapy

Only use single therapy if local resistance data confirm susceptibility to the antibiotic

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated



Cefixime 400 mg ORAL
WATCH

OR



Ceftriaxone 250 mg IM
WATCH

A single dose of 500 mg or 1 g ceftriaxone IM is recommended in some international guidelines

OR



Spectinomycin 2 g IM
ACCESS

Gonococcal infection

Sexually transmitted infection • Page 3 of 3

Rx Treatment (Section 2 of 2)

Antibiotic Treatment Duration

Single Dose

Rx Retreatment after Treatment Failure

Consider treatment failure if symptoms persist after 5 days of adequate treatment

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

 Cefixime 800 mg ORAL

OR-----

 Ceftriaxone 500 mg IM

OR-----

 Gentamicin 240 mg IM

OR-----

 Spectinomycin 2 g IM

Do not use for spectinomycin for oropharyngeal infections

COMBINED WITH-----

 Azithromycin 2 g ORAL

Oropharyngeal Infections

All dosages are for normal renal function

Dual Therapy

First Choice

 Ceftriaxone 250 mg IM

COMBINED WITH-----

 Azithromycin 1 g ORAL

Second Choice

 Cefixime 400 mg ORAL

COMBINED WITH-----

 Azithromycin 1 g ORAL

Single Therapy

Only use single therapy if local resistance data confirm susceptibility to the antibiotic

 Ceftriaxone 250 mg IM

A single dose of 500 mg or 1 g ceftriaxone IM is recommended in some international guidelines



Definition

Gonococcal infection is an STI caused by the bacterium *Neisseria gonorrhoeae*.

Pathogen

Neisseria gonorrhoeae, the organism causing gonorrhoea, is a Gram-negative bacterium.

The bacterium easily develops resistance to antibiotics, which has led to infections that are difficult to treat. As a result, resistance to antibiotics used for treatment (including third-generation cephalosporins) is a serious problem worldwide. Therefore, in 2012, WHO launched a global action plan to control the spread and impact of resistance in *Neisseria gonorrhoeae* (201).

Data on *Neisseria gonorrhoeae* resistance are collected through the WHO Global Antimicrobial Resistance Surveillance System (GLASS) and the WHO Global Gonococcal Antimicrobial Surveillance Programme (GASP network) and are regularly published (202–205).

Pathophysiology

Neisseria gonorrhoeae usually enters the mucosa (mostly of the genital tract) during sexual contact. Because of its many virulence factors, this bacterium can adapt to the local environment, evade immune response mechanisms and proliferate causing local inflammatory response and disease and, more rarely, systemic infection (i.e. gonococcal bacteraemia). If left untreated, or if it is inappropriately treated, complications may occur. In particular in women, pelvic inflammatory disease (i.e. an infection of the upper female reproductive tract) with inflammation of the uterine tubes (i.e. salpingitis), endometrium (i.e. endometritis) or abscess formation in the ovary/ovaries and tubes can occur. In men, complications include epididymitis and periurethritis with abscess formation. These complications can lead to infertility.

Disseminated gonococcal infection can occur as a result of bacteraemia secondary to mucosal infection (mostly of the genital tract) and can lead to arthritis, skin manifestations and other complications.

Infants of mothers with gonococcal infection can be infected at delivery, resulting in neonatal conjunctivitis which manifests as purulent ocular discharge and swollen eyelids. Untreated conjunctivitis may lead to scarring and blindness.

Epidemiology

Gonococcal infection is one of the most common STIs worldwide.

The 2021 WHO global progress report on HIV, viral hepatitis and STIs reported an estimated 82 million new gonococcal infections in 2020 among adults aged 15 to 49 years (193).

The highest incidence of gonococcal infection is in the Africa and Western Pacific regions; this includes China and Australia among others (206). Gonococcal infection increases the risk of HIV infection two- or three-fold.

Risk factors for gonococcal infection include HIV infection, young age, having multiple sexual partners or a new sexual partner, having partners with STIs, having had previous gonococcal infection and/or other STIs and several socioeconomic factors, such as low socioeconomic or educational level or substance abuse. Infection does not induce protective immunity therefore reinfection is possible. Resistance of *Neisseria gonorrhoeae* to antibiotics used to treat the infection is a concern; see the pathogen section for more information about resistance (204).

Clinical presentation

Signs and symptoms of gonococcal infection vary in men and women and overlap with those of chlamydial infection. Some people with gonococcal infection may be asymptomatic even though they can still transmit the infection. When symptoms occur (usually a few days after being infected), the most common clinical presentation in men is acute urethritis characterized by profuse mucopurulent urethral discharge and dysuria; testicular discomfort can also be present. In women, mucopurulent vaginal discharge and dysuria are the most common symptoms. Several women may have lower abdominal pain because of ascending infection causing pelvic inflammatory disease. Gonorrhoea causes cervical infection that presents with cervical discharge, cervical ectopy and friability and easy bleeding on contact.

In both sexes (but in males more than females), symptoms of acute proctitis with pain, pruritus, discharge and bleeding of the rectum may occur. Pharyngitis (mostly manifesting as a mild sore throat) and conjunctivitis are other conditions that usually coexist with genital infection.

Rarely, the infection can disseminate (i.e. gonococcal bacteraemia) and this can typically lead to localized infection in one or more joints (i.e. gonococcal arthritis). Please refer to the chapter on septic arthritis for more information on this topic.

In pregnant women, the infection can be transmitted to the child during vaginal delivery. In newborns, gonococcal infection can present with acute ocular infection (i.e. conjunctivitis) or pharyngitis which manifest a few days after birth. Disseminated infection with septic arthritis (usually with multiple joints involved) can also occur in newborns.

Laboratory tests

Patient microbiology tests

Molecular testing has greatly improved the detection of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* among both symptomatic and asymptomatic men and women. Molecular testing has become the recommended gold standard technology to diagnose

and screen populations for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. Table 20.1 indicates the types of specimens that can be used for this purpose.

Culture of *Neisseria gonorrhoeae* is still the standard method for performing antibiotic susceptibility testing. However, this organism is not easy to grow in the laboratory and requires special training and a special culture medium. For this reason, culture of *Neisseria gonorrhoeae* is not routinely performed as part of managing people with gonococcal infection in resource-limited settings.

Neisseria gonorrhoeae can also be identified by light microscopy of Gram-stained samples and a presumptive diagnosis can be made if intracellular Gram-negative diplococci are observed in polymorphonuclear leukocytes, best seen when there is a urethral discharge. Gram-stained smears from the cervix are also considered positive for the presumptive diagnosis of gonorrhoea in women if intracellular Gram-negative diplococci are observed in polymorphonuclear leukocytes. Gram stain of urethral samples among women has low yield and may not be cost-effective.

For more comprehensive information on the diagnosis of gonococcal infection, please refer to the most recent (2013) WHO guideline for the laboratory diagnosis of STIs (192). Please check the WHO website regularly for possible updates. Patients with gonococcal infection are also usually evaluated for other STIs, such as chlamydial infection, hepatitis B, hepatitis C, HIV infection and syphilis.

Tests to consider when gonococcal infection is suspected are listed in Table 20.1. Additional tests for other STIs that could be considered when gonococcal infection is confirmed or suspected are shown in Table 20.2.

Table 20.1 – Microbiology tests to consider when gonococcal infection is suspected as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
This is the recommended reference standard Qualitative test for <i>Neisseria gonorrhoeae</i> and <i>Chlamydia trachomatis</i> infections (i.e. nucleic acid amplification test) ^{a,b}	To diagnose gonorrhoeal and/or chlamydial urogenital disease and extragenital infection	Health care facilities with clinical laboratories
Microscopy (Gram stain) ^c	To assess microbial morphology, and presence or absence of white blood cells	Health care facilities with clinical laboratories

continues

■ PRIMARY HEALTH CARE

20. Sexually transmitted infections – gonococcal infection

Table 20.1 *continued*

Diagnostic test	Purpose of the test	Settings where the test should be available
Culture ^d and antimicrobial susceptibility testing Consider if symptoms persist despite adequate treatment and for surveillance purposes.	Initial step to detect and identify bacterial species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories
Blood cultures Consider if disseminated infection is suspected.	To detect bacterial bloodstream infections (sepsis)	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics.

^a Usually gonococcal and chlamydial infections are tested at the same time since their clinical presentations are very similar.

^b Possible specimens among women include a vulvovaginal specimen, which may be self-collected. An endocervical swab can be an alternative but requires a speculum. First-catch urine is another option, but the sensitivity and specificity tend to be lower in women. Among men, first-catch urine or urethral swabs are appropriate. Anorectal and pharyngeal samples are also adequate. Nucleic acid amplification tests also perform well for pharyngeal and anorectal samples.

^c Possible specimens are: urethral swabs, endocervical swabs and conjunctival swabs. Note. Urine samples are not good specimens for microscopy.

^d Possible specimens are: urethral swabs, endocervical swabs, vaginal swabs, rectal swabs, oropharyngeal swabs and conjunctival swabs. Note. Urine samples are not good specimens for culture. Culture is the standard method for performing antibiotic susceptibility testing.

Table 20.2 – Additional tests for other sexually transmitted infections to consider in patients with confirmed or suspected gonococcal infection as indicated in the WHO EDL (6)

Infection	Diagnostic test	Purpose of the test	Settings where the test should be available
Chlamydial urogenital infection	<i>Chlamydia trachomatis</i> NAAT	To diagnose chlamydial urogenital disease and extragenital infection	Health care facilities with clinical laboratories
HIV	Anti-HIV-1 and -HIV-2 antibody (RDT)	Self-testing to screen for HIV	Community settings and health facilities without laboratories ^a

continues

Table 20.2 *continued*

Infection	Diagnostic test	Purpose of the test	Settings where the test should be available
HIV	Anti-HIV-1 and -HIV-2 antibody (RDT and immunoassay)	To screen for HIV infection	Community settings and health facilities without laboratories ^a (RDT) Health care facilities with clinical laboratories (immunoassay)
HIV	Combined anti-HIV-1/HIV-2 antibody and p24 antigen (RDT and immunoassay)	To screen for HIV infection	Community settings and health facilities without laboratories ^a (RDT) Health care facilities with clinical laboratories (immunoassay)
Hepatitis B	Hepatitis B virus surface antigen (RDT, immunoassay)	To screen for acute and chronic hepatitis B virus infection in people aged > 12 months	Community settings and health facilities without laboratories ^a (RDT) Health care facilities with clinical laboratories (immunoassay)
Hepatitis B	IgM-specific antibodies to hepatitis B core antigen (immunoassay)	To aid in the diagnosis of acute HBV infection in the context of outbreak investigation	Health care facilities with clinical laboratories
Hepatitis C	Anti-hepatitis C antibody (RDT, immunoassay)	To screen for hepatitis C virus infection in people aged > 18 months	Community settings and health facilities without laboratories ^a (RDT) Health care facilities with clinical laboratories (immunoassay)

continues

Table 20.2 *continued*

Infection	Diagnostic test	Purpose of the test	Settings where the test should be available
Syphilis	Antibodies to <i>Treponema pallidum</i> ^b (RDT)	To diagnose or help to diagnose <i>Treponema pallidum</i>	Community settings and health facilities without laboratories ^a
Syphilis and HIV (combined test)	Combined antibodies to <i>Treponema pallidum</i> and to HIV-1 and HIV-2 (RDT)	To diagnose or help to diagnose HIV and/or <i>Treponema pallidum</i>	Community settings and health facilities without laboratories ^a
Trichomoniasis	Microscopy	To assess microbial morphology, and presence or absence of white blood cells	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics; HIV: human immunodeficiency virus; NAAT: nucleic acid amplification test; RDT: rapid diagnostic test.

^a Community and health settings without laboratories are defined as community and health facilities such as health posts and centres, doctors' offices, outreach clinics and ambulatory care. These tests are also assumed to be available at health care facilities with laboratories.

^b Usually a non-treponemal test (e.g. rapid plasma reagent, Venereal Disease Research Laboratory test) is used for screening. Please refer to the chapter on syphilis for more details on testing.

Other tests

When gonococcal infection is suspected, laboratory tests other than microbiology are not usually needed. However, microscopy of vaginal or urethral secretions will usually show the presence of leukocytes (> 10 leukocytes/field).

Using microbiology surveillance data

Monitoring antibiotic resistance in *Neisseria gonorrhoeae* is recommended to inform local, national and global guidance.

Imaging

When gonococcal infection is suspected, imaging is not usually needed.

Antibiotic treatment

The recommendations on antibiotic treatment reported here are based on the most recent WHO guidelines for the treatment of gonorrhoea and on the management of symptomatic STIs (89,191). Because of increasing antibiotic resistance to azithromycin in *Neisseria gonorrhoeae* and *Mycoplasma genitalium* and reduced susceptibility of *Neisseria gonorrhoeae* to cephalosporins, **WHO is currently revising treatment recommendations and dosages (please check the WHO website regularly for possible updates)**.

All people (including pregnant women) diagnosed with gonorrhoea should receive adequate antibiotic treatment. Antibiotic treatment options are shown in Table 20.3.

When choosing treatment, local resistance data should determine the choice of the most appropriate therapy. If data are not available, dual therapy (i.e. two antibiotics) should be given. If symptoms do not resolve within about 5 days of adequate antibiotic treatment, a resistant infection should be suspected, or an alternative diagnosis sought.

Table 20.3 – Antibiotic treatment for gonococcal infection as indicated in the 2016 WHO guidelines for the treatment of gonorrhoea (89)

Type of gonococcal infection	Treatment	Total treatment duration
Genital and anorectal infections (dual therapy^a)	First choice Ceftriaxone (IM): 250 mg AND Azithromycin (oral): 1 g Second choice Cefixime (oral): 400 mg AND Azithromycin (oral): 1 g	Single dose
Genital and anorectal infections (single therapy), if local resistance data confirm susceptibility to the antibiotic	Cefixime (oral): 400 mg OR Ceftriaxone (IM): 250 mg ^b OR Spectinomycin (IM): 2 g	Single dose

continues

Table 20.3 *continued*

Type of gonococcal infection	Treatment	Total treatment duration
Oropharyngeal infections ^c (dual therapy^a)	First choice Ceftriaxone (IM): 250 mg AND Azithromycin (oral): 1 g Second choice Cefixime (oral): 400 mg AND Azithromycin (oral): 1 g	Single dose
Oropharyngeal infections ^c (single therapy), if local resistance data confirm susceptibility to the antibiotic	Ceftriaxone (IM): 250 mg ^b	Single dose
Gonococcal ophthalmia neonatorum (i.e. gonococcal conjunctivitis)	Ceftriaxone ^d (IM): 50mg/kg	Single dose
Ocular prophylaxis ^e (topical treatment for the prevention of both chlamydial and gonococcal ophthalmia neonatorum)	Erythromycin (eye ointment): 0.5%	Antibiotic needs to be applied to both eyes soon after birth (single dose)
Retreatment after treatment failure Consider treatment failure if symptoms persist after 5 days of adequate treatment	Cefixime (oral): 800 mg AND Azithromycin (oral): 2 g OR Ceftriaxone (IM): 500 mg AND Azithromycin (oral): 2 g OR Gentamicin (IM): 240 mg AND Azithromycin (oral): 2 g OR Spectinomycin ^c (IM): 2 g AND Azithromycin (oral): 2 g	Single dose

IM: intramuscular.

Note. All dosages are for normal renal and hepatic function.

^a Dual therapy should be given if no reliable local data on resistance are available.

continues

**Table 20.3** *continued*

- ^b A single dose of 500 mg or 1 g of ceftriaxone (IM) is recommended in some international guidelines (207–209).
- ^c Do not use spectinomycin to treat cases of oropharyngeal infection.
- ^d Ceftriaxone should not be administered in neonates receiving calcium-containing intravenous fluids and it should be avoided in infants with hyperbilirubinaemia. Cefotaxime can be used as an alternative. Alternatives to ceftriaxone indicated in the 2016 WHO guidelines include kanamycin (IM) 25mg/kg or spectinomycin (IM) 25mg/kg (89).
- ^e Alternatives indicated in the 2016 WHO guidelines include tetracycline hydrochloride (eye ointment) 1%; povidone–iodine (water-based solution. Do not use alcohol-based solutions) 2.5%; silver nitrate (solution) 1%; chloramphenicol (eye ointment) 1%.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Prevention

No effective vaccine against *Neisseria gonorrhoeae* is available. Prevention is therefore one of the key elements included in the 2012 WHO global action plan to control the spread and impact of AMR in *Neisseria gonorrhoeae* (201).

Important elements of prevention include counselling and behavioural approaches including comprehensive sexuality education, pre- and post-test counselling, safe sex and risk reduction counselling and promoting consistent use of condoms. Interventions targeting high-risk groups (e.g. men who have sex with men, transgender people, sex workers, people who inject drugs) and offering HIV pre-exposure prophylaxis to people at high risk of HIV infection may be considered. Sexual partners should always be informed of the infection and treated. Reporting of this infection to health authorities according to local regulations should also be done.

21. Sexually transmitted infections – syphilis

Note

In general this chapter applies to adults and young people older than 12 years. In children, specialist advice should be sought where possible. Consideration should be given that an STI in a child may be due to child sexual abuse.

Key messages

- Syphilis has several stages of infection with different clinical presentations and remains common worldwide.
- All pregnant women should be screened for syphilis and treated if infected to prevent congenital syphilis in the child.
- Asymptomatic people should also be treated because they can transmit the infection to others, and all people with syphilis should also be evaluated for other sexually transmitted infections.
- Preventive services should be offered (e.g. condoms, brief sexuality education, HIV pre-exposure prophylaxis to people at high risk for HIV infection) and sexual partners should be informed and treated.
- Reporting of this infection to health authorities is encouraged according to local regulations.

Other relevant WHO resources (please check regularly for updates)

- Sexually transmitted infections (STIs) – fact sheets (189).
- Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021 (193).
- WHO guidelines for the treatment of *Treponema pallidum* (syphilis) (210).
- WHO guidelines for the management of symptomatic sexually transmitted infections (191).
- Laboratory diagnosis of sexually transmitted infections including human immunodeficiency virus (192).
- WHO guideline on syphilis screening and treatment for pregnant women (211).

Definition

Syphilis is an STI caused by the bacterium *Treponema pallidum* subspecies *pallidum*. Syphilis is one of other treponematoses, that is, diseases caused by spirochaetes of the species *Treponema pallidum*. Other *Treponema pallidum* subspecies causing human diseases include subspecies *pertenue*, the causative pathogen of yaws (212), subspecies *endemicum*, the causative pathogen of endemic syphilis or bejel, and subspecies *carateum*, the causative pathogen of pinta (213). This chapter will only address disease caused by *Treponema pallidum* subspecies *pallidum* (syphilis). Information about other treponematoses is available on the WHO website (212).

Syphilis can be classified as early or late based on the time since becoming infected. Usually infections of ≤ 2 years duration are defined as early and infections of > 2 years are defined as late. Furthermore, infections can be classified as primary, secondary or tertiary based on the clinical presentation (210). There is usually a long latent phase with no clinical manifestations between secondary and tertiary infection; the tertiary phase only develops in untreated or inadequately treated infections. Overlap between these definitions exists, with early infection including primary and secondary syphilis and late infection including the latent phase and tertiary syphilis.

The latent phase can also be divided into two phases – early latent and late latent. Early latent syphilis is usually defined as infection of < 2 years, whereas late latent syphilis is defined as the presence of the disease of ≥ 2 years (210). However, this distinction is difficult to apply because it is often impossible to establish the time of the initial infection.

Syphilis

Sexually transmitted infection • Page 1 of 2

In general this guidance applies to adults and young people aged over 12 years. In children, specialist advice should be sought where possible. Consideration should be given that an STI in a child may be due to child sexual abuse



Pathogen

Treponema pallidum subspecies *pallidum* is a bacterium of the phylum Spirochaetes

- Slow growing, difficult to culture *in vitro*, thin



Definition

- A sexually transmitted infection (STI) caused by the bacterium *Treponema pallidum* subspecies *pallidum*
- The infection can be transmitted from the mother to her fetus because the pathogen can cross the placenta

Classification based on:

- Timing since acquisition
 - *Early*: ≤2 years (includes primary and secondary infections and the early latent phase)
 - *Late*: >2 years (includes the late latent phase and tertiary infections)
- Clinical presentation (see below)



Diagnosis



Clinical Presentation

Early syphilis:

- *Primary infection*: Often asymptomatic, localized non painful ulcerative lesion with indurated margins (usually on genitalia, mouth or rectum) +/- local lymphadenopathy
- *Secondary infection*:
 - Skin and mucosal manifestations over trunk and extremities including palms of hands and soles of feet
 - Rash is commonly maculopapular and non-irritant
 - Mucous membranes of mouth/perineum can show lesions
 - Fever (≥ 38.0 °C), generalized lymphadenopathy and malaise usually present
 - Meningitis, hepatitis and ocular involvement can occur

Late syphilis:

- *Tertiary infection*: Can affect different organ systems
 - Cardiovascular system: usually aortitis
 - Skin/soft tissues/bones: nodular lesions (gummata)
 - Central nervous system: often progressive dementia, psychiatric symptoms, problems with coordination of movements



Microbiology Tests

• See WHO guidance "Laboratory diagnosis of sexually transmitted infections"
<https://apps.who.int/iris/handle/10665/85343>

- **Important**: all patients with suspected syphilis should also be tested for other STIs (e.g. HIV, gonococcal infection)

Direct detection methods:

- Can detect the pathogen in specimens from skin or tissue lesions

Serological tests:

- **Treponemal tests**: detect antibodies to treponemal antigens; they usually remain positive after infection even with successful treatment
 - Type of tests: **FTA-ABS, TPPA, TPHA**
- **Nontreponemal tests**: detect antibodies that react to lipids released in response to cellular damage caused by infection; usually become negative with successful treatment
 - Type of tests: **VDRL, RPR**
- All tests are negative initially in primary infection
- **Both treponemal and non-treponemal tests need to be positive to confirm the diagnosis**
- To increase access and same-day treatment, a rapid treponemal test followed (if positive) by a nontreponemal test is recommended; but starting with a non-treponemal test and confirming positive results with a treponemal test is also appropriate



Other Laboratory Tests

Primary syphilis: Usually not needed

Secondary or tertiary syphilis: May be required depending on the clinical presentation



Imaging

Usually not needed unless a complication of late syphilis is suspected

Syphilis

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Prevention

Important elements of prevention include:

- Sexuality education
- Promoting consistent use of condoms
- Pre- and post-test counselling
- Safe sex and risk reduction counselling
- Interventions targeting high risk groups
- Access of pregnant women to early and adequate prenatal care to prevent congenital syphilis

Important:

- Sexual partners should be informed of the disease and treated
- Reporting of this infection to health authorities is encouraged according to local regulations

Treatment

Clinical Considerations

Treatment is aligned with the WHO 2016 guidelines for the treatment of *Treponema pallidum* (<https://apps.who.int/iris/handle/10665/249572>) and the WHO 2021 guidelines for the management of symptomatic sexually transmitted infections (<https://apps.who.int/iris/handle/10665/342523>) but only options listed in the 2021 EML are reported below

- Treatment is always indicated when infection is diagnosed, including in asymptomatic patients because they can transmit the infection to others
- In early syphilis (primary/secondary), partners should also be treated if exposed within 90 days
- Assess serological response by repeating non-treponemal test to detect a reduction in titer; a 4-fold reduction in titers confirms adequate response (repeat 3, 6 and 12 months after the end of treatment)



Antibiotic Treatment Duration

Since treatment duration varies according to the antibiotic used and the stage of the infection, please refer to the corresponding antibiotic section for treatment duration

Neurosyphilis

All dosages are for normal renal function

 Benzylpenicillin 2.4 million IU (1.2-2.4 g) q4h **IV**
Treatment duration: 14 days

OR -----

 Procaine benzylpenicillin 1.2 million IU (1.2 g) q24h **IM**
Treatment duration: 14 days

----- COMBINED WITH -----

 Probencid 500 mg q6h **ORAL**
Treatment duration: 14 days

Early Syphilis

All dosages are for normal renal function

First Choice

 Benzathine benzylpenicillin 2.4 million IU (≈ 1.8 g) **IM**
Treatment duration: single dose

Second Choice

 Procaine benzylpenicillin 1.2 million IU (1.2 g) q24h **IM**
Treatment duration: 10-14 days

Syphilis in Pregnancy

All dosages are for normal renal function

 Benzathine benzylpenicillin 2.4 million IU (≈ 1.8 g) **IM**

Treatment duration:

- Early Syphilis: Single dose
- Late or Unknown Stage Syphilis: One dose per week for 3 consecutive weeks (total of 3 administrations, the interval between doses should not exceed 14 days)

Late or Unknown Stage Syphilis

All dosages are for normal renal function

First Choice

 Benzathine benzylpenicillin 2.4 million IU (≈ 1.8 g) **IM**
Treatment duration: One dose per week for 3 consecutive weeks (total of 3 administrations, the interval between doses should not exceed 14 days)

Second Choice

 Procaine benzylpenicillin 1.2 million IU (1.2 g) q24h **IM**
Treatment duration: 20 days

Pathogen

Syphilis is caused by *Treponema pallidum* subspecies *pallidum*, a bacterium of the phylum Spirochaetes; other members of this phylum include *Leptospira* and *Borrelia*.

Treponema pallidum is characterized by slow growth, difficulty in culturing in vitro, and its thinness – 0.2 µm compared to about 0.5 µm for a bacterium like *Escherichia coli* – which makes it difficult to see with conventional microscopy.

Resistance to penicillin has not yet been reported and therefore it remains the antibiotic of choice for the treatment of syphilis. Resistance to azithromycin has been reported in some settings (214).

Pathophysiology

Syphilis is usually acquired through sexual contact with infectious lesions on the mucosa or skin or, much more rarely, through the bloodstream. The infection can also be transmitted from the mother to her fetus because *Treponema pallidum* subspecies *pallidum* can cross the placenta and cause fetal death and congenital infection.

With sexual transmission, once *Treponema pallidum* subspecies *pallidum* enters the subcutaneous tissue, infection develops within 2–6 weeks (usually about 3 weeks) with formation of an ulcerative lesion that occurs at the site of inoculation. Usually, the immune system is able to control the early infection and, even if left untreated, the primary ulcerative lesion (i.e. chancre) resolves. However, dissemination of *Treponema pallidum* through the bloodstream can occur at the time of primary infection and this can result over time in secondary or tertiary syphilis in the absence of adequate treatment. In particular, tertiary syphilis has a long incubation period (up to years or decades after the initial infection) and develops in about a third of patients with untreated syphilis. In 2017, 370 000 prevalent cases of tertiary syphilis were reported worldwide but this number is probably an underestimation of the true burden of the disease (44).

Congenital syphilis can occur as a result of vertical transmission of the pathogen from an infected mother to the fetus. The risk of transmission depends on a combination of factors, including maternal titres of non-treponemal tests (see Table 21.1 for an explanation about tests), timing, adequacy of maternal treatment and stage of maternal infection. The estimated total number of cases of congenital syphilis worldwide in 2016 was 661 000, or 473 per 100 000 live births (215).

Epidemiology

Syphilis is a common curable STI and its incidence is increasing globally. WHO estimates there were 7 million new cases in 2020 (193). Other bacterial STIs occur more frequently, for

example, in 2020 more than 82 million new cases of gonorrhoea and about 128 million new cases of chlamydial infection were reported (193). However, syphilis has an important public health impact because of the potential serious consequences if left untreated, including maternal transmission to the fetus resulting in congenital syphilis and fetal death, and complications such as neurosyphilis and cardiovascular syphilis.

Moreover, as with other STIs, syphilis affects quality of life and increases the risk of transmitting or acquiring other STIs including HIV infection. This HIV risk is of particular concern because STIs characterized by the presence of ulcerative lesions have the highest risk of HIV transmission (216).

The risk factors for syphilis include: having multiple sexual partners or a new sexual partner; having partners with STIs; having had a previous STI; and several socioeconomic factors, such as low socioeconomic or educational level, substance abuse and young age (217,218). Lack of access to adequate prenatal care is an important risk factor for congenital syphilis.

Clinical presentation

Signs and symptoms of syphilis vary depending on the stage of the disease, early or late.

Early syphilis has the following signs and symptoms.

- Primary infection (localized disease). This is characterized by the presence of a localized non-painful ulcerative lesion (i.e. chancre) with indurated margins, usually associated with local lymphadenopathy. The lesion is usually located on the genitalia, mouth or rectum but other locations are possible depending on the site of inoculation. The lesion is often asymptomatic and can remain unnoticed, particularly among women. If left untreated, the lesion usually resolves within a few weeks without leaving a scar.
- Secondary infection (disseminated disease). This is characterized by skin and mucosal manifestations. Generally, a maculopapular non-irritant rash appears which is usually diffuse and extends bilaterally over the trunk and the extremities. A characteristic feature is the involvement of the palms of the hands and soles of the feet. The mucous membranes of the mouth and perineum can also show lesions (mostly flat lesions) that are highly infectious. Systemic manifestations (e.g. fever $\geq 38.0^{\circ}\text{C}$, generalized lymphadenopathy and malaise) are usually present. Neurological manifestations (e.g. meningitis), hepatitis and ocular involvement can also occur in this phase.

Late syphilis has the following signs and symptoms.

- Tertiary syphilis (disseminated disease). This can occur as the result of an untreated early syphilis after a period of latency, with no clinical manifestations, that may last

years. Usually tertiary syphilis develops more rapidly in patients with HIV. In this phase, different organ systems can be affected, particularly: the cardiovascular system (typically with signs and symptoms of aortitis); the skin, soft tissues and bones (typically with granulomatous or nodular lesions also known as gummas); and the central nervous system (typically with symptoms of progressive dementia, psychiatric syndrome and tabes dorsalis, which is characterized by problems with coordination of movements, pain radiating from the spine and impaired response of the pupils to light).

Congenital syphilis infection during pregnancy can lead to spontaneous abortion or premature birth. Most babies with congenital syphilis are asymptomatic at birth but when symptoms are present, they usually develop days or weeks after birth. These symptoms often include anaemia, thrombocytopenia, rash (maculopapular, desquamative rash particularly over the palms, soles, mouth and anus), generalized lymphadenopathy, hepatomegaly and jaundice, nasal discharge (that may turn bloody), painful osteitis (mostly in long bones) and teeth abnormalities. The cerebrospinal fluid is abnormal, indicating neurological disease, in up to half of all babies. Of note, neurological consequences can be expressed later in life and this should always be considered with congenital syphilis.

Laboratory tests

For more comprehensive information on diagnosis of syphilis, please refer to the most recent (2013) WHO guideline for the laboratory diagnosis of STIs (192). Please check the WHO website regularly for possible updates.

Patient microbiology tests

In patients with suspected syphilis, microbiology tests can support the diagnosis (Table 21.1). Certain microbiology tests are also used to screen asymptomatic pregnant women. For screening during pregnancy, please refer to the most recent (2017) WHO guideline on syphilis screening and treatment for pregnant women (211).

Direct detection methods

These methods can be used to detect the pathogen in specimens obtained from skin or tissues lesions (Table 21.1). Direct detection methods include: dark-field microscopy where *Treponema pallidum* from lesions of primary syphilis can be observed (of note, a negative dark-field result does not exclude syphilis); and nucleic acid amplification tests to detect DNA sequences specific to *Treponema pallidum*. Direct detection is considered the gold standard but it is much less frequently used today because it is more time-consuming than serological tests.

Serological tests

Two types of serological test can be used, treponemal and non-treponemal.

- Treponemal tests detect antibodies to treponemal antigens and usually remain positive after infection even after successful treatment. These tests include: fluorescent treponemal antibody absorption test; *Treponema pallidum* particle agglutination assay; and *Treponema pallidum* haemagglutination assay. Treponemal rapid diagnostic tests for syphilis are available and prequalified by WHO.
- Non-treponemal tests detect antibodies that react to lipids, for example, cardiolipin released during cellular damage that occurs in response to *Treponema pallidum*. These are qualitative and quantitative tests that can also be used to monitor response to treatment because their titres tend to decline after adequate treatment and may become negative (i.e. non-reactive) over time. These tests include: rapid plasma reagent test and Venereal Disease Research Laboratory test.

Initially, a two-step approach is used to test for syphilis and both types of tests – treponemal and non-treponemal – need to be positive to confirm the diagnosis. In order to increase access to testing and ensure same-day treatment, WHO recommends the use of a rapid treponemal test followed (if positive) by a non-treponemal test.

However, starting with a non-treponemal test and confirmation of positive results with a treponemal test is also appropriate.

All serological tests for syphilis (non-treponemal and treponemal tests) are negative in the early phase of primary syphilis and take 1–4 weeks after the chancre appears to become reactive. Both treponemal and non-treponemal tests are reactive in secondary or tertiary syphilis.

Non-treponemal tests can rarely give false positive results, for example, during pregnancy or during an acute febrile illness. Figure 21.1 and Figure 21.2 and Table 21.2 can be used to help with the interpretation of the results of serological tests.

Additional tests for other STIs that could be considered when syphilis is confirmed or suspected are shown in Table 21.3.

Table 21.1 – Microbiology tests to consider when syphilis is suspected as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
Microscopy of specimens obtained from skin and tissues lesions ^a	To assess microbial morphology	Health care facilities with clinical laboratories
Antibodies to <i>Treponema pallidum</i> (RDT)	To diagnose or help to diagnose <i>Treponema pallidum</i>	Community settings and health facilities without laboratories ^b
Combined antibodies to <i>Treponema pallidum</i> and to HIV-1 and HIV-2 (RDT)	To diagnose or help to diagnose HIV and/or <i>Treponema pallidum</i>	Community settings and health facilities without laboratories ^b
Non-treponemal test: rapid plasma reagin	To screen for syphilis and monitor effectiveness of treatment	Health care facilities with clinical laboratories
Non-treponemal test: VDRL test ^c	To screen for syphilis and monitor effectiveness of treatment and also to screen for, diagnose and confirm neurosyphilis ^c	Health care facilities with clinical laboratories
Treponemal test: TPHA test ^d	To confirm syphilis and diagnose early and late syphilis	Health care facilities with clinical laboratories
Treponemal test: TPPA test ^d	To confirm syphilis and diagnose early and late syphilis	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics; HIV: human immunodeficiency virus; RDT: rapid diagnostic test; TPHA: *Treponema pallidum* haemagglutination; TPPA: *Treponema pallidum* particle agglutination; VDRL: Venereal Disease Research Laboratory.

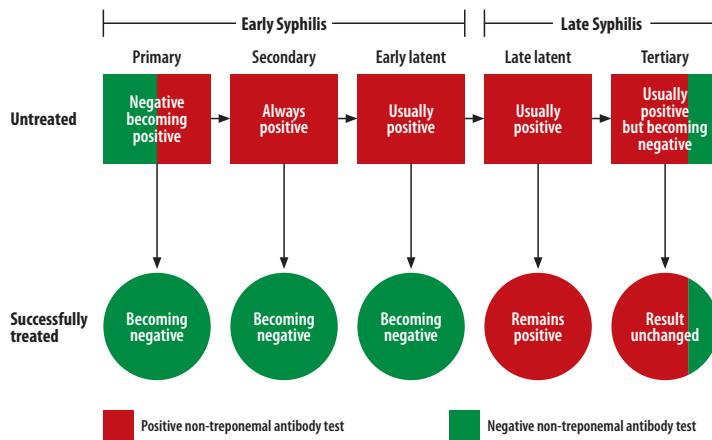
^a Nucleic acid amplification tests (e.g. polymerase chain reaction) of specimens obtained from skin and tissues lesions could also be considered if available.

^b Community and health settings without laboratories are defined as community and health facilities such as health posts and centres, doctors' offices, outreach clinics and ambulatory care. These tests are also assumed to be available at health care facilities with laboratories.

^c If neurosyphilis is suspected (this can occur at any stage of infection including in the first few months), the VDRL test can also be used on the cerebrospinal fluid in the presence of a positive syphilis serology. The test has a high specificity (i.e. few false-positive results) but a low sensitivity (i.e. many false-negative results). Examination of the cerebrospinal fluid is recommended where there is clinical evidence of neurological involvement. It is also highly desirable in all patients with syphilis of more than 2 years duration or of uncertain duration in order to evaluate the possible presence of asymptomatic neurosyphilis (219).

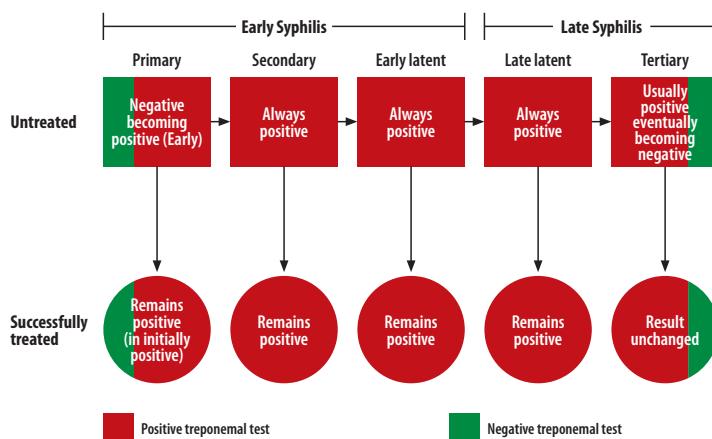
^d Treponemal tests usually remain positive after the infection has been cleared.

Figure 21.1 – Reactivity of non-treponemal serological tests by stage of syphilis and effect of treatment



Source: *Laboratory diagnosis of sexually transmitted infections including human immunodeficiency virus*, 2013 (192).

Figure 21.2 – Reactivity of treponemal serological tests by stage of syphilis and effect of treatment



Source: *Laboratory diagnosis of sexually transmitted infections including human immunodeficiency virus*, 2013 (192).

■ PRIMARY HEALTH CARE

21. Sexually transmitted infections – syphilis

Table 21.2 – Possible interpretation of combinations of non-treponemal and treponemal test results

Non-treponemal test (RPR or VDRL)	Treponemal test (FTA-ABS, TPPA, TPHA, RDT)	Interpretation
Positive	Positive	<p>This supports the diagnosis of syphilis (the stage of disease and need for treatment should be determined on a case-by-case basis).</p> <p>Note. These cases should be notified to the local authority according to national guidance for disease notification.</p>
Negative	Positive	Usually this can occur as a result of a successfully treated previous infection because treponemal tests tend to remain positive. Otherwise it could be a very early (or late) phase of the infection.
Positive	Negative	Usually this can be considered a false positive result (e.g. during pregnancy).
Negative	Negative	Usually the diagnosis of syphilis can be excluded.

FTA-ABS: fluorescent treponemal antibody absorption; RDT: rapid diagnostic test; RPR: rapid plasma reagin; TPHA: *Treponema pallidum* haemagglutination assay; TPPA: *Treponema pallidum* particle agglutination; VDRL: Venereal Disease Research Laboratory.

Table 21.3 – Additional tests for other sexually transmitted infections to consider in patients with confirmed or suspected syphilis as indicated in the WHO EDL (6)

Infection	Diagnostic test	Purpose of the test	Settings where the test should be available
Chlamydial urogenital infection and gonococcal infection	Qualitative test for <i>Chlamydia trachomatis</i> and <i>Neisseria gonorrhoeae</i> infections (NAAT)	To diagnose chlamydial and/or gonorrhoeal urogenital disease and extragenital infection	Health care facilities with clinical laboratories

continues

Table 21.3 *continued*

Infection	Diagnostic test	Purpose of the test	Settings where the test should be available
HIV	Anti-HIV-1 and -HIV-2 antibody (RDT)	Self-testing to screen for HIV	Community settings and health facilities without laboratories ^a
HIV	Anti-HIV-1 and -HIV-2 antibody (RDT and immunoassay)	To screen for HIV infection	Community settings and health facilities without laboratories ^a (RDT) Health care facilities with clinical laboratories (immunoassay)
HIV	Combined anti-HIV-1/HIV-2 antibody and p24 antigen (RDT and immunoassay)	To screen for HIV infection	Community settings and health facilities without laboratories ^a (RDT) Health care facilities with clinical laboratories (immunoassay)
Hepatitis B	Hepatitis B virus surface antigen (RDT, immunoassay)	To screen for acute and chronic hepatitis B virus infection in people older than 12 months	Community settings and health facilities without laboratories ^a (RDT) Health care facilities with clinical laboratories (immunoassay)
Hepatitis B	IgM-specific antibodies to hepatitis B core antigen (immunoassay)	To aid in the diagnosis of acute HBV infection in the context of outbreak investigation	Health care facilities with clinical laboratories
Hepatitis C	Anti-hepatitis C antibody (RDT, immunoassay)	To screen for hepatitis C virus infection in people older than 18 months	Community settings and health facilities without laboratories ^a (RDT) Health care facilities with clinical laboratories (immunoassay)

continues

Table 21.3 *continued*

Infection	Diagnostic test	Purpose of the test	Settings where the test should be available
Trichomoniasis	Microscopy	To assess microbial morphology, and presence or absence of white blood cells	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics; HIV: human immunodeficiency virus; NAAT: nucleic acid amplification test; RDT: rapid diagnostic test.

^a Community and health settings without laboratories are defined as community and health facilities such as health posts and centres, doctors' offices, outreach clinics and ambulatory care. These tests are also assumed to be available at health care facilities with laboratories.

Other tests

When primary syphilis is suspected, blood tests other than serology are not usually needed. However, in case of secondary or tertiary syphilis, laboratory tests may be required. If signs and symptoms of neurological disease (i.e. neurosyphilis) are present, a lumbar puncture to test the cerebrospinal fluid is indicated if available (Table 21.4).

Table 21.4 – Laboratory tests (other than microbiology) to consider when late syphilis is suspected as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
Basic CSF profile: CSF leukocyte count ^a , CSF differential leukocyte count and CSF protein ^b and glucose ^c	To aid in the diagnosis of neurosyphilis	Health care facilities with clinical laboratories

CSF: cerebrospinal fluid; EDL: Model List of Essential In Vitro Diagnostics.

^a CSF leukocyte count: usually > 5 white blood cell/ μL ($> 0.005 \times 10^9/\text{L}$), or a higher cut-off > 20 cell/ μL ($> 0.02 \times 10^9/\text{L}$) in HIV-positive patients even though these are not specific findings of neurosyphilis.

^b CSF protein levels: protein concentration is usually increased (> 45 mg/dL or > 0.45 g/L) but not a specific finding of neurosyphilis.

^c CSF glucose levels: glucose concentrations are usually decreased but not a specific finding of neurosyphilis.

Using microbiology surveillance data

Routine surveillance is not helpful to inform empiric guidance.

Imaging

When syphilis is suspected, imaging is not usually needed unless a complication of late syphilis is suspected.

Antibiotic treatment

All patients, including pregnant women, diagnosed with syphilis should receive a full course of antibiotic treatment. Serological response to treatment can be assessed by repeating a non-treponemal quantitative test – ideally the same type of non-treponemal test used at the time of diagnosis – to detect a reduction in titre. A four-fold reduction, or higher, in titres should be seen to confirm an adequate response to treatment for early syphilis. Usually assessments are repeated at 3, 6 and 12 months after the end of treatment.

In the case of early syphilis (primary or secondary), the partners of infected people should also be treated if they had sexual relations with the infected person in the 90 days before the person was diagnosed with syphilis. If more than 90 days have elapsed, serological testing is usually suggested and treatment is given accordingly.

The antibiotic treatment recommendations reported here (Table 21.5) are aligned with the most recent WHO guidelines for the treatment of syphilis and for the management of symptomatic STIs (191,210).

Table 21.5 – Antibiotic treatment for syphilis by stage of the disease as indicated in the most recent WHO guidelines for the treatment of syphilis (210)

Please check the WHO website regularly for possible updates

Type of infection	Treatment	Total treatment duration
Early syphilis (adults and adolescents)	First choice Benzathine benzylpenicillin ^a (IM): 2.4 million IU (\approx 1.8 g)	Benzathine benzylpenicillin: single dose
Early syphilis includes primary, secondary and early latent syphilis of no more than 2 years duration	Second choice Procaine benzylpenicillin (IM): 1.2 million IU (1.2 g) given once a day	Procaine benzylpenicillin: 10–14 days

continues

Table 21.5 *continued*

Type of infection	Treatment	Total treatment duration
Late syphilis or unknown stage (adults and adolescents) This includes infection of more than 2 years duration without evidence of treponemal infection (i.e. asymptomatic infection)	First choice Benzathine benzylpenicillin ^b (IM): 2.4 million IU (\approx 1.8 g) Second choice Procaine benzylpenicillin (IM): 1.2 million IU (1.2 g) given once a day	Benzathine benzylpenicillin: one dose per week for 3 consecutive weeks (e.g. on days 1, 8 and 15) The interval between doses should not exceed 14 days Procaine benzylpenicillin: 20 days
Congenital syphilis Infants with confirmed disease or infants who are clinically normal but whose mother had untreated or inadequately treated syphilis ^c Inadequate treatment refers to treatment received < 30 days before delivery and/or treatment with a non-penicillin regimen	Benzylpenicillin (IV): 50 000–75 000 IU/kg/dose (30–45 mg/kg/dose) given every 12 hours OR Procaine benzylpenicillin (IM): 50 000 IU/kg (50 mg/kg) given once a day If IV access is available, benzylpenicillin is preferred over procaine benzylpenicillin.	10–15 days
Neurosyphilis ^d	Benzylpenicillin ^e (IV): 2–4 million IU (1.2–2.4 g) given every 4 hours OR Procaine benzylpenicillin ^f (IM): 1.2 million IU (1.2 g) given once a day AND Probenecid (oral): 500 mg given every 6 hours	14 days

continues

Table 21.5 *continued*

Type of infection	Treatment	Total treatment duration
Syphilis in pregnancy	<p>Early syphilis</p> <p>Benzathine benzylpenicillin (IM): 2.4 million IU (\approx 1.8 g)</p> <p>Alternative options (not in the EML) in case of allergy to penicillin (or stock-outs):</p> <p>Ceftriaxone 1 g for 10–14 days</p> <p>Azithromycin (2 g single dose) or erythromycin (500 mg every 6 hours for 14 days) can also be used but neither of them crosses the placental barrier completely, therefore only the mother is treated, not the fetus.</p> <p>Late syphilis or unknown stage</p> <p>Benzathine benzylpenicillin (IM): 2.4 million IU (\approx 1.8 g)</p> <p>Alternative option (not in the EML) in case of allergy to penicillin (or stock-outs): Erythromycin 500 mg every 6 hours for 30 days, but this does not treat the fetus since erythromycin does not cross the placental barrier completely, therefore only the mother is treated.</p>	<p>Early syphilis</p> <p>Single dose</p> <p>Late syphilis or unknown stage</p> <p>One dose per week for 3 consecutive weeks (e.g. on days 1, 8 and 15).</p> <p>The interval between doses should not exceed 14 days.</p>

EML: Model List of Essential Medicines; IM: intramuscular; IU: international units; IV: intravenous;

Note. All dosages are for normal renal and hepatic function.

^a Alternative options in case of allergy to penicillin or stock-outs are indicated in the 2016 WHO guidelines but these are not included in the EML for this indication. These alternatives are doxycycline (oral) 100 mg every 12 hours (except in pregnant women) for 14 days, or ceftriaxone 1 g (IM) for 10–14 days (210). In special circumstances (i.e. when susceptibility is likely, based on local epidemiology) azithromycin 2 g (oral) as a single dose can be given. If penicillin cannot be used, doxycycline is the preferred choice (except in pregnant women) because of its lower cost and oral administration (210).

^b An alternative option, in case of allergy to penicillin or stock-outs, is indicated in the 2016 WHO guidelines but this option is not included in the EML for this indication. This option is doxycycline (oral) 100 mg every 12 hours (except in pregnant women) for 30 days (210).

^c If the mother was adequately treated and the infant is clinically normal, close monitoring of the infant is suggested. If treatment is provided, the 2016 WHO guidelines indicate benzathine benzylpenicillin (IM) 50 000 IU/kg (37.5 mg/kg) per day single dose as an option.

continues

Table 21.5 continued

^d From the 2003 WHO guidelines on management of sexually transmitted infections (219).

^e Alternative options are indicated in the 2003 WHO guidelines for non-pregnant patients allergic to penicillin but they are not included in the EML. These options are: doxycycline (oral) 200 mg every 12 hours; and tetracycline (oral) 500 mg every 6 hours. Treatment duration is 30 days in both cases.

^f Some authorities recommend adding benzathine benzylpenicillin 2.4 million IU (\approx 1.8 g) by IM injection, in three consecutive doses once weekly after completing this regimen, but there are no data to support this approach. Benzathine benzylpenicillin 2.4 million IU (\approx 1.8 g) by IM injection does not give adequate therapeutic levels in the cerebrospinal fluid (210).

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Prevention

Sexual transmission typically occurs only during primary, secondary and early latent infection. Mother-to-child transmission, however, has been documented to occur up to several years after the initial infection (210).

Prevention of infection is a key strategy; no effective vaccine against *Treponema pallidum* is yet available therefore other preventive measures can be used.

The main elements of prevention include: comprehensive sexuality education, pre- and post-test counselling, safe sex and risk reduction counselling, and promoting consistent use of condoms. Interventions targeting groups who have a higher risk of infection – for example, men who have sex with men, transgender people, sex workers, people who inject drugs, indigenous communities and people in prison – should be considered. Offering HIV pre-exposure prophylaxis to people at high risk of HIV infection may be considered.

Access of pregnant women to early and adequate prenatal care, including screening at first visit and immediate treatment initiation if needed, are key to prevent congenital syphilis.

Sexual partners should always be informed of the infection and treated (189). Reporting of this infection to health authorities according to local regulations should also be done.

22. Sexually transmitted infections – trichomoniasis

Note

In general this chapter applies to adults and young people older than 12 years. In children, specialist advice should be sought where possible. Consideration should be given that an STI in a child may be due to child sexual abuse.

Key messages

- Trichomoniasis is the most common curable sexually transmitted infection (STI) and in women it can manifest as a vaginal discharge; men are usually asymptomatic.
- Asymptomatic people should also be treated because they can transmit the infection to others and all people with trichomoniasis should also be evaluated for other STIs.
- Preventive services should be offered (e.g. condoms, brief sexuality education, human immunodeficiency virus (HIV) pre-exposure prophylaxis to people at high risk of HIV infection) and sexual partners should be informed and treated
- Reporting of this infection to health authorities is encouraged according to local regulations.

Other relevant WHO resources (please check regularly for updates)

- Sexually transmitted infections (STIs) – fact sheets (189).
- WHO guidelines for the management of symptomatic sexually transmitted infections (191).
- Laboratory diagnosis of sexually transmitted infections including human immunodeficiency virus (192).
- Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021 (193).

Definition

Trichomoniasis is an STI caused by the protozoan *Trichomonas vaginalis*.

Trichomoniasis

Sexually transmitted infection

In general this guidance applies to adults and young people aged over 12 years. In children, specialist advice should be sought where possible. Consideration should be given that an STI in a child may be due to child sexual abuse

Definition

A sexually transmitted infection (STI) caused by *Trichomonas vaginalis*

Diagnosis

Clinical Presentation

- Most persons have mild symptoms or remain asymptomatic (especially men) though they can still transmit the infection

Symptomatic infection:

- In women: acute onset of vaginal inflammation and discharge (frothy and with a bad smell), dysuria and pelvic pain
- In men: urethral discharge, dysuria and testicular discomfort or pain; rarely epididymitis and prostatitis can be present

Microbiology Tests

- See WHO guidance "Laboratory diagnosis of sexually transmitted infections"
<https://apps.who.int/iris/handle/10665/85343>
- Important: all patients with suspected trichomoniasis should also be tested for other STIs (e.g. HIV, syphilis, gonococcal infection)

Tests to consider:

- Wet mount microscopy (easy and inexpensive but should be read within 10 minutes of sample collection)
- Nucleic acid amplification tests for *T. vaginalis* (very good sensitivity; preferred if available)
- Culture (good sensitivity but requires long incubation)
- Samples that can be used: Urethral, endocervical, and vaginal swabs

Other Laboratory Tests

Usually not needed

Imaging

Usually not needed



Pathogen

Trichomonas vaginalis is an anaerobe flagellated protozoan



Prevention

Important elements of prevention include:

- Sexuality education
- Promoting consistent use of condoms
- Pre- and post-test counselling
- Safe sex and risk reduction counselling
- Interventions targeting high-risk groups

Important:

- Sexual partners should be informed of the disease and treated
- Reporting of this infection to health authorities is encouraged according to local regulations

Treatment



Clinical Considerations

Treatment is aligned with the WHO 2021 guidelines for the management of symptomatic sexually transmitted infections (<https://apps.who.int/iris/handle/10665/342523>)

Treatment is always indicated when infection is diagnosed, including in asymptomatic persons because they can transmit the infection to others



Antibiotic Treatment Duration

Since treatment duration varies, please refer to the corresponding antibiotic section for treatment duration

- Evidence supports better cure rates with 7-day course (consider if treatment adherence is not an issue)



Antibiotic Treatment

All dosages are for normal renal function



Metronidazole 2 g ORAL

Treatment duration: single dose

OR



Metronidazole 400 or 500 mg q12h ORAL

Treatment duration: 7 days



Pathogen

Trichomoniasis is caused by *Trichomonas vaginalis*, an anaerobe flagellated protozoan.

Pathophysiology

Trichomonas vaginalis infects the mucosa of the urogenital tract during sexual contact and produces a local inflammatory response that causes vaginal or urethral discharge.

Epidemiology

Trichomoniasis is the most prevalent STI worldwide with an estimated 156 million new cases in 2020 as reported by WHO (193).

The infection most commonly affects women older than 40 years. As with other STIs, the risk of acquiring or transmitting HIV is higher in cases of trichomoniasis and the infection is associated with adverse outcomes in pregnancy, such as preterm delivery, premature rupture of membranes and low birth weight (220). If left untreated, trichomoniasis can persist for months or years and in pregnant women, it can be transmitted to the baby during delivery. Common risk factors for infection include multiple sex partners, a history of having other STIs (e.g. HIV infection) and substance abuse.

Clinical presentation

Most cases of trichomoniasis are asymptomatic, especially in men, or have mild symptoms. In women, symptoms include acute onset of vaginal inflammation and discharge (usually characterized by a bad smell and with a frothy appearance), dysuria and pelvic pain. In men, symptomatic infection usually presents with urethral discharge, dysuria, and testicular discomfort or pain. Epididymitis and prostatitis can also occur in a minority of cases.

Laboratory tests

For more comprehensive information on the diagnosis of trichomoniasis, please refer to the most recent (2013) WHO guideline on the laboratory diagnosis of STIs (192). Please check the WHO website regularly for possible updates.

Patient microbiology tests

All people with trichomoniasis are also usually evaluated for other STIs, such as chlamydial infection, gonococcal infection, hepatitis B and hepatitis C, HIV infection and syphilis.

Tests to consider when trichomoniasis is suspected are indicated in Table 22.1.

Molecular assays such as nucleic acid amplification tests have the highest sensitivity of all diagnostic methods to detect *Trichomonas vaginalis* but they are not currently widely available as rapid point-of-care tests. However, if available, they should be used. Vaginal swabs are the samples of choice, but endocervical samples and urine can be used for some assays.

Historically, trichomoniasis has been diagnosed by performing wet mount microscopy. Although this is not the gold standard technique, a wet mount is frequently used because it is quick, inexpensive and easy to perform. However, to have a good chance of successfully identifying the motile trichomonads, the slide should be read within 10 minutes of collection of the sample since trichomonads quickly lose their motility. Non-motile cells cannot be diagnosed as trichomonads due to possible misidentification; for example, a non-motile trichomonad is difficult to differentiate from the nucleus of a vaginal epithelial cell.

Culture of *Trichomonas vaginalis*, which has a higher sensitivity than the wet mount microscopic examination, was the cornerstone for detecting this organism before the advent of point-of-care antigen tests and nucleic acid amplification tests. Although a culture medium is commercially available, cultures of samples from women with trichomoniasis are usually positive in the first 3 days of inoculation, but they have to be incubated for up to 7 days to rule out infection. Routine culture methods detecting *Trichomonas vaginalis* are no longer widely performed.

Additional tests for other STIs that could be considered when trichomoniasis is confirmed or suspected are shown in Table 22.2.

Table 22.1 – Microbiology tests to consider when trichomoniasis is suspected as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
Microscopy ^{a,b}	To assess microbial morphology and presence or absence of white blood cells	Health care facilities with clinical laboratories
Culture ^b	Initial step to detect and identify bacterial species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics.

^a If available, nucleic acid amplification tests for *Trichomonas vaginalis* could be considered, especially if the microscopy examination is negative. Nucleic acid tests for trichomoniasis are not listed in the third version of the EDL.

^b Possible specimens are urethral swabs, endocervical swabs and vaginal swabs.

Table 22.2 – Additional tests for other sexually transmitted infections to consider in patients with confirmed or suspected trichomoniasis as indicated in the WHO EDL (6)

Infection	Diagnostic test	Purpose of the test	Settings where the test should be available
Chlamydial urogenital infection and gonococcal infection	Qualitative test for <i>Chlamydia trachomatis</i> and <i>Neisseria gonorrhoeae</i> infections (NAAT)	To diagnose chlamydial and/or gonorrhoeal urogenital disease and extragenital infection	Health care facilities with clinical laboratories
HIV	Anti-HIV-1 and -HIV-2 antibody (RDT)	Self-testing to screen for HIV	Community settings and health facilities without laboratories ^a
HIV	Anti-HIV-1 and -HIV-2 antibody (RDT and immunoassay)	To screen for HIV infection	Community settings and health facilities without laboratories ^a (RDT) Health care facilities with clinical laboratories (immunoassay)
HIV	Combined anti-HIV-1/HIV-2 antibody and p24 antigen (RDT and immunoassay)	To screen for HIV infection	Community settings and health facilities without laboratories ^a (RDT) Health care facilities with clinical laboratories (immunoassay)
Hepatitis B	Hepatitis B virus surface antigen (RDT, immunoassay)	To screen for acute and chronic hepatitis B virus infection in people > 12 months	Community settings and health facilities without laboratories ^a (RDT) Health care facilities with clinical laboratories (immunoassay)
Hepatitis B	IgM-specific antibodies to hepatitis B core antigen (immunoassay)	To aid in the diagnosis of acute HBV infection in the context of outbreak investigation	Health care facilities with clinical laboratories

continues

Table 22.2 *continued*

Infection	Diagnostic test	Purpose of the test	Settings where the test should be available
Hepatitis C	Anti-hepatitis C antibody (RDT, immunoassay)	To screen for hepatitis C virus infection in people > 18 months	Community settings and health facilities without laboratories ^a (RDT)
			Health care facilities with clinical laboratories (immunoassay)
Syphilis	Antibodies to <i>Treponema pallidum</i> ^b (RDT)	To diagnose or help to diagnose <i>Treponema pallidum</i>	Community settings and health facilities without laboratories ^a
Syphilis and HIV combined test	Combined antibodies to <i>Treponema pallidum</i> and HIV-1/HIV-2 (RDT)	To diagnose or help to diagnose HIV and/or <i>Treponema pallidum</i>	Community settings and health facilities without laboratories ^a

EDL: Model List of Essential In Vitro Diagnostics; HIV: human immunodeficiency virus; NAAT: nucleic acid amplification test; RDT: rapid diagnostic test.

^a Community and health settings without laboratories are facilities such as health posts and centres, doctors' offices, outreach clinics, ambulatory care and home-based and self-testing. These tests are also assumed to be available at health care facilities with laboratories.

^b Usually a non-treponemal test, such as rapid plasma reagent, Venereal Disease Research Laboratory test, is used for screening. Please refer to the chapter on syphilis for more details on testing.

Other tests

When trichomoniasis is suspected, laboratory tests (other than microbiology) are not usually needed.

Using microbiology surveillance data

Routine surveillance is not helpful to inform empiric guidance.

Imaging

When trichomoniasis is suspected, imaging is not usually needed.

Antibiotic treatment

Antibiotic treatment is always indicated when trichomoniasis is diagnosed (Table 22.3), including in asymptomatic patients, to stop transmission. Sexual partners should also be tested and treated if infected.



Table 22.3 – Antibiotic treatment for trichomoniasis as indicated in the 2021 WHO guidelines for the management of symptomatic sexually transmitted infections (191)

Please check the WHO website regularly for possible updates

Treatment	Total treatment duration
Metronidazole (oral): 2 g	Single dose
OR	
Metronidazole (oral): 400 or 500 mg given every 12 hours ^a	7 days

Note. All dosages are for normal renal and hepatic function.

^a If compliance is not a problem, consider giving 500 mg (oral) every 12 hours for 7 days. Evidence supports better cure rates with a 7-day course of treatment compared with a single dose (221).

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Prevention

No effective vaccine against *Trichomonas vaginalis* is available. Prevention of infection is therefore a key strategy. Important elements of prevention include counselling and behavioural approaches including comprehensive sexuality education, pre- and post-test counselling, safe sex and risk reduction counselling, and promoting consistent use of condoms. Interventions targeting high-risk groups (e.g. men who have sex with men, transgender people, sex workers and people who inject drugs) may be considered. Offering HIV pre-exposure prophylaxis to people at high risk of HIV infection may be considered.

Sexual partners should always be informed of the infection and treated (189). Reporting of this infection to health authorities according to local regulations should also be done.

23. Lower urinary tract infection

Note

The focus of this chapter is community-acquired acute cystitis.

Key messages

- Urinary tract infections (UTIs) are more common in women and increase with age and frequency of sexual activity.
- Most cases are caused by *Escherichia coli*.
- Urine culture should be considered in children and in people at higher risk of complicated infections (e.g. men, pregnant women) or in the case of recurrent infections.
- Oral nitrofurantoin for 5 days is the main recommended treatment for lower UTIs.
- A positive urine culture in asymptomatic patients is not an indication for antibiotic treatment in the great majority of cases.

Other relevant WHO resources (please check regularly for updates)

- Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, 2013 (31).

Definition

Lower UTIs are acute infections in which only the lower part of the urinary tract is affected, such as the bladder (e.g. cystitis). These infections are often classified as either complicated or uncomplicated based on the presence of risk factors that make them more difficult to treat.

Complications can occur with lower UTIs because of certain patient-related risk factors. While there is no universally accepted definition of what constitutes a complicated UTI, lower UTIs in individuals with certain conditions of the urinary tract (e.g. anatomical anomalies and kidney stones) are generally complicated. Infections in pregnant women are also usually included in this category. Examples of factors that may increase the risk of a complicated lower UTI are shown in Box 23.1 but should not be considered a complete list.

Box 23.1 – Factors that may increase the risk of a complicated lower urinary tract infection

- Obstruction at any site of the urinary tract
- Foreign body (e.g. urinary catheters and stents)
- Incomplete voiding
- Vesicoureteral reflux
- Recent history of instrumentation
- Male sex
- Pregnancy
- Diabetes
- Immunosuppression

Notes. The list gives some examples but is not aimed to be complete. No widely accepted definition of a complicated urinary tract infection currently exists. Some experts suggest that the list above is too long and may result in diagnosing too many patients with a complicated infection. The presence of one or more of these risk factors does not mean that the infection is complicated and in need of a different treatment approach.

Source: *Guidelines on urological infections of the European Association of Urology* (222).

Lower urinary tract infection

Urinary tract infection • Page 1 of 2

Definition

- Infection of the lower part of the urinary tract (e.g. the bladder-cystitis)
- Urinary tract infections (UTI) in individuals with structural anomalies of the urinary tract or who are immunocompromised and in pregnant women are generally considered at greater risk of complicated evolution (complicated UTI)

Most Likely Pathogens

Bacteria:

• Most common:

- Enterobacteriales (mostly *Escherichia coli* including multidrug-resistant strains such as those producing ESBL)

• More rarely:

- Coagulase-negative Staphylococci: *S. saprophyticus* (mostly in young women)
- *Streptococcus agalactiae* (group B *Streptococcus*)
- *Enterococcus* spp.
- *Pseudomonas aeruginosa* or *Acinetobacter baumannii* (including multidrug-resistant strains such as those producing ESBL especially in patients with recent antibiotic exposure)

Diagnosis

Clinical Presentation

Acute (< 1 week) dysuria, increased urinary urgency and frequency, lower abdominal pain or discomfort and sometimes gross hematuria

- In women, a vaginal source of the symptoms (vaginal discharge or irritation) should be excluded first
- In elderly patients with pre-existing urinary symptoms the most reliable symptoms of infection are acute urinary changes compared to the baseline

Microbiology Tests

In symptomatic patients:

- Urine culture if risk of complicated UTI and/or recurrent UTI (to confirm the diagnosis and adapt empiric treatment)

Important:

- A positive urine culture in an asymptomatic patient indicates bacterial colonization and does not require treatment except in pregnant women or in patients undergoing urological procedures in which bleeding is anticipated
- The absence of urine leucocytes has a good negative predictive value but the positive predictive value of leucocyturia is suboptimal

Other Laboratory Tests

In symptomatic patients:

- Urinalysis (dipstick or microscopy) to detect bacteriuria and/or indirect signs of infection (positive leucocyte esterase and nitrites)
- Blood tests usually not needed

Imaging

Usually not needed unless need to investigate possible underlying abnormalities of the urinary tract

Lower urinary tract infection

Urinary tract infection - Page 2 of 2

R_X Treatment

Clinical Considerations

- Antibiotic treatment recommended if compatible clinical presentation AND a positive test** (positive urine leucocytes/leucocyte esterase or positive urine culture)
- If tests could not be performed, treat based on clinical presentation
 - Clinical improvement should be evident within 48-72h
 - Antibiotics shorten duration of symptoms by 1-2 days

Antibiotic Treatment Duration

Duration varies according to the antibiotic used - see corresponding antibiotic section

Note: in general consider longer treatments for pregnant women (usually 5 days) and men (usually 7 days)

R_X Antibiotic Treatment

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

-  Amoxicillin+clavulanic acid 500 mg+125 mg
q8h ORAL
Treatment duration: 3-5 days

Active against some ESBL-producing isolates

OR

-  Nitrofurantoin ORAL
• 100 mg q12h (modified release formulation)
• 50 mg q6h (immediate release formulation)
Treatment duration: 5 days

Nitrofurantoin is the preferred treatment option for acute lower UTI and is active against most ESBL-producing isolates

OR

-  Sulfamethoxazole+trimethoprim 800 mg+160 mg q12h ORAL
Treatment duration: 3 days

Resistance is high in many settings and NOT active against most ESBL-producing isolates

OR

-  Trimethoprim 200 mg q12h ORAL
Treatment duration: 3 days

Resistance is high in many settings and NOT active against most ESBL-producing isolates

Lower urinary tract infection

Urinary tract infection • Page 1 of 2

Definition

- Infection of the lower part of the urinary tract (e.g. the bladder-cystitis)
- Urinary tract infections (UTI) in children with structural anomalies of the urinary tract (e.g. vesicoureteral reflux or other congenital anomalies) or who are immunocompromised are generally considered at greater risk of complicated evolution (complicated UTI)

Most Likely Pathogens

Bacteria:

• Most common:

- Enterobacteriales (mostly *Escherichia coli* including multidrug-resistant strains such as those producing ESBL)

• More rarely:

- *Streptococcus agalactiae* (group B *Streptococcus*)
- *Enterococcus* spp.
- *Pseudomonas aeruginosa* or *Acinetobacter baumannii* (including multidrug-resistant strains such as those producing ESBL especially in patients with recent antibiotic exposure)

Diagnosis

Clinical Presentation

- Acute (< 1 week) dysuria, increased urinary urgency and frequency, incontinence/wetting, lower abdominal pain or discomfort and sometimes hematuria
- Generally no systemic signs/symptoms (e.g. fever)
- In girls, a vaginal source of the symptoms (vaginal discharge or irritation) should be excluded first

Microbiology Tests

In symptomatic patients:

- Urine culture (always in children) to confirm the diagnosis and adapt empiric treatment

Important:

- A positive urine culture in an asymptomatic patient indicates bacterial colonization and does not require treatment except in patients undergoing urological procedures in which bleeding is anticipated
- The absence of urine leucocytes has a good negative predictive value but the positive predictive value of leucocyturia is suboptimal

Other Laboratory Tests

In symptomatic patients:

- Urinalysis (dipstick or microscopy) to detect bacteriuria and/or indirect signs of infection (positive leucocyte esterase and nitrites)
- Blood tests usually not needed

Imaging

Usually not needed unless need to investigate possible underlying abnormalities of the urinary tract

Lower urinary tract infection

Urinary tract infection - Page 2 of 2

Rx Treatment

Clinical Considerations

- Antibiotic treatment recommended if compatible clinical presentation AND a positive test** (positive urine leucocytes/leucocyte esterase or positive urine culture)
- If tests could not be performed, treat based on clinical presentation
 - Clinical improvement should be evident within 48-72h
 - Antibiotics shorten duration of symptoms by ~2 days

Antibiotic Treatment Duration

Duration varies according to the antibiotic used - see corresponding antibiotic section

Rx Antibiotic Treatment

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated



Ampicillin+clavulanic acid 80-90 mg/kg/day
of amoxicillin component **ORAL**

• Oral weight bands:

3-<6 kg	250 mg of amox/dose q12h
6-<10 kg	375 mg of amox/dose q12h
10-<15 kg	500 mg of amox/dose q12h
15-<20 kg	750 mg of amox/dose q12h
≥20 kg	500 mg of amox/dose q8h or 1 g of amox/dose q12h

Treatment duration: 3-5 days

Amox = amoxicillin

Active against some ESBL-producing isolates

Must refrigerate oral liquid after reconstitution

OR



Nitrofurantoin 2 mg/kg/dose q12h OR 1 mg/
kg/dose q6h (immediate-release formulation)
ORAL

Treatment duration: 5 days

Nitrofurantoin is the preferred treatment option for acute lower UTI and is active against most ESBL-producing isolates

OR



Sulfamethoxazole+trimethoprim 20 mg/kg +
4 mg/kg q12h **ORAL**
• Oral weight bands:

3-<6 kg	100 mg+20 mg q12h
6-<10 kg	200 mg+40 mg q12h
10-<30 kg	400 mg+80 mg q12h
≥30 kg	800 mg+160 mg q12h

Treatment duration: 3 days

Resistance is high in many settings and NOT active against
most ESBL-producing isolates

OR



Trimethoprim 4 mg/kg q12h **ORAL**
• Oral weight bands:

3-<6 kg	20 mg q12h
6-<10 kg	40 mg q12h
10-<30 kg	80 mg q12h
≥30 kg	200 mg q12h

Treatment duration: 3 days

Resistance is high in many settings and NOT active against
most ESBL-producing isolates

Pathophysiology

Lower UTIs occur when pathogens (usually ascending the urethra from the perineal area) reach the bladder and overcome the host defences, which leads to parenchymal damage and an inflammatory response. Microorganisms in the urine do not inevitably lead to infection. Infection will depend on the interaction between the organism (for example, because of virulence factors of the pathogen), the patient (who may have more infections because of underlying diseases) and the environment (for example, the presence of a urinary catheter).

Epidemiology

Lower UTIs are very common worldwide and can affect people of any age. According to the Global Burden of Disease study, in 2017 there were an estimated 274 million new cases of UTIs (lower and upper) globally, combining all ages and both sexes (44).

The incidence of UTIs is highest in women and increases with age (e.g. UTIs increase after menopause) and frequency of sexual activity. These infections are particularly common in women because of the anatomy of their lower urinary tract; women have a shorter urethra than men and so microorganisms colonizing the skin of the perineal area can more easily reach the bladder. However, after 65 years of age, rates of lower UTIs in men and women tend to be more similar (223). It is estimated that more than 50% of women experience at least one episode of lower UTI in their lifetime. After a first episode, the risk of recurrence in young women has been estimated to be about 70% within a year (224). Risk factors for UTIs include anatomical and functional abnormalities of the urinary tract, for example, conditions that predispose to incomplete emptying of the bladder, renal insufficiency and urinary incontinence. Defective host immune factors (e.g. poorly controlled diabetes or neutropenia) and instrumentation of the urinary tract (e.g. urinary catheters and stents) are also predisposing factors.

Most likely pathogens

Lower UTIs are usually caused by bacteria that are part of the human intestinal microbiota, most frequently *Escherichia coli*. In clinical practice a causative pathogen is usually only identified in more severe cases when urinary cultures are obtained. Pathogens that most frequently cause UTIs are shown in Table 23.1. Data on causative organisms from low- and middle-income countries are limited; however, if a difference exists in the proportion of less common pathogens, it is unlikely to affect management. In Africa and the Middle East *Schistosoma haematobium* can present with haematuria and signs of a UTI, particularly in children.

Table 23.1 – Pathogens most frequently associated with urinary tract infections (in descending order of frequency)

Bacteria
Enterobacterales (including multidrug-resistant strains such as those producing ESBL)
<ul style="list-style-type: none">• <i>Escherichia coli</i> (responsible for > 80% of cases)• <i>Klebsiella pneumoniae</i>• <i>Proteus mirabilis</i>
Coagulase-negative staphylococci
<ul style="list-style-type: none">• <i>Staphylococcus saprophyticus</i> (in young women)
<i>Streptococcus agalactiae</i> (group B <i>Streptococcus</i>)
<i>Enterococcus</i> spp.
<i>Pseudomonas aeruginosa</i> ^a (including multidrug-resistant strains)
<i>Acinetobacter baumannii</i> ^a (including multidrug-resistant strains)

ESBL: extended-spectrum beta-lactamases.

^a Especially in patients with recent antibiotic exposure.

Clinical presentation

Classical symptoms of lower UTIs include a combination of acute (< 1 week) dysuria, increased urinary urgency and frequency, lower abdominal pain or discomfort, and sometimes gross haematuria, that is, blood can be seen in the urine. In women, vaginal discharge or irritation should be excluded before concluding a diagnosis of lower UTI. In elderly patients with pre-existing urinary symptoms (e.g. urinary incontinence), the evaluation may be more difficult. However, the most reliable symptoms in these cases are still acute urinary changes compared with the baseline. Atypical symptoms, such as falls and altered mental status, are unreliable. In addition, cloudy urine and smelly urine alone are not reliable signs of a UTI.

In children, symptoms can include vomiting, low-grade fever, increased urgency and frequency, dysuria, new incontinence, smelly urine, or lower abdominal pain and discomfort.

Laboratory tests

Patient microbiology tests

In symptomatic patients at a higher risk of complications and in children, a urine culture may be performed (Table 23.2). The rationale is to confirm the diagnosis and to adjust empiric treatment based on susceptibility results.

In children, a clean catch specimen is difficult to obtain but is preferred to a specimen obtained with a urine collection bag. Positive urine cultures in patients without symptoms (asymptomatic bacteriuria) are frequent and not indicative of bacterial cystitis. Except for very select cases (for example, pregnant women, or before invasive urological interventions), asymptomatic bacteriuria should not be treated with antibiotics.

Table 23.2 – Microbiology tests to consider for diagnosis of lower urinary tract infections as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
Urine culture ^a and antimicrobial susceptibility testing	Initial step to detect and identify bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics.

^a A positive urine culture in an asymptomatic patient indicates bacterial colonization and does not require treatment except in pregnant women or in patients undergoing urological procedures in which bleeding is anticipated. Bacterial colonization of the urine is a common finding, especially in women, the elderly (both sexes) and individuals with underlying urological abnormalities. Of note, the absence of urine leukocytes has a good negative predictive value but the positive predictive value of leukocyturia is poor.

Other tests

In patients with symptoms of a UTI, a urinalysis (dipstick or microscopy) may be done to detect the presence of bacteriuria and pyuria (Table 23.3), while blood tests are not generally used to confirm infection – tests results would be normal in case of lower UTI. In a symptomatic patient, leukocyturia (> 10 leukocytes/ μL , $0.01 \times 10^9/\text{L}$), the presence of leukocyte esterase and/or positive nitrites are indirect signs of infection. Of note, leukocyturia or the presence of leukocyte esterase without symptoms is not an indication for antibiotic treatment.

Table 23.3 – Laboratory tests to consider for diagnosis of lower urinary tract infections as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
Urinalysis test strips	To detect urinary tract infections	Community settings and health facilities without laboratories ^a

EDL: Model List of Essential In Vitro Diagnostics.

^a Community and health settings without laboratories are settings such as health posts and centres, doctors' offices, outreach clinics and ambulatory care. These tests are also assumed to be available at health care facilities with laboratories.

Using microbiology surveillance data

Empiric treatment would ideally be guided by recent clinically relevant local microbiology surveillance data, however these data are not routinely available. This would include clinical microbiology surveys of urine culture data from patients with lower UTI in the primary care/community setting, not hospital outpatient clinic data which likely over-estimate the prevalence of resistance. These surveys would ideally include information on the current and previous recent antibiotic treatment, clinical disease severity, patient risk factors and clinical outcomes. The focus would be on significant urine bacterial isolates resistant to antibiotics recommended in the EML and EMLc, such as nitrofurantoin.

Imaging

Initial imaging (e.g. ultrasound) of the urinary tract is not needed to diagnose a lower UTI. Imaging to investigate possible underlying abnormalities of the urinary tract could be considered, mostly in children and male patients.

No antibiotic care

Analgesic treatment should be complementary to antibiotic treatment to relieve pain associated with lower UTIs (Table 23.4). In young women who are not pregnant, clinically well, with a mild infection and who may wish to avoid or delay antibiotic treatment, symptomatic treatment alone (with a back-up antibiotic prescription) could be considered.

Table 23.4 – Medicines to consider for pain control of lower urinary tract infections

! Important		
Medicines are listed in alphabetical order and they should all be considered equal treatment options.		
Medicine	Formulation	Dose and frequency
Ibuprofen ^a	Oral liquid: 200 mg/5 mL Tablet: 200 mg; 400 mg; 600 mg	Adults: 200–400 mg given every 6 to 8 hours (maximum dose of 2.4 g a day) Children: Pain control/antipyretic treatment: 5–10 mg/kg given every 6 to 8 hours Weight bands: 6–< 10 kg: 50 mg given every 8 hours 10–< 15 kg: 100 mg given every 8 hours 15–< 20 kg: 150 mg given every 8 hours 20–< 30 kg: 200 mg given every 8 hours ≥ 30 kg: use adult dose
Paracetamol (acetaminophen) ^b	Oral liquid: 120 mg/5 mL; 125 mg/5 mL Suppository: 100 mg Tablet: 100 mg to 500 mg	Adults: 500 mg–1 g given every 4 to 6 hours (maximum dose of 4 g a day) ^c Children: Pain control/antipyretic treatment: 10–15 mg/kg given every 6 hours Weight bands: 3–< 6 kg: 60 mg given every 6 hours 6–< 10 kg: 100 mg given every 6 hours 10–< 15 kg: 150 mg given every 6 hours 15–< 20 kg: 200 mg given every 6 hours 20–< 30 kg: 300 mg given every 6 hours ≥ 30 kg: use adult dose

^a Not for children < 3 months.

^b Not recommended for use as an anti-inflammatory as it has not been proven to have such an effect.

^c In patients with hepatic impairment or cirrhosis, maximum daily dose should be 2 g.

Antibiotic treatment

Antibiotic treatment is usually given empirically if there are compatible signs and symptoms of a UTI **AND** a positive test (urinalysis or urine culture). If diagnostic tests cannot be performed, treatment may be given based on clinical presentation alone. If a urine culture is performed, empiric treatment should be reassessed once the results of susceptibility testing are available.

Clinical improvement should be within 48–72 hours of starting treatment. In general, antibiotics shorten the duration of symptoms by about 2 days (225). Efforts to reduce patient self-medication with antibiotics should be made as self-medication is still very common in some settings (226).

Local patterns of AMR, mostly to *Escherichia coli*, should be considered when available but interpreted with caution. In most cases, the summary prevalence of resistance reported by hospital microbiology laboratories will probably not be representative of first infections in the primary health care setting and may overestimate the true prevalence of resistance for lower UTIs because of selection bias. Most urine cultures are done on patients who have relapsed after their first empiric treatment and are being re-treated or have underlying reason for a higher risk of resistant infections. Most lower UTIs in patients who are not at risk of complications are still caused by pathogens that are susceptible to commonly used antibiotics. However, patterns of resistance based on good quality local data when available and on individual risk factors (e.g. previous urine culture results and recent antibiotic exposure) should be considered (227–229). In particular, *Escherichia coli* may have varying levels of resistance to first-choice antibiotics (230) and resistance is associated with higher rates of clinical failure (15).

Nitrofurantoin for 5 days is the main antibiotic recommended for acute cystitis. However, the paediatric formulation (syrup) may not be widely available and is currently expensive, even in high-income settings. Nitrofurantoin still has activity against most isolates producing ESBL (231).

Different empiric antibiotic options for treating lower UTIs are shown in Table 23.5.

Treatment duration is influenced by the antibiotic used, the age and sex of the patient, and for women by the presence of pregnancy.

Table 23.5 – Empiric antibiotic treatment for lower urinary tract infections

Adults	Children	Total treatment duration ^d
Amoxicillin+clavulanic acid ^a (oral): 500 mg + 125 mg given every 8 hours	Amoxicillin+clavulanic acid ^{a,c} (oral): 80–90 mg/kg/day of amoxicillin component Oral weight bands: 3–< 6 kg: 250 mg of amoxicillin/dose given every 12 hours 6–< 10 kg: 375 mg of amoxicillin/dose given every 12 hours 10–< 15 kg: 500 mg of amoxicillin/dose given every 12 hours 15–< 20 kg: 750 mg of amoxicillin/dose given every 12 hours ≥ 20 kg: 500 mg of amoxicillin/dose given every 8 hours or 1 g of amoxicillin/dose given every 12 hours	3–5 days
Nitrofurantoin (oral): <ul style="list-style-type: none">• 100 mg given every 12 hours (modified-release formulation)• 50 mg given every 6 hours (immediate-release formulation)	Nitrofurantoin (oral): <ul style="list-style-type: none">• 2 mg/kg/dose given every 12 hours• 1 mg/kg/dose given every 6 hours (immediate release formulation)	5 days

continues

Table 23.5 continued

Adults	Children	Total treatment duration ^d
Sulfamethoxazole+trimethoprim ^b (oral): 800 mg + 160 mg given every 12 hours	Sulfamethoxazole+trimethoprim (oral): 4 mg/kg (of trimethoprim component), every 12 hours Oral weight bands: mg of sulfamethoxazole(trimethoprim component) 3-< 6 kg: 100 mg/20 mg given every 12 hours 6-< 10 kg: 200 mg/40 mg given every 12 hours 10-< 30 kg: 400 mg/80 mg given every 12 hours ≥ 30 kg: use adult dose	3 days
Trimethoprim (oral): 200 mg given every 12 hours	Trimethoprim (oral): 4 mg/kg, every 12 hours Oral weight bands: 3-< 6 kg: 20 mg given every 12 hours 6-< 10 kg: 40 mg given every 12 hours 10-< 30 kg: 80 mg given every 12 hours ≥ 30 kg: use adult dose	3 days

Note. All dosages are for normal renal and hepatic function.

^a Amoxicillin+clavulanic acid: *Escherichia coli* resistance rates to amoxicillin+clavulanic acid are lower than to amoxicillin alone. This combination still has activity against some extended-spectrum beta-lactamase-producing isolates and it can be considered an acceptable option, particularly in young children.

^b Resistance to sulfamethoxazole+trimethoprim is high in many settings (232,233). It is ineffective against most isolates producing extended-spectrum beta-lactamases. It is not recommended in the first trimester of pregnancy.

^c Oral liquid formulations must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures.

^d In general, shorter treatments are indicated for children or non-pregnant women (3–5 days depending on the antibiotic), while longer treatments are indicated for pregnant women (usually 5 days) or men (usually 7 days).

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.



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24. Sepsis in adults (including septic shock)

Key messages

- Sepsis is an acute life-threatening condition characterized by organ dysfunction due to a dysregulated host response to infection. Its most severe form – associated with high mortality – is septic shock.
- Usually signs and symptoms are non-specific, the presence of any danger signs of severe illness should always be assessed to guide clinical management.
- Antibiotic treatment should be started as soon as possible when sepsis is suspected. However, not every patient with an infection has sepsis and the term sepsis should therefore be used carefully.
- Diagnostic tests and imaging should not delay treatment and should be guided by the suspected site of primary infection.
- Antibiotic treatment should be regularly re-evaluated including the possibility to simplify or stop antibiotics.



Other relevant WHO resources (please check regularly for updates)

- Sepsis – fact sheet (234).
- Global report on the epidemiology and burden of sepsis: current evidence, identifying gaps and future directions (235).
- Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper –February 2019 (35).
- Typhoid vaccines: WHO position paper – March 2018 (154).
- Meningococcal A conjugate vaccine: updated guidance, February 2015 (236).

Definition

In some patients with infection, a dysregulated host immune response to the infection contributes to the severity of the disease and organ dysfunction. These patients are at increased risk of death and severe sequelae and should be identified and treated rapidly.

The definition of sepsis has remained a challenge because sepsis is not a single entity (the pathogens and primary sites of infection causing sepsis, for example, vary widely) but a continuum of many different clinical presentations.

Because of the serious clinical consequences of sepsis (see section on epidemiology), many attempts have been made to provide clinicians with simple and easy-to-use criteria for identifying patients with sepsis.

 **Note**

Sepsis in adults was last defined in 2016 by the Third International Consensus Definitions for Sepsis and Septic Shock, known as SEPSIS-3 (237). According to this definition, sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection.

Compared with previous definitions (SEPSIS-1 in 1991 and SEPSIS 2 in 2001), SEPSIS-3 removed the criteria for "systemic inflammatory response syndrome (SIRS)" from the definition because the criteria lacked specificity. SIRS referred to an exaggerated inflammatory response of the body to a noxious cause characterized by a combination of symptoms such as fever or hypothermia, increased heart and/or respiratory rate and increased white blood cell count. SEPSIS-3 also dropped the term severe sepsis because the concept of non-severe sepsis was not helpful – all sepsis is a severe disease – and could be misleading and divert attention from providing rapid and effective treatment. Instead, SEPSIS-3 differentiates only between sepsis and septic shock. Septic shock is defined as a type of sepsis in which underlying circulatory and cellular and/or metabolic abnormalities are severe enough to substantially increase mortality. Patients with septic shock have persistent hypotension that requires vasopressor medication to maintain a mean arterial pressure of 65 mmHg or more and a level of serum lactate more than 2 mmol/L ($> 18 \text{ mg/dL}$) in the absence of hypovolaemia (238).

It should be noted that the definition of sepsis does not include the detection of bacteria in blood cultures (i.e. bacteraemia). See Box 24.1 for terms and definitions related to bloodstream infections.

Box 24.1 – Bacteraemia

Bacteraemia (i.e. the detection of bacteria in blood cultures) is not part of the definition of sepsis. While many patients with sepsis have bacteraemia, this is not a universal finding and most patients with bacteraemia do not meet sepsis criteria. The term septicaemia should be avoided. The terms bacteraemia and bloodstream infection, are often used interchangeably. However bloodstream infections can also be caused by pathogens other than bacteria (e.g. fungi).

The Global Antimicrobial Resistance Surveillance System (GLASS) uses the following definition of suspected bloodstream infection (239):

Presence of two or more of the following clinical signs in an adult patient:

- Hyperthermia ($> 38.0^{\circ}\text{C}$) or hypothermia ($< 36.0^{\circ}\text{C}$)
- Respiratory rate ≥ 20 breaths/minute
- Heart rate > 90 beats/minute.

A confirmed bloodstream infection requires the isolation of a clinically relevant pathogen from a blood sample of a patient (all ages) seeking health care at a health care facility.

The criteria to identify sepsis according to SEPSIS-3 are difficult to apply in low- and middle-income countries because severity is based on criteria and tests that may not be routinely available in these settings, for example, the use of inotropes, and determination of arterial oxygen partial pressure, bilirubin levels, creatinine concentrations and platelet counts. Furthermore, the Sequential Organ Failure Assessment (SOFA) score (see Table 24.1) has been validated mostly in high-income settings. Its performance in low- and middle-income countries, where causes of sepsis rarely encountered in most high-income settings (e.g. dengue and malaria) are frequent and HIV infection is more prevalent, is unclear.

To implement the SEPSIS-3 definition, clinical and laboratory signs are graded to give an overall SOFA score, and an acute change of two or more points in the baseline score is proposed to identify organ dysfunction due to infection and predict the short-term mortality risk (237).

The SOFA score (range 0–24) includes six parameters – two clinical and four laboratory ones. Each parameter can have a value from 0 to 4 (Table 24.1). The baseline SOFA score can be assumed to be zero in patients with no known pre-existing organ dysfunction.

Table 24.1 – Sequential Organ Failure Assessment (SOFA) score

Parameter	Score			
	0	1	2	3
PaO ₂ /FiO ₂ , mmHg (kPa) (53.3)	≥ 400 (40.0 - 53.2)	300 - 399 (26.7 - 39.9)	200 - 299 (13.3 - 26.6)	100 - 199 (13.3)
MAP mmHg (kPa) and catecholamine doses needed, µg/kg/min for ≥ 1 h	MAP: ≥ 70 (9.3)	MAP: < 70 (9.3)	Dopamine: < 5 OR Dobutamine any dose	Dopamine: 5.1-15 OR Epinephrine/ norepinephrine: ≤ 0.1
Platelets, × 10 ³ /µL (or × 10 ⁹ /L)	≥ 150	100 - 149	50 - 99	20 - 49
Bilirubin, mg/dL (µmol/L)	< 1.2 (20)	1.2-1.9 (20-32)	2-5.9 (33-101)	6.0-11.9 (102-204)
Glasgow coma scale ^a	15	13-14	10-12	6-9
Creatinine, mg/dL (µmol/L)	< 1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)
Urine output, mL/day			< 500	< 200

FiO₂: fractional inspired oxygen; MAP: mean arterial pressure; PaO₂: arterial oxygen partial pressure.

^aThe Glasgow coma scale is a clinical scale used to measure a person's level of consciousness based on the assessment of three parameters: eye opening response (maximum 4 points assigned), best verbal response (maximum 5 points assigned) and best motor response (maximum 6 points assigned). The total score can range from 3 (completely unresponsive) to 15 (responsive). Scores lower than 8 usually indicate a comatose state. To calculate the Glasgow coma scale, several online calculators exist.



A simplified quick version of the SOFA score called qSOFA (Table 24.2) exists that only includes three clinical criteria (mental status, blood pressure and respiratory rate) and an increase by two points can be used at the bedside for early identification of sepsis, even in low-resource settings (240). A retrospective analysis of cohort studies conducted in 17 hospitals in 10 low- and middle-income countries in sub-Saharan Africa, Asia and the Americas found that a high qSOFA score identified patients with infections who were at an increased risk of death (beyond the risk they had based on their baseline risk factors), with some variability among cohorts (241).

Table 24.2 – Quick Sequential Organ Failure Assessment (qSOFA) score

Parameter	Value
Respiratory rate	≥ 22 breaths/min
Altered mental status	Glasgow coma scale < 15 ^a
Systolic blood pressure	≤ 100 mmHg (≤ 13.3 kPa)

^aThe Glasgow come scale is a clinical scale used to measure a person's level of consciousness based on the assessment of three parameters: eye opening response (maximum 4 points assigned), best verbal response (maximum 5 points assigned) and best motor response (maximum 6 points assigned). The total score can range from 3 (completely unresponsive) to 15 (responsive). Scores lower than 8 usually indicate a comatose state. To calculate the Glasgow coma scale, several online calculators exist.



Sepsis & septic shock

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Definition

Sepsis (Sepsis 3):

- A life-threatening organ dysfunction caused by a dysregulated host response to infection

Septic Shock:

- A type of sepsis in which underlying circulatory and cellular and/or metabolic abnormalities substantially increase short-term mortality
- Patients have persistent hypotension and require vasopressors to maintain a mean arterial pressure ≥ 65 mmHg (8.7 kPa) and present with a level of serum lactate > 2 mmol/L (> 18 mg/dL) in the absence of hypovolaemia

Important: bacteraemia is not part of the definition of sepsis, while many patients with sepsis have bacteraemia, most patients with bacteraemia do not fulfill sepsis criteria



Most Likely Pathogens

- Sepsis can originate from any type of infection in any organ system. Bacteria, viruses, fungi and protozoa can all cause sepsis (but only sepsis of bacterial origin is addressed here)
- Consider pathogens other than bacteria based on local epidemiology (e.g. malaria, viral haemorrhagic fevers, influenza, COVID-19)

Community Setting (in alphabetical order):

- Enterobacteriales
 - Escherichia coli*, *Klebsiella pneumoniae* and others
 - Invasive non-typhoidal *Salmonella* (elderly patients and patients with HIV)
 - Salmonella Typhi* and *Paratyphi* (causing enteric fever)
- Staphylococcus aureus* (including MRSA)
- S. pyogenes* (group A *Streptococcus*)
- S. pneumoniae* (including penicillin non-susceptible strains)

Others to consider:

- Burkholderia pseudomallei* (pathogen causing melioidosis, endemic in South-East Asia and Australia)
- Neisseria meningitidis*

Hospital Setting (in alphabetical order):

- Acinetobacter baumannii**
- Enterobacteriales* (*Escherichia coli*, *Klebsiella pneumoniae* and others)
- Pseudomonas aeruginosa**
- Staphylococcus aureus* (including MRSA)

*Including multidrug-resistant strains such as those producing ESBL and carbapenemases

Maternal Sepsis:

- Consider *Listeria monocytogenes* and *Streptococcus agalactiae*, however the urinary tract represents main source of infection

Diagnosis

Clinical Presentation

- Early recognition of the source of infection and treatment is fundamental and impacts mortality
- Symptoms are highly variable and mostly non-specific
- Patients often present with fever (≥ 38.0 °C) or hypothermia (< 36.0 °C); tachycardia, respiratory distress, acute altered mental status and hypotension. Reduced urine output may be present

Important:

- Accurate identification of patients with sepsis is difficult and no single reference standard test exists
- Adoption and use of the internationally accepted definitions is critical to avoid overdiagnosis and overtreatment
- While it is important to rapidly treat patients with sepsis and septic shock with antibiotics it should be kept in mind that only a very small proportion of patients with an infection have sepsis



Microbiology Tests

- Guided by the suspected primary site of infection but should always include blood cultures (ideally two sets)
- Tests should ideally be performed before initiating antibiotics



Other Laboratory Tests

To Identify a Bacterial Infection:

- White blood count, CRP and/or procalcitonin
- In initial patient assessment, inflammatory markers in the normal range do not rule out sepsis if high pre-test probability

To Identify Organ Dysfunction:

- Bilirubin, blood pH and gases**, blood urea nitrogen (required for CURB-65 score calculation if suspected pneumonia), complete blood count with **platelets, creatinine, electrolytes, glucose, whole blood lactate**
- Tests in bold are required for SOFA score calculation

Imaging

Guided by the suspected primary site of infection

Prevention

- Preventing infections includes vaccinations, adequate nutrition, and access to safe water and sanitation
- Preventing evolution of infection to sepsis relies on timely diagnosis and adequate treatment of the underlying infection

Sepsis & septic shock

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Organ Dysfunction Assessment Scores

Sequential Organ Failure Assessment (SOFA)

Parameter	Score				
	0	1	2	3	4
Pa _O ₂ /FiO ₂ , mmHg (kPa)	≥ 400 (53.3)	300 - 399 (40.0 - 53.2)	200 - 299 (26.7 - 39.9)	100 - 199 (13.3 - 26.6)	< 100 (13.3)
MAP mmHg (kPa) and catecholamine doses needed (µg/kg/min for ≥ 1h)	MAP ≥ 70 (9.3)	MAP < 70 (9.3)	Dopamine < 5 OR dobutamine any dose	Dopamine 5.1–15 OR epinephrine (adrenaline)/ norepinephrine ≤ 0.1	Dopamine > 15 OR epinephrine/ norepinephrine > 0.1
Platelets (x 10 ³ /µL, x 10 ³ /L)	≥ 150	100 - 149	50 - 99	20 - 49	< 20
Bilirubin mg/dL (µmol/L)	< 1.2 (20)	1.2 - 1.9 (20 - 32)	2.0 - 5.9 (33-101)	6.0 - 11.9 (102 - 204)	> 12.0 (204)
Glasgow coma scale	15	13 - 14	10 - 12	6 - 9	< 6
Creatinine mg/dL (µmol/L)	< 1.2 (110)	1.2 - 1.9 (110 - 170)	2.0 - 3.4 (171 - 299)	3.5 - 4.9 (300-440)	> 5.0 (440)
Urine output (mL/day)				< 500	< 200

Definitions: FiO₂: fractional inspired oxygen; PaO₂: arterial oxygen partial pressure; MAP: mean arterial pressure

Quick SOFA (qSOFA)

Parameter	Value
Respiratory Rate	≥ 22 breaths/min
Altered Mental Status	Glasgow Coma Scale < 15
Systolic Blood Pressure	≤ 100 mmHg

Interpretation

An acute change of ≥ 2 points from the baseline score suggests organ dysfunction due to infection

These scores have not been extensively validated for use in low- and middle-income settings

Sepsis & septic shock

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Rx Treatment (Section 1 of 2)

Clinical Considerations

- Treatment includes treatment of the underlying infection, source control, and life-saving interventions (not addressed here)
- Many infections require surgical source control; antibiotics are complementary in these cases
- Start IV antibiotics as soon as possible if sepsis is suspected; results of tests should not delay antibiotics
- To choose the best empiric treatment consider most likely infection site and pathogens, local prevalence of antibiotic resistance, comorbidities, and risk of multidrug-resistant organisms
- If pathogen and susceptibilities are known, review antibiotics and adapt treatment

Important:

- Simplify** empiric treatment to a more narrow spectrum antibiotic based on culture results or rapid clinical improvement if culture results unavailable
- Step down to oral treatment** is based on improvement of symptoms, signs of infection and the ability to take oral antibiotics



Antibiotic Treatment Duration

- Varies based on underlying disease, degree of immunosuppression and clinical response
- Clinical Sepsis of Unknown Origin: **7 days**
- Meningitis: **10 days** (may differ in epidemics and with different pathogens)
- Lower Respiratory Tract Infection: **5 days**

Rx Clinical Sepsis of Unknown Origin

All dosages are for normal renal function

Cefotaxime 2 g q8h IV

WATCH

OR

Ceftriaxone 2 g q24h IV

WATCH

COMBINED WITH

Amikacin 15 mg/kg q24h IV

ACCESS

OR

Gentamicin 5 mg/kg q24h IV

ACCESS

Amikacin (and to a lesser extent gentamicin) retain activity against ESBL-producing strains and can be considered as a carbapenem-sparing option

Although (for each infection) antibiotics are listed in alphabetical order they should all be considered equal treatment options

Rx Meningitis

Refer also to the bacterial meningitis infographic

All dosages are for normal renal function

Consider second choice options only when first choice options are not available

First Choice

Cefotaxime 2 g q6h IV

WATCH

OR

Ceftriaxone 2 g q12h IV

WATCH

Second Choice

Amoxicillin 2 g q4h IV

ACCESS

OR

Ampicillin 2 g q4h IV

ACCESS

OR

Benzylpenicillin 4 million IU (2.4 g) q4h IV

ACCESS

OR

Chloramphenicol 1 g q6h IV

ACCESS

Use chloramphenicol only when no other option is available

Rx Lower Respiratory Tract Infection

Refer also to the community-acquired pneumonia infographic

All dosages are for normal renal function

Cefotaxime 2 g q8h IV

WATCH

OR

Ceftriaxone 2 g q24h IV

WATCH

COMBINED WITH

Clarithromycin 500 mg q12h IV

WATCH

Sepsis & septic shock

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Rx Treatment (Section 2 of 2)

Antibiotic Treatment Duration

- Varies based on underlying disease, degree of immunosuppression and clinical response
- Enteric Fever: **10 days**
- Intra-abdominal and Skin & Soft Tissue infections: **generally 7 days** depending on infection type, if adequate surgical source control achieved and on clinical recovery
- Urinary Tract Infection: **7 days**

Although (for each infection) antibiotics are listed in alphabetical order they should all be considered equal treatment options

Rx Enteric Fever

Refer also to the enteric fever infographic

All dosages are for normal renal function

 Ceftriaxone 2 g q24h IV

Some countries may have problems of increasing ceftriaxone resistance

Rx Intra-abdominal Infection

Refer also to the appendicitis, cholecystitis/cholangitis, diverticulitis and liver abscess infographics

All dosages are for normal renal function

First Choice

 Cefotaxime 2 g q8h IV

OR

 Ceftriaxone 2 g q24h IV

COMBINED WITH

 Metronidazole 500 mg q8h IV

OR

 Piperacillin+tazobactam 4 g+500 mg q6h IV

First choice options do not provide adequate activity against many ESBL-producing isolates; consider meropenem

Second Choice

 Meropenem 2 g q8h IV

Rx Skin and Soft Tissues Infection

Refer also to the necrotizing fasciitis infographic

All dosages are for normal renal function

 Ceftriaxone 2 g q24h IV

COMBINED WITH

 Metronidazole 500 mg q8h IV

In case of suspected necrotizing fasciitis ceftriaxone and metronidazole should ONLY be used if *Streptococcus pyogenes* has been excluded

OR

 Piperacillin+tazobactam 4 g+500 mg q6h IV

COMBINED WITH

 Clindamycin 900 mg q8h IV

Preferred option in case of confirmed or suspected necrotizing fasciitis

IF MRSA SUSPECTED, ADD

 Vancomycin 15-20 mg/kg q12h IV

Rx Urinary Tract Infection

Refer also to the upper urinary tract infection infographic

All dosages are for normal renal function

 Cefotaxime 2 g q8h IV

OR

 Ceftriaxone 2 g q24h IV

COMBINED WITH

 Amikacin 15 mg/kg q24h IV

Amikacin retains activity against ESBL-producing strains and can be considered as a carbapenem sparing option

Pathophysiology

Sepsis is a serious and complex clinical condition caused by a complicated interplay between an infectious agent and a dysregulated systemic immunological response by the patient, which could potentially result in multiple organ dysfunction and possibly death. Risk factors for sepsis mostly overlap with those that predispose patients to infection, for example, being very old or very young, immunosuppression due to HIV infection, cancer, on medications, cirrhosis, alcohol abuse, poorly controlled diabetes, indwelling catheters and malnutrition. Genetic factors are also implicated in the likelihood of developing sepsis in patients with an infection (242).

