Chapter 67

How antibiotic resistance occurs: the mechanisms of antibiotic resistance

Glendee Reynolds-Campbell
Cayman Islands Health Services Authority, Grand Cayman, Cayman Islands.

Camille Blake
Cayman Islands Health Services Authority, Grand Cayman, Cayman Islands.

Introduction

With the continued mounting resistance by bacteria to all classes of antibiotics, it is imperative that the mechanisms of resistance used by organisms be understood. Antibiotic resistance can be achieved through several mechanisms which can be categorized as intrinsic (e.g., naturally low permeability), adaptive (triggered by changes in the availability of environmental nutrients or low concentrations of an antibiotic) or acquired (from exogenous horizontal transfer of genetic material e.g., plasmids or via mutations to chromosomal genes).

Intrinsic mechanisms centre around the reduced permeability of the organism to the antibiotic, however, mechanisms related to the production of efflux pumps can be both intrinsic and acquired. Bacteria also share resistance genes that assist with the production of enzymes that directly inactivate, degrade, or modify antibiotics, preventing them from completing their tasks. Bacteria can also produce or acquire genes that cause modification, overproduction or replacement of antibiotic target sites rendering them useless in their bacterial eradication.

Pathogens continuously adapt to antibiotics, developing ways to evade the drugs and survive. Some bacteria have even evolved to flourish and rely on specific antibiotics in their surroundings to survive.

It is crucial to enhance monitoring for these mechanisms in clinical and environmental samples to combat the spread of antibiotic resistance and preserve the limited resources to fight bacterial infections. This chapter outlines various common resistance mechanisms against the primary antibiotic classes used in clinical settings. **Table 1** summarizes the major antibiotic classes, members, and resistance mechanisms.

Beta-lactam antibiotics (BLAs)

Beta-lactam (or β-lactam) antibiotics were the first to be discovered and remain the largest and most widely used agents. The members are subclassified into five basic structures, capable of exerting different antimicrobial activities: -penam, -penem, cephem, monobactam, and -clavam. For example, the penams aka penicillins are subdivided into natural penicillins, β-lactamase-resistant agents, aminopenicillins, carboxypenicillins, and ureidopenicillins. The cephems or cephalosporins are classified as first, second, third, fourth and

fifth generation. The BLAs derive their antimicrobial ability via a biochemically shared β-lactam ring (3-carbon and 1-nitrogen ring) and target bacterial penicillin-binding protein (PBPs) via acylation. This disrupts terminal peptidoglycan transpeptidation resulting in failure of cell wall synthesis and subsequent cell lysis. Indications for use will vary by the subclass, however, this class is suitable for a variety of infectious bacterial conditions.

Resistance mechanisms

The following mechanisms of resistance are common for β-lactam antibiotics.

Drug inactivating enzymes (β-lactamases)

Drug inactivation is the most common mechanism of resistance for BLAs. Gram-negative and Gram-positive organisms may possess genes that encode β-lactamases which hydrolyze the β-lactam amide rendering them ineffective. β-lactamases are either chromosomally mediated (i.e., inducible) or plasmid-mediated (i.e., constitutive). They are classified functionally (Bush-Jacoby) or based on molecular homology (Ambler) systems. Chromosomally mediated cephalosporinases in Group 1 correspond to Ambler class C. Group 2 (Bush-Jacoby) contains serine enzymes and may be classified in either class A or D. The metallo-β-lactamases of group 3 (Bush-Jacoby) correspond to Ambler class B. In the medical or clinical setting, functional classification is often used to guide antibiotic therapy and infection prevention intervention.

Group 1/ Class C β-lactamases are cephalosporinases with resistance to common β-lactamase inhibitors. Chromosomally mediated AmpC expression is usually induced by antibiotic pressure. There are also plasmid-mediated β-lactamases belonging to this group including MIR-1, and FOX.

Group 2/Class A and D is the largest group. The limited spectrum, class A penicillinase PC1 is common in *Staphylococcus* spp. and belongs to group 2a. This represents one of the earliest recognized β-lactamases. In contrast, broad-spectrum β-lactamases, belonging to group 2b are commonly isolated from Gram-negative organisms of the Enterobacteriaceae group. TEM-1, TEM-2 and SHV-1 which hydrolyze early-generation cephalosporins were the first recognized followed by group 2be enzymes, TEM-3, SHV-2 and CTX-M capable of hydrolyzing third generation cephalosporins. Groups 2a, 2b and 2be all retain susceptibility to βlactamase inhibitors including clavulanic acid. However, enzymes of group 2br (TEM-30, SHV-10) have relative resistance to common inhibitors including tazobactam, sulbactam and clavulanic acid.

Group 2d/ Class D β-lactamases are also resistant to the effects of commonly used inhibitors. The oxacillin hydrolyzing aka OXA enzymes are commonly plasmid-mediated and have been widely described in *Acinetobacter baumannii*, *Pseudomonas* spp. and *Burkholderia* spp. Notably, OXA-11 and OXA-15 from group 2de are unable to hydrolyze carbapenems, whilst OXA-48, (group2df) are carbapenamases. Class A carbapenemases i.e., Bush- Jacoby 2f, are distinguished by their susceptibility to β-lactamase inhibitors. The archetype of this group is plasmid-mediated KPC-2 (*Klebsiella pneumoniae* carbapenemase). Others include GES (Guiana extended-spectrum β-lactamase), SME (*Serratia marcescens* enzyme), and SHV (sulfhydryl variable lactamase).

Group 3/ Class B represent the metallo-β-lactamases (MBL). Their activity is inhibited by chelators e.g., EDTA. Resistance via class B β-lactamases is described in *K. pneumoniae*, and *P. aeruginosa*. Examples include imipenemase (IMP), Verona integrated-encoded MBL (VIM) and New Delhi MBL (NDM).

Regulation of porins and efflux pumps

Gram-negative bacteria allow the movement of hydrophilic compounds into their cell via β-barrel protein channels known as porins through which BLAs enter cells. Some bacteria possess the capacity to control the intracellular concentrations of various antibiotics by actively pumping them out of the cell using efflux pumps.

Pseudomonas aeruginosa exhibits multiple mechanisms of resistance and its regulation of porins and efflux pumps is widely studied. Porin, OprD (OccD1), the most investigated *Pseudomonas aeruginosa* porin, supports the entry of peptides and carbapenems. Open reading frame mutations as well as regulators control the expression of OprD. Physiologic stress and metal ions can negatively impact the expression of OprD resulting in porin loss and decreased intake of BLAs.
P. aeruginosa uses efflux pumps associated with resistance-nodulation-division (RND), multidrug and toxic compound extrusion (MATE), major facilitator superfamily (MFS), small multidrug resistance (SMR) and ATP-binding cassette (ABC) superfamilies of efflux pumps.

Target modification
BLAs depend on their affinity for PBP to be effective. Alteration of PBP target to PBP2a is a resistance mechanism utilized by *Staphylococcus aureus* which has 4 native PBPs (PBP1-PBP4) and a fifth PBP2a, encoded by the *mecA* gene. The source of *mecA* is not known. PBP2a has a low affinity for most BLAs, including penicillin, first to third generation cephalosporins and carbapenems. methicillin-resistant *Staphylococcus aureus* (MRSA) was first reported in 1961 in the UK. Today MRSA has been detected globally and is endemic in the U.S.A. Treatment options are limited to linezolid, daptomycin, ceftaroline, and vancomycin.

Fluoroquinolone antibiotics (FQAs)

DNA gyrase and topoisomerase are essential to bacterial replication, recombination, and DNA repair. These complex enzymes have two subunits each. DNA gyrase has subunits GyrA and GyrB. Topoisomerase IV has subunits ParC and ParE. Quinolones inhibit these enzymes causing relaxation of the supercoiled bacterial DNA, interfering with the gene expression and replication. The affinity of each fluoroquinolone to target enzymes vary by drug and organism. In Gram-negative bacteria, gyrase is more susceptible to inhibition by quinolones than is topoisomerase IV, whereas, in Gram-positive bacteria, topoisomerase IV is usually the primary target.

Resistance mechanisms
Quinolone resistance occurs primarily through the following mechanisms.

Target modification
Amino acid substitutions in the “quinolone-resistance—determining region” (QRDR) cause mutations in structural genes *gyrA, gyrB, parC* and *parE*. Mutations in *gyrA* and *parC* are far more common than *gyrB* and *parE*. Due to the relative affinity of each drug to its target, multiple QRDR mutations are usually needed to result in significant increases in the minimum inhibitory concentration.
Qnr genes are another method of resistance. These genes are chromosomal in Gram-positive organisms, in Gram-negative they are plasmid mediated. Qnr is a pentapeptide protein which binds to bacterial topoisomerase subunits inhibiting the action of quinolones. Plasmids containing *qnr* genes often also encode for ESBLs. *PMQR* genes have been found in *E. coli, Klebsiella* spp. and *Salmonella* spp.

Drug inactivating enzymes
Plasmid-mediated resistance via AAC(6')-Ib-cr encodes a variant aminoglycoside acetyltransferase. This is usually associated with the acetylation of aminoglycoside; however, it is also able to acetylate the amino

nitrogen of piperazinyl substituent of select fluoroquinolones. This causes only low-level resistance to ciprofloxacin and norfloxacin; levofloxacin is unaffected.

Efflux pumps

Overexpression of efflux pumps confers only low-level resistance to quinolones. In Gram-positive organisms like *S. aureus*, NorA, NorB or NorC MFS system overexpression is associated with increasing minimum inhibitory concentrations (MICs). NorA affects the efflux of hydrophilic fluoroquinolones i.e., norfloxacin, ciprofloxacin and enrofloxacin. In *Enterobacteriaceae*, AcrAB-TolC efflux pump (RND family) plays a significant role in quinolone efflux and has multiple controls. Plasmids may encode for efflux pumps QepA and OqxAB. QepA, a member of MFS transporters, can extrude hydrophilic fluoroquinolones. OqxAB is nonspecific and can extrude quinolones, trimethoprim, and chloramphenicol.

Aminoglycosides

Aminoglycoside antibiotics originated from the *Actinomycetales*, are broad-spectrum. Currently, there are more effective semi-synthetic versions available. These antibiotics synergize well with other antibiotic groups like β-lactams, particularly for combating multidrug-resistant (MDR) Gram-positive, Gram-negative, and tuberculosis strains. Some notable anti-pseudomonal members include amikacin, gentamicin, and tobramycin. Their mechanism involves irreversibly binding to the aminoacyl site (A-site) of the 16S rRNA component within the 30S ribosomal subunit, disrupting protein synthesis. Additionally, they impede the elongation of the nascent chain, affecting bacterial mRNA proofreading, altering membrane permeability, and enhancing drug uptake.

Resistance mechanisms

Three main resistance mechanisms exist for aminoglycoside globally.

Aminoglycoside modifying enzymes (AMEs)

There are three subclasses of these enzymes that work by modifying the acetyl and/or hydroxyl group of the drug, each at a different site as per their names: acetyltransferases (AACs), Aminoglycoside O-nucleotidyltransferases (ANTs) and Aminoglycoside O-phosphotransferases (APHs). Each subclass has variations in the enzymes that work on specific aminoglycosides and are produced at higher frequencies in particular bacteria resulting in over one hundred AMEs being noted globally (**Table 2**). Once modified the drug is unable to bind due to weaker affinity for their 30S ribosomal subunit binding site.

16S rRNA methyltransferase enzymes (RMTs)

First noted to be produced in *Streptomyces* spp., the genes for these enzymes are transferable to other organisms via integrons of plasmids and transposons as well as on chromosomes. These methylation enzymes reduce the ability of 16S rRNA within bacteria to bind with aminoglycosides. They can result in high-level resistance to the aminoglycosides. Currently, there are eleven known gene variations: *ArmA, RmtA, RmtB, RmtC, RmtD1, RmtD2, RmtE, RmtF, RmtG* and *RmtH* which all methylate the N7 position of nucleotide G1405 and *NpmA* and *NpmB* which methylate the N1 position of A1408. The prevalence of these genes is rising globally.

Efflux pumps

The resistance nodulation division (RND) family of efflux pumps includes but is not limited to; the AcrAD pump in several Gram-negatives, the MexXY-OprM pump in *Pseudomonas aeruginosa* and the AmrAB-OprA and BpeAB-OprB efflux pumps in *Burkholderia pseudomallei* are used to actively pump aminoglycosides out of cells.

Other 16S rRNA mutations

Whilst the cell wall structure of *Mycobacterium tuberculosis* naturally acts as a barrier to aminoglycosides, modifications to the permeability make them even more resistant. The aminoglycosides enter through porin channels, which organisms can in turn down-regulate.

A rare means of resistance to aminoglycosides can occur through mutations in the *rrs* gene that codes for 16S rRNA. This method may prove lethal to organisms but has been noted to occur in some strains of *Mycobacterium tuberculosis*.

Glycopeptide antibiotics (GPAS)

Glycopeptides are primarily used to treat serious infections caused by Gram-positive organisms as the outer membrane of Gram-negatives hinders the entrance of the GPAs. GPAs were also first discovered in the Actinomycetales. GPAs disrupt bacterial cell wall synthesis by binding to D-alanyl-D-alanine (D-Ala-D-Ala) terminuses of peptidoglycan building blocks, affecting the availability of this substrate during the cross-linking stage. This compromises cell wall integrity and causes the death of the organism. Vancomycin and teicoplanin were the first members of this class. Second-generation GPAs (include oritavancin, telavancin and dalbavancin), are known to be less toxic and less resistance prone. These were succeeded by the production of other semisynthetic products such as type-V GPAs such as complestatin and kistamicin. Notably, avoparcin and ristocetin GPAs used in animal husbandry are thought to have contributed to the emergence of vancomycin-resistant enterococci (VRE) in animals, subsequently becoming reservoirs for humans.

Resistance mechanisms

Acquired resistance

GPA resistance was first noted in enterococci (1987) and later spread to other Gram-positives such as Staphylococci (2002). GPA resistance results from diminishing the affinity of the antibiotic for its target by replacing the terminal D-Ala of peptidoglycan precursors with D-lactate (D-Ala- D-Lac which has one thousand times reduced affinity) or D-serine (D-Ala-D-Ser which has six times reduced affinity). The genes associated with resistance are termed *van* genes. Species with D-lac usually carry the *vanA, vanB*, (the two most clinically relevant), *vanD* and *vanM*. The operons responsible are found on plasmids and chromosomes. This group shows a high level of inducible resistance to both vancomycin and teicoplanin. The exception to this rule is *vanB* carrying enterococci which remain sensitive to teicoplanin and *vanD* which shows mid to high level resistance to vancomycin and low-level resistance to teicoplanin. The D-Ser group includes *vanC, vanE, vanG, vanL* (all found on bacterial chromosomes) and *vanN* (constitutive resistance gene found on plasmids in *E. faecium*). This group shows resistance to vancomycin only with *vanG* and *vanE* showing low level inducible resistance (MIC 8-32 ug/ml). *VanC*, which is found in motile Enterococcal species, shows constitutive non-inducible intrinsic low-level resistance.

Vancomycin-dependent enterococci are strains that have evolved to only produce D-ala-D-lac precursors for their cell walls, which can only be done in the presence of vancomycin (*in vivo* or *in vitro*).
Methicillin-resistant *Staphylococcus aureus* (MRSA) strains with reduced or intermediate resistance to vancomycin (VISA) developed due to overuse of the antibiotic in MRSA infections (vancomycin MIC 4-8 ug/ml for VISA). Vancomycin-resistant *Staphylococcus aureus* (VRSA) are MRSA strains which gained inducible vancomycin resistance through uptake of *vanA* genes on TN1548 plasmids from VRE (MIC ≥ 32 ug/ml). Heterogenous vancomycin intermediate *S. aureus* (hVISA) represents another group of staphylococci which when grown in culture have subpopulations with varying degrees of reduced susceptibility to vancomycin. Several species of coagulase-negative staphylococci have also shown vancomycin resistance (MIC ≥ 32 ug/ml), the mechanism of which is yet to be completely confirmed. The phenomenon of vancomycin tolerance in some strains of *Streptococcus pneumoniae* has resulted in treatment failure and the eminent threat of the emergence of resistant strains.

Macrolides and lincosamides

Although these antibiotics share similar modes of action, they are chemically distinct. Their spectrum of activity is primarily over Gram-positive organisms however the macrolides have some added activity for, intracellular organisms, Gram-negative cocci, and a few Gram-negative rods. Lincosamides may also have activity against protozoans. Both classes of bacteriostatic agents act on the 50S ribosomal subunit to reversibly block protein synthesis. Examples of macrolides include clarithromycin, dithromycin, erythromycin, and roxithromycin (14 membered lactone ring), azithromycin (15 membered ring) and josamycin, midecamycin, miocamycin, rokitamycin and spiramycin (16 membered ring). These agents have historically been employed to treat upper and lower respiratory tract infections inclusive of atypical pneumonias. Lincosamides include clindamycin and lincomycin which are devoid of lactone rings.

Resistance mechanisms

Target-site modification
Methylation of the 50S ribosomal target site results in resistance to macrolides, lincosamides and streptogramin B antibiotics (MLS_B phenotype). These enzymes attack the A2058 residue of the 23S component of the 50S ribosomal subunit and is encoded for by the erythromycin ribosome methylase or *erm* gene. These genes can be expressed constitutively or inducibly. There are many erm genes which have been categorized into 21 classes with 4 major classes as follows:

1. The *ermA* gene typically found in staphylococci, has a subset referred to as *ermTR* that has been detected in B-haemolytic streptococci.
2. The *ermC* also found in staphylococci.
3. The *ermB* in streptococci and enterococci
4. The *ermF* gene found in *Bacteroides* and other anaerobes.

Efflux
Active efflux of macrolides occurs using the ATP binding cassette (ABC) transporter superfamily or major facilitator (MFS) superfamily of pumps. The *msrA* gene along with other chromosomal genes work together to create fully functional ABC pumps in staphylococci. The production is induced by erythromycin and other

14 and 15 membered macrolides. Clindamycin is not affected by this pump. In Streptococci efflux pumps are encoded by the *mefA* gene.

Drug inactivation
The production of esterases and phosphotransferases in several enterobacteria causes resistance to erythromycin and other 14 and 15 membered macrolides. In staphylococci, the production of phosphotransferases by the *mphC* gene results in macrolide resistance. Where lincosamides are concerned, drug inactivation of lincomycin in staphylococci and *Enterococcus faecium* commonly occurs through production of nucleotidyltransferases encoded by *InuA*, and *InuB* genes, respectively. Clindamycin is however not affected.

Sulphonamides

Sulphonamides are a large group of agents that through several mechanisms of action produce a myriad of useful activities within the human body. Their broad-spectrum bacteriostatic effects on both Gram-positive and negative organisms occur through chemical mimicry or direct competitive inhibition of a co-substrate (p-aminobenzoic acid, p-ABA) of the bacterial enzyme dihydropteroate synthase (DHPS). DHPS is encoded by the bacterial *folP* gene and is used by bacteria in folate synthesis to produce their DNA. The incorporation of sulphonamides instead of p-ABA leads to unusable substrates and halts cell production.

Resistance mechanisms
Sulphonamide resistance is mediated through two main mechanisms.

Target modification
Target modification of the *folP* gene or acquisition of divergent codes for DHPS results in a newly formed DHPS enzyme that is used preferentially in the presence of sulphonamides.

Drug inactivation
Plasmid borne *sul* genes 1-4 is typically found in several of the more common Gram-negative pathogens such as *E. coli* and *Klebsiella pneumoniae*, as a part of multiple resistance gene clusters. Recent studies have shown the emergence of other inducible *sul* genes i.e., *sulX* (a flavin monooxygenase) and *sulR* (a flavin reductase) found in several actinobacteria. These are also capable of horizontal gene transfer.

Tetracyclines and glycylcyclines

Tetracycline antibiotics target and reversibly bind to the 16S rRNA of bacterial 30S ribosomal subunits, resulting in steric hindrance of the translation process of protein synthesis. The actinomycetes naturally produced the original batetracycline antibiotics (chlortetracycline, oxytetracycline, tetracyline and methyl-tetracycline) [26]. Newer semi-synthetic versions include methacycline, rolitetracycline, lymecycline, doxycycline and minocycline[26]. Two of the newest agents are omadacycline (a semisynthetic minocycline derivative) and eravacycline (a fully synthetic fluorocycline).

Tetracycline antibiotics are bacteriostatic broad-spectrum with the capacity to act on protozoan parasites as well as spirochaetes, obligate intracellular, Gram-positive, and Gram-negative bacteria. They are used in the treatment of pathogens associated with the genital, respiratory and gastrointestinal tracts.
The glycylcycline antibiotic class consists of the semisynthetic tetracycline-based agent Tigecycline. This agent has activity against several multidrug-resistant isolates such as MRSA, VRE, ESBL producers, carbapenem-resistant *Enterobacteriaceae* and MDR *Acinetobacter* spp. It is useful in skin and soft tissue, intrabdominal and respiratory tract illnesses.

Resistance mechanisms

Target modification
This mechanism is seen in organisms with low rRNA gene copy numbers such as *Propionibacterium acnes*, *Helicobacter pylori*, and *Streptococcus pneumoniae*. The mutation occurs at the Tet1 binding site. In *S. pneumoniae* reduced tigecycline susceptibility occurs because of the presence of a gene that encodes 16SrRNA methyltransferase.

Efflux
Over 30 different efflux pumps belonging to 7 distinct groups have been identified to differentially pump tetracyclines out of bacterial cells. They include members of the major facilitator superfamily (MFS) of transporters. Most commonly found are Tet(A) and Tet(B) which belong to group 1 and are harbored in Gram-negative organisms. Tet(K) and Tet(L), both group 2 pumps, are found in Gram-positives. Pumps from groups 3-7 are much rarer in clinical isolates. Of note, Tet(A) is the most efficient at extruding Tigecycline.

Drug inactivation
The *Tet(X)* gene confers the production of a flavin-dependent monooxygenase enzyme that can inactivate most if not all tetracyclines.

Ribosomal protection
Organisms such as *Campylobacter jejuni* and streptococcal spp. produce GTPases which provide tetracycline specific ribosomal protection proteins (RPPs), the most common of which are Tet(O) and Tet(M). The proteins work by directly preventing the binding of the drug to its target site whilst enhancing the binding of GTP/aa-tRNA based complexes to the target site. The translation step of protein synthesis therefore continues uninterrupted.

Intrinsic multidrug resistance mechanisms
Bacteria have the capacity to use a combination of intrinsic resistance mechanisms which usually assist with their normal function to evade the effects of several unrelated antibiotics, inclusive of tetracyclines. These non-drug-specific mechanisms include the repression or activation of regulatory genes, that control pumps and porins. Gram-negative bacteria use transcriptional activators that usually assist the organism when exposed to environmental stress (such as antibiotics) to regulate e.g., those from the AraC-family that includes MarA, RamA, SoxS, RobA and RarA. These activators when primed and overexpressed by stressors result in upregulation of efflux pumps that work against multiple different antibiotics. MarA also controls expression of the OmpF porin. Another example seen in *Acinetobacter baumannii* is the AdeRS-two component system

(AdeRS-TCS) regulator that controls the AdeABC major multidrug efflux pump which plays an active role in tigecycline resistance in these organisms.

Furadantoins

Nitrofurantoin is a bactericidal urinary bladder sterilant used as first-line therapy for uncomplicated infections with Gram-positive or Gram-negative pathogens. The mechanism of action of nitrofurantoin is so encompassing that resistance is relatively rare. Its reactive intermediate metabolites produced by bacterial nitroreductases, bind to bacterial ribosomes in such a way as to affect enzymes involved in DNA, RNA, protein, and cell wall synthesis. Resistance has been noted to occur through the production of mutated versions of nitroreductase; *nfsA* and *nfsB* genes are notably produced by some *E. coli* strains. Efflux pumps (via the acquired oqxAB system) or chromosomal mutations in the *ribE* gene have also been utilized for nitrofurantoin resistance.

Polymixins

Polymixins, cyclic lipopeptides, represent one of the last classes of antibiotics to have retained much usefulness against multidrug-resistant organisms, a status maintained due to limited use globally for fear of their capacity for nephro- and neuro- toxicity. They act on the Gram-negative pathogens by:

A. Binding to the lipid A component or domain of lipopolysaccharides (LPS) of the outer membrane (OM) resulting in membrane lysis.
B. Mediating contact between the inner and outer membranes leading to osmotic imbalance and cell lysis.
C. Cause accumulation of hydroxyl radicals resulting in oxidative damage to bacterial genetic material and lipids and death.