Epidemiology

Sepsis is an important global health problem that can be difficult to diagnose and manage, especially in low-income settings (234,243). According to the Global Burden of Disease study, about 49 million new cases of sepsis occurred worldwide in 2017, a decrease of almost 19% compared with 1990 (244). The most common underlying cause of sepsis is still diarrhoeal disease – 9 million attributable cases in 2017. Since 2017, the number of sepsis-related deaths has decreased worldwide (a 29% decrease compared with 1990) but deaths were still high (11 million in 2017) with the highest burden in sub-Saharan Africa. The most common underlying cause of sepsis-related death was lower respiratory tract infections, 1.8 million attributable deaths in 2017. Children were more affected by sepsis than adults; in 2017, 20 million new cases of sepsis were in children < 5 years of age (see the chapter on sepsis in children and neonates). However, a second peak in incidence in older adults was reported. About one in four cases of sepsis is estimated to be hospital-acquired with high mortality rates (245).

Sepsis can also develop during pregnancy or in the first weeks after delivery. This form of sepsis is called maternal sepsis. In 2017, about 12 million new cases of maternal sepsis were reported (244). In the period 2003–2009, sepsis was the third leading cause of maternal death worldwide (10.7% of all maternal deaths or about 260 000 deaths) after haemorrhage and hypertensive disorders (246). Based on results of the global maternal sepsis study of more than 700 facilities in 52 countries, 70 pregnant women per 1000 live births in the study cohort were hospitalized with an infection, mostly of bacterial origin – 77% of those where a pathogen was identified (247). Infections with severe maternal outcomes (e.g. death) were frequent (11 per 1000 live births); however, large variations existed across countries – 15 per 1000 live births in low- and middle-income countries and 0.6 per 1000 in high-income countries. Infections originated most often from the genital (endometritis and chorioamnionitis) or urinary tract followed by skin, respiratory and abortion-related infections (247).

Infections with antibiotic-resistant bacteria are an increasingly important cause of sepsis worldwide with important implications for the management, especially in settings with limited resources. Antibiotic resistance can affect patient outcomes, increasing short-term mortality, mostly because in these cases effective antibiotic treatment active against the resistant pathogen may not be available or given late. In a 2015 European study, 170 DALYs per 100 000 population were due to infections caused by antibiotic-resistant bacteria, of which about 70% were caused by bloodstream infections (248).

In 2017, the World Health Assembly adopted a resolution on sepsis to urge WHO Member States to implement measures to reduce the burden of sepsis by increasing efforts to improve sepsis prevention, diagnosis and treatment, including through increased research, training of health care professionals and public awareness campaigns (234,249).

Most likely pathogens

Sepsis can originate from any type of infection (bacterial, viral, fungal and protozoal) in any organ system. Infections can be community-acquired or hospital-acquired (or health care-associated). The bacterial pathogens associated with sepsis will vary widely depending on the primary site of infection, geography and place of acquisition (community or hospital, see Table 24.3).

Pathogens other than bacteria should be considered according to the local epidemiology. For example, certain settings are endemic for *Plasmodium* spp., the pathogen causing malaria, and this should always be considered where appropriate, including after travel to endemic areas. Many other pathogens, including viruses causing viral haemorrhagic fevers or respiratory viruses such as the influenza virus and SARS-CoV-2 and fungal infections, also need to be considered where appropriate (community- and hospital-acquired infections).

The mortality from sepsis is higher with infections caused by multidrug-resistant bacteria, which are commonly identified in hospital-acquired infections.

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24. Sepsis in adults (including septic shock)

Table 24.3 – Bacteria most frequently identified in blood cultures in patients with sepsis (also refer to Box 24.1 on bacteraemia)

Setting of acquisition of the infection	Bacteria (in alphabetical order)
Community	<i>Enterobacteriales</i> ^a (<i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> and others) <i>Invasive non-typhoidal Salmonella</i> (elderly patients and patients living with HIV) <i>Salmonella Typhi</i> and <i>Paratyphi</i> (causative agent of enteric fever) <i>Staphylococcus aureus</i> (including MRSA) <i>Streptococcus pneumoniae</i> (including penicillin non-susceptible strains) <i>Streptococcus pyogenes</i> (group A <i>Streptococcus</i>)
	Other pathogens to consider <i>Burkholderia pseudomallei</i> (causative agent of melioidosis which is endemic in South-East Asia and Australia) <i>Neisseria meningitidis</i> (including strains resistant to third-generation cephalosporins)
Hospital	<i>Acinetobacter baumannii</i> ^b <i>Enterobacteriales</i> ^a (<i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> and others) <i>Pseudomonas aeruginosa</i> ^a <i>Staphylococcus aureus</i> (including MRSA)
Maternal sepsis (additional pathogens to consider) ^b	<i>Listeria monocytogenes</i> <i>Streptococcus agalactiae</i> (group B <i>Streptococcus</i>)

HIV: human immunodeficiency virus; MRSA: methicillin-resistant *Staphylococcus aureus*.

Note. Most data on the pathogens associated with sepsis come from high-income settings.

^a Including multidrug-resistant strains such as those producing extended-spectrum beta-lactamases and carbapenemases.

^b In cases of maternal sepsis, however, the urinary tract represents the main source of infection (see epidemiology section).



Clinical presentation

Note

Presenting symptoms and signs and the clinical course of sepsis are highly variable and depend on the underlying pathogen, the main organ affected and the host response. Early recognition and treatment of sepsis is essential and can affect mortality. Therefore, signs of severe infection and organ dysfunction should be identified promptly.

Patients with sepsis usually present with non-specific signs and symptoms. The most frequent symptoms include fever ($\geq 38.0^{\circ}\text{C}$) or hypothermia ($< 36.0^{\circ}\text{C}$), some degree of respiratory distress (e.g. increased respiratory rate), tachycardia, acute altered mental status (e.g. disorientation and agitation) and hypotension. Oliguria (i.e. reduced urine output) may also be present.

Sepsis may be more difficult to diagnose in countries where vector-transmitted diseases (e.g. malaria and dengue) are endemic; therefore, sepsis should always be considered if there are any signs and symptoms of sepsis in these settings.

As outlined earlier, bacteraemia (i.e. the detection of bacteria in blood cultures) may be present depending on the type of pathogen, the primary site of infection and whether antibiotic treatment was administered before obtaining blood cultures. However, bacteraemia is not always found in patients with sepsis and most patients with bacteraemia do not have sepsis.

Note

Accurate identification of patients with sepsis is difficult and no single gold standard test exists. Therefore, adoption and use of internationally accepted case definitions (e.g. the SEPSIS-3 definition) is critical to avoid over-diagnosis and overtreatment. Not every patient with an infection has sepsis, in fact, only a very small proportion of patients with infection have sepsis. The term sepsis should therefore be used carefully.

Sepsis of unknown origin. The treatment of this type of sepsis is based on the most probable clinical situation. Patients should be carefully examined to localize a source of infection, including pressure ulcers, deep-seated abscesses and indwelling vascular and urinary catheters. In patients with central lines, the possibility of a central line-associated bloodstream infection should be considered with a positive blood culture and no other apparent source of infection. Bloodstream infections can also be associated with peripheral vascular lines.

Laboratory tests

Patient microbiology tests

Note

Diagnostic tests should be guided by the suspected primary site of infection. Tests, and management, which are outlined in the following paragraphs, will be different for suspected pneumonia, intra-abdominal infection, urinary tract infection, meningitis or sepsis of unknown origin. Please also refer to specific chapters of the AWaRe book based on the suspected underlying infection.

Microbiology tests help establish a definitive diagnosis of sepsis and identify the causative pathogen and underlying infection. Isolating a pathogen from a normally sterile body site (e.g. blood, cerebrospinal fluid) that is compatible with the clinical signs and symptoms usually confirms the diagnosis. However, the causative pathogen is not identified in a substantial proportion of cases, especially in patients pretreated with antibiotics.

Tests to consider when sepsis of bacterial origin is suspected include those listed in Table 24.4. Ideally, these tests should be done before starting antibiotic treatment.

Table 24.4 – Microbiology tests to consider when sepsis of bacterial origin in suspected depending on the most likely source of infection as indicated in the WHO EDL (6)

Suspected underlying infection	Diagnostic test	Purpose of the test	Settings where the test should be available
All cases where sepsis is suspected	Blood cultures and antimicrobial susceptibility testing	To detect bacterial bloodstream infections	Health care facilities with clinical laboratories
Lower respiratory tract infection	Sputum microscopy (Gram stain)	To assess microbial morphology and adequacy of the specimen for culture by identifying white blood cells and squamous epithelial cells	Health care facilities with clinical laboratories

continues

Table 24.4 *continued*

Suspected underlying infection	Diagnostic test	Purpose of the test	Settings where the test should be available
Lower respiratory tract infection	Sputum culture and antimicrobial susceptibility testing	Initial step to detect and identify bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories
Meningitis	Cerebrospinal fluid Gram stain, bacterial culture and antimicrobial susceptibility testing	Initial step to detect and identify bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories
Meningitis	Cerebrospinal fluid microscopy	To assess microbial morphology, number of white blood cells and red blood cells	Health care facilities with clinical laboratories
Diarrhoeal disease, enteric fever ^a	Stool culture and antimicrobial susceptibility testing	Initial step to detect and identify bacterial species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories
Abscess (e.g. in the context of intra-abdominal infections, skin and soft-tissue infections and dental infections)	Culture and antimicrobial susceptibility testing of abscess and/or fluid collections that can be drained	Initial step to detect and identify bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories
Urinary tract infection	Urine culture and antimicrobial susceptibility testing	Initial step to detect and identify bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics.

^a If enteric fever is suspected, note that stool cultures have a low sensitivity and are not useful in the early phase (first week) of the disease when the test is often negative.

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24. Sepsis in adults (including septic shock)

Other tests

Laboratory tests can be used to complement the clinical examination and history. Table 24.5 and Table 24.6 indicate the tests that could be considered to make an initial assessment of the patient and to help guide the duration of antibiotic treatment. Additional laboratory tests may be considered based on local availability and on the most likely source of infection. Further tests are detailed in the corresponding chapter.

Table 24.5 – Laboratory tests (other than microbiology) to consider when sepsis is suspected to identify a bacterial infection as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
White blood count	To help in the diagnosis of infections	Health care facilities with clinical laboratories but also in primary care settings
C-reactive protein ^a	To detect inflammation as an indicator of various conditions (e.g. sepsis)	Health care facilities with clinical laboratories
Procalcitonin ^a	To guide antibiotic therapy or discontinuation in sepsis	Only in tertiary health care facilities

EDL: Model List of Essential In Vitro Diagnostics.

^a Biomarkers C-reactive protein and procalcitonin may help determine whether an infection is caused by bacteria. Regular serial measurement of these biomarkers can also help decide when antibiotic therapy can be stopped (250–252). It is important to note that the probability of sepsis based on the patient's initial clinical assessment before testing (pre-test probability) needs to be considered. If the pre-test probability is high, inflammatory markers in the normal range do not rule out sepsis.

Table 24.6 – Laboratory tests (other than microbiology) to consider when sepsis is suspected to identify organ dysfunction as indicated in the WHO EDL (6)

Diagnostic test ^a	Purpose of the test	Settings where the test should be available
Bilirubin	To detect or monitor liver disease, bile duct disorders and red cell destruction Required for SOFA score calculation	Community settings and health facilities without laboratories ^b
Blood pH and gases	To assess lung function and metabolic or kidney disorders, and monitor oxygen therapy Required for SOFA score calculation (for PaO₂/FiO₂)	Health care facilities with clinical laboratories

continues

Table 24.6 *continued*

Diagnostic test^a	Purpose of the test	Settings where the test should be available
Blood urea nitrogen	To assess kidney function Required for CURB-65 score calculation (if pneumonia is suspected ^c)	Health care facilities with clinical laboratories
Complete blood count	To detect a wide range of disorders, including infections	Health care facilities with clinical laboratories
Creatinine	To monitor kidney function for management of severe infections (i.e. sepsis) and to adjust antimicrobial regimen Required for SOFA score calculation	Health care facilities with clinical laboratories
Electrolytes	To monitor fluid, electrolyte and acid-base balance	Health care facilities with clinical laboratories
Glucose	To diagnose intermediate hyperglycaemia and hypoglycaemia	Community settings and health facilities without laboratories ^b
Haemoglobin	To diagnose and monitor anaemia This is a clinical marker for some severe infections (e.g. malaria and viral haemorrhagic fevers)	Community settings and health facilities without laboratories ^b
Platelet count	To diagnose thrombocytopenia or thrombocytosis. This is a marker to manage severe infections associated with sepsis (e.g. viral haemorrhagic fever and meningococcaemia) Required for SOFA score calculation	Health care facilities with clinical laboratories
White blood cell count	To aid in the diagnosis of infections	Health care facilities with clinical laboratories
Whole blood lactate	To assess metabolic acidosis, sepsis and dehydration	Community settings and health facilities without laboratories ^b

EDL: Model List of Essential In Vitro Diagnostics; FiO_2 : fractional inspired oxygen; PaO_2 : arterial oxygen partial pressure; SOFA: Sequential Organ Failure Assessment.

^aThe tests are listed in alphabetical order.

^bCommunity and health settings without laboratories are facilities such as health posts and centres, doctors' offices, outreach clinics, ambulatory care. These tests are assumed to be available at health care facilities with laboratories.

^cSee the chapter on community-acquired pneumonia for more information.

Using microbiology surveillance data

Empiric guidance given by the AWaRe book could be reviewed and adapted based on local clinically relevant microbiology surveillance data.

Imaging

Note

Imaging studies should be guided by the suspected primary site of infection. Please also refer to specific chapters of the AWaRe book for the suspected underlying infection.

When sepsis is suspected and respiratory distress is present, a chest X-ray (or lung ultrasound) is indicated to confirm a lower respiratory tract infection. If an abdominal source of infection is suspected, in settings where it is available, a CT scan of the abdomen could be considered, for example, to confirm an intra-abdominal infection. A low-dose CT scan is an acceptable option, including in pregnant women (253). However, because abdominal ultrasound is more widely available, it can be a very helpful alternative depending on the exact site of infection. If sepsis caused by an infection of the urinary tract is suspected, initial imaging (e.g. ultrasound) of the urinary tract or during follow-up could be considered if an outflow obstruction (e.g. because of urolithiasis) or an abscess are suspected. If a dental infection is suspected, then X-rays are recommended, as detailed in the corresponding chapter.

Treatment

Treatment of sepsis includes treatment of the underlying infection, source control and life-saving interventions such as fluid resuscitation and vital organ support which are beyond the scope of the AWaRe book. For more specific guidance on treating sepsis, please refer to the 2016 international guidelines for management of sepsis and septic shock (254). Please also consult a 2016 review on the pathophysiology and clinical management of sepsis (255).

Antibiotic treatment (if bacterial sepsis is suspected)

Note

Intravenous antibiotic treatment should be started as soon as possible when sepsis of bacterial origin is suspected. Taking laboratory and microbiology tests or waiting for the results should not delay administration of the first dose of antibiotic treatment.

When selecting empiric antibiotic treatment, several factors should be considered, such as the most likely site of primary infection, the infecting pathogens and the local pattern of AMR. Comorbidities of the patient, including malnutrition and immunosuppression (e.g. due to HIV infection or neutropenia) and other factors, such as known colonization and/or previous infection with multidrug-resistant organisms, are also important factors to consider. Many variables must be considered to provide the best treatment to patients with sepsis.

Table 24.7 outlines suggested empiric treatment regimens for common primary sites of infection. In many infections (e.g. necrotizing fasciitis and intra-abdominal infections), source control (e.g. drainage of an abscess, surgical debridement) is essential.

If the pathogen causing the infection is identified and once its antibiotic susceptibilities are known, antibiotics should be reviewed and modified accordingly. However, even if enough suitable samples have been obtained and tested, a pathogen is identified only in a minority of patients with sepsis (256). When no pathogen is identified, antibiotic treatment should be guided by available laboratory results and clinical response. If an alternative cause of a non-bacterial cause of sepsis has been identified, the possibility to stop treatment should be evaluated.

Treatment duration is often decided on an individual basis according to clinical response and, if available, changes in laboratory markers of infection.

Simplify empiric treatment to a more narrow-spectrum antibiotic (often also called de-escalation) based on culture results (targeted treatment) or based on rapid clinical improvement when no microbiology test results are available. In general, the intravenous route is preferred for the initial phase of treatment.

Step-down to oral treatment is based on improvement of symptoms, signs of infection and the ability to take oral antibiotics allowing discharge of the patient home when clinically appropriate.

In patients with suspected sepsis of bacterial origin, a risk assessment based on clinical factors needs to be done, followed by appropriate tests and investigations to choose the best empiric antibiotic treatment. Patient-level and setting-level risk factors for infections caused by resistant bacteria need to be carefully considered.

- **Low-risk patients:** patients with no clinical risk factors for adverse outcomes. These patients have a low risk of infections caused by multidrug-resistant bacteria.
- **High-risk patients:** patients with major pre-existing comorbidities or immunocompromised and/or previous colonization or infection with a resistant pathogen. These patients have a higher risk of infections caused by multidrug-resistant bacteria.

Table 24.7 – Empiric antibiotic treatment for community-acquired sepsis of bacterial origin in adults

Most probable source of infection	Empiric antibiotic treatment	Total treatment duration (may vary also based on degree of immunosuppression)
Clinical sepsis of unknown origin ^a	<p>Cefotaxime^b (IV): 2 g given every 8 hours OR Ceftriaxone^b (IV): 2 g given once a day COMBINED WITH Amikacin^c (IV): 15 mg/kg given once a day OR Gentamicin^c (IV): 5 mg/kg given once a day</p>	<p>7 days</p> <p>But duration depends on the patient's underlying disease, the degree of immunosuppression, the causative pathogen (if any identified later on) and clinical progression)</p>
Enteric fever	Ceftriaxone ^d (IV): 2 g given once a day	10 days
Intra-abdominal infection	<p>First choice Cefotaxime (IV): 2 g given every 8 hours AND Metronidazole (IV): 500 mg given every 8 hours OR Ceftriaxone (IV): 2 g given once a day AND Metronidazole (IV): 500 mg given every 8 hours OR Piperacillin+tazobactam^e (IV): 4 g + 500 mg given every 6 hours Second choice Meropenem^f (IV): 2 g given every 8 hours</p>	<p>Generally 7 days.</p> <p>Duration depends on type of infection, whether adequate surgical source control was achieved, the degree of immunosuppression and on clinical recovery.</p> <p>Please refer to specific chapters of the AWaRe book based on the suspected underlying infection</p>

continues

Table 24.7 *continued*

Most probable source of infection	Empiric antibiotic treatment	Total treatment duration (may vary also based on degree of immunosuppression)
Meningitis	First choice Cefotaxime (IV): 2 g given every 6 hours OR Ceftriaxone (IV): 2 g given every 12 hours Second choice (only when first choice options are not available) Amoxicillin (IV): 2 g given every 4 hours OR Ampicillin (IV): 2 g given every 4 hours OR Benzylpenicillin (IV): 4 million IU (2.4 g) given every 4 hours OR Chloramphenicol ^g (IV): 1 g given every 6 hours	10 days ^h
Lower respiratory tract infection	Cefotaxime (IV): 2 g given every 8 hours AND Clarithromycin (IV): 500 mg given every 12 hours OR Ceftriaxone (IV): 2 g given once a day AND Clarithromycin (IV): 500 mg given every 12 hours	5 days

continues

Table 24.7 *continued*

Most probable source of infection	Empiric antibiotic treatment	Total treatment duration (may vary also based on degree of immunosuppression)
Skin and soft tissues infection	<p>Ceftriaxoneⁱ (IV): 2 g given once a day AND Metronidazoleⁱ (IV): 500 mg given every 8 hours (In case of necrotizing fasciitis, use this treatment option only if <i>Streptococcus pyogenes</i> infection has been excluded first)</p> <p>If MRSA is suspected, ADD Vancomycin (IV): 15–20 mg/kg given every 12 hours OR Piperacillin+tazobactam^j (IV): 4 g + 500 mg given every 6 hours AND Clindamycin (IV): 900 mg given every 8 hours</p> <p>If MRSA is suspected, ADD Vancomycin (IV): 15–20 mg/kg given every 12 hours</p>	Generally 7 days. Duration depends on type of infection, whether adequate surgical source control was achieved, the degree of immunosuppression, and clinical recovery. Please refer to specific chapters of the AWaRe book based on the suspected underlying infection
Urinary tract infection	<p>Cefotaximeⁱ (IV): 2 g given every 8 hours AND Amikacin^k (IV): 15 mg/kg given once a day OR Ceftriaxoneⁱ (IV): 2 g given once a day AND Amikacin^k (IV): 15 mg/kg given once a day</p>	7 days

AWaRe: Access, Watch and Reserve; ESBL: extended-spectrum beta-lactamases; IU: international units; IV: intravenous; MRSA: methicillin-resistant *Staphylococcus aureus*.

Note. All dosages are for normal renal and hepatic function. Dose adjustments may be required in patients with septic shock.

^a If the source of the infection is determined please follow infection-specific guidance.

^b Ceftriaxone or cefotaxime are alternative options. The choice can be made based on local availabilities.

^c Gentamicin and amikacin are alternative options. The choice can be made based on local availabilities. In addition, amikacin (and to a lesser extent gentamicin) is still effective against many isolates producing ESBL and is considered an appropriate carbapenem-sparing option in settings where ESBL-producing isolates are very prevalent.

continues

Table 24.7 *continued*

- ^d Some countries may have problems of increasing ceftriaxone resistance.
- ^e In patients considered at risk of infections with ESBL-producing Enterobacteriales, piperacillin+tazobactam does not provide adequate activity against many ESBL-producing isolates. In these cases, meropenem can be considered.
- ^f Meropenem should be considered only in settings with a high prevalence of ESBL-producing Enterobacteriales.
- ^g Use chloramphenicol only when no other choice is available.
- ^h Duration differs in the context of epidemics as indicated by WHO (257) and also depending on the pathogen identified.
- ⁱ Ceftriaxone and metronidazole is the preferred option if the suspected source of infection is polymicrobial (type 1) necrotizing fasciitis but it is also an adequate option in case of severe cellulitis.
- ^j Piperacillin+tazobactam (or penicillin) and clindamycin is the preferred option if the suspected source of infection is necrotizing fasciitis caused by *Streptococcus pyogenes* but it is also an adequate option in case of severe cellulitis.
- ^k Amikacin is still effective against ESBL-producing isolates and is considered an appropriate carbapenem-sparing option in settings where ESBL-producing isolates are prevalent.
- ^l Alternative antibiotics to consider based on local resistance data are piperacillin+tazobactam and carbapenems.
- Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Prevention

Any infection can progress to sepsis; therefore, preventing sepsis requires either preventing the infection or preventing the progression of the infection to sepsis.

Factors that contribute to preventing infections in the community include vaccinations (Table 24.8), adequate nutrition and healthy living environments (including access to safe water and sanitation). It is beyond the scope of this chapter to address in detail these topics.

Table 24.8 – Vaccinations to consider for prevention of certain infections

Vaccination ^a	Population where the vaccine should be considered
Meningococcal vaccination (236)	Countries with high (> 10 cases per 100 000 population/year) or intermediate (2–10 cases per 100 000 population/year) incidence of meningococcal disease or with frequent epidemics. All individuals aged 1–29 years (including pregnant women) should be vaccinated with the meningococcal A conjugate vaccine. Countries with low incidence of meningococcal disease (< 2 cases per 100 000 population/year). Vaccination is advised only for defined high-risk groups such as children and young adults or individuals with immunodeficiency. The choice of the recommended vaccine depends on the local prevalence of the meningococcal serogroups.

continues

Table 24.8 *continued*

Vaccination ^a	Population where the vaccine should be considered
Pneumococcal vaccination (35)	All children should be vaccinated with pneumococcal conjugate vaccines. In adults, the vaccine is recommended in many countries for elderly people (> 65 years) and for high-risk groups (e.g. patients with chronic pulmonary disease or who have had a splenectomy).
<i>Salmonella</i> Typhi vaccination (154)	Individuals living in countries with a high burden of enteric fever or antibiotic-resistant <i>Salmonella</i> Typhi should be vaccinated with typhoid conjugate vaccines. Vaccination should also be offered during outbreaks.

^a References cited are to WHO position papers that support the evidence for vaccination.

25. Sepsis in neonates (< 28 days) and children (28 days–12 years)

Key messages

Both neonates and older children

- Sepsis is an acute life-threatening condition characterized by organ dysfunction due to a dysregulated host response to infection.
- Antibiotic treatment should be started as soon as possible when sepsis is suspected.
- Diagnostic tests and imaging should not delay treatment which should be guided by the suspected site of primary infection.

Neonates (< 28 days)

- Sepsis in neonates can be classified based on setting of acquisition of the infection (community/hospital) or time of onset after birth (early/late), which are used to try and predict the most likely causative pathogens and guide empiric antibiotic treatment.
- Multiple clinical signs and symptoms are used to determine whether an infant has neonatal sepsis, as well as perinatal risk factors, such as prematurity/gestational age.
- Neonates are much more likely to have a primary bloodstream infection with no underlying source of infection identified.

Older children

- Common causative pathogens vary globally and combined with the setting of acquisition of the infection, this can be used to predict the most likely causative pathogens and choose empiric antibiotic treatment.
- Usually signs and symptoms are non-specific and the presence of danger signs of illness should always be assessed to guide clinical management.

Other relevant WHO resources (please check regularly for updates)

- Sepsis – fact sheet (234).
- Global report on the epidemiology and burden of sepsis: current evidence, identifying gaps and future directions (235).
- *Haemophilus influenzae* type b (Hib) vaccination position paper – July 2013: Introduction (36).
- Meningococcal A conjugate vaccine: updated guidance, February 2015 (236).
- Typhoid vaccines: WHO position paper – March 2018 (154).

Definition

Because of differences in the microbiology, sepsis in children is often classified as neonatal sepsis (newborns < 28 days) and paediatric sepsis (28 days–12 years).

Neonatal sepsis

There is no universally accepted definition of neonatal sepsis and definitions vary among studies (258). However, the term is used to describe a serious systemic condition of infectious origin (most commonly bacterial) associated with a combination of clinical and laboratory signs that occurs in the first month of life.

Neonates are much more likely to have a primary bloodstream infection with no underlying source of infection identified. Furthermore, because of differences in the host (neonates have reduced immune responses) and the way the pathogen can be acquired (e.g. exposure to maternal pathogens at birth or in utero), the sepsis definitions currently used for adults and older children are not specifically designed for use in young infants (259,260).

Neonatal sepsis has historically been categorized based on either the timing of clinical disease onset (early-onset sepsis or late-onset sepsis) or based on where the infection was likely acquired (community-acquired infection or hospital-acquired infection) (Box 25.1). The aim of these categorizations is to predict the most likely causative pathogens and guide empiric treatment. However, these categorizations have become less helpful as more infants worldwide are born in health care facilities and are exposed to multidrug-resistant pathogens in the early neonatal period, either acquired from their mother or through nosocomial acquisition in the health facility or hospital.

Box 25.1 – Commonly used categorizations of neonatal sepsis

By timing of onset

- early onset^a (occurring ≤ 3 days after birth, often acquired vertically from the mother or in the peripartum period)
- late onset (occurring > 3 days after birth, often hospital acquired)

By setting of acquisition

- community setting
- hospital setting

^aA range of different postnatal ages have been used to define early onset sepsis, including less than 3, 5 or 7 days of life.

In settings with limited access to any laboratory tests, an alternative clinical definition used by the WHO is: possible serious bacterial infection (261,262). This definition is based on the presence of multiple clinical signs (Box 25.2). If at least one of the signs is present, the neonate or young infant requires prompt treatment with antibiotics. Relevant signs to consider include difficulty feeding, history of convulsions, movement only when stimulated, respiratory rate > 60 breaths/minute, severe chest retractions and temperature $\geq 38.0^{\circ}\text{C}$ or $< 35.5^{\circ}\text{C}$.

Box 25.2 – Definition of possible serious bacterial infection (PSBI)

A young infant is classified as having PSBI when any one or more of the following signs is present:

- Not able to feed since birth or stopped feeding well (confirmed by observation)
- No movement or movement only on stimulation
- Convulsions
- Fast breathing (60 breaths per minute or more) in infants younger than 7 days of age
- Severe chest in-drawing
- Fever ($\geq 38.0^{\circ}\text{C}$)
- Low body temperature ($< 35.5^{\circ}\text{C}$)

Clinical signs and symptoms are important predictors of neonatal sepsis, as well as perinatal risk factors, such as prematurity/gestational age. Several scores exist that measure severity of sepsis and help predict short-term mortality, but these are almost all derived in the high-income setting. Scores are used to promptly identify neonates who would benefit the most from optimal antibiotic treatment and supportive care.

Because of its simplicity, one of the most frequently used scores is the Score for Neonatal Acute Physiology–II (SNAP-II score) (263). This score was developed in 2001 to predict outcomes (usually short-term mortality) in cases of possible neonatal sepsis. It should be noted, however, that this score has not been extensively validated in low- and middle-income countries and therefore there is no clear consensus on its use. Some evidence exists from low- and middle-income country settings that SNAP-II scores differ significantly in neonates with sepsis who survive or die in the short-term irrespective of gestational age (264). The SNAPPE-II score is an extension of the SNAP-II score which includes additional perinatal parameters (263).

Sepsis in children beyond neonatal age

The definition of possible serious bacterial infection outlined in the previous section on neonatal sepsis can also be used beyond neonatal age to children younger than 5 years.

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25. Sepsis in neonates (< 28 days) and children (28 days–12 years)

Other paediatric sepsis definitions in use include:

- International Pediatric Sepsis Consensus Conference, 2005 (265). Suspected or proven infection caused by any pathogen or clinical syndrome associated with a high probability of infection AND systemic inflammatory response syndrome. Systemic inflammatory response syndrome is defined as abnormal temperature or abnormal white blood cell count AND one of the following age-adjusted signs: tachycardia or bradycardia, tachypnoea and/or mechanical ventilation (266).
- Paediatric adaptation of the Sepsis-3 adult sepsis definition, including the paediatric version of the Sequential Organ Failure Assessment score (Table 25.1) (267).

It should be noted that the definition of sepsis does not include the detection of bacteria in blood cultures (i.e. bacteraemia). See Box 25.3 for terms and definitions related to blood stream infections.

**Table 25.1 – Paediatric Sequential Organ Failure Assessment (pSOFA) score**

Parameter	Score			
	0	1	2	3
PaO ₂ /FiO ₂ , mmHg (kPa) ≥ 400 (53.3)	300 - 399 (40.0 - 53.2)	200 - 299 (26.7 - 39.9)	100 - 199 (13.3 - 26.6) with respiratory support	< 100 (13.3) with respiratory support
MAP, mmHg (kPa) by age group (in months) and catecholamine doses needed (µg/kg/min for ≥ 1 h)				
< 1	≥ 46 (6.1)	< 46 (6.1)	Dopamine < 5 OR Dobutamine any dose	Dopamine 5.1–15 OR Epinephrine / norepinephrine ≤ 0.1 Epinephrine / norepinephrine > 0.1
1–11	≥ 55 (7.3)	< 55 (7.3)	As above	As above
12–23 (1–2 years)	≥ 60 (8)	< 60 (8)	As above	As above
24–59 (2–5 years)	≥ 62 (8.2)	< 62 (8.2)	As above	As above
60–143 (6–11 years)	≥ 65 (8.6)	< 65 (8.6)	As above	As above
144–216 (12–18 years)	≥ 67 (8.9)	< 67 (8.9)	As above	As above

continues

Table 25.1 continued

Parameter	Score				
	0	1	2	3	
	4				
Platelets, $\times 10^3/\mu\text{L}$ (or $\times 10^9/\text{L}$)	≥ 150	100 - 149	50 - 99	20 - 49	< 20
Bilirubin, mg/dL ($\mu\text{mol/L}$)	< 1.2 (20)	1.2–1.9 (20–32)	2–5.9 (33–101)	6.0–11.9 (102–204)	> 12.0 (204)
Glasgow coma scale ^a	15	13–14	10–12	6–9	< 6
Creatinine, mg/dL ($\mu\text{mol/L}$) by age group (months)					
< 1	< 0.8 (71)	0.8–0.9 (71–80)	1.0–1.1 (88–97)	1.2–1.5 (110–133)	$\geq 1.6 (141)$
1–11	< 0.3 (26)	0.3–0.4 (26–35)	0.5–0.7 (44–62)	0.8–1.1 (71–97)	$\geq 1.2 (110)$
12–23 (1–2 years)	< 0.4 (35)	0.4–0.5 (35–44)	0.6–1.0 (53–88)	1.1–1.4 (97–124)	$\geq 1.5 (133)$
24–59 (2–5 years)	< 0.6 (53)	0.6–0.8 (53–71)	0.9–1.5 (79–133)	1.6–2.2 (141–195)	$\geq 2.3 (203)$
60–143 (6–11 years)	< 0.7 (62)	0.7–1.0 (62–88)	1.1–1.7 (97–150)	1.8–2.5 (159–221)	$\geq 2.6 (230)$
144–216 (12–18 years)	< 1.0 (88)	1.0–1.6 (88–141)	1.7–2.8 (150–247)	2.9–4.1 (256–362)	$\geq 4.2 (371)$

FO_2 : fractional inspired oxygen; MAP: mean arterial pressure; PaO_2 : arterial oxygen partial pressure.

^a The Glasgow coma scale is a clinical scale used to measure a person's level of consciousness based on the assessment of three parameters: eye opening response (maximum 4 points assigned), best verbal response (maximum 5 points assigned) and best motor response (maximum 6 points assigned). The total score can range from 3 (completely unresponsive) to 15 (responsive). Scores lower than 8 usually indicate a comatose state. To calculate the Glasgow coma scale, several online calculators exist.

Box 25.3 – Bacteraemia

Bacteraemia (i.e. the detection of bacteria in blood cultures) is not part of the definition of sepsis. While many patients with sepsis have bacteraemia, this is not a universal finding and most patients with bacteraemia do not meet sepsis criteria. The term septicaemia should be avoided.

The terms bacteraemia and bloodstream infection are often used interchangeably. However, bloodstream infections can also be caused by pathogens other than bacteria (e.g. fungi) and are associated with clinical signs and symptoms of inflammatory response. The Global Antimicrobial Resistance Surveillance System (GLASS) uses the following definition of suspected and confirmed bloodstream infection in children and neonates (239).

GLASS criteria for suspected bloodstream infection in children older than 28 days

All children (> 28 days–< 18 years) with two or more of the following clinical signs:

- Hyperthermia (> 38.0 °C) or hypothermia (< 36.0 °C);
- Respiratory rate > 2 standard deviations above the normal for age (Table 1), or receiving mechanical ventilation for an acute pulmonary process;
- Heart rate > 2 standard deviations above normal for age (Table 1), or for children < 1 year, mean heart rate < 10th percentile for age.

Table 1 – Age-specific criteria for suspected bloodstream infection

Age group	Heart rate (beats/min)	Respiratory rate (breaths/min)
1 month–1 year	> 180 or < 90	> 34
2–5 years	> 140	> 22
6–12 years	> 130	> 18
13–18 years	> 110	> 14

GLASS criteria for suspected bloodstream infection in neonates

All neonates with two or more of the following clinical signs:

- Temperature ≥ 37.5 °C or < 35.3 °C;
- Respiratory rate > 60 breaths/minute or severe chest in-drawing or grunting or cyanosis;
- Change in level of activity;
- History of feeding difficulty;
- History of convulsions.

GLASS criteria for confirmed bloodstream infection

- Isolation of a clinically relevant pathogen from a blood sample of a patient (all ages) seeking health care at a health care facility.

Sepsis in children

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This guideline is intended for children over the age of 1 month up to 12 years. For children 0–1 month see sepsis in neonates

Definition

- International Pediatric Sepsis Consensus Conference:
Suspected or proven infection caused by any pathogen or clinical syndrome associated with a high probability of infection AND systemic inflammatory response syndrome
- Children < 5 years of age can be classified as having "Possible Serious Bacterial Infection" (PSBI) when at least one of the following signs is present:
 - Not able to feed since birth or stopped feeding well (confirmed by observation)
 - Convulsions
 - Fast breathing (≥ 60 breaths per minute)
 - Severe chest indrawing
 - Fever (≥ 38.0 °C)
 - Low body temperature (< 35.5 °C)

Important: bacteraemia is not part of the definition of sepsis, while many patients with sepsis have bacteraemia, most patients with bacteraemia do not fulfill sepsis criteria

Prevention

Preventing infections includes:

- Vaccinations
- Adequate nutrition
- Healthy living environments (e.g. access to safe water and sanitation)

Preventing evolution of infection to sepsis relies on:

- Timely diagnosis
- Adequate treatment of the underlying infection

Diagnosis

Clinical Presentation

- Usually signs and symptoms are non-specific
- Fever (≥ 38.0 °C), respiratory symptoms, tachycardia, acute altered mental status, hypotension, vomiting

Microbiology Tests

- Diagnostic tests will be different depending on the suspected source of infection
- Ideally perform tests before initiating antibiotics; tests should not cause a major delay to the start of antibiotic treatment
- Tests for suspected sepsis would normally include blood, urine and CSF culture

Other Laboratory Tests

To Identify a Bacterial Infection:

- White blood count
- C-reactive protein and/or procalcitonin

To Identify Organ Dysfunction:

- Complete blood count with platelets
- Bilirubin
- Blood pH and gases
- Blood urea nitrogen
- Creatinine
- Electrolytes
- Glucose
- Whole blood lactate

Tests in bold are required for pSOFA score calculation

Imaging

Guided by the suspected primary site of infection

Sepsis in children

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Paediatric Sequential Organ Failure Assessment (pSOFA) Score

Parameter	Age	Score					
		0	1	2	3	4	
PaO ₂ /FiO ₂ , mmHg (kPa)	All ages	≥ 400 (53.3)	300 - 399 (40.0 - 53.2)	200 - 299 (26.7 - 39.9)	100 - 199 (13.3 - 26.6) with respiratory support	< 100 (13.3) with respiratory support	
Platelets (x 10 ³ /µL, x 10 ⁹ /L)	All ages	≥ 150	100 - 149	50 - 99	20 - 49	< 20	
Bilirubin mg/dL (µmol/L)	All ages	< 1.2 (20)	1.2 - 1.9 (20 - 32)	2.0 - 5.9 (33 - 101)	6.0 - 11.9 (102 - 204)	> 12.0 (204)	
Glasgow coma scale	All ages	15	13 - 14	10 - 12	6 - 9	< 6	
MAP mmHg (kPa) and catecholamine doses needed (µg/kg/min for ≥ 1h)		<1 mo 1-11 mo 1-2 yrs 2-5 yrs 6-11 yrs 12-18 yrs	≥ 46 (6.1) ≥ 55 (7.3) ≥ 60 (8.0) ≥ 62 (8.2) ≥ 65 (8.6) ≥ 67 (8.9)	< 46 (6.1) < 55 (7.3) < 60 (8.0) < 62 (8.2) < 65 (8.6) < 67 (8.9)	Dopamine < 5 OR dobutamine any dose ≤ 0.1	Dopamine 5.1–15 OR epinephrine (adrenaline)/ norepinephrine > 0.1	Dopamine > 15 OR epinephrine/norepinephrine > 0.1
Creatinine mg/dL (µmol/L)	<1 mo 1-11 mo 1-2 yrs 2-5 yrs 6-11 yrs 12-18 yrs	< 0.8 (71) < 0.3 (26) < 0.4 (35) < 0.6 (53) < 0.7 (62) < 1.0 (88)	0.8 - 0.9 (71 - 80) 0.3 - 0.4 (26 - 35) 0.4 - 0.5 (35 - 44) 0.6 - 0.8 (53 - 71) 0.7 - 1.0 (62 - 88) 1.0 - 1.6 (88 - 141)	1.0 - 1.1 (88 - 97) 0.5 - 0.7 (44 - 62) 0.6 - 1.0 (53 - 88) 0.9 - 1.5 (79 - 133) 1.1 - 1.7 (97 - 150) 1.7 - 2.8 (150 - 247)	1.2 - 1.5 (110 - 133) 0.8 - 1.1 (71 - 97) 1.1 - 1.4 (97 - 124) 1.6 - 2.2 (141 - 195) 1.8 - 2.5 (159 - 221) 2.9 - 4.1 (256 - 362)	≥ 1.6 (141) ≥ 1.2 (110) ≥ 1.5 (133) ≥ 2.3 (203) ≥ 2.6 (230) ≥ 4.2 (371)	

Definitions: FiO₂: fractional inspired oxygen; PaO₂: arterial oxygen partial pressure; MAP: mean arterial pressure



Bacteria Most Frequently Identified in Blood Cultures in Children with Sepsis

- Sepsis can originate from any type of infection in any organ system; it is most commonly caused by bacteria
- Hospital-acquired infections have a higher risk of being caused by multidrug-resistant organisms
- Sepsis related with malaria and viral haemorrhagic fevers should always be considered in endemic settings
- Consider sepsis related with respiratory viruses

	Low and Middle Income Setting	High Income Setting
Community Acquired	<ul style="list-style-type: none"> Gram-negative bacilli (mostly <i>Escherichia coli</i>, <i>Klebsiella</i> spp.)* <i>Salmonella</i> Typhi and Paratyphi Invasive non-typhoidal <i>Salmonella</i>** <i>Streptococcus pneumoniae</i> <i>Streptococcus pyogenes</i> <i>Staphylococcus aureus</i> <i>Neisseria meningitidis</i> <i>Haemophilus influenzae</i> type b 	<ul style="list-style-type: none"> <i>Streptococcus pneumoniae</i> <i>Streptococcus pyogenes</i> <i>Staphylococcus aureus</i> <i>Neisseria meningitidis</i> Gram-negative bacilli (mostly <i>Escherichia coli</i>, <i>Klebsiella</i> spp.)*
	<ul style="list-style-type: none"> <i>Klebsiella</i> spp.* <i>Escherichia coli</i>* <i>Staphylococcus aureus</i> (including MRSA) Other Gram-negative bacteria <i>Enterococcus</i> spp. 	<ul style="list-style-type: none"> <i>Klebsiella</i> spp.* <i>Escherichia coli</i>* <i>Staphylococcus aureus</i> (including MRSA) Other Gram-negative bacteria <i>Enterococcus</i> spp.

*Including multi-drug resistant strains such as those producing ESBL and carbapenemases

**Mostly sub-Saharan Africa, < 5 years with recent malaria, anaemia, malnutrition or HIV

Sepsis in children

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R_X Treatment



Clinical Considerations

- Start IV antibiotics as soon as possible if sepsis is suspected; results of tests should not delay antibiotics
- Choose treatment based on most likely infection site and infecting pathogens, local prevalence of antibiotic resistance, comorbidities, and risk of infection with multidrug-resistant organisms; if susceptibilities & pathogen are known, review and adapt antibiotics



Antibiotic Treatment Duration

- 7 days
- 14 days in case of meningitis

Duration may vary according to underlying condition responsible for sepsis



Referral to Hospital Not Possible

All dosages are for normal renal function



Amoxicillin 50 mg/kg/dose ORAL

- 0–2 months: q12h
- > 2 months: q8h

----- COMBINED WITH -----



Gentamicin 7.5 mg/kg/dose q24h IM



Referral to Hospital Possible

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice



Ampicillin 50 mg/kg/dose q8h IV

----- OR -----



Benzylpenicillin 30 mg/kg/dose (50 000 IU/kg/dose) q8h IV

----- COMBINED WITH -----



Gentamicin 7.5 mg/kg/dose q24h IV

Second Choice



Cefotaxime 50 mg/kg/dose q8h IV

----- OR -----



Ceftriaxone 80 mg/kg/dose q24h IV

----- OR -----



Cloxacillin 25 mg/kg/dose q6h IV

Cloxacillin is a useful second-choice option when an infection caused by *S. aureus* is suspected (in community settings with high MRSA prevalence, consider vancomycin instead). If cloxacillin is unavailable, any other IV *antistaphylococcal penicillin* could be used

----- COMBINED WITH -----



Amikacin 15 mg/kg/dose q24h IV

Amikacin would mostly be used as a treatment for infections caused by Gram-negative bacteria and when antibiotic-resistant bacteria are suspected

In settings with high prevalence of resistance, particularly for suspected health care-associated infections, a broad-spectrum antibiotic with activity against Gram-negative bacteria should also be considered (e.g. piperacillin+tazobactam)

Sepsis in neonates

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This guideline is intended for infants under the age of 1 month

Definition

A serious systemic condition of infectious origin (usually bacterial) associated with a combination of clinical and laboratory signs that occurs in the first month of life

Commonly Used Classifications:

- By timing of clinical onset:
 - *Early onset sepsis*: Occurring ≤ 3 days after birth, often acquired vertically or in peripartum period
 - *Late onset sepsis*: Occurring > 3 days after birth, often hospital acquired
- By setting of acquisition:
 - *Community-acquired*
 - *Hospital-acquired*

Alternative Definition:

• A young infant is classified as having "Possible Serious Bacterial Infection" (PSBI) when at least one of the following signs is present:

- Not able to feed since birth or stopped feeding well (confirmed by observation)
- Convulsions
- Fast breathing (≥ 60 breaths per minute)
- Severe chest indrawing
- Fever (≥ 38.0 °C)
- Low body temperature (< 35.5 °C)

Important: bacteraemia is not part of the definition of sepsis, while many patients with sepsis have bacteraemia, most patients with bacteraemia do not fulfill sepsis criteria

Prevention

Preventing infections includes:

- Vaccinations
- Adequate nutrition
- Healthy living environments (e.g. access to safe water and sanitation)

Preventing evolution of infection to sepsis relies on:

- Timely diagnosis
- Adequate treatment of the underlying infection

Diagnosis

Clinical Presentation

- Usually signs and symptoms are non-specific
- Hypothermia (< 35.5 °C) or fever (≥ 38.0 °C), severe chest indrawing, tachycardia, poor feeding, reduced spontaneous movements, hypotension, vomiting
- More rarely irritability, diarrhea, abdominal distention, convulsions

Microbiology Tests

- Diagnostic tests will be different depending on the suspected source of infection
- Ideally perform tests before initiating antibiotics; tests should not cause a major delay to the start of antibiotic treatment
- Tests for suspected sepsis in young infants would normally include blood, urine and culture of the cerebrospinal fluid (CSF)

Other Laboratory Tests

To Identify a Bacterial Infection:

- White blood count
- C-reactive protein and/or procalcitonin

To Identify Organ Dysfunction:

- Complete blood count with platelets
- Bilirubin
- Blood pH and gases
- Blood urea nitrogen
- Creatinine
- Electrolytes
- Glucose
- Whole blood lactate

Imaging

Guided by the suspected primary site of infection

Sepsis in neonates

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Pathogens Most Frequently Identified in Blood Cultures in Neonates with Sepsis

- Sepsis can originate from any type of infection in any organ system; it is most commonly caused by bacteria
- Hospital-acquired infections have a higher risk of being caused by multidrug-resistant organisms
- Sepsis related with malaria and viral haemorrhagic fevers should always be considered in endemic settings
- Consider sepsis related with respiratory viruses

	Low and Middle Income Setting	High Income Setting
Community Acquired	<ul style="list-style-type: none"> • <i>Escherichia coli</i>* • <i>Staphylococcus aureus</i> (including MRSA) • <i>Klebsiella</i> spp.* More rare <ul style="list-style-type: none"> • <i>Acinetobacter</i> spp.* • <i>Streptococcus agalactiae</i> • <i>Streptococcus pyogenes</i> • <i>Streptococcus pneumoniae</i> 	<ul style="list-style-type: none"> • <i>Escherichia coli</i>* • <i>Staphylococcus aureus</i> (including MRSA) • <i>Streptococcus agalactiae</i>
Hospital Acquired	<ul style="list-style-type: none"> • <i>Klebsiella</i> spp.* • <i>Escherichia coli</i>* • <i>Acinetobacter</i> spp.* • <i>Staphylococcus aureus</i> (including MRSA) • Other Gram-negative bacteria* • <i>Enterococcus</i> spp. 	<ul style="list-style-type: none"> • <i>Escherichia coli</i>* • <i>Klebsiella</i> spp.* • <i>Staphylococcus aureus</i> (including MRSA) • Other Gram-negative bacteria* • <i>Enterococcus</i> spp.

*Including multidrug-resistant strains such as those producing ESBL and carbapenemases

Sepsis in neonates

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Rx Treatment

Clinical Considerations

- Start IV antibiotics as soon as possible if sepsis is suspected; results of tests should not delay antibiotics
- Choose treatment based on most likely infection site and infecting pathogens, local prevalence of antibiotic resistance, comorbidities, and risk of infection with multidrug-resistant organisms; if susceptibilities & pathogen are known, review and adapt antibiotics

Important:

- Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or rapid clinical improvement if culture results unavailable
- Step down to oral treatment** is based on improvement of symptoms, signs of infection and the ability to take oral antibiotics

Antibiotic Treatment Duration

• 7 days

- **14 days** in case of meningitis

Duration may vary according to underlying condition responsible for sepsis

Prophylactic Antibiotics

- Consider giving ampicillin AND gentamicin for 2 days if significant risk factors for infection as follows:
 - Membranes ruptured > 18 hours before delivery
 - Mother had fever $\geq 38.0^{\circ}\text{C}$ before delivery or during labour
 - Amniotic fluid was foul smelling or purulent

Rx Referral to Hospital Not Possible

All dosages are for normal renal function

 Amoxicillin 50 mg/kg/dose q12h **ORAL**

----- COMBINED WITH -----

 Gentamicin 5 mg/kg/dose q24h **IM**

Rx Referral to Hospital Possible

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice

 Ampicillin 50 mg/kg/dose **IV**

ACCESS
• $\leq 1\text{wk}$ of life: q12h
• $> 1\text{wk}$ of life: q8h

----- OR -----

 Benzylpenicillin 30 mg/kg/dose (50 000 IU/kg/dose) q8h **IV**

ACCESS

----- COMBINED WITH -----

 Gentamicin 5 mg/kg/dose q24h **IV**

ACCESS

Second Choice

 Cefotaxime 50 mg/kg/dose q8h **IV**

WATCH

----- OR -----

 Ceftriaxone 80 mg/kg/dose q24h **IV**

WATCH

----- OR -----

 Cloxacillin 25-50 mg/kg/dose q12h **IV**

ACCESS

*Cloxacillin is a useful second-choice option when an infection caused by *S. aureus* is suspected (in community settings with high MRSA prevalence, consider vancomycin instead). If cloxacillin is unavailable, any other IV antistaphylococcal penicillin could be used*

----- COMBINED WITH -----

 Amikacin 15 mg/kg/dose q24h **IV**

ACCESS

Amikacin would mostly be used as a treatment for infections caused by Gram-negative bacteria and when antibiotic-resistant bacteria are suspected

In settings with high prevalence of resistance, particularly for suspected health-care-associated infections, a broad-spectrum antibiotic with activity against Gram-negative bacteria should also be considered (e.g. piperacillin+tazobactam)

Pathophysiology

Sepsis is an acute life-threatening condition characterized by organ dysfunction/s due to a dysregulated host response to infection and to the direct effect of the pathogen (268).

A combination of factors contributes to the clinical manifestation and severity of sepsis. Severity of sepsis depends on a combination of the amount and virulence of the pathogen and the immune status of the host, for example, immunological immaturity or dysfunction in preterm neonates, severe malnutrition and HIV infection. In addition, the timing of exposure to the pathogen plays an important role in neonates. In this age group, early-onset sepsis is usually associated with in utero infections (e.g. chorioamnionitis) or infections caused by pathogens that colonize the maternal genital tract and that can be acquired during delivery. Late-onset sepsis is more commonly associated with postnatal acquisition of community- or health care-associated pathogens.

Sepsis in neonates has a non-specific clinical presentation and many neonates with suspected sepsis who receive antibiotics do not have sepsis and do not have any significant infection. This should be considered when sepsis is suspected to avoid over-diagnosis and overtreatment.

Beyond the neonatal age, sepsis in children can also be a primary bacterial bloodstream infection (e.g. meningococcal or pneumococcal sepsis), most commonly community-acquired. Sepsis in children may also be the result of an underlying infection in a particular site (e.g. pyelonephritis, intra-abdominal infection or meningitis) or a health care-acquired infection.

Epidemiology

In 2015, about 6 million children younger than 5 years were estimated to have died, mostly in sub-Saharan Africa and southern Asia (122). Neonates account for about half of the deaths in this age group. Overall, about 2.7 million neonates died in 2015 and of these, about 400 000 were estimated to be the result of sepsis or meningitis, and 517 000 children younger than 5 years died from sepsis or meningitis. Sepsis is the third leading cause of death in neonates after prematurity and birth asphyxia, both of which are associated with maternal infections such as chorioamnionitis (122). Premature birth (< 37 weeks of gestation) and low birth weight are the main risk factors for neonatal sepsis and are associated with higher mortality. In early onset sepsis, additional risk factors are: intra-amniotic infections (i.e. chorioamnionitis); prolonged rupture of the membranes (> 18 hours); and maternal rectovaginal colonization with specific pathogens, such as group B streptococci (*Streptococcus agalactiae*). Neonates with underlying disease such as congenital malformations, or those undergoing invasive procedures, or those with central or peripheral catheters, or those undergoing surgical procedures or those with prolonged hospital stays are also at increased risk of sepsis.



Most likely pathogens

Sepsis can be caused by a variety of pathogens including fungi and viruses, although it is most commonly caused by bacteria (268). Differences in causative pathogens may be present based on the age of the child, presence or absence of underlying comorbidities and type of comorbidity, and geographical location, such as children in high-income versus low- and middle-income settings. Pathogens most frequently associated with sepsis in neonates 28 days or younger are shown in Table 25.2. Pathogens most frequently associated with sepsis in children beyond the neonatal age are shown in Table 25.3.

Table 25.2 – Bacteria most frequently identified in blood cultures in neonates 28 days or younger with sepsis (also refer to Box 25.3 on bacteraemia)

Setting	Infection acquired in the community	Infection acquired in hospital
Low and middle income	<p>Most common</p> <p><i>Escherichia coli</i> (including multidrug-resistant strains such as those producing ESBL)</p> <p><i>Staphylococcus aureus</i> (including MRSA)</p> <p><i>Klebsiella</i> spp. (including multidrug-resistant strains)</p> <p><i>Streptococcus agalactiae</i> (group B <i>Streptococcus</i>)</p> <p>More rarely</p> <p><i>Staphylococcus</i> spp. (other than <i>Staphylococcus aureus</i>)</p> <p><i>Acinetobacter</i> spp. (including multidrug-resistant strains)</p> <p><i>Streptococcus pyogenes</i> (group A <i>Streptococcus</i>)</p> <p><i>Streptococcus pneumoniae</i></p> <p><i>Listeria monocytogenes</i></p> <p><i>Haemophilus influenzae</i></p> <p>Gram-negative bacteria other than <i>Escherichia coli</i>, <i>Klebsiella</i> spp. and <i>Acinetobacter</i> spp.</p> <p><i>Enterococcus</i> spp.</p> <p>Invasive non-typhoidal <i>Salmonella</i></p>	<p><i>Klebsiella</i> spp.</p> <p><i>Escherichia coli</i></p> <p><i>Acinetobacter</i> spp. (including multidrug-resistant strains)</p> <p><i>Staphylococcus aureus</i> (including MRSA)</p> <p>Gram-negative bacteria other than <i>Escherichia coli</i> and <i>Klebsiella</i> spp. and <i>Acinetobacter</i> spp.</p> <p><i>Enterococcus</i> spp.</p>

continues

■ HOSPITAL FACILITY

25. Sepsis in neonates (< 28 days) and children (28 days–12 years)

Table 25.2 *continued*

Setting	Infection acquired in the community	Infection acquired in hospital
High income	<p>Most common</p> <p><i>Escherichia coli</i> (including multidrug-resistant strains such as those producing ESBL) <i>Staphylococcus aureus</i> (including MRSA) <i>Streptococcus agalactiae</i> (group B <i>Streptococcus</i>)</p> <p>More rarely</p> <p><i>Staphylococcus</i> spp. (other than <i>Staphylococcus aureus</i>) <i>Listeria monocytogenes</i> <i>Haemophilus influenzae</i></p>	<p><i>Escherichia coli</i> (including multidrug-resistant strains such as those producing ESBL) <i>Klebsiella</i> spp. (including multidrug-resistant strains such as those producing ESBL and carbapenemases) <i>Staphylococcus aureus</i> (including MRSA) Gram-negative bacteria other than <i>Escherichia coli</i> and <i>Klebsiella</i> spp. <i>Enterococcus</i> spp.</p>

ESBL: extended-spectrum beta-lactamases; MRSA: methicillin-resistant *Staphylococcus aureus*.

Note. As indicated in the definition section, the distinction between neonatal sepsis acquired in the community and in the hospital is usually used in low- and middle-income settings, but neonatal sepsis can also be classified as early or late onset based on the time of onset of sepsis (counting days after delivery). The purpose of both classifications is to help identify the most likely causative pathogens, however, overlap may exist in some settings; for example, *Acinetobacter* spp. is associated with early-onset sepsis in some settings.

Hospital-acquired infections have a higher risk of being caused by multidrug-resistant organisms.

Only bacteria are listed in the table. Other pathogens to consider are viruses (mostly herpes simplex virus and enteroviruses) and fungi (mostly *Candida* spp.).

Table 25.3 – Bacteria most frequently identified in blood cultures in children older than 28 days with sepsis (also refer to Box 25.3 on bacteraemia)

Setting	Infection acquired in the community	Infection acquired in hospital
Low and middle income	<p>Gram-negative bacteria (mostly <i>Escherichia coli</i>, <i>Klebsiella</i> spp. including multidrug-resistant strains such as those producing ESBL and carbapenemases)</p> <p><i>Salmonella</i> Typhi and Paratyphi (causing enteric fever)</p> <p>Invasive non-typhoidal <i>Salmonella</i> (mainly in sub-Saharan Africa in children < 5 years with recent/acute <i>Plasmodium falciparum</i> malaria, anaemia, malnutrition, or HIV)</p> <p><i>Streptococcus pneumoniae</i></p> <p><i>Streptococcus pyogenes</i> (group A)</p> <p><i>Streptococcus</i></p> <p><i>Staphylococcus aureus</i></p> <p><i>Neisseria meningitidis</i></p> <p><i>Haemophilus influenzae</i> type b</p>	<p><i>Klebsiella</i> spp. (including multidrug-resistant strains such as those producing ESBL and carbapenemases)</p> <p><i>Escherichia coli</i> (including multidrug-resistant strains such as those producing ESBL and carbapenemases)</p> <p><i>Staphylococcus aureus</i> (including MRSA)</p> <p>Gram-negative bacteria other than <i>Escherichia coli</i> and <i>Klebsiella</i> spp. (including multidrug-resistant strains such as those producing ESBL and carbapenemases)</p> <p><i>Enterococcus</i> spp.</p>
High income	<p><i>Streptococcus pneumoniae</i></p> <p><i>Streptococcus pyogenes</i> (group A)</p> <p><i>Streptococcus</i></p> <p><i>Staphylococcus aureus</i></p> <p><i>Neisseria meningitidis</i></p> <p>Gram-negative bacteria (mostly <i>Escherichia coli</i>, <i>Klebsiella</i> spp. including multidrug-resistant strains such as those producing ESBL and carbapenemases)</p>	<p><i>Klebsiella</i> spp.</p> <p><i>Escherichia coli</i></p> <p>(including multidrug-resistant strains such as those producing ESBL and carbapenemases)</p> <p><i>Staphylococcus aureus</i> (including MRSA)</p> <p>Gram-negative bacteria other than <i>Escherichia coli</i> and <i>Klebsiella</i> spp. (including multidrug-resistant strains such as those producing ESBL and carbapenemases)</p> <p><i>Enterococcus</i> spp.</p>

ESBL: extended-spectrum beta-lactamases; MRSA: methicillin-resistant *Staphylococcus aureus*.

Note. Hospital-acquired infections have a higher risk of being caused by multidrug-resistant organisms.

Only bacteria are listed in the table. Other pathogens to consider are viruses (mostly herpes simplex virus and enteroviruses) and fungi (mostly *Candida* spp.).

■ HOSPITAL FACILITY

25. Sepsis in neonates (< 28 days) and children (28 days–12 years)

Clinical presentation

The clinical presentation can vary according to the age of the child but usually signs and symptoms are non-specific. In general, to identify the underlying clinical infection, knowledge of local patterns of infections is helpful. Dengue and malaria related sepsis should also be considered in endemic settings (269).

Neonates with sepsis commonly present with a combination of hyper- or hypothermia (temperature $\geq 38.0^{\circ}\text{C}$ or $< 35.5^{\circ}\text{C}$), severe chest indrawing, tachycardia, poor feeding, reduced spontaneous movements, hypotension and vomiting. More rarely irritability, diarrhoea, abdominal distention and/or seizures may be present. Fast breathing alone is not a strongly predictive sign of sepsis.

In children beyond neonatal age, the most frequent signs and symptoms include fever ($\geq 38.0^{\circ}\text{C}$), respiratory symptoms, tachycardia, acute altered mental status, hypotension and vomiting.

The presence of any danger signs of illness (Box 25.4) requires prompt referral for further evaluation.

Box 25.4 – Danger signs of illness in newborns and young infants

WHO recommendations in newborn health, 2017 (261)

- stopped feeding well
- history of convulsions
- fast breathing
- severe chest indrawing
- no spontaneous movement
- temperature $> 37.5^{\circ}\text{C}$ or $< 35.5^{\circ}\text{C}$
- any jaundice in the first 24 hours of life or yellow palms and soles at any age

WHO pocket book of hospital care for children, 2013 (31)

- not feeding well
- convulsions
- drowsy or unconscious
- movement only when stimulated or no movement at all
- fast breathing (60 breaths/minute)
- grunting
- severe chest indrawing
- raised temperature, $> 38.0^{\circ}\text{C}$
- hypothermia, $< 35.5^{\circ}\text{C}$
- central cyanosis

Laboratory tests

Patient microbiology tests

Microbiology tests help establish a definitive diagnosis of sepsis and identify the causative pathogen and underlying infection. Isolating a pathogen from a normally sterile body site (e.g. blood, cerebrospinal fluid) that is compatible with the clinical signs and symptoms usually confirms diagnosis. A septic screen in young infants would normally include culture of blood, urine and cerebrospinal fluid, and a chest X-ray may be considered.

Diagnostic tests should be guided by the suspected primary site of infection and will be different for pneumonia, meningitis or sepsis of unknown origin. Please also refer to specific chapters of the AWaRe book based on the suspected underlying infection.

Tests to consider when sepsis of bacterial origin is suspected are indicated in Table 25.4. Ideally, these tests should be done before starting antibiotic treatment, but treatment should not be delayed in a very unwell child.

Table 25.4 – Microbiology tests to consider when sepsis in suspected depending on the most likely source of infection as indicated in the WHO EDL (6)

Suspected underlying infection ^a	Diagnostic test	Purpose of the test	Settings where the test should be available
All cases where sepsis is suspected	Blood culture and antimicrobial susceptibility testing	To detect bacterial bloodstream infections	Health care facilities with clinical laboratories
Urinary tract infection	Urine culture and antimicrobial susceptibility testing	Initial step to detect and identify bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories
Meningitis	Cerebrospinal fluid: Gram stain, bacterial culture ^b and antimicrobial susceptibility testing	Initial step to detect and identify bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories

continues

HOSPITAL FACILITY

25. Sepsis in neonates (< 28 days) and children (28 days–12 years)

Table 25.4 *continued*

Suspected underlying infection^a	Diagnostic test	Purpose of the test	Settings where the test should be available
Diarrhoeal disease, enteric fever ^c	Stool culture and antimicrobial susceptibility testing	Initial step to detect and identify bacterial species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories
Abscess (e.g. in the context of intra-abdominal infections, skin and soft-tissue infections, dental infections)	Culture and antimicrobial susceptibility testing of abscess and/or fluid collections that can be drained	Initial step to detect and identify bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics.

^a Additional tests may be considered in endemic settings or after travel to endemic settings (e.g. malaria, viruses causing viral haemorrhagic fevers).

^b Even though cerebrospinal fluid culture is rarely done, it is a very important test to perform.

^c If enteric fever is suspected, note that stool cultures have a low sensitivity and are not useful in the early phase (first week) of disease when the test is often negative.

Other tests

Laboratory tests can be used to complement the clinical examination and history to determine the likelihood of an underlying bacterial infection (Table 25.5) and the presence and severity of acute organ dysfunction (Table 25.6). Both tables include tests that can be considered based on local laboratory availability and local protocols.

Table 25.5 – Laboratory tests (other than microbiology) to consider when sepsis in suspected to identify a bacterial infection as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
White blood count	To help in the diagnosis of infections	Health care facilities with clinical laboratories and also in primary care settings

continues

Table 25.5 *continued*

Diagnostic test	Purpose of the test	Settings where the test should be available
C-reactive protein	To detect inflammation as an indicator of various conditions (e.g. sepsis)	Health care facilities with clinical laboratories
Procalcitonin ^a	To guide antibiotic therapy or discontinuation in sepsis	Only in tertiary and higher health care facilities

EDL: Model List of Essential In Vitro Diagnostics.

^a Procalcitonin is not widely available and has only moderate accuracy for the diagnosis of sepsis in neonates with suspected sepsis at the cut-off of 2.0–2.5 ng/mL; different cut-offs in neonates with early- versus late-onset sepsis may be necessary (270). Procalcitonin may possibly have a higher sensitivity and specificity than C-reactive protein, (271). A combination of both tests may improve the accuracy of diagnosis of neonatal sepsis (272).

Table 25.6 – Laboratory tests (other than microbiology) to consider when sepsis in suspected to identify organ dysfunction as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
Bilirubin	To detect or monitor liver disease, bile duct disorders and red cell destruction	Health care facilities with clinical laboratories
Blood pH and gases	To assess lung function, metabolic or kidney disorders and monitor oxygen therapy	Health care facilities with clinical laboratories
Blood urea nitrogen	To assess kidney function	Health care facilities with clinical laboratories
Creatinine	To monitor kidney function for management of severe infections (i.e. sepsis,) and to adjust antimicrobial regimen	Health care facilities with clinical laboratories
Electrolytes	To monitor fluid, electrolyte and acid–base balance	Health care facilities with clinical laboratories
Glucose	To diagnose intermediate hyperglycaemia and hypoglycaemia	Health care facilities with clinical laboratories and also in primary care settings

continues

Table 25.6 *continued*

Diagnostic test	Purpose of the test	Settings where the test should be available
Platelet count	To diagnose thrombocytopenia or thrombocytosis. This is a marker to manage severe infections associated with sepsis (e.g. viral haemorrhagic fever, meningococcaemia)	Health care facilities with clinical laboratories
Whole blood lactate	To assess metabolic acidosis	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics.

Using microbiology surveillance data

Targeted clinical microbiology surveys of neonates and children with confirmed sepsis, including clinical presentation and infection focus, underlying disease, bloodstream isolate and resistance phenotype, antibiotic treatment and clinical outcome, may be helpful at a local and national level to inform empiric guidance.

Imaging

If available, imaging studies should be guided by the suspected primary site of infection as for microbiological sampling. Please also refer to specific chapters of the AWaRe book based on the suspected underlying infection. When sepsis is suspected and respiratory distress is present, a chest X-ray is indicated to confirm a lower respiratory tract infection that may not always be clinically obvious.

If an abdominal source of infection is suspected, an abdominal ultrasound could be considered. As an alternative and if available, a CT scan of the abdomen could also be considered; however, limiting exposure to radiation should always be considered, especially in young children. If sepsis caused by an infection of the urinary tract is suspected, initial imaging (e.g. ultrasound) of the urinary tract or during follow-up could be considered if an outflow obstruction or collection are suspected.

Antibiotic treatment

Antibiotic treatment should be started as soon as possible when sepsis is suspected. Performance and results of laboratory and microbiology tests should not delay the first dose of antibiotic treatment.

Even though the presence of perinatal risk factors (prematurity, prolonged rupture of membranes) often leads to early empiric antibiotic use in babies, there is good evidence that these risk factors alone do not reliably predict neonatal sepsis. Therefore, antibiotic treatment should generally be started in newborn infants based on a combination of clinical and laboratory signs. In neonates with significant risk factors for infection – for example, membranes ruptured > 18 hours before delivery, mother had fever $\geq 38.0^{\circ}\text{C}$ before delivery or during labour, or amniotic fluid was foul smelling or purulent – prophylactic antibiotics (ampicillin and gentamicin) should be given for only 2 days. The neonate should be reassessed after 2 days and treatment continued only if there are signs of sepsis or a positive blood culture (261).

Empiric treatment (see Table 25.7) should always cover the most probable causative pathogens, namely:

- in neonates: Gram-negative bacteria, *Staphylococcus aureus*, Group B *Streptococcus*;
- in children beyond the neonatal age: Gram-negative bacteria, *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Neisseria meningitidis*.

Simplify empiric treatment to a more narrow-spectrum antibiotic (often also called de-escalation) based on culture results if a pathogen is isolated (targeted treatment). When no organism is identified, antibiotic treatment should be guided by available laboratory results and clinical response. Simplification of empiric antibiotic regimens for low-risk neonates, using two doses of parenteral gentamicin combined with oral amoxicillin, is being implemented in primary health care settings.

In malaria-endemic areas, in a child with shock or severe illness and decreased alertness, it is often difficult to differentiate between severe *Plasmodium falciparum* malaria and invasive bacterial infection (often caused by invasive non-typhoidal *Salmonella*), and co-infections are not uncommon. In all such cases, empiric parenteral broad-spectrum antibiotics should be started immediately, together with antimalarial treatment (273).

■ HOSPITAL FACILITY

25. Sepsis in neonates (< 28 days) and children (28 days–12 years)

Table 25.7 – Empiric antibiotic treatment for community-acquired sepsis of bacterial origin in neonates and children

 **Note**

An update of WHO guidelines for the treatment of neonatal sepsis is ongoing at the date of publication of the AWaRe book. Please regularly check the WHO website for news on this topic.

 **Important**

Where more than one antibiotic is recommended for an infection, they are listed in alphabetical order and they should be considered equal treatment options, unless otherwise indicated.

	Referral to hospital possible	Referral to hospital not possible (262)	Total treatment duration
First choice^a	Ampicillin (IV): 50 mg/kg/dose: <ul style="list-style-type: none">• Given every 12 hours (first week of life)• Given every 8 hours (> first week of life) AND Gentamicin (IV): <ul style="list-style-type: none">• Neonates: 5 mg/kg/dose given once a day• Children: 7.5 mg/kg/dose given once a day OR Benzylpenicillin (IV): 50 000 IU/kg/dose (30 mg/kg/dose) given every 8 hours AND Gentamicin (IV): <ul style="list-style-type: none">• Neonates: 5 mg/kg/dose given once a day• Children: 7.5 mg/kg/dose given once a day	Amoxicillin (oral): 50 mg/kg/dose: <ul style="list-style-type: none">• Given every 12 hours (infants 0–2 months)• Given every 8 hours (> 2 months) AND Gentamicin (IM): <ul style="list-style-type: none">• Neonates: 5 mg/kg/dose given once a day• Children: 7.5 mg/kg/dose given once a day	7 days (14 days in case of meningitis)

continues

Table 25.7 continued

	Referral to hospital possible	Referral to hospital not possible (262)	Total treatment duration
Second choice^b	<p>Cefotaxime ^b (IV): 50 mg/kg/dose given every 8 hours OR Ceftriaxone ^{b,c} (IV): 80 mg/kg/dose given once a day OR Clxacillin ^{d,e} (IV):</p> <ul style="list-style-type: none"> Neonates: 25–50 mg/kg/dose given every 12 hours Children: 25 mg/kg/dose given every 6 hours <p>AND</p> <p>Amikacin ^f (IV): 15 mg/kg/dose given once a day</p>	No specific option is indicated in the EML and EMLC as second choice option when referral to hospital is not possible.	7 days

EML: Model List of Essential Medicines; EMLC: Model List of Essential Medicines for children; IM: intramuscular; IU: international units; IV: intravenous; MRSA: methicillin-resistant *Staphylococcus aureus*.

Note. All dosages are for normal renal and hepatic function.

^a To cover for *Listeria monocytogenes* and Gram-negative bacteria.

^b In settings with high resistance, particularly for suspected health care-associated infections, a broad-spectrum antibiotic with activity against Gram-negative bacteria should also be considered (e.g. piperacillin+tazobactam). Of note, empiric treatment with third-generation cephalosporins (ceftriaxone/cefotaxime) may be more appropriate in settings where invasive non-typhoidal *Salmonella* are a major cause of bloodstream infection. The reason is that (i) > 85% of non-typhoidal *Salmonella* are multidrug-resistant, which includes ampicillin resistance and (ii) aminoglycosides have reduced clinical effectiveness in invasive non-typhoidal *Salmonella* infections.

^c Ceftriaxone should not be used in neonates with hyperbilirubinaemia and should not be administered with calcium. Age restriction: use only in neonates of > 41 weeks corrected gestational age.

^d Clxacillin is a useful second-choice option when an infection caused by *Staphylococcus aureus* is suspected; the presence of extensive skin pustules, abscess or omphalitis (i.e. infection of the umbilicus and/or surrounding tissues) may suggest a staphylococcal infection. Of note, in community setting with high prevalence of MRSA, vancomycin should be considered instead of clxacillin.

^e If clxacillin is unavailable, any other IV antistaphylococcal penicillin could be used.

^f Gentamicin can be used when amikacin is not available. Amikacin (or gentamicin) would mostly be used as a treatment for infections caused by Gram-negative bacteria and when antibiotic-resistant bacteria are suspected.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

■ HOSPITAL FACILITY

25. Sepsis in neonates (< 28 days) and children (28 days–12 years)

Prevention

Sepsis rates can be reduced by preventing infection and by preventing the progression of infection to sepsis. Infections can be prevented in the community with good hygiene, safe water and sanitation, safe food preparation, good nutrition and vaccinations (Table 25.8). To prevent neonatal sepsis, infection prevention and control practices in hospital neonatal units and labour rooms are essential. The main ways to prevent the progression of infections to sepsis include prompt and adequate medical care including appropriate antibiotic treatment of the underlying infection.

Table 25.8 – Vaccinations to consider to prevent certain infections

Vaccination ^a	Population where the vaccine should be considered
<i>Haemophilus influenzae</i> type b vaccination (36)	All children should be vaccinated with <i>Haemophilus influenzae</i> type b conjugate vaccines.
Meningococcal vaccination (36,236)	Countries with high (> 10 cases per 100 000 population/year) or intermediate (2–10 cases per 100 000 population/year) incidence of meningococcal disease or with frequent epidemics: all individuals aged 1–29 years (including pregnant women) should be vaccinated with the meningococcal A conjugate vaccine. Countries with low incidence of meningococcal disease (< 2 cases per 100 000 population/year): vaccination only for defined high-risk groups such as children and young adults or individuals with immunodeficiency. The choice of the recommended vaccine depends on the local prevalence of the meningococcal serogroups.
Pneumococcal vaccination (35)	All children should be vaccinated with pneumococcal conjugate vaccines.
<i>Salmonella</i> Typhi vaccination (154)	Individuals living in countries with a high burden of enteric fever or a high burden of antibiotic-resistant <i>Salmonella</i> Typhi should be vaccinated with typhoid conjugate vaccines; vaccination should also be offered during outbreaks.

^a References cited are to WHO position papers that support the evidence for vaccination.

26. Bacterial meningitis

Key messages

- Bacterial meningitis is a severe potentially life-threatening infection.
- Given the severity of this condition, meningitis is always considered of bacterial origin until proven otherwise.
- The first dose of antibiotic should never be delayed (ideally given within 1 hour of presentation to care) and lumbar puncture and/or imaging should not delay starting treatment.
- The types of causative pathogens varies depending on the age and immune status of the patient.

Other relevant WHO resources (please check regularly for updates)

- Defeating meningitis by 2030: a global road map (274).
- Meningitis – health topic (275).
- Managing meningitis epidemics in Africa: a quick reference guide for health authorities and health-care workers (257).
- Meningococcal vaccines: WHO position paper – November 2011 (276).
- Meningococcal A conjugate vaccine: updated guidance, February 2015 (236).
- Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper –February 2019 (35).
- *Haemophilus influenzae* type b (Hib) vaccination position paper – July 2013: Introduction (36).
- WHO recommendations for routine immunization – summary tables (277).

Definition

Meningitis is an acute inflammation of the meninges, the membranes lining the brain and spinal cord. It can be infectious or non-infectious in origin (e.g. associated with autoimmune disease) and can be associated with high morbidity and mortality, even if treated promptly.

Bacterial meningitis

Page 1 of 2

Definition

- Acute inflammation of the meninges, the membranes lining the brain and spinal cord
- The cause can be infectious or non-infectious (e.g. associated with autoimmunity)

Most Likely Pathogens

Non-immunocompromised patients:

- *Streptococcus pneumoniae*
- *Neisseria meningitidis*

Immunocompromised patients or >50 years:

- *Streptococcus pneumoniae*
 - *Neisseria meningitidis*
 - *Listeria monocytogenes* (consider also in pregnant women)
- Consider in specific situations:**
- Viral infections (especially Enteroviruses, Herpesviridae and Arboviruses)
 - *Mycobacterium tuberculosis* (mostly in endemic settings and/or in patients living with HIV)
 - Cryptococcal meningitis and cerebral toxoplasmosis in severely immunocompromised patients (HIV)
 - Cerebral malaria (in patients living or travelling to endemic settings)
 - *Staphylococcus aureus* or Gram-negative bacteria, including multidrug-resistant strains after neurosurgical interventions or (for Gram-negative bacteria) in the context of *Strongyloides* hyperinfection syndrome

Prevention

- Vaccination against meningococcal, pneumococcal and *Haemophilus influenzae* type b disease
- Post-exposure antibiotic prophylaxis with ciprofloxacin or ceftazidime for close contacts (only for meningococcal meningitis)
- https://www.who.int/health-topics/meningitis#tab=tab_3

Diagnosis

Clinical Presentation

- Acute onset (<48 h) of:
 - Fever ($\geq 38.0^{\circ}\text{C}$) and/or
 - Headache and/or confusion and/or
 - Neck stiffness
- All three signs and symptoms are present in only around half of patients but 95% of patients usually have at least two and the absence of all three symptoms significantly reduces the probability of meningitis
- Haemorrhagic rash may be present (especially in case of meningococcal infection)

Microbiology Tests

Ideally before starting antibiotic treatment:

- Microscopy and culture of cerebrospinal fluid (CSF)
 - Cryptococcal antigen in CSF and blood (patients with HIV)
 - Blood cultures
- Note: if lumbar puncture not possible immediately start antibiotics after blood cultures. Testing should not delay giving antibiotics**

Other Laboratory Tests

- Cerebrospinal fluid (CSF) examination (leukocyte count and differential leukocyte count, protein and glucose)
- Complete blood count
- Blood glucose
- CRP and/or procalcitonin
- Blood lactate

- CSF findings suggestive of bacterial etiology:**
- High opening pressure (normal range 80–200 mm H₂O or 8–20 cm H₂O)
 - Turbid aspect
 - Elevated white blood cell count (often several hundred to several thousand WBC/mm³ or >0.1 to $>1 \times 10^9/\text{L}$)
 - Elevated % of neutrophils ($>80\%$)
 - Elevated protein ($>45 \text{ mg/dL}$ or $>0.45 \text{ g/L}$)
 - Low glucose ($<40 \text{ mg/dL}$ or $<2.2 \text{ mmol/L}$)
 - CSF/Serum glucose ratio ≤ 0.4

Imaging

Consider doing a head CT scan before doing the lumbar puncture in patients with focal neurological signs, decreased level of consciousness/coma or a history of central nervous system disease or recent seizures (<1 week)

Bacterial meningitis

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Rx Treatment

Clinical Considerations

Important:

- Due to the severity of this condition all suspected cases of meningitis should be treated as soon as possible as bacterial meningitis until this has been excluded/viral cause has been clearly identified
- *Listeria* is not covered by ceftriaxone or cefotaxime therefore when *Listeria* is suspected, ampicillin should be used

Empiric treatment is based on:

- Age of the patient
- Immune status of the patient
- Local prevalence of *S. pneumoniae* isolates resistant to third-generation cephalosporins (rare but can occur especially in patients with prolonged or multiple exposures to β -lactam antibiotics in the previous three months)
- If a pathogen is isolated and its susceptibilities are known, review and modify antibiotics accordingly



Use of Corticosteroids

- Dexamethasone 0.15 mg/kg q6h

- Recommended **only in high-income settings** (no evidence of benefit in other settings)
- Give with the first dose of antibiotic to attenuate the inflammatory response and reduce the risk of neurological complications and death
- Continue only if *S. pneumoniae* is confirmed



Antibiotic Treatment Duration

Unknown pathogen: **10 days**Confirmed pneumococcal meningitis: **10-14 days**Confirmed meningoococcal meningitis: **5-7 days**Confirmed *Listeria* meningitis: **21 days**

Rx Antibiotic Treatment

*All dosages are for normal renal function**Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated*
Consider second choice options only when first choice options are not available
First Choice

- Cefotaxime 2 g q6h IV

OR

- Ceftriaxone 2 g q12h IV

*Add Ampicillin (or IV amoxicillin) to ceftriaxone/cefotaxime if risk factors for *Listeria monocytogenes* are present (e.g. patients ≥ 50 years, pregnancy)*
Second Choice

- Amoxicillin 2 g q4h IV

OR

- Ampicillin 2 g q4h IV

OR

- Benzylpenicillin 4 million IU (2.4 g) q4h IV

OR

- Chloramphenicol 1 g q6h IV

Use chloramphenicol only when no other option is available because of toxicity

Bacterial meningitis

Page 1 of 2

Definition

- Acute inflammation of the meninges, the membranes lining the brain and spinal cord
- The cause can be infectious or non-infectious in origin (e.g. associated with autoimmunity)

Most Likely Pathogens

Neonates (0-1 month):

- *Streptococcus agalactiae* (Group B Streptococcus)
- *Escherichia coli*
- *Listeria monocytogenes*
- *Streptococcus pneumoniae*

Children/adolescents:

- *Streptococcus pneumoniae*
- *Neisseria meningitidis*
- *Haemophilus influenzae* type b
- Invasive non-typhoidal *Salmonella* (HIV/sickle cell disease)
- *Salmonella Typhi* (rare)

Consider in specific situations:

- Viral infections (especially Enteroviruses, Herpesviridae and Arboviruses) and non-infectious causes
- *Mycobacterium tuberculosis* (mostly in endemic settings and/or in patients living with HIV)
- Cryptococcal meningitis and cerebral toxoplasmosis in severely immunocompromised patients
- Cerebral malaria (in patients living or travelling to endemic settings)
- *Staphylococcus aureus* or Gram-negative bacteria, including multidrug-resistant strains after neurosurgical interventions

Prevention

- Vaccination against meningococcal, pneumococcal and *Haemophilus influenzae* type b disease
- Post-exposure antibiotic prophylaxis with ciprofloxacin or ceftriaxone for close contacts (only for meningococcal meningitis)
- https://www.who.int/health-topics/meningitis#tab=tab_3

Diagnosis

Clinical Presentation

Neonates:

- Symptoms are usually non-specific; often a combination of fever, poor feeding, lethargy, drowsiness, vomiting, irritability, seizures or a full fontanelle
- Neck stiffness is very uncommon

Older children:

- Acute onset (<48 h) of:
 - Fever ($\geq 38.0^{\circ}\text{C}$) and /or
 - Headache and/or confusion and /or
 - Neck stiffness
- Haemorrhagic rash may be present (especially in case of meningococcal infection)

Microbiology Tests

Ideally before starting antibiotic treatment:

- Microscopy and culture of cerebrospinal fluid (CSF)
 - Cryptococcal antigen in CSF and blood (patients with HIV)
 - Blood cultures
- Note: testing should not delay giving antibiotics**

Other Laboratory Tests

- Cerebrospinal fluid (CSF) examination (leukocyte count and differential leukocyte count, protein and glucose

CSF findings suggestive of bacterial etiology:

- High opening pressure (normal range, 80-200 mm H₂O or 8-20 cm H₂O)
- Turbid aspect
- Elevated white blood cell count (often several hundred to several thousand WBC/mm³)
- Elevated % of neutrophils (>80%)
- Elevated protein ($>45 \text{ mg/dL}$ or $>0.45 \text{ g/L}$)
- CSF/Serum glucose ratio ≤ 0.4

Imaging

Consider doing a head CT scan before doing the lumbar puncture in patients with focal neurological signs, decreased level of consciousness/coma or a history of central nervous system disease or recent seizures (<1 week)

Bacterial meningitis

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Rx Treatment

Clinical Considerations

Important: due to the severity of this condition all suspected cases of meningitis should be treated as soon as possible as bacterial meningitis until this has been excluded/viral cause has been clearly identified

- Empiric treatment is based on:

- Age of the patient
- Immune status of the patient
- Local prevalence of *S. pneumoniae* isolates resistant to third-generation cephalosporins (rare but can occur especially in patients with prolonged or multiple exposures to β -lactam antibiotics in the previous three months)
- If a pathogen is isolated and its susceptibilities are known, review and modify antibiotics accordingly

Rx Neonates (< 1 Month)

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice

 Ampicillin IV

- 1st week of life: 50 mg/kg/dose q12h
- >1st week of life: 50 mg/kg/dose q8h

----- COMBINED WITH -----

 Gentamicin IV

- 1st week of life: 5 mg/kg q24h
- >1st week of life: 7.5 mg/kg q24h

OR

 Cefotaxime IV

- 1st week of life: 50 mg/kg/dose q12h
- >1st week of life: 50 mg/kg/dose q6h

OR

 Ceftriaxone 100 mg/kg q24h IV

----- COMBINED WITH -----

 Gentamicin IV

- 1st week of life: 5 mg/kg q24h
- >1st week of life: 7.5 mg/kg q24h

Second Choice

 Meropenem 40 mg/kg/dose q8h IV

Consider only if resistant Gram-negative organisms are suspected

Use of Corticosteroids

 Dexamethasone 0.15 mg/kg q6h

- Recommended only in high-income settings (no evidence of benefit in other settings)
- Give with the first dose of antibiotic to attenuate the inflammatory response and reduce the risk of neurological complications and death
- Continue only if *S. pneumoniae* is confirmed
- Steroids are not recommended in neonatal meningitis

Antibiotic Treatment Duration

Unknown pathogen: 10 days in older children & 3 weeks in neonates

Confirmed pneumococcal meningitis: 10-14 days

Confirmed meningoococcal meningitis: 5-7 days

Confirmed *Listeria* meningitis: 21 days

Rx Children

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated
Consider second choice options only when first choice options are not available

First Choice

 Cefotaxime 50 mg/kg/dose q8h IV

OR

 Ceftriaxone 100 mg/kg q24h IV

Second Choice

 Amoxicillin 50 mg/kg/dose q8h IV

OR

 Ampicillin 50 mg/kg/dose q8h IV

OR

 Benzylpenicillin 60 mg (100 000 IU)/kg/dose q6h IV

OR

 Chloramphenicol 25 mg/kg/dose q6h IV

Use chloramphenicol only when no other option is available because of toxicity

Pathophysiology

The pathogens that cause meningitis can colonize the upper respiratory tract and from there invade the bloodstream and get access to the central nervous system through the ventricular choroid plexus or can access the meninges by local spread. Because the central nervous system lacks effective immune defences, organisms can multiply rapidly, cause direct tissue injury to the meninges and produce an inflammatory response that contributes to neurological symptoms.

Epidemiology

Meningitis is found worldwide and can affect individuals of all ages, although some differences exist across geographic regions. Mortality is highest in children younger than 5 years. Outbreaks of meningococcal meningitis mostly occurring during cooler and drier seasons are a serious threat, especially in the so-called meningitis belt, an area in the peri-Saharan African region stretching from Senegal in the west to Ethiopia in the east. Although deaths from meningitis decreased overall by about 20% between 1990 and 2016 (from an estimated 403 000 deaths to about 318 000 a year), the burden of bacterial meningitis is still high, especially in low- and middle-income countries despite an increase in immunization programmes (278). According to data from the Global Burden of Disease study, in 2017, there were around 5 million new cases of meningitis (considering all ages and both sexes combined) (44). Almost half of the cases were of viral origin (2.4 million cases). In the same year, the number of new cases of acute pneumococcal (about 440 000) and meningococcal (about 400 000) meningitis were similar, while *Haemophilus influenzae* accounted for an estimated 262 000 new cases (44).

Tuberculous meningitis is more common in settings with a high prevalence of TB, especially among patients living with HIV. In settings where TB is endemic, children and young adults are more at risk of TB meningitis (dissemination of primary infection from the lungs to the central nervous system), while in setting with a low prevalence of TB, adults are most at risk (reactivation of a latent TB infection) (279).

The incidence and mortality of meningitis are higher in countries with limited resources. In 2016, > 90% of new cases of meningitis and > 80% of deaths (about 270 000 deaths) occurred in countries with a low to middle socioeconomic index, as defined by the Global Burden of Disease study group (278). In 2016, the highest mortality was reported for central and western sub-Saharan African regions, about 110 000 deaths. Nevertheless, of the 10 countries with the highest absolute number of meningitis deaths in 2016, four were located outside of the meningitis belt (Afghanistan, China, India and Pakistan). About 7% of new meningitis cases and 4% of deaths in 2016 occurred in countries with a high or middle-to-high socioeconomic index (278).

Most likely pathogens

Viral meningitis (usually benign and mainly caused by enteroviruses and arboviruses) and non-infectious causes (e.g. autoimmune or neoplastic diseases or as a side-effect of certain medicines) can mimic the signs and symptoms of bacterial meningitis. Therefore, it is important to consider these causes in the differential diagnosis. The most frequently implicated bacteria (beyond the neonatal age) are *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae* (serotype b and non-typeable strains). The most likely causative bacteria may differ across age groups (e.g. meningitis due to *Haemophilus influenzae* mainly affects children) and in patients with immune system deficiencies, for example, increased risk of *Listeria monocytogenes*, increased risk of meningitis caused by encapsulated bacteria such as *Neisseria meningitidis* and *Streptococcus pneumoniae* in patients with asplenia or hyposplenia (Table 26.1).

Tuberculous meningitis should also be considered in the differential diagnosis in patients living in or coming from areas where TB is endemic, especially if the onset of disease is not acute.

In patients with severe immunosuppression (e.g. with advanced HIV disease), cryptococcal meningitis and cerebral toxoplasmosis should also be considered, although the clinical presentation of these two infections is usually less acute than bacterial meningitis. In patients living in or visiting areas where malaria is endemic, cerebral malaria should also be included in the differential diagnosis. Although most cases of meningitis are community-acquired, the infection can also be health care-associated (e.g. after neurosurgical interventions and after lumbar puncture). In that case, the most likely pathogens are *Staphylococcus aureus* or aerobic Gram-negative bacilli, including multidrug-resistant strains. For prevention of health care-associated meningitis refer to the WHO global guidance on prevention of surgical site infections (280).

Table 26.1 – Pathogens most frequently associated with bacterial meningitis (in descending order of frequency)

Neonates (0–1 month)	Children and adolescents	Non- immunocompromised adults	Immunocompromised adults or all adults > 50 years	Other
<i>Streptococcus agalactiae</i> (group B) <i>Streptococcus</i> <i>Escherichia coli</i> <i>Listeria monocytogenes</i>	<i>Streptococcus pneumoniae</i> <i>Neisseria meningitidis</i> <i>Haemophilus influenzae</i> type b and non-typeable strains	<i>Streptococcus pneumoniae</i> <i>Neisseria meningitidis</i>	<i>Streptococcus pneumoniae</i> <i>Neisseria meningitidis</i> In addition to the above also consider: <i>Listeria monocytogenes</i> <i>Mycobacterium tuberculosis</i> ^a	<i>Streptococcus suis</i> ^d <i>Mycobacterium tuberculosis</i> ^a <i>Staphylococcus aureus</i> or Gram-negative bacteria ^e (including multidrug-resistant strains after neurosurgical interventions)
<i>Streptococcus pneumoniae</i>				Non-bacterial causes of meningitis Viral infections (especially Enteroviruses, Herpesviridae and Arboviruses) Cryptococcal meningitis and cerebral toxoplasmosis in severely immunocompromised patients (e.g. with HIV)
				Cerebral malaria (in patients living in or travelling to endemic settings)

HIV: human immunodeficiency virus

⁴ V. *Historia monachorum VIII.*

Mostly in settings where tuberculosis is endemic and/or in patients positive for HIV

Mainly in sub-Saharan Africa in children living with HIV and/or sickle cell disease.

Pregnant women also have an increased risk of *Listeria monocytogenes* infection.

Consider if exposure to pigs.

[Gram-negative bacterial meningitis can also occur as a consequence of *Strongyloides* infection.]

mm in non-comromised people infected with *Strongyloides stercoralis*

Meningitis caused by antibiotic-resistant pathogens

Data on the proportion of penicillin- and third-generation cephalosporin-resistant *Streptococcus pneumoniae* isolates causing meningitis are scarce in most countries with a high incidence of bacterial meningitis; however, whenever available, these data should guide empiric antibiotic treatment. Currently, because of the potential risk of penicillin-resistance in *Streptococcus pneumoniae* isolates and because meningitis is a very serious and potentially fatal disease, a third-generation cephalosporin is recommended for empiric treatment. Isolates with intermediate or complete resistance to ceftriaxone have rarely been described (mainly in patients with prolonged or multiple exposures to beta-lactam antibiotics in the previous 3 months) and some experts suggest adding intravenous vancomycin or rifampicin empirically to provide effective treatment for these isolates. Meningitis caused by multidrug-resistant Gram-negative bacteria has also been reported.

Clinical presentation

In adults, meningitis should be suspected in the case of acute onset (< 48 hours) of:

- fever ($\geq 38.0^{\circ}\text{C}$) **AND/OR**
- headache and/or change in mental status and/or confusion **AND/OR**
- neck stiffness.

Clinical factors to consider in diagnosing meningitis are shown in Box 26.1.

Box 26.1 – Clinical considerations

- All three of the classic signs and symptoms (fever, confusion and/or headache, and neck stiffness) are present in only around half of patients with bacterial meningitis.
- However, 95% of adult patients usually have at least two of these symptoms and the absence of all three symptoms significantly reduces the probability of meningitis (281).

A haemorrhagic rash may also be present, especially in cases of meningitis caused by *Neisseria meningitidis* although such a rash is not specific for meningococcal infection. Notably with *Streptococcus pneumoniae*, foci of infection outside the central nervous system, such as otitis media, sinusitis, pneumonia and endocarditis, are also often observed.

Because bacterial meningitis is a serious illness and clinical and epidemiological features alone cannot always reliably differentiate bacterial and viral origin, all severe cases

should be treated as if they were bacterial until this has been excluded or a viral cause has been clearly identified.

For the diagnosis of meningitis in children and neonates, refer to the latest edition of the *WHO Pocket book of hospital care for children* (31). In neonates, the clinical presentation is less typical and symptoms are usually non-specific. Neonates often present with a combination of fever, poor feeding, lethargy, drowsiness, vomiting, irritability, seizures or a full fontanelle. Neck stiffness is very uncommon.

Laboratory tests

Patient microbiology tests

Whenever possible, certain microbiology tests should be considered (Table 26.2); ideally samples should be obtained before antibiotic treatment is started. The rationale for these tests is to establish the diagnosis and identify the pathogen as this affects treatment.

Table 26.2 – Microbiology tests to consider for the diagnosis of meningitis as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
Blood cultures ^a and antimicrobial susceptibility testing	To detect bacterial and fungal bloodstream infections	Health care facilities with clinical laboratories
CSF microscopy (Gram stain)	To assess microbial morphology, number of white blood cells and red blood cells	Health care facilities with clinical laboratories
CSF culture and antimicrobial susceptibility testing	Initial step to detect and identify bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories
Cryptococcal antigen test (CSF, blood)	To screen and diagnose cryptococcal meningitis in people living with advanced HIV disease	Health care facilities with clinical laboratories and also in primary care settings

continues

Table 26.2 continued

Diagnostic test	Purpose of the test	Settings where the test should be available
<i>Mycobacterium tuberculosis</i> DNA (CSF)	To diagnose active tuberculosis and simultaneously or sequentially detect rifampicin resistance	Health care facilities with clinical laboratories

CSF: cerebrospinal fluid; EDL: Model List of Essential In Vitro Diagnostics; HIV: human immunodeficiency virus.

^a If blood is taken before starting antibiotic treatment, blood cultures are often positive in cases of bacterial meningitis (up to 75% of cases) (281,282).

Other tests

In the presence of compatible signs and symptoms, a definitive diagnosis of bacterial meningitis requires examination of cerebrospinal fluid. Therefore, whenever possible and if no contraindications are present (such as increased bleeding risk, risk of herniation or a skin infection at the site of the puncture), a lumbar puncture should be done before starting antibiotic treatment. However, doing a lumbar puncture should never delay giving antibiotic treatment when bacterial meningitis is suspected; if available at least blood cultures should be taken before starting treatment. In settings where CT scanning is available, certain patients may benefit from a scan of the head before the lumbar puncture because of the risk of cerebral herniation after removing cerebrospinal fluid at the lumbar level if elevated intracranial pressure is suspected. CT scanning should never delay the start of antibiotic treatment. If available, imaging is indicated in patients with focal neurological signs, decreased level of consciousness or coma or a history of central nervous system disease or recent onset of seizures (< 1 week) or severe immunosuppression (e.g. advanced HIV disease).

Laboratory tests to consider when meningitis is suspected are given in Table 26.3. In the specific context of epidemics, also consult the WHO meningitis epidemics guidelines (257).

In bacterial meningitis, the characteristics of cerebrospinal fluid vary widely (and may be normal or only slightly altered in neonates); however, certain findings suggest a probable bacterial cause. In particular, the following characteristics of the cerebrospinal fluid suggest bacterial meningitis:

- high opening pressure during lumbar puncture (reference range, 80–200 mm H₂O or 8–20 cm H₂O)
- turbid appearance of cerebrospinal fluid
- elevated cerebrospinal fluid white blood cell count (often more than several hundred to several thousand cells/mm³ or > 0.1 to > 1 × 10⁹/L)

- elevated cerebrospinal fluid percentage of neutrophils (> 80%)
- elevated cerebrospinal fluid protein (> 45 mg/dL or > 0.45 g/L)
- low cerebrospinal fluid glucose (< 40 mg/dL or < 2.2 mmol/L)
- low cerebrospinal fluid to plasma glucose ratio (≤ 0.4).

Table 26.3 – Laboratory tests that could be considered for the diagnosis of meningitis as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
Basic CSF profile (CSF leukocyte count, CSF differential leukocyte count and CSF protein and glucose)	To aid in the diagnosis of bacterial, mycobacterial, fungal and viral meningitis	Health care facilities with clinical laboratories
Complete blood count	To detect a wide range of disorders, including infections	Health care facilities with clinical laboratories
Blood glucose	To diagnose hyperglycaemia/hypoglycaemia	Health care facilities with clinical laboratories but also in primary care settings
C-reactive protein	To detect inflammation as an indicator of various conditions (e.g. sepsis)	Health care facilities with clinical laboratories
Procalcitonin	To guide antibiotic therapy or discontinuation in sepsis	Only in tertiary health care facilities
Whole blood lactate	To assess metabolic acidosis, sepsis and dehydration	Community settings and health facilities without laboratories

CSF: cerebrospinal fluid; EDL: Model List of Essential In Vitro Diagnostics.

Using microbiology surveillance data

Targeted periodic clinical surveillance, including risk factors, resistance of key pathogens and outcomes, may be helpful to inform empiric guidance at a national level.

Tuberculosis meningitis

TB meningitis should always be considered in the differential diagnosis in high-risk patients and in settings where TB is endemic. TB meningitis can have an acute presentation and, similar to bacterial meningitis, its diagnosis cannot be made or excluded only on the basis of clinical presentation. Since TB meningitis is a serious disease, prompt diagnosis and treatment are essential (119).

Use of corticosteroids

The rationale for the use dexamethasone in cases of meningitis is to reduce the inflammatory response and the risk of neurological sequelae (e.g. hearing loss) and death. The use of adjunctive steroids is suggested only in high-income settings, where it has a proven benefit. Current evidence has failed to show any significant benefit both in terms of mortality and sequelae in patients in low-income countries (283–285). In high-income countries, dexamethasone can be given before or at the time of the first antibiotic dose if bacterial meningitis is suspected and continued if *Streptococcus pneumoniae* is confirmed. The recommended dose is 0.15 mg/kg of dexamethasone every 6 hours. Steroids are not recommended in neonatal meningitis.

Antibiotic treatment

Antibiotic treatment should be started as soon as possible when bacterial meningitis is suspected (Table 26.4). The first dose of antibiotic treatment should not be delayed until the results of the lumbar puncture are available. The choice of empiric antibiotic treatment should take into account the age of the patient, presence of immunosuppression and local prevalence of *Streptococcus pneumoniae* isolates resistant to third-generation cephalosporins. The patient risk of *Listeria* meningitis should also be taken into account (e.g. pregnant women, patients who are immunocompromised or patients > 50 years of age) because ceftriaxone (and cefotaxime) do not cover this pathogen and ampicillin should be used in these cases.