Resistance mechanisms

Target modification: of lipid A by addition of protective positively charged groups accomplished using the PhoP-PhoQ regulatory system (encoded by *phoP*) and modification of all three LPS domains by the PmrA-PmrB regulatory system (encoded by *pmrCAB*). High-level resistance to polymyxin E has been achieved in *Acinetobacter baumannii* strains that have lost LPS completely.

Multidrug efflux pumps: such as MexAB-OprM in *Pseudomonas aeruginosa*, the AcrAB efflux pump used by *Klebsiella pneumoniae* and *E. coli*, and the NorM pump in *Burkholderia* species.

Other mechanisms include the use of cationic OM proteins e.g., OmpA which bind to the drug neutralizing it. High level resistance to polymyxin E has been achieved in *Acinetobacter baumannii* species that have lost LPS completely.

Conclusion

Antibiotic resistance continues to be a major global concern. As the list of resistance phenotypes and genotypes to all classes continues to grow, the production of new antibiotic agents is slowly grinding to a halt.

New methods of controlling infections or limiting their spread need to be explored to limit reliance on antibiotic agents.

Table 1. Summary of major antibiotic classes, members, and resistance mechanisms.

Class	Examples	Major mechanisms of resistance	Comment
Beta-lactams	**Natural penicillins –** Benzylpenicillin (Penicillin G), Phenoxymethylpenicillin (Penicillin V) **Semisynthetic penicillins –** Oxacillin, Dicloxacillin, Flucloxacillin **Aminopenicillins –** Ampicillin, Amoxycillin **Mecillinam –** Pivmecillinam **Carboxypenicillins –** Carbenicillin, Ticarcillin **Ureidopenicillins –** Azlocillin, Mezlocillin, Piperacillin **1st generation cephalosporins –** Cefazolin, Cephalexin, Cefadroxil **2nd generation cephalosporins –** Cefuroxime, Cefoxitin, Cefotetan, Cefaclor, Cefprozil **3rd generation cephalosporins –** Ceftazidime, Cefotaxime, Ceftriaxone, Cefpodoxime, Cefixime, Cefdinir, Cefditoren, Ceftibuten **4th Generation cephalosporins –** Cefepime **5th Generation cephalosporins –** Ceftaroline, Ceftobiprole, Ceftolozane/Tazobactam **6th Generation cephalosporins –** Cefiderocol **Carbapenems –** Imipenem, Meropenem, Doripenem, Ertapenem **Aztreonam**	● Drug inactivation by enzymes: B-lactamases ● Target modification of penicillin-binding proteins (PBPs) ● Efflux pumps e.g., RND, MATE and ABC pumps ● Regulation of membrane permeability via porin loss.	Methicillin-resistant *Staphylococcus aureus* (MRSA) and Extended-spectrum β-lactamase (ESBL)-producing *Enterobacterales* are considered serious threats by the CDC whereas Carbapenem-resistant *Enterobacterales* (CRE) and Carbapenem-resistant *Acinetobacter* are urgent threats.
Glycopeptides	Vancomycin, Dalbavancin, Teicoplanin	• Target modification: D-Ala D-Lac	Vancomycin-resistant *Enterococcus* (VRE) is recognized by the CDC as a serious antimicrobial-resistant threat.
Aminoglycosides	Gentamicin, Tobramycin, Plazomicin, Amikacin	• Drug inactivation via enzymes: AAC, ANT, APH • Target modification by methyltransferases: e.g., ArmA RMTs • Efflux pumps e.g., AcrAD pump	Each group of resistance-inducing enzymes work on specific aminoglycosides and are found in specific bacteria.

(cont.)

Table 1. Summary of major antibiotic classes, members, and resistance mechanisms *(cont.)*

Class	Examples	Major mechanisms of resistance	Comment
Fluoroquinolones	Norfloxacin, Ciprofloxacin, Moxifloxacin	• Target modification: QRDR mutations. • Drug inactivation: (plasmid-mediated; variant aminoglycoside acetyltransferase). • Efflux pumps e.g., NorA pumps	High rates of fluoroquinolone resistance have been reported in uropathogens therefore members of this class are no longer considered first-line therapy in uncomplicated cystitis.
Macrolides and lincosamides	Clarithromycin, Azithromycin, Clindamycin	• Target modification: methylation if 50S ribosomal subunit, *erm* gene • Efflux pumps e.g., ABC transporter pumps • Drug inactivation via esterases and phosphotransferases	Of note, *in vitro* macrolide resistance does not always correlate to in vivo resistance which can cloud the interpretation of susceptibility testing.
Sulfonamides	Sulfamethoxazole/trimethoprim, Sulfasalazine, Sulfisoxazole	• Target modification: resistant forms of DHPS enzymes, mutations in *dhp* gene. • Drug inactivation e.g., plasmid-borne *sul* genes.	Resistance rates in this class have resulted in reduced use globally.
Tetracyclines and glycylcyclines	Tetracycline, Tigecycline	• Target modification resulting in ribosomal protection via Tet 1 mutation. • Efflux pump e.g., Tet(A). • Drug inactivation via flavin-dependent monooxygenase enzyme. • Ribosomal protection.	Synthetic variants to this class are in greater use/ demand due to both intrinsic and class-specific resistance patterns.
Polymixins	Polymixin B, Polymixin E	• Target modification: LPS domains • *Multidrug efflux pumps* • *Drug inactivation: OmpA*	This group remains one of the few active agents against multidrug-resistant isolates. However, the side effect profile means it is rarely used.
Furadantoins	Nitrofurantoin	• Target modification: reduced expression of nitroreductases via *nfsA* and *nfsB* genes. • Efflux pump overexpression e.g., oqxAB.	Resistance is uncommon.

Table 2. Common resistance genes and enzymes associated with aminoglycoside resistance.

Resistance mechanism	Genes		Enzymes	Comment
AMINOGLYCOSIDE MODIFYING ENZYMES				
N-Acetyl-transferases	AAC(2')	I	*aac(2')-Ia/b/c/d/e*	Part of a superfamily of proteins that use acetyl coenzyme A as the donor substrate to catalyze acetylation of NH2 groups of aminoglycosides.
	AAC(3)	I	*aac(3)-I/Ia/b/c/d/e/f/g/h/i/j*	
		II	*aac(3)-IIa/b/c/d/e*	
		IV	*aac(3)-IVa*	
		VI	*aac(3)-VIa*	
			aac(3)-IIIa/b/c/VIIa/VIIIa/IXa/Xa	
	AAC(6')	I	*aac(6')-Ia/i/l/q/ae/af/ai/30/33/aacA43*	
			aac(6')-Ic/f/g/h/j/k/r/s/t/u/v/w/x/y/z/aa/ad/aacA29	
		II	*aac(6')-I31/32/IIa/c*	
		unclassified	*aac(6')-Im*	
		unclassified	*aac(6')-aph(2'')*	
O-Nucleotidyl-transferases	ANT(2")	I	*ant(2'')-Ia*	Catalyzes transfer of AMP from ATP (donor substrate) from the hydroxyl group within aminoglycosides.
	ANT(3")	I	*aadA*	
	ANT(4')	I	*ant(4')-Ia/b/aadD*	
		II	*ant(4')-IIa/b*	
	ANT (6)	I	*ant(6)-Ia/b/str*	
	ANT (9)	I	*ant(9)-Ia/b*	
O-Phospho-transferases	APH(2")	I	*aph(2'')-Ib/c/d/e*	Catalyzes addition of phosphate group to aminoglycosides
			aac(6')-aph(2'')	
	APH(3')	I	*aph(3')-Ia/b/c/d*	
		II	*aph(3')-IIa/b/c*	
		III	*aph(3')-IIIa/III*	
		VI	*aph(3')-VIa/b*	
		VII	*aph(3')-VIIa*	
		XV	*aph(3')-XV*	
		unclassified	*aph(3')-IV/Va/b/c/VIII*	
	APH(3'')	I	*aph(3'')-Ia/b*	
	APH(4)	I	*aph(4)-Ia/b*	
	APH(6)	I	*aph(6)-Ia/b*	
			aph(6)-Ic/d	
	APH(7'')	I	*aph(7'')-Ia*	
	APH(9)	I	*aph(9)-Ia/b*	
METHYLTRANSFERASE ENZYMES				
16S rRNA methyltransferases	ARM	A	*armA*	Methylates the N7 position of nucleotide G1405
	RMT	A-H	*rmtA/B/C/D1/D2/E/F/G/H*	
	NPM	A	*npmA1* and *npmA2*	Methylates at the N1 position of A1408
		B	*npmB1* and *npmB2*	
		B	*npmB1* and *npmB2*	

Competing interests

The authors have no financial or non-financial competing interests to declare.

References

1. C Reygaert W. An overview of the antimicrobial resistance mechanisms of bacteria. AIMS Microbiol. 2018;4:482-501.
2. Uddin TM, et al. Antibiotic resistance in microbes: History, mechanisms, therapeutic strategies and future prospects. J Infect Public Health. 2021;14:1750-1766.
3. Neelanjana Pandey A, et al. B-Lactam Antibiotics Continuing Education Activity; 2024.
4. Tooke CL, et al. β-Lactamases and β-Lactamase Inhibitors in the 21st Century. J Mol Biol. 2019;431:3472-3500.
5. Bush K, et al. Updated functional classification of β-lactamases. Antimicrob Agents Chemother. 2010;54:969-976.
6. Sawa T, et al. Molecular diversity of extended-spectrum β-lactamases and carbapenemases, and antimicrobial resistance. J Intensive Care. 2020;8:13.
7. Wu W, et al. Antibiotic influx and efflux in Pseudomonas aeruginosa: Regulation and therapeutic implications. Microb Biotechnol. 2024;17:e14487.
8. Fishovitz J, et al. Penicillin-binding protein 2a of methicillin-resistant Staphylococcus aureus. IUBMB Life. 2014;66:572-577.
9. Mahasenan KV, et al. Conformational dynamics in penicillin-binding protein 2a of methicillin-resistant staphylococcus aureus, allosteric communication network and enablement of catalysis. J Am Chem Soc. 2017;139:2102-2110.
10. Blondeau JM. Fluoroquinolones: mechanism of action, classification, and development of resistance. Surv Ophthalmol. 2004;49:S73-S78.
11. Aldred KJ, et al. Mechanism of quinolone action and resistance. Biochemistry. 2014;53:1565-1574.
12. Jacoby GA, et al. Protective effect of qnr on agents other than quinolones that target DNA gyrase. Antimicrob Agents Chemother. 2015;59:6689-6695.
13. Jacoby GA, et al. Plasmid-Mediated Quinolone Resistance. Microbiol Spectr. 2014;2:10.1128/microbiolspec.PLAS-0006-2013.
14. Jacoby GA. Mechanisms of Resistance to Quinolones. Clin Infect Dis. 2005;41:S120-S126.
15. Jacoby GA, et al. Protective Effect of Qnr on Agents Other than Quinolones That Target DNA Gyrase. Antimicrob Agents Chemother. 2015;59:6689.
16. Garneau-Tsodikova S, et al. Mechanisms of resistance to aminoglycoside antibiotics: Overview and perspectives. Medchemcomm. 2016;7:11-27.
17. Zhang Y, et al. The prevalence and distribution of aminoglycoside resistance genes. Biosaf Health. 2023;5:14-20.
18. Kawai A, et al. Functional and Structural Characterization of Acquired 16S rRNA Methyltransferase NpmB1 Conferring Pan-Aminoglycoside Resistance. Antimicrob Agents Chemother. 2021;65:e0100921.
19. Yushchuk O, et al. Glycopeptide Antibiotic Resistance Genes: Distribution and Function in the Producer Actinomycetes. Front Microbiol. 2020;11:1173.
20. Sujatha S, et al. Glycopeptide resistance in gram-positive Cocci: A review. Interdiscip Perspect Infect Dis. 2012;2012:781679.
21. Spížek J, et al. Lincosamides: Chemical structure, biosynthesis, mechanism of action, resistance, and applications. Biochem Pharmacol. 2017;133:20-28.
22. Leclercq R. Mechanisms of resistance to macrolides and lincosamides: nature of the resistance elements and their clinical implications. Clin Infect Dis. 2002;34:482-492.

23. Ovung A, et al. Sulfonamide drugs: structure, antibacterial property, toxicity, and biophysical interactions. Biophys Rev. 2021;13:259-272.
24. Venkatesan M, et al. Molecular mechanism of plasmid-borne resistance to sulfonamide antibiotics. Nat Commun. 2023;14:4031.
25. Kim DW, et al. A novel sulfonamide resistance mechanism by two-component flavin-dependent monooxygenase system in sulfonamide-degrading actinobacteria. Environ Int. 2019;127:206-215.
26. Grossman TH. Tetracycline antibiotics and resistance. Cold Spring Harb Perspect Med. 2016;6:a025387.
27. Vallée M, et al. Exploring the in situ evolution of nitrofurantoin resistance in clinically derived uropathogenic Escherichia coli isolates. J Antimicrob Chemother. 2023;78:373-379.
28. Yu Z, et al. Antibacterial mechanisms of polymyxin and bacterial resistance. Biomed Res Int. 2015;2015:679109.

Chapter 68

Impact of antibiotics on gut microbiome and antimicrobial resistance

Ndege Daudi Ngere
AMR Now, Nairobi, Kenya.

Judith Asin
Ecumenical Pharmaceutical Network (EPN), Nairobi, Kenya.

Nelson Wachira Gichuki
Kisii University, Kisii, Kenya.

Introduction

Inappropriate antimicrobial use has been attributed as one of the main drivers of antimicrobial resistance (AMR), which is a global health concern. Antibiotics have been used for decades to prevent the spread of bacterial pathogens and thus treat bacterial infections. Nevertheless, the rate at which bacteria are developing virulence genes enabling them to resist these antibiotics is alarming. Recently, researchers have captured the attention of the effects of antibiotics on gut microbiome composition leading to perturbations. Accumulating evidence further shows that disturbance of the gut microbiome composition can have significant effects on health, which can also indirectly affect health in the long term such as gastrointestinal disorders, obesity, cardiovascular diseases, allergies, and central nervous system-related diseases. In this review, we give an overview of the gut microbiome development, its role in the host, how overuse of antibiotics impacts their composition, and finally how this contributes to AMR.

Gut microbiome

The gut microbiota is the mammalian gut microbial ecosystem and consists of trillions of bacteria, a substantial number of viruses of both eukaryotes and prokaryotes, archaea, and fungi. All these microbes co-exist with the host and have significant roles in the host functions including nutrient acquisition, metabolism, and immunity development, more importantly, they play a role in safeguarding the host from infections associated with exogenous pathogens or indigenous pathogens, and outgrowth that may result from dysbiosis. The whole normal gut microbial community typically behaves as commensals, also called commensal microbiota, actively contributing to the host's diverse functions.

Composition gut microbiome

The human gut microbiota refers to the microbes (bacteria, fungi, archaea, viruses, and protozoans) that reside inside the gut and contribute to several beneficial functions to the host, including fermentation of food items, synthesis of vitamins and amino-acids, prevention of colonization by enteropathogenic bacteria, maturation and regulation of the immune system, modulation of gastrointestinal (GIT) hormone release and regulation of brain-behavior.

Albeit "gut microbiota" perfectly refers to the microorganisms throughout the digestive tract, the term is usually used to indicate the colonic fecal microbiota, since the microorganisms at this site are common, most studied, and appear to have more significance to the host health. Therefore, gut microorganisms are associated with both the space inside the digestive tract, called the lumen, and the innermost layer of the digestive tract, called the mucosa. The microbial content of the gastrointestinal tract (GIT) varies significantly, ranging from a narrow diversity and low numbers of microbes in the esophagus and stomach to a wider diversity and high numbers in the colon.

Studies have shown that the gut microbiota of normal health individuals is populated with five major phyla. However, it is majorly dominated by *Bacteroidetes* and *Firmicutes*, whereas in minor proportions are: *Actinobacteria*, *Verrucomicrobia*, *Proteobacteria*, *Fusobacteria*, and *Cyanobacteria*. Additionally, gut microbiota varies in different anatomical parts of the GI tract. For instance, *Proteobacteria* such as *Enterobacteriaceae* are found in the small intestine but not the colon. Instead, *Bacteriodetes* such as *Bacteroidaceae*, *Prevotellaceae*, and *Rikenellaceae* are often found in the colon. Nevertheless, studies show many species are still unidentified because many cannot be cultured *in vitro*. Consequently, several studies have shown that, in healthy individuals, the gut microbiota has a symbiotic relationship with the host, where the host provides a stable habitat to the microbes while in return, microbes benefit the host in several physiological processes such as food digestion and absorption via production of hydrolytic enzymes and co-factor molecules such as vitamin production.

Antibiotics

Antibiotics are a class of medications used to treat bacterial infections by either killing the bacteria or inhibiting their growth. They play a crucial role in modern medicine by helping to combat a wide range of bacterial diseases and infections since their discovery. The first antibiotic, penicillin, was discovered by Alexander Fleming in 1928. This ground-breaking discovery revolutionized the treatment of bacterial infections and paved the way for the development of various classes of antibiotics. They have saved many millions of lives and placed the majority of infectious diseases that plagued human history for many centuries under control. Initially, on their introduction into clinical practice in the 1940s, antibiotics were extremely efficient in clearing pathogenic bacteria leading many to believe that infectious diseases would become a problem of the past and would be wiped out from all human populations eventually.

They are classified into various categories based on their chemical structure, mechanism of action, spectrum of activity, and whether they are bactericidal or bacteriostatic. Structurally, antibiotics are grouped into classes such as β-lactams, aminoglycosides, tetracyclines, macrolides, and sulfonamides. These classes correspond to distinct mechanisms of action, including inhibition of cell wall synthesis, protein synthesis, nucleic acid synthesis, or disruption of cell membrane function. Additionally, antibiotics vary in their spectrum of activity, with some targeting specific bacteria (narrow spectrum) and others effective against a broader range

of bacterial species (broad spectrum). Bactericidal antibiotics kill bacteria directly, while bacteriostatic antibiotics inhibit bacterial growth and rely on the host immune system to eradicate the pathogen.

Antibiotic mechanisms of action

Antibiotics exert their effects through various mechanisms of action. Different classes of antibiotics target different mechanisms, such as inhibiting cell wall synthesis, protein synthesis, nucleic acid synthesis, or metabolic pathways within bacterial cells. A significant number of antibiotics function by halting the synthesis of bacterial cell walls, known as β-lactam antibiotics. The process of bacterial cell wall production involves the assembly, transportation, and cross-linking of wall components, leading to structural changes in the bacterium and ultimately its demise—other antibiotics like aminoglycosides, chloramphenicol, erythromycin, and clindamycin target protein synthesis in bacteria. By exploiting differences in protein synthesis between bacterial and human cells, these antibiotics disrupt the production of new proteins and cells.
Moreover, antibiotics like polymyxin B and colistin interfere with the cell membrane's phospholipids in bacteria, compromising its integrity and causing cell death. Despite their effectiveness, these antibiotics can exhibit some toxicity toward human cells due to shared phospholipid structures. Sulfonamides act as competitive inhibitors of folic acid synthesis, a critical step in nucleic acid production, by mimicking a key intermediate compound. By competing with this compound for the enzyme responsible for folic acid conversion, sulfonamides hinder microbial growth without necessarily causing cell death. Lastly, rifampin disrupts bacterial ribonucleic acid (RNA) synthesis by binding to a specific subunit on the bacterial enzyme involved in RNA duplication. This antibiotic's higher affinity for the bacterial enzyme than the human counterpart ensures that therapeutic doses affect bacteria without harming human cells.

Pharmacokinetics and pharmacodynamics of antibiotics

Pharmacokinetics and pharmacodynamics are critical factors that significantly influence their duration and effectiveness. Pharmacokinetics refers to how the body absorbs, distributes, metabolizes, and excretes drugs like antibiotics. The absorption phase determines how quickly and completely the antibiotic enters the bloodstream after administration, impacting how soon therapeutic levels are reached. Distribution involves how the antibiotic spreads throughout the body, influenced by factors like tissue perfusion and drug binding to proteins or tissues, which can affect its concentration at the infection site. Metabolism and excretion determine how quickly the antibiotic is broken down and eliminated from the body, affecting its concentration over time. For instance, antibiotics metabolized by the liver may have different durations of action compared to those excreted through the kidneys.
Pharmacodynamics, on the other hand, deals with the relationship between drug concentration and its effect on bacteria. This includes parameters like the minimum inhibitory concentration (MIC), which is the lowest concentration of the antibiotic that inhibits bacterial growth, and the time above MIC, which measures how long the antibiotic concentration remains above this critical level. The efficacy of antibiotics often depends on maintaining concentrations above MIC for a sufficient duration to kill or inhibit bacterial growth effectively.
Therefore, antibiotics with favorable pharmacokinetic properties (such as high bioavailability and adequate tissue penetration) and pharmacodynamic characteristics (like a prolonged time above MIC relative to the

bacteria's growth rate) tend to have longer durations of action. These factors collectively determine the dosing regimen (frequency and amount) necessary to achieve therapeutic goals and optimize clinical outcomes in treating infections. Understanding PK/PD principles helps healthcare providers tailor antibiotic therapy to individual patients, ensuring effective treatment while minimizing the risk of resistance development and adverse effects.

Misuse & overuse of antibiotics

Antibiotics are powerful germ-fighting tools when used carefully and safely. But up to half of all antibiotic use isn't necessary. Overuse has led to antibacterial resistance. Bacteria adapt over time and become "super bacteria" or "superbugs." In addition, misuse and overuse are significant concerns that can have detrimental effects on the microbiome, which refers to the collective microbial inhabitants within the body. When antibiotics are used inappropriately, such as taking them for viral infections or not completing the prescribed course, it can lead to the development of antibiotic-resistant bacteria. This can occur as bacteria evolve mechanisms to survive the antibiotic onslaught. As a result, the balance of microbial communities within the body can be disrupted, leading to a decrease in beneficial bacteria and an overgrowth of harmful or antibiotic-resistant strains. Such disruptions in the microbiome can weaken the body's natural defenses, making individuals more susceptible to infections and other health issues. Therefore, it is crucial to use antibiotics judiciously and according to proper guidelines to minimize the negative impact on the microbiome and overall health.

Antibiotic residues

Antibiotic residues are the traces of antibiotics that remain in the tissues or products of animals or plants after they have been treated with antibiotics. Several antibiotic classes are extensively administered to food-producing animals, including tetracyclines, sulfonamides, fluoroquinolones, macrolides, lincosamides, aminoglycosides, beta-lactams, cephalosporins and can pose a serious health issue. For instance, antibiotic residues in milk are of great public health concern since milk is widely consumed by infants, youngsters, and adults throughout the globe. The long-term exposure to antibiotic residues in milk may result in an alteration of the drug resistance of the gut microbiome.

Antimicrobial resistance

Antimicrobial resistance develops when microorganisms adapt and grow in the presence of drugs used to treat and control infections. The development of resistance is linked to the frequency of antimicrobials used. Antimicrobial-resistant microorganisms can also share their ability to become resistant to other microorganisms that have not been exposed to antibiotics. Resistant bacteria can be found in food animals and food products used for consumption by humans. The overuse of antimicrobials elicits resistance in two ways; the emergence of point mutations and the acquisition of foreign resistance genes, which leads to alteration of the antimicrobial target and the degradation of the antimicrobial or reduction of the cell's internal antimicrobial concentration.

AMR is a One Health challenge; the health of people is connected to animals and their shared environment. Few replacement products are in development for the existing antimicrobials. Without harmonized and immediate action on a global scale, the world is heading towards a post-antibiotic era in which common infections could once again kill. AMR leads to increasing morbidity and mortality as well as resistant infections add considerable costs to the healthcare system. Globally, it is estimated that by 2050 about 10 million people will die annually from AMR-related causes and negative economic effects.
The mechanisms of AMR include:

1. Enzyme inactivation and modification.
2. Modification of the antibiotic's target site.
3. Overproduction of the target.
4. Replacement of the target site.
5. Efflux and reduced permeability.

Colonization of the gut microbiome

Colonization of the gut microbiome refers to the establishment and growth of diverse microorganisms within the gastrointestinal tract, shaping its composition and functionality. Colonization of the human gut with microbes begins immediately at birth. Upon passage through the birth canal, infants are exposed to a diverse microbial population. This is supported by existing evidence that the intestinal microbiota of infants and the vaginal microbiota of their mothers show similarities. Consequently, infants delivered through cesarean section are harbored with a microbiota characteristic of skin and dominated by taxa such as *Staphylococcus* and *Propionibacterium* spp., which is different compared with the vaginally delivered infants.
During the first year of life, the intestinal microbiota is still establishing itself. Nevertheless, past 2.5 years of age, the intestinal microbiota of children starts to resemble those of a young adult and stabilizes. This is correlated with a change in feeding habits from breast or formula-feeding to weaning and eventually introduction of solid food. Typically, the microbial composition of the mammalian intestine is relatively simple and varies widely between different individuals and also with time.
The variability in community composition is greater in this age group than for adults, which could be attributed to the greater range of morbidities associated with age and the subsequent use of medications to treat them. The ELDERMET consortium studied the microbiota of the elderly, finding a characteristic composition different from that of young adults, particularly in the proportions of *Bacteroides* spp. and *Clostridium* groups.
Both external and internal host-related factors influence microbial succession in the GIT. External factors include the environment’s microbial load, type of food eaten, and feeding habits. Internal factors include, but are not limited to, microbial interactions, intestinal pH, environmental temperature, physiological factors (such as peristalsis; and bile acids), host secretions and immune responses; and drug therapy. For instance, Yatsunenko *et al.* compared the bacterial species of fecal samples from individuals of different geographic origins (three populations from the United States and Malawi) and different ages (0-70 years). This study showed that adults have a much higher diversity of gut microbiota than in children.

Importance of gut microbiota

Metabolism

The gastrointestinal tract of humans digests about 85% of carbohydrates, 66–95% of proteins, and all fats. Studies have shown that gut bacteria can produce a variety of vitamins, synthesize all essential and nonessential amino acids, and carry out biotransformation of bile. In addition, the microbiome provides the significant biochemical pathways for the metabolism of nondigestible carbohydrates, including large polysaccharides, such as resistant starches, cellulose, hemicellulose, pectin, and gums; some oligosaccharides that escape digestion; unabsorbed sugars and alcohols from the diet; and host-derived mucins. This function leads to the recovery of energy and absorbable substrates for the host and ensures the supply of energy and nutrients for bacterial growth and proliferation.

Host protection and immune system development

Several studies suggest that the gut microbiome plays a diversified role in maintaining human health. Through strategies such as nutrient competition and the production of antimicrobial compounds called bacteriocins, it prevents colonization by pathogens. This is also called the barrier or competitive exclusion effect. The gut wall contains host cells that have attachment sites, which can be used by pathogenic bacteria to enter the epithelial cells. Studies have shown that non-pathogenic bacteria compete for these attachment sites in the border of the host's intestinal epithelial cells, hence preventing the attachment and consequently entry of pathogenic entero-bacteria into the epithelial cells. Additionally, due to competition of nutrients by the gut microbiota, they outcompete pathogenic bacteria for resources, by a sheer force of numbers.

Gut microbiome and diseases

Whereas microbiome existing research is largely concerned with "who is there" and "what are they doing" it is also important to also ask "what affects them". Perturbation of the gut microbiome's ecological homeostasis, commonly by antibiotics, can cause dysbiosis, and eventually cause and exacerbate diseases. Dysbiosis is an imbalance in bacterial composition, deviations in bacterial metabolic activities, or fluctuations in bacterial distribution within the gut. There are three types of dysbiosis:

1. Loss of beneficial bacteria.
2. Overgrowth of potentially pathogenic bacteria.
3. Loss of overall bacterial diversity.

The most common external perturbations to the microbiome are diet, medications (especially antibiotics), and, the environment. For example, dysbiosis by antibiotics can put an individual at risk for developing infections from an opportunistic pathogen, such as *Clostridium difficile*.

Studies from both animal and human models show that dysbiosis has been implicated in a wide range of diseases including inflammatory bowel disease (IBD), obesity, allergic disorders, Type 1 diabetes mellitus, autism, obesity, and colorectal cancer. Antibiotics thus impact the gut microbiota, causing rapid and reduced levels of bacterial variety and increases and decreases in the relative abundances. Other factors that can affect gut microbiome include genetics, environment, diet, lifestyle, and hormones.

Conclusion

Antimicrobial resistance (AMR) is a complex phenomenon that often develops as a result of the widespread use of antibiotics. One significant pathway through which AMR emerges is the disruption of the gut microbiota caused by antibiotics. These medications not only target harmful bacteria causing infections but also inadvertently impact the beneficial bacteria residing in our guts. As a consequence, certain bacteria in the gut may develop resistance mechanisms to survive the antibiotic onslaught, leading to the emergence of resistant strains. This resistance can then spread within the gut microbiota and potentially to other environments.

In hospital settings, where antibiotic use is common and infections are prevalent, the implications of AMR are profound. Resistant bacteria can colonize patients, leading to healthcare-associated infections that are difficult to treat. Moreover, these resistant pathogens can spread within healthcare facilities, posing a significant risk to vulnerable patients, especially those with compromised immune systems. Managing infections in hospitals becomes increasingly challenging as the pool of effective antibiotics diminishes due to the proliferation of resistant strains. This underscores the urgent need for judicious antibiotic use, infection prevention, and control measures, as well as the development of novel antimicrobial strategies to combat AMR in healthcare settings.

Competing interests

The authors have no financial and non-financial competing interests to declare.

References

1. Bull MJ, et al. Part 1: The Human Gut Microbiome in Health and Disease. Integr Med (Encinitas). 2014;13:17-22.
2. Adak A, et al. An insight into gut microbiota and its functionalities. Cell Mol Life Sci. 2019;76:473-493..
3. Aminov RI. The role of antibiotics and antibiotic resistance in nature. Environ Microbiol. 2009;11(12):2970-2988.
4. Britannica, The Editors of Encyclopaedia. "antibiotic". Encyclopedia Britannica. Available at: https://www.britannica.com/science/antibiotic. Last accessed: 16 May 2024.
5. K Jayalakshmi, et al. Review on antibiotic residues in animal products and its impact on environments and human health. J Entomol Zool Stud. 2017;5:1446-1451.
6. Hooper LV, et al. Interactions between the microbiota and the immune system. Science. 2012;336:1268-1273.
7. DeGruttola AK, et al. Current Understanding of Dysbiosis in Disease in Human and Animal Models. Inflamm Bowel Dis. 2016;22:1137-1150.
8. Clemente JC, et al. The impact of the gut microbiota on human health: an integrative view. Cell. 2012;148:1258-1270.
9. Schwartz DJ, et al. Understanding the impact of antibiotic perturbation on the human microbiome. Genome Med. 2020;12:82.

Chapter 69

Gut microbiota as reservoir of AMR

Mahdi Asghari Ozma
Tabriz University of Medical Sciences, Tabriz, Iran.

Hossein Samadi Kafil
Drug Applied Research Center, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.

Introduction

Antimicrobials have exerted a substantial influence on the field of medicine, although their capacity to function optimally is progressively being eroded by resistance. Antibiotic resistance arises from mutations in the target of antibiotics or the presence of genes that provide resistance to antibiotics. These genes are often situated on the mobile genetic elements and plasmids except for chromosomes in microbial populations and can be transferred vertically and horizontally. Pathogenic microorganisms that are capable of defying remedies may spread to the hosts' microbiomes, where the host is symptomless, under suitable circumstances. The gut is the major reserve of antibiotic-resistant bacteria and the gut microbiome is a complex and diversified bacterial community that assists the host in the processes of nutrient acquisition and disease prevention. Nevertheless, it should be noted that antibiotics may influence the mentioned ecosystem in terms of taxonomic and functional shifts, which in turn create permissive conditions for extending the presence of resistance genes in bacteria. Dysbiosis can result in an elevation in the abundance of antibiotic-resistance genes and promote the infiltration of resistant microbes into the bloodstream, urinary tract, and other bodily systems. Therefore, understanding the importance of the gut microbiome in diseases like allergic rhinitis and developing strategies to prevent or treat dysbiosis is extremely important.
Metagenomic investigation of the gut microbiota is greatly improving our understanding of antibiotic resistance. The study reveals a wide array of genes and plasmids that exhibit resistance to antibiotics and have the ability to be transmitted to other species within the gastrointestinal tract. Thus, understanding the microbiome in brokers of the context of diagnostics and treatments of various diseases is crucial, and the transfer and storage of antibiotic-resistance genes in the gastrointestinal tract must be evaluated. The current study discusses the gut's role as a reservoir for antimicrobial resistance, its ability to prevent colonization, and the potential consequences of disruptions in the microbiome leading to the colonization of drug-resistant pathogens.

Gut microbiota

The gut microbiota has a dramatic influence on the host's nutrition and gut development and acts as the host's first line of defense against pathogens so is central to both health and disease. Changes in gut microbiota are associated with problems such as vaginosis, obesity, inflammatory bowel disease (IBD), functional

bowel disorders, allergies, and other ailments. The establishment of the indigenous microbiota commences promptly following the rupture of the fetal membranes, with bacterial populations undergoing variations in response to food and host maturation. Thus, the first days of life are colonized with bacteria from the mother's birth canal, environment, and interactions. Vaginally born babies acquire microorganisms from the feces and vagina of the mother and the environment inside the mother's womb, while, on the other hand, cesarean-born babies acquire bacteria from the hospital environment, instruments, and surgeons. Factors such as preterm birth, cleanliness, and diet might impact the composition of the gut bacteria of newborns after they are born. The neonatal gastrointestinal microbiota initially consists of a limited number of species and lineages, but their diversity quickly expands throughout the first year. A significant number of indigenous bacteria cannot be cultured under laboratory conditions. Recently, advanced sequencing techniques have allowed for thorough documenting of the human microbiota, encompassing even the rare and uncultivable species. The whole 16SrRNA gene has been analyzed using traditional cloning and sequencing methods to characterize microbial communities in mucosal and fecal samples from three healthy individuals.

Environmental and lifestyle variables influence

Some of the factors affecting the occurrence of antibiotic resistance genes (ARGs) include the use of antibiotics, hygiene, illness, age, gender, diet, geographical origin, and gut probiotics. The totality of ARGs in the gut is referred to as gut resistome and the inherent resistome acts differently to varied dietary factors. So based on the present study, it is confirmed that the vegans present a lower degree of ARGs in their gut microbiota as compared to the vegetarians or non-vegetarians. Analysis of the findings also revealed that the levels of ARG are lower for consumers of dietary fiber. This correlation is likely due to the stimulation of obligatory anaerobic bacteria and the decrease in facultative anaerobes, which are frequently resistant to antibiotics and cause inflammation. Animal-derived diets may transfer a greater number of ARGs into the gastrointestinal tract compared to plant-based foods.

Speculative studies based on four age groups such as children of preschool age, schoolchildren, high school students, and adults have established that the rate of ARGs in the human gut microbiome rises in parallel to the age. More ARGs are also reported at maturity as compared to childhood and the number and the variety of reported ARGs are also higher in the maturity period. Similarities are observed in people of different age groups, normal youths, and elderly people. This means that some ARGs are part and parcel of the resistome that is present right from the time of conception up to death. These are traits that have developed over time due to the gradual build-up of antibiotic use, thus causing an increase in the presence of ARGs and bacteria that are antibiotic-resistant. Many of the factors affecting a host's age distribution of resistance genes are its health and nutrition levels, antibiotic intake, and living environment. In certain cases, these factors could even abate the development of age-related patterns.

Gender is a factor that affects the distribution of antibiotic prescriptions. Women tend to receive more antibiotic prescriptions than males. This may result in an increased risk of antimicrobial resistance for women. While there is no clear evidence that gender itself affects the occurrence of ARG, several factors like the kind of antibiotics employed, hormone changes, and reproductive status of the patients do influence gender differences.

It is established that many factors to do with the living environment have a great impact on the consumption of antibiotics as well as the levels of ARG. Such factors relate to; the physical environment in which the people live, workplace conditions, availability of housing and services, economic status, and hospital accessibility.

Rural people particularly the women and children who have close contact with poultry have higher counts of ARGs in their gut flora.

Genomic diagnostics of antimicrobial resistance

AMR has become one of the most dangerous global health problems as it weakens antibiotics' efficacy, prolongs illnesses, and increases costs and death rates. The conventional approaches to detect AMR include culture-based assays and susceptibility testing which are generally time-consuming and lack selectivity. With the availability of new diagnostic tools, these have proven to be more rapid and definitive in detecting AMR, especially through attempting to search for genetic markers that are associated with this resistance. AMR is a condition when bacteria are able to disable the antibiotics, most often through genes, detectable with the help of whole genome sequencing (WGS). It reported that common resistance strategies are enzymatic inactivation, where the bacteria synthesizes enzymes such as β-lactamases that degrade the antibiotics, efflux pumps where genes coded for proteins that expel the antibiotics out of the bacterial cells and modification of the targets where bacteria have mutations in genes encoding proteins target by the antibiotics and reduced permeability where the bacterial cell membrane alters and restrict antibiotics from accessing the bacterial cell.

Genomic diagnostic techniques include WGS, which offers a complete view of a bacterial genome and identifies both known and new resistance genes by comparing resistant and non-resistant strains; polymerase chain reaction (PCR) and quantitative PCR (qPCR), which quickly detect specific resistance genes with high sensitivity and can target multiple genes at once; metagenomics, which sequences the combined genomes of microbial communities in a sample and identifies resistance genes in complex microbiomes without the need to culture bacteria. Another method is Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-based diagnostics, which use CRISPR technology to detect specific DNA sequences associated with resistance, providing high accuracy and usability in point-of-care settings (**Table 1**).

Proteomic diagnostics of antimicrobial resistance

With the help of proteomics which uses various technological advancements, the understanding of global systems biology has improved significantly because of the capacity to analyze proteins of any living organism. Here, proteomics is very useful in defining the entire complement of proteins of an organism and is very important in understanding bacterial pathogenesis; as well as benefitting from other systems biology techniques. In this relatively new area, the study of infectious pathogens is done to ascertain protein concentrations, changes after synthesis, locations, relationships, and time-dependent changes. Far from being exhausted, the continuity of the construction of proteome technology improves proteomics' capacity to tackle large problems in microbiology.

Table 1. Genomics and proteomics methods for the detection of AMR.

Genomics methods	Proteomics methods
Whole Genome Sequencing (WGS)	Mass Spectrometry (MS)
Polymerase Chain Reaction (PCR)	Two-Dimensional Gel Electrophoresis (2D-GE)
Quantitative PCR (qPCR)	Liquid Chromatography-Mass Spectrometry (LC-MS)
Metagenomics	Matrix-Assisted Laser Desorption Ionization–Time of Flight (MALDI-TOF)
Comparative Genomics	Tandem Mass Tagging (TMT)
Microarray Analysis	Stable Isotope Labeling by Amino acids in Cell culture (SILAC)
Next-Generation Sequencing (NGS)	Enzyme-Linked Immunosorbent Assay (ELISA)
CRISPR-based Gene Editing	Western Blotting
Long-Read Sequencing	Shotgun Proteomics
RNA Sequencing (RNA-seq)	Surface-Enhanced Laser Desorption/Ionization (SELDI)

Different techniques are employed in proteomics research, and each is beneficial in some way. Most of the proteomic studies are based on mass spectrometry (MS) since it is a technique that enables the identification and quantification of proteins based on the mass-to-charge ratio of their peptide fragments. MS/MS gives information on the protein sequences and also modifications that may accrue after the protein has been translated. Two-dimensional gel electrophoresis (2-DE) checks for proteins based on their isoelectric point and molecular weights; it is particularly valuable for comparing many proteins at one time and for finding differences in expression due to conditions such as disease states. For improving the separation as well as identification of proteins in the different samples, both mass spectrometry and liquid chromatography are used together thereby forming what is known as LC-MS where HPLC and UPLC are used often. Therefore, including these techniques, scientists can solve important tasks of microbial investigation, including the study of bacterial resistance, the definition of pathogenic factors, and the identification of new therapeutic goals. Therefore, as proteomic technologies advance, they can become central to changing the paradigm of research on infectious diseases and possible interventions (**Figure 1**).

Microbiota-based defense against antimicrobial resistance

Due to the recent surge in the desire to manipulate the resistance of gut microbiota through the consumption of probiotics and FMT and its potential usefulness in the therapy of several diseases, it is vital to undergo a complete assessment before general use. It is important to maintain this careful balancing not to create new forms of antimicrobial resistance or other forms of risk that are yet to be followed. Probiotics, which are live microorganisms intended to confer health benefits, must meet specific criteria set by the food and agriculture organization. These criteria include rigorous safety assessments, including tests for antibiotic resistance, as well as meeting functional and technological requirements and desirable physiological characteristics. Commercial probiotics are typically derived from a limited range of bacteria and yeast, predominantly *Lactobacillus* spp. and *Bifidobacterium* spp.

FMT is done through endoscopic or oral routes where fresh fecal material from a donor is instilled in the patient by use of nasogastric, naso duodenal, enema, nasojejunal channels, or colonoscopy. Newer developments have seen the formulation of FMT in oral capsules and the bottles used seek to rebalance the gut with a stable and diverse population. Unlike probiotics, which contain a low level of bacteria, FMT introduces a

complex microbiota aimed at repopulating or replacing a disturbed native microbiota, which is very beneficial to health.

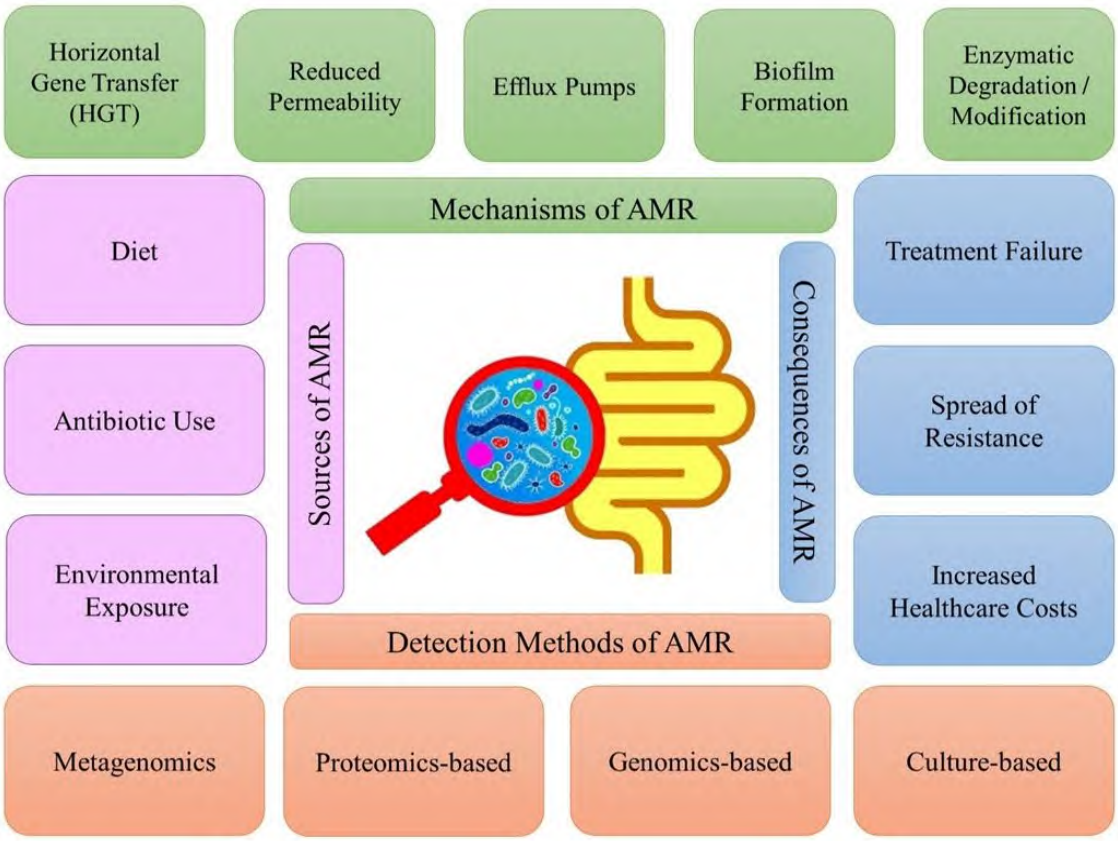

Figure 1. Investigation of the various aspects of mechanisms, sources, consequences and detection of AMR.

Conclusion

The vast and highly diverse and constantly changing microbiota of the human gastrointestinal tract is involved in metabolic, signaling and immunoregulatory processes and harbors a huge number of AMR genes. These genes can be transferred to other bacteria and the environment by commensal as well as pathogenic bacteria posing public health hazards. Three main methods help in addressing the issues of gut microbiome AMR prevalence, distribution, and source recognition, namely antibiotic susceptibility tests and functional meta-genomics. The newer techniques in genomic and proteomic analysis could potentially assist in locating and enumerating AMR genes and proteins within extensive epidemiological investigations. Foremost, it is crucial to comprehend the function of the gut microbiota and its association with AMR to create specific approaches for fighting resistant bacteria and preserving people's health.

Competing interests

The authors have no financial and non-financial competing interests to declare.

Acknowledgments

This study was supported by the Tabriz University of Medical Sciences with grant number 70277, and approved by the local ethics committee.

References

1. Ahmed SK, et al. Antimicrobial resistance: impacts, challenges, and future prospects. Journal of Medicine, Surgery, and Public Health. 2024;2:100081.
2. Bialvaei AZ, et al. Current methods for the identification of carbapenemases. J Chemother. 2016;28:1-19.
3. Partridge SR, et al. Mobile genetic elements associated with antimicrobial resistance. Clin Microbiol Rev. 2018;31:10.1128/cmr. 00088-17.
4. Leylabadlo HE, et al. Dissemination of carbapenemases producing Gram negative bacteria in the Middle East. Iran J Microbiol. 2015;7:226.
5. González R, et al. The interplay between the host microbiome and pathogenic viral infections. MBio. 2021;12:e02496-21.
6. Baquero F, et al. Evolutionary pathways and trajectories in antibiotic resistance. Clin Microbiol Rev. 2021;34:e00050-19.
7. Hu T, et al. Pathogenesis of children's allergic diseases: refocusing the role of the gut microbiota. Front Physiol. 2021;12:749544.
8. Hu Y, et al. Metagenome-wide analysis of antibiotic resistance genes in a large cohort of human gut microbiota. Nat Commun. 2013;4:2151.
9. Schlaberg R. Microbiome diagnostics. Clin Chem. 2020;66:68-76.
10. Flint HJ, et al. The role of the gut microbiota in nutrition and health. Nat Rev Gastroenterol Hepatol. 2012;9:577-589.
11. Gholizadeh P, et al. Role of oral microbiome on oral cancers, a review. Biomed Pharmacother. 2016;84:552-558.
12. Nagpal R, et al. Gut microbiota in health and disease: an overview focused on metabolic inflammation. Benef microbes. 2016;7:181-194.
13. Gholizadeh P, et al. Microbial balance in the intestinal microbiota and its association with diabetes, obesity and allergic disease. Microb Pathog. 2019;127:48-55.
14. Feizi H, et al. Gut microbiota and colorectal cancer risk factors. Curr Pharm Biotechnol. 2022;5:138920102366622100510334O.
15. Moya-Alvarez V, et al. Understanding the pathways leading to gut dysbiosis and enteric environmental dysfunction in infants: the influence of maternal dysbiosis and other microbiota determinants during early life. FEMS Microbiol Rev. 2022;46:fuac004.
16. Hajiagha MN, et al. Gut Microbiota and Human Body Interactions; Its Impact on Health: A Review. Curr Pharm Biotechnol. 2022;23:4-14.
17. Pantazi AC, et al. Development of gut microbiota in the first 1000 days after birth and potential interventions. Nutrients. 2023;15:3647.
18. Memar MY, et al. Immunologic biomarkers for diagnostic of early-onset neonatal sepsis. J Matern Fetal Neonatal Med. 2019;32:143-153.
19. Kim JE, et al. Microbial diversity and metabolic function in duodenum, jejunum and ileum of emu (Dromaius novaehollandiae). Sci Rep. 2023;13:4488.
20. Zavišić G, et al. Antibiotic resistance and probiotics: knowledge gaps, market overview and preliminary screening. Antibiotics. 2023;12:1281.
21. Behounek M. Differential Effects of Protein Isolates on the Gut Microbiome under High and Low Fiber Conditions. 2022.