As a general rule, empiric treatment in children other than neonates (< 1 month) and in adults should always cover all three of the main causative pathogens (*Haemophilus influenzae*, *Neisseria meningitidis* and *Streptococcus pneumoniae*).

If a pathogen is isolated and its susceptibilities are known, antibiotics should be reviewed and modified accordingly. When no pathogen is identified, the duration of antibiotic treatment should be guided by available laboratory results and clinical response.

Step-down to oral treatment is less commonly used in meningitis management, where the treatment is mainly parenteral where possible to maximize penetration into the cerebrospinal fluid.

Table 26.4 – Empiric antibiotic treatment for bacterial meningitis

! **Important**

Where more than one antibiotic is recommended for an infection, they are listed in alphabetical order and they should be considered equal treatment options, unless otherwise indicated.

	Adults	Children (not neonates)	Neonates (< 1 month)	Total treatment duration
First choice	Cefotaxime (IV): 2 g given every 6 hours OR Ceftriaxone (IV): 2 g given every 12 hours	Cefotaxime (IV): 50 mg/kg/dose given every 8 hours OR Ceftriaxone (IV): 100 mg/kg given once a day	Ampicillin (IV): 50 mg/kg/dose given every 12 hours (first week of life) AND Gentamicin (IV): 5 mg/kg given once a day (first week of life) OR Cefotaxime (IV): 50 mg/kg/dose given every 12 hours (first week of life) AND Gentamicin (IV): 5 mg/kg given once a day (first week of life) OR Ceftriaxone (IV); 100 mg/kg given once a day (> first week of life)	Unknown pathogen 10 days (adults and children) 3 weeks (neonates) Confirmed pneumococcal meningitis 10–14 days Confirmed meningococcal meningitis 5–7 days In epidemics, specific WHO recommendations on duration apply (257)
				Confirmed Listeria meningitis 21 days
				<i>continues</i>

Table 26.4 continued

	Adults	Children (not neonates)	Neonates (< 1 month)	Total treatment duration
Second choice^a	Amoxicillin^b OR Ampicillin^b (IV): 2 g given every 4 hours OR Benzylpenicillin (IV): 4 million IU (2.4 g) given every 4 hours OR Chloramphenicol^c (IV): 1 g given every 6 hours	Amoxicillin (IV): 50 mg/kg/dose given every 8 hours OR Ampicillin (IV): 50 mg/kg/dose given every 8 hours OR Benzylpenicillin (IV): 100 000 IU/kg/dose (60 mg/kg/dose) given every 6 hours OR Chloramphenicol ^c (IV: 25 mg/kg/dose given every 6 hours	Meropenem (IV): 40 mg/kg/dose given every 8 hours	Same as above

IU: international units; IV: intravenous.

Note: All dosages are for normal renal and hepatic function.

^a In adults and in children beyond neonatal age, consider second choice options only when first choice options are not available. In neonates, consider metropenem (second choice) only where resistant Gram-negative organisms are the suspected causative agents.

^b Ampicillin (or IV amoxicillin) in adults should be added to ceftriaxone/cefotaxime if risk factors for *Listeria monocytogenes* are present (e.g. patients ≥ 50 years, pregnant women).

^c Chloramphenicol should only be used when no other option is available because of toxicity (the most serious adverse event is bone marrow depression). Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Prevention

Vaccination and post-exposure prophylaxis

Primary prevention of bacterial meningitis relies on vaccination and antibiotic prophylaxis for close contacts of cases. Vaccination is a successful intervention to prevent bacterial meningitis. Available vaccines are active against meningococcal, pneumococcal and *Haemophilus influenzae* type b disease. Vaccines are never 100% effective and they do not protect against all strains of a bacterial pathogen. Duration of protection is also variable. As a result, even vaccinated people can develop bacterial meningitis. WHO recommendations for routine immunizations and the WHO roadmap towards defeating meningitis by 2030 are available online (274,277).

Meningococcal vaccination

Appropriate large-scale meningococcal vaccination programmes should be in place in countries with a high (> 10 cases per 100 000 population/year) or intermediate (2–10 cases per 100 000 population/year) incidence of meningococcal disease or with frequent epidemics. In countries in the meningitis belt, all individuals aged 1–29 years (including pregnant women) should be vaccinated with the meningococcal A conjugate vaccine (236,276).

In countries with a low incidence of meningococcal disease (< 2 cases per 100 000 population/year), vaccination is recommended only for defined high-risk groups such as children and young adults or individuals with immunodeficiency. The choice of the recommended vaccine depends on the local prevalence of the different meningococcal serogroups (276).

Pneumococcal vaccination

The inclusion of pneumococcal conjugate vaccines in childhood immunization programmes worldwide is recommended (35).

Haemophilus influenzae type b vaccination

The inclusion of *Haemophilus influenzae* type b conjugate vaccines in childhood immunization programmes worldwide is recommended (36).

Post-exposure antibiotic prophylaxis in case of meningococcal meningitis

Post-exposure antibiotic prophylaxis should be considered in the following situations (275):

- outside of the African meningitis belt for all close contacts within the household
- in the African meningitis belt for close contacts in non-epidemic situations.

Ciprofloxacin (usually 500 mg oral, single dose) is the antibiotic of choice, and ceftriaxone can be used as an alternative (usually 250 mg intramuscular single dose in adults and 125 mg intramuscular single dose in children).

27. Community-acquired pneumonia – severe

Key messages

- Rapidly decide if the patient has severe community-acquired pneumonia (CAP) (higher short-term mortality risk and need for hospital/intensive care admission) or mild CAP which can be managed in primary care with oral antibiotic treatment. Scores can be helpful to make this distinction.
- Laboratory tests can help assess disease severity and identify a bacterial versus a viral infection.
- Consider adding empiric antibiotic treatment with a macrolide to cover atypical pathogens (*Chlamydia* or *Mycoplasma pneumoniae*).
- Treatment duration can be limited to 5 days in most cases.

Other relevant WHO resources (please check regularly for updates)

- Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, 2013 (31).
- Revised WHO classification and treatment of pneumonia in children at health facilities: evidence summaries (118).
- Coronavirus disease (COVID-19) pandemic (32).
- Living guidance for clinical management of COVID-19: living guidance, 23 November 2021 (33).
- Therapeutics and COVID-19: living guideline, 16 September 2022 (34).
- Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper – February 2019 (35).
- *Haemophilus influenzae* type b (Hib) vaccination position paper – July 2013: Introduction (36).
- Vaccines against influenza WHO position paper – May 2022 (37).
- WHO consolidated guidelines on tuberculosis: module 4: treatment: drug-susceptible tuberculosis treatment (119).

Community-acquired pneumonia

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Definition

An acute illness affecting the lungs usually presenting with cough, sputum production, and rapid and difficult breathing with a new or worsening pulmonary infiltrate on a chest radiograph

Most Likely Pathogens

"Typical" bacteria:

- *Streptococcus pneumoniae* (most cases)
- *Haemophilus influenzae* (chronic lung diseases, smoking)
- *Moraxella catarrhalis* (chronic lung diseases, smoking)
- *Staphylococcus aureus* (often associated with influenza)
- *Enterobacteriaceae* (severe comorbidities, e.g. chronic lung diseases, dementia, stroke)

"Atypical" bacteria:

- *Mycoplasma pneumoniae* (more frequent in young adults)
- *Chlamydia pneumoniae* and *psittaci* (more frequent in young adults)
- *Legionella* spp. (chronic lung diseases or other underlying illness, travel, exposure to hot tubs)
- *Coxiella burnetii* (rural areas, exposure to livestock)

Respiratory viruses:

- Influenza viruses (A and B)
- Respiratory syncytial virus (RSV)
- Metapneumovirus
- Parainfluenza virus
- Coronavirus (including SARS-CoV-2)
- Adenovirus
- Rhinovirus
- Other respiratory viruses

Pathogens to consider in specific settings:

- *Burkholderia pseudomallei* (SE Asia, Australia)
- *Mycobacterium tuberculosis*
- *Pneumocystis jirovecii* (people with HIV or other immunosuppression)

Investigating for Tuberculosis (TB)

- Consider specific investigations for TB in endemic settings especially in high-risk patients (e.g. HIV)
- A rapid molecular test performed on a single sputum specimen is the preferred first line diagnostic test for pulmonary TB and to detect rifampicin resistance
- Consider a lipoarabinomannan rapid urinary antigen test in severely immunocompromised HIV patients with signs and symptoms of tuberculosis

Diagnosis

Clinical Presentation

- New onset (<2 weeks) or worsening cough with fever ($\geq 38.0^{\circ}\text{C}$), sputum production, dyspnea, tachypnea, reduced oxygen saturation, crepitations on lung auscultation, chest pain/discomfort without alternative explanation
- Extrapulmonary features (i.e. confusion, disorientation) may predominate in elderly, and immunocompromised patients and fever may be absent

Microbiology Tests

Mild cases: usually not needed

Severe cases (to guide antimicrobial treatment): blood cultures, urinary antigens for *L. pneumophila* and *S. pneumoniae*

Selected cases (depending on epidemiology and risk factors): sputum rapid molecular test for *M. tuberculosis*, nasopharyngeal swab for influenza viruses and SARS-CoV-2, HIV testing in settings with high HIV prevalence and in case of recurrent and/or severe pneumonia

Other Laboratory Tests

Determine disease severity: blood urea nitrogen (see CURB-65 Scoring System box), blood pH and gases, white blood cell count

Differentiate bacterial and viral (taking into account pre-test probability): C-reactive protein and/or procalcitonin

Note: tests depend on availability and clinical severity (e.g. blood gases will only be done in severe cases)

Imaging

- Chest X-ray not necessary in mild cases
- Infiltrate may not always be evident (e.g. dehydration) and non-infectious etiologies may mimic infiltrates (e.g. lung edema, pulmonary embolism)
- Radiologic appearance cannot be used to accurately predict pathogen

Community-acquired pneumonia

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CURB-65 Severity Scoring System

Signs & Symptoms (1 point each)

- Presence of confusion (new onset)
- Urea > 19 mg/dL (or > 7 mmol/L)*
- Respiratory rate > 30/min
- Systolic BP < 90 mmHg (<12 kPa) or Diastolic BP ≤ 60 mmHg (<8 kPa)
- Age ≥ 65 years

Other considerations such as severe comorbid illnesses or inability to maintain oral therapy should be taken into account. CURB-65 has not been extensively validated in low-income settings.

*The CRB-65 score, which does not require laboratory values for its calculation, can also be used, the score value interpretation is the same as for CURB-65

Score 0-1

- Consider outpatient treatment

Score 2

- Consider inpatient treatment
- Consider adding clarithromycin to beta-lactam for atypical coverage
- Perform microbiology tests

Score ≥3

- Inpatient treatment (consider ICU)
- Consider adding clarithromycin
- Perform microbiology tests

Rx Treatment

Antibiotic Treatment Duration

Treat for 5 days

If severe disease, consider longer treatment and look for complications such as empyema, if patient not clinically stable at day 5

Rx Severe Cases

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice

 Cefotaxime 2 g q8h IV/IM
WATCH

OR

 Ceftriaxone 2 g q24h IV (1 g q24h IM*)
WATCH

*A larger volume would be painful to give as intramuscular injection

IF CURB-65 ≥2,
CONSIDER ADDING

 Clarithromycin 500 mg q12h ORAL (or IV)
WATCH

Clarithromycin has excellent oral bioavailability and the intravenous route should be reserved for patients with impaired gastrointestinal function

Second Choice

 Amoxicillin+clavulanic acid 1 g+200 mg q8h IV
• A higher daily dose can be considered:
1 g+200 mg q6h

IF CURB-65 ≥2,
CONSIDER ADDING

 Clarithromycin 500 mg q12h ORAL (or IV)
WATCH

Clarithromycin has excellent oral bioavailability and the intravenous route should be reserved for patients with impaired gastrointestinal function

Rx Mild to Moderate Cases

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice

 Amoxicillin 1 g q8h ORAL
ACCESS

OR

 Phenoxymethylpenicillin (as potassium) 500 mg (800 000 IU) q6h ORAL
ACCESS

Second Choice

 Amoxicillin+clavulanic acid 875 mg+125 mg q8h ORAL
ACCESS

OR

 Doxycycline 100 mg q12h ORAL
ACCESS

Community-acquired pneumonia

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Definition

An acute illness affecting the lungs usually presenting with cough, and rapid and difficult breathing with a new or worsening pulmonary infiltrate on a chest radiograph

Most Likely Pathogens

"Typical" bacteria:

- *Streptococcus pneumoniae* (most common cause of CAP beyond the 1st week of life)
- *Haemophilus influenzae*
- *Moraxella catarrhalis*
- *Staphylococcus aureus*
- *Enterobacteriales*

"Atypical" pathogens (more frequent in children >5 years compared to younger children):

- *Mycoplasma pneumoniae*
- *Chlamydophila pneumoniae*

Respiratory viruses:

- Respiratory syncytial virus (RSV)
- Influenza viruses (A and B)
- Metapneumovirus
- Parainfluenza virus
- Coronavirus (including SARS-CoV-2)
- Adenovirus
- Rhinovirus
- Other respiratory viruses

Investigating for Tuberculosis (TB)

- Consider specific investigations for TB in endemic settings especially in high-risk patients (e.g. HIV)
- A rapid molecular test performed on a single sputum specimen is the preferred first line diagnostic test for pulmonary TB and to detect rifampicin resistance

Diagnosis

Clinical Presentation

- New onset (<2 weeks) or worsening cough with fever ($\geq 38.0^{\circ}\text{C}$), dyspnea, tachypnea, reduced oxygen saturation, crepitations, cyanosis, grunting, nasal flaring, pallor
- Pneumonia is diagnosed on: fast breathing for age and/or chest indrawing
 - Check for hypoxia with oxygen saturometer if available
- Children with runny nose and cough and no signs of severity usually do not have pneumonia and should not receive an antibiotic, only home care advice

Microbiology Tests

Mild cases: usually not needed

Severe cases (to guide antimicrobial treatment): blood cultures

Tests for COVID-19 and influenza can be considered if clinically indicated and available

Other Laboratory Tests

No test clearly differentiates viral or bacterial CAP

Consider: full blood count and C-reactive protein

Note: tests depend on availability and clinical severity (e.g. blood gases will only be done in severe cases)

Imaging

- Chest X-ray not necessary in mild cases
- Look for lobar consolidation or pleural effusion
- Radiologic appearance cannot be used to accurately predict pathogen

Community-acquired pneumonia

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Severity Assessment and Considerations

Children with **pneumonia**:

- Should be treated with oral amoxicillin at home with home care advice
- Pneumonia is diagnosed on either:
 1. Fast breathing (respiratory rate > 50 breaths/minute in children aged 2-11 months; resp rate > 40 breaths/min in children aged 1-5 years)
 2. Chest indrawing

Children with **severe pneumonia** (or a child with pneumonia who cannot tolerate oral antibiotics):

- **Should be admitted to hospital and treated with intravenous antibiotics**
- Severe pneumonia is characterized by signs of pneumonia:
 - Fast breathing (+/- chest indrawing)
 - PLUS
 - A general danger sign:
 - Inability to breastfeed or drink
 - Convulsions
 - Lethargy or reduced level of consciousness



Antibiotic Treatment Duration

3 days: in areas of low HIV prevalence and no chest indrawing

5 days: in areas of high HIV prevalence and the child has chest indrawing

If severe disease, consider longer treatment and look for complications such as empyema, if patient not clinically stable at day 5

Rx Mild to Moderate Cases

All dosages are for normal renal function

Amoxicillin 80-90 mg/kg/day **ORAL**

• Oral weight bands:

3-<6 kg	250 mg q12h
6-<10 kg	375 mg q12h
10-<15 kg	500 mg q12h
15-<20 kg	750 mg q12h
≥20 kg	500 mg q8h or 1 g q12h

Rx Treatment

Rx Severe Cases

Please see Severity Assessment and Considerations for diagnosis of severe cases

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice

Amoxicillin 50 mg/kg/dose **IV/IM**

- ACCESS • ≤1wk of life: q12h
• >1wk of life: q8h

OR

Ampicillin 50 mg/kg/dose **IV/IM**

- ACCESS • ≤1wk of life: q12h
• >1wk of life: q8h

OR

Benzylpenicillin 30 mg/kg/dose (50 000 IU/kg/dose) q8h **IV**

- ACCESS

COMBINED WITH

Gentamicin **IV/IM**

- ACCESS • Neonates: 5 mg/kg/dose q24h
• Children: 7.5 mg/kg/dose q24h

IF HIV POSITIVE AND <1 YR OLD
To treat potential *Pneumocystis jirovecii* pneumonia, **ADD**

Sulfamethoxazole+trimethoprim 40 mg/kg SMX+8 mg/kg TMP q8h **IV/ORAL** for 3 weeks

Second Choice

If NO Clinical Response to First Choice after 48-72 hours

Cefotaxime 50 mg/kg/dose q8h **IV/IM**

OR

Ceftriaxone 80 mg/kg/dose q24h **IV/IM**



Definition

CAP is an acute illness affecting the lungs caused by pathogens, most often bacteria and viruses. It usually presents with cough, sputum production (in adults), rapid and difficult breathing with new or worsening pulmonary infiltrate(s) on chest imaging.

Pathophysiology

CAP occurs when microbial pathogens (usually inhaled in the upper airways) reach the lower respiratory tract and proliferate in the alveoli. Less frequently, these pathogens can also reach the alveoli via the blood or by direct spread, for example, from an infection of the pleural or intra-abdominal space. Once in the alveoli, host immune defences are activated to eliminate the pathogens. Only when these defences fail, pneumonia manifests itself because of the tissue damage and inflammatory response triggered by the proliferation of microorganisms in the affected lung(s).

Epidemiology

CAP is common worldwide and is a leading cause of morbidity and mortality, with an especially high burden in low-income countries (120). According to the Global Burden of Disease study, in 2017, there were an estimated 471 million new cases of lower respiratory tract infections (including CAP) globally among all ages and sexes combined (44). However, a majority of these cases were viral bronchitis; therefore, caution is needed in interpreting this number. The incidence of CAP varies with age and a country's income level. The most common causative pathogen worldwide is *Streptococcus pneumoniae* and viruses (see the following section); viral–bacterial coinfections may occur.

In low-income countries, lower respiratory tract infections (including CAP) were the leading cause of death in 2016 with a crude yearly attributable mortality of about 75 per 100 000 population (721). In general, the incidence of CAP is highest in children younger than 5 years in these countries. In 2015, an estimated 0.9 million children younger than 5 years died of pneumonia and of these, about 0.5 million occurred in sub-Saharan Africa (122). Undernutrition, HIV infection, and exposure to smoke and air pollution are common risk factors for severe CAP in children younger than 5 years. As a result of better access to medical care, better nutrition and greater vaccination coverage, global mortality rates in children have declined by more than 30% since 2000. In high-income countries, CAP mainly affects adults 65 years and older and, in general, the incidence of CAP and risk of death increase with age (123).

Most likely pathogens

In **neonates and children aged up to 2 months**, pneumonia is mainly caused by *Streptococcus pneumoniae*, group B *Streptococcus*, Enterobacterales or *Staphylococcus aureus*.

In **children aged 2 months to 5 years**, pneumonia is more likely to be of viral origin (e.g. respiratory syncytial virus, and influenza and parainfluenza virus). The most important bacterial pathogen in children younger than 5 years is *Streptococcus pneumoniae*. In older children, *Streptococcus pneumoniae* is still common but “atypical” bacteria such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* may occur – atypical bacteria have intrinsic resistance to beta-lactam antibiotics and cannot be visualized by Gram staining. *Haemophilus influenzae*, *Moraxella catarrhalis* and *Staphylococcus aureus* also cause CAP in some children (Table 27.1).

In adults, viruses are common causes of CAP, either by directly causing pneumonia or by favouring superinfection with bacteria. Among bacteria, the most common causative agents are *Streptococcus pneumoniae*, followed by atypical bacteria such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella pneumophila*. *Haemophilus influenzae*, *Moraxella catarrhalis* and *Staphylococcus aureus* are also quite common (Table 27.1).

However, determining the cause of bacterial pneumonia is difficult in all age groups and no causative pathogen is identified in most cases, even if extensive microbiological tests are performed. Furthermore, there may be important geographic differences in the cause of pneumonia; for example, *Burkholderia pseudomallei* is a cause of CAP in South-East Asia, while *Coxiella burnetii* is more common in regions with exposure to livestock.

Note

- Identifying a pathogen on a specimen in the upper respiratory tract does not mean it is the cause of the pneumonia.
- Nasopharyngeal carriage of bacterial pathogens is very common.

The type of sample (upper respiratory versus lower respiratory origin, blood cultures), the test characteristics (sensitivity, specificity, predictive values), the local epidemiology, clinical presentation and, if available, other laboratory test results always need to be considered when deciding whether a positive result for a pathogen likely identifies the causative pathogen.

Table 27.1 – Pathogens most frequently associated with community-acquired pneumonia (in descending order of frequency)

"Typical" bacteria	"Atypical" bacteria ^a	Respiratory viruses	Other pathogens to consider in specific settings
<i>Streptococcus pneumoniae</i> ^b	<i>Mycoplasma pneumoniae</i> ^c	Influenza virus (A and B)	<i>Burkholderia pseudomallei</i> (South-East Asia, Australia)
<i>Haemophilus influenzae</i>	<i>Chlamydia pneumoniae</i> ^c	Respiratory syncytial virus ^d	<i>Mycobacterium tuberculosis</i>
<i>Moraxella catarrhalis</i>	<i>Chlamydia psittaci</i> ^c	Metapneumovirus	
<i>Staphylococcus aureus</i>	<i>Legionella</i> spp.	Parainfluenza virus	<i>Pneumocystis jirovecii</i>
Enterobacteriales (e.g. <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i>)	<i>Coxiella burnetii</i>	Coronavirus (including SARS-CoV-2)	(in people with HIV or other types of cellular immunosuppression)
		Adenovirus	
		Rhinovirus	
		Other respiratory viruses	

HIV: human immunodeficiency virus; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

^a Atypical bacteria remain colourless with Gram staining. They also have intrinsic resistance to beta-lactams.

^b The most common bacterial cause of community-acquired pneumonia in all age groups (beyond the first week of life) is *Streptococcus pneumoniae*.

^c *Mycoplasma pneumoniae* and *Chlamydia* spp. are more frequent in children > 5 years (compared with younger children) and in young adults.

^d Up to 50% of cases of pneumonia in children < 5 years are caused by a virus (most commonly respiratory syncytial virus).

Community-acquired pneumonia caused by antibiotic-resistant pathogens

Antimicrobial resistance is a potential problem with all pathogens associated with CAP. Clinically relevant high-level beta-lactam resistance in *Streptococcus pneumoniae* is however still rare globally. Resistance to macrolides in *Streptococcus pneumoniae* and *Mycoplasma pneumoniae* is highly prevalent in some settings (124,125). It is important to note that also in the hospital setting, parenteral Access antibiotics such as penicillin/amoxicillin/ampicillin achieve sufficient antibiotic exposure to treat the great majority of *Streptococcus pneumoniae* isolates.

Note

Community-acquired pneumonia caused by low-level and intermediate-level pneumococcal penicillin resistance can be successfully treated with higher doses of the Access antibiotics (amoxicillin, ampicillin or penicillin) in children and adults.

Clinical presentation

Nearly all respiratory diseases can mimic the symptoms of CAP. Based on clinical features alone it is often impossible to distinguish bacterial from viral pneumonia or from other non-infectious causes; local epidemiology and laboratory tests may help.

Well established clinical features of CAP include a combination of: new onset (< 2 weeks) of symptoms, worsening cough with or without sputum production, dyspnoea (difficulty in breathing), tachypnoea (abnormal respiratory rates to diagnose rapid breathing vary with age), reduced oxygen saturation, crepitations on lung auscultation, or chest pain or discomfort without an alternative explanation. Fever $\geq 38.0^{\circ}\text{C}$ for 3–4 days is usually present but may be absent, especially in elderly people. Extrapulmonary features such as confusion or disorientation may be the main symptoms in elderly people, immunocompromised patients and malnourished children. Severe pneumonia with respiratory distress and sepsis requiring intensive care and intravenous antibiotic treatment has a high associated mortality.

In children the WHO defines fast breathing pneumonia as a child with a high respiratory rate for their age (> 50 breaths/minute in children 2–11 months of age; > 40 breaths/minute in children aged 1–5 years). They may or may not have chest indrawing.

Laboratory tests

Patient microbiology tests

In severe cases the following tests could be considered to guide antimicrobial treatment (Table 27.2):

- blood cultures (ideally before starting antibiotic treatment)
- sputum microscopy and culture (ideally before starting antibiotic treatment)
- urinary antigens for *Legionella pneumophila* and *Streptococcus pneumoniae*.

Additionally, in certain cases, the following tests could also be considered (Table 27.2):

- rapid molecular test for *Mycobacterium tuberculosis* in sputum
- nucleic acid amplification test for influenza virus in a nasopharyngeal sample to help decide on antiviral treatment and for infection prevention and control purposes, for example, to prevent transmission to other patients
- nucleic acid amplification test or antigen test for SARS-CoV-2 depending on the current epidemiology
- HIV testing in low- and middle-income countries and in case of recurrent and severe pneumonia.

Routine use of nasopharyngeal swab for nucleic acid tests for respiratory viruses other than influenza or SARS-CoV-2 is usually not needed.

Table 27.2 – Microbiology tests to consider if community-acquired pneumonia is suspected as indicated in the WHO EDL (6)

Diagnostic test	Purpose of test	Setting where the test should be available	Comment
Blood cultures and antimicrobial susceptibility testing	To detect bacterial bloodstream infection	Health care facilities with clinical laboratories	Not routinely needed but suggested in severe cases ^a Some guidelines suggest blood culture also in cases of recent antibiotic exposure (< 3 months) or if MRSA or <i>Pseudomonas aeruginosa</i> infection is suspected
Sputum microscopy (Gram stain)	To assess microbial morphology and adequacy of the specimen for culture by identifying white blood cells and squamous epithelial cells	Health care facilities with clinical laboratories	Not routinely needed but suggested in severe cases ^a Some guidelines suggest sputum microscopy also in cases of recent antibiotic exposure (< 3 months) or if MRSA or <i>Pseudomonas aeruginosa</i> infection is suspected
Sputum culture and antimicrobial susceptibility testing	Initial step to detect and identify bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories	Not routinely needed but suggested in severe cases ^a Some guidelines suggest sputum culture also in cases of recent antibiotic exposure (< 3 months) or if MRSA or <i>Pseudomonas aeruginosa</i> infection is suspected

continues

Table 27.2 *continued*

Diagnostic test	Purpose of test	Setting where the test should be available	Comment
Sputum rapid molecular test for <i>Mycobacterium tuberculosis</i>	To diagnose active tuberculosis and detect rifampicin resistance	Health care facilities with clinical laboratories	If <i>Mycobacterium tuberculosis</i> infection is suspected
Urinary antigens for <i>Legionella pneumophila</i> and <i>Streptococcus pneumoniae</i>	To diagnose legionellosis and pneumococcal pneumonia	— ^b	Not routinely needed but suggested in severe cases ^a . It is often difficult or impossible to obtain high-quality sputum (e.g. from elderly people and children) Some guidelines also recommend urinary antigens in case of an outbreak of legionellosis or recent travel
Nasopharyngeal swab for NAAT for influenza viruses	To diagnose seasonal influenza infection	Health care facilities with clinical laboratories but also in primary care settings	Not routinely needed but suggested during the influenza season
SARS-CoV-2 antigen Upper respiratory specimens (e.g. nasopharyngeal or nasal swab)	To diagnose COVID-19	Community settings and health facilities without laboratories ^c	Not routinely needed but suggested depending on the epidemiologic situation
SARS-CoV-2 NAAT Upper respiratory specimens (e.g. nasopharyngeal and oropharyngeal) and lower respiratory specimens (e.g. BAL)	To diagnose COVID-19	Health care facilities with clinical laboratories	Not routinely needed but suggested depending on the epidemiologic situation

continues

Table 27.2 *continued*

Diagnostic test	Purpose of test	Setting where the test should be available	Comment
Nasopharyngeal swab for NAAT for respiratory viruses other than influenza viruses or SARS-CoV-2 (e.g. respiratory syncytial virus, adenovirus)	To diagnose respiratory viruses other than influenza or SARS-CoV-2	— ^b	Not routinely needed but suggested in severe cases ^a
Anti-HIV-1 and -HIV-2 antibody (RDT) or Combined anti-HIV-1/HIV-2 antibody and p24 antigen (RDT)	To diagnose HIV infection	Community settings and health facilities without laboratories ^c	Please consult the WHO consolidated guidelines on HIV testing services (286).

BAL: bronchoalveolar lavage; COVID-19: coronavirus disease 2019; EDL: Model List of Essential In Vitro Diagnostics; HIV: human immunodeficiency virus; MRSA: methicillin-resistant *Staphylococcus aureus*; NAAT: nucleic acid amplification test; RDT: rapid diagnostic test; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

^a Severe cases are those with CURB-65 ≥ 2 (adults); for children, refer to the section: Scores to determine disease severity and guide treatment decisions.

^b This test is not in the WHO EDL (6).

^c Community and health settings without laboratories are defined as community and health facilities such as health posts and centres, doctors' offices, outreach clinics and ambulatory care. These tests are also assumed to be available at health care facilities with laboratories.

Other tests

In severe cases, several tests could be considered based on local availability (Table 27.3) to determine disease severity, help differentiate bacterial and viral etiologies and determine treatment duration (and intravenous to oral switch) during follow up.

Table 27.3 – Laboratory tests to consider if community-acquired pneumonia is suspected as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
Blood urea nitrogen	To assess kidney function ^a	Health care facilities with clinical laboratories
White blood cell count	To help in the diagnosis of infection	Health care facilities with clinical laboratories
Blood pH and gases	To assess lung function and metabolic or kidney disorders, and monitor oxygen therapy To measure blood pH, oxygen and carbon dioxide, serum bicarbonate and anion gap	Health care facilities with clinical laboratories
C-reactive protein	To detect inflammation as an indicator of various conditions	Health care facilities with clinical laboratories
Procalcitonin	To guide antibiotic therapy or discontinuation in sepsis and lower respiratory tract infection	Only in tertiary care facilities

EDL: Model List of Essential In Vitro Diagnostics.

^a Required for the CURB-65 score calculation.

Using microbiology surveillance data

In the great majority of episodes of CAP in the hospital setting, parenteral antibiotics produce an exposure sufficient to treat most resistant isolates.

Routine clinical microbiology samples for CAP are biased towards more severe forms of CAP where more invasive sampling is performed (such as bronchoalveolar lavage) and microbiology results are therefore not representative of the general population with CAP.

Therefore, routine clinical microbiology surveillance of CAP in the hospital setting does not help to inform local empiric guidance.

Imaging

When severe CAP is suspected clinically, a chest X-ray is needed because other conditions have similar clinical features and antibiotics may be avoided if the chest X-ray does not suggest bacterial pneumonia. Furthermore, chest X-rays can be difficult to interpret,

especially those of elderly people, and many other conditions (such as heart failure) can mimic infectious infiltrates. In addition, the absence of a visible infiltrate does not always rule out pneumonia (e.g. in dehydrated patients). As with any test, the pre-test probability of pneumonia based on clinical picture and laboratory tests if available and the likelihood of alternative diagnoses need to be considered when interpreting chest X-rays. It should also be noted that the radiographic pattern cannot be used to accurately predict the microbial cause and does not reliably distinguish typical from atypical or viral pathogens.

Scores to determine disease severity and guide treatment decisions

WHO recommends that children who meet the criteria of severe pneumonia should be admitted to hospital. As a general rule for children, hospitalization is indicated in cases of severe illness (e.g. cough and severe respiratory distress, marked tachypnoea and tachycardia) and/or if the child is unable to take oral therapy.

In children, severe pneumonia is characterized by signs of pneumonia (fast breathing with or without chest indrawing) plus a general danger sign, such as inability to breastfeed or drink, convulsions, lethargy or a reduced level of consciousness (118).

In adults, several scores exist that measure severity and help predict 30-day mortality. These scores, in addition to clinical judgement, can be used to determine the need for hospitalization in immunocompetent adults diagnosed with CAP. In view of its simplicity, one of the more frequently used scores is the CURB-65 (127), or its modification, CRB-65, which does not require laboratory values for its calculation (Table 27.4). However, it should be noted that these scores have not been extensively validated in low- and middle-income countries or settings and therefore there is no clear consensus about their use in these settings (128). As well as severity scores, other factors, such as severe comorbid illnesses (e.g. HIV infection) or inability to maintain oral therapy, should always be taken into account in determining the need for hospital admission.

Table 27.4 – CURB-65 criteria and scoring, and treatment decisions

Criterion	Points
Presence of confusion (new onset)	1
Urea > 19 mg/dL (or > 7 mmol/L) ^a	1
Respiratory rate > 30 breaths/min	1

continues

Table 27.4 *continued*

Criterion	Points
Systolic blood pressure < 90 mmHg (< 12 kPa) or diastolic blood pressure ≤ 60 mmHg (≤ 8 kPa)	1
Age ≥ 65 years	1
CURB-65 score/CRB-65 score ^a	Where to treat
0–1	Candidate for outpatient treatment Low 30-day mortality risk (< 1.5%)
2	Consider inpatient treatment 30-day mortality risk ≈ 10% Consider adding clarithromycin (see Table 27.5) If tests are available, consider testing for atypical pathogens (e.g. <i>Legionella</i> spp., <i>Mycoplasma</i> spp.)
≥ 3	Inpatient treatment (consider admission to intensive care) High 30-day mortality risk (≈ 20%) Consider adding clarithromycin (see Table 27.5) Consider testing for atypical pathogens (e.g. <i>Legionella</i> spp., <i>Mycoplasma</i> spp.)

Note. The CURB score is not validated in low-and middle-income countries.

^a Urea is not required for the calculation of the CRB-65 score, a modification of the CURB-65 score that does not require laboratory tests.

Ruling out tuberculosis

TB is a cause of subacute lower respiratory tract infection and should be considered in settings endemic for TB, especially in high-risk patients (e.g. children or adults with HIV), with a slow onset of symptoms and persistent cough, or those who do not respond to the initial antibiotic treatment. In such cases, specific investigations for TB should be done. A rapid molecular test (GeneXpert® MTB/RIF assay) performed on a single sputum specimen is currently the preferred first-line diagnostic test for pulmonary TB and to detect rifampicin resistance in both children and adults. When this rapid test is not available, microscopy examination of sputum smears could be considered for the



detection of acid-fast bacilli (129). For TB management and treatment, refer to the *WHO consolidated guidelines on tuberculosis* (119).

Symptomatic care

Patients with severe CAP should receive appropriate oxygen therapy. Routine treatment with corticosteroids is usually not needed unless otherwise indicated (287–290).

Antibiotic treatment

The primary goal of empiric antibiotic treatment in CAP is to provide effective and timely treatment for *Streptococcus pneumoniae* infection, because this is the predominant bacterial pathogen, and untreated pneumococcal pneumonia is associated with high mortality (see Table 27.5 for adults and Table 27.6 for children for treatment recommendations). While ceftriaxone co-prescribed with clarithromycin is the first-choice recommended option, other less broad-spectrum options (e.g. intravenous amoxicillin or benzylpenicillin co-prescribed with clarithromycin) could be considered, especially in less severe cases not requiring intensive care unit admission.

Empiric treatment should be guided by the age of the patient, severity of symptoms, presence of comorbidities and previous antibiotic treatment. In certain cases (e.g. immunocompromised patients), the epidemiology of antibiotic resistance for common pathogens causing CAP in the setting in which the patient is being treated could be considered.

Clinical improvement should be evident within 48–72 hours of starting antibiotic therapy. If there is no response to treatment, a complication (such as empyema) should be considered. Duration of treatment should be guided by measures of clinical improvement (e.g. resolution of fever); usually 5 days of treatment are adequate for adults and 3–5 days in children.

Simplify empiric treatment to a more narrow-spectrum antibiotic (also called de-escalation) based on culture results (targeted treatment) or based on rapid clinical improvement when no microbiology test results are available.

Step-down to oral treatment is based on improvement of symptoms and signs of infection and the ability to take oral antibiotics allowing discharge of the patient home when clinically appropriate.

Table 27.5 – Empiric antibiotic treatment for severe cases of community-acquired pneumonia in adults

Important		
	Adults	Total treatment duration (130,131)
First choice	<p>Cefotaxime (IV/IM): 2 g given every 8 hours</p> <p>OR</p> <p>Ceftriaxone (IV/IM): 2 g given once a day (IV), 1 g given once a day (IM)^a</p> <p>If CURB-65 ≥ 2, CONSIDER ADDING</p> <p>Clarithromycin^b (oral or IV): 500 mg given every 12 hours</p>	<p>5 days</p> <p>Consider longer treatment and/or investigate for complications if the patient is not clinically stable at day 5</p>
Second choice	<p>Amoxicillin+clavulanic acid (IV): 1 g + 200 mg given every 8 hours (a higher dose could be considered: 1 g + 200 mg given every 6 hours)</p> <p>If CURB-65 ≥ 2, CONSIDER ADDING</p> <p>Clarithromycin^b (oral or IV): 500 mg given every 12 hours</p>	5 days

IM: intramuscular; IU: international units; IV: intravenous.

Note. All dosages are for normal renal and hepatic function.

^a The reason for giving a lower dose when the ceftriaxone is given IM (rather than IV) is that a larger volume would be painful to give as intramuscular injection.

^b The rationale of adding clarithromycin to beta-lactam is to cover for possible atypical bacteria. Azithromycin could be used as an alternative when clarithromycin is not available but there are increasing concerns about its potential for the emergence and spread of antibiotic resistance because of its long half-life. Erythromycin could also be considered but it is associated with higher toxicity (diarrhoea is frequently associated with its use). Macrolides have good bioavailability and there is no need to use the intravenous route if the patient has a functioning gastrointestinal tract.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Table 27.6 – Empiric antibiotic treatment for severe cases of community-acquired pneumonia in children (from the Revised WHO classification and treatment of childhood pneumonia at health facilities) (118)

! Important		
	Children	Total treatment duration
Severe pneumonia (pneumonia with any danger sign ^a which requires referral to facility/hospital, admission and injectable therapy)	<p>Amoxicillin OR Ampicillin (IV/IM): 50 mg/kg/dose given every 12 hours (first week of life) 50 mg/kg/dose given every 8 hours (>first week of life)</p> <p>AND</p> <p>Gentamicin (IV/IM):</p> <ul style="list-style-type: none"> Neonates: 5 mg/kg/dose given once a day Children: 7.5 mg/kg/dose given once a day <p>Amoxicillin/ampicillin can be replaced by</p> <p>Benzylpenicillin (IV): 50 000 IU/kg/dose (30 mg/kg/dose) given every 8 hours</p> <p>If no clinical response to ampicillin AND gentamicin after 48–72 hours, change to:</p> <p>Cefotaxime (IV/IM): 50mg/kg/dose given every 8 hours</p> <p>OR</p> <p>Ceftriaxone (IV/IM): 80 mg/kg/dose given once a day</p> <p>Note</p> <ul style="list-style-type: none"> if HIV-positive and older than 1 month, <i>Pneumocystis jirovecii</i> pneumonia is a risk so add empiric sulfamethoxazole+trimethoprim: 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole, given every 8 hours for 3 weeks Severe pneumonia, particularly in school-aged children, may rarely be caused by <i>Mycoplasma pneumoniae</i>, which is unresponsive to beta-lactams and would be usually treated with macrolides (e.g. clarithromycin) 	5 days (consider longer treatment if the patient is not clinically stable at day 5)

continues

■ HOSPITAL FACILITY

27. Community-acquired pneumonia – severe

Table 27.6 *continued*

HIV: human immunodeficiency virus; IM: intramuscular; IU: international units; IV: intravenous.

Note. All dosages are for normal renal and hepatic function.

^a Not able to drink, persistent vomiting, convulsions, lethargic or unconscious, stridor in a calm child or severe malnutrition.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Prevention

Vaccination can prevent many cases of CAP. Available vaccines are active against pneumococcal infection, *Haemophilus influenzae* type b disease and influenza, and several vaccines against SARS-CoV-2 are available. Vaccines are never 100% effective and because they are serogroup-specific, they do not protect against all strains of bacteria or viruses. Duration of protection is also variable. As a result, even vaccinated people can develop CAP. *Haemophilus influenzae* type b conjugate vaccines and pneumococcal conjugate vaccines should be included in all routine infant immunization programmes as they have been very successful in reducing invasive disease and, in many countries, rates of pneumococcal resistance. Countries should consider the inclusion of yearly seasonal influenza vaccination for high-risk populations (pregnant women, elderly people, patients with chronic medical conditions and health care workers) in their vaccination plan.

28. Hospital-acquired pneumonia

Key messages

- Antibiotic-resistant pathogens are more frequent in hospital-acquired pneumonia (HAP) than in community-acquired pneumonia (CAP). The frequency of multidrug-resistant pathogens as causes of HAP varies by setting (e.g. among different regions, or within a hospital) and this has implications for empiric guidance.
- HAP in ventilated patients – called ventilator-associated pneumonia (VAP) – is a special subtype of HAP with higher frequency of multidrug-resistant pathogens. It is not addressed specifically in this chapter.
- Risk factors for multidrug-resistant pathogens (e.g. longer hospital stay, previous colonization and antibiotic use) need to be considered when choosing empiric treatment.
- In people with HAP (and VAP), the respiratory tract is often colonized with bacteria and a positive culture may not indicate an acute infection.
- Potential overtreatment of HAP with broad-spectrum antibiotics of the Watch and Reserve groups should be avoided when possible, particularly in non-ventilated patients.



Other relevant WHO resources (please check regularly for updates)

- Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, 2013 (31).

Definition

Hospital-acquired pneumonia (HAP) is an acute illness affecting the lungs caused by pathogens present in the hospital setting and presenting 48 hours or more after admission. If pneumonia develops while the patient is on a ventilator, HAP is also called ventilator-associated pneumonia (VAP). Of note, the cut-off of 48 hours after admission is chosen for convenience and surveillance purposes. Depending on the situation (particularly in non-ventilated patients), even pneumonias occurring several days to weeks after hospitalization can be caused by pathogens known to cause CAP, while nosocomial pathogens can be acquired and cause infection in patients hospitalized for fewer than 48 hours.

Hospital-acquired pneumonia

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Definition

Hospital-acquired pneumonia (HAP): Acute illness affecting the lungs caused by pathogens in the hospital setting and presenting 48 hours or more after admission

Ventilator-associated pneumonia (VAP): Acute illness affecting the lungs caused by pathogens in the hospital setting and presenting 48 hours or more after admission while the patient is on a ventilator

Important: the cut-off of 48 hours is chosen for convenience and surveillance purposes



Most Likely Pathogens

- HAP may be caused by the same pathogens found in CAP or by multidrug-resistant (MDR) pathogens
- Majority of data on the microbiologic etiology of HAP is derived from ventilated patients in the intensive care setting

Bacteria most frequently associated with HAP:

- Gram-negative bacteria including *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and Enterobacteriales such as *Klebsiella pneumoniae* (including multidrug-resistant strains)
- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Staphylococcus aureus* (including MRSA)
- Anaerobes (mostly associated with large aspiration of secretions)
- *Legionella pneumophila*

Respiratory Viruses:

- Influenza viruses (A and B)
- Other respiratory viruses (including SARS-CoV-2)

Risk factors for infection with MDR pathogens:

- Previous treatment with antibiotics
- Prolonged hospital stay (particularly in the ICU)
- Prior colonization with MDR pathogens
- High local prevalence of resistant pathogens (e.g. among *S. aureus* and Gram-negative bacteria, including *P. aeruginosa*)

Diagnosis

Clinical Presentation

Non-ventilated patients: New or worsening cough +/- sputum production, difficult and rapid breathing, reduced oxygen saturation, crepitations on lung auscultation, or chest pain/discomfort with no alternative explanation; fever $\geq 38.0^{\circ}\text{C}$ usually present (may be absent, especially in the elderly)

Ventilated patients: Increased respiratory secretions, reduced oxygen saturation and a new lung infiltrate on a chest-radiograph

Note: the clinical presentation is non-specific and other diseases (e.g. pulmonary embolism) can mimic HAP. HAP/VAP may progress to sepsis



Microbiology Tests

All cases:

- Blood cultures (ideally before starting antibiotics)
- Microscopy and culture of respiratory samples (ideally before starting antibiotics)
- Urinary antigens for *L. pneumophila* and *S. pneumoniae*

Selected cases (depending on epidemiology and risk factors): Nasopharyngeal swab for influenza viruses and SARS-CoV-2

Important: a positive respiratory culture may indicate colonization rather than acute infection



Other Laboratory Tests

Determine disease severity: Blood pH and gases, white blood cell count

Differentiate bacterial and viral (taking into account pre-test probability): C-reactive protein and/or procalcitonin

Note: tests depend on availability and clinical severity (e.g. blood gases will only be done in severe cases)

• If sepsis is suspected consider additional laboratory tests (see sepsis infographic)

Imaging

Chest radiograph needed because other conditions have similar clinical features and antibiotics may be avoided if bacterial pneumonia is not suggested

Important:

- Chest radiographs can be difficult to interpret and correlate with the clinical presentation; many other conditions mimic infectious infiltrates (especially in the elderly)
- The radiographic pattern cannot be used to accurately predict the microbial cause

Hospital-acquired pneumonia

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Prevention

Key principles:

- Vaccination against pathogens that can commonly cause pneumonia
- Good hand hygiene
- Maintain mobility
- Maintain good oral and dental care
- Maintain nutrition in hospital
- Elevate the head of the bed to reduce the chances of aspirating respiratory secretions into the lungs
- Avoid intubation or reduce duration as much as possible

Bundles of care specific to the ICU also usually include:

- Minimizing sedation
- Regularly assessing if the endotracheal tube may be removed; extubate patients as soon as it is safe to do so
- Selective oral decontamination (SOD) and/or selective decontamination of the digestive tract (SDD) to reduce the bacterial burden of the upper (with SOD) and lower (with SDD) digestive tract through the administration of non-absorbable antibiotics
- SOD/SDD can help reduce the incidence of VAP, yet there is concern about the risk of selecting resistant bacteria

Treatment

Clinical Considerations

Important:

- Consider stopping treatment if HAP is ruled out or an alternative diagnosis can be made
- If not severely ill, consider targeted treatment based on microbiology results

Empiric antibiotic treatment should be guided by:

- The severity of symptoms (scoring systems exist but are not addressed here), considering local prevalence of resistant pathogens and individual risk factors for resistant pathogens

In patients with VAP specifically consider:

- Need for double anti-pseudomonal coverage (risk of infection caused by isolates resistant to an antibiotic used for monotherapy)

Important:

- Simplify empiric treatment to a more narrow-spectrum antibiotic based on culture results or rapid clinical improvement if culture results unavailable
- Step down to oral treatment is based on improvement of symptoms, signs of infection and the ability to take oral antibiotics

Antibiotic Treatment Duration

7 days; reassess diagnosis and consider longer treatment if the patient is not clinically stable at day 7

HAP (non-VAP)

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

 Amoxicillin+clavulanic acid 1 g+200 mg q8h **IV**
OR 875 mg + 125 mg q8h **ORAL**

Consider if low-risk of multidrug-resistant infections (e.g. short hospitalization before symptom onset and no prior antibiotic exposure)

OR

 Cefotaxime 2 g q8h **IV/IM**

OR

 Ceftriaxone 2 g q24h **IV** (1 g q24h **IM**)*

**A larger volume would be painful to give as intramuscular injection*

OR

 Piperacillin+tazobactam 4 g+500 mg q6h **IV**

*Piperacillin+tazobactam offers anti-pseudomonal coverage, which the other options do not (risk of *P. aeruginosa* higher in patients with recent antibiotic exposure, known previous respiratory colonization and underlying lung diseases)*

Hospital-acquired pneumonia

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Definition

Hospital-acquired pneumonia (HAP): Acute illness affecting the lungs caused by pathogens in the hospital setting and presenting 48 hours or more after admission

Ventilator-associated pneumonia (VAP): Acute illness affecting the lungs caused by pathogens in the hospital setting and presenting 48 hours or more after admission while the patient is on a ventilator

Important: the cut-off of 48 hours is chosen for convenience and surveillance purposes



Most Likely Pathogens

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- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Staphylococcus aureus* (including MRSA)
- Anaerobes (mostly associated with large aspiration of secretions)
- *Legionella pneumophila*

Respiratory Viruses:

- Influenza viruses (A and B)
- Other respiratory viruses (including SARS-CoV-2)

Risk factors for infection with MDR pathogens:

- Previous treatment with antibiotics
- Prolonged hospital stay (particularly in the ICU)
- Prior colonization with MDR pathogens
- High local prevalence of resistant pathogens (e.g. among *S. aureus* and Gram-negative bacteria, including *P. aeruginosa*)

Diagnosis

Clinical Presentation

Non-ventilated patients: New or worsening cough +/- sputum production, difficult and rapid breathing, reduced oxygen saturation, crepitations on lung auscultation, or chest pain/discomfort with no alternative explanation; fever $\geq 38.0^{\circ}\text{C}$ usually present (may be absent)

Ventilated patients: Increased respiratory secretions, reduced oxygen saturation and a new lung infiltrate on a chest-radiograph

Note: the clinical presentation is non-specific and other diseases (e.g. pulmonary embolism) can mimic HAP. HAP/VAP may progress to sepsis



Microbiology Tests

All cases:

- Blood cultures (ideally before starting antibiotics)
- Microscopy and culture of respiratory samples (ideally before starting antibiotics)

Selected cases (depending on epidemiology and risk factors): Nasopharyngeal swab for influenza viruses and SARS-CoV-2

Important: a positive respiratory culture may indicate colonization rather than acute infection



Other Laboratory Tests

Determine disease severity: Blood pH and gases, white blood cell count

Differentiate bacterial and viral (taking into account pre-test probability): C-reactive protein

Note: tests depend on availability and clinical severity (e.g. blood gases will only be done in severe cases)

• If sepsis is suspected consider additional laboratory tests (see sepsis infographic)



Imaging

Chest radiograph needed because other conditions have similar clinical features and antibiotics may be avoided if bacterial pneumonia is not suggested

Important:

- Chest radiographs can be difficult to interpret and correlate with the clinical presentation; many other conditions mimic infectious infiltrates
- The radiographic pattern cannot be used to accurately predict the microbial cause

Hospital-acquired pneumonia

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Prevention

Key principles:

- Vaccination against pathogens that can commonly cause pneumonia
- Good hand hygiene
- Maintain mobility
- Maintain good oral and dental care
- Maintain nutrition in hospital
- Elevate the head of the bed to reduce the chances of aspirating respiratory secretions into the lungs
- Avoid intubation or reduce duration as much as possible

Bundles of care specific to the ICU also usually include:

- Minimizing sedation
- Regularly assessing if the endotracheal tube may be removed; extubate patients as soon as it is safe to do so

Rx Treatment



Clinical Considerations

Important:

- Consider stopping treatment if HAP is ruled out or an alternative diagnosis can be made
- If not severely ill, consider targeted treatment based on microbiology results

Empiric antibiotic treatment should be guided by:

- The severity of symptoms (scoring systems exist but are not addressed here), considering local prevalence of resistant pathogens and individual risk factors for resistant pathogens

In patients with VAP specifically consider:

- Need for double anti-pseudomonal coverage (risk of infection caused by isolates resistant to an antibiotic used for monotherapy)

Important:

- Simplify empiric treatment to a more narrow-spectrum antibiotic based on culture results or rapid clinical improvement if culture results unavailable
- Step down to oral treatment is based on improvement of symptoms, signs of infection and the ability to take oral antibiotics



Antibiotic Treatment Duration

HAP: 7 days; reassess diagnosis and consider longer treatment if the patient is not clinically stable at day 7



HAP (non-VAP)

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated


Amoxicillin+clavulanate acid
IV:

- 1st week of life: 50 mg/kg/dose of amoxicillin component q12h
- > 1st week of life: 50 mg/kg/dose of amoxicillin component q8h
- ORAL:** 80-90 mg/kg/day of amoxicillin component
- Oral weight bands:**

3-<6 kg	250 mg of amox/dose q12h
6-<10 kg	375 mg of amox/dose q12h
10-<15 kg	500 mg of amox/dose q12h
15-<20 kg	750 mg of amox/dose q12h
≥20 kg	500 mg of amox/dose q8h or 1 g of amox/dose q12h

Amox = amoxicillin

Consider if low-risk of multidrug-resistant infections (e.g. short hospitalization before symptom onset and no prior antibiotic exposure)

Oral liquid must be refrigerated after reconstitution

OR


Cefotaxime 50 mg/kg/dose q8h IV/IM

OR


Ceftriaxone 80 mg/kg/dose q24h IV/IM

OR


Piperacillin+tazobactam 100 mg/kg/dose of piperacillin component q8h IV

*Piperacillin+tazobactam offers anti-pseudomonal coverage, which the other options do not (risk of *P. aeruginosa* higher in patients with recent antibiotic exposure, known previous respiratory colonization and underlying lung diseases)*

Pathophysiology

Colonization of the oropharynx by bacteria from the hospital environment, aspiration of secretions into the lower respiratory tract and compromised host defence mechanisms are all implicated in the pathogenesis of HAP. Pathogens can also reach the lung alveoli through the blood or by direct spread (e.g. from an infection of the pleural or intra-abdominal space). Secretions may become contaminated with bacteria (including with multidrug-resistant strains) during patient care despite infection prevention and control efforts. Inhalation of pathogens (mostly viruses) is another mechanism of infection to consider, especially during epidemic seasons or during pandemics such as COVID-19.

The presence of an endotracheal tube is a major risk factor for pneumonia (VAP) because the mechanisms that usually prevent the microaspiration of secretions into the lower respiratory tract are bypassed and also because biofilms (where bacteria can survive and multiply) can form on the internal and external surfaces of the tracheal cannula.

Epidemiology

Health care-associated infections are frequent across the world – around a quarter of all hospital antibiotic prescriptions were for health care-associated infections in a 2015 global survey in more than 50 countries (291) and HAP is an important health care-associated infection. The incidence of HAP can vary between hospitals, depending on the patient population being evaluated and the case definition used. However, the incidence is overall higher in mechanically ventilated patients treated in intensive care units than in non-ventilated patients not requiring intensive care (292).

Risk factors for HAP in non-ventilated patients include: (i) patient-related factors such as swallowing dysfunction and severe underlying medical conditions (e.g. immunosuppression, chronic lung disease); and (ii) treatment-related factors such as mechanical ventilation (for VAP) and feeding through a nasogastric tube, because their presence can lead to aspiration of oropharyngeal secretions into the lower respiratory tract. These conditions are particularly common in elderly and frail patients (293). HAP is associated with higher in-hospital mortality than CAP, and VAP is the form of HAP with the highest mortality (293,294).

Most likely pathogens

HAP may be caused by the same pathogens found in CAP or by multidrug-resistant pathogens (Table 28.1). In general antibiotic resistance is more prevalent in hospital-acquired strains but the frequency of multidrug-resistant pathogens varies between hospitals and different patient populations. Usually, the risk of infection with multidrug-

resistant pathogens is increased in patients with HAP because they have often been exposed to different regimens of antibiotics before developing HAP. The risk increases with prolonged hospitalization (higher risk of transmission, more antibiotic use) especially if in a critical care setting and in intubated patients. It is important to note that most data on the microbiological etiology of HAP come from ventilated patients in an intensive care setting because samples from the lower respiratory tract can be relatively easily obtained. In contrast, in non-ventilated patients, bronchoalveolar lavage is associated with a risk of respiratory deterioration and non-invasive sampling techniques are often not sufficient to obtain an accurate microbiological diagnosis of etiologic agents in pneumonia.

Table 28.1 – Pathogens most frequently associated with hospital-acquired pneumonia (in descending order of frequency)

Bacteria	Viruses	Fungi
Gram-negative bacteria including <i>Pseudomonas aeruginosa</i> , <i>Acinetobacter baumannii</i> and Enterobacterales such as <i>Klebsiella pneumoniae</i> (including multidrug-resistant strains such as those producing ESBL and carbapenemases) <i>Streptococcus pneumoniae</i> <i>Haemophilus influenzae</i> <i>Staphylococcus aureus</i> (including MRSA) Anaerobes (mostly associated with aspiration of a large amount of secretions) <i>Legionella pneumophila</i>	Influenza virus (A and B) Other respiratory viruses (including SARS-CoV-2)	Mostly <i>Aspergillus</i> spp. in severely immunocompromised patients or ventilated patients with influenza

ESBL: extended spectrum beta-lactamase; MRSA: methicillin-resistant *Staphylococcus aureus*; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

Clinical presentation

The clinical manifestations are the same as in all other forms of pneumonia: new or worsening cough with or without sputum production, dyspnoea (difficulty in breathing), tachypnoea (cut-off points for rapid breathing vary with age), reduced oxygen saturation, crepitations on lung auscultation, or chest pain or discomfort without an alternative explanation. Fever $\geq 38.0^{\circ}\text{C}$ is usually present but may be absent, especially in elderly people.

In ventilated patients, pneumonia is usually suspected in those with increased secretions, reduced oxygen saturation and a new lung infiltrate on a chest X-ray.

HAP and VAP may progress to sepsis and septic shock. Please refer to the sepsis chapter if this is suspected.

It is important to note that accurate diagnosis of HAP is difficult in the absence of a good reference standard. Pulmonary infiltrates on chest X-ray may be caused by a variety of non-infectious conditions and the clinical presentation may be very non-specific. There is considerable interobserver variability among specialists in the diagnosis of HAP. It is important to consider the possibility of over diagnosis of HAP and think about stopping antibiotic treatment if HAP is ruled out or an alternative diagnosis can be made.

Laboratory tests

Patient microbiology tests

Tests to be considered to guide antimicrobial treatment of HAP are shown in Table 28.2.

However, most patients will not have culture data to guide antibiotic treatment. In addition, in people with HAP, the respiratory tract is often colonized with bacteria and a positive culture may indicate colonization rather than an acute infection, especially if the sample was obtained by non-invasive methods.

Table 28.2 – Microbiology tests to consider if hospital-acquired pneumonia is suspected as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
Blood cultures and antimicrobial susceptibility testing	To detect bacterial bloodstream infection	Health care facilities with clinical laboratories
Respiratory sample microscopy ^a (Gram stain)	To assess microbial morphology and adequacy of the specimen for culture by identifying white blood cells and squamous epithelial cells	Health care facilities with clinical laboratories
Respiratory sample culture ^a and antimicrobial susceptibility testing	Initial step to detect and identify bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories

continues

Table 28.2 *continued*

Diagnostic test	Purpose of the test	Settings where the test should be available
Urinary antigens for <i>Legionella pneumophila</i> and <i>Streptococcus pneumoniae</i>	To diagnose legionellosis and pneumococcal pneumonia	— ^b
Nasopharyngeal swab for NAAT for influenza ^c	To diagnose seasonal influenza infection	Health care facilities with clinical laboratories but also in primary care settings
Nasopharyngeal swab for NAAT or antigen test for SARS-CoV-2 ^d	To diagnose COVID-19	Health care facilities with clinical laboratories (NAAT) and primary care settings (antigen test)
Nasopharyngeal swab for NAAT for respiratory viruses other than influenza or SARS-CoV-2 (e.g. respiratory syncytial virus)	To diagnose respiratory viruses other than influenza or SARS-CoV-2	— ^b

COVID-19: coronavirus disease 2019; EDL: Model List of Essential In Vitro Diagnostics; NAAT: nucleic acid amplification test; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

^a Respiratory sampling can be done using invasive or non-invasive methods depending on the patient's condition (e.g. if the patient is mechanically ventilated or not) and local availability. Invasive methods include bronchoalveolar lavage and blind bronchial sampling (usually called mini- bronchoalveolar lavage), while non-invasive methods include spontaneous expectoration, sputum induction, nasotracheal suctioning or endotracheal aspiration.

^b This test is not in the current WHO Model List of Essential In Vitro Diagnostics (6).

^c To help decide on antiviral treatment and for infection prevention and control purposes, for example, to prevent transmission to other patients.

^d Depending on the current epidemiology.

Other tests

A number of tests could be considered based on local availability to determine disease severity, help differentiate bacterial and viral causes and determine treatment duration (and the move from intravenous to oral treatment) during follow up (Table 28.3). Please also refer to the chapter on sepsis if suspected.

Table 28.3 – Laboratory tests to consider if hospital-acquired pneumonia is suspected as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
White blood cell count	To help in the diagnosis of infection	Health care facilities with clinical laboratories
Blood pH and gases	To assess lung function and metabolic or kidney disorders, and monitor oxygen therapy To measure blood pH, oxygen and carbon dioxide, serum bicarbonate and anion gap	Health care facilities with clinical laboratories
C-reactive protein	To detect inflammation as an indicator of various conditions (e.g. sepsis)	Health care facilities with clinical laboratories
Procalcitonin	To guide antibiotic therapy or discontinuation in sepsis and lower respiratory tract infection	Only in tertiary care facilities

EDL: Model List of Essential In Vitro Diagnostics.

Using microbiology surveillance data

Routine microbiology surveillance of isolates associated with HAP and their antibiotic susceptibilities could help inform local empiric guidance. Therefore, empiric guidance given by the AWaRe book could be reviewed and adapted based on local clinically relevant microbiology surveillance data.

However, clinically relevant data for this infection would be derived from local hospital blood culture and bronchoalveolar lavage fluid cultures taken from patients in intensive care who were diagnosed with HAP or VAP. Caution should be taken with surveillance of routine respiratory sampling culture data from patients with HAP or VAP due to the high rates of colonization seen in many settings.

Imaging

When HAP (or VAP) is suspected clinically, a chest X-ray should be obtained. HAP (or VAP) presents with clinical signs and symptoms along with a new or worsening pulmonary infiltrate on a chest X-ray and leukocytosis.

A chest X-ray is needed because other conditions have similar clinical features and antibiotics may be avoided if the chest X-ray does not suggest bacterial pneumonia. Chest X-rays can be difficult to interpret and to correlate with the clinical presentation (especially in elderly people where the clinical presentation is usually non-specific), and many other conditions (such as heart failure) can mimic infectious infiltrates. Therefore, caution is warranted to avoid over-diagnosis and overtreatment with antibiotics. It should also be noted that the radiographic pattern cannot be used to accurately predict the microbial etiology.

Antibiotic treatment

Empiric treatment should be guided by the severity of symptoms (scoring systems to evaluate disease severity exist but they are beyond the scope of this chapter) and by risk factors for multidrug-resistant infections. In particular, individualized assessment should be done based on risk factors such as: previous antibiotic treatment (e.g. in the 90 days preceding the infection); prolonged hospital stay, particularly in the intensive care unit (> 5 days); previous colonization with multidrug-resistant pathogens; and a high local prevalence of multidrug-resistant pathogens (among potential causative pathogens of HAP, such as *Staphylococcus aureus* and Gram-negative bacteria including *Pseudomonas aeruginosa*).

Antibiotic options to consider for empiric treatment in patients with HAP (non-VAP) are given in Table 28.4. Treatment should always be tailored to culture results once these become available.

Empiric treatment in patients with VAP should be chosen considering the time from intensive care unit admission/intubation to symptom onset. In ventilated patients (as with non-ventilated patients who develop HAP), infections that develop early (e.g. a few days after admission) are unlikely to be caused by multidrug-resistant pathogens or *Pseudomonas aeruginosa* and could safely be treated with amoxicillin+clavulanic acid. At the other end, an antibiotic with a broader spectrum of activity (and active against *Pseudomonas aeruginosa*) is preferable in cases with a longer time interval between admission to hospital and onset of symptoms.

There are some areas of uncertainty about empiric treatment for HAP.

- Adding vancomycin to the first-choice antibiotic options as an empiric treatment when MRSA infection is suspected; for example, in settings with a high prevalence of *Staphylococcus aureus* isolates that are methicillin resistant and in patients known to be colonized by MRSA.
- The need for empiric double coverage against *Pseudomonas* to improve coverage in severely ill patients (e.g. with septic shock or in need of ventilator support) because of the risk of infection caused by *Pseudomonas aeruginosa* isolates resistant to an antibiotic used for monotherapy. The need for empiric double

coverage could therefore be considered in severely ill patients with VAP (or with severe HAP requiring ventilator support) on a case-by-case basis based on local antibiotic resistance data and the personal history of the patient, such as known respiratory colonization with multidrug-resistant *Pseudomonas aeruginosa*, particularly in patients with underlying chronic lung disease. However, specific antibiotic combinations to use in these cases are not covered in the AWaRe book as they are currently not included in the EML and EMLc with which this book is closely aligned.

Simplify empiric treatment to a more narrow-spectrum antibiotic (often also called de-escalation) based on culture results (targeted treatment) or based on rapid clinical improvement when no microbiology test results are available.

Step-down to oral treatment is based on improvement of symptoms and signs of infection and the ability to take oral antibiotics allowing discharge of the patient home when clinically appropriate.

Table 28.4 – Empiric antibiotic treatment for hospital-acquired pneumonia (not for ventilator-associated pneumonia)

Adults	Children	Total treatment duration
Amoxicillin+clavulanic acid ^a (IV/oral) IV: 1 g + 200 mg given every 8 hours Oral: 875 mg + 125 mg given every 8 hours OR Cefotaxime (IV/IM): 2 g given every 8 hours OR Ceftriaxone ^b (IV/IM) IV: 2 g given once a day IM: 1 g given once a day OR Piperacillin+tazobactam ^c (IV): 4 g + 500 mg given every 6 hours	Amoxicillin+clavulanic acid ^{a,d} IV: First week of life: 50 mg/kg of amoxicillin/dose given every 12 hours Beyond first week of life: 50 mg/kg of amoxicillin/dose given every 8 hours Oral: 80–90 mg/kg/day of amoxicillin component Oral weight bands: 3–< 6 kg: 250 mg of amoxicillin/dose given every 12 hours 6–< 10 kg: 375 mg of amoxicillin/dose given every 12 hours 10–< 15 kg: 500 mg of amoxicillin/dose given every 12 hours 15–< 20 kg: 750 mg of amoxicillin/dose given every 12 hours ≥ 20 kg: 500 mg of amoxicillin/dose given every 8 hours or 1 g of amoxicillin/dose given every 12 hours OR Cefotaxime (IV/IM): 50mg/kg/dose given every 8 hours OR	7 days Reassess the diagnosis and consider longer treatment if the patient is not clinically stable at day 7

continues

Table 28.4 *continued*

Adults	Children	Total treatment duration
	<p>Ceftriaxone (IV/IM): 80 mg/kg/ dose given once a day OR Piperacillin+tazobactam ^c (IV): 100 mg/kg/dose of piperacillin component given every 8 hours</p>	

IM: intramuscular; IV: intravenous.

Note: All dosages are for normal renal and hepatic function.

^a Amoxicillin+clavulanic acid can be used in certain circumstances with low-risk of multidrug-resistant infections (e.g. short hospitalization before symptom onset and if no prior antibiotic exposure).

^b The reason for giving a lower dose when ceftriaxone is given IM (rather than IV) is that a larger volume would be painful to give as intramuscular injection.

^c Piperacillin+tazobactam offers anti-*Pseudomonas* coverage, which the other options do not. Risk of *Pseudomonas aeruginosa* is higher in patients with recent antibiotic exposure and especially in patients with known previous respiratory colonization by *Pseudomonas aeruginosa* and underlying lung diseases.

^d Oral liquid formulations must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Prevention

A detailed discussion of the prevention of HAP and VAP is beyond the scope of this chapter; however, key general principles are presented. Some measures such as vaccination against pathogens that can commonly cause pneumonia overlap with those presented in the chapter on CAP. Specific measures that apply to the hospital setting include: maintaining mobility, good oral and dental care, maintaining adequate nutritional support in hospital, elevating the head of the bed to reduce the chances of aspirating respiratory secretions into the lower lungs, avoiding intubation or reducing its duration as much as possible, and good hand hygiene. Good hand hygiene applies to patients and staff or family caregivers that come into contact with patients during the hospital stay. In addition, in the intensive care unit, locally adapted bundles of interventions to prevent VAP are usually in place and include, for example, maintaining adequate endotracheal tube cuff pressure, minimizing sedation and assessing regularly if the endotracheal tube can be removed in order to extubate patients as soon as it is safe to do so.

Selective oral decontamination and/or selective decontamination of the digestive tract can also be considered based on local intensive care unit protocols. These preventive measures have been extensively studied to prevent hospital-acquired infections. The

rationale for their use is to reduce the bacterial burden of the upper (with selective oral decontamination) and lower (with selective decontamination of the digestive tract) digestive tract through the administration of non-absorbable antibiotics – topical antibiotics applied to the oropharynx for selective oral decontamination and non-absorbable antibiotics administered through nasogastric tube for selective decontamination of the digestive tract. Evidence exists that these practices can help reduce the incidence of VAP but there is important concern about the risk of selecting resistant bacteria.

29. Intra-abdominal infections – acute cholecystitis and cholangitis

Key messages

Cholecystitis

- If cholecystectomy is performed, antibiotics should be stopped once the gallbladder is removed and there is good clinical recovery unless the patient had a severe presentation.
- Antibiotics should be chosen based on the severity of symptoms (mild or severe) with broader-spectrum agents for severe cases. The antibiotics should also be active against anaerobes as these pathogens are often involved in intra-abdominal infections.

Cholangitis

- Biliary drainage is the basis of treatment for obstructive cholangitis.
- Antibiotics should be chosen based on the severity of symptoms (mild or severe) with broader-spectrum agents for severe cases and given until drainage procedures are done. They should be continued for a total of 5 days once control of the source of infection has been achieved.

Other relevant WHO resources (please check regularly for updates)

- Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, 2013 (31).

Definition

Acute cholecystitis is an acute inflammation of the gallbladder and acute cholangitis is an acute inflammation in the bile duct system. Both conditions are classified as uncomplicated when there is no involvement of the peritoneal cavity and the inflammation is confined to the organ involved, that is no perforation, no abscess and no diffuse peritonitis. The conditions are classified as complicated when the inflammation extends to the peritoneal cavity with subsequent peritonitis or when an abscess is present.

Acute cholecystitis & cholangitis

Intra-abdominal infection • Page 1 of 2

Definition

Acute cholecystitis: Acute inflammation of the gallbladder
 • A gallstone obstructing the cystic duct for prolonged periods of time is the most frequent cause

Acute cholangitis: Acute inflammation in the bile duct system
 • A gallstone obstructing the common bile duct and malignant obstruction by tumours are the most common causes

Classification based on complexity:

- **Uncomplicated:** No involvement of the peritoneal cavity and no abscess
- **Complicated:** Involvement of the peritoneal cavity and/or abscess

Classification based on severity:

- **Mild:** Not critically ill with no signs of sepsis or septic shock
- **Severe:** Critically ill with signs of sepsis or septic shock

Most Likely Pathogens

Infections are often polymicrobial

Bacteria:

- Enterobacteriales (mostly *Escherichia coli*) and other Gram-negative bacilli (including multidrug-resistant strains)
- *Streptococcus* spp. (e.g. of the *S. anginosus* group)
- *Enterococcus* spp.
- Anaerobes (mostly *Bacteroides* spp.)

Fungi (consider if recent course of antibiotics):

- Mostly *Candida albicans*

Diagnosis

Clinical Presentation

Acute cholecystitis:

- Acute abdominal pain especially in the right upper quadrant with nausea and vomiting; fever ($\geq 38.0^{\circ}\text{C}$) may be absent

Acute cholangitis:

- Abdominal pain with fever ($\geq 38.0^{\circ}\text{C}$) and jaundice +/- nausea and vomiting

Important:

- Consider peritonitis if there is severe pain, diffuse rebound tenderness upon sudden release of pressure on the abdomen and abdominal muscular tensing
- Hypotension and signs of organ hypoperfusion (e.g. reduced urine output) are potential signs of sepsis/septic shock that need urgent treatment

Microbiology Tests

Mild uncomplicated cases:

- Not usually needed

Severe cases:

- Blood cultures (ideally before starting antibiotics)
- Microscopy and culture of abdominal fluid material and bile (if they can be drained) to adjust empiric antibiotic treatment

Other Laboratory Tests

Determine disease severity and help identify a bacterial infection: White blood cell count, C-reactive protein and/or procalcitonin

Assess liver function: AST, bilirubin and alkaline phosphatase

• If sepsis is suspected consider additional laboratory tests (see sepsis infographic)

Imaging

- Abdominal ultrasound to confirm the diagnosis
- Consider doing a CT scan of the abdomen if complications suspected or diagnosis uncertain



Acute cholecystitis & cholangitis

Intra-abdominal infection • Page 2 of 2

Rx Treatment



Antibiotic Treatment Duration

Acute cholecystitis:

- Uncomplicated cases:** Antibiotics can be stopped once gallbladder is removed
- Complicated cases:** **5 days** is adequate in most cases with good clinical recovery and source control

Acute cholangitis:

- All cases:** Give antibiotics until biliary drainage procedures are performed and continue for a total of **5 days** after successful source control



Clinical Considerations

- Cholecystectomy (for acute cholecystitis) and biliary drainage (for acute cholangitis) remain the main approaches to eliminate the source of infection**
- In both conditions empiric antibiotic treatment should be guided by:** The severity of symptoms, considering local prevalence of resistance (particularly of isolates of Enterobacteriales producing ESBL) and individual risk factors for resistant pathogens

Important for both conditions:

- Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or rapid clinical improvement if culture results unavailable
- Step down to oral treatment** is based on improvement of symptoms, signs of infection and the ability to take oral antibiotics
- If signs and symptoms persist**, abdominal imaging is suggested or an alternative extra-abdominal source of infection should be considered

Rx Mild Cases

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice



Amoxicillin+clavulanic acid 1 g +200 mg q8h IV
OR 875 mg+125 mg q8h **ORAL**

OR



Cefotaxime 2 g q8h **IV**

OR



Ceftriaxone 2 g q24h **IV**

COMBINED WITH



Metronidazole 500 mg q8h **IV/ORAL**

Second Choice



Ciprofloxacin 500 mg q12h **ORAL**

COMBINED WITH



Metronidazole 500 mg q8h **IV/ORAL**

Ciprofloxacin and metronidazole have excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function

Rx Severe Cases

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice



Cefotaxime 2 g q8h **IV**

OR



Ceftriaxone 2 g q24h **IV**

COMBINED WITH



Metronidazole 500 mg q8h **IV/ORAL**

OR



Piperacilline+tazobactam 4 g + 500 mg q6h **IV**

Second Choice



Meropenem 1 g q8h **IV**

Consider meropenem only in complicated cases if there is a high risk of infection with ESBL-producing Enterobacteriales

Acute cholecystitis & cholangitis

Intra-abdominal infection • Page 1 of 3

Definition

Acute cholecystitis: Acute inflammation of the gallbladder
 • A gallstone obstructing the cystic duct for prolonged periods of time is the most frequent cause

Acute cholangitis: Acute inflammation in the bile duct system
 • A gallstone obstructing the common bile duct and malignant obstruction by tumours are the most common causes

Classification based on complexity:

- **Uncomplicated:** No involvement of the peritoneal cavity and no abscess
- **Complicated:** Involvement of the peritoneal cavity and/or abscess

Classification based on severity:

- **Mild:** Not critically ill with no signs of sepsis or septic shock
- **Severe:** Critically ill with signs of sepsis or septic shock

Diagnosis

Clinical Presentation

Acute cholecystitis:

- Acute abdominal pain especially in the right upper quadrant with nausea and vomiting

Acute cholangitis:

- Abdominal pain with fever and jaundice +/- nausea and vomiting

Important:

- Consider peritonitis if there is severe pain, diffuse rebound tenderness upon sudden release of pressure on the abdomen and abdominal muscular tensing
- Hypotension and signs of organ hypoperfusion (e.g. reduced urine output) are potential signs of sepsis /septic shock that need urgent treatment



Most Likely Pathogens

Infections are often polymicrobial

Bacteria:

- Enterobacteriales (mostly *Escherichia coli*) and other Gram-negative bacilli (including multidrug-resistant strains)
- *Streptococcus* spp. (e.g. of the *S. anginosus* group)
- *Enterococcus* spp.
- Anaerobes (mostly *Bacteroides* spp.)

Fungi (consider if recent course of antibiotics):

- Mostly *Candida albicans*



Microbiology Tests

Mild uncomplicated cases:

- Not usually needed

Severe cases:

- Blood cultures (ideally before starting antibiotics)
- Microscopy and culture of abdominal fluid material and bile (if they can be drained) to adjust empiric antibiotic treatment



Other Laboratory Tests

Determine disease severity and help identify a bacterial infection: White blood cell count, C-reactive protein and/or procalcitonin

Assess liver function: AST, bilirubin and alkaline phosphatase

• If sepsis is suspected consider additional laboratory tests (see sepsis infographic)



Imaging

- Abdominal ultrasound to confirm the diagnosis
- Consider doing a CT scan of the abdomen if complications suspected or diagnosis uncertain

Acute cholecystitis & cholangitis

Intra-abdominal infection • Page 2 of 3

Rx Treatment (Section 1 of 2)

Clinical Considerations

- Cholecystectomy (for acute cholecystitis) and biliary drainage (for acute cholangitis) remain the main approaches to eliminate the source of infection**
- In both conditions empiric antibiotic treatment should be guided by:** The severity of symptoms, considering local prevalence of resistance (particularly of isolates of Enterobacteriales producing ESBL) and individual risk factors for resistant pathogens

Important for both conditions:

- Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or rapid clinical improvement if culture results unavailable
- Step down to oral treatment** is based on improvement of symptoms, signs of infection and the ability to take oral antibiotics
- If signs and symptoms persist**, abdominal imaging is suggested or an alternative extra-abdominal source of infection should be considered



Antibiotic Treatment Duration

Acute cholecystitis:

- Uncomplicated cases:** Antibiotics can be stopped once gallbladder is removed
- Complicated cases:** **5 days** is adequate in most cases with good clinical recovery and source control

Acute cholangitis:

- All cases:** Give antibiotics until biliary drainage procedures are performed and continue for a total of **5 days** after successful source control



Mild Cases

See the following page for treatment recommendations

Rx Severe Cases

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice

Ampicillin IV

- ACCESS • 1st week of life: 50 mg/kg/dose q12h
- > 1st week of life: 50 mg/kg/dose q8h

COMBINED WITH

Gentamicin IV

- ACCESS • Neonates: 5 mg/kg q24h
- Children: 7.5 mg/kg q24h

COMBINED WITH

Metronidazole IV/ORAL

- ACCESS • Neonates: 7.5 mg/kg/dose q12h (for IV loading dose: 15 mg/kg)
- Children: 7.5 mg/kg/dose q8h
- **Oral weight bands:**

3-<6 kg	30 mg q8h
6-<10 kg	50 mg q8h
10-<15 kg	100 mg q8h
15-<20 kg	150 mg q8h
20-<30 kg	200 mg q8h
≥30 kg	500 mg q8h

OR

Piperacillin+tazobactam 100 mg/kg/dose of piperacillin component q8h IV

Second Choice

Meropenem 20 mg/kg/dose q8h IV

Consider meropenem only in complicated cases if there is a high risk of infection with ESBL-producing Enterobacteriales

Acute cholecystitis & cholangitis

Intra-abdominal infection • Page 3 of 3

Rx Treatment (Section 2 of 2)

Rx Mild Cases

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice



Amoxicillin+clavulanic acid

IV:

- 1st week of life: 50 mg/kg/dose of amoxicillin component q12h
 - > 1st week of life: 50 mg/kg/dose of amoxicillin component q8h
- ORAL:** 80-90 mg/kg/day of amoxicillin component

• Oral weight bands:

3-<6 kg	250 mg of amox/dose q12h
6-<10 kg	375 mg of amox/dose q12h
10-<15 kg	500 mg of amox/dose q12h
15-<20 kg	750 mg of amox/dose q12h
≥20 kg	500 mg of amox/dose q8h or 1 g of amox/dose q12h

Amox = amoxicillin

Oral liquid must be refrigerated after reconstitution

OR



Ampicillin IV

- 1st week of life: 50 mg/kg/dose q12h
- > 1st week of life: 50 mg/kg/dose q8h

COMBINED WITH



Gentamicin IV

- Neonates: 5 mg/kg q24h
- Children: 7.5 mg/kg q24h

COMBINED WITH



Metronidazole IV/ORAL

- Neonates: 7.5 mg/kg/dose q12h (for IV loading dose: 15 mg/kg)
- Children: 7.5 mg/kg/dose q8h

• Oral weight bands:

3-<6 kg	30 mg q8h
6-<10 kg	50 mg q8h
10-<15 kg	100 mg q8h
15-<20 kg	150 mg q8h
20-<30 kg	200 mg q8h
≥30 kg	500 mg q8h

OR



Cefotaxime 50 mg/kg/dose q8h IV

OR



Ceftriaxone 80 mg/kg/dose q24h IV

COMBINED WITH



Metronidazole IV/ORAL

- Neonates: 7.5 mg/kg/dose q12h (for IV loading dose: 15 mg/kg)
- Children: 7.5 mg/kg/dose q8h

• Oral weight bands:

3-<6 kg	30 mg q8h
6-<10 kg	50 mg q8h
10-<15 kg	100 mg q8h
15-<20 kg	150 mg q8h
20-<30 kg	200 mg q8h
≥30 kg	500 mg q8h

Second Choice



Ciprofloxacin 15 mg/kg/dose q12h

IV/ORAL

• Oral weight bands:

3-<6 kg	50 mg q12h
6-<10 kg	100 mg q12h
10-<15 kg	150 mg q12h
15-<20 kg	200 mg q12h
20-<30 kg	300 mg q12h
≥30 kg	500 mg q12h

COMBINED WITH



Metronidazole IV/ORAL

- Neonates: 7.5 mg/kg/dose q12h (for IV loading dose: 15 mg/kg)
- Children: 7.5 mg/kg/dose q8h

• Oral weight bands:

3-<6 kg	30 mg q8h
6-<10 kg	50 mg q8h
10-<15 kg	100 mg q8h
15-<20 kg	150 mg q8h
20-<30 kg	200 mg q8h
≥30 kg	500 mg q8h

Ciprofloxacin and metronidazole have excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function

Pathophysiology

In acute cholecystitis, a gallstone obstructing the cystic duct for prolonged periods of time and causing inflammation of the gallbladder is the most frequent cause (> 90%). Acalculous cholecystitis, where there is no evidence of gallstones or cystic duct obstruction, is uncommon, especially in adults. Rarely, certain parasites (e.g. the worm *Ascaris lumbricoides*) can also cause gallbladder perforation.

In acute cholangitis, the most common cause is choledocholithiasis (i.e. gallstones in the bile duct). Infection occurs when bacteria travel up the biliary tract from the intestine or via the portal venous system. Another cause may be obstruction by tumours (e.g. pancreatic cancer) or parasites (e.g. the liver fluke *Fasciola hepatica*) (295). In addition, congenital biliary strictures or strictures following inflammation or infection can cause acute cholangitis.

In both cholecystitis and cholangitis, if bacterial contamination or chemical irritation (usually due to leakage of sterile fluids that are irritants to the peritoneum, for example, bile or blood) of the peritoneal cavity occur, peritonitis develops. Abdominal abscesses (i.e. the presence of a collection of infected fluid in the peritoneal cavity) can also form as a result of a complicated infection.

Epidemiology

Acute cholecystitis is a common surgical emergency worldwide. The incidence of acute cholecystitis is declining where cholecystectomy (surgical removal of the gallbladder) has become a common procedure in cases of recurrent attacks of biliary colic, that is, intermittent pain in the upper abdomen, usually on the right side. Acute cholecystitis mostly affects adults; children are rarely affected. The disease is more prevalent in men and elderly people. Obesity and diabetes are also well known risk factors (296,297). Short-term 30-day mortality is about 5% in severe cases and 1% in mild cases (298).

Acute cholangitis is a condition associated with high mortality if left untreated. Choledocholithiasis and malignant obstruction by tumours are the most common causes of cholangitis and their risk factors overlap (299).

Most likely pathogens

The most common pathogens involved in acute cholecystitis or cholangitis are Gram-negative bacilli and anaerobic bacteria from the intestinal microbiota (Table 29.1). Infections are often caused by more than one pathogen and may include fungal pathogens, especially in patients who have recently received antibiotic treatment. Certain parasites (*Ascaris lumbricoides*, *Fasciola hepatica*) need to be considered in endemic settings as they may cause biliary obstruction leading to bacterial complications.

Table 29.1 – Pathogens most frequently associated with acute cholecystitis and cholangitis (in descending order of frequency)

Bacteria	Fungi
Enterobacteriales (mostly <i>Escherichia coli</i>) and other Gram-negative bacteria such as <i>Pseudomonas aeruginosa</i> and <i>Acinetobacter baumannii</i> (including multidrug-resistant strains such as those producing ESBL and carbapenemases)	Mostly <i>Candida albicans</i>
<i>Streptococcus</i> spp. (e.g. of the <i>Streptococcus anginosus</i> group – old name: <i>Streptococcus milleri</i>)	
<i>Enterococcus</i> spp.	
Anaerobes (mostly <i>Bacteroides</i> spp.)	

ESBL: extended-spectrum beta-lactamases.

Clinical presentation

Acute cholecystitis should be considered as a possible diagnosis in all cases of acute abdominal pain, especially if the pain is predominantly located in the right upper quadrant.

Acute cholangitis should be considered a possible diagnosis in all cases presenting with abdominal pain, fever and jaundice, that is, yellow skin colour and sclera due to increased levels of bilirubin.

Fever ($\geq 38.0^{\circ}\text{C}$), chills, nausea and vomiting may be present, mostly in complicated infections. Severe pain, diffuse rebound tenderness on sudden release of pressure on the abdomen and abdominal muscular defence are usually present in cases of peritonitis. Hypotension and signs of organ hypoperfusion (e.g. reduced urine output) may be present in cases of organ failure and are a medical and/or surgical emergency. Please also refer to the chapter on sepsis if suspected.

Laboratory tests

Patient microbiology tests

In mild cases, routine microbiology tests are not usually needed and basing antibiotic treatment on pathogens cultured from the abdominal cavity at the time of operation is not recommended. Blood cultures and other microbiology tests could be considered in severely ill patients in order to adjust empiric antibiotic treatment once the results of susceptibility tests are available (see Table 29.2).

Table 29.2 – Microbiology tests to consider in severe cases of acute cholecystitis or cholangitis as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
Blood cultures and antimicrobial susceptibility testing	To detect bacterial bloodstream infections	Health care facilities with clinical laboratories
Microscopy, culture and antimicrobial susceptibility testing of fluid material or bile when these can be drained	Initial step to detect and identify bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics.

Other tests

Laboratory tests can be used to complement the clinical examination and medical history. Based on availability, Table 29.3 indicates tests that could be considered in the patient's initial assessment and to help guide the duration of antibiotic treatment.

Table 29.3 – Laboratory tests (other than microbiology) that may help assess the severity of disease and identify a bacterial infection as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
White blood cell count	To help in the diagnosis of infections	Health care facilities with clinical laboratories
Aspartate aminotransferase	To assess liver function	Health care facilities with clinical laboratories
Bilirubin	To detect or monitor liver disease, bile duct disorders and red cell destruction	Health care facilities with clinical laboratories
Alkaline phosphatase	To aid in diagnosis of hepatobiliary diseases	Health care facilities with clinical laboratories

continues

Table 29.3 *continued*

Diagnostic test	Purpose of the test	Settings where the test should be available
C-reactive protein	To detect inflammation as an indicator of various conditions (e.g. sepsis)	Health care facilities with clinical laboratories
Procalcitonin	To guide antibiotic therapy or discontinuation in sepsis	Only in tertiary care facilities

EDL: Model List of Essential In Vitro Diagnostics.

Using microbiology surveillance data

Routine surveillance of pathogens cultured from the abdominal cavity is not recommended.

Empiric guidance given by the AWaRe book could be reviewed and adapted based on local clinically relevant microbiology surveillance data. For example, clinically relevant isolates for this infection would be blood culture data from patients on surgical wards with intra-abdominal infections.

Imaging

Imaging is helpful to confirm cholecystitis and cholangitis. An abdominal ultrasound should always be considered when these conditions are suspected. Where available, a CT scan of the abdomen may also be considered, especially if complications are suspected or the diagnosis is uncertain.

Treatment of acute cholecystitis

Patients with suspected or confirmed acute cholecystitis should be promptly referred for surgical consultation. Eliminating the source of infection and the ongoing contamination of the peritoneal cavity (e.g. in case of perforation) is the most important surgical intervention. Cholecystectomy (i.e. removal of the gallbladder) is the only definitive treatment and an antibiotic should be given until the gallbladder is removed (300). After surgery, in uncomplicated cases, antibiotic treatment can be stopped provided the source of infection was adequately controlled and there is good clinical recovery. In severe cases (i.e. critically ill patients), 5 days of antibiotic treatment are usually adequate, provided there is good clinical recovery and the source of infection was adequately controlled and eliminated with surgery (301).

Treatment of acute cholangitis

Biliary drainage is the main surgical intervention for acute cholangitis and antibiotic treatment should be given in all cases irrespective of severity. Antibiotic treatment should be given until drainage procedures are done and continued for a total of 5 days once control of the source of infection has been achieved (301). Shorter courses of antibiotics (e.g. 3 days) have been evaluated in observational studies (and in a systematic review) and were not associated with a higher occurrence of complications; however, this practice remains controversial because the evidence is not strong (302,303).

Antibiotic treatment

Empiric antibiotic treatment should be chosen based on the severity of symptoms, mild or severe (Table 29.4), considering local prevalence of resistance, particularly isolates producing ESBLs since the prevalence can vary greatly in different settings (304). Individual risk factors for resistant pathogens (e.g. recent antibiotic treatment, colonization with resistant pathogens) should also be considered.

Simplify empiric treatment to a more narrow-spectrum antibiotic (often also called de-escalation) based on culture results (targeted treatment) or based on rapid clinical improvement when no microbiology test results are available.

Step-down to oral treatment is based on improvement of symptoms and signs of infection and the ability to take oral antibiotics allowing discharge of the patient home when clinically appropriate.

If signs and symptoms persist, abdominal imaging is suggested, or an alternative extra-abdominal source of infection should be considered.

Table 29.4 – Empiric antibiotic treatment for acute cholecystitis or cholangitis

Severity	Adults	Children	Total treatment duration
Mild cases	<p>First choice</p> <p>Amoxicillin+clavulanic acid^b</p> <p>IV: 1g + 200 mg given every 8 hours Oral: 875 + 125 mg given every 8 hours</p> <p>OR</p> <p>Cefotaxime (IV): 2 g given every 8 hours AND Metronidazole (IV/oral): 500 mg given every 8 hours</p> <p>OR</p> <p>Ceftriaxone (IV): 2 g given once a day AND Metronidazole (IV/oral): 500 mg given every 8 hours</p>	<p>Amoxicillin+clavulanic acid^b</p> <p>IV: First week of life: 50 mg/kg of amoxicillin/dose given every 12 hours Beyond first week of life: 50 mg/kg of amoxicillin/dose given every 8 hours</p> <p>Oral: 80–90 mg/kg/day of amoxicillin component Oral weight bands 3–<6 kg: 250 mg of amoxicillin/dose given every 12 hours 6–<10 kg: 375 mg of amoxicillin/dose given every 12 hours 10–<15 kg: 500 mg of amoxicillin/dose given every 12 hours 15–<20 kg: 750 mg of amoxicillin/dose given every 12 hours ≥20kg: 500 mg of amoxicillin/dose given every 8 hours or 1 g of amoxicillin/dose given every 12 hours</p>	<p>Uncomplicated cases treated with cholecystectomy: stop antibiotic after surgery if adequate control of the source of infection has been achieved and symptoms have resolved.</p>

**Note**

Mild cases are defined as patients who are not critically ill with no signs of sepsis or septic shock.
Severe cases are defined as patients who are critically ill with signs of sepsis or septic shock.



Where more than one antibiotic is recommended for an infection, they are listed in alphabetical order and they should be considered equal treatment options, unless otherwise indicated.

continues

Table 29.4 continued

Severity	Adults	Children	Total treatment duration
Mild cases	<p>Second choice</p> <p>Ciprofloxacin^a (oral): 500 mg given every 12 hours AND</p> <p>Metronidazole (IV/oral): 500 mg given every 8 hours</p> <p>(Ciprofloxacin and metronidazole have excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function.)</p>	<p>OR</p> <p>Ampicillin (IV):</p> <ul style="list-style-type: none"> First week of life: 50 mg/kg/dose given every 12 hours Beyond first week of life: 50 mg/kg/dose given every 8 hours <p>AND</p> <p>Gentamicin (IV):</p> <ul style="list-style-type: none"> Neonates: 5 mg/kg given once daily Children: 7.5 mg/kg given once daily <p>AND</p> <p>Metronidazole (IV/oral):</p> <ul style="list-style-type: none"> Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg) Children: 7.5 mg/kg/dose given every 8 hours <p>Oral weight bands</p> <p>3-< 6 kg: 30 mg given every 8 hours</p> <p>6-< 10 kg: 50 mg given every 8 hours</p> <p>10-< 15 kg: 100 mg given every 8 hours</p> <p>15-< 20 kg: 150 mg given every 8 hours</p> <p>20-< 30 kg: 200 mg given every 8 hours</p> <p>≥ 30 kg: use adult dose</p> <p>OR</p>	

continues



Table 29.4 continued

Severity	Adults	Children	Total treatment duration
Mild cases			<p>Cefotaxime (IV): 50 mg/kg/dose given every 8 hours AND</p> <p>Metronidazole (IV/oral):</p> <ul style="list-style-type: none"> Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg) Children: 7.5 mg/kg/dose given every 8 hours <p>Oral weight bands</p> <p>3–< 6 kg: 30 mg given every 8 hours</p> <p>6–< 10 kg: 50 mg given every 8 hours</p> <p>10–< 15 kg: 100 mg given every 8 hours</p> <p>15–< 20 kg: 150 mg given every 8 hours</p> <p>20–< 30 kg: 200 mg given every 8 hours</p> <p>≥ 30 kg: use adult dose</p> <p>OR</p>

continues

Table 29.4 continued

Severity	Adults	Children	Total treatment duration
Mild cases		<p>Ceftriaxone (IV): 80 mg/kg/dose given once a day AND</p> <p>Metronidazole (IV/oral):</p> <ul style="list-style-type: none"> Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg) Children: 7.5 mg/kg/dose given every 8 hours <p>Oral weight bands</p> <p>3–< 6 kg: 30 mg given every 8 hours</p> <p>6–< 10 kg: 50 mg given every 8 hours</p> <p>10–< 15 kg: 100 mg given every 8 hours</p> <p>15–< 20 kg: 150 mg given every 8 hours</p> <p>20–< 30 kg: 200 mg given every 8 hours</p> <p>≥ 30 kg: use adult dose</p>	

Second choice

Ciprofloxacin (IV/oral): 15 mg/kg/dose, given every 12 hours

continues



Table 29.4 continued

Severity	Adults	Children	Total treatment duration
Mild cases			<p>Oral weight bands</p> <ul style="list-style-type: none"> 3–< 6 kg: 50 mg given every 12 hours 6–< 10 kg: 100 mg given every 12 hours 10–< 15 kg: 150 mg given every 12 hours 15–< 20 kg: 200 mg given every 12 hours 20–< 30 kg: 300 mg given every 12 hours ≥ 30 kg: use adult dose <p>AND</p> <p>Metronidazole (IV/oral):</p> <ul style="list-style-type: none"> • Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg) • Children: 7.5 mg/kg/dose given every 8 hours <p>Oral weight bands</p> <ul style="list-style-type: none"> 3–< 6 kg: 30 mg given every 8 hours 6–< 10 kg: 50 mg given every 8 hours 10–< 15 kg: 100 mg given every 8 hours 15–< 20 kg: 150 mg given every 8 hours 20–< 30 kg: 200 mg given every 8 hours ≥ 30 kg: use adult dose <p>(Ciprofloxacin and metronidazole have excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function)</p>

continues

Table 29.4 continued

Severity	Adults	Children	Total treatment duration
Severe cases	<p>First choice</p> <p>Cefotaxime (IV): 2 g given every 8 hours</p> <p>AND Metronidazole (IV/oral): 500 mg given every 8 hours</p> <p>OR</p> <p>Ceftriaxone (IV): 2 g given once a day</p> <p>AND Metronidazole (IV/oral): 500 mg given every 8 hours</p> <p>OR</p> <p>Piperacillin+tazobactam ^c (IV): 4 g + 500 mg given every 6 hours</p>	<p>First choice</p> <p>Ampicillin (IV):</p> <ul style="list-style-type: none"> First week of life: 50 mg/kg/dose given every 12 hours Beyond first week of life: 50 mg/kg/dose given every 8 hours <p>AND</p> <p>Gentamicin (IV):</p> <ul style="list-style-type: none"> Neonates: 5 mg/kg given once daily Children: 7.5 mg/kg given once daily <p>AND</p> <p>Metronidazole (oral/IV):</p> <ul style="list-style-type: none"> Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg) Children: 7.5 mg/kg/dose given every 8 hours <p>Second choice</p> <p>Meropenem ^d (IV): 1 g given every 8 hours</p>	<p>Acute cholecystitis: 5 days in total if adequate control of the source of infection has been achieved with surgery and symptoms have resolved.</p> <p>Acute cholangitis: continue antibiotic treatment for a total of 5 days once control of the source of infection has been achieved with biliary drainage and symptoms have resolved.</p> <p>OR</p>

continues

Table 29.4 continued

Severity	Adults	Children	Total treatment duration
Severe cases		Piperacillin+tazobactam (IV): 100 mg/kg/dose of piperacillin component given every 8 hours	

IV: intravenous.

Note: All dosages are for normal renal and hepatic function.

* The use of fluoroquinolones (such as ciprofloxacin) can be associated with important side-effects including: (i) mental health disturbances such as disorientation, agitation, nervousness, memory impairment and delirium; (ii) serious blood sugar disturbances such as hypoglycaemic coma; (iii) increased risk of tendinitis and tendon rupture; (iv) worsening symptoms in those with myasthenia gravis; and (v) potential irreversible neuropathy (serious nerve damage).

^b Oral liquid formulations must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures.

^c Of note, piperacillin+tazobactam offers anti-*Enterococcus* coverage, which the other options listed for adults do not. Ampicillin would be another appropriate option, but it was not listed in this table as it is not currently in the EML for this indication, while it is listed for children.

^d Meropenem should not be considered for routine use for all severe cases but only in complicated cases (i.e. abscess and/or peritonitis) in settings with a high prevalence of extended-spectrum beta-lactamase-producing Enterobacteriales or in patients with known prior colonization, treated with multiple antibiotic courses or at risk of infections with pathogens resistant to the first-choice option. Empiric use of a Reserve antibiotic could be considered exceptionally in very select cases of seriously ill patient who are failing to respond to carbapenems; or who have previously been treated for infections caused by carbapenem-resistant pathogens; or who are known to be colonized with multidrug-resistant Gram-negative bacteria that are known to be susceptible to the selected Reserve antibiotic. Please refer to the chapter on Reserve antibiotics for the definition and list of Reserve antibiotics included in the EML and EMLC.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

30. Intra-abdominal infections – pyogenic liver abscess

Key messages

- In clinically stable patients, targeted antibiotic treatment based on the results of microbiology tests (cultures of abscess material, blood cultures) is always preferable.
- Early source control (i.e. drainage of the abscess) is usually required when feasible in addition to antibiotic treatment, especially for large abscesses > 5 cm in diameter.
- The intravenous route is preferred for initial treatment.
- Consider the possibility of an amoebic abscess and hydatid disease in the differential diagnosis because these diagnoses require different management.

Definition

A pyogenic liver abscess is defined as a collection of pus within the liver.

Pyogenic liver abscess

Intra-abdominal infection • Page 1 of 2

Definition

A collection of pus within the liver

Classification based on severity:

- **Mild:** Not critically ill with no signs of sepsis or septic shock
- **Severe:** Critically ill with signs of sepsis or septic shock

Diagnosis

Clinical Presentation

Fever ($\geq 38.0^{\circ}\text{C}$) and abdominal pain (mostly localized in the right upper abdominal quadrant) +/- vomiting, nausea, anorexia, malaise and jaundice

Microbiology Tests

- Blood cultures (ideally before starting antibiotics)
- Microscopy and culture of abscess fluid material (if this can be drained) to adjust empiric antibiotic treatment
- Tests for *Entamoeba histolytica*:
 - Antigen or nucleic acid amplification tests of abscess aspirate material
 - Serology (however in endemic settings, serology can remain positive for months/years after resolution of infection)

Other Laboratory Tests

Determine disease severity and help identify a bacterial infection: White blood cell count, C-reactive protein and/or procalcitonin

Assess liver function: AST, bilirubin and alkaline phosphatase

- If sepsis is suspected consider additional laboratory tests (see sepsis infographic)

Imaging

- Abdominal ultrasound to confirm the diagnosis
- Consider a CT scan of the abdomen especially if complications are suspected or diagnosis is uncertain



Most Likely Pathogens

Infections are often polymicrobial

Bacteria:

- Enterobacteriales (mostly *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* spp.) including multidrug-resistant strains
- *Burkholderia pseudomallei* (mostly Southeast Asia and northern Australia)
- *Staphylococcus* spp.
- *Streptococcus* spp. (e.g. of the *S. anginosus* group)
- *Enterococcus* spp.
- Anaerobes (mostly *Bacteroides* spp.)