22. Palleja A, et al. Recovery of gut microbiota of healthy adults following antibiotic exposure. Nat Microbiol. 2018;3:1255-1265.
23. Gibson MK, et al. Developmental dynamics of the preterm infant gut microbiota and antibiotic resistome. Nat Microbiol. 2016;1:1-10.
24. Schröder W, et al. Gender differences in antibiotic prescribing in the community: a systematic review and meta-analysis. J Antimicrob Chem. 2016;71:1800-1806.
25. Xie J, et al. Seasonal disparities in airborne bacteria and associated antibiotic resistance genes in PM2. 5 between urban and rural sites. Environmental Science & Technology Letters. 2018;5:74-79.
26. Tang KWK, et al. Antimicrobial resistance (AMR). Br J Biomed Sci. 2023;80:11387.
27. Avershina E, et al. Clinical Diagnostics of Bacterial Infections and Their Resistance to Antibiotics—Current State and Whole Genome Sequencing Implementation Perspectives. Antibiotics. 2023;12:781.
28. Alfei S, et al. β-lactam antibiotics and β-lactamase enzymes inhibitors, part 2: our limited resources. Pharmaceuticals. 2022;15:476.
29. Chen C, et al. Integrating CRISPR-enabled trackable genome engineering and transcriptomic analysis of global regulators for antibiotic resistance selection and identification in Escherichia coli. Msystems. 2020;5:10.1128/msystems. 00232-20.
30. Ozma MA, et al. Induction of proteome changes involved in biofilm formation of Enterococcus faecalis in response to gentamicin. Microb Pathog. 2021;157:105003.
31. Asghari Ozma M, et al. Application of Proteomics in Medical Bacteriology with Emphasis on Proteomic Analysis of Postbiotics. Medical Journal of Mashhad University of Medical Sciences. 2024;67.
32. de Souza N, et al. Mass spectrometry analysis of the structural proteome. Curr Opin Struct Biol. 2020;60:57-65.
33. Ozma MA, et al. Bacterial proteomics and its application in pathogenesis studies. Curr Pharm Biotechnol. 2022;23:1245-1256.
34. Zhao Y-Y, et al. UPLC–MSE application in disease biomarker discovery: the discoveries in proteomics to metabolomics. Chem Biol Interact. 2014;215:7-16.
35. Ozma MA, et al. A critical review of novel antibiotic resistance prevention approaches with a focus on postbiotics. Crit Rev Food Sci Nutr. 2023:1-19.
36. Ozma MA, et al. Postbiotics as the key mediators of the gut microbiota-host interactions. Le Infezioni in Medicina. 2022;30:180.
37. Merrick B, et al. Modulation of the gut microbiota to control antimicrobial resistance (AMR)—a narrative review with a focus on faecal microbiota transplantation (FMT). Infect Dis Rep. 2023;15:238-254.

Chapter 70

Challenges and opportunities for incentivising antimicrobial research

Daniela Zinzi
REVIVE Advancing Antimicrobial R&D Expert;
External Expert Evaluator at European Commission.

Introduction

Antimicrobial resistance (AMR) is a global health crisis of alarming proportions, casting shadows over the progress in medicine and public health. The rise of drug-resistant pathogens, fuelled by misuse of antibiotics, impacted 4.95 million deaths associated with resistant bacteria in 2019. This silent pandemic undermines our ability to effectively treat infections, and strains healthcare systems worldwide. A recent study has predicted that more than 39 million people would die by 2050 in the absence of stronger One Health actions supporting antimicrobials development. Based on these findings, the World Health Organization (WHO) has identified AMR as one of the top 10 global health threats, underscoring the urgent need for action.

The burden of AMR is not evenly distributed, with low- and middle-income countries (LMICs) bearing the brunt of its impact. In these regions, AMR exacerbates existing health inequities and contributes to a disproportionate number of deaths. The human cost of AMR cannot be separated by related economic consequences, with a potential loss of > $100 trillion to the global economy by 2050.

The high cost of research and development, associated with elevated failure rates, the limited market size for new antibiotics, and the slow clinical uptake of novel drugs, have stifled investment in this field, leaving the pipeline of novel drugs alarmingly thin. Discovery and development of new agents requires appropriate financial support. Currently, expertise resides mainly in small and mid-enterprises (SMEs), that struggle to find more streamlined paths of development and approval of novel molecules, to demonstrate effectiveness against pathogens with acquired or intrinsic resistance to available antimicrobials. The WHO report on antibacterials in clinical development reveals that only 1.2 new antibacterials/year received market approval in the past 12 years, highlighting the slow pace of progress in this area. The need for solutions to revamp the antibacterial pipeline and acceptable reimbursement models for product commercialization, ensuring the sustainability of research and development, and, finally, access, is huge.

The COVID-19 pandemic has further exposed the fragility of healthcare systems exacerbating the AMR crisis through the inappropriate use of antibiotics.

By understanding the current landscape and examining potential solutions, we can envision a path towards a more sustainable and equitable future where effective antimicrobials are available to all who need them.

The Complex landscape of antimicrobial research and development

The path to developing new antimicrobials is fraught with challenges, spanning scientific, regulatory, and economic domains. The scientific complexities of identifying novel targets and overcoming resistance mechanisms are compounded by stringent regulatory requirements and the economic realities of the market. These hurdles have contributed to a dwindling pipeline of new antimicrobials, leaving us increasingly vulnerable to the threat of untreatable infections.

Scientific challenges in antimicrobial discovery

The discovery of new antibiotics is a scientifically intricate process. Identifying novel targets that are unique to pathogens and do not harm human cells is a major hurdle. The development of new antifungal treatments also faces significant scientific challenges, as it is difficult to find candidate treatments that are both effective and well-tolerated by humans due to the close relationship between fungal and human cells. Additionally, the remarkable ability of some species to rapidly develop resistance mechanisms further complicates the discovery process. The high attrition rate in antimicrobial Research and Development (R&D), with a very low estimated success rate of antimicrobial candidates reaching the patient's bedside, highlights the difficulty of this endeavor. New paradigms supporting the development and approval of innovative approaches, like the potential use of bacteriophages to treat multidrug-resistant infections, are under discussion and mostly needed.

Regulatory and economic hurdles

Beyond the scientific challenges, the development of new antimicrobials is hindered by a complex regulatory landscape and economic realities. The traditional regulatory pathway, with its requirement for large-scale phase III clinical trials, often proves to be a major obstacle, particularly when dealing with specific challenging pathogens or emerging resistance patterns. The need for extensive clinical data and the challenges associated with enrolling patients targeting difficult-to-treat infections due to multi-drug-resistant pathogens can significantly prolong development timelines and escalate costs, and, at the same time, requires agreement with Regulatory agencies on innovative and more streamlined development paths, in order to speed up approval and access to selected patients' populations. The O'Neill report estimates that over 80% of the costs of bringing an antibiotic to market are related to clinical trials.

The economic landscape for antimicrobials is equally daunting. The low return on investment, coupled with the availability of cheaper generic alternatives, has led to a decline in investment from large pharmaceutical companies. Smaller companies and biotech firms, while crucial for innovation, often struggle to secure the necessary funding and navigate the complex regulatory pathways. The misalignment between the societal value of antimicrobials and their market value further exacerbates the economic challenges, faced by companies investing in antimicrobial R&D.

Evolving regulatory pathways

Recognizing the need for change, regulatory agencies such as the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) have introduced tiered frameworks that offer more flexible pathways for antimicrobial development. These frameworks leverage the predictive power of pharmacokinetics/pharmacodynamics (PK/PD) data and allow for smaller, more focused clinical trials, particularly for agents targeting specific pathogens or resistance mechanisms. While these tiered approaches offer a promising avenue for accelerating antimicrobial development, they also present challenges. The (FDA has launched the Limited Population Pathway for Antibacterial and Antifungal Drugs - the LPAD Pathway – "a tool to help with the

approval of antibacterial and antifungal drugs to treat serious and life-threatening infections in a limited population of patients with unmet needs". The LPAD supports approval based on limited, however strong evidence, in the selected limited population for whom the Agency determined a positive benefit/risk assessment. The WHO policy brief acknowledges the need for further support in moving forward non-traditional agents and recommends that regulators cooperate with developers to explore how current clinical trials can support their final approval.

The imperative of incentivization

The complex landscape of antimicrobial R&D necessitates a multifaceted approach to incentivization. Push and pull mechanisms, coupled with streamlined regulatory pathways and innovative funding models, are essential to stimulate investment, foster innovation, and ensure the timely development and delivery of new antimicrobials. By addressing the scientific, regulatory, and economic challenges, we can revitalize the antibiotic pipeline and mitigate the devastating impact of AMR on global health. It is worth emphasising the need for cross-disciplinary and multi-sector collaborations to develop effective solutions to minimize AMR, highlighting the importance of a holistic approach that goes beyond just financial incentives.

Push incentives: catalyzing early-stage research

The high-risk, high-cost nature of antimicrobial R&D necessitates substantial upfront investment to de-risk early-stage research and incentivize innovation. Push incentives, which provide direct funding and support to researchers and developers, are crucial in overcoming the financial and scientific barriers that impede the discovery and development of new antimicrobials.

Understanding push incentives

Push incentives operate by providing upfront financial and technical support to researchers and developers, enabling them to pursue promising projects that might otherwise be deemed too risky or commercially unattractive. These incentives can take various forms, including direct research grants, public-private partnerships, and tax credits. By de-risking early-stage research, push incentives can attract investment, stimulate innovation, and ultimately expand the pipeline of new antimicrobials.

Exploring push mechanisms

- **Direct research grants and public funding**. Governments and philanthropic organizations play a crucial role in supporting basic research, target discovery, and preclinical development through direct research grants. Initiatives such as the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) program, which has provided consistent funding to accelerate the development of new antibiotics, exemplify the impact of such grants[14]. The US Government, through agencies like the National Institutes of Health (NIH) and the Biomedical Advanced Research and Development Authority (BARDA), has also been a major contributor to AMR-related research. However, as highlighted in Walsh *et al.*, the allocation of funds specifically for AMR remains relatively low compared to other areas like cancer research. This disparity in funding allocation underscores the need for increased public investment in AMR research to address the growing threat of drug-resistant infections.
- **Tax credits and other fiscal incentives**. Tax breaks and other fiscal measures can incentivize private sector investment in antimicrobial R&D by reducing the financial burden and increasing the potential return on

investment. These incentives can be particularly attractive to SMEs (Small and Medium Enterprises), which often play a crucial role in early-stage innovation but may lack the resources of larger pharmaceutical companies. Clancy and Nguyen emphasize the importance of such incentives in attracting private investment and fostering a sustainable pipeline of new antimicrobials.

- **Public-private partnerships**. Collaborations between public and private entities, such as the Innovative Medicines Initiative (IMI), can leverage resources and expertise to accelerate early-stage research. The IMI's New Drugs for Bad Bugs (ND4BB) program, for example, has supported the development of several new antibiotics by fostering collaboration between academia, industry, and regulatory agencies. Such partnerships can help bridge the gap between basic research and clinical development, facilitating the translation of promising discoveries into new treatments.

Success stories and lessons learned

Several push initiatives have demonstrated success in advancing the antimicrobial pipeline. The CARB-X program, for instance, has supported the development of a diverse range of new antibiotics, including novel classes and agents targeting multidrug-resistant pathogens. The ND4BB program has also facilitated the development of several promising new antibiotics, highlighting the value of public-private partnerships in this field. These success stories underscore the importance of sustained investment in early-stage research and the need for flexible and collaborative funding models. The AMR Action Fund is the world’s largest public-private partnership investing in the development of new antimicrobial therapeutics, with the goal to provide at least 2 new effective antimicrobials by 2030.

Addressing challenges and limitations

While push incentives are essential, they are not without their challenges. The difficulty in selecting promising projects, the potential for crowding out private investment, and the need for long-term sustainability are all important considerations. As Clancy and Nguyen point out, push incentives alone may not be sufficient to address the fundamental market failures in the antibiotic market. They must be complemented by pull incentives, which create a suitable market for new antibiotics, and by efforts to address the regulatory and scientific hurdles that impede progress.

The importance of a balanced approach

A balanced approach that combines push and pull incentives, along with streamlined regulatory pathways and a focus on global collaboration, is essential to revitalize the antimicrobial pipeline and effectively combat the growing threat of AMR. By supporting early-stage research, fostering innovation, and enabling industry to retain a focus on developing innovative AMR solutions, we can ensure that future generations have access to the life-saving treatments they need.

Pull incentives: creating a viable market

While push incentives are essential for catalyzing early-stage research, they alone cannot address the economic challenges that hinder the development and commercialization of new antimicrobials. Pull incentives, which create a viable market for new antimicrobials by providing financial rewards for successful development and market entry, are crucial in bridging this gap.

Understanding pull incentives

Pull incentives operate by creating a market for new antimicrobials, ensuring that developers can recoup their investments and generate a reasonable return. These incentives can take various forms, including market entry rewards, transferable exclusivity vouchers, and subscription models. By addressing the economic disincentives associated with antimicrobial development, pull incentives can attract investment, encourage innovation, and ultimately ensure that new and effective treatments reach patients in need.

Exploring pull mechanisms

- **Market entry rewards**. These rewards, such as lump-sum payments or extended market exclusivity, provide a direct financial incentive for companies to bring new antimicrobials to market. The DISARM (Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms) and the PASTEUR (Pioneering Antimicrobial Subscriptions to End Upsurging Resistance) Act, proposed in the US, aim to stimulate the Federal Government's and industry's development and use of new antimicrobials.
- **Transferable exclusivity vouchers**. These vouchers, which grant additional market exclusivity for another product, can incentivize antimicrobial development by providing a valuable asset that can be sold or used to extend the market life of a profitable drug. While this mechanism does not directly address the economic challenges of antimicrobial development, it can provide a significant financial incentive for companies to invest in this area.
- **Subscription models**. Subscription-based payment models, where governments or healthcare systems pay a fixed fee for access to new antimicrobials, delink revenue from sales volume and ensure a sustainable market. Pilot programs in the UK and Sweden have explored this approach, demonstrating its potential to incentivize development and ensure access to new antibiotics.

Global pull mechanisms and access

The global nature of the AMR crisis necessitates the development of pull mechanisms that incentivize the development of antimicrobials that address the needs of LMICs. These mechanisms should ensure equitable access to new treatments, particularly for vulnerable populations disproportionately affected by AMR. Okeke *et al.* highlight the urgent need for such global pull mechanisms to address the inequities in access to effective antimicrobials.

Pull incentives offer a promising solution for revitalizing the antimicrobial market and ensuring the development of new and effective treatments. However, concerns about the impact on drug pricing and affordability, as well as the potential for unintended consequences such as over-prescription, must be carefully considered, besides their potential and effectiveness in attracting investment and fostering innovation.

A balanced approach to incentivization

Push and pull incentives are complementary and essential components of a comprehensive strategy to incentivize antimicrobial research and development. By combining these mechanisms with streamlined regulatory pathways and a focus on global collaboration, we can create a sustainable and effective ecosystem that fosters innovation, ensures access, and ultimately combats the growing threat of AMR.

The value of new antimicrobials

While the economic challenges of antimicrobial development are undeniable, the value of new antimicrobials extends far beyond their market price, including the potential benefits of new antimicrobials in reducing AMR and improving patient outcomes. The diversified use of a new antibiotic could lead to a significant reduction

in antimicrobial resistance (12.8% *vs.* 16.1%) and an increase in quality-adjusted life years (QALYs) at both the patient and population levels. These findings underscore the societal value of new antimicrobials and highlight the need for pull incentives that recognize and reward this value.

The global context: fostering collaboration and access

The interconnectedness of the modern world, coupled with the ease with which microbes traverse borders, underlines the global nature of the AMR crisis. No single nation can effectively combat AMR in isolation; a concerted, collaborative effort is required to address this shared threat. International cooperation, equitable access to antimicrobials, and a focus on vulnerable populations are all critical components of a comprehensive strategy to mitigate the impact of AMR.

The imperative of global collaboration

The global spread of AMR necessitates a coordinated response that transcends national boundaries. Walsh *et al.* emphasize the importance of international collaboration in tackling this challenge, highlighting the need for shared knowledge, resources, and best practices. The One Health approach, which recognizes the interconnectedness of human, animal, and environmental health, is crucial in understanding and addressing the complex dynamics of AMR transmission.

Coordinating global efforts

International organizations, such as the WHO and the Global AMR R&D Hub, play a pivotal role in coordinating research efforts, setting global priorities, and promoting equitable access to new antimicrobials. The WHO's Global Antimicrobial Resistance and Use Surveillance System (GLASS) provides a platform for harmonized reporting and sharing of AMR data, enabling countries to track trends and identify emerging threats. However, as highlighted in the Mapping Antimicrobial Resistance and Antimicrobial Use Partnership report, significant gaps in surveillance data persist, particularly in LMICs, hindering effective interventions.

Innovative financing and partnerships

Innovative financing mechanisms, such as the AMR Action Fund, are crucial in bridging the funding gap and supporting global antimicrobial development. Public-private partnerships, like the Global Antibiotic Research and Development Partnership (GARDP), can also leverage resources and expertise to accelerate R&D and ensure that new treatments reach those who need them most.

Addressing gender and equity

The impact of AMR is not evenly distributed, with women and other marginalized groups often facing greater vulnerabilities and barriers to accessing healthcare. Gender norms, roles, and relations can influence exposure and susceptibility to infections, health-seeking behaviors, and access to treatment. As highlighted in the WHO guidance document "Addressing gender inequalities in National Action Plans on Antimicrobial Resistance," integrating gender considerations into AMR research, access, and policy-making is essential to ensure equitable and effective interventions.

A collective responsibility

Combating AMR is a collective responsibility that demands a global, collaborative effort. By fostering international cooperation, promoting equitable access to antimicrobials, and addressing the underlying social and

economic factors that contribute to the spread of resistance, we can mitigate the impact of this global health crisis and protect future generations.

Conclusion

The complexities of antimicrobial research and development, coupled with market failures and inadequate investment, have created a critical need for innovative solutions to incentivize the discovery and delivery of new and effective treatments.

This chapter has explored the multifaceted challenges and opportunities in incentivizing antimicrobial research, including the scientific complexities of drug discovery, the intricate regulatory pathways, and the economic disincentives that have led to a decline in investment from large pharmaceutical companies. The current antimicrobial pipeline is worryingly sparse, with few novel drugs in development to combat the rising tide of resistance. This innovation gap has serious consequences, particularly for vulnerable populations who bear a disproportionate burden of AMR.

The role of push and pull incentives in stimulating antimicrobial innovation has been discussed as well. Push incentives, such as direct research grants and public-private partnerships, are essential for de-risking early-stage research and fostering a robust pipeline of potential new drugs. Pull incentives, such as market entry rewards and subscription models, are equally crucial in creating a viable market for new antimicrobials and ensuring that they reach patients in need.

However, incentivization alone is not enough. Addressing the regulatory and scientific hurdles that impede antimicrobial development is equally important. Streamlining regulatory pathways, promoting innovative trial designs, and fostering international collaboration are all critical components of a comprehensive strategy to combat AMR. The global nature of the AMR crisis necessitates a coordinated response that transcends national boundaries.

Furthermore, addressing the socioeconomic and gendered dimensions of AMR is imperative. The WHO has emphasized the need to consider the differential vulnerabilities and barriers to accessing healthcare faced by marginalized groups.

The development of new antimicrobials is not merely an economic endeavor; it is a moral imperative to safeguard global health and ensure a sustainable future for all.

To date, the lessons learned from the AMR crisis are more relevant than ever. The need for a proactive, collaborative, and equitable approach to global health challenges is clear. By investing in antimicrobial research and development, we are not only combating the immediate threat of drug-resistant infections but also building a more resilient and sustainable healthcare system for the future. The time to act is now!

Competing interests

Vice President, Clinical R&D at F2G, Manchester, United Kingdom.

References

1. Okeke IN, et al. The scope of the antimicrobial resistance challenge. Lancet. 2024;403:2426-2438. Erratum in: Lancet. 2024;404:1018.
2. Mohsen N, et al. Global burden of bacterial antimicrobial resistance 1990–2021: a systematic analysis with forecasts to 2050. Lancet. Published online September 16, 2024.
3. World Health Organization. Available at: https://www.who.int/news-room/spotlight/ten-threats-to-global-health-in-2019. Last accessed: 19 September 2024.
4. Walsh TR, et al. Antimicrobial Resistance: Addressing a Global Threat to Humanity. PLoS Med. 2023;20:e1004264.
5. Mendelson M, et al. Ensuring progress on sustainable access to effective antibiotics at the 2024 UN General Assembly: a target-based approach. Lancet. 2024;403:2551-2564.
6. Clancy CJ, et al. Buying Time: The AMR Action Fund and the State of Antibiotic Development in the United States 2020. Open Forum Infect Dis. 2020;7:ofaa464.
7. Gigante V, et al. Multi-year analysis of the global preclinical antibacterial pipeline: trends and gaps. Antimicrob Agents Chemother. 2024;68:e0053524.
8. Nandi A, et al. Global antibiotic use during the COVID-19 pandemic: analysis of pharmaceutical sales data from 71 countries, 2020-2022. EClinicalMedicine. 2023;57:101848.
9. Centers for Disease Control. 2022 Special report on the impact of COVID-19 on AMR Available at: https://www.cdc.gov/antimicrobial-resistance/media/pdfs/covid19-impact-report-508.pdf. Last accessed: 19 September 2024.
10. Rex JH, et al. The evolution of the regulatory framework for antibacterial agents. Ann N Y Acad Sci. 2014;1323:11-21.
11. O'Neill J. Review on antimicrobial resistance: tackling drug-resistant infections globally: final report and recommendations. 2016. Available at: https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf. Last accessed: 19 September 2024.
12. U.S Food and Drug Administration. Limited Population Pathway for Antibacterial and Antifungal Drugs – the LPAD Pathway. Available at: https://www.fda.gov/drugs/development-resources/limited-population-pathway-antibacterial-and-antifungal-drugs-lpad-pathway. Last accessed: 19 September 2024.
13. World Health Organization. Antibacterial pipeline trends and recommendations to enhance research and development: policy brief. Available at: https://www.who.int/publications/i/item/9789240097735. Last accessed: 19 September 2024.
14. Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X). 2021-2022 annual report. Available at: https://carb-x.org/carb-x-news/2021-22-annual-report/. Last accessed: 19 September 2024.
15. Robert W Eisinger, et al. A call to action—stopping antimicrobial resistance, JAC-Antimicrobial Resistance, Volume 5, Issue 1, February 2023. Available at: https://doi.org/10.1093/jacamr/dlac142. Last accessed: 19 September 2024.
16. Gordon J, et al. Estimating the Value of New Antimicrobials in the Context of Antimicrobial Resistance: Development and Application of a Dynamic Disease Transmission Model. Pharmacoeconomics. 2020;38:857-869.
17. Africa Centres for Disease Control and Prevention. Mapping Antimicrobial Resistance and Antimicrobial Use Partnership (MAAP) Country Reports. Available at: https://africacdc.org/download/mapping-antimicrobial-resistance-and-antimicrobial-use-partnership-maap-country-reports/. Last accessed: 19 September 2024.
18. Bertagnolio S., et al. WHO global research priorities for antimicrobial resistance in human health. Lancet Microbe. Published Online 2024. Available at: https://doi.org/10.1016/S2666-5247(24)00134-4. Last accessed: 19 September 2024.
19. Rex JH, et al. Progress in the Fight Against Multidrug-Resistant Bacteria 2005-2016: Modern Noninferiority Trial Designs Enable Antibiotic Development in Advance of Epidemic Bacterial Resistance. Clin Infect Dis. 2017;65:14.

Chapter 71

Why is it so difficult to change behaviours in antibiotic prescribing practices?

Adrian J. Brink
Division of Medical Microbiology, Department of Pathology, National Health Laboratory Services, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa;
Institute Infectious Diseases and Molecular Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa.

Esmita Charani
Division of Infectious Diseases and HIV Medicine, Department of Medicine, Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa;
Faculty of Health and Life Sciences, University of Liverpool, Liverpool, United Kingdom.