Fungi:

- Mostly *Candida albicans* (not a cause of "pyogenic" abscess but consider in immunocompromised patients or recent course of antibiotics)

Parasites (consider in endemic settings):

- *Entamoeba histolytica* (not a cause of "pyogenic" abscess but consider in the differential diagnosis)



Treatment (Section 1 of 2)



Clinical Considerations

- **Drainage of the abscess remains the main approach to eliminate the source of infection** (especially for large abscesses > 5 cm with higher risk of rupture)
- Drainage is also important to identify the causative pathogen and its resistance profile
- **Mild:** Targeted antibiotic treatment preferred (risk of infection due to Enterobacteriales producing ESBL or carbapenemases)
- **Severe:** Empiric treatment considering local prevalence of resistance (particularly of isolates of Enterobacteriales producing ESBL or carbapenemases) and individual risk factors for resistant pathogens

Important:

- **Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or rapid clinical improvement if culture results unavailable
- **Step down to oral treatment** is based on improvement of symptoms, signs of infection and the ability to take oral antibiotics
- **If signs and symptoms persist**, abdominal imaging is suggested, or an alternative extra-abdominal source of infection should be considered

Pyogenic liver abscess

Intra-abdominal infection • Page 2 of 2

Rx Treatment (Section 2 of 2)

Antibiotic Treatment Duration

- Usually long (at least 4 weeks) depending on adequate source control with drainage procedures
- Longer treatment in case of *Burkholderia pseudomallei* infection (months)
- Follow up imaging can help defining antibiotic treatment duration

Mild Cases

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice

Amoxicillin+clavulanic acid 1 g+200 mg q8h IV
OR 875 mg+125 mg q8h ORAL

OR

Cefotaxime 2 g q8h IV
WATCH

OR

Ceftriaxone 2 g q24h IV
WATCH

COMBINED WITH

Metronidazole 500 mg q8h IV/ORAL
ACCESS

Second Choice

Ciprofloxacin 500 mg q12h ORAL
WATCH

COMBINED WITH

Metronidazole 500 mg q8h IV/ORAL
ACCESS

Ciprofloxacin and metronidazole have excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function

Severe Cases

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice

Cefotaxime 2 g q8h IV
WATCH

OR

Ceftriaxone 2 g q24h IV
WATCH

COMBINED WITH

Metronidazole 500 mg q8h IV/ORAL
ACCESS

OR

Piperacillin+tazobactam 4 g + 500 mg q6h IV
WATCH

Second Choice

Meropenem 1 g q8h IV
WATCH

Consider meropenem only in complicated cases if there is a high risk of infection with ESBL-producing Enterobacteriales

Amoebic Abscess

All dosages are for normal renal function

Metronidazole 750 mg q8h ORAL
ACCESS

FOLLOWED BY

Paromomycin 25-35 mg/kg divided in 3 doses ORAL

Pyogenic liver abscess

Intra-abdominal infection • Page 1 of 3

Definition

A collection of pus within the liver

Classification based on severity:

- **Mild:** Not critically ill with no signs of sepsis or septic shock
- **Severe:** Critically ill with signs of sepsis or septic shock

Diagnosis

Clinical Presentation

Fever ($\geq 38.0^{\circ}\text{C}$) and abdominal pain (mostly localized in the right upper abdominal quadrant) +/- vomiting, nausea, anorexia, malaise and jaundice

Microbiology Tests

- Blood cultures (ideally before starting antibiotics)
- Microscopy and culture of abscess fluid material (if this can be drained) to adjust empiric antibiotic treatment
- Tests for *Entamoeba histolytica*:
 - Antigen or nucleic acid amplification tests of abscess aspirate material
 - Serology (however in endemic settings, serology can remain positive for months/years after resolution of infection)

Other Laboratory Tests

Determine disease severity and help identify a bacterial infection: White blood cell count, C-reactive protein and/or procalcitonin

Assess liver function: AST, bilirubin and alkaline phosphatase

- If sepsis is suspected consider additional laboratory tests (see sepsis infographic)

Imaging

- Abdominal ultrasound to confirm the diagnosis
- Consider a CT scan of the abdomen especially if complications are suspected or diagnosis is uncertain



Most Likely Pathogens

Infections are often polymicrobial

Bacteria:

- Enterobacteriales (mostly *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* spp.) including multidrug-resistant strains
- *Burkholderia pseudomallei* (mostly Southeast Asia and northern Australia)
- *Staphylococcus* spp.
- *Streptococcus* spp. (e.g. of the *S. anginosus* group)
- *Enterococcus* spp.
- Anaerobes (mostly *Bacteroides* spp.)

Fungi:

- Mostly *Candida albicans* (not a cause of "pyogenic" abscess but consider in immunocompromised patients or recent course of antibiotics)

Parasites (consider in endemic settings):

- *Entamoeba histolytica* (not a cause of "pyogenic" abscess but consider in the differential diagnosis)



Treatment (Section 1 of 3)



Clinical Considerations

- **Drainage of the abscess remains the main approach to eliminate the source of infection** (especially for large abscesses > 5 cm with higher risk of rupture)
- Drainage is also important to identify the causative pathogen and its resistance profile
- **Mild:** Targeted antibiotic treatment preferred (risk of infection due to Enterobacteriales producing ESBL or carbapenemases)
- **Severe:** Empiric treatment considering local prevalence of resistance (particularly of isolates of Enterobacteriales producing ESBL or carbapenemases) and individual risk factors for resistant pathogens

Important:

- **Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or rapid clinical improvement if culture results unavailable
- **Step down to oral treatment** is based on improvement of symptoms, signs of infection and the ability to take oral antibiotics
- **If signs and symptoms persist**, abdominal imaging is suggested, or an alternative extra-abdominal source of infection should be considered

Pyogenic liver abscess

Intra-abdominal infection • Page 2 of 3

Rx Treatment (Section 2 of 3)



Antibiotic Treatment Duration

- Usually long (at least 4 weeks) depending on adequate source control with drainage procedures
- Longer treatment in case of *Burkholderia pseudomallei* infection (months)
- Follow up imaging can help defining antibiotic treatment duration



Amoebic Abscess

All dosages are for normal renal function



Metronidazole 10-15 mg/kg/dose q8h ORAL



Mild Cases

See the following page for treatment recommendations



Severe Cases

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice



Ampicillin IV

- 1st week of life: 50 mg/kg/dose q12h
- > 1st week of life: 50 mg/kg/dose q8h

COMBINED WITH



Gentamicin IV

- Neonates: 5 mg/kg q24h
- Children: 7.5 mg/kg q24h

COMBINED WITH



Metronidazole IV/ORAL

- Neonates: 7.5 mg/kg/dose q12h (for IV loading dose: 15 mg/kg)
- Children: 7.5 mg/kg/dose q8h

Oral weight bands:

3-<6 kg	30 mg q8h
6-<10 kg	50 mg q8h
10-<15 kg	100 mg q8h
15-<20 kg	150 mg q8h
20-<30 kg	200 mg q8h
≥30 kg	500 mg q8h

OR



Piperacillin+tazobactam 100 mg/kg/dose of piperacillin component q8h IV

Second Choice



Meropenem 20 mg/kg/dose q8h IV

Consider meropenem only in complicated cases if there is a high risk of infection with ESBL-producing Enterobacteriales

Pyogenic liver abscess

Intra-abdominal infection • Page 3 of 3

Rx Treatment (Section 3 of 3)

Rx Mild Cases

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice



Amoxicillin+clavulanic acid

IV:

- 1st week of life: 50 mg/kg/dose of amoxicillin component q12h
 - > 1st week of life: 50 mg/kg/dose of amoxicillin component q8h
- ORAL:** 80-90 mg/kg/day of amoxicillin component

• Oral weight bands:

3-<6 kg	250 mg of amox/dose q12h
6-<10 kg	375 mg of amox/dose q12h
10-<15 kg	500 mg of amox/dose q12h
15-<20 kg	750 mg of amox/dose q12h
≥20 kg	500 mg of amox/dose q8h or 1 g of amox/dose q12h

Amox = amoxicillin

Oral liquid must be refrigerated after reconstitution

OR



Ampicillin IV

- 1st week of life: 50 mg/kg/dose q12h
- > 1st week of life: 50 mg/kg/dose q8h

COMBINED WITH



Gentamicin IV

- Neonates: 5 mg/kg q24h
- Children: 7.5 mg/kg q24h

COMBINED WITH



Metronidazole IV/ORAL

- Neonates: 7.5 mg/kg/dose q12h (for IV loading dose: 15 mg/kg)
- Children: 7.5 mg/kg/dose q8h

• Oral weight bands:

3-<6 kg	30 mg q8h
6-<10 kg	50 mg q8h
10-<15 kg	100 mg q8h
15-<20 kg	150 mg q8h
20-<30 kg	200 mg q8h
≥30 kg	500 mg q8h

OR



Cefotaxime 50 mg/kg/dose q8h IV

OR



Ceftriaxone 80 mg/kg/dose q24h IV

COMBINED WITH



Metronidazole IV/ORAL

- Neonates: 7.5 mg/kg/dose q12h (for IV loading dose: 15 mg/kg)
- Children: 7.5 mg/kg/dose q8h

• Oral weight bands:

3-<6 kg	30 mg q8h
6-<10 kg	50 mg q8h
10-<15 kg	100 mg q8h
15-<20 kg	150 mg q8h
20-<30 kg	200 mg q8h
≥30 kg	500 mg q8h

Second Choice



Ciprofloxacin 15 mg/kg/dose q12h

IV/ORAL

• Oral weight bands:

3-<6 kg	50 mg q12h
6-<10 kg	100 mg q12h
10-<15 kg	150 mg q12h
15-<20 kg	200 mg q12h
20-<30 kg	300 mg q12h
≥30 kg	500 mg q12h

COMBINED WITH



Metronidazole IV/ORAL

- Neonates: 7.5 mg/kg/dose q12h (for IV loading dose: 15 mg/kg)
- Children: 7.5 mg/kg/dose q8h

• Oral weight bands:

3-<6 kg	30 mg q8h
6-<10 kg	50 mg q8h
10-<15 kg	100 mg q8h
15-<20 kg	150 mg q8h
20-<30 kg	200 mg q8h
≥30 kg	500 mg q8h

Ciprofloxacin and metronidazole have excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function

Pathophysiology

A pyogenic liver abscess develops when a biliary infection spreads directly to the liver or when a complicated intra-abdominal infection spreads to the liver via the portal circulation. In cases of systemic infection, the infection may also spread to the liver via the bloodstream.

Epidemiology

Pyogenic liver abscess is the most common type of visceral abscess (305). It is frequently associated with male sex and diabetes. Pyogenic liver abscess is more common in South-East Asia (306) probably due to the different epidemiology of certain causative pathogens, such as *Klebsiella pneumoniae*. Underlying hepatobiliary or pancreatic diseases (e.g. malignancy, cirrhosis, recent abdominal or biliary surgery) are common risk factors. Abscess rupture is a rare but severe complication associated with a high mortality if not treated immediately.

Most likely pathogens

Most cases of liver abscess are caused by enteric Gram-negative bacteria and anaerobes and most cases involve more than one pathogen (Table 30.1) (307). A hypervirulent strain of *Klebsiella pneumoniae* is an increasingly common cause of liver abscess in Asia (308,309). *Burkholderia pseudomallei* (a Gram-negative bacterium found in soil and water and transmitted by inhalation or ingestion or inoculation) is also a cause of liver abscess in endemic countries, mostly in South-East Asia and in Australia.

Parasites, notably *Entamoeba histolytica* (acquired by ingestion of contaminated food or water), are another frequent cause of liver abscess in endemic settings: Indian subcontinent, Africa, and Central and South America (310,311).

Table 30.1 – Pathogens most frequently associated with liver abscess (in descending order of frequency)

Bacteria	Parasites	Fungi
Enterobacterales (mostly <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> ^a , <i>Enterobacter</i> spp.) including multidrug-resistant strains such as those producing ESBL and carbapenemases	<i>Entamoeba histolytica</i> ^c	<i>Candida</i> spp. ^d
<i>Staphylococcus</i> spp.		
<i>Streptococcus</i> spp. (e.g. of the <i>Streptococcus anginosus</i> group – old name: <i>Streptococcus milleri</i>)		
<i>Enterococcus</i> spp.		
Anaerobes (mostly <i>Bacteroides</i> spp.)		
In endemic settings consider		
<i>Burkholderia pseudomallei</i> ^b		

ESBL: extended-spectrum beta-lactamases.

^a In Asia, *Klebsiella pneumoniae* is currently the main cause of liver abscess.

^b *Burkholderia pseudomallei* is an important cause of liver abscess in South-East Asia and northern Australia.

^c This pathogen is not a cause of pyogenic abscess but needs to be considered in the differential diagnosis, especially in patients who live in or have travelled to settings where *Entamoeba histolytica* is endemic.

^d This pathogen is not a cause of pyogenic abscess and is infrequent in immunocompetent individuals but should be considered in the context of immunosuppression. Often it is in combination with bacteria.

Clinical presentation

Pyogenic liver abscess should be considered in all cases of fever ($\geq 38.0^{\circ}\text{C}$) and abdominal pain, mostly localized in the right upper abdominal quadrant. Vomiting, nausea, anorexia, malaise and jaundice are other common symptoms.

Laboratory tests

Patient microbiology tests

Whenever possible, a microbiology sample should be obtained (see Table 30.2) to guide antibiotic treatment. Ideally, the sample should be obtained before antibiotic treatment is started. The reason for doing microbiology tests is to determine the type of pathogen causing infection and its resistance profile in order to provide adequate treatment (312).

Table 30.2 – Microbiology tests to consider when a liver abscess is suspected (including testing for *Entamoeba histolytica*) as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
Blood cultures and antimicrobial susceptibility testing	To detect bacterial bloodstream infections	Health care facilities with clinical laboratories
Microscopy, culture and antimicrobial susceptibility testing of abscess or pus aspirate	Initial step to detect and identify bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories
Microscopy of stool sample for <i>Entamoeba histolytica</i>	To diagnose <i>Entamoeba histolytica</i> ^a	Health care facilities with clinical laboratories
Antigen or nucleic acid amplification test (i.e. polymerase chain reaction ^b) of abscess aspirate material for <i>Entamoeba histolytica</i>	To diagnose <i>Entamoeba histolytica</i> ^a	— ^c
Serology for <i>Entamoeba histolytica</i> ^d	To diagnose <i>Entamoeba histolytica</i> ^a	— ^c

EDL: Model List of Essential In Vitro Diagnostics.

^a *Entamoeba histolytica* is not a cause of pyogenic abscess but a cause of liver abscess that needs to be considered in the differential diagnosis in endemic settings. However, patients with amoebic liver abscess usually have no bowel symptoms; therefore, stool testing (microscopy or antigen) has a low sensitivity and is of limited usefulness for diagnosis.

^b Antigen or nucleic acid amplification testing of abscess aspirate material for *Entamoeba histolytica* could be considered where available. Diagnosis is often difficult in low- and middle-income countries due to limited laboratory resources and the fact that most patients present after a failed course of antibiotic treatment for pyogenic abscess; therefore the yield of any microbiology tests is lower (311,312).

^c This test is not in the WHO EDL (6).

^d Serology is a useful test in the diagnosis of invasive amoebiasis and is positive in more than 90% of patients with the disease. A positive serology combined with a compatible clinical presentation suggests active disease. However, in endemic settings, a positive result is more difficult to interpret since serology can remain positive for months and even years after resolution of the infection. Therefore, past and current infections become difficult to distinguish. With negative results, if the clinical suspicion of invasive amoebiasis is still strong, serology could be repeated after 1 week.

Other tests

Laboratory tests can be used to complement the clinical examination and medical history even though they are not specific for the diagnosis. Table 30.3 indicates tests that could be considered in the patient's initial assessment. Please also refer to the chapter on sepsis if suspected.

Table 30.3 – Laboratory tests (other than microbiology) to consider if pyogenic liver abscess is suspected as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
White blood count	To help in the diagnosis of infections	Health care facilities with clinical laboratories
Aspartate aminotransferase	To assess liver function	Health care facilities with clinical laboratories
Alanine aminotransferase	To assess liver function	Health care facilities with clinical laboratories
Bilirubin	To detect or monitor liver disease	Community settings and health facilities without laboratories ^a
Direct and indirect bilirubin	To detect or monitor liver disease, bile duct disorders and haemolytic anaemia, and to differentiate between these causes of jaundice	Health care facilities with clinical laboratories
Alkaline phosphatase	To aid in the diagnosis of hepatobiliary diseases	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics.

^a Community and health settings without laboratories are settings such as health posts and centres, doctors' offices, outreach clinics and ambulatory care. These tests are also assumed to be available at health care facilities with laboratories.

Using microbiology surveillance data

There is no role for routine surveillance to inform empiric guidance.

Imaging

Imaging is very helpful in the diagnosis of pyogenic liver abscess. An abdominal ultrasound should always be considered when this condition is suspected. In settings where it is available, a CT scan of the abdomen may also be considered, especially if complications are suspected or the diagnosis is uncertain.

Treatment

Early control of the source of infection through drainage of the abscess is usually required when feasible in addition to antibiotic treatment, especially for large (> 5 cm) abscesses. Drainage is recommended because larger abscesses have a higher risk of rupture.

Drainage techniques include:

- Percutaneous drainage (image-guided procedure that is usually performed by an interventional radiologist where available). A drain – usually a pigtail catheter – is inserted through the skin into the abscess and left in place until the collection is drained.
- Surgical drainage. This is done either as a conventional open procedure (i.e. laparotomy) or by laparoscopy.

In both cases, the drainage procedure is also important for diagnostic purposes to identify the type of pathogen causing the abscess and its resistance profile. Abscess material should therefore be obtained for culture when the drain is placed or the abscess is surgically removed.

Antibiotic treatment

In patients who are clinically stable, targeted treatment based on the results of microbiology tests is always preferred. In particular, infections caused by Enterobacteriales producing ESBL or carbapenemases need to be considered in patients with history of hospitalization or previously colonized or infected with these resistant pathogens as their prevalence varies greatly in different settings.

In more severe cases, empiric treatment is given, taking into account the most probable type of causative pathogen (including the possibility of *Entamoeba histolytica* infection) and local prevalence of resistance, especially for ESBL- and carbapenemase-producing isolates (see Table 30.4). Individual risk factors for resistant pathogens (e.g. recent antibiotic treatment, colonization or previous infections with resistant isolates) should also be considered.

The total duration of treatment is usually long (weeks) and depends on whether control of the source of infection is achieved and on the causative pathogen. Therefore, early control of the source of infection and identification of the causative pathogen are encouraged. In most cases, at least 4 weeks of antibiotic treatment are needed with follow-up imaging (if available) to monitor response and define treatment duration.

Longer duration of treatment is required in cases of liver abscess caused by *Burkholderia pseudomallei* – usually 2 weeks of intravenous treatment followed by > 3 months of oral treatment with sulfamethoxazole+trimethoprim to eradicate the infection and prevent relapse or recurrence. In cases of amoebic liver abscess, a 10-day course of treatment (with oral metronidazole) is usually adequate.

Simplify empiric treatment to a more narrow-spectrum antibiotic (often also called de-escalation) based on culture results (targeted treatment) or based on rapid clinical



improvement when no microbiology test results are available. In general, the intravenous route is preferred for the initial phase of treatment.

Step-down to oral treatment is based on improvement of symptoms and signs of infection and the ability to take oral antibiotics allowing discharge of the patient home when clinically appropriate.

Oral step-down therapy can be considered quickly for mild cases after adequate drainage and confirmed microbiology and susceptibility.

If signs and symptoms persist, abdominal imaging is suggested, or an alternative extra-abdominal source of infection should be considered.

Table 30.4 – Empiric antibiotic treatment for pyogenic or amoebic liver abscess**Note**

In clinically stable patients, targeted treatment based on the results of microbiology tests is preferred.

Mild cases are defined as patients who are not critically ill with no signs of sepsis or septic shock.

Severe cases are defined as patients who are critically ill with signs of sepsis or septic shock.

**Important**

Where more than one antibiotic is recommended for an infection, they are listed in alphabetical order and they should be considered equal treatment options, unless otherwise indicated.

Condition	Adults	Children	Total treatment duration
Mild cases of pyogenic liver abscess		<p>First choice Amoxicillin+clavulanic acid^a:</p> <p>IV: First week of life: 50 mg/kg of amoxicillin/dose given every 12 hours</p> <p>Beyond first week of life: 50 mg/kg of amoxicillin/dose given every 8 hours</p> <p>OR</p> <p>Cefotaxime (IV): 2 g given every 8 hours AND Metronidazole (IV/oral): 500 mg given every 8 hours</p> <p>OR</p> <p>Ceftriaxone (IV): 2 g given once a day AND Metronidazole (IV/oral): 500 mg given every 8 hours</p>	<p>At least 4 weeks if adequate control of the source of infection is achieved (follow-up imaging is usually performed to guide treatment duration)</p>

continues

continues

Table 30.4 continued

Condition	Adults	Children	Total treatment duration
Mild cases of pyogenic liver abscess	<p>Second choice</p> <p>Ciprofloxacin^a (oral): 500 mg given every 12 hours</p> <p>Metronidazole (IV/oral): 500 mg given every 8 hours</p> <p>(Ciprofloxacin and metronidazole have excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function)</p> <p>AND</p> <p>Gentamicin (IV):</p> <ul style="list-style-type: none"> • Neonates: 5 mg/kg given once daily • Children: 7.5 mg/kg given once daily <p>AND</p> <p>Metronidazole (IV/oral):</p> <ul style="list-style-type: none"> • Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg) • Children: 7.5 mg/kg/dose given every 8 hours <p>Oral weight bands</p> <p>3–< 6 kg: 30 mg given every 8 hours</p> <p>6–< 10 kg: 50 mg given every 8 hours</p> <p>10–< 15 kg: 100 mg given every 8 hours</p> <p>15–< 20 kg: 150 mg given every 8 hours</p> <p>20–< 30 kg: 200 mg given every 8 hours</p> <p>≥ 30 kg: use adult dose</p> <p>OR</p>		

Table 30.4 *continued*

Condition	Adults	Children	Total treatment duration
Mild cases of pyogenic liver abscess		<p>Cefotaxime (IV): 50 mg/kg/dose given every 8 hours AND</p> <p>Metronidazole (IV/oral):</p> <ul style="list-style-type: none"> Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg) Children: 7.5 mg/kg/dose given every 8 hours <p>Oral weight bands</p> <p>3–< 6 kg: 30 mg given every 8 hours</p> <p>6–< 10 kg: 50 mg given every 8 hours</p> <p>10–< 15 kg: 100 mg given every 8 hours</p> <p>15–< 20 kg: 150 mg given every 8 hours</p> <p>20–< 30 kg: 200 mg given every 8 hours</p> <p>≥ 30 kg: use adult dose</p> <p>OR</p>	

continues

Table 30.4 *continued*

Condition	Adults	Children	Total treatment duration
Mild cases of pyogenic liver abscess		<p>Ceftriaxone (IV): 80 mg/kg/dose given once a day AND</p> <p>Metronidazole (IV/oral):</p> <ul style="list-style-type: none"> Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg) Children: 7.5 mg/kg/dose given every 8 hours <p>Oral weight bands</p> <p>3–< 6 kg: 30 mg given every 8 hours</p> <p>6–< 10 kg: 50 mg given every 8 hours</p> <p>10–< 15 kg: 100 mg given every 8 hours</p> <p>15–< 20 kg: 150 mg given every 8 hours</p> <p>20–< 30 kg: 200 mg given every 8 hours</p> <p>≥ 30 kg: use adult dose</p>	

continues

■ HOSPITAL FACILITY

30. Intra-abdominal infections – pyogenic liver abscess

Table 30.4 *continued*

Condition	Adults	Children	Total treatment duration
Mild cases of pyogenic liver abscess		<p>Second choice</p> <p>Ciprofloxacin (IV/oral): 15 mg/kg/dose, given every 12 hours</p> <p>Oral weight bands</p> <p>3-< 6 kg: 50 mg given every 12 hours</p> <p>6-< 10 kg: 100 mg given every 12 hours</p> <p>10-< 15 kg: 150 mg given every 12 hours</p> <p>15-< 20 kg: 200 mg given every 12 hours</p> <p>20-< 30 kg: 300 mg given every 12 hours</p> <p>≥ 30 kg: use adult dose</p> <p>AND</p>	

continues

Table 30.4 continued

Condition	Adults	Children	Total treatment duration
Mild cases of pyogenic liver abscess			<p>Metronidazole (IV/oral):</p> <ul style="list-style-type: none"> • Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg) • Children: 7.5 mg/kg/dose given every 8 hours <p>Oral weight bands</p> <p>3–< 6 kg: 30 mg given every 8 hours</p> <p>6–< 10 kg: 50 mg given every 8 hours</p> <p>10–< 15 kg: 100 mg given every 8 hours</p> <p>15–< 20 kg: 150 mg given every 8 hours</p> <p>20–< 30 kg: 200 mg given every 8 hours</p> <p>≥ 30 kg: use adult dose</p> <p>(Ciprofloxacin and metronidazole have excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function)</p>

continues

Table 30.4 continued

Condition	Adults	Children	Total treatment duration
Severe cases of pyogenic liver abscess	<p>First choice</p> <p>Cefotaxime (IV): 2 g given every 8 hours AND Metronidazole (IV/oral): 500 mg given every 8 hours</p> <p>OR</p> <p>Ceftriaxone (IV): 2 g given once a day AND Metronidazole (IV/oral): 500 mg given every 8 hours</p> <p>OR</p> <p>Piperacillin+tazobactam ^c (IV): 4 g + 500 mg given every 6 hours</p> <p>Second choice</p> <p>Meropenem ^d (IV): 1 g given every 8 hours</p>	<p>First choice</p> <p>Ampicillin (IV): <ul style="list-style-type: none"> First week of life: 50 mg/kg/dose given every 12 hours Beyond first week of life: 50 mg/kg/dose given every 8 hours AND</p> <p>Gentamicin (IV): <ul style="list-style-type: none"> Neonates: 5 mg/kg given once daily Children: 7.5 mg/kg given once daily AND</p> <p>Metronidazole (IV/oral) <ul style="list-style-type: none"> Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg) Children: 7.5 mg/kg/dose given every 8 hours </p> <p>Oral weight bands</p> <ul style="list-style-type: none"> 3–< 6 kg: 30 mg given every 8 hours 6–< 10 kg: 50 mg given every 8 hours 10–< 15 kg: 100 mg given every 8 hours 15–< 20 kg: 150 mg given every 8 hours 20–< 30 kg: 200 mg given every 8 hours ≥ 30 kg: use adult dose <p>OR</p>	<p>At least 4 weeks if adequate control of the source of infection is achieved (follow-up imaging is usually performed to guide treatment duration)</p>

continues

Table 30.4 continued

Condition	Adults	Children	Total treatment duration
Severe cases of pyogenic liver abscess		Piperacillin+tazobactam (IV): 100 mg/kg/dose of piperacillin component given every 8 hours	
Amoebic liver abscess	Metronidazole (oral ^c): 750 mg given every 8 hours, followed by paromomycin (oral): 25–35 mg/kg divided in 3 doses (to eradicate colonic colonization)	Metronidazole (oral ^b): 10–15 mg/kg/dose given every 8 hours	10 days of metronidazole, followed by 7 days of paromomycin

EML: Model List of Essential Medicines; EMLc: Model List of Essential Medicines for children; IV: intravenous.

Note: All dosages are for normal renal and hepatic function.

The EML and EMLc currently does not have specific recommendations for antibiotic treatment of pyogenic or amoebic liver abscess; therefore the options presented in the table are extrapolated from the recommended treatment for complicated intra-abdominal infections.

^a The use of fluoroquinolones (such as ciprofloxacin) can be associated with important side-effects including: (i) mental health disturbances such as disorientation, agitation, nervousness, memory impairment and delirium; (ii) serious blood sugar disturbances such as hypoglycaemia; (iii) increased risk of tendinitis and tendon rupture; (iv) worsening symptoms in those with myasthenia gravis; and (v) potential irreversible neuropathy (serious nerve damage).

^b Oral liquid formulations must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperature.

^c Of note, piperacillin+tazobactam offers anti-*Enterococcus* coverage, which the other options listed for adults do not. Ampicillin would be another appropriate option, but it was not listed in this table as it is not currently in the EML for this indication, while it is listed for children.

^d Meropenem should not be considered for routine use in all severe cases but only in complicated cases in settings with a high prevalence of extended-spectrum beta-lactamase-producing Enterobacteriales or in patients with known prior colonization, treated with multiple antibiotic courses or at risk of infections with pathogens resistant to the first choice option. Empiric use of a Reserve antibiotic could be considered exceptionally in very select cases of seriously ill patients failing to respond to carbapenems or who have previously been treated for infections caused by carbapenem-resistant pathogens or who are known to be colonized with multidrug-resistant Gram-negative bacteria known to be susceptible to the selected Reserve antibiotic. Please refer to the chapter on Reserve antibiotics for the definition and list of Reserve antibiotics included in the EML and EMLc. When *Burkholderia pseudomallei* is suspected, empiric use of meropenem or imipenem could be considered, although the preferred option is ceftazidime.

^e If the patient is unable to tolerate oral treatment or in severe infections, IV metronidazole should be given: dose in adults: 500 mg every 8 hours.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

31. Intra-abdominal infections – acute appendicitis

Key messages

- Appendectomy remains the main approach to treatment in children.
- In adults, treatment with antibiotics alone (without surgery) can be considered if follow up is possible. About one in three patients treated with antibiotics alone will experience a recurrence within 2 years.
- Antibiotics should be chosen based on the severity of symptoms (mild or severe) with broader-spectrum agents for severe cases.
- Treatment should also be active against anaerobes as these pathogens are often involved in intra-abdominal infections.
- Antibiotics should be stopped once the source of infection has been controlled (e.g. after appendectomy) if there is good clinical recovery.



Other relevant WHO resources (please check regularly for updates)

- Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, 2013 (31).

Definition

Appendicitis is an acute inflammation of the appendix sometimes followed by ischaemia and perforation. It is usually classified as uncomplicated (or simple) when there is no involvement of the peritoneal cavity and no abscess. When the appendix is perforated with subsequent peritonitis or when an abscess is present, appendicitis is defined as complicated. Most cases of appendicitis are uncomplicated (70%).

Acute appendicitis

Intra-abdominal infection • Page 1 of 2

Definition

Acute inflammation of the appendix sometimes followed by ischemia and perforation

Classification based on complexity:

- **Uncomplicated** (> 70% of cases): No involvement of the peritoneal cavity and no abscess
- **Complicated**: Involvement of the peritoneal cavity and/or presence of an abscess

Classification based on severity:

- **Mild**: Not critically ill with no signs of sepsis or septic shock
- **Severe**: Critically ill with signs of sepsis or septic shock



Most Likely Pathogens

Bacteria:

- Enterobacteriales (mostly *Escherichia coli* including multidrug-resistant strains)
- *Streptococcus* spp. (e.g. of the *S. anginosus* group)
- *Enterococcus* spp.
- Anaerobes (mostly *Bacteroides* spp.)

Fungi (consider if recent course of antibiotics):

- Mostly *Candida albicans*

Parasites (consider in endemic settings):

- *Enterobius vermicularis* (pinworm) can contribute by causing obstruction of the appendix

Diagnosis

Clinical Presentation

Acute abdominal pain (usually located in the right lower quadrant or migrating from the periumbilical area to the right lower quadrant), with nausea and vomiting; fever ($\geq 38.0^{\circ}\text{C}$) may be absent

Important:

- Consider peritonitis if there is severe pain, diffuse rebound tenderness upon sudden release of pressure on the abdomen and abdominal muscular tensing
- Hypotension and signs of organ hypoperfusion (e.g. reduced urine output) are potential signs of sepsis /septic shock that need urgent treatment



Microbiology Tests

Mild uncomplicated cases:

- Not usually needed

Severe cases:

- Blood cultures (ideally before starting antibiotics)
- Microscopy and culture of abscess fluid material (taken at the time of surgery) is not routinely recommended, but may be considered in specific cases to adjust empiric antibiotic treatment

Imaging

- Abdominal ultrasound to confirm the diagnosis
- Consider doing a CT scan of the abdomen if complications suspected or diagnosis uncertain



Other Laboratory Tests

Identify an alternative cause of abdominal pain:

- Urinalysis (dipstick or microscopy) to exclude an infection of the urinary tract
- Pregnancy test in women: to exclude an ectopic pregnancy

Determine disease severity and help identify a bacterial infection:

White blood cell count, C-reactive protein and/or procalcitonin

If sepsis is suspected consider additional laboratory tests (see sepsis infographic)

Acute appendicitis

Intra-abdominal infection • Page 2 of 2

Rx Treatment



Antibiotic Treatment Duration

Antibiotic treatment complementary to surgery

- Uncomplicated cases:** Antibiotics can be stopped once appendix is removed
- Complicated cases:** Antibiotics can be continued for a total of **5 days** provided that symptoms resolved and the source of infection was eliminated with surgery

Treatment with antibiotics alone: 7 days

- Consider in selected cases if close clinical monitoring is feasible and considering patient preference (avoiding risks associated with surgery versus higher risk of recurrences and later need for surgery - about 30-40% over 5 years)

Rx Mild Cases

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice

 Amoxicillin+clavulanic acid 1 g+200 mg q8h IV
ACCESS OR 875 mg+125 mg q8h **ORAL**

OR

 Cefotaxime 2 g q8h **IV**
WATCH

OR

 Ceftriaxone 2 g q24h **IV**
WATCH

----- COMBINED WITH -----

 Metronidazole 500 mg q8h **IV/ORAL**
ACCESS

Second Choice

 Ciprofloxacin 500 mg q12h **ORAL**
WATCH

----- COMBINED WITH -----

 Metronidazole 500 mg q8h **IV/ORAL**
ACCESS

Metronidazole has excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function



Clinical Considerations

- Appendectomy remains the main approach to eliminate the source of infection**
- Empiric antibiotic treatment should be guided by:** The severity of symptoms, considering local prevalence of resistance (particularly of isolates of Enterobacteriales producing ESBL) and individual risk factors for resistant pathogens

Important:

- Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or rapid clinical improvement if culture results unavailable
- Step down to oral treatment** is based on improvement of symptoms, signs of infection and the ability to take oral antibiotics
- If signs and symptoms persist**, abdominal imaging is suggested, or an alternative extra-abdominal source of infection should be considered

Rx Severe Cases

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice

 Cefotaxime 2 g q8h **IV**
WATCH

OR

 Ceftriaxone 2 g q24h **IV**
WATCH

----- COMBINED WITH -----

 Metronidazole 500 mg q8h **IV/ORAL**
ACCESS

OR

 Piperacillin+tazobactam 4 g + 500 mg q6h **IV**
WATCH

Second Choice

 Meropenem 1 g q8h **IV**
WATCH

Consider meropenem only in complicated cases if there is a high risk of infection with ESBL-producing Enterobacteriales

Acute appendicitis

Intra-abdominal infection • Page 1 of 3

Definition

Acute inflammation of the appendix sometimes followed by ischemia and perforation

Classification based on complexity:

- **Uncomplicated** (>70% of cases): No involvement of the peritoneal cavity and no abscess
- **Complicated**: Involvement of the peritoneal cavity and/or abscess

Classification based on severity:

- **Mild**: Not critically ill with no signs of sepsis or septic shock
- **Severe**: Critically ill with signs of sepsis or septic shock



Most Likely Pathogens

Bacteria:

- Enterobacteriales (mostly *Escherichia coli* including multidrug-resistant strains)
- *Streptococcus* spp. (e.g. of the *S. anginosus* group)
- *Enterococcus* spp.
- Anaerobes (mostly *Bacteroides* spp.)

Fungi (consider if recent course of antibiotics):

- Mostly *Candida albicans*

Parasites (consider in endemic settings):

- *Enterobius vermicularis* (pinworm) can contribute by causing obstruction of the appendix

Diagnosis

Clinical Presentation

Acute abdominal pain (usually located in the right lower quadrant or migrating from the periumbilical area to the right lower quadrant), with nausea and vomiting; fever ($\geq 38.0^{\circ}\text{C}$) may be absent

Important:

- Consider peritonitis if there is severe pain, diffuse rebound tenderness upon sudden release of pressure on the abdomen and abdominal muscular tensing
- Hypotension and signs of organ hypoperfusion (e.g. reduced urine output) are potential signs of sepsis /septic shock that need urgent treatment



Microbiology Tests

Mild uncomplicated cases:

- Not usually needed

Severe cases:

- Blood cultures (ideally before starting antibiotics)
- Microscopy and culture of abscess fluid material (taken at the time of surgery) is not routinely recommended, but may be considered in specific cases to adjust empiric antibiotic treatment

Imaging

- Abdominal ultrasound if available is helpful to confirm the diagnosis
- Consider doing a CT scan of the abdomen if complications suspected or diagnosis uncertain



Other Laboratory Tests

Identify an alternative cause of abdominal pain:

- Urinalysis (dipstick or microscopy) to exclude an infection of the urinary tract
- Consider pregnancy test where appropriate to exclude an ectopic pregnancy

Determine disease severity and help identify a bacterial infection:

White blood cell count, C-reactive protein and/or procalcitonin

If sepsis is suspected consider additional laboratory tests (see sepsis infographic)

Acute appendicitis

Intra-abdominal infection • Page 2 of 3

Rx Treatment (Section 1 of 2)

Clinical Considerations

- Appendectomy remains the main approach to eliminate the source of infection**
- Treatment with antibiotics alone is not recommended in children by WHO
- Empiric antibiotic treatment should be guided by:**
The severity of symptoms, considering local prevalence of resistance (particularly of isolates of Enterobacteriales producing ESBL) and individual risk factors for resistant pathogens

Important:

- Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or rapid clinical improvement if culture results unavailable
- Step down to oral treatment** is based on improvement of symptoms, signs of infection and the ability to take oral antibiotics
- If signs and symptoms persist**, abdominal imaging is suggested, or an alternative extra-abdominal source of infection should be considered



Antibiotic Treatment Duration

- Uncomplicated cases:** Antibiotics can be stopped once surgery has been performed and child is well
- Complicated cases:** Antibiotics can be continued for a total of **5 days** provided that symptoms resolved and the source of infection was eliminated with surgery



Mild Cases

See the following page for treatment recommendations

Rx Severe Cases

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice

Ampicillin IV

- ACCESS • 1st week of life: 50 mg/kg/dose q12h
- > 1st week of life: 50 mg/kg/dose q8h

COMBINED WITH

Gentamicin IV

- ACCESS • Neonates: 5 mg/kg q24h
- Children: 7.5 mg/kg q24h

COMBINED WITH

Metronidazole IV/ORAL

- ACCESS • Neonates: 7.5 mg/kg/dose q12h (for IV loading dose: 15 mg/kg)
- Children: 7.5 mg/kg/dose q8h
- Oral weight bands:

3-<6 kg	30 mg q8h
6-<10 kg	50 mg q8h
10-<15 kg	100 mg q8h
15-<20 kg	150 mg q8h
20-<30 kg	200 mg q8h
≥30 kg	500 mg q8h

OR

Piperacillin+tazobactam 100 mg/kg/dose of piperacillin component q8h IV

Second Choice

Meropenem 20 mg/kg/dose q8h IV

Consider meropenem only in complicated cases if there is a high risk of infection with ESBL-producing Enterobacteriales

Acute appendicitis

Intra-abdominal infection • Page 3 of 3

Rx Treatment (Section 2 of 2)

Rx Mild Cases

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice



Ampicillin+clavulanic acid

IV:

- 1st week of life: 50 mg/kg/dose of amoxicillin component q12h
 - > 1st week of life: 50 mg/kg/dose of amoxicillin component q8h
- ORAL:** 80-90 mg/kg/day of amoxicillin component

• Oral weight bands:

3-<6 kg	250 mg of amox/dose q12h
6-<10 kg	375 mg of amox/dose q12h
10-<15 kg	500 mg of amox/dose q12h
15-<20 kg	750 mg of amox/dose q12h
≥20 kg	500 mg of amox/dose q8h or 1 g of amox/dose q12h

Amox = amoxicillin

Oral liquid must be refrigerated after reconstitution

OR



Ampicillin IV

- 1st week of life: 50 mg/kg/dose q12h
- > 1st week of life: 50 mg/kg/dose q8h

COMBINED WITH



Gentamicin IV

- Neonates: 5 mg/kg q24h
- Children: 7.5 mg/kg q24h

COMBINED WITH



Metronidazole IV/ORAL

- Neonates: 7.5 mg/kg/dose q12h (for IV loading dose: 15 mg/kg)
- Children: 7.5 mg/kg/dose q8h

• Oral weight bands:

3-<6 kg	30 mg q8h
6-<10 kg	50 mg q8h
10-<15 kg	100 mg q8h
15-<20 kg	150 mg q8h
20-<30 kg	200 mg q8h
≥30 kg	500 mg q8h

OR



Cefotaxime 50 mg/kg/dose q8h IV

OR



Ceftriaxone 80 mg/kg/dose q24h IV

COMBINED WITH



Metronidazole IV/ORAL

- Neonates: 7.5 mg/kg/dose q12h (for IV loading dose: 15 mg/kg)
- Children: 7.5 mg/kg/dose q8h

• Oral weight bands:

3-<6 kg	30 mg q8h
6-<10 kg	50 mg q8h
10-<15 kg	100 mg q8h
15-<20 kg	150 mg q8h
20-<30 kg	200 mg q8h
≥30 kg	500 mg q8h

Second Choice



Ciprofloxacin 15 mg/kg/dose q12h

IV/ORAL

• Oral weight bands:

3-<6 kg	50 mg q12h
6-<10 kg	100 mg q12h
10-<15 kg	150 mg q12h
15-<20 kg	200 mg q12h
20-<30 kg	300 mg q12h
≥30 kg	500 mg q12h

COMBINED WITH



Metronidazole IV/ORAL

- Neonates: 7.5 mg/kg/dose q12h (for IV loading dose: 15 mg/kg)
- Children: 7.5 mg/kg/dose q8h

• Oral weight bands:

3-<6 kg	30 mg q8h
6-<10 kg	50 mg q8h
10-<15 kg	100 mg q8h
15-<20 kg	150 mg q8h
20-<30 kg	200 mg q8h
≥30 kg	500 mg q8h

Ciprofloxacin and metronidazole have excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function

Pathophysiology

The exact mechanism leading to appendicitis is poorly understood. Conditions associated with a higher risk of weakening and disrupting the normal anatomical barrier of the appendix or that can cause its luminal obstruction could be involved. In children, lymphoid hyperplasia can contribute to the risk of developing appendicitis. Rarely, parasitic infections (mostly *Enterobius vermicularis* (pinworm)) can contribute to the development of acute appendicitis (313).

Perforation is usually the result of gangrene and a necrotic process and can lead to localized abscess formation or to peritonitis when the leak is not contained by structures surrounding the appendix.

Epidemiology

Acute appendicitis is a common surgical emergency worldwide, especially in children and young adults. The yearly incidence of appendicitis has been declining in western European and North American countries since the 1990s and has stabilized in the past 20 years to about 100–150 cases per 100 000 person-years. However, increasing trends are reported in Asia, South America and the Middle East with the incidence of appendicitis higher than in many western European and North American countries (314). In 2017, there were an estimated 19 million new cases worldwide (44). The lifetime risk of appendicitis reported in the literature varies across countries, ranging from about 2% in Africa to 16% in South Korea (315). Mortality attributable to appendicitis has declined and with prompt diagnosis and management, mortality is now < 1% in uncomplicated cases in most settings (316). Complicated cases or cases in elderly people are associated with a higher mortality.

Most likely pathogens

The most common pathogens involved in appendicitis are Gram-negative bacilli and anaerobes from the intestinal microbiota (Table 31.1). Infections are often caused by more than one pathogen and may include fungal pathogens, especially in patients who have recently received antibiotic treatment. Certain parasites need to be considered in the differential diagnosis of abdominal pain in endemic settings.

Table 31.1 – Pathogens most frequently associated with complicated acute appendicitis (in descending order of frequency)

Bacteria	Fungi	Parasites
Enterobacteriales (mostly <i>Escherichia coli</i>) and other Gram-negative bacteria such as <i>Pseudomonas aeruginosa</i> and <i>Acinetobacter baumannii</i> , including multidrug-resistant strains such as those producing ESBL and carbapenemases	Mostly <i>Candida albicans</i>	Mostly <i>Enterobius vermicularis</i> (pinworm) – can contribute by causing obstruction of the appendix
<i>Streptococcus</i> spp. (e.g. of the <i>Streptococcus anginosus</i> group – old name: <i>Streptococcus milleri</i>)		
<i>Enterococcus</i> spp.		
Anaerobes (mostly <i>Bacteroides</i> spp.)		

ESBL: extended spectrum beta-lactamases.

Clinical presentation

Acute appendicitis should be considered as a possible diagnosis in all cases of acute abdominal pain, especially if the pain is in the right lower quadrant or is moving from the periumbilical area to the right lower quadrant. Nausea and vomiting are usually present. Fever ($\geq 38.0^{\circ}\text{C}$) and rigors can be present.

Severe pain, diffuse rebound tenderness on sudden release of pressure on the abdomen and abdominal muscular tensing are usually present in cases of peritonitis. Hypotension and signs of organ hypoperfusion (e.g. reduced urine output) may be present in cases of organ failure and are a medical and/or surgical emergency. Please also refer to the chapter on sepsis if suspected.

Laboratory tests

Patient microbiology tests

Routine microbiology tests are not usually needed and basing antibiotic treatment on pathogens cultured from the abdominal cavity at the time of operation is not recommended. However, certain microbiology tests could be considered in severely ill patients to adjust empiric antibiotic treatment once the results of antibiotic susceptibility tests are available (Table 31.2).

In more severe cases, blood cultures should be taken and samples from the abdominal cavity may be useful in certain situations such as severely immunocompromised

■ HOSPITAL FACILITY

31. Intra-abdominal infections – acute appendicitis

patients or patients known to be colonized with multidrug-resistant organisms or in patients presenting with septic shock.

Table 31.2 – Microbiology tests to consider in severe cases of appendicitis as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
Blood cultures and antimicrobial susceptibility testing	To detect bacterial bloodstream infections	Health care facilities with clinical laboratories
Microscopy, culture and antimicrobial susceptibility testing of abscess fluid material when this can be drained	Not routinely recommended, but may be used in specific cases to identify bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics.

Other tests

Laboratory tests can be used to complement the clinical examination and medical history. Based on availability, Table 31.3 and Table 31.4 indicate tests that could be considered in the patient's initial assessment and to help guide the duration of antibiotic treatment.

Table 31.3 – Laboratory tests (other than microbiology) that may help identify an alternative cause of abdominal pain that could mimic appendicitis as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
Pregnancy test	In the context of suspected appendicitis the purpose of the test is to exclude an ectopic pregnancy	Community settings and health facilities without laboratories ^a
Urinalysis test (dipstick)	To exclude a urinary tract infection	Community settings and health facilities without laboratories ^a

EDL: Model List of Essential In Vitro Diagnostics.

^a Community and health settings without laboratories are settings such as health posts and centres, doctors' offices, outreach clinics and ambulatory care. These tests are also assumed to be available at health care facilities with laboratories.

Table 31.4 – Laboratory tests (other than microbiology) that may help assess the severity of disease and identify a bacterial infection as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
White blood cell count	To help in the diagnosis of infections	Health care facilities with clinical laboratories
C-reactive protein	To detect inflammation as an indicator of various conditions (e.g. sepsis)	Health care facilities with clinical laboratories
Procalcitonin	To guide antibiotic therapy or discontinuation in sepsis	Only in tertiary care facilities

EDL: Model List of Essential In Vitro Diagnostics.

Using microbiology surveillance data

Routine surveillance of pathogens cultured from the abdominal cavity is not recommended.

Empiric guidance given by the AWaRe book could be reviewed and adapted based on local clinically relevant microbiology surveillance data. For example, clinically relevant isolates for this infection would be blood culture data from patients on surgical wards with intra-abdominal infections.

Imaging

Imaging is helpful to confirm acute appendicitis. An abdominal ultrasound should always be considered when this condition is suspected. Where available a CT scan of the abdomen may also be considered, especially if complications are suspected or the diagnosis is uncertain.

Treatment

Surgery to eliminate/control the source of infection (e.g. abscess, perforated appendix) and reduce contamination of the peritoneal cavity (e.g. in cases of perforation) are the foundation of treatment. Patients with suspected or confirmed appendicitis should be promptly referred for surgical consultation and antibiotic treatment should be started quickly.

Uncomplicated cases treated with antibiotics alone

Treating appendicitis with antibiotics alone is controversial – and not recommended by WHO for children – mostly because of the higher risk of recurrences within a year (317–319).

However, this approach can be considered in adults in certain cases if close monitoring is possible, given that one in three patients treated this way will experience a recurrence within 2 years (320). Patient preference should be one element considered when deciding the approach, that is, avoidance of surgery versus higher risk of recurrence with antibiotics.

When antibiotic treatment alone is offered, the suggested duration of treatment is 7 days provided there is a good clinical response with resolution of symptoms. Patients should be re-evaluated to assess the need for surgical intervention if they do not improve on antibiotics alone.

As stated above, in children with acute appendicitis, WHO discourages this approach in the *Pocket book of hospital care for children*: "appendectomy should be done as soon as possible to prevent perforation, peritonitis and abscess formation. It is better to operate and be wrong about the diagnosis than to delay and have peritonitis occur" (31).

Antibiotic treatment

In general, empiric antibiotic treatment should be chosen based on the severity of symptoms (mild or severe), considering local prevalence of resistance, particularly isolates producing ESBLs, since prevalence can vary greatly among different settings (Table 31.5). Individual risk factors for resistant pathogens (e.g. recent antibiotic treatment, colonization with resistant pathogens) could also be considered.

Simplify empiric treatment to a more narrow-spectrum antibiotic (often also called de-escalation) based on culture results (targeted treatment) or based on rapid clinical improvement when no microbiology test results are available. It should be noted that anaerobes are difficult to culture and anaerobic coverage should usually be continued even if no anaerobes are detected in microbiologic samples.

Step-down to oral treatment is based on improvement of symptoms and signs of infection and the ability to take oral antibiotics allowing discharge of the patient home when clinically appropriate.

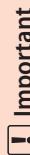
If signs and symptoms persist, abdominal imaging is suggested, or an alternative extra-abdominal source of infection should be considered.

Table 31.5 – Empiric antibiotic treatment for acute appendicitis

Severity	Adults	Children	Total treatment duration	Uncomplicated cases treated with appendectomy: stop antibiotics after surgery if adequate control of the source of infection has been achieved and symptoms have resolved.
Mild cases	First choice Amoxicillin+clavulanic acid ^a IV: 1 g + 200 mg given every 8 hours Oral: 875 + 125 mg given every 8 hours OR Cefotaxime (IV): 2 g given every 8 hours AND Metronidazole (IV/oral): 500 mg given every 8 hours OR Ceftriaxone (IV): 2 g given once a day AND Metronidazole (IV/oral): 500 mg given every 8 hours	First choice Amoxicillin+clavulanic acid ^{a,c} IV: First week of life: 50 mg/kg of amoxicillin/dose given every 12 hours Beyond first week of life: 50 mg/kg of amoxicillin/dose given every 8 hours Oral: 80–90 mg/kg/day of amoxicillin component Oral weight bands: 3–< 6 kg: 250 mg of amoxicillin/dose given every 12 hours 6–< 10 kg: 375 mg of amoxicillin/dose given every 12 hours 10–< 15 kg: 500 mg of amoxicillin/dose given every 12 hours 15–< 20 kg: 750 mg of amoxicillin/dose given every 12 hours ≥ 20 kg: 500 mg of amoxicillin/dose given every 8 hours or 1 g of amoxicillin/dose given every 12 hours		

**Note**

Mild cases are defined as patients who are not critically ill with no signs of sepsis or septic shock.
 Severe cases are defined as patients who are critically ill with signs of sepsis or septic shock.



Where more than one antibiotic is recommended for an infection, they are listed in alphabetical order and they should be considered equal treatment options, unless otherwise indicated.

continues

Table 31.5 continued

Severity	Adults	Children	Total treatment duration
Mild cases	<p>Second choice</p> <p>Ciprofloxacin^b (oral): 500 mg given every 12 hours AND</p> <p>Metronidazole (IV/oral): 500 mg given every 8 hours</p> <p>(Ciprofloxacin and metronidazole have excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function.)</p>	<p>OR</p> <p>Ampicillin (IV):</p> <ul style="list-style-type: none"> First week of life: 50 mg/kg/dose given every 12 hours Beyond first week of life: 50 mg/kg/dose given every 8 hours <p>AND</p> <p>Gentamicin (IV):</p> <ul style="list-style-type: none"> Neonates: 5 mg/kg given once daily Children: 7.5 mg/kg given once daily <p>AND</p> <p>Metronidazole (IV/oral):</p> <ul style="list-style-type: none"> Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg) Children: 7.5 mg/kg/dose given every 8 hours <p>Oral weight bands:</p> <ul style="list-style-type: none"> 3–< 6 kg: 30 mg given every 8 hours 6–< 10 kg: 50 mg given every 8 hours 10–< 15 kg: 100 mg given every 8 hours 15–< 20 kg: 150 mg given every 8 hours 20–< 30 kg: 200 mg given every 8 hours ≥ 30 kg: use adult dose <p>OR</p>	<p>Complicated cases treated with appendectomy: 5 days if adequate control of the source of infection has been achieved and symptoms have resolved.</p> <p>Uncomplicated cases treated with antibiotics alone: 7 days with close clinical monitoring and re-evaluation for surgery if symptoms do not resolve.</p>

continues



Table 31.5 continued

Severity	Adults	Children	Total treatment duration
Mild cases		<p>Cefotaxime (IV): 50 mg/kg/dose given every 8 hours AND</p> <p>Metronidazole (IV/oral):</p> <ul style="list-style-type: none"> Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg) Children: 7.5 mg/kg/dose given every 8 hours <p>Oral weight bands</p> <p>3–< 6 kg: 30 mg given every 8 hours 6–< 10 kg: 50 mg given every 8 hours 10–< 15 kg: 100 mg given every 8 hours 15–< 20 kg: 150 mg given every 8 hours 20–< 30 kg: 200 mg given every 8 hours ≥ 30 kg: use adult dose</p> <p>OR</p>	

Continues

Table 31.5 continued

Severity	Adults	Children	Total treatment duration
Mild cases		<p>Ceftriaxone (IV): 80 mg/kg/dose given once a day AND</p> <p>Metronidazole (IV/oral):</p> <ul style="list-style-type: none"> Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg) Children: 7.5 mg/kg/dose given every 8 hours <p>Oral weight bands</p> <p>3–< 6 kg: 30 mg given every 8 hours 6–< 10 kg: 50 mg given every 8 hours 10–< 15 kg: 100 mg given every 8 hours 15–< 20 kg: 150 mg given every 8 hours 20–< 30 kg: 200 mg given every 8 hours ≥ 30 kg: use adult dose</p>	

continues

Table 31.5 continued

Severity	Adults	Children	Total treatment duration
Mild cases			
		Second choice Ciprofloxacin (IV/oral): 15 mg/kg/dose, given every 12 hours Oral weight bands 3-< 6 kg: 50 mg given every 12 hours 6-< 10 kg: 100 mg given every 12 hours 10-< 15 kg: 150 mg given every 12 hours 15-< 20 kg: 200 mg given every 12 hours 20-< 30 kg: 300 mg given every 12 hours ≥ 30 kg: use adult dose AND	

continues

Table 31.5 continued

Severity	Adults	Children	Total treatment duration
Mild cases			
		Metronidazole (IV/oral): <ul style="list-style-type: none"> • Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg) • Children: 7.5 mg/kg/dose given every 8 hours Oral weight bands	
		3–< 6 kg: 30 mg given every 8 hours 6–< 10 kg: 50 mg given every 8 hours 10–< 15 kg: 100 mg given every 8 hours 15–< 20 kg: 150 mg given every 8 hours 20–< 30 kg: 200 mg given every 8 hours ≥ 30 kg: use adult dose	(Ciprofloxacin and metronidazole have excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function)

continues

continues

Table 31.5 continued

Severity	Adults	Children	Total treatment duration
Severe cases	<p>First choice</p> <p>Cefotaxime (IV): 2 g given every 8 hours AND Metronidazole (IV/oral): 500 mg given every 8 hours</p> <p>OR</p> <p>Ceftriaxone (IV): 2 g given once a day AND Metronidazole (IV/oral): 500 mg given every 8 hours</p> <p>OR</p> <p>Piperacillin+tazobactam^d (IV): 4 g + 500 mg given every 6 hours</p>	<p>First choice</p> <p>Ampicillin (IV):</p> <ul style="list-style-type: none"> First week of life: 50 mg/kg/dose given every 12 hours Beyond first week of life: 50 mg/kg/dose given every 8 hours <p>AND</p> <p>Gentamicin (IV):</p> <ul style="list-style-type: none"> Neonates: 5 mg/kg given once a day Children: 7.5 mg/kg given once a day <p>AND</p> <p>Metronidazole (IV/oral)</p> <ul style="list-style-type: none"> Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg) Children: 7.5 mg/kg/dose given every 8 hours <p>Second choice</p> <p>Meropenem^e (IV): 1 g given every 8 hours</p>	<p>Uncomplicated cases treated with appendectomy:</p> <ul style="list-style-type: none"> stop antibiotics after surgery if adequate control of the source of infection has been achieved and symptoms have resolved. <p>Complicated cases treated with appendectomy:</p> <ul style="list-style-type: none"> 5 days if adequate control of the source of infection has been achieved and symptoms have resolved. <p>Second choice</p> <p>Meropenem^d (IV): 20 mg/kg/dose given every 8 hours</p>

Table 31.5 continued

Severity	Adults	Children	Total treatment duration
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Uncomplicated cases treated with antibiotics alone: 7 days
with close clinical monitoring and re-evaluation for surgery if symptoms do not resolve.

IV. intravenous.

Note: All dosages are for normal renal and hepatic function.

^a Prevalence of resistance to amoxicillin+clavulanic acid among *Escherichia coli* isolates is high in some settings and this option should be considered taking local microbiology data into consideration where available.

^b The use of fluoroquinolones (such as ciprofloxacin) can be associated with important side-effects including: (i) mental health disturbances such as disorientation, agitation, nervousness, memory impairment and delirium; (ii) serious blood sugar disturbances such as hypoglycaemic coma; (iii) increased risk of tendonitis and tendon rupture; (iv) worsening symptoms in those with myasthenia gravis; and (v) potential irreversible neuropathy (serious nerve damage).

^c Oral liquid formulations must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures.

^d Of note, piperacilllin+tazobactam offers anti-*Enterococcus* coverage, which the other options listed for adults do not. Ampicillin would be another appropriate option, but it was not listed in this table as it is not currently in the EML for this indication, while it is listed for children.

^e Meropenem should not be considered for routine use for all severe cases but only in complicated cases (i.e. abscess and/or peritonitis) in settings with a high prevalence of extended-spectrum beta-lactamase-producing Enterobacteriaceae or in patients with known prior colonization, treated with multiple antibiotic courses or at risk of infections with pathogens resistant to the first-choice option. Empiric use of a Reserve antibiotic could be considered exceptionally in very select cases of seriously ill patients with peritonitis failing to respond to carbapenems or that have previously been treated for infections caused by carbapenem-resistant pathogens or that are known to be colonized with multidrug-resistant Gram-negative bacteria. Known to be susceptible to the selected Reserve antibiotic. Please refer to the chapter on Reserve antibiotics for the definition and list of Reserve antibiotics included in the EML and EMLC.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.



Uncomplicated cases treated with appendectomy

In patients with uncomplicated appendicitis, antibiotic treatment can be stopped once surgery is performed provided adequate control of the source of infection was achieved and symptoms have resolved. The rationale for stopping antibiotics is that in these cases the source of infection is considered to have been eliminated with surgery.

Complicated cases treated with appendectomy

In patients with complicated appendicitis, a total of **5 days** of antibiotic treatment is usually adequate, provided there is good clinical recovery and the source of infection was eliminated with surgery (321–323).

32. Intra-abdominal infections – acute diverticulitis

Key messages

- Uncomplicated cases (without peritonitis or abscess) in an immunocompetent patient are usually self-limiting and do not require antibiotic treatment.
- Complicated cases and cases in immunocompromised patients need treatment based on severity of symptoms (mild or severe) with broader-spectrum agents for severe cases.
- Treatment should also be active against anaerobes as these pathogens are often involved in intra-abdominal infections.
- In complicated cases, treatment with 4 days of antibiotics is sufficient once primary source control is achieved surgically.

Definition

Acute diverticulitis is the acute inflammation of diverticula (sac-like protrusions of the wall of the colon) that can cause severe abdominal pain. Acute diverticulitis is usually classified as uncomplicated when there is no involvement of the peritoneal cavity and the inflammation is localized to the diverticula, for example, no perforation, no abscess, no diffuse peritonitis. When the inflammation extends to the peritoneal cavity or when an abscess is present, the condition is considered complicated.

Acute diverticulitis

Intra-abdominal infection • Page 1 of 2

Definition

Acute inflammation of diverticula (sac-like protrusions of the wall of the colon) that can cause severe abdominal pain

Classification based on complexity:

- **Uncomplicated:** No involvement of peritoneal cavity and no abscess
- **Complicated:** Involvement of the peritoneal cavity and/or abscess

Classification based on severity:

- **Mild:** Not critically ill with no signs of sepsis or septic shock
- **Severe:** Critically ill with signs of sepsis or septic shock

Diagnosis

Clinical Presentation

- Acute pain in the left or right lower abdominal quadrants with chills, nausea and vomiting; fever ($\geq 38.0^{\circ}\text{C}$) may be absent
- Left diverticulitis is more common in Europe and North America, right diverticulitis in Asia

Important:

- Consider peritonitis if severe pain, diffuse rebound tenderness upon sudden release of pressure on the abdomen and abdominal muscular tensing
- Hypotension and signs of organ hypoperfusion (e.g. reduced urine output) are potential signs of sepsis /septic shock that need urgent treatment

Microbiology Tests

Mild cases:

Severe cases:

- Blood cultures (ideally before starting antibiotics)
- Microscopy and culture of abscess fluid material (if this can be drained) to adjust empiric antibiotic treatment

Other Laboratory Tests

- **Determine disease severity and help identify a bacterial infection:** White blood cell count, C-reactive protein and/or procalcitonin
- If sepsis is suspected consider additional laboratory tests (see sepsis infographic)(see sepsis infographic)

Imaging

Abdominal ultrasound or CT of the abdomen (depending on availability) to confirm the diagnosis



Most Likely Pathogens

Bacteria:

- Enterobacteriales (mostly *Escherichia coli* including multidrug-resistant strains)
- *Streptococcus* spp. (e.g. of the *S. anginosus* group)
- *Enterococcus* spp.
- Anaerobes (mostly *Bacteroides* spp.)

Fungi (consider if recent course of antibiotics):

- Mostly *Candida albicans*

Parasites (consider in endemic settings):

- *Enterobius vermicularis* (pinworm)

Rx Treatment (Section 1 of 2)



Clinical Considerations

• **Uncomplicated cases in immunocompetent patients:** antibiotics **not** needed if there are no systemic signs of infection; if these cases do not resolve spontaneously after 2-3 days, consider antibiotics

• **Uncomplicated cases in severely immunocompromised patients:** treat with antibiotics alone (if close follow up possible)

• **Complicated cases:** treat with antibiotics and surgical source control (e.g. drainage of large abscesses >5 cm or colonic resection)

Empiric antibiotic treatment should be guided by:

The severity of symptoms, considering local prevalence of resistance (particularly of isolates of Enterobacteriales producing ESBL) and individual risk factors for resistant pathogens

Important:

• **Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or rapid clinical improvement if culture results unavailable

• **Step down to oral treatment** is based on improvement of symptoms, signs of infection and the ability to take oral antibiotics

• **If signs and symptoms persist**, abdominal imaging is suggested, or an alternative extra-abdominal source of infection should be considered

Acute diverticulitis

Intra-abdominal infection • Page 2 of 2

Rx Treatment (Section 2 of 2)



Antibiotic Treatment Duration

- Most mild cases do not need antibiotic treatment
- Treatment with antibiotics alone: 4 days (if good clinical recovery and symptoms resolved)
- Treatment with antibiotics & surgical source control: Stop 4 days after adequate source control (surgery) is achieved otherwise, continue until clinically stable and afebrile



Severe Cases

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice



Cefotaxime 2 g q8h IV

OR



Ceftriaxone 2 g q24h IV

COMBINED WITH



Metronidazole 500 mg q8h IV/ORAL

OR



Piperacillin+tazobactam 4 g + 500 mg q6h IV

Second Choice



Meropenem 1 g q8h IV

Consider meropenem only in complicated cases if there is a high risk of infection with ESBL-producing Enterobacteriales



Mild Cases

Most mild cases do not need antibiotic treatment

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice



Amoxicillin+clavulanic acid 875 mg + 125 mg
ACCESS q8h ORAL

OR



Cefotaxime 2 g q8h IV

OR



Ceftriaxone 2 g q24h IV

COMBINED WITH



Metronidazole 500 mg q8h IV/ORAL

Second Choice



Ciprofloxacin 500 mg q12h ORAL

COMBINED WITH



Metronidazole 500 mg q8h IV/ORAL

Metronidazole has excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function



Pathophysiology

In cases of acute diverticulitis, the first step in the pathogenesis is the formation of diverticula (i.e. diverticulosis). Diverticula are sac-like protrusions of the colonic wall. The mechanism leading to diverticulitis of the colon is the erosion of the wall of the diverticula by increased intraluminal pressure. If bacterial contamination and chemical irritation (usually due to leakage of sterile fluids that are irritants to the peritoneum; for example, bile or blood) of the peritoneal cavity occur, peritonitis develops. Intra-abdominal abscesses (i.e. the presence of a collection of infected fluid in the peritoneal cavity) can also form as a result of a complicated diverticulitis.

Epidemiology

Acute diverticulitis is common in high-income countries and mostly affects adults older than 50 years; its incidence increases with age. The condition is less frequent in many low- and middle-income countries, probably because of differences in the fibre content of diets. The overall risk of developing acute diverticulitis in patients with diverticulosis is low (324,325) and most cases (> 80%) are uncomplicated. Nonetheless, acute diverticulitis is still a common cause of colonic resection (326).

Most likely pathogens

The most common pathogens involved in acute diverticulitis are Gram-negative bacilli and anaerobic bacteria from the intestinal microbiota (Table 32.1). Infections are often caused by more than one pathogen and may include fungal pathogens, especially in patients pre-treated with antibiotics. Certain parasites need to be considered in the differential diagnosis of abdominal pain in endemic settings.

Table 32.1 – Pathogens most frequently associated with acute diverticulitis (in descending order of frequency)

Bacteria	Fungi	Parasites
Enterobacteriales (mostly <i>Escherichia coli</i>) and other Gram-negative bacteria such as <i>Pseudomonas aeruginosa</i> and <i>Acinetobacter baumannii</i> (including multidrug-resistant strains such as those producing ESBL and carbapenemases)	Mostly <i>Candida albicans</i>	<i>Enterobius vermicularis</i> (pinworm)
<i>Streptococcus</i> spp. (e.g. of the <i>Streptococcus anginosus</i> group – old name: <i>Streptococcus milleri</i>)		
<i>Enterococcus</i> spp.		
Anaerobes (mostly <i>Bacteroides</i> spp.)		

ESBL: extended spectrum beta-lactamases.

Clinical presentation

Acute diverticulitis should be considered as a possible diagnosis in all cases of acute pain in the left lower abdominal quadrant. It should be noted that while left lower diverticulitis is more prevalent in European countries and North America, right lower diverticulitis is more common in Asia.

Fever ($\geq 38.0^{\circ}\text{C}$), chills, nausea and vomiting may be present, mostly in complicated diverticulitis. Severe pain, diffuse rebound tenderness on sudden release of pressure on the abdomen and abdominal muscular defence are usually present in cases of peritonitis. Hypotension and signs of organ hypoperfusion (e.g. reduced urine output) can be present in cases of organ failure and are a medical and /or surgical emergency. Please also refer to the chapter on sepsis if suspected.

Laboratory tests

Patient microbiology tests

In mild cases, routine microbiology tests are not usually needed and basing antibiotic treatment on pathogens cultured from the abdominal cavity at the time of operation is not recommended. Certain microbiology tests (Table 32.2) could be considered in severely ill patients to adjust empiric antibiotic treatment once the results of antibiotic susceptibility tests are available.

Table 32.2 – Microbiology tests to consider in severe cases as indicated in the EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
Blood cultures and antimicrobial susceptibility testing	To detect bacterial bloodstream infections	Health care facilities with clinical laboratories
Microscopy, culture and antimicrobial susceptibility testing of abscess fluid material when this can be drained	First step to detect and identify bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics.

Other tests

Laboratory tests can be used to complement the clinical examination and medical history. Based on availability, Table 32.3 indicates several tests that could be considered in the patient's initial assessment and to help guide the duration of antibiotic treatment.

Table 32.3 – Laboratory tests (other than microbiology) that may help assess the severity of disease and the identification of a bacterial infection as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
White blood cell count	To help in the diagnosis of infections	Health care facilities with clinical laboratories
C-reactive protein	To detect inflammation as an indicator of various conditions (e.g. sepsis) ^a	Health care facilities with clinical laboratories
Procalcitonin	To guide antibiotic therapy or discontinuation in sepsis	Only in tertiary care facilities

EDL: Model List of Essential In Vitro Diagnostics.

^a A cut-off value of 150–170 mg/L for C-reactive protein is sometimes used to discriminate between mild/uncomplicated cases and severe/complicated cases (327,328).

Using microbiology surveillance data

Routine surveillance of pathogens cultured from the abdominal cavity is not recommended.

Empiric guidance given by the AWaRe book could be reviewed and adapted based on local clinically relevant microbiology surveillance data. For example, clinically relevant isolates for this infection would be blood culture data from patients on surgical wards with intra-abdominal infections.

Imaging

Imaging is helpful to confirm acute diverticulitis. In settings where CT scanning is available, a scan of the abdomen is the best imaging method to confirm acute diverticulitis and grade its severity. However, because ultrasound is more widely available, abdominal ultrasound can also be considered a valid alternative.

Treatment

Complicated cases

Patients with suspected or confirmed complicated acute diverticulitis or with recurrent attacks should be promptly referred for surgical consultation.

Uncomplicated cases

In immunocompetent patients with uncomplicated diverticulitis (i.e. localized diverticular inflammation) and no signs of systemic inflammation, antibiotic treatment is usually not needed. In these patients, uncomplicated diverticulitis can be considered a self-limiting condition where antibiotics do not offer a benefit in terms of clinical resolution and recurrence (329,330).

Antibiotic treatment

In patients with complicated acute diverticulitis or in uncomplicated cases requiring antibiotic treatment (e.g. cases that did not resolve spontaneously after 2–3 days without antibiotic treatment) or in severely immunocompromised patients, empiric antibiotic treatment should be chosen based on the severity of symptoms (mild or severe). It is important to take into account local prevalence of resistance, particularly isolates of Enterobacteriales producing ESBLs, since the prevalence can vary greatly among settings (Table 32.4). Individual risk factors for resistant pathogens (e.g. recent antibiotic treatment, colonization with resistant

pathogens) should also be considered. In settings where resistance to carbapenems is highly prevalent, alternative antibiotic options including Reserve antibiotics – see chapter on Reserve antibiotics – could be considered in severely ill patients who are deteriorating. In complicated cases (i.e. presence of perforation or abscess), empiric antibiotic treatment should be started as soon as the diagnosis is suspected and could be stopped 4 days after control of the source of infection is achieved provided there is good clinical recovery.

Patients with small abscesses (< 5 cm) or pericolic gas are usually treated with systemic antibiotic treatment alone provided close clinical follow up is possible and there is a good clinical response and symptoms have resolved (331).

In patients with large abscesses (e.g. percutaneous drainage of abscesses > 5 cm) and patients with peritonitis, control of the source of infection (e.g. colonic resection), in addition to systemic antibiotic treatment, is needed.

Simplify empiric treatment to a more narrow-spectrum antibiotic (often also called de-escalation) based on culture results (targeted treatment) or based on rapid clinical improvement when no microbiology test results are available.

Step-down to oral treatment is based on improvement of symptoms and signs of infection and the ability to take oral antibiotics allowing discharge of the patient home when clinically appropriate.

If signs and symptoms persist, abdominal imaging is suggested, or an alternative extra-abdominal source of infection should be considered.

Table 32.4 – Empiric antibiotic treatment for acute diverticulitis**Note**

Mild cases are defined as patients who are not critically ill with no signs of sepsis or septic shock.

Severe cases are defined as patients who are critically ill with signs of sepsis or septic shock.

! Important

Antibiotics are listed in alphabetical order but they should all be considered equal treatment options, unless otherwise indicated.

Severity	Adults	Total treatment duration
Mild cases These can be uncomplicated cases that did not resolve spontaneously after 2–3 days without antibiotics or complicated cases with mild symptoms.	<p>First choice</p> <p>Amoxicillin+clavulanic acid IV: 1 g + 200 mg given every 8 hours Oral: 875 + 125 mg given every 8 hours</p> <p>OR</p> <p>Cefotaxime (IV): 2 g given every 8 hours AND Metronidazole (IV/oral): 500 mg given every 8 hours</p> <p>OR</p> <p>Ceftriaxone (IV): 2 g given once a day AND Metronidazole (IV/oral): 500 mg given every 8 hours</p> <p>Second choice</p> <p>Ciprofloxacin^a (oral): 500 mg given every 12 hours AND Metronidazole (IV/oral): 500 mg given every 8 hours</p> <p>(Ciprofloxacin and metronidazole have excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function.)</p>	Continue for 4 days after control of the source of infection is achieved provided that there is good clinical recovery.

continues

Table 32.4 *continued*

Severity	Adults	Total treatment duration
Severe cases	<p>First choice</p> <p>Cefotaxime (IV): 2 g given every 8 hours AND Metronidazole (IV/oral): 500 mg given every 8 hours OR Ceftriaxone (IV): 2 g given once a day AND Metronidazole (IV/oral): 500 mg given every 8 hours OR Piperacillin+tazobactam^b (IV): 4 g + 500 mg given every 6 hours</p> <p>Second choice</p> <p>Meropenem^c (IV): 1 g given every 8 hours</p>	Continue for 4 days after control of the source of infection is achieved provided that there is good clinical recovery.

EML: Model List of Essential Medicines; IV: intravenous.

Note: All dosages are for normal renal and hepatic function.

^a The use of fluoroquinolones (such as ciprofloxacin) can be associated with important side-effects including: (i) mental health disturbances such as disorientation, agitation, nervousness, memory impairment and delirium; (ii) serious blood sugar disturbances such as hypoglycaemic coma; (iii) increased risk of tendinitis and tendon rupture; (iv) worsening symptoms in those with myasthenia gravis; and (v) potential irreversible neuropathy (serious nerve damage).

^b Of note, piperacillin+tazobactam offers anti-*Enterococcus* coverage, which the other options listed for adults do not. Ampicillin would be another appropriate option, but it was not listed in this table as it is not currently in the EMR for this indication, while it is listed for children.

^c Meropenem should not be considered for routine use for all severe cases but only in complicated cases (i.e. abscess and/or peritonitis) in settings with a high prevalence of extended-spectrum beta-lactamase-producing Enterobacteriales or in patients with known prior colonization, treated with multiple antibiotic courses or at risk of infections with pathogens resistant to the first choice option. Empiric use of a Reserve antibiotic could be considered exceptionally in very select cases of seriously ill patients failing to respond to carbapenems or who have previously been treated for infections caused by carbapenem-resistant pathogens or who are known to be colonized with multidrug-resistant Gram-negative bacteria known to be susceptible to the selected Reserve antibiotic. Please refer to the chapter on Reserve antibiotics for the definition and list of Reserve antibiotics included in the WHO EMR.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

33. Intra-abdominal infections – *Clostridioides difficile* infection

Key messages

- Most cases of *Clostridioides difficile* infection occur in patients with current or recent antibiotic use. Good antibiotic prescribing practices – avoidance of antibiotics when not needed, preference for Access antibiotics wherever possible – are key for the control of *Clostridioides difficile* infection.
- If *Clostridioides difficile* infection is confirmed or suspected, all antibiotics that are not necessary should be stopped.
- Use oral antibiotics to treat *Clostridioides difficile* infection wherever possible.
- Adopt infection control measures to prevent transmission.
- *Clostridioides difficile* diarrhoea may resolve slowly over days, but a clinical deterioration of a patient on appropriate antibiotics should lead to escalation of treatment and a surgical referral.



Other relevant WHO resources (please check regularly for updates)

- Infection prevention and control – health topic (332).

Definition

Clostridioides difficile (formerly *Clostridium difficile*) infection is an infection of the colon caused by the bacterium *Clostridioides difficile*. The infection occurs mostly in patients with current or recent antibiotic use. For surveillance purposes, *Clostridioides difficile* infection is usually classified as either health care-associated or community-associated based on where the infection was acquired, which is determined by the timing of onset of symptoms in relation to last contact with any health care setting.

Clostridioides difficile infection (CDI)

Intra-abdominal infection

Definition

Infection of the colon caused by the bacterium *C. difficile* that occurs mostly in patients with current/recent antibiotic use and with regular exposure to healthcare settings

Diagnosis

Clinical Presentation

Usually diarrhea (≥ 3 unformed/liquid stools in 24 hrs or more than normal for individual) with no other plausible cause +/- abdominal pain, cramping and fever

Severe cases (e.g. pseudomembranous colitis):

- Severe abdominal pain, high fever; organ dysfunction
- Toxic megacolon presents with signs of acute surgical abdomen and/or sepsis (diarrhea is often absent)

Microbiology Tests

- Consider testing symptomatic patients with no other plausible reason for diarrhea especially if recent or current exposure to antibiotics
- Currently no single test to diagnose CDI is completely reliable and the best approach remains controversial

Two commonly used approaches:

1. Start with highly sensitive test to detect *C. difficile*, if positive follow with a test to confirm toxin production
 - If toxin test negative: Consider *C. difficile* colonization
2. Perform two tests simultaneously, one to detect the presence of *C. difficile* and one to detect toxin production
 - Concordant results can reliably confirm (both tests positive) or exclude (both tests negative) infection
 - If results conflict and patient is symptomatic, treatment should be based on the pre-test probability of *C. difficile* infection

Important: in case of confirmed CDI, do not repeat testing during the same episode and do not test to confirm the resolution of the infection at the end of treatment

Other Laboratory Tests

Mild cases: Not usually needed

Severe cases:

- White blood cell count
- Creatinine and electrolytes

Imaging

Usually not needed unless a complication is suspected; in these cases, consider abdominal CT

Pathogen

C. difficile

- Gram-positive spore-forming bacterium widely present in the environment that can be acquired through ingestion of spores
- Infection can be caused by strains producing toxins when the intestinal mucosa of the colon is inflamed and disrupted

NAP1/027

- *C. difficile* toxigenic strain with a particular virulence that caused outbreaks in recent years especially in North America

Rx Treatment

Clinical Considerations

- Discontinue any other antibiotics except those treating *C. difficile* infection as soon as possible and adopt infection control measures to prevent transmission
- Always recommend rehydration in patients with diarrhea; anti-diarrheal drugs not routinely necessary
- Diarrhea may resolve slowly over days, but clinical deterioration of a patient on appropriate treatment should precipitate escalation of treatment and a surgical referral

Antibiotic Treatment Duration

10 days

Rx Antibiotic Treatment

Refers to a first episode, not recurrences (within 8 weeks of previous episode)

All dosages are for normal renal function

First Choice

 Metronidazole 500 mg q8h ORAL
ACCESS

Second Choice

 Vancomycin 125 mg q6h ORAL
WATCH

In severe cases: Oral vancomycin is preferred; vancomycin dose can be increased to 500 mg q6h and can be given in combination with IV metronidazole

***Clostridioides difficile* infection (CDI)**

Intra-abdominal infection • Page 1 of 2

Definition

Infection of the colon caused by the bacterium *C. difficile* that occurs mostly in patients with current/recent antibiotic use and with regular exposure to healthcare settings

Pathogen

C. difficile

- Gram-positive spore-forming bacterium widely present in the environment that can be acquired through ingestion of spores
- Infection can be caused by toxigenic strains when the intestinal mucosa of the colon is inflamed and disrupted

NAP1/027

- C. difficile* toxigenic strain with a particular virulence that caused outbreaks in recent years especially in North America

Diagnosis

Clinical Presentation

Usually diarrhea (≥ 3 unformed/liquid stools in 24 hrs or more than normal for individual) with no other plausible cause +/- abdominal pain, cramping and fever

Severe cases (e.g. pseudomembranous colitis):

- Severe abdominal pain, high fever, organ dysfunction
- Toxic megacolon presents with signs of acute surgical abdomen and/or sepsis (diarrhea is often absent)

Clinical disease is rare in young children (esp. <2 years); they are often asymptomatic carriers

Microbiology Tests

- Consider testing symptomatic patients with no other plausible reason for diarrhea especially if recent or current exposure to antibiotics
- Testing <1 year of age is not recommended due to high prevalence of colonization in this age group**
- Currently no single test to diagnose CDI is completely reliable and the best approach remains controversial

Two commonly used approaches:

- Start with highly sensitive test to detect *C. difficile*, if positive follow with a test to confirm toxin production
 - If toxin test negative: Consider *C. difficile* colonization
- Perform two tests simultaneously, one to detect the presence of *C. difficile* and one to detect toxin production
 - Concordant results can reliably confirm (both tests positive) or exclude (both tests negative) infection
 - If results conflict and patient is symptomatic, treatment should be based on the pre-test probability of *C. difficile* infection

Other Laboratory Tests

Mild cases:

- Not usually needed

Severe cases:

- White blood cell count
- Creatinine and electrolytes

Imaging

Usually not needed unless a complication is suspected; in these cases, consider abdominal CT

Important: in case of confirmed CDI, do not repeat testing during the same episode and do not test to confirm the resolution of the infection at the end of treatment

***Clostridioides difficile* infection (CDI)**

Intra-abdominal infection • Page 2 of 2

Rx Treatment

Clinical Considerations

- Discontinue any other antibiotics except those treating *C. difficile* infection as soon as possible and adopt infection control measures to prevent transmission
- Always recommend rehydration in patients with diarrhea; anti-diarrheal drugs not routinely necessary
- Diarrhea may resolve slowly over days, but clinical deterioration of a patient on appropriate treatment should precipitate escalation of treatment and a surgical referral



Antibiotic Treatment Duration

10 days

Rx Antibiotic Treatment

First episode, not recurrences (within 8 weeks of previous episode)

All dosages are for normal renal function

First Choice



Metronidazole ORAL

- ACCESS**
- Neonates: 7.5 mg/kg/dose q12h
 - Children: 7.5 mg/kg/dose q8h
 - Oral weight bands:

3-<6 kg	30 mg q8h
6-<10 kg	50 mg q8h
10-<15 kg	100 mg q8h
15-<20 kg	150 mg q8h
20-<30 kg	200 mg q8h
≥30 kg	500 mg q8h

Second Choice



Vancomycin 5-10 mg/kg/dose q6h ORAL

In severe cases: Oral vancomycin is preferable to metronidazole

Pathogen

Clostridioides difficile is a Gram-positive anaerobic spore-forming bacterium that is widely present in the environment, especially in hospitals and long-term care facilities where spores can persist in the environment for months. Toxigenic and non-toxigenic strains exist but *Clostridioides difficile* infection is only associated with toxigenic strains. Of these strains, BI/NAP1/027 is particularly virulent and in recent years has caused outbreaks, especially in North America.

Pathophysiology

Clostridioides difficile infection is acquired through the ingestion of toxigenic spores of the Gram-positive bacterium *Clostridioides difficile*. Spores are present in stools of symptomatic patients and asymptomatic carriers. Once ingested, the spores can colonize the colonic mucosa, germinate into vegetative bacteria, multiply and produce toxins (toxin A and/or B, binary toxin). In most cases, patients remain asymptomatic. However, if disruption of the normal colonic mucosa and intestinal microbiota occurs (e.g. after exposure to antibiotics or cytotoxic chemotherapy) and if there is no adequate antibody response to *Clostridioides difficile* toxins, clinical disease can occur. This disease ranges in severity, from mild diarrhoea to life-threatening pseudomembranous colitis and toxic megacolon. Not all strains of *Clostridioides difficile* produce toxins. Recurrent infections are a frequent problem, especially in elderly and immunocompromised patients, and the risk of relapse increases with each episode.

Epidemiology

Clostridioides difficile infection is the most frequent cause of health care-associated infectious diarrhoea and is associated with prolonged hospital stay and increased costs (333,334).

Common risk factors for *Clostridioides difficile* infection include age ≥ 65 years, recent use of antibiotics and previous hospital admission (335). Almost all antibiotics can increase the risk of infection but clindamycin, cephalosporins and fluoroquinolones have been most consistently associated with increased risk of *Clostridioides difficile* infection – the risk may vary across time and settings based on the resistance/susceptibility of *Clostridioides difficile* to certain antibiotics. Cytotoxic chemotherapy can also increase the risk of infection because inflammation of the intestinal mucosa (i.e. mucositis) is often present. Patients regularly exposed to health care settings (e.g. patients on dialysis) are also at increased risk.

In young children (especially younger than 2 years), clinical disease is rare, probably because cellular receptors to *Clostridioides difficile* toxins develop later in life; therefore, young children are often asymptomatic carriers.

Clinical presentation

The most common symptom of *Clostridioides difficile* infection is diarrhoea, usually defined as the presence of at least three unformed or liquid stools in 24 hours (with no other plausible cause), or more than what is normal for that individual. Abdominal pain, cramping and fever may also be present. Signs of severe disease include marked leukocytosis (e.g. white blood cell count $> 15 \times 10^9/\text{L}$ or $15\ 000/\mu\text{L}$), severe abdominal pain, high fever and organ dysfunction, for example, elevated serum creatinine and decreased serum albumin.

Rarely, *Clostridioides difficile* infection can present with signs and symptoms of toxic megacolon. Patients with this presentation often do not have diarrhoea but have signs of acute surgical abdomen and/or sepsis and may need to be admitted to the intensive care unit. The absence of diarrhoea does therefore not exclude *Clostridioides difficile* infection. Severe cases may require a colectomy for source control.

Laboratory tests

Patient microbiology tests

Where available, a stool test in a symptomatic patient to detect toxigenic *Clostridioides difficile* (or toxin production) should be considered if the patient has no other reasons for diarrhoea, such as recent use of laxatives. The rationale is that, if infection is detected, an effective treatment can be provided, other antibiotics can be stopped if possible and infection control measures can be put in place (or reinforced) to limit transmission. Testing is not usually recommended in infants because of the high prevalence of colonization; colonization here refers to the presence of *Clostridioides difficile* in the stool of healthy children.

Even though the current version of the WHO EDL (6) does not include specific tests for *Clostridioides difficile* detection, Table 33.1 suggests tests that could be considered based on local availability.

Currently, no single test is completely reliable in diagnosing *Clostridioides difficile* infection and the best diagnostic approach to use is controversial (336). The two following approaches are commonly used and could be considered based on local available tests and laboratory protocols. For both approaches, it is important to limit testing to patients with a sufficiently high pre-test probability of *Clostridioides difficile* infection, for example, with diarrhoea and risk factors such as current or recent antibiotic use.

- Start with a highly sensitive test (nucleic acid amplification test or glutamate dehydrogenase test depending on local availability) that can detect the presence of *Clostridioides difficile*. Then, confirm positive results with a test that can detect toxin production such as the toxin A/B enzyme immunoassay. It should be noted

that if the toxin production test is negative, the patient could be colonized with *Clostridioides difficile* and therefore an alternative reason for diarrhoea should be sought.

- Start with two tests at the same time – glutamate dehydrogenase test and toxin A/B enzyme immunoassay. If both tests are positive, *Clostridioides difficile* infection can be reliably confirmed; if both are negative, *Clostridioides difficile* infection can be excluded. If the results conflict, then symptomatic patients should be treated if the pre-test probability of *Clostridioides difficile* infection is sufficiently high, for example, with recent antibiotic exposure and absence of alternative causes of diarrhoea.

In patients diagnosed with *Clostridioides difficile* infection, repeat testing during the same episode and test of cure are not needed and should be avoided.

Table 33.1 – Microbiology tests to consider if *Clostridioides difficile* infection is suspected (no test for *Clostridioides difficile* is listed in the third version of the EDL, 2021) (6)

Type of test	Purpose of the test	Comment
<ul style="list-style-type: none"> Culture NAAT GDH antigen test 	To detect toxigenic <i>Clostridioides difficile</i> strains	Usually NAAT (culture would be the reference standard but it is complex to perform and has a long turnaround time). With NAAT [®] , the main disadvantage is the high sensitivity of the test that could lead to over-diagnosis and overtreatment.
GDH antigen test	To detect <i>Clostridioides difficile</i> toxigenic and non-toxigenic strains	The main disadvantage is that this test cannot predict the ability of the strain to produce toxins. However, a negative test will generally exclude <i>Clostridioides difficile</i> infection.

continues

Table 33.1 continued

Type of test	Purpose of the test	Comment
<ul style="list-style-type: none"> • Cytotoxicity assay • Toxin A/B EIA 	To detect <i>Clostridioides difficile</i> toxins	Usually EIA (cytotoxicity assay) would be the reference standard but it is hard to do and has a long turnaround time). With EIA, the main disadvantage is the low sensitivity (i.e. high risk of false negative results).

EDL: Model List of Essential In Vitro Diagnostics; EIA: enzyme immunoassay; GDH: glutamate dehydrogenase; NAAT: Nucleic acid amplification test.

^a NAAT detect the presence of the gene for the toxin not its expression.

Other tests

Routine (non-microbiological) laboratory testing is not always needed. However, for severe cases, certain tests could be considered (Table 33.2) to assess disease severity.

Table 33.2 – Laboratory tests (other than microbiology) to consider if *Clostridioides difficile* infection is suspected as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
White blood cell count	To help in the diagnosis of infections	Health care facilities with clinical laboratories
Creatinine	To monitor kidney function for management of severe infections (i.e. sepsis) and adjustment of the antimicrobial regimen	Health care facilities with clinical laboratories
Electrolytes	To monitor fluid, electrolytes and acid–base balance	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics.

Using microbiology surveillance data

Resistance to metronidazole, vancomycin and multiple other antibiotics has been reported.

Imaging

Imaging is usually not needed unless a complication is suspected. In these cases, a CT scan of the abdomen could be considered.

No antibiotic care

Rehydration (oral or intravenous) should always be recommended in patients with diarrhoea. Anti-diarrhoea medicines are not routinely required because they do not prevent dehydration and do not improve nutritional status (145).

Antibiotic treatment

Note

It is important to discontinue any other antibiotics except those treating the *Clostridioides difficile* infection as soon as possible.

Symptomatic patients diagnosed with *Clostridioides difficile* infection should promptly receive adequate antibiotic treatment as indicated in Table 33.3. Whenever possible, it is also important to stop any other antibiotic that could have favoured *Clostridioides difficile* infection by disrupting the microbiota in the colon. If it is necessary to continue the antibiotic treatment (e.g. because of a clearly documented or high suspicion of a concomitant infection), it is advisable to select antibiotics with lower risk of selecting *Clostridioides difficile* infection, thus avoid ceftriaxone, fluoroquinolones and clindamycin.

Oral treatment with metronidazole is appropriate for a first episode of mild to moderate severity. This antibiotic is also suggested because of concerns that oral vancomycin could favour selection of vancomycin-resistant enterococci in the intestinal microbiota and that the oral formulation may be unavailable or too expensive to consider in some low-resource settings (337,338). However, in severe cases of infection, the current evidence supports the use of oral vancomycin rather than metronidazole, in part because of its benefit in reducing recurrent episodes (337–339). Treatment of recurrent episodes (usually defined as *Clostridioides difficile* infection within 8 weeks of a previous episode) with antibiotics or faecal microbiota transplantation is beyond the scope of this chapter.

Table 33.3 – Antibiotic treatment for a first episode of *Clostridioides difficile* infection

Adults	Children	Total treatment duration
<p>First choice</p> <p>Metronidazole (oral): 500 mg given every 8 hours</p>	<p>First choice</p> <p>Metronidazole (oral):</p> <ul style="list-style-type: none"> • Neonates: 7.5 mg/kg/dose given every 12 hours • Children: 7.5 mg/kg/dose given every 8 hours <p>Oral weight bands:</p> <p>3–< 6 kg: 30 mg given every 8 hours</p> <p>6–< 10 kg: 50 mg given every 8 hours</p> <p>10–< 15 kg: 100 mg given every 8 hours</p> <p>15–< 20 kg: 150 mg given every 8 hours</p> <p>20–< 30 kg: 200 mg given every 8 hours</p> <p>≥ 30 kg: use adult dose</p>	10 days
<p>Second choice</p> <p>Vancomycin (oral^a): 125 mg given every 6 hours</p>	<p>Second choice</p> <p>Vancomycin (oral):</p> <ul style="list-style-type: none"> • Neonates: 5–10 mg/kg/dose given every 6 hours • Children: 5–10 mg/kg/dose given every 6 hours 	

Note: All dosages are for normal renal and hepatic function.

^a Oral vancomycin is preferable to metronidazole in severe cases. If needed, the dose could be increased to 500 mg given every 6 hours. In severe fulminant cases, intravenous metronidazole could be added to treatment with oral vancomycin.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

34. Upper urinary tract infection

Key messages

- Most cases of upper urinary tract infection are caused by *Escherichia coli*.
- A urine culture should be obtained before starting antibiotic treatment.
- Mild cases can be treated with oral antibiotics in the outpatient setting.
- Empiric treatment varies depending on the severity of clinical presentation and underlying risk factors.
- The local prevalence of resistance among *Escherichia coli* urinary isolates needs to be considered if data are available.



Other relevant WHO resources (please check regularly for updates)

- Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, 2013 (31).

Definition

Upper UTIs are acute infections in which pathogens (mostly bacteria from the intestinal microbiota colonizing the skin in the perineal area) reach the kidney/s by ascending through the urethra, bladder and the ureter/s. In addition, pathogens can gain access to the kidney/s through the bloodstream. An infection of the kidney/s is commonly referred to as pyelonephritis. Infections can be community acquired or hospital acquired. The focus of this chapter is on community-acquired pyelonephritis in immunocompetent patients without a urinary catheter.

Complications can occur with upper UTIs because of patient-related risk factors that make the infection more difficult to treat. While there is no universally accepted definition of what constitutes a complicated UTI, upper UTIs in individuals with pre-existing conditions of the urinary tract (e.g. anatomical anomalies and kidney stones) are generally considered complicated. Upper UTIs in pregnant women are also usually considered complicated. Examples of factors that may increase the risk of a complicated upper UTI are shown in Box 34.1.

Box 34.1 – Factors that may increase the risk of a complicated upper urinary tract infection

- Obstruction at any site of the urinary tract
- Foreign body (e.g. urinary catheters and stents)
- Incomplete voiding
- Vesicoureteral reflux
- Recent history of instrumentation
- Male sex
- Pregnancy
- Diabetes
- Immunosuppression
- Health care-associated urinary tract infection

Notes. The list gives some examples but is not aimed to be complete. No widely accepted definition of a complicated urinary tract infection currently exists. Some experts argue that the list above is too long and may result in diagnosing too many patients with a so-called complicated infection. The presence of one or more of these risk factors does not mean that the infection is complicated and in need of a different treatment approach.

Source: Guidelines on urological infections of the European Association of Urology (222).

Upper urinary tract infection

Urinary tract infection • Page 1 of 2

This chapter focuses on community-acquired pyelonephritis in patients with no catheter

Definition

Infection of the kidneys (pyelonephritis) in which microorganisms ascend the urinary tract via the urethra, bladder, ureters or reach the kidneys through the bloodstream

Classification based on complexity:

- **Uncomplicated:** Urinary tract infections (UTI) in individuals with no risk factors for complicated UTI
- **Complicated:** UTI in individuals with structural anomalies of the urinary tract (e.g. kidney stones, anatomical anomalies) or who are immunocompromised and in pregnant women are generally considered complicated (or at risk of complications). UTI in patients with urinary catheters or stents are also considered complicated (not discussed here)



Most Likely Pathogens

Bacteria:

- **Most common:**
 - Enterobacteriales (mostly *Escherichia coli* including multidrug resistant strains such as those producing ESBL and carbapenemases)
- **More rarely:**
 - *Enterococcus* spp.
 - *Streptococcus agalactiae* (group B *Streptococcus*)
 - *Staphylococcus aureus* (rare in uncomplicated UTI, usually in patients with urinary catheters, can be associated with bacteremia)
 - *Pseudomonas aeruginosa*, *Acinetobacter baumannii* (including multidrug-resistant strains especially in patients with recent antibiotic exposure or instrumentation of the urinary tract, rare in uncomplicated UTI)



Diagnosis



Clinical Presentation

- Flank pain, costovertebral angle tenderness, nausea and vomiting, fever and signs of systemic illness +/- symptoms of cystitis
- Severity varies from mild disease (most cases) that can be managed with oral treatment (no nausea/vomiting, low-grade fever) to severe cases requiring intravenous treatment and hospital admission



Other Laboratory Tests

All cases (if upper UTI is suspected clinically):

- Urinalysis (dipstick or microscopy) to detect bacteruria and/or indirect signs of infection (positive leucocyte esterase and nitrites)

Additionally in severe cases:

- White blood cell count, C-reactive protein and/or procalcitonin
- If sepsis is suspected consider additional laboratory tests (see sepsis infographic)



Microbiology Tests

All cases (if upper UTI is suspected clinically):

- Urine culture: Ideally before starting antibiotic treatment
 - The test is considered positive when bacteria are above a certain minimum cut-off that can vary between laboratories
 - A positive urine culture is not always a sign of urinary tract infection or an indication for antibiotic treatment (and urine can also become contaminated during sampling)

Additionally in severe cases:

- Blood cultures: Ideally before starting antibiotic treatment



Imaging

Routine imaging is not necessary but can be considered if urine flow is blocked or an abscess is suspected

Upper urinary tract infection

Urinary tract infection • Page 2 of 2

Rx Treatment

Clinical Considerations

- Patients with upper urinary tract infection are generally symptomatic
- Patients with a positive urine test but no UTI symptoms usually **do not require treatment** (exceptions exist, e.g. pregnant women or if invasive urologic procedure is scheduled, for whom pre-emptive antibiotic therapy may be indicated)
- Empiric antibiotic treatment should be guided by:** The severity of symptoms, considering local prevalence of resistance (particularly of isolates of Enterobacteriales producing ESBL) and individual risk factors for resistant pathogens

Important:

- Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or rapid clinical improvement if culture results unavailable
- Step down to oral treatment** is based on improvement of symptoms, signs of infection and the ability to take oral antibiotics
- Clinical improvement is usually evident within 48-72 hours of starting treatment; **if signs and symptoms persist**, consider and investigate a possible complication (e.g. abscess) and review the results of the urine culture to verify that the pathogen is susceptible to the antibiotic used



Antibiotic Treatment Duration

7 days

Rx Mild Cases

All dosages are for normal renal function



Ciprofloxacin 500 mg q12h **ORAL**

Rx Severe Cases

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated



Cefotaxime 1 g q8h **IV/IM**

OR



Ceftriaxone 1 g q24h **IV/IM**

AND/OR



Amikacin 15 mg/kg q24h **IV**

AND/OR



Gentamicin 5 mg/kg q24h **IV**

Consider amikacin or gentamicin where ESBL-producing isolates are highly prevalent

In very sick patients, amikacin or gentamicin can be given in combination with cefotaxime or ceftriaxone

Upper urinary tract infection

Urinary tract infection • Page 1 of 2

Definition

Infection of the kidneys (pyelonephritis) in which microorganisms ascend the urinary tract via the urethra, bladder, ureters or reach the kidneys through the bloodstream

Classification based on complexity:

- **Uncomplicated:** Urinary tract infections (UTI) in children with no risk factors for complicated UTI
- **Complicated:** More common in girls, infants and children with structural malformations of the urinary tract (e.g. vesicoureteral reflux or other congenital anomalies)



Most Likely Pathogens

Bacteria:

- **Most common:**
 - Enterobacteriales (mostly *Escherichia coli* including multidrug resistant strains such as those producing ESBL and carbapenemases)
- **More rarely:**
 - *Enterococcus* spp.
 - Other Gram-negative bacilli (e.g. *Klebsiella* spp.)
 - *Staphylococcus aureus* (rare in uncomplicated UTIs, usually in patients with urinary catheters)
 - Group B *Streptococcus* (*Streptococcus agalactiae*)



Diagnosis



Clinical Presentation

- Fever is most common symptom, with irritability, vomiting and diarrhoea
- In older children (e.g. over 2 years of age) abdominal pain, urgency, frequency and dysuria are more common, along with flank pain/tenderness and increased wetting
- Severity varies from mild disease (most cases) that can be managed with oral treatment (no nausea/vomiting, low-grade fever) to severe cases requiring intravenous treatment and hospital admission



Other Laboratory Tests

All cases (if upper UTI is suspected clinically):

- Urinalysis (dipstick or microscopy) to detect bacteriuria and/or indirect signs of infection (positive leucocyte esterase and nitrites)

Additionally in severe cases:

- White blood cell count, C-reactive protein and/or procalcitonin
- If sepsis is suspected consider additional laboratory tests (see sepsis infographic)



Microbiology Tests

All cases (if upper UTI is suspected clinically):

- Urine culture: Ideally before starting antibiotic treatment
 - The test is considered positive when bacteria are above a certain minimum cut-off that can vary between laboratories
 - A positive urine culture is not always a sign of urinary tract infection or an indication for antibiotic treatment (and urine can also become contaminated during sampling)

Additionally in severe cases:

- Blood cultures: Ideally before starting antibiotic treatment



Imaging

Ultrasound is helpful if available

Upper urinary tract infection

Urinary tract infection - Page 2 of 2

Rx Treatment

Clinical Considerations

- In young children with mild cases** it is often difficult to clearly distinguish between lower and upper UTI, therefore oral options recommended for lower UTI can be used initially (if no need for IV treatment) or as step down treatment (see Lower Urinary Tract for antibiotic options)
- Empiric antibiotic treatment should be guided by:** The severity of symptoms, considering local prevalence of resistance (particularly of isolates of Enterobacteriales producing ESBL) and individual risk factors for resistant pathogens

Important:

- Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or rapid clinical improvement if culture results unavailable
- Step down to oral treatment** is based on improvement of symptoms, signs of infection and the ability to take oral antibiotics
- Clinical improvement is usually evident within 48-72 hours of starting treatment; **if signs and symptoms persist**, consider and investigate a possible complication (e.g. abscess) and review the results of the urine culture to verify that the pathogen is susceptible to the antibiotic used

Antibiotic Treatment Duration

7 days

Rx Severe Cases

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

 Cefotaxime 50 mg/kg/dose q8h **IV/IM**
WATCH

OR

 Ceftriaxone 80 mg/kg/dose q24h **IV/IM**
WATCH

AND/OR

 Amikacin 15 mg/kg q24h **IV**
ACCESS

AND/OR

 Gentamicin **IV**
ACCESS
• Neonates: 5 mg/kg/dose q24h
• Children: 7.5 mg/kg/dose q24h

Consider amikacin or gentamicin where ESBL-producing isolates are highly prevalent

In very sick patients, amikacin or gentamicin can be given in combination with cefotaxime or ceftriaxone

Rx Mild Cases

All dosages are for normal renal function

 Ciprofloxacin 15 mg/kg/dose q12h **IV/ORAL**
WATCH

• Oral weight bands:

3-<6 kg	50 mg q12h
6-<10 kg	100 mg q12h
10-<15 kg	150 mg q12h
15-<20 kg	200 mg q12h
20-<30 kg	300 mg q12h
≥30 kg	500 mg q12h

Ciprofloxacin has excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function

Pathophysiology

Upper UTIs occur when pathogens reach the upper urinary tract and overcome the host defences, which leads to tissue damage and an inflammatory response. Pathogens in the urine do not inevitably lead to infection. Infection will depend on the interaction between the pathogen (e.g. the presence of specific virulence factors in the pathogen), the host (who may be more or less likely to have infections because of, for example, underlying diseases) and the local conditions within the urinary tract, for example, because of abnormalities of the urinary tract or the presence of foreign material such as a urinary catheter. Furthermore, it is important to note that urine can also become contaminated during sampling so that the presence of bacteria in a urine sample does not necessarily mean bacteria are present in the urinary tract.

Epidemiology

UTIs are very common worldwide and can affect people at any age. In 2017, there were an estimated 274 million new cases of UTIs globally (upper and lower), combining all ages and both sexes (44).

The incidence of UTIs is highest in women and increases with age (e.g. UTIs increase after menopause) and frequency of sexual activity. These infections are particularly common in women because of the anatomy of their lower urinary tract; women have a shorter urethra than men and so microorganisms colonizing the skin of the perineal area can more easily reach the bladder. Risk factors for UTIs include anatomical and functional abnormalities of the urinary tract, such as conditions that predispose to incomplete emptying of the bladder, renal insufficiency and urinary incontinence. Defective host immune factors (e.g. poorly controlled diabetes or neutropenia) and instrumentation of the urinary tract (e.g. urinary catheters and stents) are also predisposing factors.

Most likely pathogens

Most UTIs are caused by enteric Gram-negative bacteria, most frequently *Escherichia coli*, which is responsible for about 80% of cases in children and adults. Other causative pathogens are shown in Table 34.1. Data on causative pathogens from low- and middle-income countries are limited.

Table 34.1 – Pathogens commonly causing upper urinary tract infections (in descending order of frequency)

Most cases	Enterobacterales (including multidrug-resistant strains such as those producing ESBL and carbapenemases) <ul style="list-style-type: none"> • <i>Escherichia coli</i> (> 80% of cases) • <i>Klebsiella pneumoniae</i> • <i>Proteus mirabilis</i> • Other Enterobacterales
More rarely	<i>Enterococcus</i> spp. <i>Streptococcus agalactiae</i> (group B <i>Streptococcus</i>) <i>Staphylococcus aureus</i> (rare in uncomplicated urinary tract infections, often in patients with urinary catheters; can be associated with bacteraemia)
Additionally in patients with recent antibiotic exposure, hospitalization or instrumentation of the urinary tract (e.g. insertion of a catheter)	<i>Pseudomonas aeruginosa</i> <i>Acinetobacter baumannii</i> (including multidrug-resistant strains)

ESBL: extended-spectrum beta-lactamases.

Clinical presentation

Classical symptoms of pyelonephritis include flank pain, costovertebral angle tenderness, nausea and vomiting, fever ($\geq 38.0^{\circ}\text{C}$) and signs of systemic illness. Symptoms of cystitis (dysuria, suprapubic tenderness, increased urgency and frequency) may or may not be present.

Severity of signs and symptoms may range from mild disease (e.g. no nausea or vomiting, low-grade fever) that can be safely managed in an outpatient setting with oral antibiotic treatment to severe cases that require hospitalization and intravenous treatment to septic shock requiring admission to intensive care.

In younger children, symptoms are often non-specific, including high fever, irritability, vomiting and diarrhoea. In children older than 2 years, abdominal pain, urgency, frequency and dysuria are more common.

Laboratory tests

Patient microbiology tests

If upper UTI is suspected clinically, a urine culture should be done whenever possible, ideally before starting antibiotic treatment. The rationale is to confirm the diagnosis and to adjust empiric treatment based on susceptibility results.

- Urine culture is considered positive when bacteria concentration in the urine is higher than a certain cut-off concentration in symptomatic patients (e.g. $\geq 10^5$ microorganisms/mL of urine).
- Minimum cut-offs to diagnose an infection can vary by laboratory.
- Lower cut-offs are often used to diagnose infections in females compared with males or in patients with urinary catheters.

Note

- The presence of bacteria in the urine alone is not a sign of infection or an indication for antibiotic treatment. This condition is referred to as asymptomatic bacteriuria when no symptoms suggestive of UTI are present.
- Cut-offs of concentration of bacteria in the urine alone cannot distinguish infection from colonization. The pre-test probability of UTI always needs to be considered when interpreting urine culture results.
- Patients with positive urine cultures without symptoms suggestive of a UTI usually do not require treatment. There may be some exception such as pregnant women or patients who have an invasive urological procedure scheduled, for whom pre-emptive antibiotic therapy may be indicated.

For patients requiring hospitalization, a blood culture should be done where possible before starting antibiotic treatment to guide treatment.

Table 34.2 summarizes the microbiology tests that can be done to diagnose upper UTIs.

Table 34.2 – Microbiology tests for upper urinary tract infections as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
Urine culture and antimicrobial susceptibility testing	Initial step to detect and identify bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories
Blood cultures and antimicrobial susceptibility testing	To detect bacterial bloodstream infections	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics.

Other tests

In patients with symptoms of a UTI, a urinalysis (dipstick or microscopy) may be done to detect the presence of bacteriuria and/or indirect signs of infection (leukocyturia and nitrites). In a symptomatic patient, leukocyturia (> 10 leukocytes/ μL ; $> 0.01 \times 10^9/\text{L}$), the presence of leukocyte esterase and/or positive nitrites are indirect signs of infection.

In patients with a severe clinical presentation and when sepsis of urinary origin is suspected, a white blood cell count may be done to support the diagnosis of bacterial infection as well as testing for biomarkers of infection, such as C-reactive protein. Table 34.3 summarizes the laboratory tests that can be done to assist with the diagnosis of upper UTIs.

Table 34.3 – Laboratory tests (other than microbiology) to consider for the diagnosis of upper urinary tract infections as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
Urinalysis test strips	To detect urinary tract infections	Community settings and health facilities without laboratories ^a
Urine microscopy	Presence or absence of: white blood cells, red blood cells; presence of casts and crystals in urine	Health care facilities with clinical laboratories

continues

Table 34.3 *continued*

Diagnostic test	Purpose of the test	Settings where the test should be available
White blood cell count ^b	To aid in the diagnosis of infections	Health care facilities with clinical laboratories
C-reactive protein ^b	To detect inflammation as an indicator of various conditions (e.g. sepsis)	Health care facilities with clinical laboratories
Procalcitonin ^b	To guide antibiotic therapy or discontinuation in sepsis	Only in tertiary care facilities

EDL: Model List of Essential In Vitro Diagnostics.

^a Community and health settings without laboratories are settings such as health posts and centres, doctors' offices, outreach clinics and ambulatory care. These tests are also assumed to be available at health care facilities with laboratories.

^b Only in severe cases when sepsis of urinary origin is suspected.

Using microbiology surveillance data

Empiric guidance given by the AWaRe book should be reviewed and adapted based on local clinically relevant microbiology surveillance data. For example, clinically relevant isolates for this infection would be blood and urine culture data from patients being treated in the hospital with community-acquired upper UTIs. Data on severity of clinical presentation, underlying patient risk factors, previous and current antibiotic treatment, current microbiology and clinical outcome would help to inform the development of local guidance.

Imaging

Routine imaging of all cases of upper UTI is not necessary. Initial imaging (e.g. ultrasound) of the urinary tract could be done in severely ill patients or during follow-up if an outflow obstruction or a fluid collection (i.e. abscess) is suspected.

Symptomatic care

Medicines that could be considered to control pain in upper UTI are given in Table 34.4.

Table 34.4 – Medicines to consider for pain control of upper urinary tract infections

Medicine	Formulation	Dose and frequency
Ibuprofen ^a	Oral liquid: 200 mg/5 mL Tablet: 200 mg; 400 mg; 600 mg	Adults: 200–400 mg given every 6 to 8 hours (maximum dose of 2.4 g a day) Children: 5–10 mg/kg given every 6 to 8 hours (pain control/antipyretic treatment) 6–< 10 kg: 50 mg given every 8 hours 10–< 15 kg: 100 mg given every 8 hours 15–< 20 kg: 150 mg given every 8 hours 20–< 30 kg: 200 mg given every 8 hours ≥ 30 kg: use adult dose
Paracetamol (acetaminophen) ^b	Oral liquid: 120 mg/5 mL; 125 mg/5 mL Suppository: 100 mg Tablet: 100 mg to 500 mg	Adults: 500 mg–1 g given every 4 to 6 hours (maximum dose of 4 g a day) ^c Children: 10–15 mg/kg given every 6 hours (pain control/antipyretic treatment) 3–< 6 kg: 60 mg given every 6 hours 6 <10 kg: 100 mg given every 6 hours 10–< 15 kg: 150 mg given every 6 hours 15–< 20 kg: 200 mg given every 6 hours 20–< 30 kg: 300 mg given every 6 hours ≥ 30 kg: use adult dose

^a Not for children < 3 months.^b Not recommended for use as an anti-inflammatory as it has not been proven to have such an effect.^c In patients with hepatic impairment or cirrhosis, maximum daily dose should be 2 g.

Antibiotic treatment

The primary goal of empiric antibiotic treatment is to provide effective and timely treatment for the main bacterial pathogens in upper UTI, most commonly *Escherichia coli*. The choice of empiric treatment should be based on the severity of symptoms (mild/moderate or severe). Many upper UTIs can be managed with oral antibiotics in the outpatient setting (340).

Mild/moderate cases (adults and children)

Mild/moderate cases of upper UTIs are defined as patients who are not critically ill and there are no clinical signs of sepsis or septic shock. In these cases, for adults, a 7-day treatment course with oral ciprofloxacin should be considered if there is no nausea and vomiting, (Table 34.5). For young children it is clinically more difficult to make a clear distinction between upper and lower UTIs, with fever and general systemic signs of infection seen in both groups. If systemic intravenous treatment is required, a third-generation cephalosporin (ceftriaxone or cefotaxime) is an option. Clinical improvement should be evident within 48–72 hours of starting treatment. If no improvement is seen in that time, a complication (such as an abscess) should be considered and investigated by imaging, and the susceptibility of bacteria isolated in the urine culture should be reviewed.

Step-down to oral treatment is based on improvement of symptoms and signs of infection and the ability to take oral antibiotics allowing discharge of the patient home when clinically appropriate.

Severe cases (adults and children)

Severe cases of upper UTIs are defined as patients who are critically ill, with sepsis and/or septic shock. Please also refer to the chapter on sepsis if suspected. These cases should be treated rapidly with systemic antibiotics. A third-generation cephalosporin (ceftriaxone or cefotaxime) or gentamicin or amikacin (Table 34.5) for 7 days, for both children and adults, is recommended (341,342). Clinical improvement is usually evident within 48–72 hours of starting treatment when a switch to oral antibiotics should be considered.

Simplify empiric treatment to a more narrow-spectrum antibiotic (often also called de-escalation) based on culture results (targeted treatment) or based on rapid clinical improvement when no microbiology test results are available.

Step-down to oral treatment is based on improvement of symptoms and signs of infection and the ability to take oral antibiotics allowing discharge of the patient home when clinically appropriate.

Settings with high rates of resistant isolates

Enterobacteriales can develop resistance to antibiotics through different mechanisms, for example, production of ESBL, ampicillinase C (AmpC) beta-lactamases and carbapenemases. Resistance to beta-lactam antibiotics (e.g. in ESBL-producing strains) is often associated with resistance to other classes of antibiotics, such as fluoroquinolones. Although resistance is higher in hospital-acquired strains, it is also present in community-acquired infections. Specific thresholds for when not to use particular antibiotics are given in some guidelines; however, these lack a strong evidence base with no clear rationale for the suggested cut-

offs. Therefore, local knowledge of the prevalence of resistance to antibiotic classes used to treat UTIs should be considered, as well as individual risk factors (e.g. previous infection or colonization with a resistant pathogen) and severity of clinical presentation.

In hospital settings where resistance to first-choice antibiotics (Table 34.5) is highly prevalent and in severely ill patients with acute clinical deterioration, piperacillin+tazobactam or a carbapenem could be considered, even though the EML and EMLc do not explicitly recommend these options. Empiric use of a Reserve antibiotic could be considered exceptionally in very select cases of seriously ill patients failing to respond to carbapenems or who have previously been treated for infections caused by carbapenem-resistant pathogens or who are known to be colonized with multidrug-resistant Gram-negative bacteria known to be susceptible to the selected Reserve antibiotic. Please refer to the chapter on Reserve antibiotic for the definition and list of Reserve antibiotics included in the EML and EMLc.

Table 34.5 – Empiric antibiotic treatment for upper urinary tract infections

! Important			
Severity	Adults	Children	Total treatment duration
Mild to moderate cases	Ciprofloxacin ^{a,b} (oral): 500 mg given every 12 hours (Ciprofloxacin has excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function.)	Ciprofloxacin ^a (IV/oral): 15 mg/kg/dose given every 12 hours Oral weight bands: 3-< 6 kg: 50 mg given every 12 hours 6-< 10 kg: 100 mg given every 12 hours 10-< 15 kg: 150 mg given every 12 hours 15-< 20 kg: 200 mg given every 12 hours 20-< 30 kg: 300 mg given every 12 hours ≥ 30 kg: use adult dose (Ciprofloxacin has excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function.)	7 days ^c

continues

Table 34.5 *continued*

Severity	Adults	Children	Total treatment duration
Severe cases	Cefotaxime ^d (IV/IM): 1 g given every 8 hours OR Ceftriaxone ^d (IV/IM): 1 g given once a day AND/OR Amikacin ^e (IV): 15 mg/kg given once a day AND/OR Gentamicin ^e (IV): 5 mg/kg given once a day	Cefotaxime ^d (IV/IM): 50mg/kg/dose given every 8 hours OR Ceftriaxone ^d (IV/IM): 80 mg/kg/dose given once a day AND/OR Amikacin ^e (IV): 15 mg/kg/dose given once a day AND/OR Gentamicin ^e (IV) <ul style="list-style-type: none"> • Neonates: 5 mg/kg/dose given once a day • Children: 7.5 mg/kg/dose given once a day 	7 days

ESBL: extended-spectrum beta-lactamases; IM: intramuscular; IV: intravenous.

Notes. All dosages are for normal renal and hepatic function.

Escherichia coli resistance rates to amoxicillin+clavulanic acid are lower than to amoxicillin alone. This combination still has activity against some ESBL-producing isolates and it can be considered an acceptable option, particularly in young children.

^a Resistance to fluoroquinolones is increasing including in low-and middle-income countries and in children (343–345).

^b The use of fluoroquinolones (such as ciprofloxacin) can be associated with important side-effects including: (i) mental health disturbances such as disorientation, agitation, nervousness, memory impairment and delirium; (ii) serious blood sugar disturbances such as hypoglycaemic coma; (iii) increased risk of tendinitis and tendon rupture; (iv) worsening symptoms in those with myasthenia gravis; and (v) potential irreversible neuropathy (serious nerve damage).

^c In men with upper urinary tract infections, prostatitis can also be present and longer treatment may therefore be warranted, but not universally as not each urinary tract infection episode in a male is associated with prostatitis.

^d Resistance to third-generation cephalosporins is increasing including in low- and middle-income countries and in children (343–345). In very sick patients, gentamicin (or amikacin) can be given in combination with ceftriaxone (or cefotaxime).

^e Amikacin and gentamicin are still effective against isolates producing ESBL and are considered appropriate carbapenem-sparing options in settings where ESBL-producing isolates are very prevalent. Use of aminoglycosides can be associated with nephrotoxicity and/or ototoxicity, especially when used for more than 7 days.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

35. Acute bacterial osteomyelitis

Key messages

- Osteomyelitis can occur alone or in combination with septic arthritis.
- In clinically stable adult patients, targeted treatment based on the results of microbiology tests is always preferable because of the large number of potential causes, risk of resistant pathogens and long treatment.
- In children there is less variability in causative pathogens (mostly *Staphylococcus* spp. and *Streptococcus* spp.) and empiric treatment is common practice.
- In general, the intravenous route is preferred for initial treatment but rapid oral step down is increasingly used.
- Duration of treatment in children is usually shorter than in adults.
- Dead bone, which is usually present in chronic infections, needs to be removed surgically for antibiotic treatment to be successful.

Other relevant WHO resources (please check regularly for updates)

- Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, 2013 (31).
- WHO consolidated guidelines on tuberculosis: module 3: diagnosis: rapid diagnostics for tuberculosis detection, 2021 update (346).
- WHO consolidated guidelines on tuberculosis: module 5: management of tuberculosis in children and adolescents (347).

Definition

Osteomyelitis is an infection of the bone characterized by inflammation and bone destruction. Infection can be classified according to how the pathogen spreads in the body (via the bloodstream or by local spread from nearby tissue or through direct inoculation, for example in cases of open fractures) or the duration of symptoms (acute or chronic). Acute infections develop and evolve over days or weeks, while chronic infections evolve over months or years. Chronic infections are also characterized by the presence of dead bone fragments (sequestrum).

Both classifications have implications for the management of osteomyelitis. For example, the pathogens infecting bone by local spread are more variable than those infecting bone via the bloodstream. In addition, dead bone, which is usually present in chronic infections, needs to be removed surgically for antibiotic treatment to be successful.

Acute bacterial osteomyelitis

Bone and joint infection • Page 1 of 2

This guidance does not cover prosthetic-joint infections in detail

Definition

An infection of the bone characterized by inflammation and bone destruction

Classification based on:

- *Mechanism of dissemination in the body:* Through the bloodstream (less common in adults), local spread or direct inoculation
- *Duration of symptoms:* Acute (days to weeks), chronic (months to years with presence of dead bone fragments)

Consequences of classification for management:

- Differences in the causative pathogens:
 - Local spread: more variability in possible causative pathogens
 - Spread through the bloodstream: more common with certain pathogens (e.g. *S. aureus*)
- Necessity for surgery (e.g. dead bone, usually present in chronic infections, needs removal for antibiotic treatment to be successful)



Most Likely Pathogens

Bacteria (most cases):

- *Staphylococcus aureus* (including MRSA)
- *Staphylococcus* spp. other than *S. aureus*
- *Streptococcus* spp. (mostly in patients with splenic dysfunction (*S. pneumoniae*))

Additionally in immunocompromised patients:

- *Candida* spp.
- *Cryptococcus* spp.
- *Histoplasma* spp.
- *Mycobacterium tuberculosis*
- *Pseudomonas aeruginosa*

Consider in specific situations:

- *Acinetobacter baumannii* (open fractures)
- *Bartonella* spp. (history of cat bite wounds)
- *Brucella* spp. (exposure to infected animals or ingestion of contaminated food, mostly dairy products)
- Enterobacteriases and anaerobes (pressure ulcers, diabetic foot infections, open fractures)
- Invasive non-typhoidal *Salmonella* spp. (sickle cell disease)

Diagnosis



Clinical Presentation

- Gradual onset of localized pain with redness, swelling, and warmth of the affected area +/- fever and other signs of systemic infection
- If vertebral spine, hip and pelvis involved, pain is usually the main symptom
- Suspect in case of defective healing of a fractured bone
- Osteomyelitis can occur with/without septic arthritis
- Tuberculous osteomyelitis: consider when illness is chronic (less ill, less marked local signs), pus drains from the infected bone to the surface of the skin or patient has other signs of tuberculosis



Microbiology Tests

All microbiology tests ideally before starting antibiotics

- Blood cultures
- Microscopy and culture of bone biopsy material
- Microscopy and culture of deep samples of tissue/bone collected during debridement to adjust empiric antibiotic treatment

It is **important** to determine the causative pathogen to adequately target antibiotic treatment because the number of potential pathogens is large and antibiotic resistant pathogens (e.g. MRSA) are not infrequent

- Samples should also be tested for special pathogens (e.g. mycobacteria, fungi, *Brucella* spp.) based on clinical/epidemiological features



Other Laboratory Tests

To differentiate between bacterial and reactive viral infections:

- White blood cell count

To detect inflammation:

- C-reactive protein (CRP) and/or procalcitonin
- Erythrocyte sedimentation rate (ESR could complement CRP especially during follow up)

To help exclude other bone diseases:

- Calcium, phosphate and alkaline phosphatase tests
- These tests are usually normal in osteomyelitis but abnormal in other bone diseases

Imaging

- X-ray of the affected bone
- Normal X-ray on admission does not rule out acute osteomyelitis but can help exclude alternative diagnosis
- CT or MRI could also be considered if available
- MRI has a high sensitivity/specificity to detect bone changes (especially in early phase)

Acute bacterial osteomyelitis

Bone and joint infection • Page 2 of 2

Rx Treatment

Clinical Considerations

- Surgical treatment not required in most cases**
- Surgical debridement of the bone can be considered in some selected cases to reduce the risk of complications
- Prosthetic-joint infections: Surgical approach depends on the location of the prosthesis, characteristics of the patient and local practices

Antibiotic treatment:

- The intravenous route is preferred at least in the first week of treatment
- Targeted antibiotic treatment** based on microbiology results always preferred (many potential causative pathogens and high levels of resistance)
- If **empiric treatment** is required consider most likely pathogens including local prevalence and individual risk factors for MRSA
- Adjust therapy once microbiology results available

Important:

- Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or rapid clinical improvement if culture results unavailable
- Step down to oral treatment** is based on improvement of symptoms, signs of infection and the ability to take oral antibiotics



Antibiotic Treatment Duration

4 to 6 weeks

Based on:

- Presence/absence of dead bone or foreign bodies
- Causative organism and its resistance profile
- Ability of the antibiotic to penetrate into bone tissues
- Imaging studies are usually not useful to determine duration

Rx Antibiotic Treatment

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice



Cloxacillin 2 g q6h IV

ACCESS

If cloxacillin is unavailable, any other IV antistaphylococcal penicillin could be used. A higher dose (e.g. 12 g/day) could be considered given the concerns with bone penetration

Second Choice



Amoxicillin+clavulanic acid 1 g + 200 mg q8h IV

ACCESS

OR



Cefazolin 2 g q8h IV

WATCH

OR



Cefotaxime 2 g q8h IV

WATCH

OR



Ceftriaxone 2 g q24h IV

WATCH

Ceftriaxone or cefotaxime are the preferred options if invasive non-typhoidal *Salmonella* or *Enterobacteriales* infection is suspected

OR



Clindamycin 600 mg q8h IV/ORAL

ACCESS

Acceptable option for community-acquired-MRSA if MRSA is susceptible or in settings where MRSA maintains high levels of susceptibility to clindamycin, otherwise consider vancomycin

Acute bacterial osteomyelitis

Bone and joint infection • Page 1 of 2

Definition

An infection of the bone characterized by inflammation and bone destruction

Classification based on:

- *Mechanism of dissemination in the body:* Through the bloodstream (less common in adults), local spread or direct inoculation
- *Duration of symptoms:* Acute (days to weeks), chronic (months to years with presence of dead bone fragments)

Consequences of classification for management:

- Differences in the causative pathogens:
 - Local spread: more variability in possible causative pathogens
 - Spread through the bloodstream: more common with certain pathogens (e.g. *S. aureus*)
- Necessity for surgery (e.g. dead bone, usually present in chronic infections, needs removal for antibiotic treatment to be successful)



Most Likely Pathogens

Bacteria (most cases):

- *Staphylococcus aureus* (including MRSA)
- *Streptococcus* spp. (mostly Group A *Streptococcus*)
- *Kingella kingae* (young children, usually with milder clinical disease)
- *Haemophilus influenzae* type b (young children not vaccinated against Hib)
- Invasive non-typhoidal *Salmonella* spp. (in children with sickle cell disease)
- *Acinetobacter baumannii* (open fractures)

Additional bacteria in immunocompromised children:

- Enterobacteriales (open fractures)
- *Pseudomonas aeruginosa*

Diagnosis

Clinical Presentation

- Gradual onset of localized pain with redness, swelling, and warmth of the affected area +/- fever and other signs of systemic infection
- If vertebral spine, hip and pelvis involved, pain is usually the main symptom
- Suspect in case of defective healing of a fractured bone
- Osteomyelitis can occur with/without septic arthritis
- Tuberculous osteomyelitis: consider when illness is chronic (less ill, less marked local signs), pus drains from the infected bone to the surface of the skin or patient has other signs of tuberculosis

Microbiology Tests

All microbiology tests ideally before starting antibiotics

- Blood cultures
- Microscopy and culture of bone biopsy material
- Microscopy and culture of deep samples of tissue/bone collected during debridement to adjust empiric antibiotic treatment

It is **important** to determine the causative pathogen to adequately target antibiotic treatment because the number of potential pathogens is large and antibiotic resistant pathogens (e.g. MRSA) are not infrequent

• Samples should also be tested for special pathogens (e.g. mycobacteria, fungi, *Brucella* spp.) based on clinical/epidemiological features

Other Laboratory Tests

To differentiate between bacterial and reactive viral infections:

- White blood cell count

To detect inflammation:

- C-reactive protein (CRP)
- Erythrocyte sedimentation rate (could complement CRP especially during follow up)

Imaging

- X-ray of the affected bone

- Normal X-ray on admission does not rule out acute osteomyelitis but can help exclude alternative diagnosis

- CT or MRI could also be considered if available

- MRI has a high sensitivity/specificity to detect bone changes (especially in early phase)

Acute bacterial osteomyelitis

Bone and joint infection • Page 2 of 2

Rx Treatment

Clinical Considerations

Surgical treatment not required in most cases

Antibiotic Treatment

- The intravenous route is preferred at least in the first few days of treatment
- In children empiric treatment is common practice** and *S. aureus* remains the most common pathogen
- In neonates, *S. aureus*** is also the most common pathogen but empiric treatment should also cover Enterobacteriales (very rare in older children)
 - For Enterobacteriales use:
 - Cefotaxime or
 - Ceftriaxone (not in infants with hyperbilirubinemia)

Important:

- Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or rapid clinical improvement if culture results unavailable
- Step down to oral treatment** is based on improvement of symptoms, signs of infection and the ability to take oral antibiotics

Antibiotic Treatment Duration

Around **3 weeks** in children with uncomplicated infections

Based on:

- Clinical recovery
 - Causative organism and its resistance profile
- Imaging studies are usually not useful to determine duration

Rx Antibiotic Treatment

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice



Cloxacillin IV

ACCESS

- Neonates: 25-50 mg/kg/dose q12h
- Children: 25 mg/kg/dose q6h
- ORAL:** 15 mg/kg/dose q6h

Oral weight bands:

3-<6 kg	62.5 mg q6h
6-<10 kg	125 mg q6h
10-<15 kg	250 mg q6h
15-<20 kg	375 mg q6h
≥20 kg	500 mg q6h

If cloxacillin is unavailable, any other IV *antistaphylococcal penicillin* could be used. For oral administration, dicloxacillin and flucloxacillin are preferred options within the class as they have better oral bioavailability

Second Choice



Amoxicillin+clavulanic acid IV:

ACCESS

- 1st week of life: 50 mg/kg/dose of amoxicillin component q12h
- > 1st week of life: 50 mg/kg/dose of amoxicillin component q8h
- ORAL:** 80-90 mg/kg/day of amoxicillin component

Oral weight bands:

3-<6 kg	250 mg of amox/dose q12h
6-<10 kg	375 mg of amox/dose q12h
10-<15 kg	500 mg of amox/dose q12h
15-<20 kg	750 mg of amox/dose q12h
≥20 kg	500 mg of amox/dose q8h or 1 g of amox/dose q12h

Amox = amoxicillin

Oral liquid must be refrigerated after reconstitution

OR



Cefazolin 25 mg/kg/dose q12h IV

WATCH

OR



Cefotaxime 50 mg/kg/dose q8h IV

WATCH

OR



Ceftriaxone 80 mg/kg/dose q24h IV

WATCH

Ceftriaxone or cefotaxime are the preferred options if invasive non-typhoidal *Salmonella* or *Enterobacteriales* infection is suspected

OR



Clindamycin IV

ACCESS

- Neonates: 5 mg/kg/dose q8h
- Children: 10 mg/kg/dose q8h

Acceptable option for community-acquired-MRSA if MRSA is susceptible or in settings where MRSA maintains high levels of susceptibility to clindamycin, otherwise consider vancomycin

Pathophysiology

Bacteria can reach the bone from a source of infection by spreading through the bloodstream or by local spread or by direct inoculation, for example, after trauma, bone surgery, prosthetic joint implantation, pressure or decubitus ulcers or diabetic foot infections. The infection can affect a single portion of the bone or can extend to the surrounding soft tissue. Infections can rapidly lead to destruction of the affected bone.

The pathophysiology of osteomyelitis differs between children and adults; osteomyelitis caused by spread through the bloodstream is much more common in children (mostly < 5 years of age) where it usually affects long bones (mostly the tibia and femur) because the bones are more heavily vascularized in children. In adults, spread of the infection via the bloodstream is less common; nonetheless, it can occur (e.g. as a metastatic infection of infective endocarditis) and in most cases if osteomyelitis is caused, it concerns the vertebra and intervertebral disc (vertebral osteomyelitis). However, in the adult population, dissemination by local spread (e.g. after trauma) is far more common.

Epidemiology

Risk factors for osteomyelitis are those associated with bacteraemia (e.g. presence of indwelling vascular catheters, injection drug use, haemodialysis) and those making the bone vulnerable to infection, such as bone surgery, open bone fracture, presence of foreign material such as prosthetic joint implants, sickle-cell disease, diabetes and impaired bone vascularization. Acute suppurative and non-suppurative osteomyelitis of the jaw may also result from oral and dental infections.

Acute osteomyelitis in children is more frequent in low- and middle-income countries and is more common in boys than in girls. If left untreated or managed late, acute osteomyelitis can leave children with long-term disability.

The global burden of osteomyelitis is still high, mostly in low- and middle-income countries where the disease disproportionately affects the young and where delays in diagnosis and adequate management can lead to acute forms that evolve into chronic osteomyelitis, which is very difficult to treat (348).

Most cases globally develop after a traumatic event, for example, infections in open fractures following road traffic incidents or combat. In addition, in high-income settings, diabetes (which can lead to foot osteomyelitis; not specifically addressed in this chapter) and spinal interventions (which can lead to vertebral osteomyelitis) contribute to the burden of disease.

Most likely pathogens

The most frequent pathogens associated with acute osteomyelitis in children and adults are shown in Table 35.1 and Table 35.2, respectively.

Table 35.1 – Pathogens most frequently associated with acute osteomyelitis in children (in descending order of frequency)

Pathogen	Most common way of spreading	Patients most at risk
<i>Staphylococcus aureus</i> (including MRSA)	Bloodborne or local spread	Usually, no risk factors are identified but consider with penetrating injuries, recent surgical procedures or bite wounds
<i>Streptococcus</i> spp. (mostly <i>Streptococcus pyogenes</i> , often called group A <i>Streptococcus</i> , and less commonly <i>Streptococcus pneumoniae</i>). <i>Streptococcus agalactiae</i> (group B <i>Streptococcus</i>) is a potential pathogen for neonates.	Bloodborne	Mostly no risk factor identified
<i>Kingella kingae</i> (a species of anaerobic Gram-negative bacilli)	Bloodborne	Young children with generally mild disease
<i>Haemophilus influenzae</i> type b	Bloodborne	Young children not vaccinated against <i>Haemophilus influenzae</i> type b
Invasive non-typhoidal <i>Salmonella</i>	Bloodborne	Children with sickle-cell disease
Enterobacteriales	Bloodborne, local spread	Neonates and immunocompromised children. Also consider in case of open fractures
<i>Acinetobacter baumannii</i>	Bloodborne, local spread	Consider in case of open fractures
<i>Pseudomonas aeruginosa</i>	Bloodborne or local spread	Immunocompromised patients and immunocompetent children following wound puncture

MRSA: methicillin-resistant *Staphylococcus aureus*.

Table 35.2 – Pathogens most frequently associated with acute osteomyelitis in adults (in descending order of frequency)

Pathogen	Most common way of spreading	Patients most at risk
<i>Staphylococcus aureus</i> (including MRSA)	Bloodborne or local spread	Usually, no risk factors are identified but consider with penetrating injuries, recent surgical procedures, bite wounds or injection drug use
<i>Staphylococcus</i> spp. other than <i>Staphylococcus aureus</i>	Bloodborne or local spread	Patients with recent prosthetic joint implants or arthroscopy or patients with bite wounds
<i>Streptococcus</i> spp.	Bloodborne or local spread	Splenic dysfunction
Less frequent pathogens (in alphabetical order)		
<i>Acinetobacter baumannii</i>	Bloodborne, local spread	Consider in case of open fractures
Anaerobes	Local spread	Patients with bite wounds or recent abdominal surgery; diabetic foot infection
<i>Bartonella</i> spp.	Bloodborne	Patients with cat bite wounds
<i>Brucella</i> spp.	Bloodborne	Patients with occupational or domestic exposure to infected animals (e.g. farmers, sheep herders, veterinarians) or ingestion of contaminated food, mostly dairy products

continues

Table 35.2 *continued*

Pathogen	Most common way of spreading	Patients most at risk
<i>Candida</i> spp.	Bloodborne or local spread	Immunocompromised patients, patients with invasive devices, patients who inject drugs (haematogenous spread) or patients with deep wounds (dissemination by local spread)
<i>Cryptococcus</i> spp.	Bloodborne	Immunocompromised patients
Enterobacteriales	Bloodborne or local spread	Patients with decubitus (pressure) ulcers, diabetic foot infections and burn wounds, especially if the wound is close to the perineum, and abdominal surgery
<i>Histoplasma</i> spp.	Bloodborne	Immunocompromised patients
<i>Mycobacterium tuberculosis</i>	Bloodborne or local spread (e.g. from adjacent paravertebral lymph nodes)	Immunocompromised patients because of the risk of reactivation of tuberculosis. Often a cause of chronic rather than acute infection.
<i>Pseudomonas aeruginosa</i>	Bloodborne or local spread	Immunocompromised patients and following wound puncture, including injection drug use
Invasive non-typhoidal <i>Salmonella</i>	Bloodborne	Adults with sickle-cell disease

MRSA: methicillin-resistant *Staphylococcus aureus*.

Clinical presentation

Note

Osteomyelitis can occur alone or in combination with septic arthritis

Acute osteomyelitis is characterized by gradual onset of localized pain and/or tenderness with a combination of redness, swelling, pain and warmth of the affected area. Fever ($\geq 38.0^{\circ}\text{C}$) and other signs of systemic infection (e.g. tachycardia, leukocytosis) may be present. In the context of osteomyelitis involving the vertebral spine, hip and pelvis, pain is usually the main symptom.

Osteomyelitis should also be suspected in case of defective healing of a fractured bone.

In children where acute osteomyelitis often involves the femur and tibia, difficulty and/or inability to walk or reluctance to move the limb may be a presenting symptom.

Note

Osteomyelitis can sometimes present as chronic illness; the patient appears less ill, with fewer marked local signs, and perhaps without a fever. Consider tuberculous osteomyelitis (mostly vertebral also known as Pott disease) when the illness is chronic, discharging sinuses are present (i.e. when a passage (sinus) forms from the infected bone to the surface of the skin and pus drains through) or the patient has other signs of tuberculosis.

Laboratory tests

Patient microbiology tests

Determining the causative pathogen of osteomyelitis is important to target antibiotic treatment because the number of potential causative pathogens is large and antibiotic resistant pathogens (e.g. MRSA) are not infrequent; this makes it difficult to define appropriate empiric treatment. Duration of treatment may be long, thus increasing the risk of side-effects of the antibiotic therapy. Whenever possible, a microbiology sample should therefore be obtained to guide antibiotic treatment (Table 35.3).

Table 35.3 – Microbiology tests to consider when osteomyelitis is suspected as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
Blood culture and antimicrobial susceptibility testing	To detect bacterial bloodstream infections	Health care facilities with clinical laboratories
Bone biopsy for microscopy, culture ^a and antimicrobial susceptibility testing	Initial step in detection and identification of bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories
Microscopy, culture and antimicrobial susceptibility testing of deep samples of tissue and/or bone collected during debridement (i.e. when the surgeon removes as much of the diseased bone as possible) ^a	Initial step in detection and identification of bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics.

^a Samples should be tested for special pathogens, such as mycobacteria, fungi and *Brucella* spp., if compatible clinical/epidemiological features are evident.

Other tests

Laboratory tests can be used to complement the clinical examination and history. Table 35.4 gives several tests that could be considered in the initial patient assessment to differentiate between bacterial and reactive viral infections and to help guide the timing of changing to oral treatment and total duration of antibiotic treatment.

Table 35.4 – Laboratory tests (other than microbiology) to identify a bacterial infection, as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
White blood count	To help in the diagnosis of infections	Health care facilities with clinical laboratories
C-reactive protein	To detect inflammation as an indicator of various conditions	Health care facilities with clinical laboratories

continues

Table 35.4 *continued*

Diagnostic test	Purpose of the test	Settings where the test should be available
Erythrocyte sedimentation rate	Erythrocyte sedimentation rate could be used to complement C-reactive protein especially during follow-up when clinical improvements may be slower to detect than laboratory improvements	Community settings and health facilities without laboratories ^a
Procalcitonin	To guide antibiotic therapy or discontinuation in sepsis	Only in tertiary care facilities

EDL: Model List of Essential In Vitro Diagnostics.

^a Community health settings without laboratories are settings such as health posts and centres, doctors' offices, outreach clinics and ambulatory care. These tests are also assumed to be available at health care facilities with laboratories.

Additional tests that could be considered mostly to help exclude other bone diseases in adults (e.g. metastatic or metabolic bone disease) include calcium, phosphate and alkaline phosphatase. The rationale is that these tests are usually normal in case of osteomyelitis but they are usually abnormal in other bone diseases.

Using microbiology surveillance data

Routine clinical microbiology surveillance is generally not helpful in informing empiric guidance.

Imaging

Initial imaging with an X-ray is important when bone infections are suspected. However, a normal X-ray on admission does not rule out acute osteomyelitis but it can help exclude alternative diagnoses, such as a fracture or a malignant condition. In an X-ray, changes such as soft tissue swelling, periosteal thickening and/or elevation and lytic lesions are often found later than clinical disease. An X-ray could also help identify a sequestrum (dead bone) that needs to be removed surgically. Where available, a CT scan or magnetic resonance imaging (MRI) could also be considered in certain patients, for example, in cases of diagnostic uncertainty with X-ray. MRI has a high degree of sensitivity and specificity to detect bone changes, especially in the early phase. Nuclear imaging (e.g. bone scan or bone scintigraphy) could also be considered as an alternative where available.

Surgical treatment

In adults, no surgical intervention is required in most cases of acute osteomyelitis that are diagnosed and managed early in the course of illness. These cases can be treated with an antibiotic alone with good bone penetration. However, in certain cases of acute osteomyelitis (and always in case of chronic infections), surgical debridement of the bone may be required to reduce the risk of complications because of impaired local vascularization (e.g. avascular necrosis of the bone, permanent bone damage) and to remove "dead" bone and clean the surrounding soft tissue.

In children, acute osteomyelitis is usually treated with medical management alone (i.e. no surgery).

Note

For prosthetic joint infections, treatment usually requires the surgical removal of the device. This can be done in one stage (the new prosthesis is immediately inserted) or two stages (the infected prosthesis is removed, the area is debrided, antibiotic treatment is given for several weeks and finally the new prosthesis is inserted). The choice of one stage or two stages depends on the location of the prosthesis (e.g. hip, knee), characteristics of the patient (e.g. advanced age, comorbidities) and local practices.

A detailed discussion of prosthetic-joint infections is beyond the scope of the AWaRe book.

Antibiotic treatment

Note

In adults with osteomyelitis, targeted antibiotic treatment based on microbiology is always preferred. In children, it is unusual to identify the pathogen and empiric treatment is usually given.

In adults, empiric treatment is sometimes required, for example, in severely ill patients requiring immediate treatment or when it is not possible to obtain a clinical sample for microbiological examination. In these cases, the choice of the antibiotic needs to be based on the pathogens most commonly identified in this type of infections (Table 35.5). In addition, empiric treatment against community-acquired MRSA could be considered in some cases based on individual risk factors (e.g. MRSA colonization) and on the local prevalence of community-acquired MRSA.

Duration of treatment is usually long (weeks) but it differs in acute or chronic infections. Duration is also influenced by the presence, absence or removal of foreign bodies

(including dead bone), the type of causative organism and its resistance profile, the use of antibiotics with an optimal antibiotic spectrum (i.e. based on microbiology results), and good bone penetration.

Total treatment duration of about 3 weeks is usually adequate in patients with uncomplicated disease and good clinical recovery, while complicated disease may require 6 weeks of treatment.

Uncomplicated infections are those with symptoms for < 14 days, no underlying disease, no penetrating trauma and no need for extensive surgical intervention.

Imaging studies are usually not useful to determine the duration of treatment.

Simplify empiric treatment to a more narrow-spectrum antibiotic (often also called de-escalation) based on culture results (targeted treatment) or rapid clinical improvement if culture results unavailable. Historically, the intravenous route has always been preferred, at least in the initial phase of treatment.

Step down to oral antibiotics at home is increasingly being used early in the treatment course (e.g. in the first week) when the disease is uncomplicated (349). Step down to oral treatment is based on improvement of symptoms and signs of infection, improved clinical function and the ability to take oral antibiotics with good bone penetration, especially in adults (e.g. clindamycin).

Table 35.5 – Empiric antibiotic treatment for osteomyelitis

Adults	Children	Total treatment duration
First choice Cloxacillin ^a (IV): 2 g given every 6 hours	First choice Cloxacillin ^a IV: <ul style="list-style-type: none">• Neonates: 25–50 mg/kg/dose given every 12 hours• Children: 25 mg/kg/dose given every 6 hours Oral: 15 mg/kg/dose given every 6 hours Oral weight bands 3–< 6 kg: 62.5 mg given every 6 hours 6–< 10 kg: 125 mg given every 6 hours 10–< 15 kg: 250 mg given every 6 hours 15–< 20 kg: 375 mg given every 6 hours ≥ 20 kg: 500 mg given every 6 hours	3 weeks ^b (in children with uncomplicated infections) 4–6 weeks ^c (in adults)

continues

Table 35.5 *continued*

Adults	Children	Total treatment duration
Second choice	Second choice	Same as above
Amoxicillin+clavulanic acid (IV): 1g + 200 mg given every 8 hours	Amoxicillin+clavulanic acid ^f IV: First week of life: 50 mg/kg of amoxicillin/dose given every 12 hours Beyond first week of life: 50 mg/kg of amoxicillin/dose given every 8 hours	
OR		
Cefazolin (IV): 2 g given every 8 hours	Oral: 80–90 mg/kg/day of amoxicillin component	
OR		
Cefotaxime ^d (IV) 2 g given every 8 hours	Oral weight bands	
OR	3-< 6 kg: 250 mg of amoxicillin/dose given every 12 hours	
Ceftriaxone ^d (IV): 2 g given once a day	6-< 10 kg: 375 mg of amoxicillin/dose given every 12 hours	
OR	10-< 15 kg: 500 mg of amoxicillin/dose given every 12 hours	
Clindamycin ^e (IV/oral): 600 mg given every 8 hours	15-< 20 kg: 750 mg of amoxicillin/dose given every 12 hours	
	≥ 20kg: 500 mg of amoxicillin/dose given every 8 hours or 1 g of amoxicillin/dose given every 12 hours	
OR		
	Cefazolin (IV): 25 mg/kg/dose given every 12 hours	
OR		
	Cefotaxime ^d (IV): 50mg/kg/dose given every 8 hours	
OR		
	Ceftriaxone ^d (IV): 80 mg/kg/dose given once a day	
OR		
	Clindamycin ^e (IV/oral):	
	<ul style="list-style-type: none"> • Neonates: 5 mg/kg/dose given every 8 hours • Children: 10 mg/kg/dose given every 8 hours 	

continues

Table 35.5 continued

IV: intravenous; MRSA: methicillin-resistant *Staphylococcus aureus*.

Notes. All dosages are for normal renal and hepatic function.

As mentioned in the text, empiric treatment should be avoided whenever possible in adults because there are many potential causative pathogens and high levels of resistance (e.g. MRSA) making it difficult to specify appropriate empiric treatment. In children, there is usually less variability in the most likely causative pathogens (in children the disease is mostly caused by spread of *Staphylococcus* spp. and *Streptococcus* spp. through the bloodstream) and therefore empiric treatment is common practice.

In neonates, empirical antibiotic therapy should also cover Enterobacterales because infections caused by Gram-negative bacteria can occur in neonates, but *Staphylococcus aureus* remains the most common pathogen. Therefore, in neonates, empiric use of cefotaxime (or ceftazidime) is appropriate; ceftazidime should be avoided in infants with hyperbilirubinaemia. In older children, bone infections caused by Enterobacterales are very rare.

^a If cloxacillin is unavailable, any other IV antistaphylococcal penicillin could be used. For oral administration, dicloxacillin and flucloxacillin are preferred options within the class as they have better oral bioavailability. In adults, a higher dose (e.g. 12 g/day) could be considered given the concerns with bone penetration.

^b Three weeks of treatment (usually starting with 3–5 days IV treatment and then changing to oral treatment) are now commonly used in children with acute bloodborne osteomyelitis based on response to fever, ability to move the limb and reduction in levels of C-reactive protein (if available).

^c Longer treatments may be required if implants or foreign material are present or in case of inadequate control at the source of infection; for example, where there is an abscess that has not been adequately drained.

^d Ceftriaxone or cefotaxime is preferred if invasive non-typhoidal *Salmonella* or Enterobacterales infection are suspected. In neonates, cefotaxime is recommended in these cases.

^e Clindamycin is still an acceptable option when community-acquired MRSA is suspected or detected if antimicrobial susceptibility tests show that MRSA is sensitive to clindamycin or in settings where MRSA maintains high levels of susceptibility to clindamycin. Clindamycin can also be used when changing from the IV to the oral route, and in patients allergic to penicillin. In case of MRSA isolates resistant to clindamycin and in settings where the prevalence of community-acquired MRSA is high, the use of vancomycin could be considered when *Staphylococcus aureus* is suspected. Oral options to consider to complete the course of treatment in case of MRSA or methicillin-susceptible *Staphylococcus aureus* infections could be sulfamethoxazole+trimethoprim and doxycycline.

^f Oral liquid formulations must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

36. Septic arthritis

Key messages

- Septic arthritis can occur alone or in combination with osteomyelitis.
- Ideally microbiology test (e.g. synovial fluid culture) results should be obtained before starting antibiotics.
- Targeted treatment is preferable whenever possible in adults because of the large number of potential causative pathogens, while in children empiric treatment is usually given.
- In general, the intravenous route is preferred for initial antibiotic treatment, but rapid oral step down is increasingly used.
- Surgical lavage or needle aspiration as a form of source control is important in adults.



Other relevant WHO resources (please check regularly for updates)

- Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, 2013 (31).

Definition

Septic arthritis is an infection usually of bacterial origin of one or several joints. Infections can be classified based on the causative pathogen (gonococcal or non-gonococcal), on the type of affected joint (large or small joint) and on the concomitant presence or absence of osteomyelitis.

Septic arthritis

Bone and joint infection • Page 1 of 2

This guidance does not cover prosthetic-joint infections in detail

Definition

An infection of one or several joints, usually of bacterial origin

Gonococcal arthritis:

- Rare complication of gonococcal infection (predominantly affects women)
- Characterized by dissemination of the infection via the bloodstream

Classification based on:

- **Causative pathogen:** Gonococcal or non-gonococcal
- **Type of affected joint:** Large or small joint
- **Mechanism of dissemination in the body:**
 - Spread through the bloodstream (more common)
 - Local spread or direct inoculation



Most Likely Pathogens

Bacteria (most cases):

- *Staphylococcus aureus* (including MRSA)
- *Staphylococcus* spp. other than *S. aureus*
- *Streptococcus* spp.

Additionally in immunocompromised patients:

- *Candida* spp.
- *Cryptococcus* spp.
- *Histoplasma* spp.
- *Mycobacterium tuberculosis*
- *Pseudomonas aeruginosa*

Consider in specific situations:

- *Acinetobacter baumannii* (open skin wounds with exposed joint)
- Anaerobes (penetrating injuries)
- *Bartonella* spp. (history of cat bite wounds)
- *Brucella* spp. (exposure to infected animals or ingestion of contaminated food, mostly dairy products)
- Enterobacteriales (pressure ulcers, diabetic foot infections, and open skin wounds with exposed joint)
- *Neisseria gonorrhoeae* (if gonococcal infection)

Diagnosis

Clinical Presentation

- Acute onset (usually a few days, but up to 2 weeks) of joint pain and reduced range of motion with redness, swelling, warmth of the joint (may be less evident in "deep" joints)
- Usually, a single joint is affected (often knee)
- Polyarticular infection is more common in patients with underlying rheumatoid arthritis
- Other signs of systemic infection are usually present
- Septic arthritis can occur with/without osteomyelitis

Gonococcal arthritis:

- Typical signs and symptoms of septic arthritis (usually affecting knees and ankles) + skin manifestations (rash, small papules)
- Often no signs/symptoms of cervicitis/urethritis

Important: if left untreated, septic arthritis can rapidly lead to destruction of the cartilage; it therefore needs to be rapidly diagnosed and treated

Microbiology Tests

All microbiology tests ideally before starting antibiotics

- Blood cultures
- Microscopy and culture of synovial fluid
 - Culture is usually negative in gonococcal arthritis
- Microscopy and culture of deep samples of tissue collected during debridement in prosthetic joint implant to adjust empiric antibiotic treatment
- Nucleic acid amplification test of urogenital specimens and urine for *Neisseria gonorrhoeae* infection

It is **important** to determine the causative pathogen to adequately target antibiotic treatment because the number of potential pathogens is large and antibiotic resistant pathogens (e.g. MRSA) are not infrequent

• Samples should also be tested for special pathogens (e.g. mycobacteria, fungi, *Brucella* spp., *Neisseria gonorrhoeae*) based on clinical/epidemiological features

Other Laboratory Tests

To differentiate between bacterial and reactive viral infections:

- White blood cell count (WBC)

To detect inflammation:

- C-reactive protein (CRP)
- Erythrocyte sedimentation rate (ESR could complement CRP especially during follow up)

Synovial fluid examination:

- WBC and microscopy for crystals
- WBC usually $> 20\,000 \text{ cells}/\mu\text{L}$ ($> 20 \times 10^9/\text{L}$) with $> 90\%$ neutrophils

Imaging

- Ultrasound of the affected joint to detect joint effusion and synovial swelling (due to increased intra-articular fluid)

- Consider MRI if available, especially if concomitant osteomyelitis is suspected (more sensitive/specific to detect bone changes)

Septic arthritis

Bone and joint infection • Page 2 of 2

Rx Treatment

Clinical Considerations

- Prompt surgical drainage of purulent material and lavage of the joint is a key part of the management of septic arthritis** (antibiotic treatment alone is usually not sufficient) and can reduce risk of complications
- Immobilization of the joint is not necessary except for pain control
- Prosthetic-joint infections: Surgical approach depends on the location of the prosthesis, characteristics of the patient and local practices

Antibiotic treatment:

- The intravenous route is preferred at least in the first week of treatment
- Targeted antibiotic treatment** based on microbiology results always preferred (many potential causative pathogens and high levels of resistance)
- If **empiric treatment** is required consider most likely pathogens including local prevalence and individual risk factors for MRSA or *N. gonorrhoeae* based on individual risk factors
- Adjust therapy once microbiology results available

Important:

- Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or rapid clinical improvement if culture results unavailable
- Step down to oral treatment** is based on improvement of symptoms, signs of infection and the ability to take oral antibiotics



Antibiotic Treatment Duration

- 4 to 6 weeks**
- 2 weeks** in case of gonococcal infection

Based on:

- Presence/absence/removal of foreign bodies
- Causative organism and its resistance profile
- Presence/absence of osteomyelitis

Rx Antibiotic Treatment

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice



Cloxacillin 2 g q6h IV

ACCESS

If cloxacillin is unavailable, any other IV antistaphylococcal penicillin could be used. A higher dose (e.g. 12 g/day) could be considered given the concerns with bone penetration

Second Choice



Amoxicillin+clavulanic acid 1 g + 200 mg q8h IV

ACCESS

OR



Cefazolin 2 g q8h IV

WATCH

OR



Cefotaxime 2 g q8h IV

WATCH

OR



Ceftriaxone 2 g q24h IV

WATCH

Ceftriaxone or cefotaxime are the preferred options if invasive non-typhoidal *Salmonella* or *Enterobacteriales* infection is suspected

OR



Clindamycin 600 mg q8h IV/ORAL

ACCESS

Acceptable option for community-acquired-MRSA if MRSA is susceptible or in settings where MRSA maintains high levels of susceptibility to clindamycin, otherwise consider vancomycin

Septic arthritis

Bone and joint infection • Page 1 of 2

Definition

An infection of one or several joints, usually of bacterial origin

Classification based on:

- Type of affected joint: Large or small joint
- Mechanism of dissemination in the body:
 - Spread through the bloodstream (more common)
 - Local spread or direct inoculation



Most Likely Pathogens

Bacteria (most cases):

- *Staphylococcus aureus* (including MRSA)
- *Streptococcus* spp. (mostly Group A *Streptococcus*)
- *Kingella kingae* (young children, usually with milder clinical disease)
- *Haemophilus influenzae* type b (young children not vaccinated against Hib)
- Invasive non-typhoidal *Salmonella* spp. (in children with sickle cell disease)

Diagnosis



Clinical Presentation

- Acute onset (usually a few days, but up to 2 weeks) of joint pain and reduced range of motion with redness, swelling, warmth of the joint (may be less evident in "deep" joints)
- Usually, a single joint is affected (often knee)
- Other signs of systemic infection are usually present
- Septic arthritis can occur alone or with osteomyelitis

Important: if left untreated, septic arthritis can rapidly lead to destruction of the cartilage (especially in young children); it therefore needs to be rapidly diagnosed and treated



Microbiology Tests

All microbiology tests ideally before starting antibiotics

- Blood cultures
- Microscopy and culture of synovial fluid
- Microscopy and culture of deep samples of tissue collected during debridement in case of prosthetic joint implant to adjust empiric antibiotic treatment

It is **important** to determine the causative pathogen to adequately target antibiotic treatment because the number of potential pathogens is large and antibiotic resistant pathogens (e.g. MRSA) are not infrequent

- Samples should also be tested for special pathogens (e.g. mycobacteria, fungi, *Brucella* spp.) based on clinical/epidemiological features



Other Laboratory Tests

To differentiate between bacterial and reactive viral infections:

- White blood cell count (WBC)

To detect inflammation:

- C-reactive protein (CRP)
- Erythrocyte sedimentation rate (ESR could complement CRP especially during follow up)

Synovial fluid examination:

- WBC and microscopy for crystals
- WBC usually $>20\,000$ cells/ μL ($>20 \times 10^9/\text{L}$) with $>90\%$ neutrophils



Imaging

- Ultrasound of the affected joint to detect joint effusion and synovial swelling (due to increased intra-articular fluid)
- Consider MRI if available, especially if concomitant osteomyelitis is suspected (more sensitive/specific to detect bone changes)

Septic arthritis

Bone and joint infection • Page 2 of 2

Rx Treatment

Clinical Considerations

- Prompt surgical drainage of purulent material and lavage of the joint can reduce risk of complications
- Immobilization of the joint is not necessary except for pain control
- Prosthetic-joint infections: Surgical approach depends on the location of the prosthesis, characteristics of the patient and local practices

Antibiotic treatment:

- The intravenous route is preferred at least in the first few days of treatment
- In children empiric treatment is common practice**
- In neonates**, empiric treatment should also cover Enterobacteriales (very rare in older children)
 - For Enterobacteriales use:
 - Cefotaxime or
 - Ceftriaxone (not in infants with hyperbilirubinemia)

Important:

- Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or rapid clinical improvement if culture results unavailable
- Step down to oral treatment** is based on improvement of symptoms, signs of infection and the ability to take oral antibiotics
- Early oral step down in the first week may be used in uncomplicated patients

Rx Antibiotic Treatment

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice



Cloxacillin IV

ACCESS

- Neonates: 25-50 mg/kg/dose q12h
- Children: 25 mg/kg/dose q6h
- ORAL:** 15 mg/kg/dose q6h
- Oral weight bands:**

3-<6 kg	62.5 mg q6h
6-<10 kg	125 mg q6h
10-<15 kg	250 mg q6h
15-<20 kg	375 mg q6h
≥20 kg	500 mg q6h

If cloxacillin is unavailable, any other IV *antistaphylococcal penicillin* could be used. For oral administration, dicloxacillin and flucloxacillin are preferred options within the class as they have better oral bioavailability

Second Choice



Amoxicillin+clavulanic acid

IV:

- 1st week of life: 50 mg/kg/dose of amoxicillin component q12h
- > 1st week of life: 50 mg/kg/dose of amoxicillin component q8h
- ORAL:** 80-90 mg/kg/day of amoxicillin component
- Oral weight bands:**

3-<6 kg	250 mg of amox/dose q12h
6-<10 kg	375 mg of amox/dose q12h
10-<15 kg	500 mg of amox/dose q12h
15-<20 kg	750 mg of amox/dose q12h
≥20 kg	500 mg of amox/dose q8h or 1 g of amox/dose q12h

Amox = amoxicillin

Oral liquid must be refrigerated after reconstitution

OR



Cefazolin 25 mg/kg/dose q12h IV

WATCH

OR



Cefotaxime 50 mg/kg/dose q8h IV

WATCH

OR



Ceftriaxone 80 mg/kg/dose q24h IV

WATCH

Ceftriaxone or cefotaxime are the preferred options if invasive non-typhoidal *Salmonella* or *Enterobacteriales* infection is suspected

OR



Clindamycin IV/ORAL

ACCESS

- Neonates: 5 mg/kg/dose q8h
- Children: 10 mg/kg/dose q8h

Acceptable option for community-acquired-MRSA if MRSA is susceptible or in settings where MRSA maintains high levels of susceptibility to clindamycin, otherwise consider vancomycin

Pathophysiology

In septic arthritis, bacteria can reach the joint through dissemination through the bloodstream, by local spread or by direct inoculation from a contiguous infected bone or soft tissue, for example, local spread following trauma or bites, bone surgery, prosthetic joint implantation, pressure and decubitus ulcers and diabetic foot infections (350). Dissemination through the bloodstream is more common in both children and adults. Once bacteria gain access to the joint space, they can adhere to the articular cartilage, produce an inflammatory response and promote cartilage destruction within hours. If left untreated, septic arthritis can rapidly lead to destruction of the cartilage. It therefore needs to be rapidly diagnosed and treated.

Epidemiology

Septic arthritis is associated with substantial morbidity (e.g. adverse joint outcomes) and low mortality (350,351). People at risk of septic arthritis are people with a higher risk of bacteraemia (e.g. those with indwelling vascular catheters, injection drug users, patients on haemodialysis) and those with a higher likelihood of the joint becoming infected, for example, patients with rheumatoid arthritis, diabetes, sickle-cell disease and prosthetic joints and other foreign material. Post-surgical infections are common in adults. Community-acquired infections are quite rare in adults, while they are common in children.

In children, septic arthritis is more frequent in low- and middle-income countries and in boys more than girls. If left untreated or managed late, septic arthritis can leave children with long-term disability.

Gonococcal arthritis, characterized by dissemination of the infection through the bloodstream, is a rare complication of gonorrhoea that mostly affects women.

Most likely pathogens

A large variety of pathogens can cause septic arthritis with some differences between children and adults (Table 36.1 and Table 36.2).

Table 36.1 – Pathogens most frequently associated with acute septic arthritis in children (in descending order of frequency)

Pathogen	Most common mechanism of dissemination	Patients most at risk
<i>Staphylococcus aureus</i> (including MRSA)	Bloodborne or by local spread	Usually, no risk factors are identified but consider with penetrating injuries, recent surgical procedures or bite wounds
<i>Streptococcus pyogenes</i> (group A <i>Streptococcus</i>) and less commonly <i>Streptococcus pneumoniae</i> <i>Streptococcus agalactiae</i> (group B <i>Streptococcus</i>) is a potential pathogen for neonates	Bloodborne	Usually, no risk factors are identified but consider with penetrating injuries or recent surgical procedures
<i>Kingella kingae</i> (a species of anaerobic Gram-negative bacilli)	Bloodborne	Young children, usually with milder clinical disease
<i>Haemophilus influenzae</i> type b	Bloodborne	Young children not vaccinated against <i>Haemophilus influenzae</i> type b
Invasive non-typhoidal <i>Salmonella</i>	Bloodborne	Children with sickle-cell disease
Enterobacteriales	Bloodborne	Neonates and immunocompromised children. Consider also in case of open skin wounds with exposed joint

MRSA: methicillin-resistant *Staphylococcus aureus*.**Table 36.2 – Pathogens most frequently associated with acute septic arthritis in adults**

Pathogen	Main dissemination mechanism	Patients most at risk
<i>Staphylococcus aureus</i> (including MRSA)	Bloodborne or by local spread	Patients with penetrating injuries, recent surgical procedures, bite wounds or intravenous drug injection
<i>Staphylococcus</i> spp. other than <i>Staphylococcus aureus</i>	Bloodborne or by local spread	Patients who had implantation of prosthetic joint implants or arthroscopy, and patients with bite wounds
<i>Streptococcus</i> spp.	Bloodborne or by local spread	Splenic dysfunction (<i>S. pneumoniae</i>)

continues

Table 36.2 *continued*

Pathogen	Main dissemination mechanism	Patients most at risk
Less frequent (in alphabetical order)		
<i>Acinetobacter baumannii</i>	Bloodborne or by local spread	Consider in case of open skin wounds with exposed joint
Anaerobes	By local spread	Patients with penetrating injuries (e.g. bite wounds)
<i>Bartonella</i> spp.	Bloodborne	Patients with cat bite wounds
<i>Brucella</i> spp.	Bloodborne	Patients with occupational or domestic exposure to infected animals (e.g. farmers, shepherds, veterinarians) or who have ingested contaminated food, mostly dairy products. Endemic in the Middle East and Mediterranean regions
<i>Candida</i> spp.	Bloodborne or by local spread	Immunocompromised patients, patients with invasive devices, patients who inject drugs (haematogenous spread) or patients with deep wounds (dissemination by local spread)
<i>Cryptococcus</i> spp.	Bloodborne	Immunocompromised patients
Enterobacterales	Bloodborne or by local spread	Patients with decubitus or pressure ulcers, diabetic foot infections, burn wounds (especially if the wound is close to the perineum) and those having undergone recent abdominal surgery. Consider also in case of open skin wounds with exposed joint.
<i>Histoplasma</i> spp.	Bloodborne	Immunocompromised patients
<i>Neisseria gonorrhoeae</i>	Bloodborne	Mostly women with disseminated gonococcal infection
<i>Mycobacterium tuberculosis</i>	Bloodborne	Immunocompromised patients because of the risk of reactivation of tuberculosis
<i>Pseudomonas aeruginosa</i>	Bloodborne or by local spread	Immunocompromised patients and people who inject drugs

MRSA: methicillin-resistant *Staphylococcus aureus*.

Clinical presentation

Note

Septic arthritis can occur alone or in combination with osteomyelitis.

Septic arthritis is characterized by acute onset (usually a few days, but up to 2 weeks) of joint pain (moderate to severe) and reduced range of motion with redness, swelling and warmth of the joint. The condition may be less evident when “deep” joints such as the hip, shoulder or sacroiliac joint are affected. In most cases, one single joint is affected (often the knee). Involvement of more than one joint (polyarticular infection) is more common with underlying rheumatoid arthritis. Other signs of systemic infection (e.g. fever $\geq 38.0^{\circ}\text{C}$, tachycardia, increased biomarkers of inflammation) are usually present.

In certain situations (e.g. septic arthritis of multiple joints), it is important to exclude an extra-articular source of infection such as endocarditis.

In young children permanent destruction of the joint cartilage and long-term disability can occur rapidly, therefore rapid diagnosis and prompt empiric antibiotic treatment are essential.

In case of gonococcal arthritis, typical signs and symptoms of septic arthritis (mostly affecting one or a few joints and usually the knees and ankles) are usually accompanied by skin manifestations such as rash or small papules on the trunk and distal extremities. Often patients with gonococcal arthritis have no signs or symptoms of cervicitis or urethritis.

Laboratory tests

Patient microbiology data

Determining the causative pathogen of septic arthritis is important for targeted antibiotic treatment because the number of potential causative pathogens is large (making it difficult to select empiric treatment) and treatment duration may be long, increasing the risk of side-effects from the antibiotic therapy.

Whenever possible, a microbiology sample should therefore be obtained to guide antibiotic treatment (Table 36.3). Ideally microbiology test results should be obtained before starting antibiotic treatment. However, because cartilage destruction can occur within hours, tests should never delay the start of antibiotic treatment.

Table 36.3 – Microbiology tests to consider when septic arthritis is suspected, as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
Synovial fluid for microscopy, culture ^a and antimicrobial susceptibility testing	Initial step to detect and identify bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories
Blood cultures and antimicrobial susceptibility testing	To detect bacterial bloodstream infections	Health care facilities with clinical laboratories
Microscopy, culture and antimicrobial susceptibility testing of deep samples collected at debridement in case of prosthetic joint implant	Initial step to detect and identify bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories
Nucleic acid amplification test of urogenital specimens and urine for <i>Neisseria gonorrhoeae</i> infection ^b	To diagnose gonorrhoeal urogenital disease and extragenital infection	Health care facilities with clinical laboratories
Synovial fluid for <i>Mycobacterium tuberculosis</i> DNA	To diagnose active tuberculosis and detect rifampicin resistance	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics.

^a Examination for particular pathogens (e.g. mycobacteria, fungi, *Brucella* spp.) should be done if clinical/epidemiological features are compatible. In cases of gonococcal arthritis, the culture of the synovial fluid is usually negative.

^b This test is not validated on the synovial fluid but is used in some settings.

Other tests

Laboratory tests can be used to complement the clinical examination and history and may help decide between bacterial septic arthritis and a viral reactive arthritis. Table 36.4 and Table 36.5 list tests that could be considered in the initial assessment of the patient to help make a diagnosis and guide the duration of antibiotic treatment.

Table 36.4 – Laboratory tests (other than microbiology) to consider to identify a bacterial joint infection, as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
White blood count	To help in the diagnosis of infections	Health care facilities with clinical laboratories but also in primary care settings
C-reactive protein	To detect inflammation as an indicator of various conditions	Health care facilities with clinical laboratories
Procalcitonin	To guide antibiotic therapy or discontinuation in sepsis	Only in tertiary care facilities
Erythrocyte sedimentation rate	To detect inflammation as an indicator of various conditions when C-reactive protein is not available	Community settings and health facilities without laboratories ^a

EDL: Model List of Essential In Vitro Diagnostics.

^a Community and health settings without laboratories are settings such as health posts and centres, doctors' offices, outreach clinics and ambulatory care. These tests are also assumed to be available at health care facilities with laboratories.

Table 36.5 – Synovial fluid examination

Diagnostic test	Purpose of the test	Settings where the test should be available
Synovial fluid: white cell count and crystals ^a	To detect the presence or absence of white blood cells and crystals	Health care facilities with clinical laboratories

^a With septic arthritis, it is helpful to know the number of white blood cells in the synovial fluid and microscopy should also be done to investigate alternative diagnoses such as gout or chondrocalcinosis. Compared to non-infectious arthritis, acute bacterial infections are characterized by a much higher white cell count in the synovial fluid, usually $> 20\,000$ cells/ μL (20×10^9 cells/L) with $> 90\%$ being neutrophils.

Using microbiology surveillance data

Due to the wide number of pathogens identified, there is no role for routine surveillance cultures to inform empiric guidance.

Imaging

Initial imaging with an ultrasound is useful when joint infections are suspected to detect joint effusion and synovial swelling due to the presence of increased intra-articular fluid.

MRI could also be considered, if available, in certain patients particularly when concomitant osteomyelitis is suspected, because MRI is more sensitive and specific than ultrasound in detecting bone changes.

Treatment

Prompt surgical drainage of any purulent material (aspiration) and washing of the joint (lavage) is a key part of the management of septic arthritis since antibiotics alone are usually not sufficient to control the source of the infection, at least in adults. Aspiration and lavage can reduce the risk of complications, such as permanent cartilage destruction, joint deformity and instability and degenerative arthritis. Immobilization of the joint is not necessary except for pain control.

Note

For prosthetic-joint infections, treatment can be in one or two stages depending on the location of the prosthesis (e.g. hip, knee), characteristics of the patient (e.g. older age, comorbidities) and on local practices. In the one-stage procedure, the old device is surgically removed and the new prosthesis is immediately inserted. In the two-stage procedure, the infected prosthesis is removed, the area is debrided and antibiotic treatment is given for several weeks. Then, in the second stage, the new prosthesis is inserted.

A detailed discussion of prosthetic-joint infections is beyond the scope of this chapter.

Antibiotic treatment

Note

In adults, targeted antibiotic treatment based on microbiology results is always preferred (unless the patient is severely ill or it is impossible to obtain a clinical sample for microbiological examination) because there are many potential causative pathogens, which makes it difficult to select an appropriate empiric treatment.

In young children, the treatment is often empiric.

When patients require empiric treatment (mostly young children or severely ill patients or when it is impossible to obtain a clinical sample for microbiological examination), the

choice should be based on the most probable pathogens in this type of infection, mostly *Staphylococcus aureus* and *Streptococcus* spp. (Table 36.6). In addition, empiric treatment against community-acquired MRSA or *Neisseria gonorrhoeae* may be considered in certain cases based on individual risk factors (e.g. known MRSA colonization) and compatible clinical and epidemiological features.

The duration of treatment is long – several weeks, except for gonococcal arthritis which requires shorter treatment. Duration of treatment is influenced by: duration of symptoms (acute or chronic); presence, absence or removal of foreign bodies (including devitalized bone if concomitant osteomyelitis is present); type of causative pathogen and its resistance profile; and concomitant presence of osteomyelitis, and therefore the availability of antibiotics with good bone penetration.

The total treatment duration is generally 3 weeks in children and 4–6 weeks in adults. With gonococcal arthritis, a shorter treatment duration (10–14 days) is adequate.

Simplify empiric treatment to a more narrow-spectrum antibiotic (often also called de-escalation) based on culture results (targeted treatment) or rapid clinical improvement if culture results unavailable. Historically, the intravenous route has always been preferred at least in the first week of treatment. However, recent evidence suggests that a change to oral antibiotics in the first week of treatment can be used for patients with uncomplicated disease.

Step down to oral treatment is based on improvement of symptoms and signs of infection, improvement in joint function and the ability to take oral antibiotics allowing discharge of the patient home when clinically appropriate.

Table 36.6 – Empiric antibiotic treatment for septic arthritis

Adults	Children	Total treatment duration
First choice Cloxacillin ^a (IV): 2 g given every 6 hours	First choice Cloxacillin ^a IV: <ul style="list-style-type: none">• Neonates: 25–50 mg/kg/dose given every 12 hours• Children: 25 mg/kg/dose given every 6 hours Oral: 15 mg/kg/dose given every 6 hours Oral weight bands 3–< 6 kg: 62.5 mg given every 6 hours 6–< 10 kg: 125 mg given every 6 hours 10–< 15 kg: 250 mg given every 6 hours 15–< 20 kg: 375 mg given every 6 hours ≥ 20 kg: 500 mg given every 6 hours	Children: 3 weeks Adults: 4–6 weeks ^b

continues

Table 36.6 *continued*

Adults	Children	Total treatment duration
Second choice	Second choice	
Amoxicillin+clavulanic acid	Amoxicillin+clavulanic acid ^e	Children: 3 weeks
(IV): 1g + 200 mg given every 8 hours	IV: First week of life: 50 mg/kg of amoxicillin/dose given every 12 hours Beyond first week of life: 50 mg/kg of amoxicillin/dose given every 8 hours Oral: 80–90 mg/kg/day of amoxicillin component	Adults: 4–6 weeks ^b
OR		
Cefazolin (IV): 2 g given every 8 hours		
OR		
Cefotaxime ^c (IV) 2 g given every 8 hours	Oral weight bands 3–< 6 kg: 250 mg of amoxicillin/dose given every 12 hours	
OR		
Ceftriaxone ^c (IV): 2 g given once a day	6–< 10 kg: 375 mg of amoxicillin/dose given every 12 hours 10–< 15 kg: 500 mg of amoxicillin/dose given every 12 hours	
OR		
Clindamycin ^d (IV/oral): 600 mg given every 8 hours	15–< 20 kg: 750 mg of amoxicillin/dose given every 12 hours ≥ 20kg: 500 mg of amoxicillin/dose given every 8 hours or 1 g of amoxicillin/dose given every 12 hours	
OR		
	Cefazolin (IV): 25 mg/kg/dose given every 12 hours	
OR		
	Cefotaxime ^c (IV): 50mg/kg/dose given every 8 hours	
OR		
	Ceftriaxone ^c (IV): 80 mg/kg/dose given once a day	
OR		
	Clindamycin ^d (IV/oral):	
	<ul style="list-style-type: none"> • Neonates: 5 mg/kg/dose given every 8 hours • Children: 10 mg/kg/dose given every 8 hours 	

continues

Table 36.6 continued

IV: intravenous; MRSA: methicillin-resistant *Staphylococcus aureus*.

Notes. All dosages are for normal renal and hepatic function.

As mentioned in the text, targeted treatment is preferable whenever possible in adults because of the large number of potential causative pathogens, while in children empiric treatment is often given.

In neonates, empirical antibiotic therapy should also cover Enterobacteriales because infections caused by Gram-negative bacteria can occur, but *Staphylococcus aureus* remains the most common pathogen. Therefore, in neonates, empiric use of cefotaxime (or ceftriaxone) is appropriate; ceftriaxone should be avoided in infants with hyperbilirubinaemia. In older children, joint infections caused by Enterobacteriales are very rare.

^aIf cloxacillin is unavailable, any other IV antistaphylococcal penicillin could be used. For oral administration, dicloxacillin and flucloxacillin are preferred options within the class as they have better oral bioavailability. In adults, a higher dose (e.g. 12 g/day) could be considered given the concerns with bone penetration.

^bShorter duration (10–14 days) in cases of gonococcal arthritis.

^cCeftriaxone or cefotaxime is preferred in cases of suspected invasive non-typhoidal *Salmonella* infection or Enterobacteriales infection or gonococcal arthritis. In neonates, cefotaxime is recommended in these cases.

^dClindamycin is still an acceptable option when community-acquired MRSA is suspected if antimicrobial susceptibility tests show that MRSA is sensitive to clindamycin or in settings where MRSA maintains high levels of susceptibility to clindamycin; suspicion should be based on local prevalence of community-acquired MRSA. Clindamycin can also be used when changing from the IV to oral route, and in patients allergic to penicillin. For severe disease potentially caused by MRSA, vancomycin can be considered in settings with local high prevalence of community-acquired MRSA, even though this is not a recommendation included in the current EML and EMLc (8,9). In case of MRSA and based on susceptibility results, alternative oral options that could be considered to complete the course of treatment include sulfamethoxazole+trimethoprim and doxycycline.

^eOral liquid formulations must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

37. Skin and soft tissue infections – necrotizing fasciitis

Key messages

- Necrotizing fasciitis is a life-threatening rapidly progressing infection of the deep soft tissue with pain out of proportion to skin findings.
- Surgery is both diagnostic and therapeutic (surgical exploration and debridement of necrotic tissue) and delays in surgery are associated with higher mortality.
- Antibiotic treatment is important but needs to be accompanied by source control (surgery).
- Children are rarely affected. Cases occur mostly in immunocompromised children or as a complication of chickenpox.

Definition

Necrotizing fasciitis is a life-threatening necrotizing infection of the deep soft tissues that specifically affects the muscular fascia – the fascia is the connective tissue surrounding the muscle. The disease is caused mostly by bacteria and is characterized by acute and fulminant (severe and sudden onset) necrosis with tissue destruction and signs of systemic toxicity. Necrotizing fasciitis can be classified based on: the causative pathogen (type 1 or polymicrobial necrotizing fasciitis (caused by multiple pathogens); or type 2 or monomicrobial necrotizing fasciitis (caused by a single pathogen)); the presence or absence of gas in tissues (polymicrobial infections are more often associated with the presence of gas); the site of the infection (e.g. leg, head and neck, perineum); or the risk of a poor outcome (high versus low or moderate risk). Necrotizing fasciitis affecting the perineum is also called Fournier gangrene.



Necrotizing fasciitis

Skin and soft tissue infection • Page 1 of 2

Definition

Life-threatening necrotizing infection of the deep soft tissues affecting the muscular fascia; caused mostly by bacteria and characterized by acute/fulminant necrosis with tissue destruction and systemic signs of toxicity

Classification based on:

- **Causative pathogen:**
 - Type 1/polymicrobial
 - Type 2/monomicrobial
- **Presence or absence of gas in tissues**
 - For example, presence of gas is common in polymicrobial infections
- **Involved site:**
 - Leg
 - Head and neck
 - Perineum (Fournier gangrene)
- **Risk of poor outcome:**
 - High versus moderate risk

Most Likely Pathogens

Monomicrobial / Type 2:

• Most cases:

- *Streptococcus pyogenes* (group A *Streptococcus*)
- *Streptococcus agalactiae* (group B *Streptococcus*)
- *Streptococcus dysgalactiae* (mostly in elderly and chronically ill patients)

• Less frequently:

- *Staphylococcus aureus* (including MRSA)

• Specific environmental exposures:

- *Aeromonas hydrophila* (freshwater)
- *Vibrio vulnificus* (seawater)

Polymicrobial / Type 1:

- Anaerobes (e.g. *Bacteroides* spp., *Clostridium perfringens*, *Pasteurelloctococcus* spp. or mouth anaerobes when head/neck involved)
- Enterobacteriales
- *Pseudomonas* spp.
- *Streptococcus* spp.
- *Staphylococcus aureus* (including MRSA)

Diagnosis

Clinical Presentation

- Acute onset of localized pain out of proportion to physical findings accompanied by rapid onset of systemic signs
- Signs and symptoms of skin and soft tissue infections (redness, warmth, swelling) usually present when portal of entry is the skin but severe pain is the main symptom; rapid progression of redness, ecchymosis and bullae is also suggestive
- Definitive diagnosis requires direct visualization of necrotic tissue in the muscular fascia through surgical exploration

Fournier gangrene:

- Severe pain accompanied by signs of necrosis in the perineal area; rapid progression of the infection to the abdominal wall and gluteal muscles is possible

Microbiology Tests

- Blood cultures (ideally before starting antibiotics)
- Microscopy and culture of deep samples of tissue collected at debridement to adjust empiric antibiotic treatment

Other Laboratory Tests

Determine disease severity and help identify a bacterial infection: White blood cell count, C-reactive protein and/or procalcitonin

- If sepsis is suspected consider additional laboratory tests (see sepsis infographic)

Initial evaluation for suspected necrotizing fasciitis:

- Complete blood count
- Creatinine
- Electrolytes
- Glucose

Imaging

- Ultrasound may be helpful to evaluate the extent of the affected tissue and gas and fluid along the muscular fascia
- Consider CT scan of the affected area

Imaging should not delay surgical exploration/inspection since surgery is the best way to diagnose/treat this infection

Necrotizing fasciitis

Skin and soft tissue infection • Page 2 of 2

Rx Treatment

Clinical Considerations

- Clinical progression to severe disease is rapid, carefully monitor signs of sepsis/septic shock
- **Early surgical removal of necrotic tissue through drainage/debridement is key; delays are associated with increased mortality**
- Antibiotic treatment is a complementary measure to surgical source control
- Intravenous immunoglobulin sometimes used when shock complicates necrotizing fasciitis (and toxic shock syndrome suspected) however very expensive and unclear effect on mortality

Important:

- **Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or rapid clinical improvement if culture results unavailable
- **Step down to oral treatment** is based on improvement of symptoms, signs of infection and the ability to take oral antibiotics

Antibiotic Treatment Duration

Usually 2-3 weeks

Based on:

- Clinical response
- Surgical source control, and
- Evolution of laboratory markers of infection

Rx Antibiotic Treatment

All dosages apply to normal renal function

 Piperacillin+tazobactam 4 g+500 mg q6h IV

----- COMBINED WITH -----

 Clindamycin 900 mg q8h IV

----- OR -----

Use this treatment option only if *Streptococcus pyogenes* infection has been excluded first

 Ceftriaxone 2 g q24h IV

----- COMBINED WITH -----

 Metronidazole 500 mg q8h IV

IF MRSA SUSPECTED,
CONSIDER ADDING

 Vancomycin 15-20 mg/kg q12h IV

Necrotizing fasciitis

Skin and soft tissue infection • Page 1 of 2

Definition

Life-threatening necrotizing infection of the deep soft tissues, specifically affecting the muscular fascia; caused mostly by bacteria and characterized by acute/fulminant necrosis with tissue destruction and systemic signs of toxicity

Classification based on:

- Causative pathogen:
 - Type 1/polymicrobial
 - Type 2/monomicrobial
- Presence or absence of gas in tissues
 - For example, presence of gas is common in polymicrobial infections
- Involved site:
 - Leg
 - Head and neck
 - Perineum (Fournier gangrene)
- Risk of poor outcome:
 - High versus moderate risk



Most Likely Pathogens

Monomicrobial / Type 2:

• Most cases:

- *Streptococcus pyogenes* (group A *Streptococcus*)
- *Streptococcus agalactiae* (group B *Streptococcus*)
- *Streptococcus dysgalactiae* (mostly in elderly and chronically ill patients)

• Less frequently:

- *Staphylococcus aureus* (including MRSA)

• Specific environmental exposures:

- *Aeromonas hydrophila* (freshwater)
- *Vibrio vulnificus* (seawater)

Polymicrobial / Type 1:

- Anaerobes (e.g. *Bacteroides* spp., *Clostridium perfringens*, *Peptostreptococcus* spp. or mouth anaerobes when head/neck involved)

- Enterobacteriales

- *Pseudomonas* spp.

- *Streptococcus* spp.

- *Staphylococcus aureus* (including MRSA)

Diagnosis

Clinical Presentation

- **Very rare**, may occur as a complication of varicella/chicken pox (or associated with a compromised immune system)
- Most elements described for adults also apply to children, but certain specificities exist:
 - Areas affected: torso (neonates and infants); extremities and face (older children)
 - Early signs and symptoms: fever $\geq 38.0^{\circ}\text{C}$, redness/skin discolouration, localized swelling, marked tenderness and pain of the affected area



Microbiology Tests

- Blood cultures (ideally before starting antibiotics)
- Microscopy and culture of deep samples of tissue collected at debridement to adjust empiric antibiotic treatment



Other Laboratory Tests

Determine disease severity and help identify a bacterial infection: White blood cell count, C-reactive protein and/or procalcitonin

- If sepsis is suspected consider additional laboratory tests (see sepsis infographic)

Initial evaluation for suspected necrotizing fasciitis:

- Complete blood count
- Creatinine
- Electrolytes
- Glucose



Imaging

Imaging should not delay surgical exploration/inspection since surgery is the best way to diagnose/treat this infection

- Ultrasound may be helpful to evaluate the extent of the affected tissue and gas and fluid along the muscular fascia
- Consider CT scan of the affected area

Necrotizing fasciitis

Skin and soft tissue infection • Page 2 of 2

Rx Treatment

Clinical Considerations

- Clinical progression to severe disease is rapid, carefully monitor signs of sepsis/septic shock
- **Early surgical removal of necrotic tissue through drainage/debridement is key; delays associated with increased mortality**
- Antibiotic treatment is a complementary measure to surgical source control
- Intravenous immunoglobulin sometimes used when shock complicates necrotizing fasciitis (and toxic shock syndrome suspected) however very expensive and unclear effect on mortality

Important:

- **Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or rapid clinical improvement if culture results unavailable
- **Step down to oral treatment** is based on improvement of symptoms, signs of infection and the ability to take oral antibiotics

Antibiotic Treatment Duration

Usually 2-3 weeks

Based on:

- Clinical response
- Surgical source control, and
- Evolution of laboratory markers of infection

Rx Antibiotic Treatment

All dosages apply to normal renal function

 **Piperacillin+tazobactam 100 mg/kg/dose of piperacillin component q8h IV**

----- COMBINED WITH -----

 **Clindamycin IV**
 • Neonates: 5 mg/kg/dose q8h
 • Children: 10 mg/kg/dose q8h

----- OR -----

Use this treatment option only if Streptococcus pyogenes infection has been excluded first

 **Ceftriaxone 80 mg/kg/dose q24h IV**

----- COMBINED WITH -----

 **Metronidazole IV/ORAL**
 • Neonates: 7.5 mg/kg/dose q12h (for IV starting with a loading dose of 15 mg/kg)
 • Children: 7.5 mg/kg/dose q8h
 • **Oral weight bands:**

3-<6 kg	30 mg q8h
6-<10 kg	50 mg q8h
10-<15 kg	100 mg q8h
15-<20 kg	150 mg q8h
20-<30 kg	200 mg q8h
≥30 kg	500 mg q8h

IF MRSA SUSPECTED,
CONSIDER ADDING

 **Vancomycin IV**
 • Neonates: 15 mg/kg/dose q12h
 • Children: 15 mg/kg/dose q8h

Pathophysiology

In necrotizing fasciitis, bacteria can reach the muscular fascia by local spread through a skin lesion or a break in the skin barrier (e.g. wounds, bites, injection of drugs, surgery) or through a breach in the mucosal barrier – usually in the intestine where the source could be a diverticulum or a malignancy, or in the oropharynx. Infections can thus be both exogenous (i.e. pathogens that enter the body from the environment) and endogenous (i.e. pathogens that naturally reside in the body). Often a clear place of entry is not identified. Bacteria can also reach the muscular fascia via the bloodstream, although this is less common.

Necrotizing fasciitis is characterized by tissue damage with necrosis and inflammatory fluid accumulation along the fascia and between muscle groups. The muscle is usually not affected; however, sometimes muscular abscesses can form. Legs and arms are the most commonly affected sites.

Epidemiology

Necrotizing fasciitis is a rare but life-threatening disease. Polymicrobial (type 1) forms occur most frequently in older adults and/or individuals with underlying comorbidities (mostly diabetes (352), peripheral vascular disease, immunosuppression) or traumatic or surgical wounds. Intravenous drug injection is also a risk factor. Monomicrobial (type 2) forms can occur at any age, including in otherwise healthy individuals, and they are the most common form in children (353). Toxic shock syndrome is a rare life-threatening complication of necrotizing fasciitis due to toxin production by *Streptococcus pyogenes* (often referred to as group A *Streptococcus*) or *Staphylococcus aureus* and can also be the cause of septic shock when these pathogens are involved.

Most likely pathogens

The most common pathogens causing mono- and polymicrobial necrotizing fasciitis are listed in Table 37.1.

Table 37.1 – Pathogens most frequently associated with necrotizing fasciitis (in descending order of frequency)

Monomicrobial (single pathogen)/type 2	Polymicrobial (multiple pathogens)/type 1
Most cases	Combination of anaerobes
<i>Streptococcus pyogenes</i> (group A <i>Streptococcus</i>)	<i>Bacteroides</i> spp.
<i>Streptococcus agalactiae</i> (group B <i>Streptococcus</i>)	<i>Clostridium perfringens</i>
<i>Streptococcus dysgalactiae</i> (mostly in elderly people and patients with chronic illness)	<i>Pestostreptococcus</i> spp. or oral anaerobic organisms when the head and/or neck are affected
Less frequently	and
<i>Staphylococcus aureus</i> (including MRSA)	<i>Enterobacteriales</i>
Pathogens to consider in cases with specific environmental exposure	<i>Pseudomonas</i> spp.
<i>Aeromonas hydrophila</i> (exposure to fresh water)	<i>Streptococcus</i> spp.
<i>Vibrio vulnificus</i> (exposure to seawater)	<i>Staphylococcus aureus</i> (including MRSA)

MRSA: methicillin-resistant *Staphylococcus aureus*; MSSA: methicillin-susceptible *Staphylococcus aureus*.

Clinical presentation

Clinical progression to severe disease is rapid. Therefore, the patient should always be carefully monitored for signs of sepsis or septic shock. Please also refer to the chapter on sepsis if suspected.

Adults

Necrotizing fasciitis is usually characterized by acute onset of pain out of proportion to physical findings in the affected area and rapid onset of systemic signs – for example, fever $\geq 38.0\text{ }^{\circ}\text{C}$, tachycardia and increased biomarker levels – leukocytosis, C-reactive protein and procalcitonin (354).

Signs and symptoms of skin and soft tissue infections (i.e. redness, skin discolouration, swelling, induration (hardening of soft tissue) and warmth of the affected area) are usually present when pathogen entry is through the skin. However, at least initially, the overlying skin often appears only minimally affected and skin changes – typically bullae and necrosis – only become apparent as the infection progresses. Rapid progression of redness, ecchymosis and bullae is also suggestive of this infection.

In cases of necrotizing fasciitis of the perineum (Fournier gangrene), severe pain is accompanied by signs of necrosis in the perineal area, often the scrotum in men. Rapid progression of the infection to the abdominal wall and gluteal muscles is possible.

While in patients with cellulitis, skin abnormalities are the usual symptoms, in patients with necrotizing fasciitis, severe pain (often disproportionate to skin changes) is the characteristic symptom, at least in the initial phase. A definitive diagnosis requires the direct visualization of necrotic tissue in the muscular fascia through surgical exploration.

Children

Necrotizing fasciitis is very rare in children but may occur as a complication of varicella (chickenpox) or can be associated with a compromised immune system. Most characteristics described for adults also apply to children, but certain specific features exist (355). For example, in neonates and infants, the torso is often affected, while in older children the arms and legs and the face are affected.

Laboratory tests

Patient microbiology tests

Whenever possible, a microbiology sample of the affected tissue should be obtained to guide antibiotic treatment; samples can be collected at the time of surgical exploration. This will allow the causative pathogen(s) to be determined so that adequate antibiotic treatment can be given, for example, single versus multiple causative pathogens. Blood cultures should also be obtained, ideally before antibiotic treatment is started (Table 37.2).

Table 37.2 – Microbiology tests to consider in a patient with suspected necrotizing fasciitis as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
Blood cultures and antimicrobial susceptibility testing	To detect bacterial and fungal bloodstream infections	Health care facilities with clinical laboratories
Microscopy, culture and antimicrobial susceptibility testing of deep samples of tissue collected at debridement ^a	Initial step in detection and identification of bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics.

^a Intraoperative tissue samples should also be sent for histopathology examination.



Other tests

Laboratory tests can be used to complement clinical examination and history. Table 37.3 and Table 37.4 give several tests that could be considered in the initial assessment of the patient suspected of having necrotizing fasciitis and to help guide the length of antibiotic treatment. Please also refer to the chapter on sepsis if suspected.

Table 37.3 – Laboratory tests (other than microbiology) to consider to identify a bacterial infection as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
White blood count	To help in the diagnosis of infections	Health care facilities with clinical laboratories but also in primary care settings
C-reactive protein	To detect inflammation as an indicator of various conditions	Health care facilities with clinical laboratories
Procalcitonin	To guide antibiotic therapy or discontinuation in sepsis	Only in tertiary health care facilities

EDL: Model List of Essential In Vitro Diagnostics.

Table 37.4 – Laboratory tests (other than microbiology) to consider in a patient with suspected necrotizing fasciitis as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
Complete blood count	To detect a wide range of disorders, including infections	Health care facilities with clinical laboratories
Creatinine	To monitor kidney function for management of severe infections (i.e. sepsis) and adjustment of the antimicrobial regimen	Health care facilities with clinical laboratories
Electrolytes	To monitor fluid, electrolyte and acid–base balance	Health care facilities with clinical laboratories
Glucose	To diagnose intermediate hyperglycaemia and hypoglycaemia	Community settings and health facilities without laboratories

continues

Table 37.4 *continued*

Diagnostic test	Purpose of the test	Settings where the test should be available
Haemoglobin	To diagnose and monitor anaemia Clinical marker for certain severe infections	Community settings and health facilities without laboratories

EDL: Model List of Essential In Vitro Diagnostics.

Note. If sepsis is suspected, additional tests may be needed; please refer to the chapter on sepsis.

Using microbiology surveillance data

There is no role for routine surveillance to inform empiric guidance.

Imaging

Imaging should not delay surgical exploration (or surgical inspection) since surgery is still the most reliable tool to diagnose and treat necrotizing fasciitis.

If available, ultrasound imaging may help in the diagnosis of necrotizing fasciitis and to evaluate the extent to which the tissue is affected and the presence or absence of gas and fluid along the muscular fascia. A CT scan of the affected area could also be considered.

Management

Prompt surgical removal of the necrotic tissue through drainage and debridement is the cornerstone of treatment of necrotizing fasciitis. Delays in this step are usually associated with higher mortality (356). Antibiotic treatment is a complementary measure to adequate surgical source control of the infection.

Intravenous immunoglobulin is occasionally used when shock is a complication in necrotizing fasciitis and therefore toxic shock syndrome (mostly due to *Streptococcus pyogenes* or *Staphylococcus aureus*) is suspected; however, the effect of the use of high-cost intravenous immunoglobulin on mortality is unclear (357).

Antibiotic treatment

Because of the seriousness of necrotizing fasciitis and the speed at which it can progress, empiric antibiotic treatment should be given immediately when necrotizing fasciitis is suspected. The antibiotics should cover both Gram-positive bacteria (including methicillin-resistant *Staphylococcus aureus*) and anaerobic pathogens (Table 37.5).

In patients at higher risk of a Gram-negative bacterial infection (e.g. patients with severe immunosuppression), additional empiric medicines should be considered that have activity against these pathogens.

Simplify empiric treatment to a more narrow-spectrum antibiotic (often also called de-escalation) based on culture results (targeted treatment) or rapid clinical improvement if culture results are unavailable.

Step-down to oral treatment is based on improvement of symptoms and signs of infection and the ability to take oral antibiotics allowing discharge of the patient home when clinically appropriate.

Table 37.5 – Empiric antibiotic treatment for suspected or confirmed necrotizing fasciitis

Adults	Children	Total treatment duration
Piperacillin+tazobactam (IV): 4 g + 500 mg given every 6 hours AND Clindamycin ^a (IV): 900 mg given every 8 hours ADD Vancomycin (IV) if MRSA is suspected: 15–20 mg/kg given every 12 hours OR (If <i>Streptococcus pyogenes</i> necrotizing fasciitis is considered unlikely): Ceftriaxone (IV): 2 g given once a day AND Metronidazole (IV): 500 mg given every 8 hours ADD Vancomycin (IV) if MRSA is suspected: 15–20 mg/kg given every 12 hours	Piperacillin+tazobactam (IV): 100 mg/kg/dose of piperacillin component given every 8 hours AND Clindamycin ^a (IV): <ul style="list-style-type: none">• Neonates: 5 mg/kg/dose given every 8 hours• Children: 10 mg/kg/dose given every 8 hours ADD Vancomycin (IV) if MRSA is suspected: <ul style="list-style-type: none">• Neonates: 15 mg/kg/dose given every 12 hours• Children: 15 mg/kg/dose given every 8 hours OR (If <i>Streptococcus pyogenes</i> necrotizing fasciitis is considered unlikely): Ceftriaxone (IV): 80 mg/kg given once a day AND Metronidazole (IV/oral): <ul style="list-style-type: none">• Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg)• Children: 7.5 mg/kg/dose given every 8 hours	2–3 weeks ^b

continues

■ HOSPITAL FACILITY

37. Skin and soft tissue infections – necrotizing fasciitis

Table 37.5 *continued*

Adults	Children	Total treatment duration
	<p>Oral weight bands:</p> <p>3-< 6 kg: 30 mg given every 8 hours</p> <p>6-< 10 kg: 50 mg given every 8 hours</p> <p>10-< 15 kg: 100 mg given every 8 hours</p> <p>15-< 20 kg: 150 mg given every 8 hours</p> <p>20-<30 kg: 200 mg given every 8 hours</p> <p>≥ 30 kg: use adult dose</p> <p>ADD</p> <p>Vancomycin (IV) if MRSA is suspected:</p> <ul style="list-style-type: none">• Neonates: 15 mg/kg/dose given every 12 hours• Children: 15 mg/kg/dose given every 8 hours	

IV: intravenous, MRSA: methicillin-resistant *Staphylococcus aureus*.

Note: All dosages are for normal renal and hepatic function.

^a Clindamycin has the ability to suppress the expression of virulence factors in *Staphylococcus aureus* (i.e. it has an anti-toxin effect).

^b Knowledge on the most appropriate duration of treatment is limited. Therefore, duration is often individualized based on clinical response, on the success of surgical source control and, if available, changes in laboratory markers of infection. Usually total treatment duration is about 2–3 weeks.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

38. Skin and soft tissue infections – pyomyositis

Key messages

- Most cases of pyomyositis occur in tropical countries in young children and adults.
- Most cases (> 90%) are caused by *Staphylococcus aureus* and *Streptococcus* spp. and Access group antibiotics are the mainstay of treatment.
- If an abscess is present, source control and antibiotic treatment have a complementary role in controlling the infection.
- Immunosuppression is a risk factor.



Other relevant WHO resources (please check regularly for updates)

- Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, 2013 (31).

Definition

Pyomyositis is an infection of a skeletal muscle caused by bacteria usually accompanied by abscess formation.