Introduction

Using behavioural and cultural insights (BCI) offers an innovative, evidence-based and people-centred approach to reshape how we address antimicrobial resistance (AMR). BCI was recently recognized as a high-impact intervention by the WHO European Region's new AMR roadmap. It employs methods from social and behavioral sciences to understand health behaviors, aiming to reshape AMR strategies.

Hospital antibiotic prescribing is a complex process influenced by various social and contextual factors. Changing these practices requires addressing communication barriers among disciplines, clarifying responsibilities, and minimizing fears associated with altering antibiotic prescribing and infection management decisions. In this regard, many antimicrobial stewardship (AMS) interventions lack integration of social sciences and behavioral theories, leading to a gap in understanding effective behavior change strategies in hospital settings. More research is essential to identify effective behavior change interventions that are adaptable and sustainable across diverse environments and cultural contexts.

The primary aim of AMS should be to foster sustained behavioral change towards optimising prescribing practices. This necessitates exploring the determinants influencing antibiotic decision-making among different prescriber groups, and the wider healthcare workforce engaged in infection prevention and AMS including nurses and pharmacists. Notably, qualitative studies are beginning to shed light on the challenges associated with changing antibiotic prescribing practices, indicating that deeper understanding is crucial for driving sustainable change. Incorporating behavioral insights into AMS can ultimately help to create a more effective response to inappropriate antibiotic prescribing, leading to improved health outcomes.

Discussion

Several models can be used to explore the behaviours of health-care workers (HCWs). The Theoretical Domains Framework (TDF) and the COM-B model are widely used frameworks for understanding the behaviors of HCWs in relation to antibiotic prescribing and AMR interventions. It highlights the interconnectedness of four key elements that influence practices:

Capability: This emphasizes the need for HCWs to possess the necessary knowledge, skills, and training to appropriately select, prescribe, and monitor the use of antibiotics. Ensuring that HCWs are well-prepared and educated can enhance their ability to improve appropriate antibiotic use.

Motivation: Motivation is a crucial factor that encompasses not only the confidence of HCWs in their capabilities but also their understanding of the impact of their actions. Emotional responses and situational pressures can significantly shape their decision-making processes regarding antibiotic use.

Social Opportunity: This component focuses on the social context in which HCWs operate. Peer norms, values, and the dynamics of interaction with others and seniors can greatly influence prescribing behaviors and create an environment conducive to responsible antibiotic use.

Physical Opportunity: Physical opportunity refers to the environmental and tangible aspects that facilitate or hinder antibiotic prescribing. Access to necessary resources, equipment, tools and clear guidelines are essential to support HCWs in making informed and appropriate decisions.

A recent meta-synthesis (n=63 studies) informed by the TDF, confirmed that prescriber's capabilities, motivation and opportunities to be the main drivers of antibiotic prescribing behaviour. Specifically, knowledge, skills, beliefs, expectations, the influence of patients and colleagues, organizational culture and infrastructure characteristics have a significant impact on prescribing behaviours. In this regard, in a recent systematic review and meta-ethnography Wojcik *et al.* also reviewed the complexities of antibiotic prescribing behavior in acute hospitals. Synthesizing the experiences of doctors from various levels of seniority across multiple countries, the study findings were grouped into overarching themes that highlight the multifaceted challenges of appropriate antibiotic prescribing in hospital settings, and why it is difficult to change behaviours in antibiotic prescribing practices.

Loss of ownership of prescribing decisions

The transition of patients between wards, a busy work environment, a high workload, and poor documentation and communication contribute to ambiguity of ownership over antibiotic decisions. Out-of-hours care presents unique challenges in healthcare delivery, particularly regarding the allocation of prescribing responsibilities. During nights and weekends, junior doctors often find themselves in situations where they must manage complex cases independently. They may be required to make critical decisions, such as prescribing antibiotics, with limited support from senior colleagues. This scenario can lead to ambiguity in responsibility and potentially affect the quality of care, as junior doctors might not have immediate access to the necessary guidance or feedback.

While antibiotic decision-making is inherently team-based and interprofessional, the responsibility of stopping or de-escalating therapy is perceived to lie primarily with consultants or senior specialists. In this regard, non-infectious disease/clinical microbiology (ID/CM) consultants often feel a strong sense of ownership over clinical decision-making, expressing concerns about their autonomy being challenged by ID/CM advice. Ownership is also compromised due to a lack of clarity around the specific roles and responsibilities of clinicians

in antibiotic prescribing, leading to disparities in expectations. Junior clinicians are often expected to start antibiotics but not review or stop them, creating a gap in ownership during transitions of care. In this respect, Charani *et al.* in an observational study at a London teaching hospital, highlighted that loss of ownership often occurs during the transition of care between the emergency department and inpatient teams. This issue is prevalent across different hospital settings and complicates collective responsibility for AMR. This observation is important as most stewardship interventions target junior doctors and overlook the hierarchical decision-making process within surgical and medical teams in hospitals.

Tension between individual care and public health concerns

It is also evident that a significant tension exists between providing individual patient care and addressing public health concerns related to AMR. The existing evidence emphasizes the challenges clinicians face in balancing immediate patient needs with long-term societal risks. Therefore, balancing risks is at the core of prescribing behaviour and the dilemma clinicians face is described as 'the tragedy of the commons'. When there is uncertainty about an infection, clinicians often prioritize immediate clinical risks over long-term population risks i.e. starting antibiotics might benefit the individual patient despite excessively contributing to future AMR. Notably, the threat of AMR is generally perceived to be distant and not immediate. The immediate need to resolve clinical concerns for the patient being considered can lead to behaviours that counter those required to mitigate the risk of AMR in the long-term. This requires infectious diseases experts to reconsider how they discuss the concept of risk associated with AMR to non-expert colleagues.
In a systematic review of antibiotic prescribing behaviour, focusing on balancing the risks to individual and society, Crockow *et al.*, fear of consequences was found to be another determinant driving antibiotic prescribing. The fear of negative outcomes and the perception that conservative prescribing is not good practice can lead to antibiotic use outside clinical guidelines. This might involve prescribing broader-spectrum antibiotics or extending the duration beyond what is clinically necessary, without any added benefit to the individual patient. In this context, the fear of patient deterioration can overshadow adherence to evidence-based practice. As a result, optimizing antibiotic use becomes a lower priority, and the risks of over-prescribing are often downplayed. Crockow *et al.* also established that antibiotic prescribing decisions in low-income countries were shaped by a context of heightened uncertainty and risk due to poor microbiology and infection control services.

Evidence-based practice versus bedside medicine

A significant conflict between evidence-based practice and experiential learning and bedside medicine poses major challenges for appropriate antibiotic prescribing in hospitals. Hence, there is a tension between the evidence-based practices promoted by AMS teams and the experiential learning that clinicians value most in clinical settings. Despite the benefits of experience in identifying and treating severely ill patients, a common tendency across all levels of experience in the medical field is to err on the side of caution. This often means prescribing antibiotics "just in case," as this approach provides reassurance both to the doctor and the patient.
This prescribing behaviour can become the default option for several reasons. Immediate patient safety is safe guarded in that prescribing antibiotics ensures that if there is a bacterial infection, it is being treated promptly, which minimizes the risk of complications or deterioration in the patient's condition. Furthermore,

in the event of an adverse outcome, doctors might feel more protected legally and professionally if they have prescribed antibiotics. This practice can be seen as a precaution to avoid potential accusations of negligence. During busy in- and out-of-hours shifts, the pressure to manage a high volume of patients quickly may lead to more inappropriate prescribing practices. Antibiotics can be seen as a straightforward, immediate intervention. Diagnostic uncertainty also plays a major role. In settings without immediate access to comprehensive diagnostic tools and tests, the uncertainty of a diagnosis might lead doctors to prescribe antibiotics as a precautionary measure. In addition, positive patient outcomes, maintaining a professional reputation and approval from supervisors take priority. Guideline-based advice, often provided remotely without direct patient assessment, can clash with clinicians' sense of ownership and responsibility for their patients. This can lead to a preference for intuitive, subjective decision-making over theoretical, evidence-based guidance, especially in situations requiring immediate medical judgment. Another key theme is the distinction between laboratory-based medicine and bedside medicine. Clinicians often perceive antibiotic prescribing as a skill learned through direct experience and mentorship from consultants, rather than interpreting laboratory results appropriately. In particular, this experiential learning often relies on practices observed many years prior, which may not align with current evidence-based diagnostic stewardship principles.

Diverse priorities and competing hierarchical influences

The review by Wojcik *et al.* further explores the impact of diverse priorities among different clinical teams on antibiotic prescribing behaviour in acute hospitals. It also highlights the complexities and hierarchical challenges doctors face when navigating between various authoritative figures. Diverse priorities in antibiotic decision-making are evident among different specialty groups. Although there is a common overall approach to managing infections, the emphasis placed on various phases of the decision-making process varies significantly between emergency department (ED) clinicians, surgical specialties, and medical specialties. In particular, the primary focus of ED clinicians and surgical specialities is immediate patient care and infection prevention including initiating antibiotics promptly.

This proactive approach aims to mitigate immediate risks associated with infections, particularly in acute and post-surgical scenarios. Medical specialties, on the other hand, are more focused on the longer-term management of infections. Their approach involves careful monitoring and ongoing assessment of the patient's response to initial antibiotic treatment and stopping antibiotics. In an ethnographic study of culture and team dynamics, Charani *et al.* confirmed that in medicine, accepted norms of the decision-making process are characterized as collectivist (input from pharmacists, infectious disease, and medical microbiology teams), rationalized, and policy-informed. In contrast, in surgery, antibiotic decision-making is perceived as a nonsurgical intervention that can be delegated to junior staff or other specialties.

In this regard, antibiotic prescribing is inherently interprofessional, involving multiple authoritative figures including the immediate clinical team and other specialties. Discord in interpersonal relationships can significantly influence prescribing decisions, sometimes leading to poor continuity of care. Inconsistent advice and misunderstandings regarding roles and responsibilities further hinder successful collaboration. Competing hierarchical influences is another factor to consider. Challenging the decisions of senior colleagues is often perceived as unacceptable, creating additional barriers for junior doctors in advocating for evidence-based antibiotic use. The concept of "prescribing etiquette" reflects the unspoken cultural norms and practices that influence how healthcare professionals prescribe antibiotics. This culture of "noninterference" suggests that there is a reluctance among peers to question or intervene in each other's prescribing decisions. This

noninterference is driven by professional hierarchy and the dynamics within clinical groups, which act as significant determinants of prescribing behaviours.

A collaborative culture that fosters a multidisciplinary approach and normalizes the involvement of other specialists in the decision-making process is crucial for improving antibiotic prescribing and AMS. However, the involvement of other specialties in decision-making often depends on the familiarity and acceptance of those colleagues by senior clinicians. Challenges in managing multidisciplinary interactions should also be recognized. Junior doctors described managing interactions with other healthcare professionals as challenging. The "unspoken" yet widely accepted rules on how to manage multidisciplinary dynamics mean that doctors face difficulties navigating the complex system of interrelationships with colleagues who could potentially assist them.

The presence of ward clinical pharmacists generates conflicting opinions, whereas some clinicians described pharmacists as helpful in discussing and prompting antibiotic review and de-escalation etc., however, they were perceived by some participants (mostly male physicians from internal medicine) as interference. Furthermore, the success of AMS initiatives can be significantly limited by the lack of partnership with nurses. Despite their crucial role in patient care, nursing involvement in antibiotic decision-making remains minimal, despite their crucial role in antibiotic administration, review, monitoring, and related infection care practices. This situation arises from several factors, including perceptions about the expertise required for antibiotic prescribing. Antibiotic decision-making is seen as a domain exclusive to medical professionals with prescribing powers. This leads to underestimating the potential contributions of nurses and results in the exclusion of nurses from important discussions and decisions about antibiotic use and infection management, even though they are integral to patient care and monitoring.

Bonaconsa *et al.* at a tertiary care hospital in South Africa, recently employed sociograms, a visual mapping method, to analyse the content and flow of communication and the social interactions among participants during surgical ward rounds. Their study provided valuable insights into several aspects of infection management and AMS. The study mapped out how discussions on infection management and AMS are started and it identified who leads and who participates in these conversations. It detailed how decisions are made and communicated to those responsible for implementing them. The ethnographic study established that leadership styles affect ward-round dynamics, determining whether nurses and patients are actively engaged in discussions on infection management and antibiotic therapy.

In addition, the findings from another qualitative study in South Africa and India highlight several critical barriers to effective infection management within the surgical pathway.

The implicit roles and potential contributions of HCWs including nurses and senior surgeons are not fully recognized as interventions primarily target junior doctors, missing opportunities for integrating infection-related care across the surgical team. Operating surgeons hold the primary ownership of decisions, and entrenched hierarchies was shown to exclude other HCWs from the decision-making process. Notably, there is a lack of structural support to enable HCWs to change their behaviours and actively participate in infection-related surgical care. Similarly, to influence infection control behaviours in surgery, interventions to prevent surgical site infections need to consider the social team structure and shared ownership of the clinical outcome.

Facilitators for changing behaviour

An understanding of and accounting for cultural norms in antibiotic decision-making and infection management are critical to the effective design, implementation and adoption of AMS. To this end, HCW co-design and involvement in interventions are critical for enabling HCWs to have a sense of ownership can lead to

greater personal investment in clinical decisions. Clarifying roles and responsibilities at the individual level to ensure that all HCWs understand their specific contributions to antibiotic prescribing, may address the loss of ownership and is essential to improve antibiotic prescribing practices. This includes clearly defining who is responsible for initiating, reviewing, and discontinuing antibiotic therapy.

The tension between individual care and public health impact is a major concern. Understanding the cultural norms within hospitals and enhancing training to support evidence-based antibiotic prescribing can help support risk stratification in infection management and optimise clinical practice. This includes reinforcing the importance of adhering to clinical guidelines and recognizing the broader impact of antibiotic misuse. Implementing support systems and better risk communication can help clinicians make informed decisions that consider both immediate clinical needs and long-term public health outcomes. Notably, decision support tools such as the innovative tool to support clinicians to safely initiate antibiotic reassessment ("antibiotic time-out") which involved the development of a digital antibiotic review tracking toolkit (DARTT) can support this process.

There is a need to better integrate evidence-based guidelines with the realities of bedside medicine. This could involve more direct involvement of AMS teams in clinical settings and ensuring that guidelines are practical and adaptable to real-time decision-making. Understanding the context-specific determinants of non-adherence to guidelines, such as antibiotic recommendations for surgical prophylaxis, involves examining various factors that can influence healthcare providers' behavior and decision-making processes. Furthermore, training programs should emphasize the importance of evidence-based practice while also respecting the value of experiential learning. Implementing regular feedback loops where junior and senior doctors can receive constructive feedback on their antibiotic-prescribing decisions may assist in identifying areas of improvement and reinforcing evidence-based practices.

Mentorship from senior clinicians should include discussions on current guidelines and the rationale behind evidence-based recommendations. Efforts should also be made to bridge the gap between laboratory-based medicine and bedside practice. This might include improved communication and collaboration between laboratory staff and clinicians to ensure that diagnostic stewardship and advice is perceived as relevant and practical. By resolving these conflicts through a collaborative culture and promoting a more integrated approach to antibiotic prescribing, it may be possible to enhance adherence to evidence-based practices while still valuing the experiential knowledge of clinicians.

Promoting multidisciplinary collaboration may represent one strategy for positively influencing prescribing behaviour among different clinical teams, with diverse priorities. Efforts should be made to promote a collaborative culture where the roles of different specialists are recognized and valued. This can be achieved through multidisciplinary team meetings, joint training sessions, and clear communication channels. In addition, clear definitions of roles and responsibilities related to antibiotic prescribing can help reduce misunderstandings and ensure consistent advice across teams. This may involve creating formal protocols and guidelines that outline the specific contributions of various specialties. Therefore, on a macro-level, institutionalizing policies mandate the inclusion of multiple specialties in developing antibiotic prescribing guidelines and protocols. This ensures diverse perspectives are considered and integrated into practice.

Providing support for junior doctors in negotiating complex hierarchical dynamics is essential. Mentorship programs, open forums for discussion, and encouraging a culture where questioning and challenging decisions are seen as part of professional growth can empower junior doctors to participate more actively in AMS interventions. Addressing the hierarchical barriers that prevent junior doctors from consulting with ID/CM clinicians and other specialists can improve antibiotic prescribing practices. This includes creating an environment where interdisciplinary consultation is encouraged and facilitated, and where junior doctors feel confident in seeking guidance from all relevant authorities. By addressing diverse priorities and hierarchical

challenges, hospitals can improve the effectiveness of AMS programs and ensure more appropriate antibiotic prescribing practices.

By focusing on these key areas, hospitals can make significant strides in optimizing antibiotic prescribing practices, thereby improving patient outcomes and combating the growing threat of AMR. However, whilst behavioral, normative, and control beliefs play a significant role in antibiotic prescribing practices, to design and implement effective AMS interventions, it is crucial to conduct quantitative studies that assess the relative weight of individual determinants. Similarly, is prioritizing other research areas for AMS from a behavioural perspective.

Conclusion

This short overview highlights the complexity of changing antibiotic use in hospitals and the importance of adopting diverse strategies that consider various behavioural, cultural, and systemic factors. The key determinants and facilitators for improving antibiotic prescribing are summarized in **Table 1**. In essence, effective antibiotic therapy optimization requires a comprehensive approach that integrates behavioural insights, fosters interprofessional relationships and is sensitive to socio-cultural contexts. This holistic perspective can contribute to the successful implementation of AMS interventions and ultimately improve antibiotic prescribing and thus enhance patient safety and quality of care.

Table 1. Key determinants and facilitators for changing behaviours in antibiotic prescribing practices.

Determinant	Facilitator
Behavioural diversity and change	Recognizing that healthcare professionals have diverse learning processes and responses to change is essential. Strategies to improve prescribing should be tailored to accommodate these differences.
Role of relationships	Empowering interprofessional relationships fosters collaboration and communication among team members, which is critical for improving prescribing. Encouraging teamwork can enhance the transmission of knowledge and adherence to best practices.
Cognitive biases in decision-making	Understanding predictable errors resulting in illogical and irrational prescribing is crucial. Interventions must be designed to mitigate these biases and encourage evidence-based decision-making.
Socio-cultural awareness	Strategies should be rooted in an understanding of local socio-cultural dynamics that affect antibiotic use. This includes considering institutional history, norms, and values that shape professional practice.
Focus on habit and norms	Developing a culture that values patient safety and quality of care can facilitate better antibiotic prescribing practices. This might involve integrating AMS principles into routine clinical practices and decision-making.
Collective ownership of decisions	Encouraging a sense of collective responsibility among team members can improve antibiotic prescribing. Empowering teams to take ownership can lead to more accountable and sustainable best practices.
Education and training	Embedding experiential learning opportunities and ensuring ongoing education on the latest evidence can help healthcare professionals adapt to changes and challenges in antibiotic use.

Competing interests

AJ Brink has received research funding from Oppenheimer Generations, GARDP, FEND and Pfizer.
E Charani is a Wellcome Trust Career Development Fellow at the University of Cape Town. She holds research grants from Wellcome Trust, GARDP, and WHO TDR. In the last three years, she has provided unrestricted educational lectures on stewardship at meetings funded by Pfizer and Biomerieux and has received honoraria for these lectures.

References

1. World Health Organization. Behavioural and cultural insights: a game-changer in tackling antimicrobial resistance. Available at: https://www.who.int/azerbaijan/news/item/29-11-2023-behavioural-and-cultural-insights--a-game-changer-in-tackling-antimicrobial-resistance. Published November 2023. Last accessed: 30 July 2024.
2. Sartelli M, et al. Antimicrobials: a global alliance for optimizing their rational use in intra-abdominal infections (AGORA). World J Emerg Surg. 2016;11:33.
3. Wojcik G, et al. Understanding the complexities of antibiotic prescribing behaviour in acute hospitals: a systematic review and meta-ethnography. Archives Public Health. 2021;79:134.
4. Van den Bergh D, et al. A commitment and call to strengthen and expand qualitative research efforts to improve the impact of antimicrobial stewardship. JAC Antimicrob Resist. 2021;3:dlab151.
5. Lorencatto F, et al. Driving sustainable change in antimicrobial prescribing practice: How can social and behavioural sciences help? J Antimicrob Chemother. 2018;73:2613-2624.
6. Sartelli M, et al. The Global Alliance for Infections in Surgery: defining a model for antimicrobial stewardship—results from an international cross-sectional survey. World J Emerg Surg. 2017;12:34.
7. Michie S, et al. The behaviour change wheel: A new method for characterising and designing behaviour change interventions. Implement Sci. 2011;6:42.
8. Acampora M, et al. Uncovering influential factors in human antibiotic prescribing: a meta-synthesis study informed by the Theoretical Domains Framework. J Hosp Infect. 2024;144:28-55.
9. Mattick K, et al. A window into the lives of junior doctors: narrative interviews exploring antimicrobial prescribing experiences. J Antimicrob Chemother. 2014;69:2274-2283.
10. Broom J, et al. Barriers to uptake of antimicrobial advice in a UK hospital: a qualitative study. J Hospital Infect. 2016; 93:418-422.
11. Broom A, et al. The social dynamics of antibiotic use in an Australian hospital. J Sociol. 2016;52:824-839.
12. Rawson TM, et al. Mapping the decision pathways of acute infection management in secondary care among UK medical physicians: a qualitative study. BMC Med. 2016;14:208.
13. Broom A, et al. A Bourdieusian analysis of doctors' antibiotic prescribing. Soc Sci Med. 2014;110:81-88.
14. Livorsi D, et al. Factors Influencing Antibiotic-Prescribing Decisions Among Inpatient Physicians: A Qualitative Investigation. Infect Control Hosp Epidemiol. 2015;36:1065-1072.
15. Skodvin B, et al. An antimicrobial stewardship program initiative: a qualitative study on prescribing practices among hospital doctors. Antimicrob Resist Infect Control. 2015;4:24.
16. Charani E, et al. The differences in antibiotic decision-making between acute surgical and acute medical teams: An ethnographic study of culture and team dynamics. Clin Infect Dis. 2019;69:12-20
17. Bjorkman I, et al. Perceptions among Swedish hospital physicians on prescribing of antibiotics and antibiotic resistance. Qual Saf Health Care. 2010;19(6):e8.
18. Broom J, et al. Individual care versus broader public health: A qualitative study of hospital doctors' antibiotic decisions. Infect Dis Heal. 2017;22:97-104.

19. Krockow EM, et al. Balancing the risks to individual and society: A systematic review and synthesis of qualitative research on antibiotic prescribing behaviour in hospitals. J Hosp Infect. 2018;101:428-439.
20. Chaves NJ, et al. Analysis of knowledge and attitude surveys to identify barriers and enablers of appropriate antimicrobial prescribing in three Australian tertiary hospitals. Intern Med J. 2014;44:568-567.
21. Cortoos PJ, et al. Opposing expectations and suboptimal use of a local antibiotic hospital guideline: a qualitative study. J Antimicrob Chemother. 2008;62:189-195.
22. May L, et al. Multisite exploration of clinical decision making for antibiotic use by emergency medicine providers using quantitative and qualitative methods. Infect Control Hosp Epidemiol. 2014;35:1114-1125.
23. Sedrak A, et al. Enablers and barriers to the use of antibiotic guidelines in the assessment and treatment of community acquired pneumonia—A qualitative study of clinicians' perspectives. Int J Clin Pract. 2017;71:e12959.
24. Charani E, et al. Understanding the determinants of antimicrobial prescribing within hospitals: The role of "prescribing etiquette". Clin Infect Dis. 2013;57:188-196.
25. Castro-Sánchez E, et al. European Commission guidelines for the prudent use of antimicrobials in human health: a missed opportunity to embrace nursing participation in stewardship. Clin Microbiol Infect. 2018;24:914-915.
26. Bonaconsa C, et al. Visual mapping of team dynamics and communication patterns on surgical ward rounds: an ethnographic study. BMJ Qual Saf. 2021;30:812-824.
27. Singh S, et al. Investigating infection management and antimicrobial stewardship in surgery: a qualitative study from India and South Africa. Clin Microbiol Infect. 2021;27:1455-1464.
28. Troughton R, et al. Understanding determinants of infection control practices in surgery: the role of shared ownership and team hierarchy. Antimicrob Resist Infect Control. 2019; 8:116.
29. Wojcik G, et al. Improving antibiotic use in hospitals: development of a digital antibiotic review tracking toolkit (DARTT) using the behaviour change wheel. Psychol Health 2023;1-21.
30. Lohiniva AL, et al. Developing a theory-based behavior change intervention to improve the prescription of surgical prophylaxis. Int J Clin Pharm. 2022;44:227-234.
31. Rzewuska M, et al. Prioritizing research areas for antibiotic stewardship programmes in hospitals: a behavioural perspective consensus paper. Clin Microbiol Infect. 2019;25:163.