Pyomyositis

Skin and soft tissue infection

Definition

An infection of a skeletal muscle caused by bacteria usually accompanied by abscess formation

Diagnosis

Clinical Presentation

- Acute onset of localized muscle pain with cramping usually in the lower limbs/gluteal muscles with fever $\geq 38.0^{\circ}\text{C}$ +/– swelling and induration of the affected area
- Other signs of systemic infection are usually present (e.g. tachycardia, leukocytosis)
- Abscess can form within days/weeks
- Signs of severe clinical progression (e.g. signs of sepsis/septic shock) should always be carefully monitored
- Complications due to bacteraemia can occur (e.g. septic emboli, septic arthritis, endocarditis)

Microbiology Tests

- Blood cultures (ideally before starting antibiotics)
- Microscopy and culture of abscess fluid material (if this can be drained) to adjust empiric antibiotic treatment

Other Laboratory Tests

Determine disease severity and help identify a bacterial infection: White blood cell count, C-reactive protein and/or procalcitonin

Imaging

- Initial X-ray is important to localize the site and extent of the infection and/or to exclude alternative diagnosis
- Ultrasound is helpful to detect the presence of abscess (and to guide its drainage)
 - If available, also consider MRI or CT-scan because of their higher sensitivity to identify muscle swelling (i.e. inflammation) and the presence of purulent material

Most Likely Pathogens

- *Staphylococcus aureus* (>90%, including MRSA*)
 - Some strains can produce the Panton-Valentine leukocidin, a toxin that can cause a more severe disease. Consider especially in case of recurrent skin infections (decolonization measures can be considered to prevent recurrence and transmission)
- *Streptococcus* spp. (mostly *Streptococcus pyogenes*)
- *Escherichia coli* (sometimes, especially in oncology patients)

Rx Treatment

Clinical Considerations

• Drainage of the abscess remains the main approach to eliminate the source of infection

• Drainage is also important to obtain material for culture and identify the causative pathogen and its resistance profile

• **Mild:** Targeted antibiotic treatment preferred after having obtained culture results

• **Severe or impossible to obtain a clinical sample for microbiological examination:** Empiric treatment considering most likely pathogens including local prevalence and individual risk factors for MRSA

Important:

- **Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or rapid clinical improvement if culture results unavailable
- **Step down to oral treatment** is based on improvement of symptoms, signs of infection and the ability to take oral antibiotics

Antibiotic Treatment Duration

Treat for 2-3 weeks:

- 2 weeks in otherwise healthy patients and adequate source control
- 3 weeks if source control is not optimal or underlying diseases

Rx Antibiotic Treatment

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

 Amoxicillin+clavulanic acid 1 g+200 mg q8h **IV**
OR 875 mg+125 mg q8h **ORAL**

OR-----

 Cefalexin 500 mg q8h **ORAL**

OR-----

 Cloxacillin 2 g q6h **IV** OR 500 mg q6h **ORAL**

If cloxacillin is unavailable, any other IV antistaphylococcal penicillin could be used. For oral administration, dicloxacillin and flucloxacillin are preferred options within the class as they have better oral bioavailability

Pyomyositis

Skin and soft tissue infection • Page 1 of 2

Definition

An infection of a skeletal muscle caused by bacteria usually accompanied by abscess formation



Most Likely Pathogens

- *Staphylococcus aureus* (>90%, including MRSA*)
 - Some strains can produce the Panton-Valentine leukocidin, a toxin that can cause a more severe disease. Consider especially in case of recurrent skin infections (decolonization measures can be considered to prevent recurrence and transmission)
- *Streptococcus* spp. (mostly *Streptococcus pyogenes*)
- *Escherichia coli* (sometimes, especially in oncology patients)



Diagnosis



Clinical Presentation

- Acute onset of localized muscle pain with cramping usually in the lower limbs/gluteal muscles with fever $\geq 38.0^{\circ}\text{C}$ +/- swelling and induration of the affected area
- Other signs of systemic infection are usually present (e.g. tachycardia, leukocytosis)
- Abscess can form within days/weeks
- Signs of severe clinical progression (e.g. signs of sepsis/septic shock) should always be carefully monitored
- Complications due to bacteremia can occur (e.g. septic emboli, septic arthritis, endocarditis)



Microbiology Tests

- Blood cultures (ideally before starting antibiotics)
- Microscopy and culture of abscess fluid material (if this can be drained) to adjust empiric antibiotic treatment



Other Laboratory Tests

Determine disease severity and help identify a bacterial infection: White blood cell count, C-reactive protein and/or procalcitonin



Imaging

- Initial X-ray is important to localize the site and extent of the infection and/or to exclude alternative diagnosis
- Ultrasound is helpful to detect the presence of abscess (and to guide its drainage)
 - If available, also consider MRI or CT-scan because of their higher sensitivity to identify muscle swelling (i.e. inflammation) and the presence of purulent material

Pyomyositis

Skin and soft tissue infection • Page 2 of 2

Rx Treatment

Clinical Considerations

- Drainage of the abscess remains the main approach to eliminate the source of infection**
- Drainage is also important to obtain material for culture and identify the causative pathogen and its resistance profile
- Mild:** Targeted antibiotic treatment preferred after having obtained culture results
- Severe or impossible to obtain a clinical sample for microbiological examination:** Empiric treatment considering most likely pathogens including local prevalence and individual risk factors for MRSA

Important:

- Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or rapid clinical improvement if culture results unavailable
- Step down to oral treatment** is based on improvement of symptoms, signs of infection and the ability to take oral antibiotics

Rx Antibiotic Treatment

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated



Ampicillin+clavulanic acid

IV:

- 1st week of life: 50 mg/kg/dose of ampicillin component q12h

- > 1 week of life: 50 mg/kg/dose of ampicillin component q8h

- ORAL:** 80-90 mg/kg/day of ampicillin component

Oral weight bands:

3-<6 kg	250 mg of amox/dose q12h
6-<10 kg	375 mg of amox/dose q12h
10-<15 kg	500 mg of amox/dose q12h
15-<20 kg	750 mg of amox/dose q12h
≥20 kg	500 mg of amox/dose q8h or 1 g of amox/dose q12h

Amox = amoxicillin

Oral liquid must be refrigerated after reconstitution

OR



Cefalexin 25 mg/kg/dose q12h ORAL

Oral weight bands:

3-<6 kg	125 mg q12h
6-<10 kg	250 mg q12h
10-<15 kg	375 mg q12h
15-<20 kg	500 mg q12h
20-<30 kg	625 mg q12h
≥30 kg	500 mg q8h

OR



Cloxacillin IV

- Neonates: 25-50 mg/kg/dose q12h
- Children: 25 mg/kg/dose q6h
- ORAL:** 15 mg/kg/dose q6h
- Oral weight bands:**

3-<6 kg	62.5 mg q6h
6-<10 kg	125 mg q6h
10-<15 kg	250 mg q6h
15-<20 kg	375 mg q6h
≥20 kg	500 mg q6h

If cloxacillin is unavailable, any other IV antistaphylococcal penicillin could be used. For oral administration, dicloxacillin and flucloxacillin are preferred options within the class as they have better oral bioavailability

Pathophysiology

In pyomyositis, bacteria reach the muscle from another source of infection spread through the bloodstream. Once bacteria reach the muscle, an inflammatory reaction develops with initial swelling of the muscle and progressive abscess formation and increasing oedema. The process may take days to a few weeks for the signs of systemic infection to appear and the presence of a pus collection large enough to be drained to become clinically evident.

Epidemiology

Most cases of pyomyositis occur in tropical countries often in young children (< 5 years) or in adults (aged 20–45 years), and males are more affected than females. History of trauma or muscle strain are usually present. HIV infection, malnutrition and malignancies may be risk factors in the tropics, even though most patients are otherwise healthy. In non-tropical countries, the disease is more common in adults with underlying severe medical conditions, such as immunocompromised patients (358).

Clinical presentation

Pyomyositis is characterized by acute onset (usually days to a few weeks) of localized muscle pain with cramping usually in the lower limbs or in the gluteal muscles (although any muscle can be affected) with a fever $\geq 38.0^{\circ}\text{C}$. Swelling and induration (hardening of soft tissue) of the affected area are also usually present when the disease becomes clinically evident. Other signs of systemic infection (e.g. tachycardia, increased biomarker levels such as leukocytosis, C-reactive protein and procalcitonin) are usually present. Abscess can form within days to weeks. Complications of bacteraemia (e.g. septic emboli, septic arthritis and endocarditis) can occur. The patient should always be monitored for signs of severe clinical progression, such as signs of sepsis or septic shock.

Please also refer to the chapter on sepsis if suspected.

Most likely pathogens

Most cases (> 90%) of pyomyositis are caused by *Staphylococcus aureus* including MRSA or by *Streptococcus* spp. (mostly *Streptococcus pyogenes* often referred to as group A *Streptococcus*) (Table 38.1). *Escherichia coli* can sometimes be implicated, especially in patients with cancer. Mycobacteria (*Mycobacterium tuberculosis* and certain non-tuberculous mycobacteria) can also be responsible for this infection.

Table 38.1 – Pathogens most frequently associated with pyomyositis (in descending order of frequency)

Most cases	More rarely
<i>Staphylococcus aureus</i> (including MRSA) ^a	<i>Escherichia coli</i> (mostly in patients with cancer)
<i>Streptococcus pyogenes</i> (group A <i>Streptococcus</i>)	<i>Mycobacterium tuberculosis</i> and certain non-tuberculous mycobacteria

MRSA: methicillin-resistant *Staphylococcus aureus*.

^a Some strains can produce the Panton–Valentine leukocidin, a toxin associated with a higher pathogenic potential (i.e. the risk of causing a more severe disease). The possibility of *Staphylococcus aureus* positive for Panton–Valentine leucocidin should be considered especially in case of recurrent skin infections. In these cases, topical decolonization measures might be considered to prevent recurrence and transmission to others.

Laboratory tests

Patient microbiology tests

Microbiology tests (cultures of blood and abscess material) can be done to determine the causative pathogen and its resistance profile, ideally before starting antibiotic treatment (Table 38.2). In patients with severe disease, microbiology tests should however not delay antibiotic treatment.

Table 38.2 – Microbiology tests to consider in a patient with suspected pyomyositis as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
Blood cultures and antimicrobial susceptibility testing	To detect bacterial and fungal bloodstream infections	Health care facilities with clinical laboratories
Microscopy, culture and antimicrobial susceptibility testing of deep samples collected at aspiration/drainage of abscess	Initial step to detect and identify bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics.

Other tests

Laboratory tests can be used to complement the clinical examination and history. Table 38.3 indicates tests that could be considered in the initial assessment of the patient and to help guide the duration of antibiotic treatment.

Table 38.3 – Laboratory tests (other than microbiology) to consider to identify a bacterial infection as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
White blood count	To aid in the diagnosis of infections	Health care facilities with clinical laboratories but also in primary care settings
C-reactive protein	To detect inflammation as an indicator of various conditions (e.g. sepsis)	Health care facilities with clinical laboratories
Procalcitonin	To guide antibiotic therapy or discontinuation in sepsis	Only in tertiary and higher health care facilities

EDL: Model List of Essential In Vitro Diagnostics.

Using microbiology surveillance data

There is no role for routine surveillance to inform empiric guidance.

Imaging

Initial imaging with an X-ray is important when pyomyositis is suspected to locate the site and extent of the infection, any bony involvement or to exclude an alternative diagnosis. However, if available, MRI or a CT scan could also be considered because they have greater sensitivity (compared to conventional X-ray) in identifying muscle swelling (i.e. inflammation) and the presence of infected tissue.

Ultrasound is helpful, if available, to detect the presence of an abscess and to guide its drainage.

Management

Prompt drainage of the abscess (if present) is important for adequate control of the source of infection and is complementary to antibiotic treatment. If extensive muscle necrosis is present or if it is not possible to drain the collection of pus percutaneously, surgery may be necessary.

Antibiotic treatment

Targeted antibiotics based on microbiology tests are preferred in the treatment of pyomyositis. However, when patients require immediate treatment (e.g. are severely ill) or when it is impossible to obtain a clinical sample for microbiological examination, the choice of antibiotic should be based on the pathogens most commonly seen in this type of infection – *Staphylococcus aureus* and *Streptococcus* spp. (Table 38.4). In addition, empiric treatment against community-acquired MRSA may be considered in some cases based on individual risk factors (e.g. known MRSA colonization) and on the local prevalence of community-acquired MRSA. In these cases, some international guidance documents suggest using vancomycin (359).

Intravenous antibiotics may be needed, at least in the first phase of treatment.

Treatment duration is long (usually 2–3 weeks) and is influenced by the clinical and radiological response and by the adequacy of drainage of the abscess, if present. Shorter duration of treatment (2 weeks) could be considered in otherwise healthy patients and when adequate source control is achieved, that is the abscess is well drained. Longer duration (3 weeks) could be considered if source control is inadequate or in patients with underlying diseases.

Simplify empiric treatment to a more narrow-spectrum antibiotic (often also called de-escalation) based on culture results (targeted treatment) or rapid clinical improvement if culture results unavailable.

Step-down to oral treatment is based on improvement of symptoms and signs of infection and the ability to take oral antibiotics allowing discharge of the patient home when clinically appropriate.

Table 38.4 – Empiric antibiotic treatment for pyomyositis

Important		
Adults	Children	Total treatment duration
Amoxicillin+clavulanic acid	Amoxicillin+clavulanic acid ^b	2–3 weeks
IV: 1 g + 200 mg given every 8 hours Oral: 875 mg + 125 mg given every 8 hours	IV: First week of life: 50 mg/kg of amoxicillin/dose given every 12 hours Beyond first week of life: 50 mg/kg of amoxicillin/dose given every 8 hours Oral: 80–90 mg/kg/day of amoxicillin component Oral weight bands: 3–< 6 kg: 250 mg of amoxicillin/dose given every 12 hours 6–< 10 kg: 375 mg of amoxicillin/dose given every 12 hours 10–< 15 kg: 500 mg of amoxicillin/dose given every 12 hours 15–< 20 kg: 750 mg of amoxicillin/dose given every 12 hours ≥ 20 kg: 500 mg of amoxicillin/dose given every 8 hours or 1 g of amoxicillin/dose given every 12 hours	
OR Cefalexin (oral): 500 mg given every 8 hours	OR Cloxacillin ^a	
IV: 2 g given every 6 hours Oral: 500 mg given every 6 hours	3–< 6 kg: 125 mg given every 12 hours 6–< 10 kg: 250 mg given every 12 hours 10–< 15 kg: 375 mg given every 12 hours 15–< 20 kg: 500 mg given every 12 hours 20–<30 kg: 625 mg given every 12 hours ≥ 30 kg: use adult dose	
OR Cefalexin (oral): 25 mg/kg/dose given every 12 hours	OR	
Oral weight bands: 3–< 6 kg: 125 mg given every 12 hours 6–< 10 kg: 250 mg given every 12 hours 10–< 15 kg: 375 mg given every 12 hours 15–< 20 kg: 500 mg given every 12 hours 20–<30 kg: 625 mg given every 12 hours ≥ 30 kg: use adult dose	OR	

continues

Table 38.4 *continued*

Adults	Children	Total treatment duration
Cloxacillin^a		

IV:

- Neonates: 25–50 mg/kg/dose given every 12 hours
- Children: 25 mg/kg/dose given every 6 hours

Oral: 15 mg/kg/dose given every 6 hours

Oral weight bands:

- 3–< 6 kg: 62.5 mg given every 6 hours
- 6–< 10 kg: 125 mg given every 6 hours
- 10–< 15 kg: 250 mg given every 6 hours
- 15–< 20 kg: 375 mg given every 6 hours
- ≥ 20 kg: 500 mg given every 6 hours

EML: Model List of Essential Medicines; IV: intravenous.

Notes: All dosages are for normal renal and hepatic function.

The recommendations given in the table are not included in the WHO EML but were extrapolated from the EML recommendations for skin and soft tissue infections (8).

Vancomycin is not listed as first choice because in most settings methicillin-resistant *Staphylococcus aureus* is not a frequent cause of community-acquired infections.

^a If cloxacillin is unavailable, any other IV antistaphylococcal penicillin could be used. For oral administration, dicloxacillin and flucloxacillin are preferred options within the class as they have better oral bioavailability.

^b Oral liquid formulations must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

39. Febrile neutropenia

This chapter focuses on empiric treatment of suspected or confirmed bacterial infections in patients with neutropenia (including neutropenic sepsis) but it does not cover antiviral or antifungal treatment or antibiotic prophylaxis for patients with afebrile neutropenia, which are beyond the scope of this chapter.

Key messages

- Neutropenia is the most common complication of cancer treatment with cytotoxic chemotherapy.
- Patients can be at low or high risk of serious infections based on the duration of neutropenia.
- Febrile neutropenia often presents as unexplained fever with no site of infection or pathogen identified.
- Diagnostic tests depend on the most likely site of primary infection.
- Empiric antibiotic treatment should be started in febrile patients with a neutrophil count of $< 500 \text{ cells}/\mu\text{L}$ ($< 0.5 \times 10^9 \text{ cells/L}$) with treatment duration based on the clinical response irrespective of the neutrophil count.

Definition

Febrile neutropenia is a severe condition that can be caused by common Gram-positive and Gram-negative bacteria, fungi and other opportunistic pathogens. Febrile neutropenia occurs mostly in patients with neoplastic diseases who are receiving cytotoxic myelosuppressive chemotherapy.

Two elements need to be considered in defining febrile neutropenia: fever and neutropenia.

For fever, there are no universally accepted temperature cut-offs and slightly different cut-offs are used in different centres. Generally, a pragmatic definition of fever is $\geq 38.0^\circ\text{C}$. A more precise definition is used by the Infectious Diseases Society of America in their 2010 *Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer* (360) which is:

- a single oral temperature measurement of $\geq 38.3^\circ\text{C}$ or
- a temperature of $\geq 38.0^\circ\text{C}$ sustained over 1 hour.

There is less variation in definition of neutropenia, which is defined as a temporary reduction in the absolute neutrophil count; an absolute neutrophil count of < 1000 (sometimes < 1500) cells/ μ L ($< 1.0 \times 10^9$ cells/L) is considered indicative of neutropenia. Neutropenia can be classified as severe when the absolute neutrophil count is < 500 cells/ μ L ($< 0.5 \times 10^9$ cells/L) – also called agranulocytosis – and profound when absolute neutrophil count is < 100 cells/ μ L ($< 0.1 \times 10^9$ cells/L).

Febrile neutropenia can be characterized according to identification of the causative pathogen and source of infection as:

- microbiologically proven infection (i.e. the causative pathogen is identified)
- clinical source of infection diagnosed but no pathogen identified (e.g. pharyngitis)
- unexplained fever (no pathogen identified and no clear source of infection)
- non-infectious fever (e.g. medicine-induced).

Unexplained fever with no focus or positive culture is the most common situation observed in clinical practice.

Febrile neutropenia

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This guidance covers suspected bacterial infections in neutropenic patients (including neutropenic sepsis) but not antiviral or antifungal treatment nor antibiotic prophylaxis for patients with afebrile neutropenia or prophylaxis with granulocyte colony-stimulating factors

Definition

- A severe syndrome that can occur in patients with neoplastic diseases receiving cytotoxic myelosuppressive chemotherapy
- Two elements need to be considered:
 - Fever: Body temperature $\geq 38.0^{\circ}\text{C}$
 - Neutropenia: Temporary reduction of the absolute neutrophil count (ANC) $<1000 \text{ cells}/\mu\text{L} (<1.0 \times 10^9/\text{L})$

Severity:

- Severe neutropenia: ANC $<500 \text{ cells}/\mu\text{L} (<0.5 \times 10^9/\text{L})$
- Profound neutropenia: ANC $<100 \text{ cells}/\mu\text{L} (<0.1 \times 10^9/\text{L})$

Categorized by risk of developing severe infections (requiring or prolonging hospitalization):

- Low risk: ≤ 7 days of severe neutropenia and no ongoing comorbidities (beside cancer) or renal or hepatic dysfunction
- High risk: >7 days of severe neutropenia and ongoing comorbidities (beside cancer) or renal or hepatic dysfunction

Note: these are ways to classify neutropenia and narrow down the differential diagnosis

Characterized according to identification of causative pathogen and source of infection:

1. Microbiologically proven infection (causative pathogen identified)
2. Clinical source of infection diagnosed but no pathogen identified (e.g. pharyngitis)
3. Unexplained fever (no pathogen identified and no clear source of infection) (most common scenario)
4. Non-infectious fever (e.g. drug-induced)

Most Likely Pathogens

Mostly bacteria that colonize patient's own skin and bowel including multidrug-resistant organisms

Gram-positive bacteria:

- *Staphylococcus* spp. (including MRSA)
- *Streptococcus* spp.
- *Enterococcus* spp. (including vancomycin-resistant Enterococci)

Gram-negative bacteria:

- Enterobacteriales and *Pseudomonas aeruginosa* (including ESBL and carbapenemase-producing strains)

Other pathogens:

- Anaerobes
- Consider fungi (mostly *Candida albicans* and *Aspergillus* spp.) and viruses (e.g. cytomegalovirus, human herpesvirus 6) if longer duration of neutropenia

Diagnosis

Clinical Presentation

- Presentation is highly variable depending on the underlying infection
- Fever is usually present but because patients with neutropenia fail to produce effective inflammatory responses, they can sometimes present with few clinical findings and no fever despite infection
- Clinical progression to severe disease or death can be very rapid (over a few hours); signs of sepsis/septic shock should always be carefully monitored

Microbiology Tests

Important: microbiology tests to consider in the initial assessment depend on the most likely source of infection and should ideally be taken before starting antibiotic treatment

Always obtain:

- Blood cultures
- Urine culture
- In selected cases, consider:**
- Sputum microscopy and culture
- Nasopharyngeal swab for nucleic acid test for influenza and other respiratory viruses (including SARS-CoV-2)
- Cerebrospinal fluid (CSF) microscopy and bacterial culture
- Stool culture
- *C. difficile* testing
- Tests to diagnose invasive fungal infections and other viral etiologies (especially in high-risk patients)

Other Laboratory Tests

Important: tests to consider in the initial assessment depend on the most likely source of infection

- Complete blood count, bilirubin, creatinine, electrolytes, blood pH and gases, whole blood lactate, C-reactive protein and/or procalcitonin

Imaging

- Consider imaging in initial assessment to identify the source of infection (depending on clinical presentation)
- Consider additional imaging to expand diagnostic work-up or to exclude a complicated infection if no clinical improvement after a few days of treatment

Febrile neutropenia

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Rx Treatment

Clinical Considerations

- Antibiotic treatment should consider the most likely site of infection, local prevalence of resistance and individual risk factors for resistant pathogens (especially ESBL, carbapenemase-producing isolates and MRSA)
- In addition to antibiotic treatment, it is important that source control is achieved; consider removal of an infected central venous catheter
- If fever persists and there is no clinical improvement after 48–72 hours, consider further tests to identify source or assess whether a local complication has developed (consider a resistant organism or non-bacterial infection)

Patients with severe neutropenia (<500 cells/ μ L or $<0.5 \times 10^9/L$) who develop fever:

- Should promptly receive antibiotic treatment even when a clear site of infection is not identified

Low-risk patients:

- Outpatient setting with monitoring and follow-up, if oral treatment tolerated

High-risk patients (or close follow-up unfeasible):

- Hospitalization and initial IV treatment
- Step down from IV to oral antibiotics is suggested when the patient has clinically improved, is afebrile and is able to tolerate oral treatment

Rx Low Risk

Important: treatment escalation in case of persistent fever is beyond the scope of this guidance

All dosages are for normal renal function

 Amoxicillin+clavulanic acid 500 mg + 125 mg q8h **ORAL**
ACCESS WATCH

CONSIDER ADDING

 Ciprofloxacin 500 mg q12h **ORAL**
WATCH

Antibiotic Treatment Duration

Low-risk patients: 7 days

High-risk patients: Until clinical signs of infection resolved AND no fever for at least 48 hours

- Mostly depends on clinical response and (if identified) infectious site and causative pathogen
- Current evidence suggests discontinuation based on clinical approach and not neutrophil count

Important: If using combination therapy, reassess the need to continue combination over time based on microbiology test results and clinical response

Rx High Risk

Important: treatment escalation in case of persistent fever is beyond the scope of this guidance

All dosages are for normal renal function

First Choice

 Piperacillin+tazobactam 4 g + 500 mg q6h **IV**
WATCH

Second Choice

 Meropenem 1 g q8h **IV**
WATCH

Consider meropenem only in settings with high prevalence of ESBL-producing Enterobacteriales or in patients with known prior colonization or infection with resistant pathogens

CONSIDER ADDING TO EITHER REGIMEN

 Amikacin 15 mg/kg q24h **IV**
ACCESS

If resistant Gram-negative bacteria suspected

----- AND/OR -----

 Vancomycin 15–20 mg/kg q12h **IV**
WATCH

If MRSA suspected

Febrile neutropenia

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This guidance covers suspected bacterial infections in neutropenic patients (including neutropenic sepsis) but not antiviral or antifungal treatment nor antibiotic prophylaxis for patients with afebrile neutropenia or prophylaxis with granulocyte colony-stimulating factors

Definition

- A severe infection that can occur in patients with neoplastic diseases receiving cytotoxic myelosuppressive chemotherapy
- Two elements need to be considered:
 - Fever: Temperature $\geq 38.0^{\circ}\text{C}$
 - Neutropenia: Temporary reduction of the absolute neutrophil count (ANC) $<1000 \text{ cells}/\mu\text{L} (<1.0 \times 10^9/\text{L})$

Severity:

- Severe neutropenia: ANC $<500 \text{ cells}/\mu\text{L} (<0.5 \times 10^9/\text{L})$
- Profound neutropenia: ANC $<100 \text{ cells}/\mu\text{L} (<0.1 \times 10^9/\text{L})$

Categorized by risk of developing severe infections (requiring or prolonging hospitalization):

- Low risk:* ≤ 7 days of severe neutropenia and no ongoing comorbidities (beside cancer) or renal or hepatic dysfunction
- High risk:* >7 days of severe neutropenia and ongoing comorbidities (beside cancer) or renal or hepatic dysfunction

Note: these are ways to classify neutropenia and narrow down the differential diagnosis

Characterized according to identification of causative pathogen and source of infection:

- Microbiologically proven infection (causative pathogen identified)
- Clinical source of infection diagnosed but no pathogen identified (e.g. pharyngitis)
- Unexplained fever (no pathogen identified and no clear source of infection) (most common scenario)
- Non-infectious fever (e.g. drug-induced)



Most Likely Pathogens

Mostly bacteria that colonize patient's own skin and bowel including multidrug-resistant organisms

Gram-positive bacteria:

- Staphylococcus* spp. (including MRSA)
- Streptococcus* spp.
- Enterococcus* spp. (including vancomycin-resistant Enterococci)

Gram-negative bacteria:

- Enterobacteriales and *Pseudomonas aeruginosa* (including ESBL and carbapenemase-producing strains)

Other pathogens:

- Anaerobes
- Consider fungi (mostly *Candida albicans* and *Aspergillus* spp.) and viruses (e.g. cytomegalovirus, human herpesvirus 6) if longer duration of neutropenia

Diagnosis

Clinical Presentation

- Presentation is highly variable depending on the underlying infection
- Fever is usually present but symptoms and signs are masked and a child can present with no fever and few signs despite infection
- Clinical progression to severe disease or death can be very rapid (over a few hours); signs of sepsis/septic shock should always be carefully monitored

Microbiology Tests

Important: microbiology tests to consider in the initial assessment depend on the most likely source of infection and should ideally be taken before starting antibiotic treatment

Always obtain:

- Blood cultures
- Urine culture

In selected cases, consider:

- Sputum microscopy and culture
- Nasopharyngeal swab for nucleic acid test for influenza and other respiratory viruses (including SARS-CoV-2)
- Cerebrospinal fluid (CSF) microscopy and bacterial culture
- Stool culture
- C. difficile* testing
- Tests to diagnose invasive fungal infections and other viral etiologies (especially in high-risk patients)

Other Laboratory Tests

Important: tests to consider in the initial assessment depend on the most likely source of infection

- Complete blood count, bilirubin, creatinine, electrolytes, blood pH and gases, whole blood lactate, C-reactive protein and/or procalcitonin

Imaging

- Consider imaging in initial assessment to identify the source of infection (depending on clinical presentation)
- Consider additional imaging - CT chest and abdominal ultrasound to expand diagnostic work-up or to exclude a complicated infection if no clinical improvement after a few days of treatment

Febrile neutropenia

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Rx Treatment

Clinical Considerations

- Antibiotic treatment should consider the most likely site of infection, local prevalence of resistance and individual risk factors for resistant pathogens (especially ESBL, carbapenemase-producing isolates and MRSA)
 - In addition to antibiotic treatment, it is important that source control is achieved; consider removal of an infected Central Venous Catheter
 - If fever persists and there is no clinical improvement after 48–72 hours, consider further tests to identify source or assess whether a local complication has developed (consider a resistant organism or non-bacterial infection)
- Patients with severe neutropenia (<500 cells/ μ L or $<0.5 \times 10^9/L$) who develop fever:**
- Should promptly receive antibiotic treatment even when a clear site of infection is not identified

Low-risk patients:

- Outpatient setting with monitoring and follow-up, if oral treatment tolerated

High-risk patients (or close follow-up unfeasible):

- Hospitalization and initial IV treatment
- Step down from IV to oral antibiotics is suggested when the patient has clinically improved, is afebrile and is able to tolerate oral treatment

Rx Low Risk

All dosages are for normal renal function



Amoxicillin+clavulanic acid 80–90 mg/kg/day of amoxicillin component **ORAL**

• Oral weight bands:

3-<6 kg	250 mg of amox/dose q12h
6-<10 kg	375 mg of amox/dose q12h
10-<15 kg	500 mg of amox/dose q12h
15-<20 kg	750 mg of amox/dose q12h
≥20 kg	500 mg of amox/dose q8h or 1 g of amox/dose q12h

Amox = amoxicillin

Oral liquid must be refrigerated after reconstitution

CONSIDER ADDING



Ciprofloxacin 15 mg/kg/dose q12h **ORAL**

• Oral weight bands:

3-<6 kg	50 mg q12h
6-<10 kg	100 mg q12h
10-<15 kg	150 mg q12h
15-<20 kg	200 mg q12h
20-<30 kg	300 mg q12h
≥30 kg	500 mg q12h

Antibiotic Treatment Duration

Low-risk patients: **7 days**

High-risk patients: Until clinical signs of infection resolved AND no fever for at least 48 hours

- Mostly depends on clinical response and (if identified) infectious site and causative pathogen
- Current evidence suggests discontinuation based on clinical approach and not neutrophil count

Important: If using combination therapy, reassess the need to continue combination over time based on microbiology test results and clinical response

Rx High Risk

All dosages are for normal renal function

First Choice



Piperacillin+tazobactam 100 mg/kg/dose of piperacillin component q8h **IV**

Second Choice



Meropenem 20 mg/kg/dose q8h **IV**

Consider meropenem only in settings with high prevalence of ESBL-producing *Enterobacteriales* or in patients with known prior colonization or infection with resistant pathogens

CONSIDER ADDING TO EITHER REGIMEN



Amikacin 15 mg/kg q24h **IV**

If resistant Gram-negative bacteria suspected

----- AND/OR -----



Vancomycin **IV**

- Neonates: 15 mg/kg/dose q12h
- Children: 15 mg/kg/dose q8h

If MRSA suspected

Pathophysiology

Neutropenia (i.e. decreased number of circulating neutrophils) can develop as the result of a reduced production of neutrophils by the bone marrow, or increased peripheral destruction or sequestration at localized inflammatory sites. Once neutrophils fall below a certain threshold, the risk of developing infections increases. Severity and duration of neutropenia are independent risk factors for serious infection, that is, the risk is higher with longer and more severe neutropenia.

It is beyond the scope of this chapter to describe how cytotoxic chemotherapies and cancer affect the immune system and predispose to infection. As well as a reduced absolute neutrophil count, patients with cancer and on cytotoxic chemotherapy often also have dysfunctional lymphocytes or immunoglobulin deficiencies, impaired natural barriers to infection (e.g. mucositis) and malnutrition, which additionally weaken their ability to control infections. Furthermore, the presence of invasive devices (e.g. intravascular catheters) is an additional risk factor for infection to consider.

Epidemiology

Neutropenia is the most common complication of cytotoxic cancer treatment that can lead to treatment delays and reductions in the chemotherapy dose (361). The risk of developing febrile neutropenia depends on: the type of underlying tumour (e.g. very high in patients with acute leukaemia and lower in patients with solid tumours); the type and dose of chemotherapy used; and individual risk factors, such as older age, advanced stage of disease, comorbidities, other concomitant myelotoxic medications (362). The risk of developing severe infection depends on the duration and severity of neutropenia; therefore, initial risk assessment is an important step to identify patients at low or high risk of developing serious complications, such as complications requiring hospitalization or prolonging hospitalization. As well as the physician's assessment, several scoring systems exist (e.g. Multinational Association of Supportive Care in Cancer (MASCC) score) to help predict this risk (363). These systems usually include a combination of factors, such as general clinical status of the patient, presence of comorbidities, age and whether the patient is hospitalized or not. However, no system can distinguish patients at low or high risk of infection with complete accuracy (364).

Low-risk patients are those expected to have a shorter duration of severe neutropenia (≤ 7 days) and have no comorbidities (other than cancer) or renal or hepatic dysfunction. High-risk patients are expected to remain neutropenic for longer periods (> 7 days) or are those with ongoing comorbidities (other than cancer) and renal or hepatic dysfunction.

Neutropenia is also common in children receiving myelosuppressive treatment – especially for acute lymphoblastic leukaemia or lymphoma (the most common forms of

cancer in childhood (365)) and for acute myeloid leukaemia – or after haemopoietic stem cell transplantation or treatment for certain aggressive solid tumours, such as neuroblastoma (366,367).

Most likely pathogens

A fever of infectious origin in a patient with neutropenia is most likely caused by bacteria that colonize the patient's own skin and bowel, including multidrug-resistant organisms such as ESBL-producing or carbapenemase-producing Gram-negative bacteria (Table 39.1). These patients often receive broad-spectrum antibiotics while in hospital and are therefore at increased risk of antibiotic-resistant infections. Furthermore, certain pathogens (e.g. fungi) become more frequent with longer duration of neutropenia.

Table 39.1 – Pathogens most frequently associated with febrile neutropenia (in descending order of frequency)

Bacteria	Viruses	Parasites
<i>Staphylococcus epidermidis</i>	Cytomegalovirus	<i>Candida</i> spp.
<i>Staphylococcus aureus</i> (including MRSA)	Human herpesvirus 6	<i>Aspergillus</i> spp. (in case of prolonged neutropenia)
<i>Streptococcus</i> spp.	(Consider viruses in high-risk patients mostly because of reactivation of latent infections)	
Other Gram-positive bacteria (e.g. <i>Enterococcus</i> spp. including VRE)		
Enterobacteriales (including multidrug-resistant strains such as those producing ESBL and carbapenemases)		
<i>Pseudomonas aeruginosa</i>		
Anaerobes		

ESBL: extended-spectrum beta-lactamases; MRSA: methicillin-resistant *Staphylococcus aureus*; VRE: vancomycin-resistant Enterococci.

Notes. The risk of multidrug-resistant pathogens should always be carefully considered in patients with neutropenia because often infections in these patients are health care-associated.

Most data come from tertiary care centres in high-income settings.

Clinical presentation

Apart from fever, other accompanying signs and symptoms of febrile neutropenia vary greatly depending on the underlying infection, for example, pneumonia, UTI, skin infection, meningitis, colitis. Bacteraemia (i.e. the detection of bacteria in blood cultures) may be present. Because patients with neutropenia fail to produce effective inflammatory responses, they can sometimes present with few clinical findings and no fever despite infection.

A detailed clinical examination should always be done to help identify the site of infection. Skin changes (e.g. rash, ulcers, signs of vascular infection), changes in the oral mucosa and pharynx (e.g. ulcers inside the mouth, dental disease, thrush), abnormalities in the perineal and perirectal area, symptoms and signs of typhlitis (inflammation of the cecum) and colitis with abdominal pain, diarrhoea and sometimes rectal bleeding often due to mucositis should therefore always be carefully investigated.

Clinical progression to severe disease or death can be very rapid (over a few hours); therefore, the presence of any signs of sepsis or septic shock should always be carefully monitored. Please also refer to the chapter on sepsis if suspected.

Laboratory tests

Patient microbiology tests

Whenever possible a microbiology sample (e.g. blood cultures) should be obtained – ideally before antibiotic treatment is started – because results of the test can help establish the diagnosis and treatment can be adapted accordingly.

Tests to consider depend on the most likely primary site of infection and should therefore be adapted based on the clinical presentation (Table 39.2). Some tests should always be performed (indicated as routine tests in Table 39.2), while others could be considered in certain cases, including for surveillance purposes and based on local availability. Additional tests not presented in the table but that could be considered, especially in high-risk patients, include tests to diagnose invasive fungal infections (e.g. *Aspergillus* galactomannan antigen screening) and those for other viral infections, such as nucleic acid amplification test for cytomegalovirus.

Other tests

Laboratory tests to consider if febrile neutropenia is suspected depend on the most likely source of infection and are shown in Table 39.3.

Table 39.2 – Microbiology tests to consider when febrile neutropenia is suspected depending on the most likely source of infection as indicated in the WHO EDL (6)

Test priority	Diagnostic test	Purpose of the test	Settings where the test should be available
Routine	Blood cultures and antimicrobial susceptibility testing	To detect bacterial and fungal bloodstream infections	Health care facilities with clinical laboratories
Routine	Urine culture and antimicrobial susceptibility testing	Initial step to detect and identify bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories
Consider in certain cases	Sputum microscopy (Gram stain)	To assess microbial morphology and adequacy of the specimen for culture by identifying white blood cells and squamous epithelial cells	Health care facilities with clinical laboratories
Consider in certain cases	Sputum culture and antimicrobial susceptibility testing	Initial step to detect and identify bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories
Consider in certain cases (including for infection control purposes)	Nasopharyngeal swab for NAAT for influenza ^a	To diagnose seasonal influenza infection	Health care facilities with clinical laboratories but also in primary care settings
Consider in certain cases (including for infection control purposes)	Nasopharyngeal swab for NAAT or antigen test for SARS-CoV-2	To diagnose COVID-19	Health care facilities with clinical laboratories (NAAT) and primary care settings (antigen test)
Consider in certain cases	Aspergillus antigen test	To diagnose invasive aspergillosis in Immunocompromised patients	Health care facilities with clinical laboratories

continues

Table 39.2 *continued*

Test priority	Diagnostic test	Purpose of the test	Settings where the test should be available
Consider in certain cases	Cerebrospinal fluid microscopy	To assess microbial morphology, number of white blood cells and red blood cells	Health care facilities with clinical laboratories
Consider in certain cases	Cerebrospinal fluid Gram stain, bacterial culture and antimicrobial susceptibility testing	Initial step to detect and identify bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories
Consider in certain cases	Stool culture and antimicrobial susceptibility testing	Initial step to detect and identify bacterial species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories
Consider in certain cases	<i>Clostridioides difficile</i> testing (usually NAAT)	To diagnose <i>Clostridioides difficile</i> infection	— ^b

COVID-19: coronavirus disease 2019; EDL: Model List of Essential In Vitro Diagnostics; NAAT: nucleic acid amplification test; SARS CoV-2: severe acute respiratory syndrome coronavirus 2.

^a Testing for respiratory viruses other than influenza (e.g. respiratory syncytial virus) could be considered based on availability and local epidemiology.

^b This test is not in the WHO EDL (6).

Table 39.3 – Laboratory tests to consider when febrile neutropenia is suspected as indicated in the WHO EDL (6)

Diagnostic test	Purpose of the test	Settings where the test should be available
Complete blood count	To detect a wide range of disorders (e.g. severity of neutropenia, anaemia, thrombocytopenia), including infections	Health care facilities with clinical laboratories
C-reactive protein ^a	To detect inflammation as an indicator of various conditions (e.g. sepsis)	Health care facilities with clinical laboratories
Procalcitonin ^a	To guide antibiotic therapy or discontinuation in sepsis	Only in tertiary care facilities
Bilirubin	To detect or monitor liver disease	Community settings and health facilities without laboratories ^b
Creatinine	To monitor kidney function for management of severe infections (i.e. sepsis) and to adjust antimicrobial regimens	Health care facilities with clinical laboratories
Electrolytes	To monitor fluid, electrolyte and acid–base balance	Health care facilities with clinical laboratories
Blood pH and gases	To assess lung function, metabolic or kidney disorders and monitor oxygen therapy	Health care facilities with clinical laboratories
Whole blood lactate	To assess metabolic acidosis, sepsis and dehydration	Community settings and health facilities without laboratories ^b

EDL: Model List of Essential In Vitro Diagnostics.

^a Measurement of biomarkers on admission (C-reactive protein and procalcitonin) might help identify high-risk patients and predict severe outcomes, such as sepsis (368–370).

^b Community and health settings without laboratories are facilities such as health posts and centres, doctors' offices, outreach clinics, ambulatory care and home-based and self-testing. These tests are assumed to be available at health care facilities with laboratories.

Using microbiology surveillance data

Empiric guidance given by the AWaRe book could be reviewed and adapted based on local clinically relevant microbiology surveillance data. This would include blood culture data from local haemato-oncology patients, ideally risk-stratified by underlying diagnosis.

Imaging

Imaging based on clinical presentation should be considered in the patient's initial assessment to identify the source of infection. If there is no clinical improvement and the fever does not resolve with treatment in a few days, additional imaging could be considered (e.g. CT scan of the lungs and sinuses, and other tests based on clinical suspicion) to expand diagnostic work-up or to exclude a complicated infection such as invasive fungal disease.

Treatment

This chapter focuses on antibiotic treatment of suspected or confirmed bacterial infections but it does not cover antiviral or antifungal treatment. It also does not cover prophylaxis with granulocyte colony-stimulating factors (i.e. growth factors that stimulate the bone marrow to produce more neutrophils) such as filgrastim listed on the EML since 2015 for the treatment of acquired neutropenia.

The use of granulocyte colony-stimulating factors for therapeutic purposes (i.e. in febrile patients) is controversial and guidelines vary in their recommendations. Evidence shows that their use in combination with antibiotics does not reduce mortality compared with antibiotics alone; however, granulocyte colony-stimulating factors could be considered in certain patients because their use is associated with shorter hospital stay and duration of antibiotic use (reduced by 1–2 days) most likely due to the faster neutrophil recovery (371).

It is important that source control is achieved as early as possible, this includes drainage of any abscesses and removal or change of invasive devices such as central venous catheters, where appropriate.

Antibiotic treatment

Patients with neutropenia who develop fever should promptly receive antibiotic treatment even when a clear site of infection is not identified (372).

Low-risk patients can be managed in an outpatient setting if adequate monitoring and follow-up are available and if they are able to tolerate oral treatment (373). High-risk patients, or patients where close follow-up is not feasible, require hospitalization and initial intravenous treatment to start with.

The choice of empiric treatment should always consider a combination of factors, including the most likely site of primary infection and the infecting pathogens (including risk of viral and invasive fungal infections) and the local pattern of AMR. Other factors, such as known colonization or previous infection with multidrug-resistant organisms and recent

antibiotic exposure (including antibiotic prophylaxis) are also important factors to consider. Recommended empiric antibiotic options are given in Table 39.4.

 **Note**

Table 39.4 refers to empiric treatment not to treatment escalation in case of persistent fever which is beyond the scope of the chapter.

Simplify empiric treatment to a more narrow-spectrum antibiotic (often also called de-escalation) based on culture results (targeted treatment) or rapid clinical improvement if culture results unavailable.

Step down to oral antibiotics is suggested when the patient has made a good clinical response, the fever has settled and the patient can tolerate oral antibiotics.

Antibiotic treatment for patients with febrile neutropenia may require adjustments in dose and frequency of administration because pharmacokinetic and pharmacodynamic parameters could be altered in these patients and renal and hepatic toxicity related to chemotherapy is common (374).

If the causative pathogen is identified, once susceptibilities are known, antibiotics should be reviewed and modified accordingly. However, even if adequate microbiological sampling is performed, a pathogen is often not identified.

If fever persists (e.g. patient still has a temperature 48–72 hours after the start of antibiotic treatment) and there is no clinical improvement, further diagnostic tests (e.g. imaging) could be performed to identify the source of infection (if this is still unclear) or to assess whether a local complication has developed such as a fluid collection. In addition, a resistant pathogen or an invasive fungal disease should be considered as they could be responsible for the prolonged fever.

Duration of treatment will mostly depend on the clinical response (e.g. resolution of fever and clinical recovery) and, if identified, on the infectious site and the causative pathogen.

Continuation of antibiotic treatment until neutrophil recovery (absolute neutrophil count $> 500 \text{ cells}/\mu\text{L}$; $> 0.5 \times 10^9 \text{ cells/L}$) is controversial with guidelines varying in their recommendations. Evidence suggests that discontinuation of antibiotics based on a positive clinical assessment – for example, if the clinical recovery is good and no source is identified or if an infection has been adequately treated and irrespective of the neutrophil count – can safely reduce exposure to antibiotics (375,376).

Table 39.4 – Initial empiric antibiotic treatment for febrile neutropenia (absolute neutrophil count < 500 cells/ μ L ($< 0.5 \times 10^9$ cells/L)) based on the patient's initial risk assessment

Patient risk	Adults	Children	Total treatment duration
Low risk: expected duration of neutropenia < 7 days, no major comorbidities, no organ dysfunction, possible outpatient treatment	<p>Amoxicillin+clavulanic acid (oral); 500 mg+125mg given every 8 hours</p> <p>CONSIDER ADDING</p> <p>Ciprofloxacin^a (oral); 500 mg given every 12 hours</p>	<p>Amoxicillin+clavulanic acid^b (oral); 80–90 mg/kg/day of amoxicillin component</p> <p>Oral weight bands:</p> <ul style="list-style-type: none"> 3–< 6 kg: 250 mg of amoxicillin/dose given every 12 hours 6–< 10 kg: 375 mg of amoxicillin/dose given every 12 hours 10–< 15 kg: 500 mg of amoxicillin/dose given every 12 hours 15–< 20 kg: 750 mg of amoxicillin/dose given every 12 hours \geq 20 kg: 500 mg of amoxicillin/dose given every 8 hours or 1 g of amoxicillin/dose given every 12 hours <p>CONSIDER ADDING</p> <p>Ciprofloxacin (oral) 15 mg/kg/dose given every 12 hours</p> <p>Oral weight bands:</p> <ul style="list-style-type: none"> 3–< 6 kg: 50 mg given every 12 hours 6–< 10 kg: 100 mg given every 12 hours 10–< 15 kg: 150 mg given every 12 hours 15–< 20 kg: 200 mg given every 12 hours 20–<30 kg: 300 mg given every 12 hours \geq 30 kg: use adult dose 	

continues

Table 39.4 continued

Patient risk	Adults	Children	Total treatment duration
High risk: expected duration of neutropenia > 7 days, major comorbidities, organ dysfunction	<p>First choice</p> <p>Piperacillin-tazobactam (IV): 4g + 500 mg given every 6 hours</p> <p>Second choice</p> <p>Meropenem ^c (IV): 1g given every 8 hours</p> <p>CONSIDER ADDING</p> <p>Amikacin ^d (IV): 15 mg/kg/dose given once a day</p> <p>AND/OR</p> <p>Vancomycin ^e (IV):</p> <ul style="list-style-type: none"> • Neonates: 15 mg/kg/dose given every 12 hours • Children: 15 mg/kg/dose given every 8 hours given every 12 hours 	<p>First choice</p> <p>Piperacillin-tazobactam (IV): 100 mg/kg/dose of piperacillin component given every 8 hours</p> <p>Second choice</p> <p>Meropenem ^c (IV): 20 mg/kg/dose given every 8 hours</p> <p>CONSIDER ADDING</p> <p>Amikacin ^d (IV): 15 mg/kg/dose given once a day</p> <p>AND/OR</p> <p>Vancomycin ^e (IV):</p> <ul style="list-style-type: none"> • Neonates: 15 mg/kg/dose given every 12 hours • Children: 15 mg/kg/dose given every 8 hours given every 12 hours 	Until clinical signs of infection have resolved, including absence of fever for at least 48 hours. If a pathogen is identified, the duration of therapy will be based on the particular pathogen and site of infection. If the patient still has neutropenia, he/she should be closely monitored for 24–48 hours and if fever returns, antibiotics should be restarted.

Continues

Table 39.4 continued

ESBL: extended-spectrum beta-lactamase; IV: intravenous; MRSA: methicillin-resistant *Staphylococcus aureus*.

Note. All dosages are for normal renal and hepatic function.

^aThe use of fluoroquinolones (such as ciprofloxacin) can be associated with important side-effects including: (i) mental health disturbances such as disorientation, agitation, nervousness, memory impairment and delirium; (ii) serious blood sugar disturbances such as hypoglycaemic coma; (iii) increased risk of tendonitis and tendon rupture; (iv) worsening symptoms in those with myasthenia gravis; and (v) potential irreversible neuropathy (serious nerve damage).

^bOral liquid formulations must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures.

^cEmpiric meropenem should only be considered in settings with a high prevalence of ESBL-producing Enterobacteriales or in patients with known prior colonization or infection with resistant pathogens.

^dConsider adding amikacin in combination with piperacillin+tazobactam or meropenem when infections with resistant Gram-negative bacteria are suspected based on local epidemiology and clinical presentation; for example, severely ill patients including those who become clinically unstable after initial empiric monotherapy, and patients with known prior colonization or infection with ESBL-producing Enterobacteriales. The need to continue combination treatment should be reassessed over time (e.g. after 48–72 hours) based on microbiology test results and clinical response.

^eConsider adding vancomycin in combination with piperacillin+tazobactam or meropenem when infection with MRSA is suspected (e.g. patients with MRSA colonization) or where a line infection is strongly suspected because of the risk of multidrug-resistant coagulase-negative *Staphylococcus* infection. The need to continue combination treatment should be reassessed over time (e.g. after 48–72 hours) based on microbiology test results and clinical response.

40. Surgical prophylaxis

Antibiotic prophylaxis prior to dental surgeries is not addressed in this chapter.

Key messages

- Surgical site infections are an important complication of surgical procedures and appropriate antibiotic prophylaxis can reduce the risk of surgical site infections for certain procedures.
- Access group antibiotics are recommended as the first-choice options in most cases.
- Depending on the type of surgery, antibiotic prophylaxis may need to be adapted in people colonized with multidrug-resistant organisms.
- The indication and choice of antibiotic prophylaxis depends on the type of surgical procedure. Not all surgical procedures require prophylaxis.
- Prophylaxis should not be continued after surgery to prevent infection. One antibiotic dose covers the entire duration of potential contamination during surgery in most cases.



Other relevant WHO resources (please check regularly for updates)

- Global guidelines for the prevention of surgical site infection, second edition (280).

Definition of terms used in this chapter

Definitions are taken from the 2018 WHO publication: *Global guidelines for the prevention of surgical site infections* (280).

Antibiotic prophylaxis: prevention of infectious complications by administering an effective antimicrobial agent before exposure to contamination during surgery.

Surgical procedure: an operation where at least one incision (including laparoscopic incisions) is made through the skin or mucous membrane, or a reoperation through an incision that was left open after a previous operative procedure, and takes place in the operating room.

Surgical site infection: an infection that occurs after surgery in the part of the body where the surgery took place. Surgical site infections can sometimes be superficial infections involving the skin only. Other surgical site infections are more serious and can involve tissues under the skin, organs or implanted material.

Surgical site infection is also defined as an infection that occurs up to 30 days after an operation and affects:

- the skin and subcutaneous tissue of the surgical incision (superficial incisional); and/or
- the deep soft tissue (for example, fascia or muscle) of the incision (deep incisional) and/or
- any part of the anatomy (e.g. organs and spaces) other than the incision that was opened or manipulated during an operation (organ or space).

Surgical wound: a wound created when an incision is made with a scalpel or other sharp cutting device and then closed in the operating room by suture, staple, adhesive tape, or glue and bringing the skin edges together.

Categories of surgical wound

- *Clean:* an uninfected surgical wound in which no inflammation is found, and which is not in the respiratory, alimentary, genital or urinary tracts. In addition, clean wounds are usually closed and, if necessary, drained with closed drainage. Surgical incisional wounds that are done after non-penetrating (blunt) trauma should be included in this category if they meet the criteria.
- *Clean-contaminated:* a surgical wound in the respiratory, alimentary, genital or urinary tracts which was made under controlled conditions and without unusual contamination. Operations involving the biliary tract, appendix, vagina and oropharynx are included in this category, provided no evidence of infection or major (i.e. significant) break in sterile technique is found.
- *Contaminated:* open, fresh, accidental wounds. Also included in this category are: operations with major break in sterile technique (e.g. open cardiac massage) or substantial spillage (of gastrointestinal contents) from the gastrointestinal tract; and incisions in which acute, non-purulent inflammation is found, including necrotic tissue, without evidence of purulent drainage such as dry gangrene.
- *Dirty or infected:* old traumatic wounds with retained dead tissue and those that involve existing clinical infection or perforated viscera. Such wounds suggest that the organisms causing postoperative infection were present at the site of the surgery before the operation.

Surgical prophylaxis

Page 1 of 2

Antibiotic prophylaxis prior to dental surgeries is not addressed

Definition

Prevention of infectious complications by administering an effective antibiotic before exposure to contamination during surgery

Types of surgical procedures:

- **Clean:** Respiratory, alimentary, genital or urinary tracts are not entered during surgery
- **Clean-contaminated:** Respiratory, alimentary, genital or urinary tracts are entered under controlled conditions and without unusual contamination
- **Contaminated:** Significant interruptions in sterile technique or gross spillage from the gastrointestinal tract

WHO guidelines for the prevention of surgical site infections: <https://apps.who.int/iris/handle/10665/277399>

Most Likely Pathogens

Depends on the anatomical site of the procedure; often bacteria belonging to the human microbiota



Antibiotic Prophylaxis Before Surgical Procedures (Section 1 of 2)



Clinical Considerations

- Choice of antibiotic prophylaxis depends on the type and anatomical site of surgical procedure
- Patients colonized with multidrug-resistant Gram-negative bacteria: Lack of high-quality evidence to support expanding the spectrum of antibiotic prophylaxis; decisions usually made on a case-by-case basis
- Patients colonized with MRSA who will have a skin incision: Consider adding vancomycin to the routinely recommended surgical regimen



Timing of Antibiotic Prophylaxis

120 minutes or less before starting surgery

Single dose before surgery. Do not continue the antibiotic after the surgical procedure to prevent infection. Consider an additional dose only for prolonged procedures or if major blood loss.



Bowel Surgery

Includes appendectomy, small intestine and colorectal surgical procedures

All dosages are for normal renal function

First Choice



Cefazolin 2 g single dose IV

----- COMBINED WITH -----



Metronidazole 500 mg single dose IV

Second Choice



Amoxicillin+clavulanic acid 2 g+200 mg single dose IV

Surgical prophylaxis

Page 2 of 2

R_X Antibiotic Prophylaxis Before Surgical Procedures (Section 2 of 2)

R_X Clean or Clean-Contaminated Procedure

All dosages are for normal renal function

First Choice

 Cefazolin 2 g single dose IV
ACCESS WATCH

Second Choice

 Cefuroxime 1.5 g single dose IV
WATCH

R_X Urologic Procedure

All dosages are for normal renal function

First Choice

 Cefazolin 2 g single dose IV
ACCESS

Second Choice

 Gentamicin 5 mg/kg single dose IV
ACCESS

R_X Contaminated Procedure

All dosages are for normal renal function

First Choice

 Cefazolin 2 g single dose IV
ACCESS

----- COMBINED WITH -----

 Metronidazole 500 mg single dose IV
ACCESS

Second Choice

 Amoxicillin+clavulanic acid 2 g+200 mg single dose IV
ACCESS

OR

 Gentamicin 5 mg/kg single dose IV
ACCESS

----- COMBINED WITH -----

 Metronidazole 500 mg single dose IV
ACCESS

Gentamicin should be given in combination with metronidazole because, if given alone, it provides insufficient coverage of anaerobic bacteria

Surgical prophylaxis

Page 1 of 2

Antibiotic prophylaxis prior to dental surgeries is not addressed

Definition

Prevention of infectious complications by administering an effective antibiotic before exposure to contamination during surgery

Types of surgical procedures:

- **Clean:** Respiratory, alimentary, genital or urinary tracts are not entered
- **Clean-contaminated:** Respiratory, alimentary, genital or urinary tracts are entered under controlled conditions and without unusual contamination
- **Contaminated:** Significant interruptions in sterile technique or gross spillage from the gastrointestinal tract

WHO guidelines for the prevention of surgical site infections: <https://apps.who.int/iris/handle/10665/277399>



Most Likely Pathogens

Depends on the anatomical site of the procedure; often bacteria belonging to the human microbiota



Antibiotic Prophylaxis Before Surgical Procedures (Section 1 of 2)



Clinical Considerations

- Choice of antibiotic prophylaxis depends on the type and anatomical site of surgical procedure
- Patients colonized with multidrug-resistant Gram-negative bacteria: Lack of high-quality evidence to support expanding the spectrum of antibiotic prophylaxis; decisions usually made on a case-by-case basis
- Patients colonized with MRSA who will have a skin incision: Consider adding vancomycin to the routine recommended surgical regimen



Timing of Antibiotic Prophylaxis

120 minutes or less before starting surgery

Single dose before surgery. Do not continue the antibiotic after the surgical procedure to prevent infection. Consider an additional dose only for prolonged procedures or if major blood loss.



Bowel Surgery

Includes appendectomy, small intestine and colorectal surgical procedures

All dosages are for normal renal function

First Choice



Cefazolin 50 mg/kg single dose IV

----- COMBINED WITH -----



Metronidazole 7.5 mg/kg single dose IV

Second Choice



Amoxicillin+clavulanic acid 50 mg/kg of amoxicillin component single dose IV

Surgical prophylaxis

Page 2 of 2

Rx Antibiotic Prophylaxis Before Surgical Procedures (Section 2 of 2)

Rx Clean or Clean-Contaminated Procedure

All dosages are for normal renal function

First Choice

 Cefazolin 50 mg/kg single dose **IV**
ACCESS WATCH

Second Choice

 Cefuroxime 50 mg/kg single dose **IV**
WATCH

Rx Contaminated Procedure

All dosages are for normal renal function

First Choice

 Cefazolin 50 mg/kg single dose **IV**
ACCESS

----- COMBINED WITH -----

 Metronidazole 7.5 mg/kg single dose **IV**
ACCESS

Rx Urologic Procedure

All dosages are for normal renal function

First Choice

 Cefazolin 50 mg/kg single dose **IV**
ACCESS

Second Choice

 Gentamicin single dose **IV**
• Neonates: 5 mg/kg
• Children: 7.5 mg/kg

Second Choice

 Amoxicillin+clavulanic acid 50 mg/kg of amoxicillin component single dose **IV**
ACCESS

OR

 Gentamicin single dose **IV**
• Neonates: 5 mg/kg
• Children: 7.5 mg/kg
ACCESS

----- COMBINED WITH -----

 Metronidazole 7.5 mg/kg single dose **IV**
ACCESS

Gentamicin should be given in combination with metronidazole because, if given alone, it provides insufficient coverage of anaerobic bacteria

Epidemiology

The percentage of surgical site infections varies depending on the type of surgical procedure. For example, in 2017 in 13 European countries reporting data on > 600 000 surgical procedures, the overall percentage of infections per 100 operations ranged from 0.5% after knee prosthesis surgery to 10.1% after colon surgery. For most types of surgery, more than 80% of patients received antibiotic prophylaxis. The only exception was cholecystectomy for which a lower percentage of patients received antibiotic prophylaxis – 44% in case of laparoscopic and 66% in case of open cholecystectomy (377).

Another study included data collected in 2016 from more than 12 000 patients from 66 countries with different human development indexes; 10.2% of patients were from countries with a low human development index. Overall, 12.3% of patients undergoing gastrointestinal surgery developed a surgical site infection within 30 days. However, statistically significant differences in the incidence of surgical site infections were found based on the human development indexes. In particular, the incidence of surgical site infections was 9.4% in countries with a high human development index, 14.0% in countries with a medium human development index and 23.2% in those with a low human development index. Patients in countries with a low human development index were 1.6 times more likely to develop an infection than patients in countries with a higher human development index (378). Variation in infection rates was also found after caesarean sections with rates of infections ranging from 3% to 11% in high-income countries compared to 3% to 24% in low- and middle-income countries (379).

Surgical site infections and surgical prophylaxis to prevent them are a frequent cause of antibiotic use in hospitals. The 2015 global point prevalence survey on antibiotic use (reporting data from 303 hospitals in 53 countries) reported that on the day of the survey, 1.6% of admitted patients were receiving antibiotics for a postoperative surgical site infection (291). Of note, 34.4% of adult inpatients were receiving at least one antibiotic on the day of the survey. Of the total antibiotic prescriptions, 17.8% were for surgical prophylaxis. The most frequently prescribed antibiotic was cefazolin, prescribed in 27.5% of patients receiving surgical prophylaxis. Prolonged surgical prophylaxis (> 1 day) was common in all regions, ranging from 40.6% in Oceania to 86.3% in eastern Europe (291).

Most likely pathogens

The pathogens causing surgical site infections vary based on the type of surgical procedure (Table 40.1).

Table 40.1 – Pathogens most frequently associated with surgical site infections by anatomical site of the procedure

Type of procedure	Pathogens most frequently associated with surgical site infections
Cardiac procedures	<i>Staphylococcus aureus</i> and coagulase-negative staphylococci
Cardiac device insertion procedures (e.g. pacemaker implantation)	<i>Staphylococcus aureus</i> and coagulase-negative staphylococci
Non-cardiac thoracic procedures (e.g. pulmonary resection)	<i>Staphylococcus aureus</i> and coagulase-negative staphylococci <i>Haemophilus influenzae</i> <i>Enterobacter cloacae</i> <i>Klebsiella pneumoniae</i> <i>Acinetobacter</i> spp. <i>Pseudomonas aeruginosa</i> <i>Moraxella catarrhalis</i>
Gastroduodenal procedures	<i>Staphylococcus aureus</i> and coagulase-negative staphylococci <i>Enterococcus</i> spp. Enterobacterales Anaerobes (<i>Bacteroides</i> spp.)
Biliary tract procedures	Enterobacterales Anaerobes <i>Enterococcus</i> spp. <i>Streptococcus</i> spp. <i>Staphylococcus aureus</i> and coagulase-negative staphylococci
Appendectomy	<i>Escherichia coli</i> Anaerobes (<i>Bacteroides fragilis</i>)
Small intestine procedures	Enterobacterales Anaerobes <i>Enterococcus</i> spp. <i>Streptococcus</i> spp. <i>Staphylococcus aureus</i> and coagulase-negative staphylococci

continues

Table 40.1 continued

Type of procedure	Pathogens most frequently associated with surgical site infections
Hernia repair procedures	<i>Enterococcus</i> spp. <i>Streptococcus</i> spp. <i>Staphylococcus aureus</i> and coagulase-negative staphylococci
Colorectal procedures	<i>Escherichia coli</i> Anaerobes (<i>Bacteroides fragilis</i>)
Head and neck procedures	<i>Streptococcus</i> spp. <i>Staphylococcus aureus</i> and coagulase-negative staphylococci Enterobacterales Anaerobes (from the oral microbiota)
Neurosurgical procedures	<i>Staphylococcus aureus</i> and coagulase-negative staphylococci Gram-negative bacteria
Gynaecological procedures	<i>Streptococcus agalactiae</i> (group B streptococcus) <i>Staphylococcus aureus</i> <i>Enterococcus</i> spp. Anaerobes
Ophthalmic procedures	<i>Staphylococcus aureus</i> and coagulase-negative staphylococci
Orthopaedic procedures	<i>Staphylococcus aureus</i> and coagulase-negative staphylococci
Urological procedures	Enterobacterales (mostly <i>Escherichia coli</i>) <i>Enterococcus</i> spp.
Vascular procedures	<i>Staphylococcus aureus</i> and coagulase-negative staphylococci

Note. This list is based on data from high-income settings and aims to give a general overview (380). The distribution of the pathogens most frequently associated with surgical site infections may vary in other settings.

Antibiotic prophylaxis

The choice of the antibiotic should be based on the type of surgical procedure because not all procedures are associated with the same risk of developing infection (Table 40.2).

In general, antibiotic prophylaxis before surgery where the most likely pathogens causing infection are Gram-positive bacteria should consist of intravenous first- or second-

generation cephalosporins – cefazolin or, as an alternative second choice, cefuroxime. These surgeries include clean procedures such as cardiac and vascular surgery but also procedures that involve the placement of a prosthesis or implant.

If additional pathogens (e.g. anaerobes) could cause infection (e.g. in abdominal procedures), antibiotic prophylaxis should be adapted accordingly. In these cases, cefazolin in combination with metronidazole would be an appropriate option.

In patients known to be colonized with MRSA and who will have a skin incision, vancomycin prophylaxis (in addition to the routine recommended antibiotic prophylaxis) may be justified. This is recommended because vancomycin alone is less effective than cefazolin (the antibiotic recommended as prophylaxis in most surgical procedures) against methicillin-sensitive *Staphylococcus aureus* and because vancomycin has no activity against Gram-negative bacteria. It should be noted that in patients colonized with MRSA, procedure-specific preventive measures other than antibiotic prophylaxis (e.g. nasal decolonization with mupirocin ointment, skin antisepsis) may be beneficial but such measures are not specifically addressed in this chapter. Please refer to the WHO guidelines for the prevention of surgical site infections (280) for information on such preventive measures.

In the context of patients known to be colonized with multidrug-resistant Gram-negative bacteria (e.g. bacteria producing ESBLs or carbapenemases), the WHO guidelines acknowledged a lack of high quality evidence to make recommendations on the need to include other antibiotics for prophylaxis to cover these pathogens (280). However, certain factors, such as the closeness of the likely reservoir of these bacteria to the operative site or characteristics of the patient, could help to make decision on a case-by-case basis.

Table 40.2 – Antibiotic prophylaxis before surgical procedures (all single dose)

Type of procedure	First choice	Second choice
Clean procedure ^a	Cefazolin (IV): <ul style="list-style-type: none"> Children: 50 mg/kg Adults: 2 g^b 	Cefuroxime (IV): <ul style="list-style-type: none"> Children: 50 mg/kg Adults: 1.5 g
Clean contaminated procedure ^c (except bowel surgery and urological procedures)	Cefazolin (IV): <ul style="list-style-type: none"> Children: 50 mg/kg Adults: 2 g^b 	Cefuroxime (IV): <ul style="list-style-type: none"> Children: 50 mg/kg Adults: 1.5 g
Contaminated procedure ^d	Cefazolin (IV): <ul style="list-style-type: none"> Children: 50 mg/kg Adults: 2 g^b AND Metronidazole (IV): <ul style="list-style-type: none"> Children: 7.5 mg/kg Adults: 500 mg 	Amoxicillin+clavulanic acid (IV): <ul style="list-style-type: none"> Children: 50 mg/kg of amoxicillin component Adults: 2 g + 200 mg OR Gentamicin ^e (IV): <ul style="list-style-type: none"> Neonates: 5 mg/kg Children: 7.5 mg/kg Adults: 5 mg/kg AND Metronidazole (IV): <ul style="list-style-type: none"> Children: 7.5 mg/kg Adults: 500 mg
Bowel surgery ^f	Cefazolin (IV): <ul style="list-style-type: none"> Children: 50 mg/kg Adults: 2 g^b AND Metronidazole (IV): <ul style="list-style-type: none"> Children: 7.5 mg/kg Adults: 500 mg 	Amoxicillin+clavulanic acid (IV): <ul style="list-style-type: none"> Children: 50 mg/kg of amoxicillin component Adults: 2 g + 200 mg
Urologic procedures	Cefazolin (IV): <ul style="list-style-type: none"> Children: 50 mg/kg Adults: 2 g^b 	Gentamicin (IV): <ul style="list-style-type: none"> Neonates: 5 mg/kg Children: 7.5 mg/kg Adults: 5 mg/kg

continues

Table 40.2 *continued*

IV: intravenous.

Note: All dosages are for normal renal and hepatic function.

^a Surgical procedures where the respiratory, alimentary, genital or urinary tracts are not entered.

^b Higher doses of cefazolin (e.g. 3 g) may be required in obese patients, > 120 kg.

^c Surgical procedures where the respiratory, alimentary, genital or urinary tracts are entered under controlled conditions and without unusual contamination. Operations involving the biliary tract, appendix, vagina and oropharynx are included in this category.

^d Operations with major (i.e. significant) interruptions in sterile technique (e.g. open cardiac massage) or substantial spillage from the gastrointestinal tract.

^e Gentamicin should be given in combination with metronidazole and not as a stand-alone option in contaminated surgical procedures because, if given alone, it provides insufficient coverage of anaerobic bacteria. Amikacin could be used instead of gentamicin based on local availability.

^f Bowel surgery includes appendectomy, small intestine and colorectal surgical procedures.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Timing of antibiotic prophylaxis before surgery

According to the previously cited WHO guidelines, the antibiotic should be given 120 minutes or less before incision (280).

Duration of antibiotic prophylaxis

Antibiotic prophylaxis should not be continued after surgery for the purpose of preventing surgical site infections including in the presence of a surgical wound drain (280). This is because one dose of the prophylactic antibiotic should cover the entire period of potential contamination (i.e. from the time of the incision until final closure of the wound) in most cases and continuing prophylaxis does not offer additional benefit in reducing the incidence of surgical site infections compared with discontinuing it (381). At the same time, limiting the duration to one single dose reduces the risk of selecting resistant bacteria in the patient's own microbiota and the risk of developing *Clostridioides difficile* infections.

Only in certain cases may a further dose of antibiotic be required, such as for prolonged surgical procedures (exceeding about two times the half-life of the antibiotic) or when there is major blood loss (380). If another dose is necessary, the half-life of the antibiotic should be considered, for example, giving a second dose of cefazolin 4 hours after the initial preoperative dose in long surgeries (Table 40.3).

Table 40.3 – Half-life of the antibiotics recommended for surgical prophylaxis in the WHO EML (8)

Antibiotic	Half-life ^a (hours)
Amoxicillin+clavulanic acid	1–2
Cefazolin	1.2–2.2
Cefuroxime	1–2
Gentamicin	2–3
Metronidazole	6–8

EML: Model List of Essential Medicines.

^a In adults with normal renal function

A close-up photograph showing a person's hands wearing black nitrile gloves. One hand holds a petri dish containing a red agar medium with several green bacterial colonies. The other hand holds a white cotton swab, dipping it into one of the colonies. In the background, a white tray with multiple small wells is visible.

RESERVE ANTIBIOTICS

41. Overview

Key messages

- Reserve antibiotics are antibiotics that retain activity against some of the multidrug-resistant bacteria listed in the WHO priority pathogen list.
- Countries should consider developing formal methods to monitor and control the use of Reserve antibiotics.
- The AWaRe classification and the list of Reserve antibiotics is updated every 2 years by the EML Expert Committee considering the availability of new antibiotics, new efficacy/effectiveness and safety data, updates of the WHO priority pathogen list or changing epidemiology.
- The list of Reserve antibiotics on the EML is closely aligned with the WHO list of critically important antimicrobials and WHO analysis of the clinical antibacterial pipeline.

Other relevant WHO resources (please check regularly for updates)

- WHO Antibiotic characterization – AWaRe portal (11).
- WHO AWaRe classification of antibiotics, 2021 (10).

The Reserve group of antibiotics includes antibiotics that still have relevant levels of activity against some of the multidrug-resistant bacteria listed in the WHO priority pathogen list, including bacteria which are resistant to most or all of the EML antibiotics in the Access and Watch groups (Table 41.1).

In addition, all Reserve antibiotics are categorized as either high priority or highest priority in the WHO list of critically important antimicrobials for human medicine (382). This list is intended for public health and animal health authorities who should ensure that critically important antibiotics for humans are also used sensibly in veterinary medicine. Use of any Reserve antibiotics in animals should be avoided wherever possible.

Reserve antibiotics can either be older off-patent antibiotics that have been reintroduced into clinical practice (e.g. polymyxin B, colistin, fosfomycin) or new antibiotics that have been recently licensed for the treatment of multidrug-resistant bacteria. It is important to note that not all antibiotics that have activity against strains of multidrug-resistant bacteria have been included in the EML (8). Between 2017 and 2021, the list of Reserve antibiotics was updated and some antibiotics were removed and others added to this group. Only antibiotics listed on the EML and EMLc are considered essential for all health systems.

The EML needs to be continually updated as more evidence on the antibiotics in the list and new antibiotics become available. The list of Reserve antibiotics in the 2021 EML is closely aligned with the WHO analysis of the clinical antibacterial pipeline (383), which assesses how antibacterial drugs in the development pipeline address the WHO priority pathogens list. Ideally an antibiotic under development will progress through the pipeline and, after licensing, would be considered for listing in the EML as a Reserve antibiotic.

The overarching principle for listing an antibiotic as a Reserve antibiotic in the EML is evidence of its usefulness to effectively treat a severe clinical infection for which the currently available treatment options are very limited, indicating a clear unmet global public health need. Other important considerations are strong evidence that the antibiotic has: better efficacy, safety and durability (low likelihood of selection of resistance on treatment) than comparable medicines; low impact on the microbiome; and simplicity of administration. There is therefore likely to be a range of Reserve antibiotics that cover different serious clinical infections. These antibiotics would include, for example, systemic antibiotics targeted at particular multidrug-resistant phenotypes (e.g. carbapenem-resistant organisms) or targeted at important pathogens (e.g. *Pseudomonas* spp. or *Acinetobacter* spp.). Equally, there is an important unmet clinical need for active oral drugs that can be used as targeted treatment of multidrug-resistant pathogens (e.g. *Klebsiella* spp.). This focus on public health emphasizes the importance for Reserve antibiotics to have phenotypic and genotypic activity that is globally relevant. For example, Reserve antibiotics that are active against carbapenem-resistant pathogens should ideally also have activity against the most common genetic types identified in low- and middle-income countries, e.g. metallo-beta-lactamases.

Reserve antibiotics are considered the so-called last-resort antibiotics which are still effective for the treatment of specific patient populations. There is a complex balance between using Reserve antibiotics effectively in sick patients where needed and their overuse potentially leading to a rapid decline in their effectiveness. The great majority of Reserve antibiotics are intravenous and used in the hospital facility setting. There is wider use of Reserve antibiotics in high-income countries than in low- and middle-income countries, raising concerns about equity of access to Reserve antibiotics which are generally more expensive than Access or Watch antibiotics.

Therefore, these antibiotics should be available for clinical care when needed but used only in certain situations where their use is likely to have clear clinical benefits. Reserve antibiotics are ideally used for **targeted** treatment once multidrug-resistant bacteria are confirmed; for example, following laboratory identification of the pathogen from a blood culture and susceptibility testing demonstrating wide multidrug resistance but sensitivity to a Reserve antibiotic. However, high quality rapid culture and sensitivity data are often not available in many settings and identification of a pathogen may not always be feasible even with access to state-of-the-art microbiologic techniques. The AWaRe book focuses on empiric treatment when diagnostic test results, including microbiological cultures, are not available.

Reserve antibiotics could be considered for empiric therapy in very select cases where a multidrug-resistant pathogen as the cause of the infection can be strongly suspected based on the clinical infection, local microbiology, previous treatment or known colonization with a multidrug-resistant pathogen.

Reserve antibiotics are not listed as first- or second-choice options for any of the infections included in the AWaRe book. However, to help with the appropriate use of Reserve antibiotics, a comment about their potential role for empiric therapy has been added to specific chapters where they are most likely to be used, for example, for severe hospital-acquired infections or severe infections in patients who have received multiple antibiotic treatments in the recent past. The risks and benefits of treatment need to be carefully considered in high-risk patient populations with multidrug-resistant infections that have a high associated mortality. Some antibiotics on the Reserve list have substantial toxicity but may still be used for treatment if there are no or few other treatment options and the risk of death or permanent sequelae due to the infection are high. Ensuring the optimal use of Reserve antibiotics is complex and difficult at both a patient and country level, but control of the use of Reserve antibiotics is critical to maintaining their future effectiveness. For example, colistin in South Africa is only authorized for use if specific criteria are met and with approval from the Medicines Control Council, as in section 21 of the Medicines and Related Substances Act 101 of 1965 (384).

The need for stewardship of Reserve antibiotics and what countries should do to contribute to good stewardship are outlined in Box 41.1.

Box 41.1 – Reserve antibiotic stewardship

- Preserving the effectiveness of Reserve antibiotics (i.e. preventing the development of resistance to these antibiotics in the future) is key to maintaining their longevity in clinical use.
- Therefore, all efforts should be made to ensure careful use of Reserve antibiotics within local and national stewardship strategies, which should include routine local and/or national monitoring and reporting of their use.
- Countries should consider developing formal guidance on and control of the use of Reserve antibiotics at a national and local level, including through medicines regulation.

Prescribers need to recognize the very limited data available on the clinical efficacy of most Reserve antibiotics in treating multidrug-resistant infections. Regulatory approval is usually obtained through non-inferiority trials (usually trials on complicated UTI and/or complicated intraabdominal infections) containing few high-risk patients with multidrug-resistant infections. Vulnerable patient populations at particular risk for infections by multidrug-resistant pathogens such as the very young, the very old and

immunocompromised individuals are often underrepresented in these trials. Therefore, the effectiveness of these new molecules on multidrug-resistant isolates is often based on in vitro data or case reports and retrospective observational studies with a high inherent risk of bias. Furthermore, recruitment of patients with carbapenem-resistant pathogens into pathogen-focused or limited-population trials has been difficult, which has led to estimates of clinical efficacy based on small studies. Strategic comparative public health-focused (rather than regulatory) trials for multidrug-resistant infections that directly compare multiple agents in high-risk populations for clinical efficacy, toxicity, resistance and health economic outcomes are urgently needed to inform the serious unmet public health priorities in this critical area.

The expected activity of Reserve antibiotics against beta-lactamase-producing bacteria are shown in Table 41.1.

Table 41.1 – Expected activity of Reserve antibiotics against third-generation cephalosporin- and carbapenem-resistant bacteria based on the type of beta-lactamase produced

Type of beta-lactamase	ESBL ^a	KPC ^b	NDM, VIM, IMP ^b	AmpC	OXA-48 ^b	Non-fermenters ^c
Ambler class^d	A ^e	A ^e	B	C ^e	D ^e	NA
			(MBLs)			
Cefiderocol	+	+	+	+	+	+ ^f
Ceftazidime+ avibactam	+	+	-	+	+	- <i>Acinetobacter baumannii</i>
						+ <i>Pseudomonas aeruginosa</i>
Fosfomycin (IV) (consider using only in combination therapy)	+	+/-	+/-	+	+/-	- <i>Acinetobacter baumannii</i>
						+/- <i>Pseudomonas aeruginosa</i>
Meropenem+ vaborbactam	+	+	-	+	-	+/-

continues

Table 41.1 continued

Type of beta-lactamase	ESBL ^a	KPC ^b	NDM, VIM, IMP ^b	AmpC	OXA-48 ^b	Non-fermenters ^c
Plazomicin	+	+	+/-	+	+	-
Polymyxin B and colistin	+	+	+	+	+	+

AmpC: ampicillinase C; ESBL: extended-spectrum beta-lactamases; IMP: imipenemase; IV: intravenous; KPC: *Klebsiella pneumoniae* carbapenemase; MBLs: metallo-beta-lactamases; NA: not applicable; NDM: New Delhi metallo-beta-lactamase; OXA-48: oxacillinase-48; VIM: Verona integron-encoded metallo-beta-lactamase.

Expected activity: + active; +/- possibly active; - not or insufficiently active.

^aESBL are a group of different beta-lactamases conferring resistance to most beta-lactam antibiotics (with the notable exception of carbapenems).

^bCarbapenemases.

^cNon-fermenters refer to bacteria that cannot catabolize glucose and thus are unable to ferment. The most relevant in this context are *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. Please note when using this table, always consider that even when activity of a certain Reserve antibiotic is reported against carbapenem-resistant non-fermenters, this activity ultimately depends on the type of carbapenemase produced and the resistance mechanism. For plazomicin, some in vitro studies have shown activity against *Pseudomonas aeruginosa* similar to amikacin (426).

^dThe Ambler classification of beta-lactamases is the most widely used classification. According to this classification beta-lactamases are divided into four classes (A, B, C and D) based upon similarities in their amino acid sequence.

^eAmbler class A, C and D are serine beta-lactamases.

^fHigher mortality has been reported with carbapenem-resistant *Acinetobacter baumannii* infections.

42. Cefiderocol

Key messages

- The primary use of cefiderocol is for the treatment of infections caused by metallo-beta-lactamases (MBL)-producing carbapenem-resistant Enterobacteriales.
- There is very limited evidence for the use of cefiderocol in children.
- Caution is needed with the use of cefiderocol for *Acinetobacter baumannii* infections because it was reported to have higher mortality than the best available alternative therapy in one clinical trial.

Cefiderocol is the first clinically available siderophore cephalosporin. Siderophore-antibiotic conjugates exploit the ability of siderophores to bind extracellular free iron and use iron transporters to cross bacterial cell membranes (in the case of cefiderocol the outer membrane of aerobic Gram-negative bacteria), which results in active accumulation of the antibiotic at the site of action. In addition, cefiderocol can also enter the bacterial cell by passively diffusing through porin channels similar to other beta-lactams.

Cefiderocol has been licensed for the treatment of complicated UTIs, hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia in patients 18 years or older. Its indications include severe infections caused by certain strains of carbapenem-resistant Enterobacteriales, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* depending on the type of carbapenemase produced and the resistance mechanism in patients with limited treatment options.

The primary use of cefiderocol is for the treatment of infections caused by metallo-beta-lactamases-producing carbapenem-resistant Enterobacteriales for which alternative treatment options are very limited (at the time of publication of the AWaRe book).

Particular caution is needed in patients with *Acinetobacter baumannii* infections because of concerning data from a randomized clinical trial that reported higher mortality with cefiderocol in this patient population (385,386).

Its current indications in the EML and EMLc (8,9) include infections caused by certain strains of carbapenem-resistant Enterobacteriales and *Pseudomonas aeruginosa* depending on the type of carbapenemase produced and the resistance mechanism.

Cefiderocol

Rx Pharmacology

- Siderophore cephalosporin
- **Mechanism of action:** Inhibition of bacterial enzymes responsible for cell-wall synthesis



Indications for Use



Targeted Treatment

- Severe infections caused by laboratory-confirmed carbapenem-resistant Enterobacteriales and/or *P. aeruginosa* (particularly infections caused by MBL-producing pathogens)
 - Caution needed with *A. baumannii* infections because of higher mortality than best available alternative therapy described in a clinical trial (<https://pubmed.ncbi.nlm.nih.gov/33058795/>)



Empiric Use

- Only in very selected cases of seriously ill patients (e.g. sepsis/septic shock):
 - who have not responded to carbapenems if other causes of treatment failure have been excluded first and there is strong suspicion that the infection is caused by a carbapenem-resistant pathogen (especially in settings with a high prevalence of MBL-producing pathogens)
 - who have previously been treated for infections caused by carbapenem-resistant pathogens susceptible to cefiderocol
 - who are known to be colonized with carbapenem-resistant pathogens susceptible to cefiderocol



Important Considerations

- Efficacy demonstrated in clinical trials for empiric use for complicated UTI, VAP/HAP, BSI and sepsis in adults
- Very limited evidence for other infections and use in children



Formulations

- Powder for intravenous infusion: 1 g/vial



Spectrum of Activity

Active against:

- Aerobic Gram-negative bacteria including many carbapenem-resistant Enterobacteriales, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*
- Carbapenemases: KPC, OXA-48 and MBLs
- ESBL and AmpC β-lactamases

Not active against:

- Gram-positive bacteria and anaerobes

Emerging resistance to cefiderocol in Enterobacteriales, *A. baumannii* and *P. aeruginosa*:

- The proportion of isolates resistant to cefiderocol is low but data is very limited



Toxicity

Well tolerated with side effects similar to other beta-lactams (mostly gastrointestinal)



Dose



Antibiotic Treatment Duration

- Treatment duration varies according to indication and should be as short as possible
- Usually between **7-14 days**



Adults

Dosage is for normal renal function; dose adjustment required in case of renal impairment



Cefiderocol 2 g q8h IV



Children or Neonates

No data for children or neonates

Administration

Cefiderocol is currently available as powder for intravenous infusion (1 g/vial). It is administered by intravenous infusion over 3 hours.

Mechanism of action

Cefiderocol acts by inhibiting bacterial enzymes responsible for cell-wall synthesis, primarily penicillin-binding proteins. This leads to cell lysis and death.

Spectrum of activity

Cefiderocol is only active against aerobic Gram-negative bacteria (Table 42.1). Specifically, it is active against many carbapenem-resistant Enterobacterales, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* clinical isolates. Cefiderocol has no, or only limited, activity against Gram-positive bacteria or anaerobes.

In vitro, cefiderocol is not degraded by ESBL and by certain types of carbapenemase, in particular *Klebsiella pneumoniae* carbapenemases, oxacillinase-48 (OXA-48) beta-lactamases and metallo-beta-lactamases such as New Delhi metallo-beta-lactamases, Verona integron-encoded, or imipenemase metallo-beta-lactamases.

Of note, cefiderocol is one of the few Reserve antibiotics with reported activity against metallo-beta-lactamases. The other such antibiotics are colistin/polymyxin B, fosfomycin and aztreonam combined with avibactam, in the form of ceftazidime+avibactam.

Table 42.1 – Expected activity of cefiderocol against third-generation cephalosporin and carbapenem-resistant bacteria based on the type of beta-lactamase produced

Type of beta-lactamase	ESBL ^a	KPC ^b	NDM, VIM, IMP ^b	AmpC	OXA-48 ^b	Non-fermenters ^c
Ambler class^d	A ^e	A ^e	B (MBLs)	C ^e	D ^e	NA
Expected activity of cefiderocol	+	+	+	+	+	+

AmpC: ampicillinase C; ESBL: extended-spectrum beta-lactamases; IMP: imipenemase; KPC: *Klebsiella pneumoniae* carbapenemase; MBLs: metallo-beta-lactamases; NA: not applicable; NDM: New Delhi metallo-beta-lactamase; OXA-48: oxacillinase-48; VIM: Verona integron-encoded metallo-beta-lactamase.

Expected activity: + active.

^a ESBL are a group of different beta-lactamases.

^b Carbapenemases.

^c Non-fermenters refer to bacteria that cannot catabolize glucose and thus are unable to ferment. The most relevant in this context are *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. When using this table, always consider that even when activity of a certain Reserve antibiotic is reported against carbapenem-resistant non-fermenters, this ultimately depends on the type of carbapenemase produced and the resistance mechanism.

^d The Ambler classification of beta-lactamases is the most widely used classification. According to this classification beta-lactamases are divided into four classes (A, B, C and D) based upon similarities in their amino acid sequence.

^e Ambler class A, C and D are serine beta-lactamases.

^f Higher mortality has been reported with carbapenem-resistant *Acinetobacter baumannii* infections.

Clinical efficacy

At the time of publication of the AWaRe book, three randomized clinical trials had assessed the efficacy and safety of cefiderocol in adults (385,387,388). The results of these trials provide evidence that cefiderocol is not inferior to carbapenems for the treatment of infections caused by Gram-negative bacteria (not specifically multidrug-resistant) particularly for complicated UTIs, HAP including VAP and bloodstream infections or sepsis.

One study that enrolled 150 patients with confirmed carbapenem-resistant Gram-negative infection and compared cefiderocol to the best available therapy reported higher mortality in the cefiderocol group, which appeared to be driven by a worse outcome in the subgroup of patients with *Acinetobacter baumannii* infections (385). Mortality at day 28 was 24.8% (25/101) in the cefiderocol group versus 18.4% (9/49) in the best available therapy group (difference 6.4%, 95% confidence interval (CI): -8.6% to 19.2%). The statistically significant difference persisted at day 49: 34/101 (33.7%) in the cefiderocol group versus 10/49 (20.4%) in the best available therapy group; difference 13.3%, 95% CI: -2.5% to 26.9%.

A possible explanation given by the authors for this difference was that, despite randomization, a higher mortality risk was present at the time of randomization in the cefiderocol group; for example, more patients were in the intensive care unit or had experienced shock in the month preceding randomization. The increase in mortality remains, however, a major concern in this patient population and requires further investigation in clinical trials.

Although very small numbers of patients with metallo-beta-lactamase-producing Enterobacteriales were included in these trials, outcomes in this group of patients were favourable.

At the time of publication of the AWaRe book, cefiderocol is being assessed in phase II trials (i.e. trials that assess safety and effectiveness in small groups of patients) in children and good evidence about its efficacy and safety in the paediatric setting is lacking.

Toxicity

Cefiderocol has a good safety profile similar to other beta-lactams and is well tolerated. In clinical trials, side-effects were described in proportions similar to those experienced by patients in control groups. Gastrointestinal effects (e.g. diarrhoea) are the most commonly reported side-effects.

Dose

Cefiderocol requires dose adjustments in cases of renal impairment (Table 42.2). Renal function should be closely monitored and doses adjusted accordingly. Dose adjustments are not covered in the AWaRe book. Please also refer to the chapter on dosing for more information.

Table 42.2 – Cefiderocol suggested doses

Dose in adults	Dose in children	Dose in neonates
2 g given every 8 hours	There are no data for children or neonates	There are no data for children or neonates

Note. All dosages are for normal renal and hepatic function.

Indication for the use as a Reserve antibiotic

Targeted treatment

Cefiderocol could be considered as a last-resort option for the targeted treatment of severe invasive infections (e.g. positive blood culture) caused by laboratory-confirmed

carbapenem-resistant Enterobacteriales and *Pseudomonas aeruginosa*, particularly if the resistance is caused by metallo-beta-lactamases. The use of cefiderocol should be limited to situations where no other adequate therapeutic options are available. Given the increased mortality observed in the trial mentioned before (385), cefiderocol should be used with caution in patients with *Acinetobacter baumannii* infection.

To preserve its effectiveness (i.e. to prevent the development of resistance), cefiderocol should not be used to treat infections caused by isolates only producing ESBLs when there are other options available.

Empiric treatment

Cefiderocol could be considered for empiric use exceptionally in very select cases of seriously ill patients with invasive infections (e.g. patients with sepsis/septic shock) including the following patients.

- Patients who have not responded to carbapenems if: (i) other causes of treatment failure have been excluded first, and (ii) there is a strong suspicion that the infection is caused by carbapenem-resistant bacteria, especially in settings with a high prevalence of metallo-beta-lactamase-producing Enterobacteriales. However, if a patient is not improving, antibiotic failure is not the only possible cause to consider. Alternative reasons include: alternative diagnosis; development of complications (e.g. an abscess); inadequate control of the source of infection; suboptimal dose of the antibiotic; or impossibility for the antibiotic to reach an adequate concentration at the site of infection. These possible causes of the lack of improvement in a patient are always important to consider before changing or adding new antibiotics.
- Patients who have previously been treated for infections caused by carbapenem-resistant bacteria that are susceptible only to cefiderocol.
- Patients who are known to be colonized with carbapenem-resistant bacteria found to be susceptible only to cefiderocol.

To help prescribers identify clinical scenarios where empiric use of Reserve antibiotics could exceptionally be considered, suggestions are given in the relevant chapters of the AWaRe book for certain infections – only for infections where empiric use could potentially be adequate on a case-by-case basis.

Emerging resistance in Enterobacterales, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*

Most Gram-negative bacteria are susceptible to cefiderocol. However, at the time of publication of the AWaRe book, few data were available about resistance. Most evidence comes from two laboratory surveillance studies that tested the in vitro activity of cefiderocol in more than 30 000 Gram-negative aerobic isolates (years 2014–2017) and showed that cefiderocol was effective at low minimum inhibitory concentrations for more than 99% of isolates (389,390). An increase in minimum inhibitory concentrations to cefiderocol has emerged on treatment in a small proportion of patients in trials.

Data on resistance to cefiderocol are currently not reported by the GLASS.

Duration

Treatment duration varies according to indication and should be as short as possible, usually between 7 and 14 days.

43. Ceftazidime+avibactam

Key messages

- Ceftazidime+avibactam has activity against many carbapenem-resistant Enterobacteriales and *Pseudomonas aeruginosa*, but not strains producing metallo-beta-lactamases.
- When used to treat complicated intra-abdominal infections it should be given with metronidazole due to its inconsistent activity against anaerobes.

Ceftazidime+avibactam is a combination of a third-generation cephalosporin (ceftazidime) in clinical use since the 1980s and a new non-beta-lactam beta-lactamase inhibitor (avibactam). Its current indications in the EML and EMLc (8,9) include infections caused by certain strains of carbapenem-resistant Enterobacteriales and *Pseudomonas aeruginosa* depending on the type of carbapenemase produced and the resistance mechanism. Its activity against *Acinetobacter baumannii* is limited.

Administration

Ceftazidime+avibactam is currently available as powder for intravenous infusion (2 g + 0.5 g in vial). It is administered by intravenous infusion over 2 hours.

Mechanism of action

Ceftazidime acts by inhibiting bacterial enzymes responsible for cell-wall synthesis, primarily penicillin binding protein 3. Avibactam targets the site of certain serine beta-lactamases and inactivates them, thus protecting ceftazidime from degradation.

Ceftazidime+avibactam

Rx Pharmacology

- Combination of a third-generation cephalosporin (ceftazidime) and a novel non-β-lactam β-lactamase inhibitor (avibactam)
- Mechanism of action:**
 - Ceftazidime inhibits bacterial enzymes responsible for cell wall synthesis
 - Avibactam inactivates certain serine β-lactamases, protecting ceftazidime from degradation

Indications for Use

Targeted Treatment

- Severe infections caused by laboratory-confirmed carbapenem-resistant Enterobacteriales or *P. aeruginosa* (not *A. baumannii*) susceptible to ceftazidime+avibactam (CAZ-AVI)

Empiric Use

- Only in very select cases of seriously ill patients (e.g. patients with sepsis/septic shock):
 - who have not responded to carbapenems if other causes of treatment failure have been excluded first and there is strong suspicion that the infection is caused by a carbapenem-resistant pathogen
 - who have previously been treated for infections caused by carbapenem-resistant pathogens susceptible to CAZ-AVI
 - who are known to be colonized with carbapenem-resistant pathogens susceptible to CAZ-AVI

Important Considerations

- When used to treat complicated intra-abdominal infections CAZ-AVI should be given with metronidazole due to its unpredictable activity against anaerobes
- Since it is not active against MBLs, it is important to know the local epidemiology of the most prevalent genotypes for aerobic Gram-negative bacteria

Formulations

- Powder for intravenous infusion: 2 g + 500 mg in vial

Toxicity

- Side effects are similar to those previously reported for ceftazidime alone
- The most frequent are diarrhoea, nausea and vomiting



Spectrum of Activity

- Active against:**
 - Aerobic Gram-negative bacteria including ceftazidime-resistant and many carbapenem-resistant Enterobacteriales and *Pseudomonas aeruginosa*
 - Carbapenemases: KPC and OXA-48
 - ESBL and AmpC β-lactamases
- Variable activity against:**
 - Streptococcus* spp.
 - Staphylococcus* spp.
 - Anaerobes
- Not active against:**
 - MBL-producing Gram-negative bacteria (inactive against NDM, VIM, IMP carbapenemases unless co-prescribed with aztreonam)
 - Enterococcus* spp.
 - Acinetobacter* spp.
- Emerging resistance to CAZ-AVI in Enterobacteriales and *Pseudomonas aeruginosa*:**
 - The proportion of isolates resistant to CAZ-AVI is low (higher for *P. aeruginosa*) with geographical variability

Dose



Antibiotic Treatment Duration

- Treatment duration varies according to indication and should be as short as possible
- Usually between **7-14 days**



Adults

Dosage is for normal renal function; dose adjustment required in case of renal impairment



Ceftazidime+avibactam 2.5 g (2 g ceftazidime + 500 mg avibactam) q8h IV



Children

Dosage is for normal renal function; dose adjustment required in case of renal impairment



Ceftazidime+avibactam 62.5 mg/kg/dose q8h IV
(50 mg/kg/dose ceftazidime + 12.5 mg/kg/dose avibactam)
Max: 2 g ceftazidime + 500 mg avibactam per dose

Spectrum of activity

Ceftazidime+avibactam is mainly active against aerobic Gram-negative bacteria. Specifically, it is active against ceftazidime-resistant and many carbapenem-resistant Enterobacteriales and *Pseudomonas aeruginosa* clinical isolates, but its activity against *Acinetobacter* spp. is limited.

Avibactam inhibits the activity of ESBLs, AmpC beta-lactamases, *Klebsiella pneumoniae* carbapenemases and OXA-48 beta-lactamases (Table 43.1), and so preserves the activity of ceftazidime against many multidrug-resistant Gram-negative bacteria. However, avibactam does not inhibit the activity of metallo-beta-lactamases such as New Delhi metallo-beta-lactamase, Verona integron-encoded, or imipenemase metallo-beta-lactamases and therefore ceftazidime is inactive against strains expressing these beta-lactamases.

Ceftazidime+avibactam also has some antistreptococcal activity, very limited antistaphylococcal activity and no anti-enterococcal activity. Its activity against anaerobes varies: *Clostridium* spp. are resistant and *Bacteroides* spp. show unpredictable susceptibility.

Table 43.1 – Expected activity of ceftazidime+avibactam against third-generation cephalosporin- and carbapenem-resistant bacteria based on the type of beta-lactamase produced

Type of beta-lactamase	ESBL ^a	KPC ^b	NDM, VIM, IMP ^b	AmpC	OXA-48 ^b	Non-fermenters ^c
Ambler class^d	A ^e	A ^e	B (MBLs)	C ^e	D ^e	NA
Expected activity of ceftazidime+avibactam^f	+	+	-	+	+	- <i>Acinetobacter baumannii</i>
						+ <i>Pseudomonas aeruginosa</i>

AmpC: ampicillinase C; ESBL: extended-spectrum beta-lactamases; IMP: imipenemase; KPC: *Klebsiella pneumoniae* carbapenemase; MBLs: metallo-beta-lactamases; NA: not applicable; NDM: New Delhi metallo-beta-lactamase; OXA-48: oxacillinase-48; VIM: Verona integron-encoded metallo-beta-lactamase.

Expected activity: + active; – not or insufficiently active.

^a ESBL are a group of different beta-lactamases.

^b Carbapenemases.

^c Non-fermenters refer to bacteria that cannot catabolize glucose and thus are unable to ferment. The most relevant in this context are *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. When using this table, always consider that even when activity of a certain Reserve antibiotic is reported against carbapenem-resistant non-fermenters, this ultimately depends on the type of carbapenemase produced and the resistance mechanism.

continues

Table 43.1 *continued*

^d The Ambler classification of beta-lactamases is the most widely used classification. According to this classification beta-lactamases are divided into four classes (A, B, C and D) based upon similarities in their amino acid sequence.

^e Ambler class A, C and D are serine beta-lactamases.

^f Ceftazidime+avibactam co-prescribed with aztreonam retains activity against metallo-beta-lactamase-producing bacteria, however aztreonam is not currently listed in the WHO EML and EMLc.

Clinical efficacy

Several clinical trials have assessed the efficacy and safety of ceftazidime+avibactam in adults and provide evidence that it is not inferior to carbapenems for the treatment of infections caused by Gram-negative bacteria particularly for: complicated UTIs (391,392); complicated intra-abdominal infections in combination with metronidazole (392–394); and HAP (395). Of note, in the majority of trials, the infection being caused by multidrug-resistant organisms was not an inclusion criterion. In children, at the time of publication of the AWaRe book, ceftazidime+avibactam has been assessed in phase II trials (i.e. trials that assess safety and effectiveness in small groups of patients) for the treatment of complicated UTIs, compared with cefepime (396), and in combination with metronidazole for the treatment of complicated intra-abdominal infections, compared with meropenem (397).

In both studies, ceftazidime+avibactam was well tolerated with a safety profile similar to that of ceftazidime alone and appeared effective in children with complicated urinary or intra-abdominal infections caused by Gram-negative pathogens.

Toxicity

Ceftazidime+avibactam is well tolerated and has side-effects similar to those previously reported for ceftazidime alone. The most frequent side-effects are diarrhoea, nausea and vomiting.

Dose

Ceftazidime+avibactam requires dose adjustments in cases of renal impairment (Table 43.2). Renal function should be closely monitored, and doses adjusted accordingly. Please also refer to the chapter on dosing for more information.

Table 43.2 – Ceftazidime+avibactam suggested doses

Dose in adults	Dose in children
IV: 2.5 g (2 g ceftazidime + 500 mg avibactam) given every 8 hours	IV: 62.5 mg/kg/dose (50 mg/kg/dose ceftazidime + 12.5 mg/kg/dose avibactam); given every 8 hours Max: 2 g ceftazidime + 500 mg avibactam per dose

IV: intravenous.

Note. All dosages are for normal renal and hepatic function.

Indication for use as a Reserve antibiotic

Targeted treatment

Ceftazidime+avibactam could be considered as a last-resort option for the targeted treatment of severe invasive infections (e.g. septic shock with positive blood culture) caused by laboratory-confirmed carbapenem-resistant Enterobacteriales or *Pseudomonas aeruginosa* (not *Acinetobacter baumannii*), including infections caused by strains producing certain carbapenemases that have tested susceptible to this antibiotic.

Ceftazidime+avibactam is not indicated for infections caused by strains producing metallo-beta-lactamases. Sometimes ceftazidime+avibactam is combined with aztreonam for these strains but the evidence remains limited.

If ceftazidime+avibactam is used to treat intra-abdominal infections, it should be used as part of a combination treatment because it lacks activity against anaerobic organisms – therefore it is usually used in combination with metronidazole.

To preserve its effectiveness (i.e. to prevent the development of resistance), ceftazidime+avibactam should not be used to treat infections caused by isolates only producing ESBLs or by ceftazidime-resistant bacteria when there are other options available.

Empiric treatment

Ceftazidime+avibactam could be considered for empiric use exceptionally in very select cases of seriously ill patients with invasive infections (e.g. patients with sepsis/septic shock without microbiological test results) suspected to be caused by a multidrug-resistant pathogen (e.g. severe hospital-acquired infections or infections in patients who have received multiple antibiotic treatments in the recent past), such as in the following situations.

- Patients who have not responded to carbapenems if other causes of treatment failure have been excluded first and there is a strong suspicion that the infection

is caused by carbapenem-resistant bacteria. Since ceftazidime+avibactam is not active against metallo-beta-lactamases conveying carbapenem resistance, it is important to know the most prevalent genotypic variants that are circulating of aerobic Gram-negative bacteria in the setting where the patient acquired the infection. However, if a patient is not improving, antibiotic failure is not the only possible cause to consider. Alternative reasons include, for example: alternative diagnosis; development of complications (e.g. an abscess); inadequate source control; sub-optimal dose of the antibiotic; or impossibility for the antibiotic to reach an adequate concentration at the site of infection. Alternative reasons are always important to consider before changing or adding new antibiotics.

- Patients who have previously been treated for infections caused by carbapenem-resistant bacteria.
- Patients who are known to be colonized with carbapenem-resistant bacteria found to be susceptible to ceftazidime+avibactam.

To help prescribers identify clinical situations where empiric use of Reserve antibiotics could exceptionally be considered, suggestions are given in the relevant chapters of the AWaRe book for selected infections (only for infections where empiric use could potentially be adequate on a case-by-case basis).

Emerging resistance in Enterobacteriales and *Pseudomonas aeruginosa*

Most *Klebsiella pneumoniae* carbapenemase-producing Enterobacteriales and *Pseudomonas aeruginosa* are still susceptible to ceftazidime+avibactam. The proportion of isolates resistant to ceftazidime+avibactam is low (higher for *Pseudomonas aeruginosa*) with variability across geographical regions (398,399). Data on resistance to ceftazidime+avibactam are currently not reported by the GLASS. Resistance is often associated with previous exposure to ceftazidime+avibactam (400).