Chapter 72

Antibiotic side effects, adverse reactions and their implications on antimicrobial resistance

Judith Asin
Ecumenical Pharmaceutical Network, Kenya.

Ndege Ngere
AMR Now, Kenya.

Mario Medegan
Mouvement Universel pour la Survie de l'Humanite (MUSUHUM), Benin.

Lineo Grace Nyenye
Maluti Adventist Hospital, Mapoteng, Lesotho.

Introduction

Infections in hospital settings frequently require antibiotic treatment, which, despite its therapeutic benefits, carries risks such as side effects (SE), adverse drug reactions (ADR), and the potential for bacterial resistance. Antibiotics can disrupt the balance of beneficial microbiota, particularly in the gastrointestinal tract, leading to various unintended consequences.

While both SE and ADRs represent distinct outcomes of antibiotic use, they tend to differ in description and presentation. SE typically denote unintended but predictable responses to a medication often manifesting as mild and tolerable effects like *nausea, diarrhoea or mild allergic reactions.* They can happen at normal recommended doses and are unrelated to the intended medical purpose. Sometimes SE can have a positive health benefit. Regardless of whether symptoms are negative or positive, they are still considered SE. Conversely, ADRs are severe, unpredictable responses that extend beyond the medication's intended effects and can cause significant discomfort, organ damage, or life-threatening complications, requiring immediate medical intervention.

SE and ADR can range from mild to severe, negatively impacting drug prescribing practices, prolonging hospital stays, and increasing socioeconomic costs. Studies indicate that ADRs affect over 7% of the general population and 10-20% of hospitalized patients, making it essential for healthcare providers to differentiate between SE and ADR and adjust treatment plans accordingly to ensure that the benefits outweigh the potential risks and ensure patient safety. Understanding antibiotic classifications and mechanisms, along with patient awareness of prescribed antibiotics and their potential interactions, is crucial for patient compliance to treatment, reducing risk of incomplete antibiotic courses as well as the risk of antimicrobial resistance (AMR)

Given the role of antibiotic misuse and overuse in fueling the emergence of AMR, a comprehensive understanding of these medications is indispensable in addressing this global health crisis. In addition, by

addressing antibiotic SE and ADRs, through effective stewardship programs, healthcare professionals can optimize treatment outcomes while safeguarding patient well-being ultimately contributing to more effective infection control measures within hospital environments.

Overview of antibiotics

Antibiotics are a cornerstone of modern medicine, pivotal in the treatment and management of bacterial infections. These compounds are designed to either kill bacteria or inhibit their growth, thereby aiding the body's immune system in eradicating the infection. Antibiotics can be broadly classified into several types based on their mechanism of action and spectrum of activity. *Broad-spectrum antibiotics*, such as tetracyclines and cephalosporins, target a wide range of bacteria, while *narrow-spectrum antibiotics*, like penicillin and erythromycin, are effective against specific types of bacteria. The mechanisms of action of antibiotics vary: *cell wall synthesis inhibitors* (e.g., penicillins and cephalosporins) disrupt the structural integrity of bacterial cell walls, leading to cell lysis*; protein synthesis inhibitors* (e.g., tetracyclines and macrolides) impede bacterial ribosomes, thereby preventing protein production essential for bacterial growth; and *nucleic acid synthesis inhibitors* (e.g., quinolones) interfere with bacterial DNA replication or transcription. Despite their crucial role in treating infections, the use of antibiotics is fraught with challenges, including potential SE and adverse reactions. Understanding these aspects is essential for optimizing antibiotic therapy, minimizing risks, and addressing the growing concern of AMR, which can compromise patient safety and the effectiveness of treatment protocols.

Antibiotics are usually safe and effective in bacterial infections but might lead to ADR development. Factors such as reduced efficacy, overuse and misuse of antibiotics are among other contributing factors to antibiotics-related SE and ADRs occurrence. Just like any other medicines that can cause SE, antibiotics also lead to ADRs when administered to some patients. For instance, a study assessing ADRs patterns to commonly prescribed drugs in a tertiary care hospital in India found that ADRs attributed to antibiotics alone accounted for 14% of all ADR reported while Seliva and Durairajan determined that antibiotics constituted the majority of ADRs accounting for 59.1% of all ADR reported in the conducted by pharmacovigilance center of Savethia Medical College Hospital Chennai India. The two studies provided evidence that indeed some patients experience ADR when taking some antibiotics.

Impact of pharmacokinetic variability on antibiotic efficacy and adverse reactions

The pharmacokinetics of antibiotics, encompassing their *absorption, distribution, metabolism, and excretion*, play a crucial role in determining their efficacy and potential for adverse reactions. Variability in these processes can lead to a wide range of SE. For instance, antibiotics that are rapidly absorbed and widely distributed may achieve high tissue concentrations, increasing the risk of toxicity in sensitive organs such as the liver or kidneys. Conversely, drugs that are poorly metabolized or excreted can accumulate in the body, further exacerbating the potential for adverse reactions. Additionally, individual patient factors like genetic variations, age, and underlying health conditions can influence drug metabolism, thereby modifying both therapeutic outcomes and SE profiles.

In critically ill patients, the correct antibiotic regimen is very important because several physiological manifestations of a critical illness may change the pharmacokinetic behavior of administered drugs. Pharmacokinetic modifications in critically ill patients are present without exception, from absorption, distribution, and metabolism to the process of excretion. Thus, in the intensive care patient, standard antibiotic doses are expected to result in over- or underexposure to drugs, mainly due to changes in the volume of distribution

and clearance. Understanding these pharmacokinetic properties and alterations is essential for optimizing antibiotic use, minimizing ADRs, and mitigating the risk of AMR (AMR) by ensuring appropriate dosing regimens and reducing unnecessary exposure.

Exploring side effects, adverse reactions and the influence of food on antibiotic therapy

Side effects (SE)

Antibiotic SE can range from mild and transient to severe and potentially life-threatening, impacting patient safety and treatment outcomes. Common SE includes gastrointestinal disturbances such as nausea, vomiting, diarrhea, abdominal pain, loss of appetite, and bloating, which are frequently associated with antibiotics like amoxicillin, vancomycin and clindamycin often owing to disturbance of gut flora. The risk of vancomycin- and clindamycin-associated *C. difficile* colitis increases with the number of days receiving antibiotics.

Broad-spectrum antibiotics are also likely to cause secondary *Candida* species overgrowth, especially in those with diabetes. *Clostridium difficile* infections are mostly caused by ampicillin or amoxicillin, clindamycin, third-generation cephalosporins (such as cefotaxime and ceftazidime), and fluoroquinolones.

Tetracyclines are another class of antibiotics that may lead to some SE. Commonly reported SE due to tetracyclines include gastrointestinal irritation that is marked by epigastric burning and distress, abdominal discomfort as well as diarrhea. However, this SE can be avoided or minimized by taking the drug with food. Photosensitivity reaction in the skin is one of SE that occurs as the result of tetracyclines use when an individual is exposed to sunlight. Nail pigmentation and onycholysis may develop with or without accompanying photosensitivity. Therefore, avoidance of sunlight exposure can help to overcome photosensitivity reactions attributed to tetracyclines. To add more permanent brown teeth discoloration is seen in children receiving either short- or long-term therapy with tetracyclines. This is because calcium in teeth chelates with the drug. Duration of therapy with tetracyclines seemed not to be a greater risk for this SE to occur, rather the total quantity of antibiotics administered is the risk factor. The larger the drug dose relative to body weight, the more intense the enamel discoloration. It is very important to avoid the use of tetracyclines in children and expecting and breastfeeding mothers in order to avoid this SE from occurring.

Adverse reactions (ADRs)

Hypersensitivity reactions are by far the most common ADR seen with penicillins. These reactions may occur with any dosage form of penicillin appearing to either an individual with an already known history of penicillin allergy or even in the absence of a previous known exposure to the drug. It is worth noting that allergy to one penicillin exposes the patient to a greater risk of reaction if another penicillin is given. Manifestation of penicillin-related allergy any include maculopapular rash, urticaria rash, fever, bronchospasm, vasculitis, exfoliative dermatitis as well as Stevenson-Johnson syndrome and anaphylaxis. Likewise, cephalosporins also cause hypersensitivity reactions. Cephalosporins' associated allergic reactions appear to be identical to those of penicillins. This is because they both have in common a chemical structure, the beta-lactam ring. Because of this similarity, patients who are allergic to penicillin are likely to be allergic to cephalosporin. So, there are cross-hypersensitivity reactions among beta-lactam antibiotics such as penicillins, cephalosporins and carbapenems.

Aminoglycoside is another class of antibiotic that has the potential to cause either reversible or irreversible *vestibular cochlear toxicity*. This occurs predominantly with persisting elevated plasma concentration and

long exposure to the drugs. Sometimes a single dose administration of some aminoglycoside such as tobramycin is enough to induce slight but temporary cochlear dysfunction. Another frequently reported aminoglycoside ADR is *nephrotoxicity***.** This ADR occurs as a result of the accumulation of and retention of the drug in the proximal tubular cells. However, aminoglycoside-induced kidney injury can be reversible. Therefore, careful consideration should be made in administering this drug to patients with the potential to have kidney injury.

Macrolide, erythromycin, causes *cardiac arrhythmias* including QT prolongation with ventricular tachycardia. This is one of the serious ADR that can be lethal. Another serious ADR associated with macrolides use is hypersensitivity reactions presenting with fever, eosinophilia and skin eruptions. The use of macrolides in people with a known history of hypersensitivity reactions is forbidden. Oral administration of erythromycin especially in large doses is frequently followed by epigastric distress which may be severe at some times. Other gastrointestinal SE associated with macrolides use includes abdominal cramps, nausea, vomiting and diarrhea. These gastrointestinal symptoms are dose-related and self-limiting. (A Summary of antibiotic class-related adverse drug reactions is shown in **Table 1**).

Table 1. Summary of antibiotic class-related adverse drug reaction (Adapted from: Choi JH, et al. 2017, and Goparaju S, et al. 2024).

Antibiotic class	Adverse drug reaction
Antituberculosis medicines	Rash, vomiting, shortness of breath, blurred vision, abdominal pain, hemoptysis, Jaundice, hyperpigmentation, hepatitis, gastritis, low back pain, optic neuritis
Cephalosporins e.g. ceftriaxone, cefotaxime	Pruritus, rash, diarrhea, vomiting, shortness of breath, chills, angioedema, eye swelling, thrombocytopenia, swelling, low back pain
Tetracyclines e.g. doxycycline, minocycline	Pruritus, rash, photosensitivity
Sulfonamides e.g. sulfasalazine, sulfadiazine	Pruritus, ear pain, anaemia, aplastic aneamia, hypersensitivity reactions, anorexia, glossitis, stomatitis
Carbapenems e.g. meropenem, impenem	Rash, blood urea increase
Aminoglycosides e.g. gentamycin, amikacin	Diarrohea, acute renal failure, pedal oedema, ototoxicity, nephrotoxicity
Macrolide e.g. azithromycin, erythromycin	Vomiting, diarrhea, chills, fixed drug eruption, metallic taste, tingling, vaginal irritation
Nitroimidazole e.g. metronidazole, tinidazole	Pruritus, shortness of breath, fixed drug eruptions, metallic taste, tingling, vaginal irritation
Penicillins e.g. amoxicillin, cloxacillin	Rash, urticaria, vomiting, diarrhea, chills, generalized body pain, swelling
Glycopeptide e.g. vancomycin	Pruritus, red man syndrome
Lincosamide	Pruritus
Quinolones e.g. ciprofloxacin, levofloxacin	Photosensitivity, arthropathy, QT interval prolongation

Drug-to-drug interaction

Rifamycins, one of the antituberculosis drugs, are a potent inducer of a vast variety of hepatic microsomal enzymes. Its administration may significantly decrease the half-life of several compounds such as HIV protease inhibitors, oral anticoagulants and sulphonylureas leading to sub-therapeutic levels. Rifamycins may affect the clinical outcome of these drugs and hence treatment failure. Therefore, the doses of these drugs should be adjusted if concurrently taken with rifamycins to achieve the desired clinical outcomes

Also, sulfonamides happen to potentiate other drug effects by mechanisms that appear to primarily involve metabolism inhibition and possibly displacement from plasma protein, albumin leading to elevated plasma levels. These drugs include hydantoin anticonvulsants and sulphonylureas. While this might look like a favorable drug-to-drug interaction, there is a need to monitor and watch out for the toxicity of phenytoin or glibenclamide when taken concurrently with sulfonamide antibiotics.

Quinolones such as ciprofloxacin inhibit theophylline metabolism and lead to elevated methylxanthines serum concentration which may result in toxicity. Theophylline toxicities should be carefully monitored if taken with ciprofloxacin. Also, antacids, zinc, other polyvalent metal cations such as calcium or iron as well as sucralfate decrease significantly intestinal absorption of fluoroquinolones leading to low bioavailable doses after oral administration. This might lead to antibiotic treatment failure that has the potential to fuel the emergence of drug resistance. Therefore, antiacid and zinc should be taken several hours apart if prescribed together with quinolones.

Probenecid slows tubular secretions of most penicillins and cephalosporins leading to high serum concentration and longer plasma level. This may accelerate the occurrence of these antibiotics-related toxicity. Penicillins and cephalosporins toxicities should be monitored and watch out if these drugs are taken along with probenecid. Adding more combinations of non-steroidal anti-inflammatory drugs with penicillins may also lead to increased penicillin exposure attributed to competitive inhibition of both drug tubular secretions.

Clarithromycin inhibits the effect of CYP3A4 affecting serum levels of several drugs such as statins and valproic acid leading to increased drug concentrations. So, co-administration of clarithromycin with statins increases the risk of statin-induced rhabdomyolysis, while valproic acid-associated toxicity presents with low blood pressure, bradycardia, central nervous system depression, respiratory depression, cerebral oedema and progression to coma and death can be experienced. Therefore, concurrent use of clarithromycin with either statins or valproic acid increases the risks of those drugs SE.

Drug-to-food interaction

Some food may affect how these antibiotics work leading to ADR and SE. Histamine-containing food such as cheese and fish may induce a flushing reaction manifesting with headache, difficulty in breathing, nausea and tachycardia when taken with isoniazid. Even though there is no need for dietary restriction, it is necessary but the patient's diet should be looked at if this reaction occurs. So, histamine-containing food may predispose one to some isoniazid-associated flushing reaction.

Furthermore, dairy products such as milk, yoghurt and cheese can interfere with certain antibiotics like tetracycline and ciprofloxacin. This is because tetracyclines and fluoroquinolones can bind to divalent cation-containing products calcium in dairy food resulting in reduced drug absorption and potential for therapeutic failure. Concurrent administration of fluoroquinolones or tetracyclines with dairy products must be avoided to prevent therapeutic failure as well as the emergence of drug resistance.

On the other hand, alcohol can negatively interact with some antibiotics leading to unintended outcomes. Alcohol can affect doxycycline and make it less effective in people with a history of heavy drinking which might potentially lead to treatment failure and drug resistance as well. Also, concurrent use of alcohol with metronidazole or tinidazole can cause very unpleasant SE such as feeling sick, stomach pain, hot flushes, fast and irregular heartbeat, headache, dizziness and drowsiness. This is because alcohol interferes with the breakdown of metronidazole. Therefore, use of alcohol while taking doxycycline or metronidazole must be avoided.

To add more, grapefruit juice is one of the commonly consumed beverages that may interact with some antibiotics. Grapefruit juice has been reported to moderately increase the serum concentration of erythromycin through inhibition of metabolizing enzyme, CYP3A4 and therefore there is a need to watch out for

erythromycin effects and toxicities such as QTc interval lengthening (a summary of antibiotic food-drug interaction is shown in **Table 2**).

Table 2. Summary of antibiotic food-drug interaction (Adapted from: Goparaju S, *et al.* 2024, and Selva P, *et al.* 2024).

Food	Drug	Effect
Dairy products	Tetracyclines, fluoroquinolones	Reduced drug absorption
Alcohol	Metronidazole	Adverse drug reaction
	Doxycycline	Reduced drug effect
Histamine containing food	Isoniazid	Adverse drug reaction
Grapefruit juice	Erythromycin	Increase drug blood level

Implications of SE and ADRs on the emergence and spread of AMR

AMR is a natural phenomenon which occurs in microbes making them unresponsive to drugs used to treat infections. Suboptimal dosage of antimicrobials is attributed to the emergence of AMR and subsequently may lead to therapeutic failure. SE and ADRs are also attributed to limited treatment options and discontinuation of drug dosage which may result in AMR.

This results in the use of a higher class of antimicrobials increasing the treatment cost. A study was conducted following descriptive analysis of ADRs based on spontaneous reports from the European pharmacovigilance database revealed that Penicillins, which is commonly used as a first-line defense, is the most common antibiotic associated with SEs & ADRs. In addition, Linezolid, which is classified under the Reserve class in the World Health Organization (WHO) AWaRe classification, was found to have the highest reported incidences associated with ADR. This could be due to multiple reasons such as; increased use; duration of treatment, since it is used long-term; and patient population, since it is primarily used by critically ill patients who are more susceptible to ADRs due to the presence of many risk factors. In addition, the off-label use of linezolid, which is quite common, may be a reason for the higher risk of ADRs.

Several *risk factors* are also associated with increased side effects and adverse reactions to antibiotics, which can, in turn, contribute to the development of antibiotic resistance. One significant factor is polypharmacy, where the use of multiple medications can lead to complex drug-drug interactions, enhancing the risk of adverse effects and complicating treatment regimens. Additionally, patients with underlying health conditions, such as liver or kidney dysfunction, may experience heightened sensitivity to antibiotics, resulting in increased side effects and compromised drug metabolism. Age also plays a role, with both the elderly and paediatric populations being more vulnerable to adverse reactions due to physiological differences and varying drug tolerances. Inappropriate or prolonged antibiotic use, including incorrect dosing or incomplete courses, can exacerbate side effects and foster resistance by promoting the survival of partially resistant bacterial strains. Moreover, inadequate patient education and adherence issues can lead to suboptimal antibiotic use, further increasing the likelihood of resistance development. Addressing these risk factors through careful prescribing practices and patient management is essential for minimizing adverse reactions and combating the spread of antimicrobial resistance.

Conclusion

Understanding the SE and ADRs associated with antibiotics is crucial for combating AMR and enhancing patient care. Antibiotics remain some of the most commonly prescribed drugs, and as such, ADRs and SE are inherent to their use. This manuscript has outlined various ADRs, including systemic and oral reactions, and explored their implications for treatment efficacy and safety. Due to factors such as time constraints and limited understanding, clinicians often miss opportunities to gather comprehensive information about patients' reported reactions, potentially leading to underreported or misdiagnosed allergies. Therefore, clinicians should integrate proper allergy documentation and reporting into their daily practices to ensure more accurate assessment and management.

By identifying and addressing these SE, healthcare professionals can implement more effective stewardship programs that optimize antibiotic use while minimizing harm to patients. Furthermore, recognizing the role of drug-drug and drug-food interactions in altering antibiotic therapy outcomes underscores the need for vigilant prescribing practices and patient education. Effective management of these interactions not only mitigates the risk of ADRs but also contributes to more precise and effective treatment regimens.

In a hospital setting, where the stakes are particularly high due to the complexity of infections and the prevalence of multi-drug-resistant organisms, safeguarding patient well-being and improving infection control measures are inextricably linked to a nuanced understanding of antibiotic-related ADRs. This holistic approach supports the development of strategies that address immediate treatment needs and contribute to the broader goal of curbing AMR. Enhanced awareness and targeted interventions are essential to ensuring that antibiotics remain a viable and effective tool in the ongoing fight against infectious diseases

Competing interests

The authors have no financial and non-financial competing interests to declare.

References

1. Amer AA. A narrative review on clinical trials showing contraindicated drugs with grapefruit juice. Sciences of Phytochemistry. 2023;2:48-69.
2. Blondeau JM. What have we learned about antimicrobial use and the risks for Clostridium difficile-associated diarrhoea? J Antimicrob Chemother. 2009;63:238-242.
3. Cattaneo D, et al. The Issue of Pharmacokinetic-Driven Drug-Drug Interactions of Antibiotics: A Narrative Review. Antibiotics (Basel). 2022;11:1410.
4. Gomes ER, et al. Epidemiology of hypersensitivity drug reactions. Curr Opin Allergy Clin Immunol. 2005;5:309-316.
5. Goparaju S, et al. Patterns of Adverse Drug Reactions to Commonly Prescribed Antibiotics in a Tertiary Care Hospital. Natl J Physiol Pharm Pharmacol. 2024; 14: 138-143.
6. Choi JH, et al. Food and Drug Interactions. J Lifestyle Med. 2017;7:1-9.
7. Jourdan A, et al. Antibiotic hypersensitivity and adverse reactions: management and implications in clinical practice. Allergy Asthma Clin Immunol. 2020;16:6
8. Justo JA, et al. Adverse reactions associated with systemic polymyxin therapy. Pharmacotherapy. 2015;35:28-33.
9. Llor C, et al. Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem. Ther Adv Drug Saf. 2014;5:229-241.

10. Radkowski P, et al. Antibiotic-Drug Interactions in the Intensive Care Unit: A Literature Review. Antibiotics (Basel). 2024;13:503.
11. Selva P, et al. Exploration and Evaluation of Adverse Drug Reactions Documented in a Tertiary-Care Hospital in Chennai: An In-Depth Retrospective Observational Study. Cureus. 2024;16:e60977.
12. Vintila BI, et al. Adverse Drug Reactions Relevant to Drug Resistance and Ineffectiveness Associated with Meropenem, Linezolid, and Colistin: An Analysis Based on Spontaneous Reports from the European Pharmacovigilance Database. Antibiotics (Basel). 2023;12:918.

Chapter 73

The AWaRe classification and its utility to implement prescribing practice

Ibrahim Chikowe
Pharmacy Department, Kamuzu University of Health Sciences (KUHES), Blantyre, Malawi.

Daniel Kaira
Medical Laboratory Sciences (MLS), Kamuzu University of Health Sciences (KUHES), Blantyre, Malawi.

Henry Phiri
Abwenzi Pa Za Umoyo (APZU)/Partners in Health (PIH), Neno, Malawi.

King Bwaila
Pharmacy Department, Malawi College of Health Sciences (MCHS), Zomba, Malawi.

Introduction

Antimicrobial resistance has become one of the rapidly evolving public health crises worldwide, and this has been partly attributed to irrational prescribing and use of antimicrobial agents. Noting this threat, in 2015, the World Health Organization (WHO) developed a global action plan (GAP) for mitigating the problem. The GAP included optimisation of antimicrobial use, and as part of this effort, in 2017, the WHO introduced the AWaRe classification of antibiotics, revised in 2019 and 2021. AWaRe classification stands for Access, Watch, and Reserve, and this is grouping or classification of antibiotics: 41 essential antibiotics for over 30 clinical infections in primary and hospital facility health care settings; additional 257 antibiotics not listed EML; and the Not Recommended category of antibiotics (103) that are fixed-dose combinations (FDC) (containing at least 2 APIs), which are not recommended for clinical use due to a lack of full microbiological, pharmacological, clinical, and safety validation studies for their use as such. The Access group comprises the antibiotics that should be prescribed first and second for the most common clinical infections. It is composed of mostly narrow-spectrum antibiotics with fewer side effects, lower antimicrobial resistance selection potential, and lower cost, and are widely available. The Watch group contains generally broader spectrum antibiotics with higher antimicrobial resistance selection potential, usually suitable for more sick patients in hospital settings, and they require monitored use to avoid overuse. The Reserve group comprises antibiotics that should be used as a last resort, generally in severe infections, by multidrug-resistant pathogens. Accordingly, the AWaRe classification is intended as a tool for monitoring antibiotic use, defining targets, and monitoring antimicrobial stewardship policies aiming to optimize antibiotic use. For example, the WHO 13th General Programme of Work 2019–2023 and subsequent revisions included a country-level target of at least 60% of total antibiotic consumption being Access group antibiotics. Achievement of this, therefore, partly may depend on

the revision of EMLs, prescribing guidelines, and supervision of antibiotic use at the national level. It is anticipated that the effective implementation of the AWaRe classification can prolong antibiotic effectiveness.
Since the publication and implementation of the AWaRe classification, several studies have been conducted to assess how the AWaRe classification has been used in measuring prescribing practices and the extent of its adoption at the country level across the globe. Therefore, this review chapter evaluates the literature and determines the extent of AWaRe classification utilisation in prescribing practices.

Methods and materials

The study followed a scoping and qualitative review approach as described by Mak *et al.* The following search string was used to retrieve the relevant literature from Google Scholar, and PubMed: [("WHO AWaRe" OR "WHO Access Watch Reserve" OR "AWaRe classification") & (antibiotic OR antimicrobial) & (prescribing practices OR prescribing behaviour OR prescribing patterns OR antibiotic stewardship)]. The publication dates of the peer-reviewed articles were filtered to be between 2017 and September 2024 (since the AWaRe tool was developed in 2017). The search retrieved 163 articles, and after abstract title screening, 96 studies were included. The information in the articles was critically reviewed from the title, abstract, and full text. Based on the collected literature, critical issues associated with AWaRe classification were identified, which included whether the studies reported attainment of AWaRe classification goals and common challenges associated with AWaRe classification implementation.

Monitoring and evaluation of the AWaRe classification utilisation

The AWaRe classification aims to reduce the use of the watch and reserve groups of antibiotics as well as reporting the use of antibiotics using the Global Antimicrobial Resistance Surveillance System (GLASS). According to the WHO target, each country was expected to use at least 60% of the Access group in its overall country-level antibiotic use by the year 2023 if it was to manage the rising resistance and make antibiotic use safer and more effective. AWaRe implementation indicators or markers were developed, which included: i) integration of the AWaRe classification into the essential medicines list; ii) antimicrobial stewardship national action plans; iii) monitoring and evaluation systems; and iv) supply chain and logistics management systems, and training programs (MTaPS, USAID).
To assess the WHO target at least 60% of the country-level antibiotic consumption should be from the Access group by 2023, the 96 eligible studies were reviewed. **Figure 1** below shows the selected number of surveys conducted worldwide on AWaRe classification implementation.

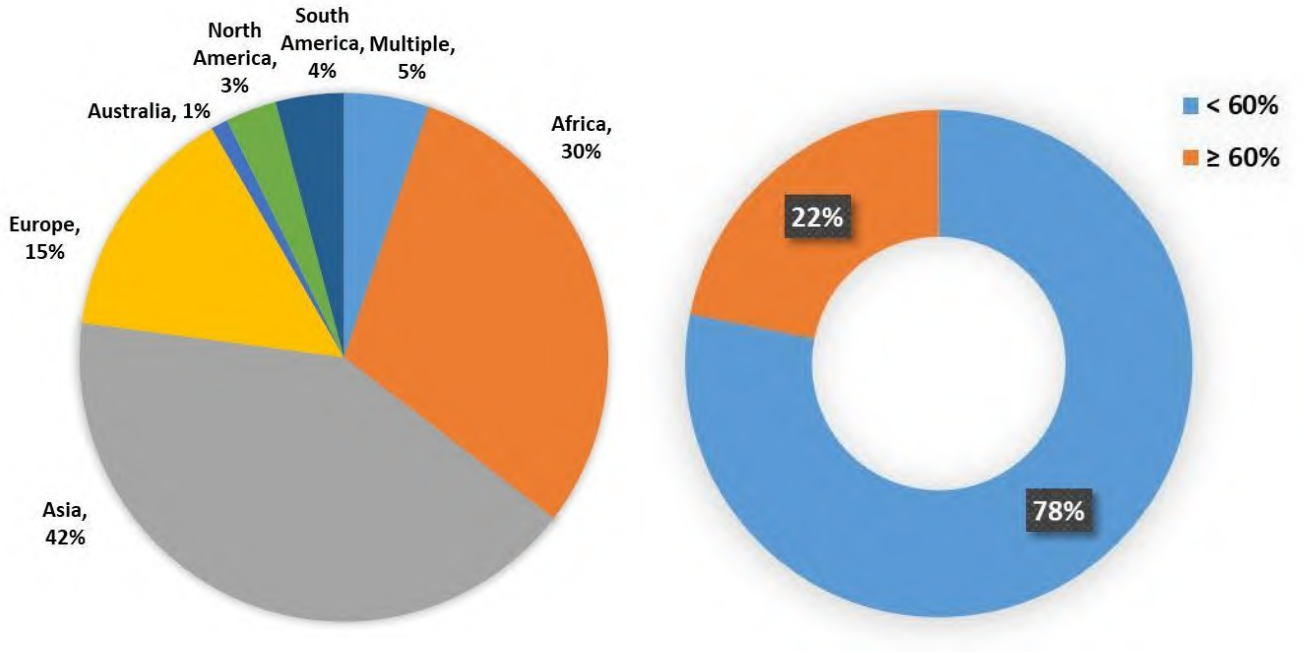

Figure 1. Study continents and proportions (on the left). The proportion of studies that reported prescriptions with 60% Access group antibiotics (on the right)

The 96 studies were conducted in 55 countries across all WHO regions, and only 22% of the studied sites in these countries had 60% Access group antibiotics in their prescriptions or supply chain records. The problem was widespread across the continents regardless of income level. While some countries had many studies, others had one to none. Additionally, there were varied results, whereby some countries such as Colombia, Ghana, India, Sierra Leone, South Africa, Vietnam, Uganda, Zambia, and Tanzania had studies reporting both ≥60% Access group antibiotics and <60% Access group antibiotics. Since the introduction of the AWaRe classification, antibiotic consumption has been varying in different countries and settings. For example, there was an increase in the Watch group and a decrease in the Access group at a public sector hospital in Limpopo province; an observation that was also noted in an Indian study; and a Zambian study where the Watch group ceftriaxone was the most prescribed. In Canada, the regional stratification of antibiotic prescription showed a varied pattern of AWaRe antibiotics groups, whereby the Access antibiotics group was mostly prescribed in western (46.4%) and eastern (44.5%) regions hospitals, while the Central region had 31.9% and 66.0% of all antibiotics from the "Watch" group.

Furthermore, this review has revealed that there is a high prevalence of non-recommended fixed-dose combination antibiotics (FDC-AB) worldwide, including low- and middle-income countries, especially in Sub-Saharan Africa. For example, one study in Tanzania showed a significant portion of non-recommended FDC-AB between 2017 and 2019 when the AWaRe classification was in use, with drug combinations like norfloxacin-tinidazole and penicillin being among the most commonly used antibiotics. The overuse of antibiotics was also reported within the AWaRe classification utilisation period in a survey done in a private pharmacy, where prescriptions containing one, two, three, and four antibiotics were reported, which shows that some pharmacies only care about their business, not the quality care and AMR drive. Furthermore, there were differences in the most widely used antibiotics overall and in the AWaRe classification group, but the most widely used, included the 3rd generation cephalosporins, with ceftriaxone, metronidazole, and amoxicillin as the

commonly used antibiotics. This variation could be due to the differences in disease burdens, availability, or costs.

Many of the studies were also conducted in different settings such as supply chain warehouses, single and multiple hospitals or clinics, and community pharmacies, in different periods, which made the trend and comparative analysis difficult. Therefore, the results might not give a true picture of what is going on the ground. For example, some results are recent while others are old within the AWaRe period (2017-2024), which makes it easier to know the status of the sites whose results are recent and difficult to know the status of the sites whose studies are old. Additionally, these are mostly reports derived from studies, not from national repositories for the AWaRe classification monitoring and evaluation or systems, where well-coordinated and routine monitoring and evaluation data can be deposited and accessed for analysis.

Several studies have been reported on training programs, and they have shown that awareness and training activities about hospital antimicrobial stewardship programs can improve the knowledge, attitude, and practices of healthcare providers about AWaRe classification. For example, training and awareness programs in Albania reduced inappropriate utilization of the Watch group antibiotics, hence AMR prevention antibiotics. In Albania, awareness activities and hospital antimicrobial stewardship programs addressed knowledge, attitude, and practice gaps about AWaRe classification, whereby inappropriate utilization of antibiotics in the Watch group was reduced and improved AMR prevention.

Integration of the aware classification into the essential medicines list has also been one of the indicators of AWaRe classification implementation. A study by Adekoya done in 2020 showed that most countries updated their national essential medicines lists (NEMLs) in alignment with the AWaRe classifications, although some countries such as Bangladesh, Bosnia and Herzegovina, Bulgaria, Latvia, Panama, Poland, and Yemen were lagging as they had very few essential Access antibiotics (fewer than ten). Although studies have shown that adoption of AWaRe can be influenced by income level, these countries showed that they had lower adoption than counterparts with comparable income levels. Another study in Nepal showed that there were differences between the NEML antibiotics list and the WHO AWaRe antibiotics list. These results confirm that there is still limited progress in the integration of AWaRe classification antibiotics into the NEMLs. It is reported that the listing of medicines in NEMLs can have a significant impact on the availability, use, and adherence to the AWaRe classification in subsequent processes such as procurement, purchasing, and prescribing. Additionally, priority bacterial infections with high global disease burdens could be limited or lack appropriate. This review also found that there are varied lists of Watch antibiotics, as shown in previous studies.

Another indicator of AWaRe is the antimicrobial stewardship national action plan development. In a study by Charani *et al.*, conducted in 2022, in which they analysed the existing national action plans (NAPs) for antimicrobial resistance worldwide, 64% (122/192) of the studied countries had a NAP, and they found that there were marked gaps and variability in the national action plan development and operationalisation levels. The evaluated NAP domains included policy and strategic planning, medicines management and prescribing systems, technology for optimised antimicrobial prescribing, context, culture, and behaviours, operational delivery, and monitoring, as well as patient and public engagement and involvement.

Common challenges related to AWaRe classification utilisation

The studies evaluated have contributed valuable insights into the AWaRe classification utilisation worldwide, the challenges faced in its utilisation, and offer recommendations for enhancing the effective implementation of the AWaRe classification for antimicrobial resistance. **Table 1** below shows the commonly reported problems and potential solutions. As shown in **Table 1**, tools for monitoring and evaluating the consumption

of antibiotics in the AWaRe as well as non-recommended FDC-AB in low- and middle-income countries, especially in Sub-Saharan Africa, have been reported as one of the challenges affecting the AWaRe classification implementation. This might have led to the persistence of nonadherence to the AWaRe classification.

Table 1. Challenges of AWaRe classification and their potential solutions.

Sector	Challenge effects	Solution
Monitoring and evaluation: lack of routine AWaRe classification data collection and reporting repository	Failure to quantify the problem, success, and progress	Indicators for each sector: public and private, disease-specific, hospital-level specific, etc.
Knowledge, attitudes, and practices of health workers (or prescribers)	Limited knowledge about the list of the drugs under AWaRe groups and the implications of nonadherence	Designing antimicrobial stewardship programmes that integrate AWaRe concepts in patient care provision.
Supply chain management	Limited availability of recommended AWaRe group drugs, which leads to prescription and/or disbursement of the wrong group due to supply choices	AWaRe classifications/NEMLs that guide the demand and supply of drugs Regulation of import of medicines by public and private sector drug supply players
Nonalignment of the NEMLs and AWaRe classification group drugs	Lack or limited availability and access to enough or appropriate antibiotics for priority bacterial infections with high global disease burdens	Revise the NEMLs to align with the AWaRe classification by increasing Access group drugs and reducing Watch and Reserve group antibiotics.
Limited funding for drugs	Convenient purchasing and selling of drugs due to pricing and budget constraints	Increase access and affordability of narrow-spectrum, safe, and affordable (Access) antibiotics while discouraging inappropriate use of broader-spectrum (Watch) and (Reserve) antibiotics.
Unclassified drugs	Confusion for health care providers, underuse of important drugs	Reclassification of antibiotics, and updating the AWaRe classification
Global crises	Changes in prescribing patterns	Robust AMR prevention measures, incorporation of AWaRe classification in prescribing decisions and increasing AMS vigilance during crises
Different disease burdens and prescribing needs	Low adherence to AWaRe classification	Adapt the AWaRe targets based on the risk, and burden of the target sites.
Lack of impact evaluation of AWaRe on AMR	Lack of informed choices for the alignment of the framework's goals and values towards AMS	Measuring the impact of the AWaRe classification on the prevalence of AMR in different settings

Abbreviations. AMR: antimicrobial resistance. NEMLs, national essential medicines lists.

The AWaRe classification itself is also without faults, as noted and reported elsewhere that some AWaRe groups contain drugs with different spectrums of action and indications, like in the case of amoxicillin, cloxacillin, and amoxicillin-clavulanate, that belong to the Access group, yet they have different characteristics. For example, in acute otitis media treatment, amoxicillin and amoxicillin-clavulanate are the first and second choices, respectively, yet cloxacillin is better than amoxicillin-clavulanate for mild soft tissue infections and bacterial lymphadenitis treatment, from an AMR perspective. This grouping challenge has led to some countries adopting the AWaRe classification to suit their objectives, prescribing needs, and disease burdens. Therefore, this calls for guidance on ways of adapting and using the AWaRe framework in different settings based on the risk and burden of the target sites or disease epidemiology and the countries' GDP.

Although this review has shown that several studies have reported the existence of programs aimed at the knowledge, attitudes, and practices as well as awareness of the AWaRe classification, the problem still exists

in many parts of the world, and there still exist significant gaps in knowledge, attitudes, and practices for the AWaRe classification. Additionally, there is limited promotion of using 'Access' antibiotics over the Watch and Reserve categories. Affordability and accessibility of antibiotics have also been cited as reasons for the use of unrecommended groups.

Global health crises are also one of the factors that have been noted as contributing to the lack of adherence to AWaRe, as noted during the COVID-19 pandemic, where AWaRe classification use was disrupted due to new guidelines for managing it that interfered with the AWaRe guidelines as well as disrupted supply chain systems and AMR drives such as resources and personnel. In a study in the UK on the impact of COVID-19 on antimicrobial stewardship measures, mixed results were reported where there were shifts in prescribing patterns for some antibiotics and no significant changes for others. It was also revealed that the AWaRe classification enabled a structured description of antibiotic use. It was recommended that there should be robust AMS measures and strengthening the AMS vigilance during crises to effectively address AMR challenges that arise. Community pharmacies have also been faulted for nonadherence and overuse of antibiotics. Several studies have reported the overuse of antibiotics and selling of Not recommended and Reserve groups due to many factors, some of which are intentional, while others are societal bottlenecks. Therefore, awareness programs should also be targeting community pharmacies.

Another challenge affecting AWaRe classification adoption is the unavailability of Access group drugs. As already shown by some studies, Access group antibiotics in many NEMLs, as well as hospitals, is limited or not available at times for many reasons, such as cost, and it is recommended that this could be solved by, among others, registration of many generic drugs, where demand and supply forces would lead to competition, price reduction, affordability, and accessibility. Furthermore, measures should be put in place to ensure that Watch and Reserve group antibiotics are more expensive than the Access group to minimise price convenience purchasing. This may call for increasing political will and resources to the health sector and players, as well as incentives to the wholesalers and distributors on some products, such as tariff or tax exemptions or reductions and discounts. This could also include the use of regulatory body involvement, whereby the wholesalers can be controlled on what they import into the countries or placing restrictions on some products, such as Watch and Reserve group antibiotics, regulation of wholesale and retail markups as well as pharmaceutical remunerations.

As noted in the review, the data collected is not enough for decision-making regarding the AWaRe framework performance due to incomparability, as a result of a lack of or limited availability of robust tools and systems for monitoring and evaluating antibiotic consumption (recommended and non-recommended FDC-AB). There are limited multinational and multisectoral antimicrobial stewardship strategies, which makes it difficult to relate the data. Dealing with these problems could minimise the use of the Watch and Reserve group as well as abolish the consumption of non-recommended FDC-AB consumption.

Conclusion

The chapter has shown that there have been several countries evaluating the AWaRe classification utilisation. The studies have shown that many countries are lagging in the utilisation of the AWaRe classification in prescribing due to many bottlenecks, such as limited integration of the AWaRe framework into the supply chain system and the NEMLs, limited integration and availability or accessibility of Access group antibiotic treatment options in the hospitals, which limits the prescribers choice; alternative cheaper treatment options in the Watch and Reserve groups than the Access group that tempt prescribers to issue Watch or Reserve group antibiotics; and a lack and limited developed AMR NAPs that limit awareness, knowledge, attitudes, and

practices of health care providers. However, at this point, it is difficult to conclude the status quo on the adherence level for each group based on the available data, as the results are variable due to many factors such as time, site, and manner of data collection, which make the monitoring, tracking, and comparability difficult. In addition, several studies evaluated the AWaRe classification utilisation assessment but did not cover all the AWaRe classification parameters, making some indicators less studied than others. Some studies did not explicitly show the proportions belonging to each AWaRe group, making it difficult to include them in the analyses. Other studies included incomplete data, for example, only for one group, and irrelevant units of measurement. Therefore, guidelines are needed for the AWaRe classification indicator to make them more useful, as literature surveys provide invaluable information that some countries cannot manage to produce due to resource constraints, and these studies can address such gaps if done well with harmonised procedures and tools. Some countries are doing well and better than others. However, those countries doing well might be affected by those lagging because they are in a global village where the resistant strains can be spread through travel. Therefore, there should be concerted efforts so that all places are doing things correctly, thereby simultaneously and across the board achieving the purpose of AWaRe. Multinational surveys do not show detailed AWaRe information figures despite showing them in figures without corresponding numbers.

Competing interests

The authors have no financial and non-financial competing interests to declare.

References

1. Vincenzo N. Introductory Chapter: Surgical Infections. In: Vincenzo N, editor. Infectious Process and Sepsis.
2. Abu-Ajaleh S, et al. An Evaluation of the Impact of Increasing the Awareness of the WHO Access, Watch, and Reserve (AWaRe) Antibiotics Classification on Knowledge, Attitudes, and Hospital Antibiotic Prescribing Practices. Antibiotics. 2023;12:951.
3. Abdelsalam Elshenawy R, et al. WHO AWaRe classification for antibiotic stewardship: tackling antimicrobial resistance – a descriptive study from an English NHS Foundation Trust prior to and during the COVID-19 pandemic. Front. Microbiol. 2023:14:1298858.
4. Adekoya I, et al. Comparison of antibiotics included in national essential medicines lists of 138 countries using the WHO Access, Watch, Reserve (AWaRe) classification: a cross-sectional study. Lancet Infect Dis. 2021;21:1429-1440.
5. Bhardwaj A, et al. Trend analysis of antibiotics consumption using WHO AWaRe classification in tertiary care hospital. International Journal of Basic & Clinical Pharmacology. 2020;9:1675.
6. Canadian Antimicrobial Resistance Surveillance System (CARSS). This dashboard presents integrated information from PHAC surveillance systems on antimicrobial use data in humans and animals. Available at: https://health-infobase.canada.ca/carss/amu/results.html?ind=01. Last accessed: 30 September 2024.
7. Charani E, et al. An analysis of existing national action plans for antimicrobial resistance-gaps and opportunities in strategies optimising antibiotic use in human populations. Lancet Glob Health. 2023;11:e466-e474.
8. Chaurasiya RK. Availability of access, watch, and reserve group antibiotics in pharmacies surrounding tertiary hospitals in Chitwan, Nepal. J Chitwan Med Coll.2024;14:54-58.
9. Gagliotti C, et al. Patterns of community antibiotic use with reference to the AWaRe classification of the World Health Organization. JAC Antimicrob Resist. 2024;6:dlae110.

10. Darwish Elhajji F, et al. Overview of Availability, Cost, and Affordability of Antibiotics for Adults in Jordan: An AWaRe Classification Perspective. Antibiotics (Basel). 2023;12:1576.
11. Moore DP, et al. Antibiotic and antifungal use in paediatric departments at three academic hospitals in South Africa. IJID Reg. 2023;10:151-158.
12. Dereje B, et al. Prescribing Pattern and Associated Factors in Community Pharmacies: A Cross-Sectional Study Using AWaRe Classification and WHO Antibiotic Prescribing Indicators in Dire Dawa, Ethiopia. Drugs Real World Outcomes. 2023;10:459-469.
13. Hoxha I, et al. 11-Year Trend in Antibiotic Consumption in a South-Eastern European Country; the Situation in Albania and the Implications for the Future. Antibiotics (Basel). 2023;12:882.
14. Hsia Y, et al. Use of the WHO Access, Watch, and Reserve classification to define patterns of hospital antibiotic use (AWaRe): an analysis of paediatric survey data from 56 countries. Lancet Glob Health. 2019;7:e861-e871
15. Jha N, et al. Availability of access, watch, and reserve (AWaRe) group of antibiotics in community pharmacies located close to a tertiary care hospital in Lalitpur, Nepal. PLoS One. 2023;18:e0294644.
16. Kakumba JM, et al. Evaluation of Antibiotic Prescribing Pattern Using WHO Access, Watch and Reserve Classification in Kinshasa, Democratic Republic of Congo. Antibiotics. 2023;12:1239.
17. Lee KS, et al. Factors Impacting Pharmaceutical Prices and Affordability: Narrative Review. Pharmacy (Basel). 2020;9:1.
18. Mak S, et al. Steps for Conducting a Scoping Review. J Grad Med Educ. 2022;14:565-567.
19. Mendelson M, et al. Ensuring progress on sustainable access to effective antibiotics at the 2024 UN General Assembly: a target-based approach. Lancet. 2024;403:2551 – 2564.
20. Moja L, et al. WHO's essential medicines and AWaRe: recommendations on first- and second-choice antibiotics for empiric treatment of clinical infections. Clin Microbiol Infect. 2024;30 Suppl 2:S1-S51.
21. MTaPS. A Technical Guide to Implementing the World Health Organization's AWaRe Antibiotic Classification in MTaPS Program Countries. Available at: https://www.mtapsprogram.org/wp-content/uploads/2021/03/USAID-MTaPS_Implementing-WHO-AWaRe-Classification.pdf. Last accessed: 30 September 2024.
22. Mthombeni TC, et al. Antibiotic consumption by Access, Watch and Reserve index in public sector of Limpopo province, South Africa: 2014–2018. S Afr J Infect Dis. 2022;37:a463.
23. Mudenda S, et al. World Health Organization AWaRe framework for antibiotic stewardship: Where are we now and where do we need to go? An expert viewpoint. Antimicrob Steward Healthc Epidemiol. 2023;3:e84.
24. Mudenda S, et al. Prescribing Patterns of Antibiotics According to the WHO AWaRe Classification during the COVID-19 Pandemic at a Teaching Hospital in Lusaka, Zambia: Implications for Strengthening of Antimicrobial Stewardship Programmes. Pharmacoepidemiology. 2023; 2:42-53.
25. Nguyen NV, et al. Community-level consumption of antibiotics according to the AWaRe (Access, Watch, Reserve) classification in rural Vietnam. JAC Antimicrob Resist. 2020;2:dlaa048.
26. Parmar B, et al. Prevalence of antibiotic resistance: an alarming threat for human. Vegetos. 2024.
27. Storehagen L, et al. Should Antibiotics Be Controlled Medicines? Lessons from the Controlled Drug Regimen. J Law Med Ethics. 2018;46:81-94.
28. Vliegenthart-Jongbloed K, et al. Not recommended fixed-dose antibiotic combinations in low- and middle-income countries - the example of Tanzania. Antimicrob Resist Infect Control. 2023;12:37.
29. World Health Organisation. Thirteenth general programme of work 2019–2023. Available at: https://iris.who.int/bitstream/handle/10665/324775/WHO-PRP-18.1-eng.pdf?sequence=1. Last accessed: 30 September 2024.
30. Web Annex C. WHO AWaRe (Access, Watch, Reserve) classification of antibiotics for evaluation and monitoring of use, 2023. In: The selection and use of essential medicines 2023: Executive summary of the report of the 24th WHO Expert Committee on the Selection and Use of Essential Medicines. 2023 (WHO/MHP/HPS/EML/2023.04).
31. Zanichelli V, et al. The WHO AWaRe (Access, Watch, Reserve) antibiotic book and prevention of antimicrobial resistance. Bull World Health Organ. 2023;101:290–296.