Duration

Treatment duration varies according to indication and should be as short as possible, usually between 7 and 14 days.

44. Fosfomycin (intravenous)

Key messages

- Fosfomycin has activity against methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci and many carbapenem-resistant Enterobacteriales.
- Fosfomycin is usually used as part of combination treatments because of concerns about the emergence of resistance.
- There is very limited evidence on the use of fosfomycin in children.
- The optimal dose of fosfomycin is not clearly defined.

Fosfomycin is an antibiotic belonging to the class of phosphonic antibiotics discovered at the end of the 1960s. Its current indications in the EML and EMLc include infections caused by carbapenem-resistant Enterobacteriales (8,9). For *Pseudomonas aeruginosa*, the activity of fosfomycin is variable.

Administration

Fosfomycin is available as powder for intravenous infusion (2 g; 4 g (as sodium) in vial). Fosfomycin has to be administered by slow intravenous infusion. Intramuscular use is discouraged by the European Medicines Agency because of insufficient data confirming benefits to patients (401). Oral formulations (fosfomycin trometamol and fosfomycin calcium) mostly used for the treatment of lower UTIs are not currently included in the EML and EMLc (8,9) and therefore they are not covered in this chapter.

Mechanism of action

Fosfomycin acts by inhibiting bacterial enzymes responsible for cell-wall synthesis, primarily pyruvyl transferase, an enzyme necessary for the synthesis of peptidoglycan.

Fosfomycin

This infographic only addresses the IV formulation of fosfomycin. Oral formulations are not currently included in the EML/EMLc

Rx Pharmacology

- Belongs to the phosphonic acid class of antibiotics
- Mechanism of action:** Inhibition of bacterial enzymes responsible for cell-wall synthesis

Indications for Use

Targeted Treatment

- Severe infections caused by laboratory-confirmed carbapenem-resistant Enterobacteriales or *Pseudomonas aeruginosa* susceptible to fosfomycin
- Salvage therapy for otherwise untreatable infections caused by MRSA and vancomycin-resistant *Enterococcus* (VRE) susceptible to fosfomycin

Empiric Use

- Only in very select cases of seriously ill patients (e.g. sepsis/septic shock):
 - who have not responded to carbapenems if other causes of treatment failure have been excluded and there is strong suspicion that the infection is caused by a carbapenem-resistant pathogen
 - who have previously been treated for infections caused by carbapenem-resistant pathogens susceptible to fosfomycin
 - who are known to be colonized with carbapenem-resistant pathogens susceptible to fosfomycin

Important Considerations

- Usually given in combination with other antibiotics due to concerns about the rapid emergence of resistance when used alone
- Very limited data from clinical trials about efficacy and safety (children and adults)

Formulations

- Powder for intravenous infusion: 2 g/vial or 4 g/vial (as sodium)



Spectrum of Activity

- Active against:**
 - ESBL and AmpC β-lactamases-producing Enterobacteriales
 - Gram-positive bacteria including MRSA, VRE and *S. epidermidis*
- Variable activity against:**
 - Pseudomonas aeruginosa*
 - Aerobic Gram-negative bacteria including many carbapenem-resistant Enterobacteriales
 - Carbapenemases: KPC, OXA-48 and metallo-β-lactamases (MBL)
- Not active against:**
 - Acinetobacter baumannii*
- Emerging resistance to fosfomycin in Enterobacteriales:**
 - Rare in clinical practice even though it can rapidly develop *in vitro*



Toxicity

- Generally well tolerated
- Consider risk of:
 - Sodium overload in patients with heart failure (related to the sodium salt formulation)
 - Hypokalaemia (need to monitor potassium levels regularly)



Dose



Antibiotic Treatment Duration

- Treatment duration varies according to indication and should be as short as possible
- Usually between **7-14 days**



Adults

Dosage is for normal renal function; dose adjustment required in case of renal impairment



Fosfomycin 6 g q8h IV

- Total daily dose may vary: range 12-24 g depending on indication and renal function



Children

Dosage is for normal renal function



Fosfomycin 200-400 mg/kg/day divided q8-12h IV

Spectrum of activity

Fosfomycin is active against several Gram-positive and Gram-negative bacteria but not as a single agent against *Streptococcus* spp., or *Acinetobacter* spp. or anaerobic bacteria. Specifically, it is usually active against *Enterococcus* spp. (including vancomycin-resistant strains), *Staphylococcus aureus* (including methicillin-resistant strains) and *Staphylococcus epidermidis*. It is also active against Gram-negative Enterobacterales (including ESBL-producing strains); however, activity against carbapenem-resistant or carbapenemases-producing strains is variable (Table 44.1). Fosfomycin's activity against *Pseudomonas aeruginosa* is variable.

Table 44.1 – Expected activity of intravenous fosfomycin against third-generation cephalosporin and carbapenem-resistant bacteria based on the type of beta-lactamase produced

Type of beta-lactamase	ESBL ^a	KPC ^b	NDM, VIM, IMP ^b	AmpC	OXA-48 ^b	Non-fermenters ^c
Ambler class^d	A ^e	A ^e	B (MBLs)	C ^e	D ^e	NA
Expected activity of IV fosfomycin	+	+/-	+/-	+	+/-	- <i>Acinetobacter baumannii</i>
(Consider using only in combination therapy)						+/- <i>Pseudomonas aeruginosa</i>

AmpC: ampicillinase C; ESBL: extended-spectrum beta-lactamases; IMP: imipenemase; IV: intravenous; KPC: *Klebsiella pneumoniae* carbapenemase; MBLs: metallo-beta-lactamases; NA: not applicable; NDM: New Delhi metallo-beta-lactamase; OXA-48: oxacillinase-48; VIM: Verona integron-encoded metallo-beta-lactamase.

Expected activity: + active; +/- possibly active; - not or insufficiently active.

^a ESBL are a group of different beta-lactamases.

^b Carbapenemases.

^c Non-fermenters refer to bacteria that cannot catabolize glucose and thus are unable to ferment. The most relevant in this context are *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. When using this table, always consider that even when activity of a certain Reserve antibiotic is reported against carbapenem-resistant non-fermenters, this ultimately depends on the type of carbapenemase produced and the resistance mechanism.

^d The Ambler classification of beta-lactamases is the most widely used classification. According to this classification beta-lactamases are divided into four classes (A, B, C and D) based upon similarities in their amino acid sequence.

^e Ambler class A, C and D are serine beta-lactamases.

Clinical efficacy

Intravenous fosfomycin could be considered for the treatment of certain severe infections when other antibiotics cannot be used or are not effective. It is usually used as part of combination treatments, mostly because of concerns about the emergence of resistance when used alone. The benefits of combination treatment compared with monotherapy in terms of better clinical efficacy are unclear as there is limited clinical evidence (402,403).

Few clinical trials have assessed the efficacy and safety of fosfomycin (intravenous) in adults. Fosfomycin has been assessed for the treatment of complicated UTIs and the results showed that fosfomycin was not inferior to piperacillin+tazobactam (404). Another non-inferiority trial which compared fosfomycin with meropenem and ceftriaxone has recently been completed (405). Fosfomycin has also been evaluated for the treatment of MRSA bacteraemia and endocarditis in combination with daptomycin and this combination was more effective than daptomycin alone (406).

Other evidence in support of the use of fosfomycin for difficult-to-treat *Staphylococcus aureus* infections (including MRSA) exists but it is anecdotal and inconclusive. This evidence is mostly from observational and in-vitro studies, including results from a clinical trial comparing fosfomycin (in combination with imipenem) to vancomycin alone for the treatment of complicated MRSA bacteraemia and endocarditis; however, this study failed to reach an adequate sample size (407).

In children, the evidence is even more limited. One pharmacokinetic and safety trial has recently been completed of fosfomycin as an empiric treatment in neonatal sepsis (408).

The use of fosfomycin for other indications (e.g. bone and joint infections, hospital-acquired pneumonia, meningitis and abdominal infections) relies on evidence from case reports or other observational and in vitro studies which is therefore less robust.

Toxicity

Fosfomycin is well tolerated. However, use of the intravenous formulation can be associated with sodium overload related to the sodium salt formulation (this could be of concern in patients with heart failure) and hypokalaemia (therefore potassium levels should be regularly monitored).

Dose

The optimal intravenous dose still needs to be clearly defined (Table 44.2). Usually, doses vary with the severity of the disease and the patient's renal function. Dose adjustments are necessary in cases of renal impairment. Please also refer to the chapter on dosing for more information.

Table 44.2 – Fosfomycin suggested doses

Dose in adults	Dose in children
IV: 6 g given every 8 hours (Note. Total daily dose may vary depending on the indication and may range between 12 g and 24 g per day divided every 8 to 12 hours.)	IV: 200–400 mg/kg/day divided every 8 to 12 hours

IV: intravenous.

Note. All dosages are for normal renal and hepatic function.

Indication for use as a Reserve antibiotic

Targeted treatment

Fosfomycin (usually as part of combination therapy to reduce the risk of the development of resistance) could be considered in the following cases.

- As a last-resort option for the targeted treatment of severe infections caused by laboratory-confirmed carbapenem-resistant Enterobacteriales or *Pseudomonas aeruginosa* (including strains producing carbapenemases) that have been shown to be susceptible to this antibiotic. Caution is needed with infections caused by *Pseudomonas aeruginosa* because the activity of fosfomycin against this pathogen is variable.
- As a last-resort option for difficult-to-treat infections caused by *Staphylococcus aureus* (including MRSA) and *Enterococcus* spp., including vancomycin-resistant strains. However, the 2021 version of the EML and EMLc does not include this use.

Empiric treatment

Usually as part of combination therapy, fosfomycin could be considered for empiric use in selected cases of seriously ill patients with invasive infections (e.g. patients with sepsis/septic shock) suspected to be caused by a multidrug-resistant pathogen (e.g. severe hospital-acquired infections or infections in patients who have received multiple antibiotic treatments in the recent past) such as in the following situations.

- Patients who have not responded to carbapenems if other causes of treatment failure have been excluded first and there is a strong suspicion that the infection is caused by a carbapenem-resistant Enterobacteriales – fosfomycin does not reliably treat *Acinetobacter* spp. and its activity against *Pseudomonas*

aeruginosa is variable. However, if a patient is not improving, antibiotic failure is not the only possible cause to consider. Alternative reasons include, for example: alternative diagnosis, development of complications (e.g. an abscess), inadequate source control, sub-optimal dose of the antibiotic or impossibility for the antibiotic to reach an adequate concentration at the site of infection. Alternative reasons are always important to consider before changing or adding new antibiotics.

- Patients who have previously been treated for infections caused by carbapenem-resistant Enterobacteriales. In certain settings *Klebsiella pneumoniae* may be resistant to fosfomycin; therefore, local knowledge of susceptibility profiles for aerobic Gram-negative bacteria is crucial (409). Fosfomycin does not reliably treat *Acinetobacter* spp. and its activity against *Pseudomonas aeruginosa* is variable.
- Patients who are known to be colonized with carbapenem-resistant pathogens found to be susceptible to fosfomycin.

To help prescribers identify clinical scenarios where empiric use of Reserve antibiotics could exceptionally be considered, suggestions are given in the relevant chapters of the AWaRe book for selected infections (only for infections where empiric use could potentially be adequate on a case-by-case basis).

Emerging resistance in Enterobacteriales

Cross-resistance is uncommon because of the unique structure and mechanism of action of fosfomycin. Both chromosomal-mediated and plasmid-mediated (i.e. transmissible) resistance can occur. Resistance can rapidly develop in vitro, but in clinical practice resistance is still uncommon, although it is increasing (410).

Data on resistance to fosfomycin are currently not reported by the GLASS.

Duration

Treatment duration varies according to indication and should be as short as possible, usually between 7 and 14 days.

45. Linezolid

Key messages

- Linezolid has activity against most strains of vancomycin-resistant *Enterococcus* spp. and methicillin-resistant *Staphylococcus aureus*.
- Linezolid has good oral bioavailability.
- Prolonged use (> 4 weeks) of linezolid is associated with increased incidence of toxicity (myelosuppression, neuropathy) and should be avoided if possible.

Linezolid is a synthetic antibiotic of the oxazolidinone class which has been in clinical use since the early 2000s for the treatment of infections caused by Gram-positive bacteria resistant to other antibiotics. Its current indications in the EML and EMLc include infections caused by MRSA, vancomycin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* spp. and multi-drug resistant *Mycobacterium tuberculosis* (8,9).

Linezolid

Rx Pharmacology

- Synthetic antibiotic of the oxazolidinone class
- **Mechanism of action:** Inhibition of bacterial protein synthesis



Spectrum of Activity

• Active against:

- Gram-positive bacteria including MRSA, VRE and penicillin non-susceptible pneumococci
- *Mycobacterium tuberculosis* including extensively drug-resistant strains

• Not active against:

- Gram-negative bacteria
- Anaerobes

• Emerging resistance to linezolid in MRSA, VRSA, VRE:

- Reported but remains low



Formulations

- Solution for intravenous infusion: 2 mg/mL in 300 mL bag
- Oral formulations:
 - Tablet: 400 mg; 600 mg
 - Tablet (dispersible): 150 mg
 - Powder for oral liquid: 100 mg/5 mL



Toxicity

- Generally well tolerated, risks increase with prolonged use (>4 weeks)
- Consider risk of:
 - Myelosuppression (mostly thrombocytopenia)
 - Monitor complete blood cell count every week
 - Severe optic neuropathy and peripheral neuropathy (both rare)



Dose



Antibiotic Treatment Duration

Treatment duration varies according to indication and should be as short as possible (increased risk of side effects if used for >4 weeks)



Adults

Dosage is for normal renal function; no need to adjust the dose in case of renal impairment



Linezolid 600 mg q12h IV/ORAL



Children

Dosage is for normal renal function; no need to adjust the dose in case of renal impairment



Linezolid 10 mg/kg/dose q8h IV/ORAL



Neonates

Dosage is for normal renal function; no need to adjust the dose in case of renal impairment



Linezolid IV/ORAL

- 1st week of life: 10 mg/kg/dose q12h
- >1st week of life: 10 mg/kg/dose q8h



Indications for Use



Targeted Treatment

- MRSA infections in selected situations:
 - Severe renal impairment
 - Hypersensitivity to vancomycin
 - Need to use oral treatment and other cheaper oral options are unavailable or not indicated
- VRSA or VRE infections
- Mycobacterial infections, including extensively drug-resistant *M. tuberculosis* (second-line option)



Empiric Use

- Only in very selected cases of seriously ill patients with invasive infections who are known to be colonized with VRE or VRSA



Important Considerations

The high oral bioavailability of linezolid allows initiation with oral treatment as an alternative to intravenous treatment

Administration

Linezolid is currently available as a solution for intravenous infusion (2 mg/mL in 300 mL bag) administered by intravenous infusion over 30–120 minutes, and as an oral formulation (tablet: 400 mg; 600 mg). A neonatal or paediatric formulation is also available (powder for oral liquid: 100 mg/5 mL). The high oral bioavailability of linezolid allows initiation with oral treatment as an alternative to intravenous treatment.

Generic versions of linezolid are available.

Mechanism of action

Linezolid acts by binding to the 50S unit of the bacterial ribosome, inhibiting the synthesis of bacterial proteins.

Spectrum of activity

Linezolid is mainly active against aerobic Gram-positive bacteria. In particular against most clinical isolates of vancomycin-resistant *Enterococcus* spp., MRSA and penicillin non-susceptible pneumococci. In addition, linezolid has some bactericidal activity against *Mycobacterium tuberculosis* including extensively drug-resistant strains and certain non-tuberculous mycobacteria.

Linezolid is not indicated for the treatment of Gram-negative infections. Even though linezolid has some in vitro activity against certain Gram-negative and anaerobic bacteria, clinical data are limited and its use is not recommended for the treatment of these pathogens.

Clinical efficacy

Several clinical trials have assessed the efficacy and safety of linezolid compared to vancomycin for the treatment of MRSA infections in general (411) and for skin and soft tissue infections in particular, including those caused by MRSA (412). Linezolid was associated with better short-term survival compared to daptomycin for the treatment of bloodstream infections caused by vancomycin-resistant *Enterococcus* spp. (413–415). However, linezolid's overall superiority to daptomycin is less clear because a large cohort study showed greater treatment failure and short-term mortality with linezolid than daptomycin (416). With health care-associated pneumonia, the results of a systematic review and meta-analysis did not show a clear benefit of linezolid for clinical cure or microbiological eradication when compared to vancomycin or teicoplanin, and linezolid was associated with more side-effects (417).

Linezolid can also be used as part of a longer regimen (longer than the standard TB treatment duration) for the treatment of patients with multidrug- and rifampicin-resistant TB as indicated in WHO guidelines for treatment of drug-resistant TB (418).

Toxicity

Linezolid is generally well tolerated; however, it can cause myelosuppression (mostly thrombocytopenia but also anaemia or leukopenia), which is usually reversible when linezolid is stopped. Therefore, a complete blood cell count should be done weekly, especially in high-risk patients, such as those with pre-existing myelosuppression or concomitant use of medicines that cause bone marrow suppression. As with any other medicine, interactions with other medicines should be checked before prescribing linezolid; this topic is, however, not addressed in the AWaRe book. Severe optic neuropathy can occur rarely, particularly if linezolid is used for more than 28 days. Patients should be advised to report all new visual symptoms. Peripheral neuropathy is also rarely associated with the (prolonged) use of linezolid. The risk of side-effects increases with prolonged use (usually > 4 weeks), which should be avoided unless there are no alternatives.

Dose

Linezolid does not require dose adjustments in case of renal impairment (Table 45.1). Please also refer to the chapter on dosing for more information.

Table 45.1 – Linezolid suggested doses

Dose in adults	Dose in children	Dose in neonates
600 mg given every 12 hours	10 mg/kg/dose given every 8 hours	10 mg/kg/dose given every 12 hours (first week of life) or every 8 hours (> first week of life)

Note. All dosages are for normal renal and hepatic function.

Indication for use as a Reserve antibiotic

Linezolid can be considered in the following situations.

- Oral treatment for MRSA is necessary and other less expensive oral alternatives to linezolid are not indicated or are likely to be ineffective due to resistance or toxicity concerns.

- Oral treatment may be necessary when maintaining access to parenteral treatment is difficult or for switching from intravenous to oral treatment when the patient could be discharged from hospital before the planned treatment course is completed.
- In case of documented hypersensitivity to vancomycin.
- In case of severe renal impairment.
- In case of infections caused by vancomycin-resistant *Enterococcus* spp. or *Staphylococcus aureus*.
- In very select cases of seriously ill patients with invasive infections that are known to be colonized with vancomycin-resistant *Enterococcus* spp. or *Staphylococcus aureus*.
- As a second-line option for the treatment of mycobacterial infections, including extensively drug-resistant *Mycobacterium tuberculosis* as recommended in WHO guidelines (418).

When using linezolid, the risk of side-effects (mostly thrombocytopenia), especially with prolonged use, should always be taken into account. Because of this and because of the risk of emergence of resistance, linezolid use as Reserve antibiotic should be limited to well defined patient populations and be as short as possible.

Emerging resistance in Gram-positive bacteria

Resistance to linezolid in usually susceptible Gram-positive bacteria most commonly arises through mutations in the bacterial 23S ribosomal RNA, but it can also be transmitted through plasmids. Resistance can develop in the absence of prior treatment with linezolid and also after short periods of exposure to the antibiotic and should be carefully monitored.

Resistant isolates of enterococci, staphylococci and streptococci have been reported worldwide but their proportion remains low and in general; most Gram-positive bacteria are still susceptible to linezolid (419). Selection for resistance could be favoured by suboptimal dosing of the antibiotic, especially in severely ill patients where volumes of distribution may be higher leading to low plasma levels (420).

Data on resistance to linezolid are currently not reported by the GLASS.

Duration

Treatment duration varies according to indication and should be as short as possible. Prolonged treatment (> 4 weeks) should be avoided whenever possible because of increased risk of toxicity (see toxicity section).

46. Meropenem+vaborbactam

Key messages

- Meropenem+vaborbactam has activity against many carbapenem-resistant Enterobacteriales, especially those producing *Klebsiella pneumoniae* carbapenemases, but not strains producing metallo-beta-lactamases and oxacillinase-48 (OXA-48).
- Meropenem+vaborbactam is currently not licensed for use in children.

Meropenem+vaborbactam is a combination of a carbapenem (meropenem) and a new non-beta-lactam beta-lactamase inhibitor (vaborbactam). Its current indications in the EML include infections caused by certain strains of carbapenem-resistant Enterobacteriales, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* (8). Its activity varies depending on the type of carbapenemase produced and the resistance mechanism.

However, for most strains of *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, the addition of vaborbactam to meropenem has no additional advantage over meropenem alone because of the presence of different resistance mechanisms. Therefore, activity of meropenem + vaborbactam against these pathogens is limited.

Administration

Meropenem+vaborbactam is currently available as powder for intravenous infusion (1 g + 1 g in vial). It should be administered by intravenous infusion over 3 hours.

Mechanism of action

Meropenem+vaborbactam acts by inhibiting bacterial enzymes responsible for cell wall synthesis, primarily penicillin-binding proteins. Vaborbactam targets the site of certain serine beta-lactamases (Ambler class B) and inactivates them, thus protecting meropenem from degradation.

Meropenem+vaborbactam

Rx Pharmacology

- Combination of a carbapenem (meropenem) and a novel non-β-lactam β-lactamase inhibitor (vaborbactam)
- Mechanism of action:**
 - Meropenem inhibits bacterial enzymes responsible for cell wall synthesis
 - Vaborbactam inactivates certain serine β-lactamases, thus protecting meropenem from degradation

Indications for Use

Targeted Treatment

- Severe infections caused by laboratory-confirmed KPC-producing Enterobacteriales, including bacteria resistant to ceftazidime+avibactam but susceptible to meropenem+vaborbactam

Empiric Use

- Only in very selected cases of seriously ill patients (e.g. sepsis/septic shock):
 - who have not responded to carbapenems if other causes of treatment failure have been excluded and there is strong suspicion that the infection is caused by a carbapenem-resistant pathogen
 - who have previously been treated for infections caused by carbapenem-resistant pathogens susceptible to meropenem+vaborbactam
 - who are known to be colonized with carbapenem-resistant pathogens susceptible to meropenem+vaborbactam

Important Considerations

- Since it is not active against metallo-β-lactamases (Ambler class B) or class D carbapenemases (such as OXA-48), it is important to know the local epidemiology of the most prevalent genotypic variants for aerobic Gram-negative bacteria

Formulations

- Powder for intravenous infusion: 1 g + 1 g in vial



Spectrum of Activity

- Active against:**
 - Aerobic Gram-negative bacteria including many carbapenem-resistant Enterobacteriales
 - KPC carbapenemases
 - ESBL and AmpC β-lactamases
 - Aerobic Gram-positive bacteria
 - Anaerobes
- Variable activity against:**
 - *Acinetobacter baumannii*
 - *Pseudomonas aeruginosa*
- Not active against:**
 - Gram-negative bacteria producing metallo-β-lactamases (NDM, VIM, IMP) or Ambler class D carbapenemases (such as OXA-48)
- Emerging resistance to meropenem+vaborbactam in Enterobacteriales:**
 - Very rare in clinical practice



Toxicity

- Generally well tolerated
- Side effects similar to meropenem alone

Dose



Antibiotic Treatment Duration

- Treatment duration varies according to indication and should be as short as possible
- Usually between **7-14 days**



Adults

Dosage is for normal renal function; dose adjustment required in case of renal impairment



Meropenem+vaborbactam 4 g (2 g meropenem + 2 g vaborbactam) q8h IV



Children or Neonates

Currently not licensed for use in children or neonates

Spectrum of activity

Meropenem+vaborbactam has a broad-spectrum of action including Gram-positive aerobic bacteria, Gram-negative aerobic bacteria and anaerobic bacteria. In particular, vaborbactam inhibits the activity of ESBLs, AmpC beta-lactamases and *Klebsiella pneumoniae* carbapenemases, and thus preserves the activity of meropenem against many multidrug-resistant Gram-negative bacteria (Table 46.1). However, vaborbactam does not inhibit the activity of metallo-beta-lactamases and OXA-48 beta-lactamases and therefore meropenem is not active against strains expressing these beta-lactamases (Table 46.1).

Table 46.1 – Expected activity of meropenem+vaborbactam against third-generation cephalosporin and carbapenem-resistant bacteria based on the type of beta-lactamase produced

Type of beta-lactamase	ESBL ^a	KPC ^b	NDM, VIM, IMP ^b	AmpC	OXA-48 ^b	Non-fermenters ^c
Ambler class ^d	A ^e	A ^e	B	C ^e	D ^e	NA
Expected activity of meropenem+vaborbactam	+	+	-	+	-	+/-

AmpC: ampicillinase C; ESBL: extended-spectrum beta-lactamases; IMP: imipenemase; KPC: *Klebsiella pneumoniae* carbapenemase; MBLs: metallo-beta-lactamases; NA: not applicable; NDM: New Delhi metallo-beta-lactamase; OXA-48: oxacillinase-48; VIM: Verona integron-encoded metallo-beta-lactamase.

Expected activity: + active; +/- possibly active; - not or insufficiently active.

^a ESBL are a group of different beta-lactamases.

^b Carbapenemases.

^c Non-fermenters refer to bacteria that cannot catabolize glucose and thus are unable to ferment. The most relevant in this context are *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. When using this table, always consider that even when activity of a certain Reserve antibiotic is reported against carbapenem-resistant non-fermenters, this ultimately depends on the type of carbapenemase produced and the resistance mechanism.

^d The Ambler classification of beta-lactamases is the most widely used classification. According to this classification beta-lactamases are divided into four classes (A, B, C and D) based upon similarities in their amino acid sequence.

^e Ambler class A, C and D are serine beta-lactamases.

Clinical efficacy

The TANGO I trial demonstrated that the efficacy and safety of meropenem+vaborbactam in adults was non-inferior to piperacillin+tazobactam for the treatment of complicated UTIs (421). The TANGO II trial (77 patients) demonstrated improved clinical cure and decreased



short-term mortality and nephrotoxicity than the best-available therapy for the treatment of infections caused by proven or suspected carbapenem-resistant Enterobacteriales (422).

Toxicity

Meropenem+vaborbactam is well tolerated and has side-effects similar to those previously reported for meropenem alone. However, meropenem+vaborbactam is less damaging to the kidneys than other antibiotics used to treat infections caused by carbapenem-resistant Enterobacteriales.

Dose

Dose adjustments are required in cases of renal impairment (Table 46.2). In children, the optimal dose is unknown because of limited paediatric-specific pharmacokinetics and pharmacodynamic data (423). Please also refer to the chapter on dosing for more information.

Table 46.2 – Meropenem+vaborbactam suggested doses

Dose in adults	Dose in children	Dose in neonates
IV: 4 g (2 g meropenem + 2 g vaborbactam) given every 8 hours	Currently not licensed for children	Currently not licensed for neonates

IV: intravenous.

Note. All dosages are for normal renal and hepatic function.

Indication for use as a Reserve antibiotic

Targeted treatment

Meropenem+vaborbactam could be considered in the following situations.

- As a last-resort option for the targeted treatment of severe infections caused by laboratory-confirmed *Klebsiella pneumoniae* carbapenemase-producing Enterobacteriales. It is not indicated in cases of metallo-beta-lactamases and OXA-48 production.
- For treatment of infections caused by bacteria resistant to ceftazidime+avibactam, unless resistance to ceftazidime+avibactam is due to the production of metallo-beta-lactamases.

- Based on the results of available trials, meropenem+vaborbactam could be considered in cases of severe complicated urinary tract and intra-abdominal infections and for HAP when other antibiotics cannot be used or are not effective.

Empiric treatment

Meropenem+vaborbactam could be considered for empiric use exceptionally in very select cases of seriously ill patients with invasive infections (e.g. patients with sepsis/septic shock) suspected to be caused by a multidrug-resistant pathogen (e.g. severe hospital-acquired infections or infections in patients who have received multiple antibiotic treatments in the recent past), such as in the following situations.

- Patients who have not responded to carbapenems if other causes of treatment failure have been excluded first and there is a strong suspicion that the infection is caused by a carbapenem-resistant pathogen. However, if a patient is not improving, antibiotic failure is not the only possible cause to consider. Alternative reasons include, for example: alternative diagnosis, development of complications (e.g. an abscess), inadequate source control, sub-optimal dose of the antibiotic or impossibility for the antibiotic to reach an adequate concentration at the site of infection. Alternative reasons are always important to consider before changing or adding new antibiotics.
- Patients who have previously been treated for infections caused by carbapenem-resistant pathogens.
- Patients who are known to be colonized with carbapenem-resistant pathogens found to be susceptible to meropenem+vaborbactam.

To help prescribers identify these specific situations where empiric use of meropenem+vaborbactam could exceptionally be considered, suggestions are given in the relevant chapters of the AWaRe book for selected infections (only for infections where empiric use could be considered on a case-by-case basis).

Emerging resistance in Enterobacteriales

Most *Klebsiella pneumoniae* carbapenemase-producing Enterobacteriales are still susceptible to meropenem+vaborbactam with very few reports of resistant strains (424).

Data on resistance to meropenem+vaborbactam are currently not reported by the GLASS.

Duration

Treatment duration varies according to indication and should be as short as possible, usually between 7 and 14 days.

47. Plazomicin

Key messages

- Plazomicin has activity against many carbapenem-resistant Enterobacteriales such as those producing *Klebsiella pneumoniae* carbapenemases and oxacillinase-48 (OXA-48) carbapenemases, but not strains producing metallo-beta-lactamases.
- Side-effects of plazomicin are similar to other aminoglycosides, usually kidney and inner ear.
- Plazomicin is currently not licensed for use in children.

Plazomicin is a new semisynthetic aminoglycoside derived from sisomicin, an older aminoglycoside (425). Its current indications in the EML include infections caused by carbapenem-resistant Enterobacteriales (8,9).

Administration

Plazomicin has been developed as injection for intravenous use (500 mg/10 mL). It is administered by intravenous infusion over 30 minutes.

Mechanism of action

Plazomicin acts by binding to the 30S unit of the bacterial ribosome, thus inhibiting the start of the synthesis of bacterial proteins.

Plazomicin

Rx Pharmacology

- New semisynthetic aminoglycoside
- **Mechanism of action:** Inhibition of bacterial protein synthesis



Indications for Use

✓ Targeted Treatment

- Severe infections caused by laboratory-confirmed carbapenem-resistant Enterobacteriales susceptible to plazomicin (not *P. aeruginosa* or *A. baumannii*)
- Infections caused by Gram-negative bacteria resistant to other aminoglycosides if non-Reserve antibiotic options cannot be used



– Empiric Use

- Only in very selected cases of seriously ill patients (e.g., sepsis/septic shock caused by urinary tract infections if used as monotherapy - for other infections aminoglycosides are usually used in combination with other antibiotics):
 - who have not responded to carbapenems; if other causes of treatment failure have been excluded first and there is strong suspicion that the infection is caused by a carbapenem-resistant pathogen
 - who have previously been treated for infections caused by carbapenem-resistant pathogens susceptible to plazomicin
 - who are known to be colonized with carbapenem-resistant pathogens susceptible to plazomicin



Important Considerations

- Efficacy demonstrated in clinical trials only for complicated urinary tract infections in adults
- Very limited evidence for other infections and use in children



Formulations

- Intravenous injection: 500 mg/10 mL



Spectrum of Activity

- **Active against:**
 - Aerobic Gram-negative bacteria including many carbapenem-resistant Enterobacteriales
 - Carbapenemases: KPC and OXA-48
 - ESBL and AmpC β -lactamases
 - Bacteria producing aminoglycoside-modifying enzymes
- **Variable activity against:**
 - Strains producing metallo- β -lactamases
- **Not active against:**
 - *Acinetobacter baumannii*
 - *Pseudomonas aeruginosa*
- **Emerging resistance to plazomicin in Enterobacteriales:**
 - Very limited data



Toxicity

- Side effects similar to other aminoglycosides
- The most frequent are:
 - Kidney damage (monitor creatinine levels regularly)
 - Hearing loss and vestibular toxicity



Dose



Antibiotic Treatment Duration

- Treatment duration varies according to indication and should be as short as possible
- Usually between 7-14 days



Adults

Weight-based once-daily dosing is used; dosage is for normal renal function



Plazomicin 15 mg/kg q24h IV



Children or Neonates

No data for children or neonates

Spectrum of activity

Plazomicin is mainly active against Gram-negative aerobic bacteria, including ESBL-producing Enterobacteriales, carbapenem-resistant (including carbapenemase-producing) Enterobacteriales (Table 47.1) and bacteria producing aminoglycoside-modifying enzymes.

Table 47.1 – Expected activity of plazomicin against third-generation cephalosporin and carbapenem-resistant bacteria based on the type of beta-lactamase produced

Type of beta-lactamase	ESBL ^a	KPC ^b	NDM, VIM, IMP ^b	AmpC	OXA-48 ^b	Non-fermenters ^c
Ambler class^d	A ^e	A ^e	B (MBLs)	C ^e	D ^e	NA
Expected activity of plazomicin	+	+	+/- ^f	+	+	-

AmpC: ampicillinase C; ESBL: extended-spectrum beta-lactamases; IMP: imipenemase; KPC: *Klebsiella pneumoniae* carbapenemase; MBLs: metallo-beta-lactamases; NA: not applicable; NDM: New Delhi metallo-beta-lactamase; OXA-48: oxacillinase-48; VIM: Verona integron-encoded metallo-beta-lactamase.

Expected activity: + active; +/- possibly active; - not or insufficiently active.

^a ESBL are a group of different beta-lactamases.

^b Carbapenemases.

^c Non-fermenters refer to bacteria that cannot catabolize glucose and thus are unable to ferment. The most relevant in this context are *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. When using this table, always consider that even when activity of a certain Reserve antibiotic is reported against carbapenem-resistant non-fermenters, this ultimately depends on the type of carbapenemase produced and the resistance mechanism. For plazomicin, some *in vitro* studies have shown activity against *Pseudomonas aeruginosa* similar to amikacin (426).

^d The Ambler classification of beta-lactamases is the most widely used classification. According to this classification beta-lactamases are divided into four classes (A, B, C and D) based upon similarities in their amino acid sequence.

^e Ambler class A, C and D are serine beta-lactamases.

^f Susceptibility to plazomicin among strains producing metallo-beta-lactamases can be > 50%.

Clinical efficacy

Plazomicin can be considered as salvage therapy for otherwise untreatable carbapenem-resistant Gram-negative infections.

Efficacy has been demonstrated only for the treatment of complicated UTIs in adults where plazomicin showed non-inferiority to meropenem (427).

Very limited evidence exists for the treatment of other types of infections and for its use in children. Plazomicin has also been compared with colistin as part of combination therapy for the treatment of severe infections caused by carbapenem-resistant Enterobacterales, such as bacteraemia and hospital-acquired pneumonia (428). The results of the study indicated that plazomicin reduced short-term mortality and disease-related complications, but the trial was stopped early because of major difficulties with enrolling patients. The study therefore provides only descriptive statistics and findings; as such its results are inconclusive.

Toxicity

Plazomicin can cause damage to the kidneys and ears, similar to other aminoglycosides. The risk of nephrotoxicity is higher in older patients (> 65 years) and in patients with pre-existing renal impairment; therefore, creatinine levels should be monitored regularly.

Dose

Weight-based, once-daily dosing is used (Table 47.2). Dose adjustments are required in cases of renal impairment. No paediatric dosing is currently available. Please also refer to the chapter on dosing for more information.

Table 47.2 – Plazomicin suggested doses

Dose in adults	Dose in children	Dose in neonates
IV: 15 mg/kg given once daily	Currently not licensed for children	Currently not licensed for neonates

IV: intravenous.

Note. All dosages are for normal renal and hepatic function.

Indication for use as a Reserve antibiotic

Targeted treatment

Plazomicin could be considered in the following situations.

- As a last-resort option for the targeted treatment of severe infections (mostly UTIs) caused by laboratory-confirmed carbapenem-resistant Enterobacterales, including infections caused by strains producing carbapenemases that have been shown to be susceptible to this antibiotic.
 - An important advantage of plazomicin is that it only needs to be given once a day, while other Reserve antibiotics that have a comparable spectrum of activity require multiple daily doses.
 - To preserve its effectiveness (i.e. to prevent the development of resistance), it should not be used to treat Enterobacterales isolates that only produce ESBLs when other choices are available.
- For infections caused by Gram-negative bacteria resistant to other aminoglycosides such as gentamicin or amikacin if non-Reserve antibiotic options cannot be used.

Empiric treatment

Plazomicin could be considered for empiric use exceptionally in very select cases of seriously ill patients with invasive infections (e.g. patients with sepsis/septic shock caused by infections of the urinary tract if used as monotherapy; in other situations, plazomicin, like other aminoglycosides, would most likely be used in combination with other antibiotics) suspected to be caused by a multidrug-resistant pathogen (e.g. severe hospital-acquired infections or infections in patients who have received multiple antibiotic treatments in the recent past), such as in the following situations.

- Patients who have not responded to carbapenems if other causes of treatment failure have been excluded first and there is a strong suspicion that the infection is caused by carbapenem-resistant bacteria. However, if a patient is not improving, antibiotic failure is not the only possible cause to consider. Alternative reasons include: alternative diagnosis; development of complications (e.g. abscess); inadequate source control; suboptimal dosing of the antibiotic; or impossibility for the antibiotic to reach an adequate concentration at the site of infection. Alternative reasons are always important to consider before changing or adding new antibiotics.

- Patients who have previously been treated for infections caused by carbapenem-resistant bacteria.
- Patients who are known to be colonized with carbapenem-resistant bacteria found to be susceptible to plazomicin.

To help prescribers identify clinical situations where empiric use of Reserve antibiotics could exceptionally be considered, suggestions are given in the relevant chapters of the AWaRe book for selected infections (only for infections where empiric use could potentially be adequate on a case-by-case basis).

Emerging resistance in Enterobacterales

The main mechanisms of resistance overlap with some of those for other aminoglycosides. In particular, ribosomal modifications of the target site within the ribosome can prevent plazomicin from binding to its target, and alterations to uptake and efflux pumps can decrease the antibiotic concentration at the site of action. However, unlike other aminoglycosides, plazomicin maintains activity against most aminoglycoside-modifying enzymes – enzymes that can reduce the affinity of the antibiotic for its ribosomal target through a mechanism that is different from ribosomal modifications. Plasmid-mediated resistance (i.e. transmissible resistance) has also been described.

Data on resistance to plazomicin are currently not reported by the GLASS.

Duration

Treatment duration varies according to indication and should be as short as possible, usually between 7 and 14 days.

48. Polymyxin B and colistin (polymyxin E)

Key messages

- Polymyxin B and colistin have the same spectrum of activity that includes many strains of multidrug-resistant Gram-negative bacteria including *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.
- Polymyxin B and colistin are usually used as part of combination treatments; however, the only currently available randomized clinical trial did not show superiority over monotherapy.
- Great care must be taken to avoid dosing errors since doses can be given in different units on labels and an initial loading dose is always necessary.
- The main side-effect of polymyxin B and colistin is kidney damage, caused more often by colistin than polymyxin B.

Polymyxin B and colistin are polypeptides belonging to the polymyxin class of antibiotics. These antibiotics became available for clinical use in the 1960s but were replaced by other classes because of their unfavourable safety profile, notably nephrotoxicity. They have, however, been rediscovered in recent years because they retain activity against many strains of multidrug-resistant Gram-negative bacteria, including carbapenemase-producing strains. Polymyxin B and colistin have very similar chemical structures; however, polymyxin B is administered directly as the active antibiotic, while colistin is administered as inactive prodrug (sodium salt of colistin methane sulfonate also known as colistimethate). Since colistimethate is produced by chemical modification of colistin molecules through addition of methanesulfonate moieties, there are many different partially methanesulfonated derivatives in a given product, which results in batch-to-batch (and brand-to-brand) variation of the exact composition. Furthermore, there is important patient-to-patient variation in the metabolism of colistimethate, making the pharmacokinetics of colistin difficult to predict (429).

The current indications for polymyxins B and colistin in the EML and EMLc include infections caused by carbapenem-resistant Enterobacterales, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* (8,9).

Polymyxin B and colistin (polymyxin E)

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Rx Pharmacology

- Polymyxin B and colistin are polypeptides belonging to the polymyxin class of antibiotics
- Polymyxin B and colistin have very similar chemical structures, however:
 - Polymyxin B is administered directly as the active antibiotic
 - Colistin is administered as inactive prodrug (colistimethate sodium)
- **Mechanism of action:** Polymyxin B and colistin act by disrupting the bacterial cell membrane, leading to cell lysis



Spectrum of Activity

- Polymyxin B and colistin have the same antibacterial spectrum
- **Active against:**
 - Aerobic Gram-negative bacteria (including many multidrug-resistant isolates)
- **Not active against:**
 - Anaerobes
 - Gram-positive bacteria
 - Gram-negative cocci (e.g. *Neisseria* spp.)
- **Emerging resistance to polymyxins in Enterobacteriales, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*:**
 - Resistance can be due to chromosomal mutations leading to changes in the bacterial membrane that impair the ability of polymyxin B and colistin to bind to their target
 - Transmissible resistance due to mobilized colistin resistance (*mcr*) genes is also being increasingly described



Toxicity

- Polymyxin B and colistin can cause kidney damage (colistin > polymyxin B) and, more rarely, neurotoxicity (e.g. paresthesia)
- Side effects are reversible in most cases and are associated with the cumulative dose and duration of therapy



Indications for Use



Targeted Treatment

- Severe infections caused by laboratory-confirmed carbapenem-resistant Gram-negative bacteria susceptible to polymyxins (including infections caused by carbapenemase-producing strains susceptible to polymyxins)



Empiric Use

- Only in very selected cases of seriously ill patients (e.g. patients with sepsis/septic shock):
 - who have not responded to carbapenems if other causes of treatment failure have been excluded first and there is a strong suspicion that the infection is caused by a carbapenem-resistant pathogen
 - who have previously been treated for infections caused by carbapenem-resistant pathogens susceptible to polymyxins
 - who are known to be colonized with carbapenem-resistant pathogens susceptible to polymyxins



Important Considerations

- If both are available, polymyxin B is usually preferred to colistin (**important:** except for urinary tract infections) because it has better pharmacokinetic characteristics and less potential to cause kidney damage
- Usually given as part of combination therapy depending on the type of infection even though currently there is no evidence from randomized clinical trials that combination therapy is superior to colistin monotherapy for short-term clinical success - at least for infections caused by extensively drug-resistant *Acinetobacter* spp.

Polymyxin B and colistin (polymyxin E)

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Formulations

Polymyxin B:

- Powder for intravenous infusion: 50 mg (500 000 IU) in vial

Colistin:

- Powder for intravenous infusion: 1 million IU (as colistimethate sodium) in vial (equivalent to 34 mg colistin base activity)



Dose



Antibiotic Treatment Duration

- Treatment duration varies according to indication and should be as short as possible
- Usually between **7-14 days**



Clinical Considerations

- Great care must be taken to avoid dosing errors with polymyxin B and colistin; errors can arise because doses can be given in different units on labels

• Polymyxin B doses can be expressed in:

- mg
- International Units (IU)
- 1 mg of polymyxin B corresponds to 10 000 IU

• Colistin (polymyxin E) doses can be expressed in:

- International Units (IU) of colistimethate sodium (CMS)
- mg of colistimethate sodium
- mg of colistin base activity (CBA)
- 34 mg of colistin base activity corresponds to:
 - 1 million IU of colistimethate sodium
 - 80 mg of colistimethate sodium

- When using polymyxins, it is crucial to start therapy with a loading dose (to achieve more rapidly effective plasma concentrations) followed by maintenance dose after 12-24 hours

- For colistin (but not for polymyxin B), dose adjustments are necessary in cases of renal impairment



Adults

All dosages are for normal renal function

Polymyxin B



Polymyxin B IV

- Loading dose: 2.5 mg/kg (25 000 IU/kg)
- Maintenance dose: 1.5 mg/kg/dose (15 000 IU/kg/dose) q12h

Colistin



Colistin IV

- Loading dose: 300 mg CBA (9 million IU CMS)
- Maintenance dose: 150 mg CBA (4.5 million IU CMS) q12h



Children

All dosages are for normal renal function

Few data are available for dosing in children; doses approved by regulatory agencies may be suboptimal for many children due to interpatient variability

Polymyxin B



Polymyxin B IV

- Loading dose: 2.5 mg/kg (25 000 IU/kg)
- Maintenance dose:
 - Children <2 years: 0.75-2.25 mg/kg/dose (7 500-22 500 IU/kg/dose) q12h
 - Children ≥2 years: 1.5 mg/kg/dose (15 000 IU/kg/dose) q12h

Colistin



Colistin IV

- Loading dose: insufficient data
- 0.625-1.25 mg/kg/dose CBA (18 750-37 500 IU/kg/dose CMS) q6h
- OR
- 1.25-2.5 mg/kg/dose CBA (37 500-75 000 IU/kg/dose CMS) q12h



Neonates

All dosages are for normal renal function

Polymyxin B



Polymyxin B IV

- Loading dose: 2.5 mg/kg (25 000 IU/kg)
- Maintenance dose: 0.75-2.25 mg/kg/dose (7 500-22 500 IU/kg/dose) q12h

Colistin



Colistin IV

- Loading dose: insufficient data
- 0.625-1.25 mg/kg/dose CBA (18 750-37 500 IU/kg/dose CMS) q6h
- OR
- 1.25-2.5 mg/kg/dose CBA (37 500-75 000 IU/kg/dose CMS) q12h

Administration

Polymyxin B and colistin are available as powder for intravenous injection formulations (polymyxin B: 500 000 IU in vial; colistin: 1 million IU (as colistemethate sodium) in vial). They are administered by intravenous infusion over 60 to 90 minutes. There are important geographical differences in the availability of these antibiotics; polymyxin B, for example, is not available in many countries. The oral non-absorbable formulation of colistin (colistin sulfate) is not currently included in the EML and EMLc (8,9) and therefore is not covered in this chapter.

Mechanism of action

Polymyxin B and colistin act by disrupting the bacterial cell membrane through interaction with lipopolysaccharides present in the membranes of Gram-negative bacteria which thus leads to cell lysis. However, the exact mechanism is unknown.

Spectrum of activity

Polymyxin B and colistin have the same antibacterial spectrum and both are active only against aerobic Gram-negative bacteria with no activity against anaerobes, Gram-positive bacteria and Gram-negative cocci, for example, *Neisseria* spp.. Polymyxins are active against many clinical isolates of carbapenem-resistant Enterobacterales, *Acinetobacter* spp. and *Pseudomonas aeruginosa*, including many of the isolates producing carbapenemases (Table 48.1).

Table 48.1 – Expected activity of polymyxins against third-generation cephalosporin and carbapenem-resistant bacteria based on the type of beta-lactamase produced

Type of beta-lactamase	ESBL ^a	KPC ^b	NDM, VIM, IMP ^b	AmpC	OXA-48 ^b	Non-fermenters ^c
Ambler class^d	A ^e	A ^e	B (MBLs)	C ^e	D ^e	NA
Expected activity of polymyxin B and colistin	+	+	+	+	+	+

AmpC: ampicillinase C; ESBL: extended-spectrum beta-lactamases; IMP: imipenemase; KPC: *Klebsiella pneumoniae* carbapenemase; MBLs: metallo-beta-lactamases; NA: not applicable; NDM: New Delhi metallo-beta-lactamase; OXA-48: oxacillinase-48; VIM: Verona integron-encoded metallo-beta-lactamase.

Expected activity: + active.

^a ESBL are a group of different beta-lactamases.

^b Carbapenemases.

^c Non-fermenters refer to bacteria that cannot catabolize glucose and thus are unable to ferment. The most relevant in this context are *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. When using this table, always consider that even when activity of a certain Reserve antibiotic is reported against carbapenem-resistant non-fermenters, this ultimately depends on the type of carbapenemase produced and the resistance mechanism.

^d The Ambler classification of beta-lactamases is the most widely used classification. According to this classification beta-lactamases are divided into four classes (A, B, C and D) based upon similarities in their amino acid sequence.

^e Ambler class A, C and D are serine beta-lactamases.

Clinical efficacy

Polymyxin B and colistin can be considered as salvage therapy for otherwise untreatable infections caused by carbapenem-resistant Gram-negative bacteria.

For severe infections, they are usually given as part of combination therapy often with high doses of carbapenems (but only if the minimum inhibitory concentration of carbapenems is $\leq 8\text{--}16 \text{ mg/L}$) or in combination with other antibiotics depending on the type of infection and in vitro susceptibility (430).

However, the only currently available randomized clinical trial did not show that combination therapy was superior to colistin monotherapy for short-term clinical success – at least for infections caused by extensively drug-resistant *Acinetobacter* spp. It is unclear whether this also applies to carbapenemase-producing Enterobacterales (431). Evidence from observational studies is available but should be interpreted with caution due to the inherent methodological limitations (432,433).

Polymyxin B and colistin were approved for use decades ago and were therefore not subjected to the same development process that would be required for the approval of a

new antibiotic today. This point should be kept in mind when interpreting data about their efficacy and safety, for example, current products of polymyxins may be less nephrotoxic than those initially used (434). There are recently licensed Reserve group beta-lactam/beta-lactamase inhibitor combinations (ceftazidime+avibactam, meropenem+vaborbactam) or siderophore-antibiotics (cefiderocol) available that some experts consider preferable to polymyxins because of their better safety profile and potentially better efficacy. However, the evidence of their superiority is weak and access and affordability of these new antibiotics is a major issue in many low- and middle-income settings.

Toxicity

The use of polymyxin B and colistin can cause kidney damage (colistin is more likely to cause damage than polymyxin B) and, more rarely, neurotoxicity (e.g. paraesthesia). The side-effects are reversible in most cases and are associated with the cumulative dose and duration of therapy and use of concomitant medicines with similar toxicities.

Dose

Great care must be taken to avoid dosing errors with polymyxin B and colistin (Table 48.2 and Table 48.3). Errors can arise because doses can be given in different units on labels (435–437).

Polymyxin B doses can be given in international units (IU) or milligrams. For example, a dose of 1 million IU corresponds to 100 mg.

Colistin doses can be given in: IU of colistimethate sodium; mg of colistimethate sodium; or mg of colistin base activity. For example, a dose of 1 million IU of colistimethate sodium corresponds to 80 mg of colistimethate sodium and to 34 mg of colistin base activity.

When using polymyxins, it is crucial to start therapy with a loading dose followed by maintenance dose after 12–24 hours. The reason is to more rapidly achieve plasma concentrations that may be effective. In addition, for colistin (but not for polymyxin B), dose adjustments are necessary in cases of renal impairment (438).

Few data are available for dosing in children. Current evidence suggests that doses approved by regulatory agencies may be suboptimal for many children due to interpatient variability (438).

Please also refer to the chapter on dosing for more information.

Table 48.2 – Polymyxin B suggested doses

	Dose in adults	Dose in children	Dose in neonates
Loading dose	2.5 mg/kg (25 000 IU/kg)	2.5 mg/kg (25 000 IU/kg)	2.5 mg/kg (25 000 IU/kg)
Maintenance dose (start 12 hours after the loading dose)	1.5 mg/kg/dose (15 000 IU/kg/dose) given every 12 hours Higher doses up to 2.5–3 mg/kg/dose (25 000–30 000 IU/kg/dose) can be used but the maximum daily dose should not exceed 200 mg (2 000 000 IU)	1.5 mg/kg/dose (15 000 IU/kg/dose) given every 12 hours In children < 2 years of age 0.75–2.25 mg/kg/dose (7 500–22 500 IU/kg/dose) given every 12 hours	0.75–2.25 mg/kg/dose (7 500–22 500 IU/kg/dose) given every 12 hours

Note. All dosages are for normal renal and hepatic function.

IU: international units.

Table 48.3 – Colistin suggested doses

 Note			
	Dose in adults	Dose in children	Dose in neonates
Loading dose	300 mg CBA (9 million IU colistimethate sodium)	Insufficient data	Insufficient data
Maintenance dose (start 12 hours after the loading dose)	150 mg CBA (4.5 million IU colistimethate sodium) given every 12 hours Maximum daily dose should not exceed 300–400 mg CBA or 9–12 million IU colistimethate sodium	0.625–1.25 mg/kg/dose CBA (18 750–37 500 IU/kg/dose colistimethate sodium) given every 6 hours OR 1.25–2.5 mg/kg/dose CBA (37 500–75 000 IU/kg/dose colistimethate sodium) given every 12 hours	0.625–1.25 mg/kg/dose CBA (18 750–37 500 IU/kg/dose colistimethate sodium) given every 6 hours OR 1.25–2.5 mg/kg/dose CBA (37 500–75 000 IU/kg/dose colistimethate sodium) given every 12 hours

CBA: colistin base activity; IU: international units.

Note. All dosages are for normal renal and hepatic function.

^a 34 mg of CBA corresponds to 1 million IU of colistimethate sodium and to 80 mg of colistimethate sodium.

Indication for use as a Reserve antibiotic

Targeted treatment

Polymyxin B or colistin could be considered, usually as part of a combination therapy, as a last-resort option for the targeted treatment of severe infections caused by laboratory-confirmed carbapenem-resistant Gram-negative bacteria, including infections caused by carbapenemase-producing strains that have been found to be susceptible to these antibiotics.

If available, polymyxin B is usually preferred to colistin because it has better pharmacokinetic characteristics and less potential to cause kidney damage.

The only situation where the use of colistin is preferred is for the treatment of UTIs because colistin reaches higher concentrations in urine compared to polymyxin B. The prodrug colistimethate is excreted primarily by the kidneys, while polymyxin B is mainly eliminated through non-renal pathways; however the fraction of colistimethate being converted to colistin in the urine remains unclear (439).

Empiric treatment

Polymyxin B or colistin should only be considered for empiric use exceptionally in selected cases of seriously ill patients with invasive infections (e.g. patients with sepsis/septic shock) suspected to be caused by a multidrug-resistant pathogen (e.g. severe hospital-acquired infections or infections in patients who have received multiple antibiotic treatments in the recent past), such as in the following situations.

- Patients who have not responded to carbapenems if other causes of treatment failure have been excluded first and there is a strong suspicion that the infection is caused by a carbapenem-resistant pathogen. However, if a patient is not improving, antibiotic failure is not the only possible cause to consider. Alternative reasons include for example: alternative diagnosis, development of complications (e.g. an abscess), inadequate source control, sub-optimal dose of the antibiotic or impossibility for the antibiotic to reach an adequate concentration at the site of infection. Alternative reasons are always important to consider before changing or adding new antibiotics.
- Patients who have previously been treated for infections caused by carbapenem-resistant pathogens susceptible to polymyxins.
- Patients who are known to be colonized with carbapenem-resistant pathogens found to be susceptible to polymyxins.



To help prescribers identify clinical scenarios where empiric use of Reserve antibiotics could exceptionally be considered, suggestions are given in the relevant chapters of the AWaRe book for selected infections (only for infections where empiric use could potentially be adequate on a case-by-case basis).

Emerging resistance in Enterobacterales, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*

Some technical challenges exist to identify resistance to polymyxin B and colistin. For example, polymyxins diffuse poorly in diffusion-based assays, such as disk-diffusion tests. Broth microdilution, which is the recommended method, is impractical and rarely used in most laboratories (440). Resistance can be related to chromosomal mutations that lead to changes in the bacterial membrane that impair the ability of polymyxin B and colistin to bind to their target. Plasmid-mediated resistance (i.e. transmissible resistance) due to mobilized colistin resistance (*mcr*) genes is also being increasingly described (441,442).

Data on resistance to colistin and polymyxin B are currently not reported by the GLASS.

Duration

Treatment duration varies according to indication and should be as short as possible, usually between 7 and 14 days.

DOSING GUIDANCE

49. Dosing guidance - Adults

Table 49.1 lists the antibiotics and suggested doses to be used in adults for the conditions covered in the AWaRe book.

Table 49.1 – Antibiotic dosing guidance: adults

All dosages are for normal renal and hepatic function.

Antibiotic (alphabetic order)	Dose	Indications for use
Amikacin	IV: 15 mg/kg/dose given once daily	Febrile neutropenia (high risk) Sepsis (unknown origin) Upper UTI (severe)
Amoxicillin	Oral: Lower dose: 500 mg given every 8 hours Higher dose: 1 g given every 8 hours IV: 2 g given every 4 hours	Lower dose (oral): Pharyngitis Acute otitis media COPD exacerbations (mild) Dental infections Higher dose (oral): Acute sinusitis CAP (mild) IV: Meningitis

continues

Table 49.1 *continued*

Antibiotic (alphabetic order)	Dose	Indications for use
Amoxicillin+clavulanic acid	<p>Oral:</p> <p>Lower dose: 500 mg + 125 mg given every 8 hours</p> <p>Higher dose: 875 mg + 125 mg given every 8 hours</p> <p>IV:</p> <p>Lower dose: 1 g + 200 mg given every 8 hours</p> <p>Higher dose: 2 g + 200 mg (single dose for prophylaxis)</p>	<p>Lower dose (oral):</p> <p>Acute otitis media</p> <p>Acute sinusitis</p> <p>Periorbital cellulitis</p> <p>COPD exacerbations (severe)</p> <p>UTI (lower)</p> <p>SSTI (mild)</p> <p>Febrile neutropenia (low risk)</p> <p>Higher dose (oral):</p> <p>CAP (mild)</p> <p>HAP</p> <p>Intra-abdominal infections (mild)</p> <p>Pyomyositis</p> <p>Lower dose (IV)</p> <p>Bone and joint infections</p> <p>CAP (severe)</p> <p>HAP</p> <p>Periorbital (or preseptal) cellulitis</p> <p>Intra-abdominal infections (mild)</p> <p>Pyomyositis</p> <p>Higher dose (IV)</p> <p>Surgical prophylaxis</p>
Ampicillin	IV: 2 g given every 4 hours	Meningitis

continues

Table 49.1 continued

Antibiotic (alphabetic order)	Dose	Indications for use
Azithromycin	<p>Oral:</p> <p>Lower dose: 500 mg given once daily</p> <p>Higher dose: 1 g (single dose)</p>	<p>Lower dose:</p> <p>Enteric fever (mild) Infectious acute diarrhoea</p> <p>Single dose:</p> <p><i>Chlamydia</i> infection^a Cholera Gonococcal infection^a Trachoma</p>
Benzathine benzylpenicillin (only for IM use)	IM: 2.4 million IU (\approx 1.8 g) (the number of doses depends on the stage of the infection)	Syphilis ^a
Benzylpenicillin (only for IV use) Also known as: - aqueous benzylpenicillin - benzylpenicillin potassium - benzylpenicillin sodium - crystalline penicillin - penicillin G potassium - penicillin G sodium	<p>IV:</p> <p>Lower dose: 2-4 million IU (1.2-2.4 g) given every 4 hours</p> <p>Higher dose: 4 million IU (2.4 g) given every 4 hours</p>	<p>Lower dose:</p> <p>Neurosypilis^a</p> <p>Higher dose:</p> <p>Meningitis</p>
Cefalexin	Oral: 500 mg given every 8 hours	COPD exacerbations (mild) Periorbital (or preseptal) cellulitis Pharyngitis Pyomyositis SSTI (mild)
Cefazolin	IV: 2 g given every 8 hours or single dose	Bone and joint infections Surgical prophylaxis (single dose)

continues

Table 49.1 *continued*

Antibiotic (alphabetic order)	Dose	Indications for use
Cefiderocol	IV: 2 g given every 8 hours	Empiric use should be exceptional (e.g. seriously ill patients with risk factors for infections due to carbapenem-resistant bacteria or failing to respond to carbapenems when other causes of treatment failure have been excluded)
Cefixime	Oral: 400 mg given once daily	Infectious acute diarrhoea Gonococcal infection ^a (single dose)
Cefotaxime	IV/IM: Lower dose: 1 g given every 8 hours Higher dose: 2 g given every 8 hours Highest dose: 2 g given every 6 hours	Lower dose (3 g/day): Upper UTI (severe) Higher dose (6 g/day): Bone and joint infections CAP (severe) HAP Intra-abdominal infections (mild and severe) Sepsis (unknown origin) Highest dose (8 g/day) Meningitis
Ceftazidime+avibactam	IV: 2 g + 500 mg given every 8 hours	Empiric use should be exceptional (e.g. seriously ill patients with risk factors for infections due to carbapenem-resistant bacteria or failing to respond to carbapenems when other causes of treatment failure have been excluded)

continues

Table 49.1 continued

Antibiotic (alphabetic order)	Dose	Indications for use
Ceftriaxone	IV/IM: Single dose: 250 mg Lower dose: 1 g given once daily Higher dose: 2 g given once daily Highest dose: 2 g given every 12 hours	Single dose: Gonococcal infection ^a Lower dose (1 g/day): Infectious acute diarrhoea (severe) Upper UTI (severe) High dose (2 g/day): Bone and joint infections CAP (severe) Endophthalmitis Enteric fever (severe) HAP Intra-abdominal infections (mild and severe) Necrotizing fasciitis Sepsis (unknown origin) Highest dose (4 g/day): Meningitis
Cefuroxime	IV: 1.5 g (single dose)	Surgical prophylaxis
Ciprofloxacin <i>Ciprofloxacin has excellent oral bioavailability and the intravenous route should be reserved for patients with impaired gastrointestinal function.</i>	Oral: 500 mg given every 12 hours 1 g (single dose)	Upper UTI (mild) Infectious acute diarrhoea Intra-abdominal infections (mild) Enteric fever Febrile neutropenia (low risk) Cholera (single dose)
Chloramphenicol	IV: 1 g given every 6 hours	Meningitis

continues

Table 49.1 continued

Antibiotic (alphabetic order)	Dose	Indications for use
Clarithromycin <i>Clarithromycin has excellent oral bioavailability and the intravenous route should be reserved for patients with impaired gastrointestinal function.</i>	Oral: 500 mg given every 12 hours IV: 500 mg given every 12 hours	Pharyngitis (oral) CAP (severe) (IV/oral)
Clindamycin	IV/oral: Lower dose: 600 mg given every 8 hours IV: Higher dose: 900 mg given every 8 hours	Lower dose: Bone and joint infections Higher dose: Necrotizing fasciitis
Cloxacillin	Lower dose: (oral) 500 mg given every 6 hours Higher dose: (IV) 2 g given every 6 hours	Lower dose: SSTI (mild) Higher dose: Bone and joint infections Periorbital (or preseptal) cellulitis Pyomyositis
Colistin (polymyxin E) CBA: colistin base activity; CMS: colistimethate sodium	IV: Loading dose: 300 mg CBA/9 million IU CMS Maintenance dose: 150 mg CBA/4.5 million IU CMS given every 12 hours Maximal daily dose should not exceed 300 (to 400) mg CBA or 9 (to 12) million IU CMS	Empiric use should be exceptional (e.g. seriously ill patients with risk factors for infections due to carbapenem-resistant bacteria or failing to respond to carbapenems when other causes of treatment failure have been excluded)

continues

Table 49.1 continued

Antibiotic (alphabetic order)	Dose	Indications for use
Doxycycline	Oral: 100 mg given every 12 hours 300 mg (single dose)	CAP (mild) COPD exacerbations (mild) Chlamdia infection ^a Cholera (single dose)
Gentamicin	IV: 5 mg/kg given once daily	Sepsis (unknown origin) Surgical prophylaxis Upper UTI (severe)
Fosfomycin (IV)	IV: 6 g given every 8 hours (range 12–24 g per day depending on the indication)	Empiric use should be exceptional (e.g. seriously ill patients with risk factors for infections due to carbapenem-resistant bacteria or failing to respond to carbapenems when other causes of treatment failure have been excluded)
Linezolid	IV/oral: 600 mg given every 12 hours	Empiric use should be exceptional (e.g. oral treatment for suspected MRSA infections when no alternatives are available) For use in tuberculosis, refer to WHO guidelines (418)
Meropenem	IV: Lower dose: 1 g given every 8 hours Higher dose: 2 g given every 8 hours	Lower dose: Febrile neutropenia (high risk) Intra-abdominal infections (severe) Higher dose: Sepsis (severe intra-abdominal infections)

continues

Table 49.1 *continued*

Antibiotic (alphabetic order)	Dose	Indications for use
Meropenem+vaborbactam	IV: 2 g + 2 g given every 8 hours	Empiric use should be exceptional (e.g. seriously ill patients with risk factors for carbapenem-resistant infections or failing to respond to carbapenems when other causes of treatment failure have been excluded)
Metronidazole <i>Metronidazole has excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function.</i>	Oral/IV: Single dose: 500 mg, 2 g Lowest dose: 500 mg given every 12 hours Lower dose: 500 mg given every 8 hours Higher dose: 750 mg given every 8 hours	Single dose: Surgical prophylaxis (500 mg) Trichomoniasis (2 g) Lowest dose: Trichomoniasis Lower dose: <i>Clostridioides difficile</i> infection Intra-abdominal infections (mild and severe) Necrotizing fasciitis Higher dose: Amoebic abscess
Nitrofurantoin	Oral: 100 mg given every 12 hours (modified release) 50 mg given every 6 hours (immediate release)	UTI (lower)
Phenoxytmethylpenicillin	Oral: 500 mg (800 000 IU ^b) given every 6 hours	Pharyngitis CAP (mild) Dental infections

continues

Table 49.1 continued

Antibiotic (alphabetic order)	Dose	Indications for use
Piperacillin+tazobactam	IV: 4 g + 500 mg given every 6 hours	HAP Intra-abdominal infections (severe) Necrotizing fasciitis Febrile neutropenia (high-risk)
Plazomicin	IV: 15 mg/kg/dose given once daily	Empiric use should be exceptional (e.g. seriously ill patients with risk factors for carbapenem-resistant infections or failing to respond to carbapenems when other causes of treatment failure have been excluded)
Polymyxin B	IV: Loading dose: 2.5 mg/kg (25 000 IU/kg) Maintenance dose: 1.5 mg/kg (15 000 IU/kg) given every 12 hours Higher doses up to 2.5-3.0 mg/kg (25 000-30 000 IU/kg) can be used but the maximum daily dose should not exceed 200 mg (2 million IU)	Empiric use should be exceptional (e.g. seriously ill patients with risk factors for carbapenem-resistant infections or failing to respond to carbapenems when other causes of treatment failure have been excluded)
Procaine benzylpenicillin	IM: 1.2 million IU (1.2 g) given once daily	Syphilis ^a Neurosypilis ^a
Sulfamethoxazole+trimethoprim	Oral: 800 mg + 160 mg given every 12 hours	UTI (lower) Infectious acute diarrhoea
Trimethoprim	Oral: 200 mg given every 12 hours	UTI (lower)

continues

Table 49.1 continued

Antibiotic (alphabetic order)	Dose	Indications for use
Vancomycin <i>Vancomycin is not absorbed from the gastrointestinal tract when given orally. The only indication for oral vancomycin is Clostridoides difficile infection</i>	IV: 15–20 mg/kg given every 12 hours Oral: 125 mg given every 6 hours or 500 mg given every 6 hours	IV: Endophthalmitis Febrile neutropenia (high risk) (if MRSA suspected) Necrotizing fasciitis (if MRSA suspected) Oral: <i>Clostridoides difficile</i> infection (higher dose for severe cases)

CAP: community-acquired pneumonia; CBA: colistin base activity; CMS: colistimethate sodium; COPD: chronic obstructive pulmonary diseases; HAP: hospital-acquired pneumonia; IM: intramuscular; IU: international units; IV: intravenous; MRSA: methicillin-resistant *Staphylococcus aureus*; SSTI: skin and soft tissue infections; UTI: urinary tract infection

^a WHO guidelines for treatment of sexually transmitted infections are currently being revised. Check the WHO website for possible updates.

^b Units of the potassium salt.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

50. Dosing guidance - Children

Table 50.1 lists the antibiotics and suggested doses to be used in children for the conditions covered in the AWaRe book.

For children, weight-based dosing is used for oral treatment when possible. The 2019 EML report on consensus guidance on paediatric antibiotic dosing regimens was used as a reference but adapted and weight-banded by infection and severity of disease (20). Local and national dosing guidance should be considered where available.

Table 50.1 – Antibiotics dosing guidance: children

All dosages are for normal renal and hepatic function.

Antibiotic (alphabetic order)	Dose	Indications for use
Amikacin	<p>IV: 15 mg/kg/dose given once daily</p> <p>Up to a maximum daily dose of 1.5 g</p>	<p>Febrile neutropenia (high risk)</p> <p>Sepsis (unknown origin)</p> <p>Upper UTI (severe)</p>

continues

Table 50.1 *continued*

Antibiotic (alphabetic order)	Dose	Indications for use
Amoxicillin	<p>Oral: 80–90 mg/kg/day Up to a maximum daily dose of 1.5 g but can be higher for serious bacterial infections Weight bands: 3–<6 kg: 250 mg given every 12 hours 6–<10 kg: 375 mg given every 12 hours 10–<15 kg: 500 mg given every 12 hours 15–<20 kg: 750mg given every 12 hours ≥ 20 kg: 500 mg given every 8 hours or 1 g given every 12 hours</p> <p>IV:</p> <ul style="list-style-type: none"> • First week of life: 50 mg/kg/dose given every 12 hours • Beyond first week of life: 50 mg/kg/dose given every 8 hours <p>Up to a maximum daily dose of 6 g (serious bacterial infections)</p>	<p>Oral: Pharyngitis Acute otitis media Dental infections Acute sinusitis CAP (mild) Sepsis (referral to hospital not possible)</p> <p>IV: Meningitis CAP</p>

continues

Table 50.1 continued

Antibiotic (alphabetic order)	Dose	Indications for use
Amoxicillin+clavulanic acid <i>Oral liquid formulations must be refrigerated after reconstitution.</i>	<p>Oral: 80–90 mg/kg/day (amoxicillin component)</p> <p>Weight bands:</p> <ul style="list-style-type: none"> 3–< 6 kg: 250 mg of amoxicillin/dose given every 12 hours 6–< 10 kg: 375 mg of amoxicillin/dose given every 12 hours 10–< 15 kg: 500 mg of amoxicillin/dose given every 12 hours 15–< 20 kg: 750 mg of amoxicillin/dose given every 12 hours ≥ 20 kg: 500 mg of amoxicillin/dose given every 8 hours or 1 g of amoxicillin/dose given every 12 hours <p>IV:</p> <p>First week of life: 50 mg/kg of amoxicillin/dose given every 12 hours</p> <p>Beyond first week of life: 50 mg/kg of amoxicillin/dose given every 8 hours</p>	<p>Oral: Acute otitis media Acute sinusitis UTI (lower) SSTI (mild) Febrile neutropenia (low risk)</p> <p>Oral/IV: Intra-abdominal infections (mild) Bone and joint infections HAP Periorbital (or preseptal) cellulitis Pyomyositis</p> <p>IV: Surgical prophylaxis</p>

continues

Table 50.1 *continued*

Antibiotic (alphabetic order)	Dose	Indications for use
Ampicillin	<p>IV:</p> <ul style="list-style-type: none"> First week of life: 50 mg/kg/dose given every 12 hours Beyond first week of life: 50 mg/kg/dose given every 8 hours <p>Up to a maximum daily dose of 6 g (serious bacterial infections)</p>	Meningitis Sepsis Intra-abdominal infections (mild and severe) CAP (severe)
Azithromycin	<p>Oral:</p> <p>Lower dose: 10 mg/kg/dose given every 24 hours</p> <p>Higher dose: 20 mg/kg/dose given every 24 hours</p> <p>Up to a maximum daily dose of 500 mg</p>	<p>Lower dose: Acute bloody diarrhoea</p> <p>Higher dose: Enteric fever (mild) Cholera (single dose) Trachoma (single dose)</p>
Benzathine benzylpenicillin (only for IM use)	IM: 50 000 IU (\approx 37.5 mg)/kg (single dose)	Congenital syphilis (only in selected cases)

continues

Table 50.1 continued

Antibiotic (alphabetic order)	Dose	Indications for use
Benzylpenicillin (only for IV use) Also known as: - aqueous benzylpenicillin - benzylpenicillin potassium - benzylpenicillin sodium - crystalline penicillin - penicillin G potassium - penicillin G sodium	IV: Lower dose: 50 000–75 000 IU/kg/dose (30–45 mg/kg/dose) given every 12 hours Higher dose: Severe CAP/sepsis Meningitis 50 000 IU/kg/dose (30 mg/kg/dose) given every 8 hours Meningitis 100 000 IU/kg/dose (60 mg/kg/dose) given every 6 hours Up to a maximum daily dose of 6 million IU (3.6 g)	Lower dose: Congenital syphilis Higher dose: Severe CAP Sepsis Meningitis
Cefalexin	Oral: 25 mg/kg/dose given every 12 hours Maximum daily dose: use adult dosing Weight bands: 3–< 6 kg: 125 mg given every 12 hours 6–< 10 kg: 250 mg given every 12 hours 10–< 15 kg: 375 mg given every 12 hours 15–< 20 kg: 500 mg given every 12 hours 20–< 30 kg: 625 mg given every 12 hours ≥ 30 kg: use adult dose	Periorbital (or preseptal) cellulitis Pharyngitis Pyomyositis SSTI (mild)

continues

Table 50.1 *continued*

Antibiotic (alphabetic order)	Dose	Indications for use
Cefazolin	IV: 25 mg/kg/dose given every 12 hours 50 mg/kg (single dose for surgical prophylaxis) Maximum daily dose: see adult dosing	Bone and joint infections Surgical prophylaxis
Cefixime	Oral: 10 mg/kg/dose given once daily Maximum daily dose: see adult dosing	Infectious acute diarrhoea
Cefotaxime	IV/IM: First week of life: 50 mg/kg/dose given every 12 hours Beyond first week of life: 50 mg/kg/dose given every 8 hours Maximum daily dose: see adult dosing	Upper UTI (severe) Bone and joint infections CAP (severe) HAP Intra-abdominal infections (mild and severe) Sepsis (unknown origin) Meningitis
Ceftazidime+avibactam	IV: 62.5 mg/kg/dose (50 mg/kg/dose ceftazidime + 12.5 mg/kg/dose avibactam) given every 8 hours Maximum daily dose: see adult dosing	Seriously ill patients with presumed infections due to multidrug-resistant bacteria

continues

Table 50.1 *continued*

Antibiotic (alphabetic order)	Dose	Indications for use
Ceftriaxone	IV/IM: Lower dose: 80 mg/kg/dose given once daily Higher dose: 100 mg/kg/dose given once daily Up to a maximum daily dose of 3 g	Lower dose: Infectious acute diarrhoea (severe) Upper UTI (severe) Bone and joint infections CAP (severe) Endophthalmitis Enteric fever (severe) HAP Intra-abdominal infections (mild and severe) Necrotizing fasciitis Sepsis (unknown origin) Higher dose: Meningitis
Cefuroxime	IV: 50 mg/kg (single dose)	Surgical prophylaxis

continues

Table 50.1 continued

Antibiotic (alphabetic order)	Dose	Indications for use
Ciprofloxacin <i>Ciprofloxacin has excellent oral bioavailability and the intravenous route should be reserved for patients with impaired gastrointestinal function.</i>	Oral: 15 mg/kg/dose given every 12 hours Weight bands: 3–< 6 kg: 50 mg given every 12 hours 6–< 10 kg: 100 mg given every 12 hours 10–< 15 kg: 150 mg given every 12 hours 15–< 20 kg: 200 mg given every 12 hours 20–<30 kg: 300 mg given every 12 hours \geq 30 kg: Use adult dose Up to a maximum daily dose of 1.5 g (oral), or 1.2 g (IV)	Upper UTI (mild) Infectious acute diarrhoea Intra-abdominal infections (mild) Enteric fever Febrile neutropenia (low risk) Cholera (single dose)
Chloramphenicol <i>Use chloramphenicol only when no other option is available due to toxicity concerns</i>	IV/IM: 25 mg/kg/dose given every 6 hours Maximum daily dose: use adult dosing	Meningitis
Clarithromycin	Oral: 7.5 mg/kg/dose given every 12 hours Up to a maximum daily dose of 1 g	Pharyngitis
Clindamycin	IV/oral: <ul style="list-style-type: none"> • Neonates: 5 mg/kg/dose given every 8 hours • Children: 10 mg/kg/dose given every 8 hours Maximum daily dose: see adult dosing	Bone and joint infections Necrotizing fasciitis

continues

Table 50.1 *continued*

Antibiotic (alphabetic order)	Dose	Indications for use
Cloxacillin	<p>IV:</p> <ul style="list-style-type: none"> Neonates: 25–50 mg/kg/dose given every 12 hours Children: 25 mg/kg/dose given every 6 hours <p>Up to a maximum daily dose of 1.5 g, but can be higher for serious bacterial infections</p> <p>Oral: 15 mg/kg/dose given every 6 hours</p> <p>Weight bands:</p> <p>3–< 6 kg: 62.5 mg given every 6 hours</p> <p>6–< 10 kg: 125 mg given every 6 hours</p> <p>10–< 15 kg: 250 mg given every 6 hours</p> <p>15–< 20 kg: 375 mg given every 6 hours</p> <p>≥ 20 kg: 500 mg given every 6 hours</p>	<p>SSTI (mild)</p> <p>Bone and joint infections</p> <p>Periorbital (or preseptal) cellulitis</p> <p>Pyomyositis</p>
Colistin (polymyxin E) CBA: colistin base activity; CMS: colistimethate sodium	<p>IV:</p> <p>0.625–1.25 mg/kg/dose CBA (18 750–37 500 IU/kg/dose CMS) given every 6 hours</p> <p>OR</p> <p>1.25–2.5 mg/kg/dose CBA (37 500–75 000 IU/kg/dose CMS) given every 12 hours</p> <p>Up to a maximum daily dose of 200 mg CBA (6 million IU CMS)</p>	Seriously ill patients with presumed infections due to multidrug-resistant bacteria

continues

Table 50.1 *continued*

Antibiotic (alphabetic order)	Dose	Indications for use
Doxycycline	Oral: <ul style="list-style-type: none"> < 45 kg (< 12 years): 2–4 mg/kg (single dose) > 45 kg (> 12 years): 300 mg (single dose) 	Cholera
Gentamicin	IV: <ul style="list-style-type: none"> First week of life: 5 mg/kg given once daily Beyond first week of life: 7.5 mg/kg given once daily 	Sepsis (unknown origin) Surgical prophylaxis Upper UTI (severe) Intra-abdominal infections (mild and severe)
Fosfomycin (IV)	IV: <ul style="list-style-type: none"> 200–400 mg/kg/day divided every 8 to 12 hours <p>Maximum daily dose: see adult dosing</p>	Seriously ill patients with presumed infections due to multidrug-resistant bacteria
Linezolid	IV/oral: <ul style="list-style-type: none"> First week of life: 10 mg/kg/dose given every 12 hours Beyond first week of life: 10 mg/kg/dose given every 8 hours <p>Up to a maximum daily dose of 1.2 g</p>	Seriously ill patients with presumed infections due to multidrug-resistant bacteria For use in tuberculosis, refer to WHO guidelines (418)
Meropenem	IV: 20 mg/kg/dose given every 8 hours Up to a maximum daily dose of 6 g	Febrile neutropenia (high risk) Intra-abdominal infections (severe)

continues

Table 50.1 continued

Antibiotic (alphabetic order)	Dose	Indications for use
Metronidazole <i>Metronidazole has excellent oral bioavailability and the intravenous route should be reserved for patients with impaired gastrointestinal function.</i>	<p>Oral/IV:</p> <ul style="list-style-type: none"> Neonates: 7.5 mg/kg/ dose given every 12 hours (starting with a loading dose if used IV: 15 mg/kg) Children: 7.5 mg/kg/ dose given every 8 hours <p>Up to a maximum daily dose of 1 g</p> <p>Weight bands:</p> <p>3–< 6 kg: 30 mg given every 8 hours</p> <p>6–< 10 kg: 50 mg given every 8 hours</p> <p>10–< 15 kg: 100 mg given every 8 hours</p> <p>15–< 20 kg: 150 mg given every 8 hours</p> <p>20–< 30 kg: 200 mg given every 8 hours</p> <p>≥ 30 kg: use adult dose</p> <p>Higher dose:</p> <p>10–15 mg/kg/dose given every 8 hours</p> <p>Maximum daily dose: see adult dosing</p>	Intra-abdominal infections (mild and severe) Necrotizing fasciitis <i>Clostridioides difficile</i> infection <p>Higher dose:</p> Amoebic abscess <p>Single dose:</p> Surgical prophylaxis

continues

Table 50.1 *continued*

Antibiotic (alphabetic order)	Dose	Indications for use
Nitrofurantoin	Oral: 2 mg/kg/dose given every 12 hours; or 1 mg/kg/dose given every 6 hours (immediate release formulation) Up to a maximum daily dose of 200 mg	UTI (lower)
Phenoxycephalothin	Oral: 10–15 mg/kg/dose (16 000–24 000 IU ^a /kg/dose) given every 6–8 hours	Pharyngitis Dental infections
Piperacillin+tazobactam	IV: 100 mg/kg/dose of piperacillin component given every 8 hours Up to a maximum daily dose of 10 g of piperacillin component	HAP Intra-abdominal infections (severe) Necrotizing fasciitis Febrile neutropenia (high-risk)
Polymyxin B	IV: Loading dose: 2.5 mg/kg (25 000 IU/kg) Maintenance dose: < 2 years: 0.75–2.25 mg/kg/dose (7500–22 500 IU/kg/dose) given every 12 hours ≥ 2 years: 1.5 mg/kg/dose (15 000 IU/kg/dose) given every 12 hours	Seriously ill patients with presumed infections due to multidrug-resistant bacteria
Procaine benzylpenicillin (only for IM use)	IM: 50 000 IU (50 mg)/kg given once daily	Congenital syphilis

continues

Table 50.1 *continued*

Antibiotic (alphabetic order)	Dose	Indications for use
Sulfamethoxazole+ trimethoprim	<p>Oral: 20 mg/kg of sulfamethoxazole + 4 mg/kg of trimethoprim given every 12 hours</p> <p>Up to a maximum daily dose of 1200 mg of sulfamethoxazole component</p> <p>Weight bands:</p> <ul style="list-style-type: none"> 3-< 6 kg: 100 mg + 20 mg given every 12 hours 6-< 10 kg: 200 mg + 40 mg given every 12 hours 10-< 30 kg: 400 mg + 80 mg given every 12 hours ≥ 30 kg: use adult dose 	UTI (lower) Infectious acute diarrhoea
Trimethoprim	<p>Oral: 4 mg/kg given every 12 hours</p> <p>Weight bands:</p> <ul style="list-style-type: none"> mg of sulfamethoxazole/ trimethoprim component 3-< 6 kg: 20 mg given every 12 hours 6-< 10 kg: 40 mg given every 12 hours 10-< 30 kg: 80 mg given every 12 hours ≥ 30 kg: use adult dose 	UTI (lower)

continues

Table 50.1 continued

Antibiotic (alphabetic order)	Dose	Indications for use
Vancomycin <i>Vancomycin is not absorbed from the gastrointestinal tract when given orally. The only indication for oral vancomycin is Clostridoides difficile infection</i>	IV: <ul style="list-style-type: none">Neonates: 15 mg/kg/dose given every 12 hoursChildren: 15 mg/kg/dose given every 8 hours <p>Up to a maximum daily dose of 2 g (IV)</p> <p>Oral: 5–10 mg/kg/dose given every 6 hours</p> <p>Up to a maximum daily dose of 2 g (oral)</p>	IV: Endophthalmitis Febrile neutropenia (high risk) (if MRSA suspected) Necrotizing fasciitis (if MRSA suspected) Oral: <i>Clostridoides difficile</i> infection (higher dose for severe cases)

CAP: community-acquired pneumonia; CBA: colistin base activity; CMS: colistimethate sodium; HAP: hospital-acquired pneumonia; IM: intramuscular; IU: international units; IV: intravenous; MRSA: methicillin-resistant *Staphylococcus aureus*; SSTI: skin and soft tissue infections; UTI: urinary tract infection.

^a Units of the potassium salt.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

References

1. WHO model prescribing information: drugs used in bacterial infections. Geneva: World Health Organization; 2001 (<https://apps.who.int/iris/handle/10665/42372>, accessed 30 August 2022).
2. WHO policy guidance on integrated antimicrobial stewardship activities. Geneva: World Health Organization; 2021 (<https://apps.who.int/iris/handle/10665/341432>, accessed 30 August 2022).
3. Antimicrobial stewardship programmes in health-care facilities in low- and middle-income countries: a WHO practical toolkit. Geneva: World Health Organization; 2019 (<https://apps.who.int/iris/handle/10665/329404>, accessed 30 August 2022).
4. The selection and use of essential medicines. Report of the WHO Expert Committee, 2017 (including the 20th WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2017 (WHO Technical Report Series, No. 1006; <https://apps.who.int/iris/handle/10665/259481>, accessed 30 August 2022).
5. The selection and use of essential medicines. Report of the WHO Expert Committee, 2019 (including the 21st WHO Model List of Essential Medicines and the 7th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2019 (WHO Technical Report Series, No. 1021; <https://apps.who.int/iris/handle/10665/330668>, accessed 30 August 2022).
6. The selection and use of essential in vitro diagnostics: report of the third meeting of the WHO Strategic Advisory Group of Experts on In Vitro Diagnostics, 2020 (including the third WHO model list of essential in vitro diagnostics). Geneva: World Health Organization; 2020 (WHO Technical Report Series, No. 1301; <https://apps.who.int/iris/handle/10665/339064>, accessed 30 August 2022).
7. Fleming-Dutra KE, Hersh AL, Shapiro DJ, Bartoces M, Enns EA, File TM, Jr, et al. Prevalence of inappropriate antibiotic prescriptions among US ambulatory care visits, 2010–2011. *JAMA*. 2016;315(17):1864–73. <https://doi.org/10.1001/jama.2016.4151>
8. World Health Organization Model List of Essential Medicines – 22nd List, 2021. Geneva: World Health Organization; 2021 (<https://apps.who.int/iris/handle/10665/345533>, accessed 30 August 2022).
9. World Health Organization Model List of Essential Medicines for Children – 8th List, 2021. Geneva: World Health Organization; 2021 (<https://apps.who.int/iris/handle/10665/345534>, accessed 30 August 2022).
10. WHO access, watch, reserve (AWaRe) classification of antibiotics for evaluation and monitoring of use, 2021. Geneva: World Health Organization; 2021 (<https://apps.who.int/iris/handle/10665/345555>, accessed 30 August 2022).
11. WHO Antibiotic characterization – AWaRe portal [internet]. Geneva: World Health Organization; 2021 (<https://aware.essentialmeds.org/groups>, accessed 30 August 2022).
12. Executive Board, 144. Proposed programme budget 2020–2021: thirteenth General Programme of Work, 2019–2023: WHO Impact Framework. Geneva: World Health Organization; 2018. (<https://apps.who.int/iris/handle/10665/327341>, accessed 30 August 2022).
13. Using indicators to measure country pharmaceutical situations: fact book on WHO level I and level II monitoring indicators. Geneva: World Health Organization; 2006 (<https://apps.who.int/iris/handle/10665/354554>, accessed 30 August 2022).
14. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ*. 2010;340:c2096. <https://doi.org/10.1136/bmj.c2096>

15. van Hecke O, Wang K, Lee JJ, Roberts NW, Butler CC. Implications of antibiotic resistance for patients' recovery from common infections in the community: a systematic review and meta-analysis. *Clin Infect Dis.* 2017;65(3):371–82. <https://doi.org/10.1093/cid/cix233>
16. Global action plan on antimicrobial resistance. Geneva: World Health Organization; 2015 (<https://apps.who.int/iris/handle/10665/193736>, accessed 30 August 2022).
17. Bortone B, Jackson C, Hsia Y, Bielicki J, Magrini N, Sharland M. High global consumption of potentially inappropriate fixed dose combination antibiotics: analysis of data from 75 countries. *PLoS One.* 2021;16(1):e0241899. <https://doi.org/10.1371/journal.pone.0241899>
18. Substandard and falsified medical products – fact sheet [internet]. Geneva: World Health Organization; 2018 (<https://www.who.int/news-room/fact-sheets/detail/substandard-and-falsified-medical-products>, accessed 30 August 2022).
19. Khare S, Purohit M, Sharma M, Tamhankar AJ, Lundborg CS, Diwan V, et al. Antibiotic prescribing by informal healthcare providers for common illnesses: a repeated cross-sectional study in rural India. *Antibiotics (Basel).* 2019;8(3). <https://doi.org/10.3390/antibiotics8030139>
20. Lutsar I. Report on consensus guidance on pediatric dosing regimens for access antibiotics on the Essential Medicine List for Children. Submitted to the 22nd WHO Expert Committee on Selection and Use of Essential Medicines, 1–5 May 2019. (https://cdn.who.int/media/docs/default-source/essential-medicines/2019-eml-expert-committee/late-papers/abwg_paediatric_dosing_ab.pdf, accessed 30 August 2022).
21. Rizk NA, Kanafani ZA, Tabaja HZ, Kanj SS. Extended infusion of beta-lactam antibiotics: optimizing therapy in critically-ill patients in the era of antimicrobial resistance. *Expert Rev Anti Infect Ther.* 2017;15(7):645–52. <https://doi.org/10.1080/14787210.2017.1348894>
22. Osthoff M, Siegemund M, Balestra G, Abdul-Aziz MH, Roberts JA. Prolonged administration of beta-lactam antibiotics – a comprehensive review and critical appraisal. *Swiss Med Wkly.* 2016;146:w14368. <https://doi.org/10.4414/smw.2016.14368>
23. Safety monitoring of medicinal products. Guidelines for setting up and running a pharmacovigilance centre. Uppsala: The Uppsala Monitoring Centre; 2000 (<https://who-umc.org/media/1703/24747.pdf>, accessed 30 August 2022).
24. Blumenthal KG, Peter JG, Trubiano JA, Phillips EJ. Antibiotic allergy. *Lancet.* 2019;393(10167):183–98. [https://doi.org/10.1016/s0140-6736\(18\)32218-9](https://doi.org/10.1016/s0140-6736(18)32218-9)
25. Sousa-Pinto B, Fonseca JA, Gomes ER. Frequency of self-reported drug allergy: a systematic review and meta-analysis with meta-regression. *Ann Allergy Asthma Immunol.* 2017;119(4):362–73.e2. <https://doi.org/10.1016/j.anai.2017.07.009>
26. Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and management of penicillin allergy: a review. *JAMA.* 2019;321(2):188–99. <https://doi.org/10.1001/jama.2018.19283>
27. Trubiano JA, Stone CA, Grayson ML, Urbancic K, Slavin MA, Thrusky KA, et al. The 3 Cs of antibiotic allergy – Classification, Cross-reactivity, and Collaboration. *J Allergy Clin Immunol Pract.* 2017;5(6):1532–42. <https://doi.org/10.1016/j.jaip.2017.06.017>
28. Macy E, Blumenthal KG. Are cephalosporins safe for use in penicillin allergy without prior allergy evaluation? *J Allergy Clin Immunol Pract.* 2018;6(1):82–9. <https://doi.org/10.1016/j.jaip.2017.07.033>
29. Devchand M, Urbancic KF, Khumra S, Douglas AP, Smibert O, Cohen E, et al. Pathways to improved antibiotic allergy and antimicrobial stewardship practice: the validation of a beta-lactam antibiotic allergy assessment tool. *J Allergy Clin Immunol Pract.* 2019;7(3):1063–5.e5. <https://doi.org/10.1016/j.jaip.2018.07.048>
30. Trubiano JA, Vogrin S, Chua KYL, Bourke J, Yun J, Douglas A, et al. Development and validation of a penicillin allergy clinical decision rule. *JAMA Intern Med.* 2020;180(5):745–52. <https://doi.org/10.1001/jamainternmed.2020.0403>

31. Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, second edition. Geneva: World Health Organization; 2013 (<https://apps.who.int/iris/handle/10665/81170>, accessed 30 August 2022).
32. Coronavirus disease (COVID-19) pandemic [internet]. Geneva: World Health Organization; 2022 (<https://www.who.int/emergencies/diseases/novel-coronavirus-2019>, accessed 30 August 2022).
33. Living guidance for clinical management of COVID-19: living guidance, 23 November 2021. Geneva: World Health Organization; 2021 (<https://apps.who.int/iris/handle/10665/349321>, accessed 30 August 2022).
34. Therapeutics and COVID-19: living guideline, 16 September 2022. Geneva: World Health Organization; 2022 (<https://apps.who.int/iris/handle/10665/362843>, accessed 30 September 2022).
35. Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper – February 2019. *Wkly Epidemiol Rec.* 2019;94(8):85–104.
36. Haemophilus influenzae type b (Hib) vaccination position paper – July 2013. *Wkly Epidemiol Rec.* 2013;88(39):413–26.
37. Vaccines against influenza: WHO position paper – May 2022. *Wkly Epidemiol Rec.* 2022;97(19):185–208.
38. Smith MP, Lown M, Singh S, Ireland B, Hill AT, Linder JA, et al. Acute cough due to acute bronchitis in immunocompetent adult outpatients: CHEST expert panel report. *Chest.* 2020;157(5):1256–65. <https://doi.org/10.1016/j.chest.2020.01.044>
39. Schwartz KL, Langford BJ, Daneman N, Chen B, Brown KA, McIsaac W, et al. Unnecessary antibiotic prescribing in a Canadian primary care setting: a descriptive analysis using routinely collected electronic medical record data. *CMAJ Open.* 2020;8(2):E360–e69. <https://doi.org/10.9778/cmajo.20190175>
40. Wang CN, Huttner BD, Magrini N, Cheng Y, Tong J, Li S, et al. Pediatric antibiotic prescribing in China according to the 2019 World Health Organization Access, Watch, and Reserve (AWaRe) antibiotic categories. *J Pediatr.* 2020;220:125–31.e5. <https://doi.org/10.1016/j.jpeds.2020.01.044>
41. Havers FP, Hicks LA, Chung JR, Gaglani M, Murthy K, Zimmerman RK, et al. Outpatient antibiotic prescribing for acute respiratory infections during influenza seasons. *JAMA Netw Open.* 2018;1(2):e180243. <https://doi.org/10.1001/jamanetworkopen.2018.0243>
42. Smith SM, Fahey T, Smucny J, Becker LA. Antibiotics for acute bronchitis. *Cochrane Database Syst Rev.* 2017;6(6):CD000245. <https://doi.org/10.1002/14651858.CD000245.pub4>
43. Chonmaitree T, Alvarez-Fernandez P, Jennings K, Trujillo R, Marom T, Loeffelholz MJ, et al. Symptomatic and asymptomatic respiratory viral infections in the first year of life: association with acute otitis media development. *Clin Infect Dis.* 2015;60(1):1–9. <https://doi.org/10.1093/cid/ciu714>
44. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 2018;392(10159):1789–858. [https://doi.org/10.1016/s0140-6736\(18\)32279-7](https://doi.org/10.1016/s0140-6736(18)32279-7)
45. Kawai K, Adil EA, Barrett D, Manganella J, Kenna MA. Ambulatory visits for otitis media before and after the introduction of pneumococcal conjugate vaccination. *J Pediatr.* 2018;201:122–7.e1. <https://doi.org/10.1016/j.jpeds.2018.05.047>
46. Marom T, Tan A, Wilkinson GS, Pierson KS, Freeman JL, Chonmaitree T. Trends in otitis media-related health care use in the United States, 2001–2011. *JAMA Pediatr.* 2014;168(1):68–75. <https://doi.org/10.1001/jamapediatrics.2013.3924>
47. Chronic suppurative otitis media: burden of illness and management options. Geneva: World Health Organization; 2004 (<https://apps.who.int/iris/handle/10665/42941>, accessed 30 August 2022).
48. Ngo CC, Massa HM, Thornton RB, Cripps AW. Predominant bacteria detected from the middle ear fluid of children experiencing otitis media: a systematic review. *PLoS One.* 2016;11(3):e0150949. <https://doi.org/10.1371/journal.pone.0150949>

49. Kozyrskyj A, Klassen TP, Moffatt M, Harvey K. Short-course antibiotics for acute otitis media. Cochrane Database Syst Rev. 2010;2010(9):CD001095. <https://doi.org/10.1002/14651858.CD001095.pub2>
50. Hoberman A, Paradise JL, Rockette HE, Kearney DH, Bhatnagar S, Shope TR, et al. Shortened antimicrobial treatment for acute otitis media in young children. *N Engl J Med.* 2016;375(25):2446–56. <https://doi.org/10.1056/NEJMoa1606043>
51. Venekamp RP, Schilder AGM. Clinical failure is more common in young children with acute otitis media who receive a short course of antibiotics compared with standard duration. *Evid Based Med.* 2017;22(3):100. <https://doi.org/10.1136/ebmed-2017-110697>
52. Rheumatic heart disease – fact sheet [internet]. Geneva: World Health Organization; 2020 (<https://www.who.int/news-room/fact-sheets/detail/rheumatic-heart-disease>, accessed 30 August 2022).
53. Rheumatic fever and rheumatic heart disease: report of a WHO expert consultation, Geneva, 20 October–1 November 2001. Geneva: World Health Organization; 2004 (WHO Technical Report Series, No. 923; <https://apps.who.int/iris/handle/10665/42898>, accessed 30 August 2022).
54. Diphtheria vaccine: WHO position paper – August 2017. *Wkly Epidemiol Rec.* 2017;92(31):417–36.
55. Barnett ML, Linder JA. Antibiotic prescribing to adults with sore throat in the United States, 1997–2010. *JAMA Intern Med.* 2014;174(1):138–40. <https://doi.org/10.1001/jamainternmed.2013.11673>
56. Mehta N, Schilder A, Fragaszy E, H ERE, Dukes O, Manikam L, et al. Antibiotic prescribing in patients with self-reported sore throat. *J Antimicrob Chemother.* 2017;72(3):914–22. <https://doi.org/10.1093/jac/dkw497>
57. Oliver J, Malliya Wadu E, Pierse N, Moreland NJ, Williamson DA, Baker MG. Group A Streptococcus pharyngitis and pharyngeal carriage: a meta-analysis. *PLoS Negl Trop Dis.* 2018;12(3):e0006335. <https://doi.org/10.1371/journal.pntd.0006335>
58. Ralph AP, Carapetis JR. Group A streptococcal diseases and their global burden. *Curr Top Microbiol Immunol.* 2013;368:1–27. https://doi.org/10.1007/82_2012_280
59. Zuhlik LJ, Beaton A, Engel ME, Hugo-Hamman CT, Karthikeyan G, Katzenellenbogen JM, et al. Group A Streptococcus, acute rheumatic fever and rheumatic heart disease: epidemiology and clinical considerations. *Curr Treat Options Cardiovasc Med.* 2017;19(2):15. <https://doi.org/10.1007/s11936-017-0513-y>
60. Little P, Stuart B, Hobbs FD, Butler CC, Hay AD, Delaney B, et al. Antibiotic prescription strategies for acute sore throat: a prospective observational cohort study. *Lancet Infect Dis.* 2014;14(3):213–9. [https://doi.org/10.1016/s1473-3099\(13\)70294-9](https://doi.org/10.1016/s1473-3099(13)70294-9)
61. Spurling GK, Del Mar CB, Dooley L, Foxlee R, Farley R. Delayed antibiotic prescriptions for respiratory infections. Cochrane Database Syst Rev. 2017;9(9):CD004417. <https://doi.org/10.1002/14651858.CD004417.pub5>
62. Cilliers AM. Rheumatic fever and its management. *BMJ.* 2006;333(7579):1153–6. <https://doi.org/10.1136/bmj.39031.420637.BE>
63. Watkins DA, Johnson CO, Colquhoun SM, Karthikeyan G, Beaton A, Bukhman G, et al. Global, regional, and national burden of rheumatic heart disease, 1990–2015. *N Engl J Med.* 2017;377(8):713–22. <https://doi.org/10.1056/NEJMoa1603693>
64. Centor RM, Witherspoon JM, Dalton HP, Brody CE, Link K. The diagnosis of strep throat in adults in the emergency room. *Med Decis Making.* 1981;1(3):239–46. <https://doi.org/10.1177/0272989x8100100304>
65. Engel ME, Cohen K, Goudien R, Kengne AP, Barth DD, Whitelaw AC, et al. The Cape Town clinical decision rule for streptococcal pharyngitis in children. *Pediatr Infect Dis J.* 2017;36(3):250–5. <https://doi.org/10.1097/INF.0000000000001413>
66. van Driel ML, De Sutter AI, Habraken H, Thorning S, Christiaens T. Different antibiotic treatments for group A streptococcal pharyngitis. Cochrane Database Syst Rev. 2016;9:CD004406. <https://doi.org/10.1002/14651858.CD004406.pub4>

67. Altamimi S, Khalil A, Khalaiwi KA, Milner RA, Pusic MV, Al Othman MA. Short-term late-generation antibiotics versus longer term penicillin for acute streptococcal pharyngitis in children. Cochrane Database Syst Rev. 2012(8):CD004872. <https://doi.org/10.1002/14651858.CD004872.pub3>
68. Skoog Ståhlgren G, Tyrstrup M, Edlund C, Giske CG, Mölstad S, Norman C, et al. Penicillin V four times daily for five days versus three times daily for 10 days in patients with pharyngotonsillitis caused by group A streptococci: randomised controlled, open label, non-inferiority study. BMJ. 2019;367:l5337. <https://doi.org/10.1136/bmj.l5337>
69. Lemiere MB, van Driel ML, Merenstein D, Liira H, Mäkelä M, De Sutter AI. Antibiotics for acute rhinosinusitis in adults. Cochrane Database Syst Rev. 2018;9(9):CD006089. <https://doi.org/10.1002/14651858.CD006089.pub5>
70. Shaikh N, Wald ER. Decongestants, antihistamines and nasal irrigation for acute sinusitis in children. Cochrane Database Syst Rev. 2014;2014(10):CD007909. <https://doi.org/10.1002/14651858.CD007909.pub4>
71. Chow AW, Benninger MS, Brook I, Brozek JL, Goldstein EJ, Hicks LA, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Clin Infect Dis. 2012;54(8):e72–e112. <https://doi.org/10.1093/cid/cir1043>
72. Falagas ME, Karageorgopoulos DE, Grammatikos AP, Matthaiou DK. Effectiveness and safety of short vs. long duration of antibiotic therapy for acute bacterial sinusitis: a meta-analysis of randomized trials. Br J Clin Pharmacol. 2009;67(2):161–71. <https://doi.org/10.1111/j.1365-2125.2008.03306.x>
73. Guideline: sugars intake for adults and children. Geneva: World Health Organization; 2015 (<https://apps.who.int/iris/handle/10665/149782>, accessed 30 August 2022).
74. Oral health – fact sheet [internet]. Geneva: World Health Organization; 2022 (<https://www.who.int/news-room/fact-sheets/detail/oral-health>, accessed 30 August 2022).
75. Ending childhood dental caries: WHO implementation manual. Geneva: World Health Organization; 2019 (<https://apps.who.int/iris/handle/10665/330643>, accessed 30 August 2022).
76. WHO monograph on tobacco cessation and oral health integration. Geneva: World Health Organization; 2017 (<https://apps.who.int/iris/handle/10665/255692>, accessed 30 August 2022).
77. Information brochure for early detection and management of noma. Brazzavile: World Health Organization Regional Office for Africa; 2016 (<https://apps.who.int/iris/handle/10665/254579>, accessed 30 August 2022).
78. Kasseebaum NJ, Smith AGC, Bernabé E, Fleming TD, Reynolds AE, Vos T, et al. Global, regional, and national prevalence, incidence, and disability-adjusted life years for oral conditions for 195 countries, 1990–2015: a systematic analysis for the global burden of diseases, injuries, and risk factors. J Dent Res. 2017;96(4):380–7. <https://doi.org/10.1177/0022034517693566>
79. Thompson W, Williams D, Pulcini C, Sanderson S, Calfon P, Verma M. The essential role of the dental team in reducing antibiotic resistance. Geneva: FDI World Dental Federation; 2020 (<https://www.fdiworlddental.org/resource/fdi-white-paper-essential-role-dental-team-reducing-antibiotic-resistance>, accessed 30 August 2022).
80. Thompson W, Williams D, Pulcini C, Sanderson S, Calfon P, Verma M. Tackling antibiotic resistance: why dentistry matters. Int Dent J. 2021;71(6):450–3. <https://doi.org/10.1016/j.identj.2020.12.023>
81. Mekonnen D, Derbie A, Abeje A, Shumet A, Nibret E, Biadglegne F, et al. Epidemiology of tuberculous lymphadenitis in Africa: a systematic review and meta-analysis. PLoS One. 2019;14(4):e0215647. <https://doi.org/10.1371/journal.pone.0215647>
82. McCulley JP, Dougherty JM. Bacterial aspects of chronic blepharitis. Trans Ophthalmol Soc U K. 1986;105 (Pt 3):314–8.
83. Viswalingam M, Rauz S, Morlet N, Dart JK. Blepharokeratoconjunctivitis in children: diagnosis and treatment. Br J Ophthalmol. 2005;89(4):400–3. <https://doi.org/10.1136/bjo.2004.052134>

84. Doan S, Gabison EE, Nghiem-Buffet S, Abitbol O, Gatinel D, Hoang-Xuan T. Long-term visual outcome of childhood blepharokeratoconjunctivitis. *Am J Ophthalmol.* 2007;143(3):528–9. <https://doi.org/10.1016/j.ajo.2006.09.058>
85. Gao YY, Di Pascuale MA, Li W, Liu DT, Baradarani-Rafii A, Elizondo A, et al. High prevalence of Demodex in eyelashes with cylindrical dandruff. *Invest Ophthalmol Vis Sci.* 2005;46(9):3089–94. <https://doi.org/10.1167/iovs.05-0275>
86. Azari AA, Barney NP. Conjunctivitis: a systematic review of diagnosis and treatment. *JAMA.* 2013;310(16):1721–9. <https://doi.org/10.1001/jama.2013.280318>
87. Friedlaender MH. A review of the causes and treatment of bacterial and allergic conjunctivitis. *Clin Ther.* 1995;17(5):800–10; discussion 779. [https://doi.org/10.1016/0149-2918\(95\)80058-1](https://doi.org/10.1016/0149-2918(95)80058-1)
88. Sheikh A, Hurwitz B, van Schayck CP, McLean S, Nurmatov U. Antibiotics versus placebo for acute bacterial conjunctivitis. *Cochrane Database Syst Rev.* 2012(9):CD001211. <https://doi.org/10.1002/14651858.CD001211.pub3>
89. WHO guidelines for the treatment of Neisseria gonorrhoeae. Geneva: World Health Organization; 2016 (<https://apps.who.int/iris/handle/10665/246114>, accessed 30 August 2022).
90. Cho H, Shin YU, Siegel NH, Yu HG, Sobrin L, Patel A, et al. Endogenous endophthalmitis in the American and Korean population: an 8-year retrospective study. *Ocul Immunol Inflamm.* 2018;26(4):496–503. <https://doi.org/10.1080/09273948.2016.1195000>
91. Celiker H, Kazokoglu H. Ocular culture-proven endogenous endophthalmitis: a 5-year retrospective study of the microorganism spectrum at a tertiary referral center in Turkey. *Int Ophthalmol.* 2019;39(8):1743–51. <https://doi.org/10.1007/s10792-018-0997-9>
92. Durand ML. Bacterial and fungal endophthalmitis. *Clin Microbiol Rev.* 2017;30(3):597–613. <https://doi.org/10.1128/cmr.00113-16>
93. Han DP, Wisniewski SR, Wilson LA, Barza M, Vine AK, Doft BH, et al. Spectrum and susceptibilities of microbiologic isolates in the Endophthalmitis Vitrectomy Study. *Am J Ophthalmol.* 1996;122(1):1–17. [https://doi.org/10.1016/s0002-9394\(14\)71959-2](https://doi.org/10.1016/s0002-9394(14)71959-2)
94. McCannel CA. Meta-analysis of endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents: causative organisms and possible prevention strategies. *Retina.* 2011;31(4):654–61. <https://doi.org/10.1097/IAE.0b013e31820a67e4>
95. Brockhaus L, Goldblum D, Eggenschwiler L, Zimmerli S, Marzolini C. Revisiting systemic treatment of bacterial endophthalmitis: a review of intravitreal penetration of systemic antibiotics. *Clin Microbiol Infect.* 2019;25(11):1364–9. <https://doi.org/10.1016/j.cmi.2019.01.017>
96. Kim CH, Chen MF, Coleman AL. Adjunctive steroid therapy versus antibiotics alone for acute endophthalmitis after intraocular procedure. *Cochrane Database Syst Rev.* 2017;2(2):CD012131. <https://doi.org/10.1002/14651858.CD012131.pub2>
97. Ung L, Bispo PJM, Shanbhag SS, Gilmore MS, Chodosh J. The persistent dilemma of microbial keratitis: global burden, diagnosis, and antimicrobial resistance. *Surv Ophthalmol.* 2019;64(3):255–71. <https://doi.org/10.1016/j.survophthal.2018.12.003>
98. Khor WB, Prajna VN, Garg P, Mehta JS, Xie L, Liu Z, et al. The Asia Cornea Society Infectious Keratitis Study: a prospective multicenter study of infectious keratitis in Asia. *Am J Ophthalmol.* 2018;195:161–70. <https://doi.org/10.1016/j.ajo.2018.07.040>
99. McDonald EM, Ram FS, Patel DV, McGhee CN. Topical antibiotics for the management of bacterial keratitis: an evidence-based review of high quality randomised controlled trials. *Br J Ophthalmol.* 2014;98(11):1470–7. <https://doi.org/10.1136/bjophthalmol-2013-304660>

100. Ambati BK, Ambati J, Azar N, Stratton L, Schmidt EV. Periorbital and orbital cellulitis before and after the advent of *Haemophilus influenzae* type B vaccination. *Ophthalmology*. 2000;107(8):1450–3. [https://doi.org/10.1016/s0161-6420\(00\)00178-0](https://doi.org/10.1016/s0161-6420(00)00178-0)
101. Baiu I, Melendez E. Periorbital and orbital cellulitis. *JAMA*. 2020;323(2):196. <https://doi.org/10.1001/jama.2019.18211>
102. Nageswaran S, Woods CR, Benjamin DK, Jr., Givner LB, Shetty AK. Orbital cellulitis in children. *Pediatr Infect Dis J*. 2006;25(8):695–9. <https://doi.org/10.1097/01.inf.0000227820.36036.f1>
103. Sobol SE, Marchand J, Tewfik TL, Manoukian JJ, Schloss MD. Orbital complications of sinusitis in children. *J Otolaryngol*. 2002;31(3):131–6. <https://doi.org/10.2310/7070.2002.10979>
104. Wong SJ, Levi J. Management of pediatric orbital cellulitis: A systematic review. *Int J Pediatr Otorhinolaryngol*. 2018;110:123–9. <https://doi.org/10.1016/j.ijporl.2018.05.006>
105. Stimes GT, Girotto JE. Applying pharmacodynamics and antimicrobial stewardship to pediatric preseptal and orbital cellulitis. *Paediatr Drugs*. 2019;21(6):427–38. <https://doi.org/10.1007/s40272-019-00357-3>
106. Botting AM, McIntosh D, Mahadevan M. Paediatric pre- and post-septal peri-orbital infections are different diseases. A retrospective review of 262 cases. *Int J Pediatr Otorhinolaryngol*. 2008;72(3):377–83. <https://doi.org/10.1016/j.ijporl.2007.11.013>
107. Chaudhry IA, Shamsi FA, Elzaridi E, Al-Rashed W, Al-Amri A, Arat YO. Inpatient preseptal cellulitis: experience from a tertiary eye care centre. *Br J Ophthalmol*. 2008;92(10):1337–41. <https://doi.org/10.1136/bjo.2007.128975>
108. Darrell RW, Wagener HP, Kurland LT. Epidemiology of uveitis. Incidence and prevalence in a small urban community. *Arch Ophthalmol*. 1962;68:502–14. <https://doi.org/10.1001/archoph.1962.00960030506014>
109. Trachoma – fact sheet [internet]. Geneva: World Health Organization; 2022 (<https://www.who.int/news-room/fact-sheets/detail/trachoma>, accessed 30 August 2022).
110. World Health Assembly Resolution WHA51.11. Global elimination of blinding trachoma. Geneva: World Health Organization; 1998 (<https://apps.who.int/iris/handle/10665/79806>, accessed 30 August 2022).
111. Solomon AW, Kello AB, Bangert M, West SK, Taylor HR, Tekerao R, et al. The simplified trachoma grading system, amended. *Bull World Health Organ*. 2020;98(10):698–705. <https://doi.org/10.2471/blt.19.248708>
112. Trachoma control: a guide for programme managers. Geneva: World Health Organization; 2006 (<https://apps.who.int/iris/handle/10665/43405>, accessed 30 August 2022).
113. Taylor HR, Burton MJ, Haddad D, West S, Wright H. Trachoma. *Lancet*. 2014;384(9960):2142–52. [https://doi.org/10.1016/s0140-6736\(13\)62182-0](https://doi.org/10.1016/s0140-6736(13)62182-0)
114. Solomon AW, Holland MJ, Burton MJ, West SK, Alexander ND, Aguirre A, et al. Strategies for control of trachoma: observational study with quantitative PCR. *Lancet*. 2003;362(9379):198–204. [https://doi.org/10.1016/s0140-6736\(03\)13909-8](https://doi.org/10.1016/s0140-6736(03)13909-8)
115. Validation of elimination of trachoma as a public health problem. Geneva: World Health Organization; 2016 (<https://apps.who.int/iris/handle/10665/208901>, accessed 30 August 2022).
116. Merbs S, Resnikoff S, Kello AB, Mariotti S, Greene G, West SK. Trichiasis surgery for trachoma, second edition. Geneva: World Health Organization; 2015 (<https://apps.who.int/iris/handle/10665/155227>, accessed 30 August 2022).
117. Amza A, Goldschmidt P, Einterz E, Huguet P, Olmiere C, Bensaid P, et al. Elimination of active trachoma after two topical mass treatments with azithromycin 1.5% eye drops. *PLoS Negl Trop Dis*. 2010;4(11):e895. <https://doi.org/10.1371/journal.pntd.0000895>
118. Revised WHO classification and treatment of pneumonia in children at health facilities: evidence summaries. Geneva: World Health Organization; 2014 (<https://apps.who.int/iris/handle/10665/137319>, accessed 30 August 2022).

119. WHO consolidated guidelines on tuberculosis: module 4: treatment: drug-susceptible tuberculosis treatment. Geneva: World Health Organization; 2022 (<https://apps.who.int/iris/handle/10665/353829>, accessed 30 August 2022).
120. Peyrani P, Mandell L, Torres A, Tillotson GS. The burden of community-acquired bacterial pneumonia in the era of antibiotic resistance. *Expert Rev Respir Med.* 2019;13(2):139–52. <https://doi.org/10.1080/17476348.2019.1562339>
121. The top 10 causes of death – fact sheet [internet]. Geneva: World Health Organization; 2020 (<https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death>, accessed 30 August 2022).
122. Liu L, Oza S, Hogan D, Chu Y, Perin J, Zhu J, et al. Global, regional, and national causes of under-5 mortality in 2000–15: an updated systematic analysis with implications for the Sustainable Development Goals. *Lancet.* 2016;388(10063):3027–35. [https://doi.org/10.1016/S0140-6736\(16\)31593-8](https://doi.org/10.1016/S0140-6736(16)31593-8)
123. Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. *Thorax.* 2012;67(1):71–9. <https://doi.org/10.1136/thx.2009.129502>
124. Kim SH, Chung DR, Song JH, Baek JY, Thamlikitkul V, Wang H, et al. Changes in serotype distribution and antimicrobial resistance of *Streptococcus pneumoniae* isolates from adult patients in Asia: emergence of drug-resistant non-vaccine serotypes. *Vaccine.* 2020;38(38):6065–73. <https://doi.org/10.1016/j.vaccine.2019.09.065>
125. Aliberti S, Cook GS, Babu BL, Reyes LF, A HR, Sanz F, et al. International prevalence and risk factors evaluation for drug-resistant *Streptococcus pneumoniae* pneumonia. *J Infect.* 2019;79(4):300–11. <https://doi.org/10.1016/j.jinf.2019.07.004>
126. Lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis of active tuberculosis in people living with HIV: policy update 2019. Geneva: World Health Organization; 2019 (<https://apps.who.int/iris/handle/10665/329479>, accessed 30 August 2022).
127. Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax.* 2003;58(5):377–82. <http://dx.doi.org/10.1136/thorax.58.5.377>
128. Aston SJ, Rylance J. Community-acquired pneumonia in sub-Saharan Africa. *Semin Respir Crit Care Med.* 2016;37(6):855–67. <https://doi.org/10.1055/s-0036-1592126>
129. Implementing tuberculosis diagnostics: policy framework. Geneva: World Health Organization; 2015 (<https://apps.who.int/iris/handle/10665/162712>, accessed 30 August 2022).
130. Uranga A, Espana PP, Bilbao A, Quintana JM, Arriaga I, Intxausti M, et al. Duration of antibiotic treatment in community-acquired pneumonia: a multicenter randomized clinical trial. *JAMA Intern Med.* 2016;176(9):1257–65. <https://doi.org/10.1001/jamainternmed.2016.3633>
131. McMullan BJ, Andresen D, Blyth CC, Avent ML, Bowen AC, Britton PN, et al. Antibiotic duration and timing of the switch from intravenous to oral route for bacterial infections in children: systematic review and guidelines. *Lancet Infect Dis.* 2016;16(8):e139–52. [https://doi.org/10.1016/S1473-3099\(16\)30024-X](https://doi.org/10.1016/S1473-3099(16)30024-X)
132. Chronic obstructive pulmonary disease (COPD) – fact sheet [internet]. Geneva: World Health Organization; 2022 ([https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-\(copd\)](https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd)), accessed 30 August 2022).
133. Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach. Geneva: World Health Organization; 2007 (<https://apps.who.int/iris/handle/10665/43776>, accessed 30 August 2022).
134. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2021 report. Global Initiative for Chronic Obstructive Lung Disease – GOLD; 2020 (https://goldcopd.org/wp-content/uploads/2020/11/GOLD-REPORT-2021-v1.1-25Nov20_WMV.pdf, accessed 30 August 2022)

135. Donaldson GC, Wedzicha JA. COPD exacerbations. 1. Epidemiology. *Thorax*. 2006;61(2):164–8. <https://doi.org/10.1136/thx.2005.041806>
136. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1736–88. [https://doi.org/10.1016/S0140-6736\(18\)32203-7](https://doi.org/10.1016/S0140-6736(18)32203-7)
137. Global status report on noncommunicable diseases 2014. Geneva: World Health Organization; 2014 (<https://apps.who.int/iris/handle/10665/148114>, accessed 30 August 2022).
138. Siddharthan T, Grigsby MR, Goodman D, Chowdhury M, Rubinstein A, Irazola V, et al. Association between household air pollution exposure and chronic obstructive pulmonary disease outcomes in 13 low- and middle-income country settings. *Am J Respir Crit Care Med*. 2018;197(5):611–20. <https://doi.org/10.1164/rccm.201709-1861OC>
139. Koul PA, Mir H, Akram S, Potdar V, Chadha MS. Respiratory viruses in acute exacerbations of chronic obstructive pulmonary disease. *Lung India*. 2017;34(1):29–33. <https://doi.org/10.4103/0970-2113.197099>
140. van Rijn AL, van Boheemen S, Sidorov I, Carbo EC, Pappas N, Mei H, et al. The respiratory virome and exacerbations in patients with chronic obstructive pulmonary disease. *PLoS One*. 2019;14(10):e0223952. <https://doi.org/10.1371/journal.pone.0223952>
141. Butler CC, Gillespie D, White P, Bates J, Lowe R, Thomas-Jones E, et al. C-reactive protein testing to guide antibiotic prescribing for COPD exacerbations. *N Engl J Med*. 2019;381(2):111–20. <https://doi.org/10.1056/NEJMoa1803185>
142. Brett AS, Al-Hasan MN. COPD exacerbations – a target for antibiotic stewardship. *N Engl J Med*. 2019;381(2):174–5. <https://doi.org/10.1056/NEJMv1905520>
143. Vollenweider DJ, Frei A, Steurer-Stey CA, Garcia-Aymerich J, Puhan MA. Antibiotics for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2018;10(10):CD010257. <https://doi.org/10.1002/14651858.CD010257.pub2>
144. Herath SC, Normansell R, Maisey S, Poole P. Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD). *Cochrane Database Syst Rev*. 2018;10:CD009764. <https://doi.org/10.1002/14651858.CD009764.pub3>
145. The treatment of diarrhoea. A manual for physicians and other senior health workers. Fourth revision. Geneva: World Health Organization; 2005 (<https://apps.who.int/iris/handle/10665/43209>, accessed 30 August 2022).
146. Diarrhoeal disease – fact sheet [internet]. Geneva: World Health Organization; 2017 (<https://www.who.int/news-room/fact-sheets/detail/diarrhoeal-disease>, accessed 30 August 2022).
147. Cholera vaccines: WHO position paper – August 2017. *Wkly Epidemiol Rec*. 2017;92(34):477–500.
148. Technical note on the use of antibiotics for the treatment and control of cholera. Global Task Force on Cholera Control; May 2018 (<https://www.gtfcc.org/wp-content/uploads/2019/10/gtfcc-technical-note-on-use-of-antibiotics-for-the-treatment-of-cholera.pdf>, accessed 30 August 2022).
149. Rotavirus vaccines: WHO position paper – July 2021. *Wkly Epidemiol Rec*. 2021;96(28):301–19.
150. Schistosomiasis (bilharzia) – health topic [internet]. Geneva: World Health Organization; 2022 (<https://www.who.int/health-topics/schistosomiasis>, accessed 30 August 2022).
151. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of diarrhoea in 195 countries: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Infect Dis*. 2018;18(11):1211–28. [https://doi.org/10.1016/S1473-3099\(18\)30362-1](https://doi.org/10.1016/S1473-3099(18)30362-1)
152. Fletcher SM, McLaws ML, Ellis JT. Prevalence of gastrointestinal pathogens in developed and developing countries: systematic review and meta-analysis. *J Public Health Res*. 2013;2(1):42–53. <https://doi.org/10.4081/jphr.2013.e9>

153. Measles vaccines: WHO position paper – April 2017. *Wkly Epidemiol Rec.* 2017;92(17):205–27.
154. Typhoid vaccines: WHO position paper – March 2018. *Wkly Epidemiol Rec.* 2018;93(13):153–72.
155. Crump JA. Progress in typhoid fever epidemiology. *Clin Infect Dis.* 2019;68(Suppl 1):S4–s9. <https://doi.org/10.1093/cid/ciy846>
156. The global burden of typhoid and paratyphoid fevers: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Infect Dis.* 2019;19(4):369–81. [https://doi.org/10.1016/S1473-3099\(18\)30685-6](https://doi.org/10.1016/S1473-3099(18)30685-6)
157. Cruz Espinoza LM, McCreedy E, Holm M, Im J, Mogeni OD, Parajulee P, et al. Occurrence of typhoid fever complications and their relation to duration of illness preceding hospitalization: a systematic literature review and meta-analysis. *Clin Infect Dis.* 2019;69(Suppl 6):S435–s48. <https://doi.org/10.1093/cid/ciz477>
158. Britto CD, Wong VK, Dougan G, Pollard AJ. A systematic review of antimicrobial resistance in *Salmonella enterica* serovar Typhi, the etiological agent of typhoid. *PLoS Negl Trop Dis.* 2018;12(10):e0006779. <https://doi.org/10.1371/journal.pntd.0006779>
159. Butt MH, Saleem A, Javed SO, Ullah I, Rehman MU, Islam N, et al. Rising XDR-typhoid fever cases in Pakistan: are we heading back to the pre-antibiotic era? *Front Public Health.* 2021;9:794868. <https://doi.org/10.3389/fpubh.2021.794868>
160. Zmora N, Shrestha S, Neuberger A, Paran Y, Tamrakar R, Shrestha A, et al. Open label comparative trial of mono versus dual antibiotic therapy for typhoid fever in adults. *PLoS Negl Trop Dis.* 2018;12(4):e0006380. [http://doi.org/10.1371/journal.pntd.0006380](https://doi.org/10.1371/journal.pntd.0006380)
161. National treatment guidelines for antimicrobial use in infectious diseases, Version 1.0. New Delhi: National Centre for Disease Control Government of India; 2016
162. Akram J, Khan AS, Khan HA, Gilani SA, Akram SJ, Ahmad FJ, et al. Extensively drug-resistant (XDR) typhoid: evolution, prevention, and its management. *Biomed Res Int.* 2020;2020:6432580. <https://doi.org/10.1155/2020/6432580>
163. Marchello CS, Carr SD, Crump JA. A systematic review on antimicrobial resistance among *Salmonella* Typhi worldwide. *Am J Trop Med Hyg.* 2020;103(6):2518–27. <https://doi.org/10.4269/ajtmh.20-0258>
164. Saha S, Sajib MSI, Garrett D, Qamar FN. Antimicrobial resistance in typhoidal *Salmonella*: around the world in 3 days. *Clin Infect Dis.* 2020;71(Suppl 2):S91–s95. <https://doi.org/10.1093/cid/ciaa366>
165. Guidance for industry. Acute bacterial skin and skin structure infections: developing drugs for treatment. Silver Spring: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research; 2013 (<https://www.fda.gov/media/71052/download>, accessed 30 August 2022).
166. Karimkhani C, Dellavalle RP, Coffeng LE, Flohr C, Hay RJ, Langan SM, et al. Global skin disease morbidity and mortality: an update from the Global Burden of Disease Study 2013. *JAMA Dermatol.* 2017;153(5):406–12. <https://doi.org/10.1001/jamadermatol.2016.5538>
167. Patel M, Lee SI, Akyea RK, Grindlay D, Francis N, Levell NJ, et al. A systematic review showing the lack of diagnostic criteria and tools developed for lower-limb cellulitis. *Br J Dermatol.* 2019;181(6):1156–65. <https://doi.org/10.1111/bjd.17857>
168. Koning S, van der Sande R, Verhagen AP, van Suijlekom-Smit LW, Morris AD, Butler CC, et al. Interventions for impetigo. *Cochrane Database Syst Rev.* 2012;1(1):CD003261. <https://doi.org/10.1002/14651858.CD003261>
169. Corcione S, De Rosa FG. The optimal duration of treatment for skin and soft tissue infections and acute bacterial skin and skin structure infections. *Curr Opin Infect Dis.* 2018;31(2):155–62. <https://doi.org/10.1097/QCO.0000000000000440>
170. Burns – fact sheet [internet]. Geneva: World Health Organization; 2018 (<https://www.who.int/news-room-fact-sheets/detail/burns>, accessed 30 August 2022).

171. Lachiewicz AM, Hauck CG, Weber DJ, Cairns BA, van Duin D. Bacterial infections after burn injuries: impact of multidrug resistance. *Clin Infect Dis.* 2017;65(12):2130–6. <https://doi.org/10.1093/cid/cix682>
172. Stewart BT, Gyedu A, Agbenorku P, Amankwa R, Kushner AL, Gibran N. Routine systemic antibiotic prophylaxis for burn injuries in developing countries: a best evidence topic (BET). *Int J Surg.* 2015;21:168–72. <https://doi.org/10.1016/j.ijsu.2015.08.002>
173. Ramos G, Cornistein W, Cerino GT, Nacif G. Systemic antimicrobial prophylaxis in burn patients: systematic review. *J Hosp Infect.* 2017;97(2):105–14. <https://doi.org/10.1016/j.jhin.2017.06.015>
174. Prevention and management of wound infection. Geneva: World Health Organization; 2013 (<https://www.who.int/publications/item/prevention-and-management-of-wound-infection>, accessed 30 August 2022).
175. Snakebite envenoming – health topic [internet]. Geneva: World Health Organization; 2022 (<https://www.who.int/health-topics/snakebite>, accessed 30 August 2022).
176. Snakebite envenoming: a strategy for prevention and control. Geneva: World Health Organization; 2019 (<https://apps.who.int/iris/handle/10665/324838>, accessed 30 August 2022).
177. Global status report on road safety 2018. Geneva: World Health Organization; 2018. (<https://apps.who.int/iris/handle/10665/276462>, accessed 30 August 2022).
178. Tetanus vaccines: WHO position paper – February 2017. *Wkly Epidemiol Rec.* 2017;92(6):53–76.
179. Rabies vaccines: WHO position paper – April 2018. *Wkly Epidemiol Rec.* 2018;93(16):201–19.
180. Hepatitis B vaccines: WHO position paper – July 2017. *Wkly Epidemiol Rec.* 2017;92(27):369–92.
181. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, 2021 update. Geneva: World Health Organization; 2021. (<https://apps.who.int/iris/handle/10665/342899>, accessed 30 August 2022).
182. Road traffic injuries – fact sheet [internet]. Geneva: World Health Organization; 2021 (<https://www.who.int/news-room/fact-sheets/detail/road-traffic-injuries>, accessed 30 August 2022).
183. Naghavi M, Marczak LB, Kutz M, Shackelford KA, Arora M, Miller-Petrie M, et al. Global mortality from firearms, 1990–2016. *JAMA.* 2018;320(8):792–814. <https://doi.org/10.1001/jama.2018.10060>
184. Animal bites – fact sheet [internet]. Geneva: World Health Organization; 2018 (<https://www.who.int/news-room/fact-sheets/detail/animal-bites>, accessed 30 August 2022).
185. Bula-Rudas FJ, Olcott JL. Human and animal bites. *Pediatr Rev.* 2018;39(10):490–500. <https://doi.org/10.1542/pir.2017-0212>
186. Davies HD. When your best friend bites: a note on dog and cat bites. *Can J Infect Dis.* 2000;11(5):227–9. <https://doi.org/10.1093/pch/5.7.381>
187. De Klerk P, Van Dijk M, Van As AB. Treatment and outcome of unusual animal bite injuries in young children. *S Afr Med J.* 2016;106(2):206–9. <https://doi.org/10.7196/SAMJ.2016.v106i2.10106>
188. Tetanus reported cases and incidence [internet]. Geneva: World Health Organization; 2022 (<https://immunizationdata.who.int/pages/incidence/TTETANUS.html?CODE=Global&DISEASE=TTETANUS&YEAR>, accessed 30 August 2022).
189. Sexually transmitted infections (STIs) – fact sheet [internet]. Geneva: World Health Organization; 2021 ([https://www.who.int/news-room/fact-sheets/detail/sexually-transmitted-infections-\(stis\)](https://www.who.int/news-room/fact-sheets/detail/sexually-transmitted-infections-(stis)), accessed 30 August 2022).
190. WHO guidelines for the treatment of Chlamydia trachomatis. Geneva: World Health Organization; 2016 (<https://apps.who.int/iris/handle/10665/246165>, accessed 30 August 2022).
191. Guidelines for the management of symptomatic sexually transmitted infections. Geneva: World Health Organization 2021 (<https://apps.who.int/iris/handle/10665/342523>, accessed 30 August 2022).

192. Laboratory diagnosis of sexually transmitted infections, including human immunodeficiency virus. Geneva: World Health Organization; 2013 (<https://apps.who.int/iris/handle/10665/85343>, accessed 30 August 2022).
193. Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021: accountability for the global health sector strategies 2016–2021: actions for impact. Geneva: World Health Organization; 2021 (<https://apps.who.int/iris/handle/10665/341412>, accessed 30 August 2022).
194. Hussen S, Wachamo D, Yohannes Z, Tadesse E. Prevalence of chlamydia trachomatis infection among reproductive age women in sub Saharan Africa: a systematic review and meta-analysis. *BMC Infect Dis.* 2018;18(1):596. <https://doi.org/10.1186/s12879-018-3477-y>
195. Chico RM, Mayaud P, Ariti C, Mabey D, Ronsmans C, Chandramohan D. Prevalence of malaria and sexually transmitted and reproductive tract infections in pregnancy in sub-Saharan Africa: a systematic review. *JAMA.* 2012;307(19):2079–86. <https://doi.org/10.1001/jama.2012.3428>
196. Xia Q, Wang T, Xian J, Song J, Qiao Y, Mu Z, et al. Relation of Chlamydia trachomatis infections to ectopic pregnancy: a meta-analysis and systematic review. *Medicine (Baltimore).* 2020;99(1):e18489. <https://doi.org/10.1097/MD.00000000000018489>
197. Tang W, Mao J, Li KT, Walker JS, Chou R, Fu R, et al. Pregnancy and fertility-related adverse outcomes associated with Chlamydia trachomatis infection: a global systematic review and meta-analysis. *Sex Transm Infect.* 2020;96(5):322–9. <https://doi.org/10.1136/sextrans-2019-053999>
198. Li B, Hocking JS, Bi P, Bell C, Fairley CK. The efficacy of azithromycin and doxycycline treatment for rectal chlamydial infection: a retrospective cohort study in South Australia. *Intern Med J.* 2018;48(3):259–64. <https://doi.org/10.1111/imj.13624>
199. Kong FY, Tabrizi SN, Fairley CK, Vodstrcil LA, Huston WM, Chen M, et al. The efficacy of azithromycin and doxycycline for the treatment of rectal chlamydia infection: a systematic review and meta-analysis. *J Antimicrob Chemother.* 2015;70(5):1290–7. <https://doi.org/10.1093/jac/dku574>
200. Lau A, Kong FYS, Fairley CK, Templeton DJ, Amin J, Phillips S, et al. Azithromycin or doxycycline for asymptomatic rectal Chlamydia trachomatis. *N Engl J Med.* 2021;384(25):2418–27. <https://doi.org/10.1056/NEJMoa2031631>
201. Global action plan to control the spread and impact of antimicrobial resistance in *Neisseria gonorrhoeae*. Geneva: World Health Organization; 2012 (<https://apps.who.int/iris/handle/10665/44863>, accessed 30 August 2022).
202. Global antimicrobial resistance and use surveillance system (GLASS) report: 2021. Geneva: World Health Organization; 2021 (<https://apps.who.int/iris/handle/10665/341666>, accessed 30 August 2022).
203. Global Health Observatory – WHO Gonococcal AMR Surveillance Programme [internet]. Geneva: World Health Organization; 2022 (<https://www.who.int/gho/data/themes/topics/who-gonococcal-amr-surveillance-programme-who-gasp>, accessed 30 August 2022).
204. Wi T, Lahra MM, Ndowa F, Bala M, Dillon JR, Ramon-Pardo P, et al. Antimicrobial resistance in *Neisseria gonorrhoeae*: Global surveillance and a call for international collaborative action. *PLoS Med.* 2017;14(7):e1002344. <https://doi.org/10.1371/journal.pmed.1002344>
205. Unemo M, Lahra MM, Escher M, Eremin S, Cole MJ, Galarza P, et al. WHO global antimicrobial resistance surveillance for *Neisseria gonorrhoeae* 2017–18: a retrospective observational study. *Lancet Microbe.* 2021;2(11):e627–e36. [https://doi.org/10.1016/s2666-5247\(21\)00171-3](https://doi.org/10.1016/s2666-5247(21)00171-3)
206. Newman L, Rowley J, Vander Hoorn S, Wijesooriya NS, Unemo M, Low N, et al. Global estimates of the prevalence and incidence of four curable sexually transmitted infections in 2012 based on systematic review and global reporting. *PLoS One.* 2015;10(12):e0143304. <https://doi.org/10.1371/journal.pone.0143304>
207. Workowski KA, Bachmann LH, Chan PA, Johnston CM, Muzny CA, Park I, et al. Sexually transmitted infections treatment guidelines, 2021. *MMWR Recomm Rep.* 2021;70(4):1–187. <https://doi.org/10.15585/mmwr.rr7004a1>

208. Unemo M, Ross J, Serwin AB, Gomberg M, Cusini M, Jensen JS. 2020 European guideline for the diagnosis and treatment of gonorrhoea in adults. *Int J STD AIDS.* 2020;956462420949126. <https://doi.org/10.1177/0956462420949126>
209. Fifer H, Saunders J, Soni S, Sadiq ST, Fitzgerald M. 2018 UK national guideline for the management of infection with *Neisseria gonorrhoeae*. *Int J STD AIDS.* 2020;31(1):4–15. <https://doi.org/10.1177/0956462419886775>
210. WHO guidelines for the treatment of *Treponema pallidum* (syphilis). Geneva: World Health Organization; 2016 (<https://apps.who.int/iris/handle/10665/249572>, accessed 30 August 2022).
211. WHO guideline on syphilis screening and treatment for pregnant women. Geneva: World Health Organization; 2017 (<https://apps.who.int/iris/handle/10665/259003>, accessed 30 August 2022).
212. Yaws – fact sheet [internet]. Geneva: World Health Organization; 2022 (<https://www.who.int/news-room/fact-sheets/detail/yaws>, accessed 30 August 2022).
213. Giacani L, Lukehart SA. The endemic treponematoses. *Clin Microbiol Rev.* 2014;27(1):89–115. <https://doi.org/10.1128/cmr.00070-13>
214. Stamm LV. Global challenge of antibiotic-resistant *Treponema pallidum*. *Antimicrob Agents Chemother.* 2010;54(2):583–9. <https://doi.org/10.1128/aac.01095-09>
215. Korenromp EL, Rowley J, Alonso M, Mello MB, Wijesooriya NS, Mahiané SG, et al. Global burden of maternal and congenital syphilis and associated adverse birth outcomes – estimates for 2016 and progress since 2012. *PLoS One.* 2019;14(2):e0211720. <https://doi.org/10.1371/journal.pone.0211720>
216. Hook EW, 3rd. Syphilis. *Lancet.* 2017;389(10078):1550–7. [https://doi.org/10.1016/s0140-6736\(16\)32411-4](https://doi.org/10.1016/s0140-6736(16)32411-4)
217. Arando M, Fernandez-Naval C, Mota-Foix M, Martinez D, Armengol P, Barberá MJ, et al. Early syphilis: risk factors and clinical manifestations focusing on HIV-positive patients. *BMC Infect Dis.* 2019;19(1):727. <https://doi.org/10.1186/s12879-019-4269-8>
218. Kojima N, Park H, Konda KA, Joseph Davey DL, Bristow CC, Brown B, et al. The PICASSO Cohort: baseline characteristics of a cohort of men who have sex with men and male-to-female transgender women at high risk for syphilis infection in Lima, Peru. *BMC Infect Dis.* 2017;17(1):255. <https://doi.org/10.1186/s12879-017-2332-x>
219. Guidelines for the management of sexually transmitted infections. Geneva: World Health Organization; 2003 (<https://apps.who.int/iris/handle/10665/42782>, accessed 30 August 2022).
220. Silver BJ, Guy RJ, Kaldor JM, Jamil MS, Rumbold AR. Trichomonas vaginalis as a cause of perinatal morbidity: a systematic review and meta-analysis. *Sex Transm Dis.* 2014;41(6):369–76. <https://doi.org/10.1097/olq.0000000000000134>
221. Kissinger P, Muzny CA, Mena LA, Lillis RA, Schwebke JR, Beauchamps L, et al. Single-dose versus 7-day-dose metronidazole for the treatment of trichomoniasis in women: an open-label, randomised controlled trial. *Lancet Infect Dis.* 2018;18(11):1251–9. [https://doi.org/10.1016/s1473-3099\(18\)30423-7](https://doi.org/10.1016/s1473-3099(18)30423-7)
222. Bonkat G, Bartoletti R, Bruyère F, Cai T, Geerlings SE, Köves B, et al. EAU Guidelines on urological infections. Arnhem: European Association of Urology; 2022 (<https://uroweb.org/guideline/uurological-infections/>, accessed 30 August 2022).
223. Tandogdu Z, Wagenlehner FM. Global epidemiology of urinary tract infections. *Curr Opin Infect Dis.* 2016;29(1):73–9. <https://doi.org/10.1097/qco.0000000000000228>
224. Foxman B, Gillespie B, Koopman J, Zhang L, Palin K, Tallman P, et al. Risk factors for second urinary tract infection among college women. *Am J Epidemiol.* 2000;151(12):1194–205. <https://doi.org/10.1093/oxfordjournals.aje.a010170>
225. Kronenberg A, Butikofer L, Odotayo A, Muhlemann K, da Costa BR, Battaglia M, et al. Symptomatic treatment of uncomplicated lower urinary tract infections in the ambulatory setting: randomised, double blind trial. *BMJ.* 2017;359:j4784. <https://doi.org/10.1136/bmj.j4784>

226. Torres NF, Chibi B, Middleton LE, Solomon VP, Mashamba-Thompson TP. Evidence of factors influencing self-medication with antibiotics in low and middle-income countries: a systematic scoping review. *Public Health.* 2019;168:92–101. <https://doi.org/10.1016/j.puhe.2018.11.018>
227. Walker E, Lyman A, Gupta K, Mahoney MV, Snyder GM, Hirsch EB. Clinical management of an increasing threat: Outpatient urinary tract infections due to multidrug-resistant uropathogens. *Clin Infect Dis.* 2016;63(7):960–5. <https://doi.org/10.1093/cid/ciw396>
228. Miotla P, Romanek-Piva K, Bogusiewicz M, Markut-Miotla E, Adamiak A, Wrobel A, et al. Antimicrobial resistance patterns in women with positive urine culture. Does menopausal status make a significant difference? *Biomed Res Int.* 2017;2017:4192908. <https://doi.org/10.1155/2017/4192908>
229. Gebremariam G, Legese H, Woldu Y, Araya T, Hagos K, Gebreyesus Wasihun A. Bacteriological profile, risk factors and antimicrobial susceptibility patterns of symptomatic urinary tract infection among students of Mekelle University, northern Ethiopia. *BMC Infect Dis.* 2019;19(1):950. <https://doi.org/10.1186/s12879-019-4610-2>
230. Mazzariol A, Bazaj A, Cornaglia G. Multi-drug-resistant Gram-negative bacteria causing urinary tract infections: a review. *J Chemother.* 2017;29(suppl 1):2–9. <https://doi.org/10.1080/1120009X.2017.1380395>
231. Raja NS. Oral treatment options for patients with urinary tract infections caused by extended spectrum beta-lactamase (ESBL) producing Enterobacteriaceae. *J Infect Public Health.* 2019;12(6):843–6. <https://doi.org/10.1016/j.jiph.2019.05.012>
232. Kot B. Antibiotic resistance among uropathogenic Escherichia coli. *Pol J Microbiol.* 2019;68(4):403–15. <https://doi.org/10.33073/pjm-2019-048>
233. Gangcuangco LM, Alejandria M, Henson KE, Alfaraz L, Ata RM, Lopez M, et al. Prevalence and risk factors for trimethoprim-sulfamethoxazole-resistant Escherichia coli among women with acute uncomplicated urinary tract infection in a developing country. *Int J Infect Dis.* 2015;34:55–60. <https://doi.org/10.1016/j.ijid.2015.02.022>
234. Sepsis – fact sheet [internet]. Geneva: World Health Organization; 2020 (<https://www.who.int/news-room/fact-sheets/detail/sepsis>, accessed 30 August 2022).
235. Global report on the epidemiology and burden of sepsis: current evidence, identifying gaps and future directions. Geneva: World Health Orgnization; 2020 (<https://apps.who.int/iris/handle/10665/334216>, accessed 30 August 2022).
236. Meningococcal A conjugate vaccine: updated guidance, February 2015. *Wkly Epidemiol Rec.* 2015;90(8):57–62.
237. Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, et al. Developing a new definition and assessing new clinical criteria for septic shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA.* 2016;315(8):775–87. <https://doi.org/10.1001/jama.2016.0289>
238. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA.* 2016;315(8):801–10. <https://doi.org/10.1001/jama.2016.0287>
239. GLASS method for estimating attributable mortality of antimicrobial resistant bloodstream infections. Geneva: World Health Organization; 2020 (<https://apps.who.int/iris/handle/10665/332457>, accessed 30 August 2022).
240. Adhikari NKJ, Rubenfeld GD. qSOFA score for patients with sepsis in low- and middle-income countries. *JAMA.* 2018;319(21):2175–7. <https://doi.org/10.1001/jama.2018.6413>
241. Rudd KE, Seymour CW, Aluisio AR, Augustin ME, Bagenda DS, Beane A, et al. Association of the Quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA) score with excess hospital mortality in adults with suspected infection in low- and middle-income countries. *JAMA.* 2018;319(21):2202–11. <https://doi.org/10.1001/jama.2018.6229>

242. Cecconi M, Evans L, Levy M, Rhodes A. Sepsis and septic shock. *Lancet*. 2018;392(10141):75–87. [https://doi.org/10.1016/S0140-6736\(18\)30696-2](https://doi.org/10.1016/S0140-6736(18)30696-2)
243. Rudd KE, Kissoon N, Limmathurotsakul D, Bory S, Mutahunga B, Seymour CW, et al. The global burden of sepsis: barriers and potential solutions. *Crit Care*. 2018;22(1):232. <https://doi.org/10.1186/s13054-018-2157-z>
244. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. *Lancet*. 2020;395(10219):200–11. [https://doi.org/10.1016/S0140-6736\(19\)32989-7](https://doi.org/10.1016/S0140-6736(19)32989-7)
245. Markwart R, Saito H, Harder T, Tomczyk S, Cassini A, Fleischmann-Struzek C, et al. Epidemiology and burden of sepsis acquired in hospitals and intensive care units: a systematic review and meta-analysis. *Intensive Care Med*. 2020;46(8):1536–51. <https://doi.org/10.1007/s00134-020-06106-2>
246. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller AB, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. *Lancet Glob Health*. 2014;2(6):e323–33. [https://doi.org/10.1016/S2214-109X\(14\)70227-X](https://doi.org/10.1016/S2214-109X(14)70227-X)
247. WHO Global Maternal Sepsis Study Research Group. Frequency and management of maternal infection in health facilities in 52 countries (GLOSS): a 1-week inception cohort study. *Lancet Glob Health*. 2020;8(5):e661–e71. [https://doi.org/10.1016/S2214-109X\(20\)30109-1](https://doi.org/10.1016/S2214-109X(20)30109-1)
248. Cassini A, Höglberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *Lancet Infect Dis*. 2019;19(1):56–66. [https://doi.org/10.1016/s1473-3099\(18\)30605-4](https://doi.org/10.1016/s1473-3099(18)30605-4)
249. World Health Assembly Resolution WHA70.7. Improving the prevention, diagnosis and clinical management of sepsis. Geneva: World Health Organization; 2017 (<https://apps.who.int/iris/handle/10665/275646>, accessed 30 August 2022).
250. de Jong E, van Oers JA, Beishuizen A, Vos P, Vermeijden WJ, Haas LE, et al. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. *Lancet Infect Dis*. 2016;16(7):819–27. [https://doi.org/10.1016/S1473-3099\(16\)00053-0](https://doi.org/10.1016/S1473-3099(16)00053-0)
251. Oliveira CF, Botoni FA, Oliveira CR, Silva CB, Pereira HA, Serufo JC, et al. Procalcitonin versus C-reactive protein for guiding antibiotic therapy in sepsis: a randomized trial. *Crit Care Med*. 2013;41(10):2336–43. <https://doi.org/10.1097/CCM.0b013e31828e969f>
252. von Dach E, Albrich WC, Brunel AS, Prendki V, Cuvelier C, Flury D, et al. Effect of C-reactive protein-guided antibiotic treatment duration, 7-day treatment, or 14-day treatment on 30-day clinical failure rate in patients with uncomplicated Gram-negative bacteremia: a randomized clinical trial. *JAMA*. 2020;323(21):2160–9. <https://doi.org/10.1001/jama.2020.6348>
253. Committee on Obstetric Practice. Committee Opinion No. 723: Guidelines for diagnostic imaging during pregnancy and lactation. *Obstet Gynecol*. 2017;130(4):e210–e6. <https://doi.org/10.1097/AOG.0000000000002355>
254. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med*. 2017;43(3):304–77. <https://doi.org/10.1007/s00134-017-4683-6>
255. Gotts JE, Matthay MA. Sepsis: pathophysiology and clinical management. *BMJ*. 2016;353:i1585. <https://doi.org/10.1136/bmj.i1585>
256. Samuel L. Direct detection of pathogens in bloodstream during sepsis: Are we there yet? *J Appl Lab Med*. 2019;3(4):631–42. <https://doi.org/10.1373/jalm.2018.028274>
257. Managing meningitis epidemics in Africa: a quick reference guide for health authorities and health-care workers, Revised 2015. Geneva: World Health Organization; 2015 (<https://apps.who.int/iris/handle/10665/154595>, accessed 30 August 2022).

258. McGovern M, Giannoni E, Kuester H, Turner MA, van den Hoogen A, Bliss JM, et al. Challenges in developing a consensus definition of neonatal sepsis. *Pediatr Res.* 2020;88(1):14–26. <https://doi.org/10.1038/s41390-020-0785-x>
259. McGovern M, Giannoni E, Kuester H, Turner MA, van den Hoogen A, Bliss JM, et al. Challenges in developing a consensus definition of neonatal sepsis. *Pediatr Res.* 2020. <https://doi.org/10.1038/s41390-020-0785-x>
260. Molloy EJ, Wynn JL, Bliss J, Koenig JM, Keij FM, McGovern M, et al. Neonatal sepsis: need for consensus definition, collaboration and core outcomes. *Pediatr Res.* 2020. <https://doi.org/10.1038/s41390-020-0850-5>
261. WHO recommendations on newborn health: guidelines approved by the WHO Guidelines Review Committee. Geneva: World Health Organization; 2017 (<https://apps.who.int/iris/handle/10665/259269>, accessed 30 August 2022).
262. Guideline: managing possible serious bacterial infection in young infants when referral is not feasible. Geneva: World Health Organization; 2015 (<https://apps.who.int/iris/handle/10665/181426>, accessed 30 August 2022).
263. Richardson DK, Corcoran JD, Escobar GJ, Lee SK. SNAP-II and SNAPP-E-II: simplified newborn illness severity and mortality risk scores. *J Pediatr.* 2001;138(1):92–100. <https://doi.org/10.1067/mpd.2001.109608>
264. Pal S, Jain A, Garg M, Sekhar JC. Predicting outcome in neonates with possible clinical sepsis by estimating an early Score for Neonatal Acute Physiology-II (SNAP-II). *J Trop Pediatr.* 2019. <https://doi.org/10.1093/tropej/fmz076>
265. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med.* 2005;6(1):2–8. <https://doi.org/10.1097/01.PCC.0000149131.72248.E6>
266. Pediatric SIRS, sepsis, and septic shock criteria [internet]. New York: MDCalc; 2022 (<https://www.mdcalc.com/pediatric-sirs-sepsis-septic-shock-criteria>, accessed 30 August 2022).
267. Matics TJ, Sanchez-Pinto LN. Adaptation and validation of a pediatric sequential organ failure assessment score and evaluation of the Sepsis-3 definitions in critically ill children. *JAMA Pediatr.* 2017;171(10):e172352. <https://doi.org/10.1001/jamapediatrics.2017.2352>
268. Shane AL, Sánchez PJ, Stoll BJ. Neonatal sepsis. *Lancet.* 2017;390(10104):1770–80. [https://doi.org/10.1016/S0140-6736\(17\)31002-4](https://doi.org/10.1016/S0140-6736(17)31002-4)
269. Kwizera A, Festic E, Dünser MW. What's new in sepsis recognition in resource-limited settings? *Intensive Care Med.* 2016;42(12):2030–3. <https://doi.org/10.1007/s00134-016-4222-x>
270. Pontrelli G, De Crescenzo F, Buzzetti R, Jenkner A, Balduzzi S, Calò Carducci F, et al. Accuracy of serum procalcitonin for the diagnosis of sepsis in neonates and children with systemic inflammatory syndrome: a meta-analysis. *BMC Infect Dis.* 2017;17(1):302. <https://doi.org/10.1186/s12879-017-2396-7>
271. Yu Z, Liu J, Sun Q, Qiu Y, Han S, Guo X. The accuracy of the procalcitonin test for the diagnosis of neonatal sepsis: a meta-analysis. *Scand J Infect Dis.* 2010;42(10):723–33. <https://doi.org/10.3109/00365548.2010.489906>
272. Ruan L, Chen GY, Liu Z, Zhao Y, Xu GY, Li SF, et al. The combination of procalcitonin and C-reactive protein or presepsin alone improves the accuracy of diagnosis of neonatal sepsis: a meta-analysis and systematic review. *Crit Care.* 2018;22(1):316. <https://doi.org/10.1186/s13054-018-2236-1>
273. WHO Guidelines for malaria. Geneva: World Health Organization; 2022 (<https://apps.who.int/iris/handle/10665/354781>, accessed 30 August 2022).
274. Defeating meningitis by 2030: a global road map. Geneva: World Health Organization; 2021. (<https://apps.who.int/iris/handle/10665/342010>, accessed 30 August 2022).
275. Meningitis – health topic [internet]. Geneva: World Health Organization; 2022 (<https://www.who.int/health-topics/meningitis>, accessed 30 August 2022).

276. Meningococcal vaccines: WHO position paper – November 2011. *Wkly Epidemiol Rec.* 2011;86(47):521–39.
277. WHO recommendations for routine immunization – summary tables [Internet]. Geneva: World Health Organization (<https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/who-recommendations-for-routine-immunization---summary-tables>, accessed 30 August 2022).
278. Global, regional, and national burden of meningitis, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* 2018;17(12):1061–82. [https://doi.org/10.1016/s1474-4422\(18\)30387-9](https://doi.org/10.1016/s1474-4422(18)30387-9)
279. Bourgi K, Fiske C, Sterling TR. Tuberculosis meningitis. *Curr Infect Dis Rep.* 2017;19(11):39. <https://doi.org/10.1007/s11908-017-0595-4>
280. Global guidelines for the prevention of surgical site infection, second edition. Geneva: World Health Organization; 2018 (<https://apps.who.int/iris/handle/10665/277399>, accessed 30 August 2022).
281. van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M. Clinical features and prognostic factors in adults with bacterial meningitis. *N Engl J Med.* 2004;351(18):1849–59. <https://doi.org/10.1056/NEJMoa040845>
282. Bijlsma MW, Brouwer MC, Kasanmoentalib ES, Kloek AT, Lucas MJ, Tanck MW, et al. Community-acquired bacterial meningitis in adults in the Netherlands, 2006–14: a prospective cohort study. *Lancet Infect Dis.* 2016;16(3):339–47. [https://doi.org/10.1016/S1473-3099\(15\)00430-2](https://doi.org/10.1016/S1473-3099(15)00430-2)
283. Molyneux EM, Walsh AL, Forsyth H, Tembo M, Mwenechanya J, Kayira K, et al. Dexamethasone treatment in childhood bacterial meningitis in Malawi: a randomised controlled trial. *Lancet.* 2002;360(9328):211–8. [https://doi.org/10.1016/S0140-6736\(02\)09458-8](https://doi.org/10.1016/S0140-6736(02)09458-8)
284. Nguyen TH, Tran TH, Thwaites G, Ly VC, Dinh XS, Ho Dang TN, et al. Dexamethasone in Vietnamese adolescents and adults with bacterial meningitis. *N Engl J Med.* 2007;357(24):2431–40. <https://doi.org/10.1056/NEJMoa070852>
285. Gudina EK, Tesfaye M, Adane A, Lemma K, Shibiru T, Wieser A, et al. Adjunctive dexamethasone therapy in unconfirmed bacterial meningitis in resource limited settings: is it a risk worth taking? *BMC Neurol.* 2016;16(1):153. <https://doi.org/10.1186/s12883-016-0678-0>
286. Consolidated guidelines on HIV testing services, 2019. Geneva: World Health Organization; 2020 (<https://apps.who.int/iris/handle/10665/336323>, accessed 30 August 2022).
287. Marti C, Grosgruin O, Harbarth S, Combescure C, Abbas M, Rutschmann O, et al. Adjunctive corticotherapy for community acquired pneumonia: a systematic review and meta-analysis. *PLoS One.* 2015;10(12):e0144032. <https://doi.org/10.1371/journal.pone.0144032>
288. Briel M, Spoorenberg SMC, Snijders D, Torres A, Fernandez-Serrano S, Meduri GU, et al. Corticosteroids in patients hospitalized with community-acquired pneumonia: systematic review and individual patient data meta analysis. *Clin Infect Dis.* 2018;66(3):346–54. <https://doi.org/10.1093/cid/cix801>
289. Siemieniuk RA, Meade MO, Alonso-Coello P, Briel M, Evaniew N, Prasad M, et al. Corticosteroid therapy for patients hospitalized with community-acquired pneumonia: a systematic review and meta-analysis. *Ann Intern Med.* 2015;163(7):519–28. <https://doi.org/10.7326/M15-0715>
290. Stern A, Skalsky K, Avni T, Carrara E, Leibovici L, Paul M. Corticosteroids for pneumonia. *Cochrane Database Syst Rev.* 2017;12(12):CD007720. <https://doi.org/10.1002/14651858.CD007720.pub3>
291. Versporten A, Zarb P, Caniaux I, Gros MF, Drapier N, Miller M, et al. Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: results of an internet-based global point prevalence survey. *Lancet Glob Health.* 2018;6(6):e619–e29. [https://doi.org/10.1016/S2214-109X\(18\)30186-4](https://doi.org/10.1016/S2214-109X(18)30186-4)
292. Barbier F, Andremont A, Wolff M, Bouadma L. Hospital-acquired pneumonia and ventilator-associated pneumonia: recent advances in epidemiology and management. *Curr Opin Pulm Med.* 2013;19(3):216–28. <https://doi.org/10.1097/MCP.0b013e32835f27be>

293. Burton LA, Price R, Barr KE, McAuley SM, Allen JB, Clinton AM, et al. Hospital-acquired pneumonia incidence and diagnosis in older patients. *Age Ageing*. 2016;45(1):171–4. <https://doi.org/10.1093/ageing/afv168>
294. Sopena N, Sabrià M. Multicenter study of hospital-acquired pneumonia in non-ICU patients. *Chest*. 2005;127(1):213–9. <https://doi.org/10.1378/chest.127.1.213>
295. Lübbert C, Schneitler S. Parasitic and infectious diseases of the biliary tract in migrants and international travelers. *Expert Rev Gastroenterol Hepatol*. 2016;10(11):1211–25. <https://doi.org/10.1080/17474124.2016.1240614>
296. Cho JY, Han HS, Yoon YS, Ahn KS. Risk factors for acute cholecystitis and a complicated clinical course in patients with symptomatic cholelithiasis. *Arch Surg*. 2010;145(4):329–33; discussion 33. <https://doi.org/10.1001/archsurg.2010.35>
297. Andercou O, Olteanu G, Mihaileanu F, Stancu B, Dorin M. Risk factors for acute cholecystitis and for intraoperative complications. *Ann Ital Chir*. 2017;88:318–25.
298. Yokoe M, Takada T, Hwang TL, Endo I, Akazawa K, Miura F, et al. Validation of TG13 severity grading in acute cholecystitis: Japan-Taiwan collaborative study for acute cholecystitis. *J Hepatobiliary Pancreat Sci*. 2017;24(6):338–45. <https://doi.org/10.1002/jhbp.457>
299. Ahmed M. Acute cholangitis – an update. *World J Gastrointest Pathophysiol*. 2018;9(1):1–7. <https://doi.org/10.4291/wjgp.v9.i1.1>
300. Regimbeau JM, Fuks D, Pautrat K, Mauvais F, Haccart V, Msika S, et al. Effect of postoperative antibiotic administration on postoperative infection following cholecystectomy for acute calculous cholecystitis: a randomized clinical trial. *JAMA*. 2014;312(2):145–54. <https://doi.org/10.1001/jama.2014.7586>
301. Gomi H, Solomkin JS, Schlossberg D, Okamoto K, Takada T, Strasberg SM, et al. Tokyo Guidelines 2018: antimicrobial therapy for acute cholangitis and cholecystitis. *J Hepatobiliary Pancreat Sci*. 2018;25(1):3–16. <https://doi.org/10.1002/jhbp.518>
302. Haal S, Ten Böhmer B, Balkema S, Depla AC, Fockens P, Jansen JM, et al. Antimicrobial therapy of 3 days or less is sufficient after successful ERCP for acute cholangitis. *United European Gastroenterol J*. 2020;8(4):481–8. <https://doi.org/10.1177/2050640620915016>
303. Tinusz B, Szapáry L, Paládi B, Tenk J, Rumbus Z, Pécsi D, et al. Short-course antibiotic treatment is not inferior to a long-course one in acute cholangitis: a systematic review. *Dig Dis Sci*. 2019;64(2):307–15. <https://doi.org/10.1007/s10620-018-5327-6>
304. Coccolini F, Sartelli M, Catena F, Montori G, Di Saverio S, Sugrue M, et al. Antibiotic resistance pattern and clinical outcomes in acute cholecystitis: 567 consecutive worldwide patients in a prospective cohort study. *Int J Surg*. 2015;21:32–7. <https://doi.org/10.1016/j.ijsu.2015.07.013>
305. Mavilia MG, Molina M, Wu GY. The evolving nature of hepatic abscess: a review. *J Clin Transl Hepatol*. 2016;4(2):158–68. <https://doi.org/10.14218/JCTH.2016.00004>
306. Shi SH, Zhai ZL, Zheng SS. Pyogenic liver abscess of biliary origin: the existing problems and their strategies. *Semin Liver Dis*. 2018;38(3):270–83. <https://doi.org/10.1055/s-0038-1661363>
307. Luo M, Yang XX, Tan B, Zhou XP, Xia HM, Xue J, et al. Distribution of common pathogens in patients with pyogenic liver abscess in China: a meta-analysis. *Eur J Clin Microbiol Infect Dis*. 2016;35(10):1557–65. <https://doi.org/10.1007/s10096-016-2712-y>
308. Lo JZ, Leow JJ, Ng PL, Lee HQ, Mohd Noor NA, Low JK, et al. Predictors of therapy failure in a series of 741 adult pyogenic liver abscesses. *J Hepatobiliary Pancreat Sci*. 2015;22(2):156–65. <https://doi.org/10.1002/jhbp.174>
309. Ren Y, Wang H, Chang Z, Liu Z. Clinical and computed tomography features of extended-spectrum β -lactamase-producing *Klebsiella pneumoniae* liver abscess. *BMC Infect Dis*. 2020;20(1):416. <https://doi.org/10.1186/s12879-020-05142-z>

310. Kumanan T, Sujanitha V, Sreeharan N. Amoebic liver abscess: a neglected tropical disease. *Lancet Infect Dis.* 2020;20(2):160–2. [https://doi.org/10.1016/S1473-3099\(19\)30696-6](https://doi.org/10.1016/S1473-3099(19)30696-6)
311. Shirley DT, Farr L, Watanabe K, Moonah S. A review of the global burden, new diagnostics, and current therapeutics for amebiasis. *Open Forum Infect Dis.* 2018;5(7):ofy161. <https://doi.org/10.1093/ofid/ofy161>
312. Khim G, Em S, Mo S, Townell N. Liver abscess: diagnostic and management issues found in the low resource setting. *Br Med Bull.* 2019;132(1):45–52. <https://doi.org/10.1093/bmb/lbz032>
313. Tayfur M, Balci MG. Pathological changes in appendectomy specimens including the role of parasites: a retrospective study of 2400 cases of acute appendicitis. *Niger J Clin Pract.* 2019;22(2):270–5.
314. Ferris M, Quan S, Kaplan BS, Molodecky N, Ball CG, Chernoff GW, et al. The Global incidence of appendicitis: a systematic review of population-based studies. *Ann Surg.* 2017;266(2):237–41. <https://doi.org/10.1097/SLA.0000000000002188>
315. Bhangu A, Sørensen K, Di Saverio S, Assarsson JH, Drake FT. Acute appendicitis: modern understanding of pathogenesis, diagnosis, and management. *Lancet.* 2015;386(10000):1278–87. [https://doi.org/10.1016/S0140-6736\(15\)00275-5](https://doi.org/10.1016/S0140-6736(15)00275-5)
316. Kotaluoto S, Ukkonen M, Paunioaho SL, Helminen M, Sand J, Rantanen T. Mortality related to appendectomy: a population based analysis over two decades in Finland. *World J Surg.* 2017;41(1):64–9. <https://doi.org/10.1007/s00268-016-3688-6>
317. Di Saverio S, Sibillo A, Giorgini E, Biscardi A, Villani S, Coccolini F, et al. The NOTA Study (Non Operative Treatment for Acute Appendicitis): prospective study on the efficacy and safety of antibiotics (amoxicillin and clavulanic acid) for treating patients with right lower quadrant abdominal pain and long-term follow-up of conservatively treated suspected appendicitis. *Ann Surg.* 2014;260(1):109–17. <https://doi.org/10.1097/sla.0000000000000560>
318. Vons C, Barry C, Maitre S, Pautrat K, Leconte M, Costaglioli B, et al. Amoxicillin plus clavulanic acid versus appendicectomy for treatment of acute uncomplicated appendicitis: an open-label, non-inferiority, randomised controlled trial. *Lancet.* 2011;377(9777):1573–9. [https://doi.org/10.1016/s0140-6736\(11\)60410-8](https://doi.org/10.1016/s0140-6736(11)60410-8)
319. Salminen P, Paajanen H, Rautio T, Nordström P, Aarnio M, Rantanen T, et al. Antibiotic therapy vs appendectomy for treatment of uncomplicated acute appendicitis: the APPAC randomized clinical trial. *JAMA.* 2015;313(23):2340–8. <https://doi.org/10.1001/jama.2015.6154>
320. Flum DR, Davidson GH, Monsell SE, Shapiro NI, Odom SR, Sanchez SE, et al. A randomized trial comparing antibiotics with appendectomy for appendicitis. *N Engl J Med.* 2020;383(20):1907–19. <https://doi.org/10.1056/NEJMoa2014320>
321. van Rossem CC, Schreinemacher MH, van Geloven AA, Bemelman WA. Antibiotic duration after laparoscopic appendectomy for acute complicated appendicitis. *JAMA Surg.* 2016;151(4):323–9. <https://doi.org/10.1001/jamasurg.2015.4236>
322. David A, Dodgion C, Zein Eddine SB, Davila D, Webb TP, Trevino CM. Perforated appendicitis: Short duration antibiotics are noninferior to traditional long duration antibiotics. *Surgery.* 2020;167(2):475–7. <https://doi.org/10.1016/j.surg.2019.08.007>
323. van den Boom AL, de Wijkerslooth EML, Wijnhoven BPL. Systematic review and meta-analysis of postoperative antibiotics for patients with a complex appendicitis. *Dig Surg.* 2020;37(2):101–10. <https://doi.org/10.1159/000497482>
324. Shahedi K, Fuller G, Bolus R, Cohen E, Vu M, Shah R, et al. Long-term risk of acute diverticulitis among patients with incidental diverticulosis found during colonoscopy. *Clin Gastroenterol Hepatol.* 2013;11(12):1609–13. <https://doi.org/10.1016/j.cgh.2013.06.020>
325. Loffeld RJ. Long-term follow-up and development of diverticulitis in patients diagnosed with diverticulosis of the colon. *Int J Colorectal Dis.* 2016;31(1):15–7. <https://doi.org/10.1007/s00384-015-2397-1>

326. Swanson SM, Strate LL. Acute colonic diverticulitis. *Ann Intern Med.* 2018;168(9):itc65–itc80. <https://doi.org/10.7326/AITC201805010>
327. Kechagias A, Rautio T, Kechagias G, Mäkelä J. The role of C-reactive protein in the prediction of the clinical severity of acute diverticulitis. *Am Surg.* 2014;80(4):391–5.
328. Mäkelä JT, Klintrup K, Takala H, Rautio T. The role of C-reactive protein in prediction of the severity of acute diverticulitis in an emergency unit. *Scand J Gastroenterol.* 2015;50(5):536–41. <https://doi.org/10.3109/00365521.2014.999350>
329. Sartelli M, Weber DG, Kluger Y, Ansaloni L, Cocolinli F, Abu-Zidan F, et al. 2020 update of the WSES guidelines for the management of acute colonic diverticulitis in the emergency setting. *World J Emerg Surg.* 2020;15(1):32. <https://doi.org/10.1186/s13017-020-00313-4>
330. Desai M, Fathallah J, Nutalapati V, Saligram S. Antibiotics versus no antibiotics for acute uncomplicated diverticulitis: a systematic review and meta-analysis. *Dis Colon Rectum.* 2019;62(8):1005–12. <https://doi.org/10.1097/DCR.0000000000001324>
331. Sawyer RG, Claridge JA, Nathens AB, Rotstein OD, Duane TM, Evans HL, et al. Trial of short-course antimicrobial therapy for intraabdominal infection. *N Engl J Med.* 2015;372(21):1996–2005. <https://doi.org/10.1056/NEJMoa1411162>
332. Infection prevention and control – health topic [internet]. Geneva: World Health Organization; 2022 (<https://www.who.int/health-topics/infection-prevention-and-control>, accessed 30 August 2022).
333. Evans CT, Safdar N. Current trends in the epidemiology and outcomes of Clostridium difficile Infection. *Clin Infect Dis.* 2015;60 Suppl 2:S66–71. <https://doi.org/10.1093/cid/civ140>
334. Dubberke ER, Olsen MA. Burden of Clostridium difficile on the healthcare system. *Clin Infect Dis.* 2012;55 Suppl 2(Suppl 2):S88–92. <https://doi.org/10.1093/cid/cis335>
335. Davies K, Lawrence J, Berry C, Davis G, Yu H, Cai B, et al. Risk factors for primary Clostridium difficile infection: results from the observational study of risk factors for Clostridium difficile infection in hospitalized patients with infective diarrhea (ORCHID). *Front Public Health.* 2020;8:293. <https://doi.org/10.3389/fpubh.2020.00293>
336. Fang FC, Polage CR, Wilcox MH. Point-counterpoint: what is the optimal approach for detection of Clostridium difficile infection? *J Clin Microbiol.* 2017;55(3):670–80. <https://doi.org/10.1128/JCM.02463-16>
337. Zar FA, Bakkanagari SR, Moorthi KM, Davis MB. A comparison of vancomycin and metronidazole for the treatment of Clostridium difficile-associated diarrhea, stratified by disease severity. *Clin Infect Dis.* 2007;45(3):302–7. <https://doi.org/10.1086/519265>
338. Stevens VW, Nelson RE, Schwab-Daugherty EM, Khader K, Jones MM, Brown KA, et al. Comparative effectiveness of vancomycin and metronidazole for the prevention of recurrence and death in patients with Clostridium difficile infection. *JAMA Intern Med.* 2017;177(4):546–53. <https://doi.org/10.1001/jamainternmed.2016.9045>
339. Johnson S, Louie TJ, Gerdling DN, Cornely OA, Chasan-Taber S, Fitts D, et al. Vancomycin, metronidazole, or tolevamer for Clostridium difficile infection: results from two multinational, randomized, controlled trials. *Clin Infect Dis.* 2014;59(3):345–54. <https://doi.org/10.1093/cid/ciu313>
340. Czaja CA, Scholes D, Hooton TM, Stamm WE. Population-based epidemiologic analysis of acute pyelonephritis. *Clin Infect Dis.* 2007;45(3):273–80. <https://doi.org/10.1086/519268>
341. Sandberg T, Skoog G, Hermansson AB, Kahlmeter G, Kyulenstierna N, Lannergard A, et al. Ciprofloxacin for 7 days versus 14 days in women with acute pyelonephritis: a randomised, open-label and double-blind, placebo-controlled, non-inferiority trial. *Lancet.* 2012;380(9840):484–90. [https://doi.org/10.1016/S0140-6736\(12\)60608-4](https://doi.org/10.1016/S0140-6736(12)60608-4)

342. Eliakim-Raz N, Yahav D, Paul M, Leibovici L. Duration of antibiotic treatment for acute pyelonephritis and septic urinary tract infection – 7 days or less versus longer treatment: systematic review and meta-analysis of randomized controlled trials. *J Antimicrob Chemother.* 2013;68(10):2183–91. <https://doi.org/10.1093/jac/dkt177>
343. Fasugba O, Gardner A, Mitchell BG, Mnatzaganian G. Ciprofloxacin resistance in community- and hospital-acquired *Escherichia coli* urinary tract infections: a systematic review and meta-analysis of observational studies. *BMC Infect Dis.* 2015;15:545. <https://doi.org/10.1186/s12879-015-1282-4>
344. Dehbanipour R, Khanahmad H, Sedighi M, Bialvaei AZ, Faghri J. High prevalence of fluoroquinolone-resistant *Escherichia coli* strains isolated from urine clinical samples. *J Prev Med Hyg.* 2019;60(1):E25–e30. <https://doi.org/10.15167/2421-4248/jpmh2019.60.1.884>
345. Alberici I, Bayazit AK, Drozdz D, Emre S, Fischbach M, Harambat J, et al. Pathogens causing urinary tract infections in infants: a European overview by the ESCAPE study group. *Eur J Pediatr.* 2015;174(6):783–90. <https://doi.org/10.1007/s00431-014-2459-3>
346. WHO consolidated guidelines on tuberculosis: module 3: diagnosis: rapid diagnostics for tuberculosis detection, 2021 update. Geneva: World Health Organization; 2021 (<https://apps.who.int/iris/handle/10665/342331>, accessed 30 August 2022).
347. WHO consolidated guidelines on tuberculosis: module 5: management of tuberculosis in children and adolescents. Geneva: World Health Organization; 2022 (<https://apps.who.int/iris/handle/10665/352522>, accessed 30 August 2022).
348. Kubwimana O, Uwizeyimana E, Legg L, Lucero-Prisno DE. Chronic osteomyelitis in sub-Saharan Africa – a review. *Glob Surg.* 2019;5:1–5. <https://doi.org/10.15761/GOS.1000207>
349. Li HK, Rombach I, Zambellas R, Walker AS, McNally MA, Atkins BL, et al. Oral versus intravenous antibiotics for bone and joint infection. *N Engl J Med.* 2019;380(5):425–36. <https://doi.org/10.1056/NEJMoa1710926>
350. Mathews CJ, Weston VC, Jones A, Field M, Coakley G. Bacterial septic arthritis in adults. *Lancet.* 2010;375(9717):846–55. [https://doi.org/10.1016/s0140-6736\(09\)61595-6](https://doi.org/10.1016/s0140-6736(09)61595-6)
351. Abram SGF, Alvand A, Judge A, Beard DJ, Price AJ. Mortality and adverse joint outcomes following septic arthritis of the native knee: a longitudinal cohort study of patients receiving arthroscopic washout. *Lancet Infect Dis.* 2020;20(3):341–9. [https://doi.org/10.1016/s1473-3099\(19\)30419-0](https://doi.org/10.1016/s1473-3099(19)30419-0)
352. Cheng NC, Tai HC, Chang SC, Chang CH, Lai HS. Necrotizing fasciitis in patients with diabetes mellitus: clinical characteristics and risk factors for mortality. *BMC Infect Dis.* 2015;15:417. 10.1186/s12879-015-1144-0
353. Zundel S, Lemaréchal A, Kaiser P, Szavay P. Diagnosis and treatment of pediatric necrotizing fasciitis: a systematic review of the literature. *Eur J Pediatr Surg.* 2017;27(2):127–37. <https://doi.org/10.1055/s-0036-1584531>
354. Diab J, Bannan A, Pollitt T. Necrotising fasciitis. *BMJ.* 2020;369:m1428. <https://doi.org/10.1136/bmj.m1428>
355. Schröder A, Gerin A, Firth GB, Hoffmann KS, Grieve A, Oetzmann von Sochaczewski C. A systematic review of necrotising fasciitis in children from its first description in 1930 to 2018. *BMC Infect Dis.* 2019;19(1):317. <https://doi.org/10.1186/s12879-019-3941-3>
356. Nawijn F, Smeeing DPJ, Houwert RM, Leenen LPH, Hietbrink F. Time is of the essence when treating necrotizing soft tissue infections: a systematic review and meta-analysis. *World J Emerg Surg.* 2020;15:4. <https://doi.org/10.1186/s13017-019-0286-6>
357. Kadri SS, Swihart BJ, Bonne SL, Hohmann SF, Hennessy LV, Louras P, et al. Impact of intravenous immunoglobulin on survival in necrotizing fasciitis with vasopressor-dependent shock: a propensity score-matched analysis from 130 US hospitals. *Clin Infect Dis.* 2017;64(7):877–85. <https://doi.org/10.1093/cid/ciw871>
358. Shittu A, Deinhardt-Emmer S, Vas Nunes J, Niemann S, Grobusch MP, Schaumburg F. Tropical pyomyositis: an update. *Trop Med Int Health.* 2020;25(6):660–5. <https://doi.org/10.1111/tmi.13395>

359. Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2014;59(2):e10–52. <https://doi.org/10.1093/cid/ciu444>
360. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. *Clin Infect Dis.* 2011;52(4):e56–93. <https://doi.org/10.1093/cid/cir073>
361. Lalami Y, Klastersky J. Impact of chemotherapy-induced neutropenia (CIN) and febrile neutropenia (FN) on cancer treatment outcomes: an overview about well-established and recently emerging clinical data. *Crit Rev Oncol Hematol.* 2017;120:163–79. <https://doi.org/10.1016/j.critrevonc.2017.11.005>
362. Lyman GH, Abella E, Pettengell R. Risk factors for febrile neutropenia among patients with cancer receiving chemotherapy: a systematic review. *Crit Rev Oncol Hematol.* 2014;90(3):190–9. <https://doi.org/10.1016/j.critrevonc.2013.12.006>
363. MASCC risk index for febrile neutropenia [internet]. New York: MDCalc; 2022 (<https://www.mdcalc.com/mascc-risk-index-febrile-neutropenia>, accessed 30 August 2022).
364. Haeusler GM, Thursky KA, Slavin MA, Babl FE, De Abreu Lourenco R, Allaway Z, et al. Risk stratification in children with cancer and febrile neutropenia: a national, prospective, multicentre validation of nine clinical decision rules. *eClinicalMedicine.* 2020;18:100220. <https://doi.org/10.1016/j.eclimn.2019.11.013>
365. Hunger SP, Mullighan CG. Acute lymphoblastic leukemia in children. *N Engl J Med.* 2015;373(16):1541–52. <https://doi.org/10.1056/NEJMra1400972>
366. Davis K, Wilson S. Febrile neutropenia in paediatric oncology. *Paediatr Child Health (Oxford).* 2020;30(3):93–7. <https://doi.org/10.1016/j.paed.2019.12.002>
367. Castagnola E, Fontana V, Caviglia I, Caruso S, Faraci M, Fioredda F, et al. A prospective study on the epidemiology of febrile episodes during chemotherapy-induced neutropenia in children with cancer or after hemopoietic stem cell transplantation. *Clin Infect Dis.* 2007;45(10):1296–304. <https://doi.org/10.1086/522533>
368. Combariza JF, Lombana M, Pino LE, Arango M. C-reactive protein and the MASCC risk index identify high-risk patients with febrile neutropenia and hematologic neoplasms. *Support Care Cancer.* 2015;23(4):1009–13. <https://doi.org/10.1007/s00520-014-2454-2>
369. Arif T, Phillips RS. Updated systematic review and meta-analysis of the predictive value of serum biomarkers in the assessment and management of fever during neutropenia in children with cancer. *Pediatr Blood Cancer.* 2019;66(10):e27887. <https://doi.org/10.1002/pbc.27887>
370. Ahn S, Lee YS, Lim KS, Lee JL. Adding procalcitonin to the MASCC risk-index score could improve risk stratification of patients with febrile neutropenia. *Support Care Cancer.* 2013;21(8):2303–8. <https://doi.org/10.1007/s00520-013-1787-6>
371. Mhaskar R, Clark OA, Lyman G, Engel Ayer Botrel T, Morganti Paladini L, Djulbegovic B. Colony-stimulating factors for chemotherapy-induced febrile neutropenia. *Cochrane Database Syst Rev.* 2014;2014(10):CD003039. <https://doi.org/10.1002/14651858.CD003039.pub2>
372. Koenig C, Schneider C, Morgan JE, Ammann RA, Sung L, Phillips B. Association of time to antibiotics and clinical outcomes in patients with fever and neutropenia during chemotherapy for cancer: a systematic review. *Support Care Cancer.* 2020;28(3):1369–83. <https://doi.org/10.1007/s00520-019-04961-4>
373. Rivas-Ruiz R, Villasis-Keever M, Miranda-Novales G, Castelán-Martínez OD, Rivas-Contreras S. Outpatient treatment for people with cancer who develop a low-risk febrile neutropaenic event. *Cochrane Database Syst Rev.* 2019;3(3):CD009031. <https://doi.org/10.1002/14651858.CD009031.pub2>
374. Lortholary O, Lefort A, Tod M, Chomat AM, Darras-Joly C, Cordonnier C. Pharmacodynamics and pharmacokinetics of antibacterial drugs in the management of febrile neutropenia. *Lancet Infect Dis.* 2008;8(10):612–20. [https://doi.org/10.1016/s1473-3099\(08\)70228-7](https://doi.org/10.1016/s1473-3099(08)70228-7)

375. Aguilar-Guisado M, Espigado I, Martín-Peña A, Gudiol C, Royo-Cebrecos C, Falantes J, et al. Optimisation of empirical antimicrobial therapy in patients with haematological malignancies and febrile neutropenia (How Long study): an open-label, randomised, controlled phase 4 trial. *Lancet Haematol.* 2017;4(12):e573–e83. [https://doi.org/10.1016/s2352-3026\(17\)30211-9](https://doi.org/10.1016/s2352-3026(17)30211-9)
376. Stern A, Carrara E, Bitterman R, Yahav D, Leibovici L, Paul M. Early discontinuation of antibiotics for febrile neutropenia versus continuation until neutropenia resolution in people with cancer. *Cochrane Database Syst Rev.* 2019;1(1):CD012184. <https://doi.org/10.1002/14651858.CD012184.pub2>
377. Healthcare-associated infections: surgical site infections. Annual Epidemiological Report for 2017. Stockholm: European Centre for Disease Prevention and Control; 2019 (<https://www.ecdc.europa.eu/en/publications-data/healthcare-associated-infections-surgical-site-infections-annual-1>, accessed 30 August 2022).
378. GlobalSurg Collaborative. Surgical site infection after gastrointestinal surgery in high-income, middle-income, and low-income countries: a prospective, international, multicentre cohort study. *Lancet Infect Dis.* 2018;18(5):516–25. [https://doi.org/10.1016/S1473-3099\(18\)30101-4](https://doi.org/10.1016/S1473-3099(18)30101-4)
379. Rickard J, Beilman G, Forrester J, Sawyer R, Stephen A, Weiser TG, et al. Surgical infections in low- and middle-income countries: a global assessment of the burden and management needs. *Surg Infect (Larchmt).* 2020;21(6):478–94. <https://doi.org/10.1089/sur.2019.142>
380. Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health Syst Pharm.* 2013;70(3):195–283. <https://doi.org/10.2146/ajhp120568>
381. de Jonge SW, Boldingh QJJ, Solomkin JS, Dellinger EP, Egger M, Salanti G, et al. Effect of postoperative continuation of antibiotic prophylaxis on the incidence of surgical site infection: a systematic review and meta-analysis. *Lancet Infect Dis.* 2020;20(10):1182–92. [https://doi.org/10.1016/s1473-3099\(20\)30084-0](https://doi.org/10.1016/s1473-3099(20)30084-0)
382. Critically important antimicrobials for human medicine, sixth revision. Geneva: World Health Organization; 2019 (<https://apps.who.int/iris/handle/10665/312266>, accessed 30 August 2022).
383. 2020 antibacterial agents in clinical and preclinical development: an overview and analysis. Geneva: World Health Organization; 2021 (<https://apps.who.int/iris/handle/10665/340694>, accessed 30 August 2022).
384. Medicines and Related Substances Act (previously Drugs Control Act) 101 of 1965 [internet]. Cape Town: Government of South Africa; 2022 (<https://www.gov.za/documents/drugs-control-act-7-jul-1965-0000>, accessed 30 August 2022).
385. Bassetti M, Echols R, Matsunaga Y, Ariyasu M, Doi Y, Ferrer R, et al. Efficacy and safety of ceferocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. *Lancet Infect Dis.* 2021;21(2):226–40. [https://doi.org/10.1016/s1473-3099\(20\)30796-9](https://doi.org/10.1016/s1473-3099(20)30796-9)
386. Heil EL, Tamia PD. Ceferocol: the Trojan horse has arrived but will Troy fall? *Lancet Infect Dis.* 2021;21(2):153–5. [https://doi.org/10.1016/s1473-3099\(20\)30828-8](https://doi.org/10.1016/s1473-3099(20)30828-8)
387. Portsmouth S, van Veenhuizen D, Echols R, Machida M, Ferreira JCA, Ariyasu M, et al. Ceferocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by Gram-negative uropathogens: a phase 2, randomised, double-blind, non-inferiority trial. *Lancet Infect Dis.* 2018;18(12):1319–28. [https://doi.org/10.1016/s1473-3099\(18\)30554-1](https://doi.org/10.1016/s1473-3099(18)30554-1)
388. Wunderink RG, Matsunaga Y, Ariyasu M, Clevenbergh P, Echols R, Kaye KS, et al. Ceferocol versus high-dose, extended-infusion meropenem for the treatment of Gram-negative nosocomial pneumonia (APEKS-NP): a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Infect Dis.* 2021;21(2):213–25. [https://doi.org/10.1016/s1473-3099\(20\)30731-3](https://doi.org/10.1016/s1473-3099(20)30731-3)
389. Yamano Y. In vitro activity of ceferocol against a broad range of clinically important gram-negative bacteria. *Clin Infect Dis.* 2019;69(Suppl 7):S544–s51. <https://doi.org/10.1093/cid/ciz827>

390. Karlowsky JA, Hackel MA, Tsuji M, Yamano Y, Echols R, Sahm DF. In vitro activity of ceftiderocol, a siderophore cephalosporin, against Gram-negative bacilli isolated by clinical laboratories in North America and Europe in 2015–2016: SIDERO-WT-2015. *Int J Antimicrob Agents*. 2019;53(4):456–66. <https://doi.org/10.1016/j.ijantimicag.2018.11.007>
391. Wagenlehner FM, Sobel JD, Newell P, Armstrong J, Huang X, Stone GG, et al. Ceftazidime-avibactam versus doripenem for the treatment of complicated urinary tract infections, including acute pyelonephritis: RECAPTURE, a phase 3 randomized trial program. *Clin Infect Dis*. 2016;63(6):754–62. <https://doi.org/10.1093/cid/ciw378>
392. Carmeli Y, Armstrong J, Laud PJ, Newell P, Stone G, Wardman A, et al. Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* complicated urinary tract infections or complicated intra-abdominal infections (REPRISE): a randomised, pathogen-directed, phase 3 study. *Lancet Infect Dis*. 2016;16(6):661–73. [https://doi.org/10.1016/S1473-3099\(16\)30004-4](https://doi.org/10.1016/S1473-3099(16)30004-4)
393. Mazuski JE, Gasink LB, Armstrong J, Broadhurst H, Stone GG, Rank D, et al. Efficacy and safety of ceftazidime-avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infection: results from a randomized, controlled, double-blind, phase 3 program. *Clin Infect Dis*. 2016;62(11):1380–9. <https://doi.org/10.1093/cid/ciw133>
394. Qin X, Tran BG, Kim MJ, Wang L, Nguyen DA, Chen Q, et al. A randomised, double-blind, phase 3 study comparing the efficacy and safety of ceftazidime/avibactam plus metronidazole versus meropenem for complicated intra-abdominal infections in hospitalised adults in Asia. *Int J Antimicrob Agents*. 2017;49(5):579–88. <https://doi.org/10.1016/j.ijantimicag.2017.01.010>
395. Torres A, Zhong N, Pachl J, Timsit JF, Kollef M, Chen Z, et al. Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial. *Lancet Infect Dis*. 2018;18(3):285–95. [https://doi.org/10.1016/S1473-3099\(17\)30747-8](https://doi.org/10.1016/S1473-3099(17)30747-8)
396. Bradley JS, Roilides E, Broadhurst H, Cheng K, Huang LM, MasCasullo V, et al. Safety and efficacy of ceftazidime-avibactam in the treatment of children ≥3 months to <18 years with complicated urinary tract infection: results from a phase 2 randomized, controlled trial. *Pediatr Infect Dis J*. 2019;38(9):920–8. <https://doi.org/10.1097/inf.0000000000002395>
397. Bradley JS, Broadhurst H, Cheng K, Mendez M, Newell P, Prchlík M, et al. Safety and efficacy of ceftazidime-avibactam plus metronidazole in the treatment of children ≥3 months to <18 years with complicated intra-abdominal infection: results from a phase 2, randomized, controlled trial. *Pediatr Infect Dis J*. 2019;38(8):816–24. <https://doi.org/10.1097/inf.0000000000002392>
398. Wang Y, Wang J, Wang R, Cai Y. Resistance to ceftazidime-avibactam and underlying mechanisms. *J Glob Antimicrob Resist*. 2019;22:18–27. <https://doi.org/10.1016/j.jgar.2019.12.009>
399. Spiliopoulou I, Kazmierczak K, Stone GG. In vitro activity of ceftazidime/avibactam against isolates of carbapenem-non-susceptible Enterobacteriaceae collected during the INFORM global surveillance programme (2015–17). *J Antimicrob Chemother*. 2020;75(2):384–91. <https://doi.org/10.1093/jac/dkz456>
400. Di Bella S, Giacobbe DR, Maraolo AE, Viaggi V, Luzzati R, Bassetti M, et al. Resistance to ceftazidime/avibactam in infections and colonisations by KPC-producing Enterobacteriales: a systematic review of observational clinical studies. *J Glob Antimicrob Resist*. 2021;25:268–81. <https://doi.org/10.1016/j.jgar.2021.04.001>
401. Fosfomycin-containing medicinal products [internet]. Amsterdam: European Medicines Agency; 2020 (<https://www.ema.europa.eu/en/medicines/human/referrals/fosfomycin-containing-medicinal-products>, accessed 30 August 2022).

402. Samonis G, Maraki S, Karageorgopoulos DE, Vouloumanou EK, Falagas ME. Synergy of fosfomycin with carbapenems, colistin, netilmicin, and tigecycline against multidrug-resistant *Klebsiella pneumoniae*, *Escherichia coli*, and *Pseudomonas aeruginosa* clinical isolates. *Eur J Clin Microbiol Infect Dis.* 2012;31(5):695–701. <https://doi.org/10.1007/s10096-011-1360-5>
403. Bakthavatchalam YD, Shankar A, Muthuirulandi Sethuvel DP, Asokan K, Kanthan K, Veeraghavan B. Synergistic activity of fosfomycin-meropenem and fosfomycin-colistin against carbapenem resistant *Klebsiella pneumoniae*: an in vitro evidence. *Future Sci OA.* 2020;6(4):Fso461. <https://doi.org/10.2144/fsoa-2019-0074>
404. Kaye KS, Rice LB, Dane AL, Stus V, Sagan O, Fedosiuk E, et al. Fosfomycin for injection (ZTI-01) versus piperacillin-tazobactam for the treatment of complicated urinary tract infection including acute pyelonephritis: ZEUS, a phase 2/3 randomized trial. *Clin Infect Dis.* 2019;69(12):2045–56. <https://doi.org/10.1093/cid/ciz181>
405. Sojo-Dorado J, López-Hernández I, Rosso-Fernandez C, Morales IM, Palacios-Baena ZR, Hernández-Torres A, et al. Effectiveness of fosfomycin for the treatment of multidrug-resistant *Escherichia coli* bacteremic urinary tract infections: a randomized clinical trial. *JAMA Netw Open.* 2022;5(1):e2137277. <https://doi.org/10.1001/jamanetworkopen.2021.37277>
406. Pujol M, Miró JM, Shaw E, Aguado JM, San-Juan R, Puig-Asensio M, et al. Daptomycin plus fosfomycin versus daptomycin alone for methicillin-resistant *Staphylococcus aureus* bacteraemia and endocarditis. A randomized clinical trial. *Clin Infect Dis.* 2021;72(9):1517–25. <https://doi.org/10.1093/cid/ciaa1081>
407. Pericàs JM, Moreno A, Almela M, García-de-la-Mària C, Marco F, Muñoz P, et al. Efficacy and safety of fosfomycin plus imipenem versus vancomycin for complicated bacteraemia and endocarditis due to methicillin-resistant *Staphylococcus aureus*: a randomized clinical trial. *Clin Microbiol Infect.* 2018;24(6):673–6. <https://doi.org/10.1016/j.cmi.2018.01.010>
408. Intravenous and oral fosfomycin in hospitalised neonates with clinical sepsis (NeoFosfo). Bethesda, MD: U.S. National Library of Medicine; 2018 (ClinicalTrials.gov Identifier: NCT03453177; <https://clinicaltrials.gov/ct2/show/NCT03453177>, accessed 30 August 2022).
409. Abbott IJ, Dekker J, van Gorp E, Wijma RA, Raaphorst MN, Klaassen CHW, et al. Impact of bacterial species and baseline resistance on fosfomycin efficacy in urinary tract infections. *J Antimicrob Chemother.* 2020;75(4):988–96. <https://doi.org/10.1093/jac/dkz519>
410. Falagas ME, Athanasaki F, Voulgaris GL, Triarides NA, Vardakas KZ. Resistance to fosfomycin: Mechanisms, frequency and clinical consequences. *Int J Antimicrob Agents.* 2019;53(1):22–8. <https://doi.org/10.1016/j.ijantimicag.2018.09.013>
411. Li J, Zhao QH, Huang KC, Li ZQ, Zhang LY, Qin DY, et al. Linezolid vs. vancomycin in treatment of methicillin-resistant *Staphylococcus aureus* infections: a meta-analysis. *Eur Rev Med Pharmacol Sci.* 2017;21(17):3974–79.
412. Yue J, Dong BR, Yang M, Chen X, Wu T, Liu GJ. Linezolid versus vancomycin for skin and soft tissue infections. *Cochrane Database Syst Rev.* 2016(1):CD008056. <https://doi.org/10.1002/14651858.CD008056.pub3>
413. Chuang YC, Wang JT, Lin HY, Chang SC. Daptomycin versus linezolid for treatment of vancomycin-resistant enterococcal bacteraemia: systematic review and meta-analysis. *BMC Infect Dis.* 2014;14:687. <https://doi.org/10.1186/s12879-014-0687-9>
414. Balli EP, Venetis CA, Miyakis S. Systematic review and meta-analysis of linezolid versus daptomycin for treatment of vancomycin-resistant enterococcal bacteraemia. *Antimicrob Agents Chemother.* 2014;58(2):734–9. <https://doi.org/10.1128/aac.01289-13>
415. Whang DW, Miller LG, Partain NM, McKinnell JA. Systematic review and meta-analysis of linezolid and daptomycin for treatment of vancomycin-resistant enterococcal bloodstream infections. *Antimicrob Agents Chemother.* 2013;57(10):5013–8. <https://doi.org/10.1128/aac.00714-13>

416. Britt NS, Potter EM, Patel N, Steed ME. Comparison of the effectiveness and safety of linezolid and daptomycin in vancomycin-resistant enterococcal bloodstream infection: a national cohort study of Veterans Affairs patients. *Clin Infect Dis.* 2015;61(6):871-8. <https://doi.org/10.1093/cid/civ444>
417. Jiang H, Tang RN, Wang J. Linezolid versus vancomycin or teicoplanin for nosocomial pneumonia: meta-analysis of randomised controlled trials. *Eur J Clin Microbiol Infect Dis.* 2013;32(9):1121-8. 10.1007/s10096-013-1867-z
418. WHO consolidated guidelines on tuberculosis: module 4: treatment: drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2020 (<https://apps.who.int/iris/handle/10665/332397>, accessed 30 August 2022).
419. Shariati A, Dadashi M, Chegini Z, van Belkum A, Mirzaii M, Khoramrooz SS, et al. The global prevalence of daptomycin, tigecycline, quinupristin/dalfopristin, and linezolid-resistant *Staphylococcus aureus* and coagulase-negative staphylococci strains: a systematic review and meta-analysis. *Antimicrob Resist Infect Control.* 2020;9(1):56. <https://doi.org/10.1186/s13756-020-00714-9>
420. Sazdanovic P, Jankovic SM, Kostic M, Dimitrijevic A, Stefanovic S. Pharmacokinetics of linezolid in critically ill patients. *Expert Opin Drug Metab Toxicol.* 2016;12(6):595-600. <https://doi.org/10.1517/17425255.2016.1170807>
421. Kaye KS, Bhowmick T, Metallidis S, Bleasdale SC, Sagan OS, Stus V, et al. Effect of meropenem-vaborbactam vs piperacillin-tazobactam on clinical cure or improvement and microbial eradication in complicated urinary tract infection: the TANGO I randomized clinical trial. *JAMA.* 2018;319(8):788-99. <https://doi.org/10.1001/jama.2018.0438>
422. Wunderink RG, Giamparellos-Bourboulis EJ, Rahav G, Mathers AJ, Bassetti M, Vazquez J, et al. Effect and safety of meropenem-vaborbactam versus best-available therapy in patients with carbapenem-resistant Enterobacteriaceae infections: the TANGO II randomized clinical trial. *Infect Dis Ther.* 2018;7(4):439-55. <https://doi.org/10.1007/s40121-018-0214-1>
423. Chiotos K, Hayes M, Gerber JS, Tammaro PD. Treatment of carbapenem-resistant Enterobacteriaceae infections in children. *J Pediatric Infect Dis Soc.* 2020;9(1):56-66. <https://doi.org/10.1093/jpids/piz085>
424. Pfaller MA, Huband MD, Mendes RE, Flamm RK, Castanheira M. In vitro activity of meropenem/vaborbactam and characterisation of carbapenem resistance mechanisms among carbapenem-resistant Enterobacteriaceae from the 2015 meropenem/vaborbactam surveillance programme. *Int J Antimicrob Agents.* 2018;52(2):144-50. <https://doi.org/10.1016/j.ijantimicag.2018.02.021>
425. Shaeer KM, Zmarlicka MT, Chahine EB, Piccicacco N, Cho JC. Plazomicin: A next-generation aminoglycoside. *Pharmacotherapy.* 2019;39(1):77-93. <https://doi.org/10.1002/phar.2203>
426. Castanheira M, Deshpande LM, Woosley LN, Serio AW, Krause KM, Flamm RK. Activity of plazomicin compared with other aminoglycosides against isolates from European and adjacent countries, including Enterobacteriaceae molecularly characterized for aminoglycoside-modifying enzymes and other resistance mechanisms. *J Antimicrob Chemother.* 2018;73(12):3346-54. <https://doi.org/10.1093/jac/dky344>
427. Wagenlehner FME, Cloutier DJ, Komirenko AS, Cebrik DS, Krause KM, Keepers TR, et al. Once-daily plazomicin for complicated urinary tract infections. *N Engl J Med.* 2019;380(8):729-40. <https://doi.org/10.1056/NEJMoa1801467>
428. McKinnell JA, Dwyer JP, Talbot GH, Connolly LE, Friedland I, Smith A, et al. Plazomicin for infections caused by carbapenem-resistant Enterobacteriaceae. *N Engl J Med.* 2019;380(8):791-3. <https://doi.org/10.1056/NEJMMc1807634>
429. Kwa A, Kasiakou SK, Tam VH, Falagas ME. Polymyxin B: similarities to and differences from colistin (polymyxin E). *Expert Rev Anti Infect Ther.* 2007;5(5):811-21. <https://doi.org/10.1586/14787210.5.5.811>

430. Falagas ME, Lourida P, Poulikakos P, Rafailidis PI, Tansarli GS. Antibiotic treatment of infections due to carbapenem-resistant Enterobacteriaceae: systematic evaluation of the available evidence. *Antimicrob Agents Chemother.* 2014;58(2):654–63. <https://doi.org/10.1128/aac.01222-13>
431. Paul M, Daikos GL, Durante-Mangoni E, Yahav D, Carmeli Y, Benattar YD, et al. Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial. *Lancet Infect Dis.* 2018;18(4):391–400. [https://doi.org/10.1016/S1473-3099\(18\)30099-9](https://doi.org/10.1016/S1473-3099(18)30099-9)
432. Zusman O, Altunin S, Koppel F, Dishon Benattar Y, Gedik H, Paul M. Polymyxin monotherapy or in combination against carbapenem-resistant bacteria: systematic review and meta-analysis. *J Antimicrob Chemother.* 2017;72(1):29–39. <https://doi.org/10.1093/jac/dkw377>
433. Paul M, Carmeli Y, Durante-Mangoni E, Mouton JW, Tacconelli E, Theuretzbacher U, et al. Combination therapy for carbapenem-resistant Gram-negative bacteria. *J Antimicrob Chemother.* 2014;69(9):2305–9. <https://doi.org/10.1093/jac/dku168>
434. Vaara M. Polymyxins and their potential next generation as therapeutic antibiotics. *Front Microbiol.* 2019;10:1689. <https://doi.org/10.3389/fmicb.2019.01689>
435. Nation RL, Garonzik SM, Thamlikitkul V, Giamparellos-Bourboulis EJ, Forrest A, Paterson DL, et al. Dosing guidance for intravenous colistin in critically-ill patients. *Clin Infect Dis.* 2017;64(5):565–71. <https://doi.org/10.1093/cid/ciw839>
436. Ahern JW, Schnoor JB. Colistin: potential for dosage error. *Clin Infect Dis.* 2012;55(9):1275; author reply 75–6. <https://doi.org/https://doi.org/10.1093/cid/cis632>
437. Nation RL, Garonzik SM, Li J, Thamlikitkul V, Giamparellos-Bourboulis EJ, Paterson DL, et al. Updated US and European dose recommendations for intravenous colistin: How do they perform? *Clin Infect Dis.* 2016;62(5):552–8. <https://doi.org/10.1093/cid/civ964>
438. Tsuji BT, Pogue JM, Zavascki AP, Paul M, Daikos GL, Forrest A, et al. International consensus guidelines for the optimal use of the polymyxins: endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP). *Pharmacotherapy.* 2019;39(1):10–39. <https://doi.org/10.1002/phar.2209>
439. Luque S, Escano C, Sorli L, Li J, Campillo N, Horcajada JP, et al. Urinary concentrations of colistimethate and formed colistin after intravenous administration in patients with multidrug-resistant Gram-negative bacterial infections. *Antimicrob Agents Chemother.* 2017;61(8). <https://doi.org/10.1128/AAC.02595-16>
440. Ezadi F, Ardebili A, Mirnejad R. Antimicrobial susceptibility testing for polymyxins: Challenges, issues, and recommendations. *J Clin Microbiol.* 2019;57(4). <https://doi.org/10.1128/JCM.01390-18>
441. Wang R, van Dorp L, Shaw LP, Bradley P, Wang Q, Wang X, et al. The global distribution and spread of the mobilized colistin resistance gene mcr-1. *Nat Commun.* 2018;9(1):1179. <https://doi.org/10.1038/s41467-018-03205-z>
442. Liu YY, Wang Y, Walsh TR, Yi LX, Zhang R, Spencer J, et al. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. *Lancet Infect Dis.* 2016;16(2):161–8. [https://doi.org/10.1016/s1473-3099\(15\)00424-7](https://doi.org/10.1016/s1473-3099(15)00424-7)
443. The selection and use of essential medicines. Report of the WHO Expert Committee, 2021 (including the 22nd WHO Model List of Essential Medicines and the 8th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2021 (WHO Technical Report Series, No. 1035; <https://apps.who.int/iris/handle/10665/351172>, accessed 30 August 2022).



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