Chapter 74

Old and modern antibiotics for today's infections

Rahnuma Ahmad
Department of Physiology, Medical College for Women and Hospital, Dhaka, Bangladesh.

Mainul Haque
The Unit of Pharmacology, Faculty of Medicine and Defence Health, Universiti Pertahanan Nasional Malaysia (National Defence University of Malaysia), Kuala Lumpur, Malaysia.

Introduction

Antibiotics were introduced into use in the twentieth century, and this was one of the groundbreaking events of the century. This allowed infectious diseases to be treated and made it possible for numerous modern medical procedures to be carried out safely, including open heart surgery, cancer treatment, and organ transplants. Unfortunately, there has been long-standing misuse of these precious compounds, and because of this, we are now facing a dangerous era of antimicrobial resistance. Such recent developments have led policymakers to realize and provide funds for continuing the research to discover and develop new antibiotics. It has been suggested that if immediate action is not taken, global mortality due to antimicrobial-resistant infection by 2050 will rise to 10 million per year.

Researchers are now looking into new microbial natural products to produce new-generation antimicrobial drugs. The reasons for this approach are that synthetic antibiotics have not been incredibly successful, and natural compounds are far more diverse chemically and as antibiotics are more effective.

Among these known natural products, 64% are of filamentous actinomycetes. Microbes-producing antibiotics have been used for thousands of years; for example, moldy bread poultices were used more than two thousand years ago to treat wounds in Egypt, China, Greece, and Serbia. The application of medicinal soil and moldy bread as remedies has been discovered in Eber's papyrus from 1551 BC. Methicillin-resistant *Staphylococcus* has been successfully killed using an Anglo-Saxon recipe dating back 1000 years. However, Paul Ehrlich is acknowledged for the development of synthetic arsenic-based prodrug salvarsan and neo-salvarsan circa for the treatment of the organism responsible for syphilis, *Treponema pallidum*, one hundred years ago. Ehrlich used dyes to stain bacteria cells precisely, and Gerhard Domagk (bacteriologist from Bayer) discovered the sulfonamide prodrug Prontosil, inspired by these dyes for staining bacteria cells. This sulfonamide was the first broad-spectrum, effective antimicrobial used clinically.

Filamentous *Actinomycetales*, which produce antimicrobials, was discovered by Selman Waksman in the 1930s. Neomycin and streptomycin were the first anti-tubercular agents. Several streptomyces are anti-bacterial, antifungal, and anti-viral. The 1940s-1960s was the golden age of antibiotic discovery following the steps of Waksman, and these antibiotics are still used today, although their effectiveness has been reduced

with rising antimicrobial resistance. Most antibiotics under clinical trial are synthetic or derived from already-known natural product classes.

The antibiotics being used as single agents may not be able to eliminate specific pathogens as they have become resistant. These pathogens, known as ESKAPE pathogens, include *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter* spp. Certain high-cost antibiotics may be found in advanced countries, but such drugs may not be affordable for a large population segment, particularly in low and middle-income countries. Therefore, researchers want to modify and/or reinvestigate previously ignored compounds because of their dosing difficulty, chemical instability, unwanted side effects, and toxic properties. The World Health Organization (WHO) in 2017 issued a list of 12 microorganisms that had become resistant to the antibiotics available. Then, in 2024, the WHO updated this list (the Bacterial Priority Pathogens List), which included fifteen families of antibiotic-resistant bacteria divided into medium, high, and critical categories per prioritization. This list may allow policymakers and health authorities to provide guidelines for using new antibiotics for investment and treatment.

This was done to urge scientists and the pharmaceutical industry to discover new antibiotics (natural products, synthetic or semisynthetic) to avoid a dangerous scenario where millions may die due to failure of treatment of infections.

Objective and methods

This work aimed to gather information concerning the antimicrobials discovered in the past now being modified. Such antibiotics are again in the limelight, as with the use of synthetic chemistry, the structures may be modified to become effective against microbes that have become resistant to the original structures. The work also looks into natural-based products and peptidic compounds that are being discovered using baiting techniques and genomic searches. The research also examines novel modern antibiotics with promising effects against ESKAPE pathogens. The information was collected with the help of databases like PubMed, Scopus, and Google Scholar between June 204 and August 2024. The keywords used for searching included 'antimicrobial,' AND 'Resistant bacteria,' AND 'Natural antimicrobial product,' AND 'Synthetic chemistry,' AND 'Vancomycin,' AND 'glycopeptides,' AND 'peptidic compounds,' AND 'cGMP,' AND 'baiting technique,' AND 'ESKAPE,' AND 'antimicrobial peptides (AMPs).'

Old and new antibiotics against microbes

This research section delves into the various old structures modified to become effective antimicrobials and natural-based antimicrobial products, and it currently produces synthetic and semisynthetic agents.

Vancomycin and glycopeptides

Vancomycin (**Figure 1**) was approved by the FDA (Food and Drug Administration) in 1958 and was structurally entirely defined in 1982 when confirmation was given regarding the presence of asparagine in its structure. This antibiotic and its chemically close antibiotics were known for many years as 'the antibiotics of last resort.' Vancomycin and naturally appearing or semisynthetic chemically similar antibiotics exerted their action of inhibiting the growth of bacteria by binding with *l-Ala-d-iso-Gln-l-Lys-d-Ala-d-Ala* terminals in the cross-links of the wall of Gram-positive cell. Vancomycin resistance occurred in the case of *vanA, vanB, and vanD* when

D -Ala residue was replaced by *D*-Lactate, and in *vanC, vanG,* and *vane D*-Ser replaced *D* -Ala residue. Bacteria like *Staphylococcus aureus* also started to become resistant to vancomycin. In recent years, 3 semisynthetic glycopeptides have been used in clinical settings. These include telavancin in 2009, dalbavancin in 2014, obtained from the A40926 complex, and oritavancin from chloroeremomycin.

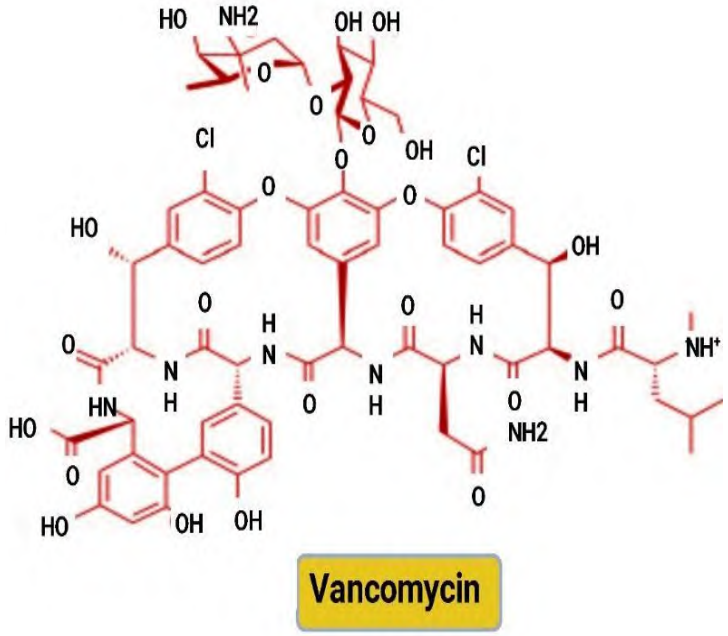

Figure 1. The structure of vancomycin.
This figure has been drawn with the premium version of BioRender (https://biorender.com/. Accessed: 3 September 2024) with license number FW279FJLT3. Image credit: Rahnuma Ahmad. O: oxygen, NH_2: amino group, OH: hydroxyl group.

Synthetic modification of vancomycin

The peptide backbone of vancomycin molecule modification through a synthetic chemical process by adding from other glycopeptides and alteration in one position of the peptide chain was carried out in Boger laboratory at the Scripps Research Institute in La Jolla, California. This alteration has been shown to potentially improve its ability to 'inhibit' Gram-positive cells and demonstrates effective activity against *E. faecalis* and methicillin-resistant *Staphylococcus aureus* (MRSA). The substitutions that were used to modify the molecule were listed by Okano *et al.* Such structural alterations to vancomycin structure led to the minimum inhibitory concentration of vancomycin for *E. faecalis* and *E. faecium* reduced from >250 µg mL-1 to 5 to 0.005 µg mL-1 for these resistant microbes. Then, guanidino modifications of the C-terminus of the molecule enhanced antimicrobial properties, giving rise to the synergistic mechanism of action. 4-chlorobiphenyl)-methyl (CBP) modification was coupled with X = O and R = a variety of guanidino substituents, and several modified vancomycins were produced, which exhibited minimum inhibitory concentration levels against resistant microbes. These molecules do not display hemolytic properties, have better pharmacokinetic properties, and show *in vivo* potency and efficacy against MRSA and *Staphylococcus aureus* strain, which is vancomycin-resistant. Thus, this vancomycin, first discovered in the late 1950s, has been chemically modified, known as maxamycins, to overcome the resistance developed by microbes.

Polymyxins and colistin

Chemists and microbiologists avoided these compounds from the 1960s to the late 1970s since these compounds and their chemical kins exhibited more toxic effects than aminoglycosides, tetracyclines, etc. Thus, these were not used then. However, with the advent of multidrug-resistant microbes, these compounds (polymyxin and colistin) (**Figure 2** and **Figure 3**) have been included in combination therapy. In 2016, it was observed that plasmid that expresses the *mcr* gene are transmissible as water-borne microbes, and resistance to currently used antibiotics, including these compounds, was noted to develop through adding phosphoethanolamine moiety to Gram-negative bacteria's cell membrane. These resistant microbes, being water-borne, have been pointed out in a study to spread to different areas of China from the mainland.

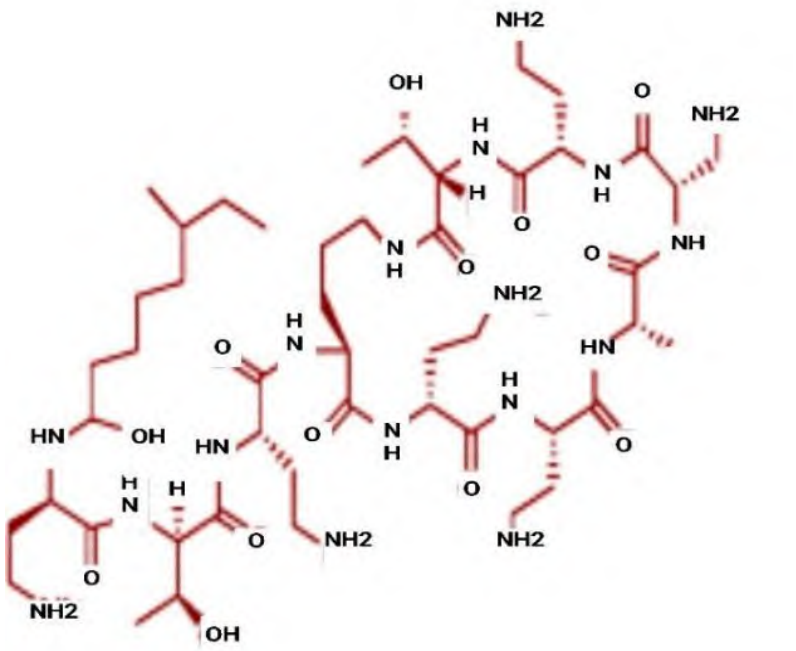

Figure 2. The structure of colistin.

This figure has been drawn with the premium version of BioRender (https://biorender.com/. Accessed: 3 September 2024) with license number HZ279FRHSN. Image credit: Rahnuma Ahmad. O: oxygen, NH_2: amino group, OH: hydroxyl group.

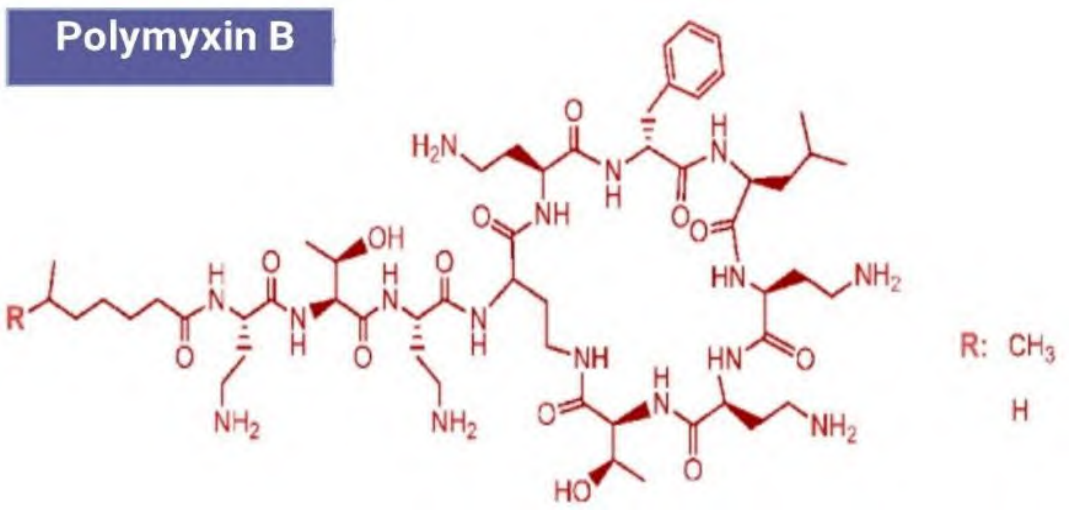

Figure 3. The structure of polymyxin.

This figure has been drawn with the premium version of BioRender (https://biorender.com/. Accessed: 3 September 2024) with license number NA279G5OT0. Image credit: Rahnuma Ahmad. O: oxygen, NH_2: amino group, OH: hydroxyl group, CH_3: methyl group.

Researchers in Germany, China, and South Australia have attempted to obtain potential antimicrobials against this resistant *A. baumannii* by producing new variations from old and well-known colistin and polymyxin B. Vaara *et al.* reported over two thousand polymyxin analogs, of which only three exhibited effectivities against the resistant Gram-negative organisms. Jiang *et al.* produced a novel and effective analog of polymyxin FADDI-287 using alanine substitution. This polymyxin analog showed the minimum inhibitory concentration of 0.125-0.5 µg mL^{-1} against *A. baumannii* in comparison to polymyxin B. Patent WO2015149131 covers FADDI-287 that has been allowed in China and USA. Colistin analogs may be produced using the semisynthetic AMP-based bacterial genomic sequence analysis done by the Brady group. Modified colistin called biphenyl macolacin was reported in 2022.

Vancomyxin

It has been known that vancomycin cannot act against Gram-negative bacteria and can only penetrate the lipid II component of the bacteria, provided the outer membrane becomes permeable. When administered together, appropriate agents that can help vancomycin penetrate the bacteria allow vancomycin to produce an effect against the Gram-negative bacteria *Escherichia coli*. In 2010, vancomycin and colistin, a combination of these 2 antibiotics, were administered simultaneously, exhibiting significant effects. In 2021, vancomycin was produced, and a spacer was added between the vancomycin, known as polymyxin E nonapeptide (PMEN). The spacer can be linked to vancomycin's C-terminus or the vancosamine amino group; thus, a compound series has been developed (**Figure 4**).

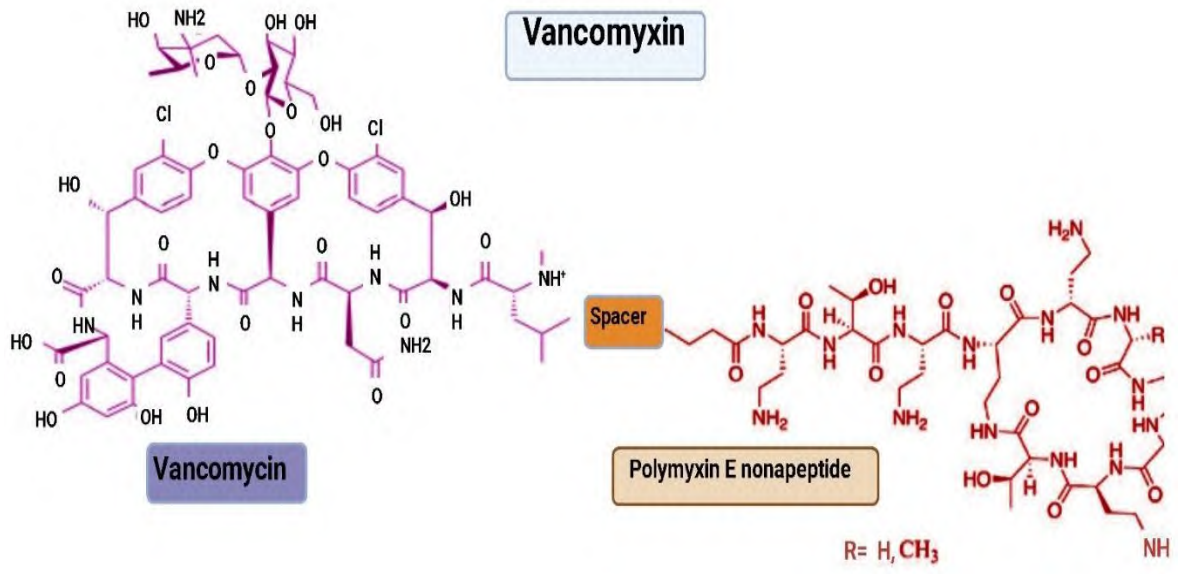

Figure 4. The structure of vancomyxin is where a spacer is placed between Vancomycin and PMEN. This figure has been drawn with the premium version of BioRender (https://biorender.com/. Accessed: 3 September 2024) with license number VT279G1ZC3. Image credit: Rahnuma Ahmad. O: oxygen, NH_2: amino group, OH: hydroxyl group, CH_3: methyl group.

Research was conducted to evaluate the efficacy of the linked vancomycin and PMENs against 5 Gram-positive and 4 Gram-negative bacteria. Six vancomycin *versus* vancomycin and PMEN separately and then again vancomycin in combination with PMEN (8 µg mL^{-1}) were tested on these Gram-positive and Gram-negative bacteria. Vancomyxin exhibited a minimum inhibitory concentration of 8-16 µg mL^{-1} against the Gram-negative bacteria, except for the *P. aeruginosa* strain (ATCC 27853) that responded to separate administration of vancomycin and PMEN, which demonstrated resistance when uncombined vancomycin and PMEN with the minimum inhibitory concentration of 128 µg mL^{-1} was applied. Vancomyxins showed a highly significant effect against Gram-positive bacteria with a minimum inhibitory concentration of 0.008 µg mL^{-1} for *Staphylococcus simulans,* while vancomycin demonstrated a minimum inhibitory concentration of 0.125 µg mL^{-1}.
Even though *in vivo* toxicities and activities of vancomycin have not been assessed, the study of the nephrotoxic and hemolytic properties have been evaluated on immortalized proximal tubule epithelial cells (ciPTECs), with relative mitochondrial activity after 24 h as the endpoint. The toxicity levels were much above the minimum inhibitory concentration *in vitro*.

Cyclic peptides other than colistin and polymyxins

The first antibiotic that was a natural product to have entered clinical usage was cyclic peptide tyrocidine, contrary to the common belief that it was penicillin and tyrocidine, an antibiotic to have been used as gramicidin derivative as reported in 1940. In 1943, gramicidin was used to treat injuries on the battlefield in the USSR. Production on a large scale and clinical use were discussed in detail by Gause in 1946. The different cyclic peptides are still being studied, and in recent years, 3 reviews have been done about natural and synthetically obtained antimicrobial peptides (AMP). In their review, Lazzaro *et al.* suggested that AMP adaptation activity may be lost, and synergy of conventional antibiotics may occur. They demonstrated synergy between AMP PGLa (an antimicrobial peptide comprising 21 amino acids that form an α-helical secondary structure) and magainin 2. These AMPs can be found in the skin of African *Xenopus laevis*. Eukaryotes can

produce different classes of AMP at the same time. AMPs have been found to show response specificity in eukaryotic phyla and may not exhibit broad-spectrum properties in all cases.
Another review of research was carried out on synthetic and semisynthetic AMPs, which highlighted a semisynthetic agent, AMP Murepavadin. It is based on protegrin (antimicrobial peptide) and is a cyclic beta-hairpin (refers to a reverse turn connecting adjacent strands in an antiparallel β sheet) peptidomimetic. It targets the transporter protein in *P. aeruginosa*. Phase I trials were permitted for this AMP via oral and inhalation routes for cystic fibrosis patients with *P. aeruginosa* infection by the UK Medicine Agency in 2020. However, in 2019, two other trials were terminated in phase III of a clinical trial due to the development of injury to the kidney. Klobucar and Brown discussed potential AMP agents, including those mentioned here, which can affect the outer membrane in Gram-negative bacteria.

Other antibiotic classes (peptide-based) that hold potential

Natural-product-derived antimicrobials, particularly peptide molecules, can be synthesized in bulk. This is done following the identification of a suitable compound, and then the compound is produced and/or modified as required for further testing.

Teixobactin

A microbe that was unknown before 2015 was isolated by the Lewis group (Northeastern University) using a 'baiting technique.' They isolated a compound (Teixobactin) that was effective against Gram-positive bacteria and resistant to multiple antibiotics. The target of this compound was noted to be the sugar moieties and pyrophosphate found in Lipid II (connected to peptidoglycan) and Lipid III (associated with cell wall teichoic and biosynthesis downregulation). The solid-phase technique has been employed for the synthesis of this compound. The first solution-phase synthesis for this agent was provided by the study done by Gao *et al.* in 2019. This compound and its derivatives can be administered via two routes into the human body. Ng *et al.* reported the modification of the agent and demonstrated its effectiveness against *P. aeruginosa*.

Grasslands DNA

The use of metagenomic research to obtain information about potential antimicrobial agents without microbe isolation was demonstrated by the Brady group (Rockefeller). Charlop-Powers and Brady published a geographic analysis and associated data of the microbiome informatics package in 2015. Biosynthetic diversity source initial data regarding Urban Park Microbiomes was brought to light by the mentioned group in 2016. They noted a cluster of genes that may be connected to a calcium-dependent antibiotic. In 2018, they covered the analogs of paenimucillin A while reporting on the synthetic-bioinformatic natural product (culture-independent) discovery approach. This resulted in the finding that paenimucillin C can inhibit the growth of *A. baumannii* isolates (multidrug-resistant). It was implied that the mechanism of action involved the cell membrane. In 2020, the research horizon was further expanded when, from 96 clusters of NRPS, 157 cyclic peptides were synthesized. These agents were used against the microbes in the ESCAPE category, and 9 antibiotics were found to be effective against some of these pathogens and against *M. tuberculosis*. There was also a report on the discovery of a CDA compound (culture-independent) in which the high effectiveness of malacidin A, having a minimum inhibitory concentration of 0.1 to 0.8 μg mL^{-1}, was demonstrated. Malacidin A was effective against microbes exhibiting resistance against tetracyclines, aminoglycosides, tetracyclines, and β-lactams. Malacidin B was also reported, which differed from malacidin A by one methylene group. Malacidin A complete synthesis was reported by Rockefeller and the University of Hongkong together in 2020, while a second complete malacidin A synthesis with its analogs was given by the Brimble Group (New Zealand).

In 2021, a research study gave details regarding the clinical trials involving peptidic antibiotics, which revealed that cyclic and linear peptide variations exhibited significant activity against antibiotic-resistant microbes. Another study showed the list of synthetic, semisynthetic, and natural product antibiotics discovered in the previous 5 years in 2021. Similarly, another study displayed an updated list of antimicrobial agents, their sources and outcomes of their clinical trials, and the mechanism of action involved.

Synthesis of cGMP products

cGMP-quality, complete, or partial natural products have been successfully synthesized recently, producing drugs like eribulin. Such research has led to clinical trials of tetracycline-like molecules. In the 1990s, the Lederle (Pfizer) laboratories had developed modified versions of tetracyclines like sarecycline, eravacycline, and omadacycline, which in 2018 received approval for clinical use. Two other compounds, Viridicatumtoxin A and B, have been derived by adding 4 ring scaffolds to the nucleus of the tetracycline. Viridicatumtoxin was first found in *Penicillium viridicatum* fungus in 1973 by Hutchinson *et al.*, and Viridicatumtoxin B was observed in 2008 by Zheng *et al.* This Viridicatumtoxin B synthesis was later reported in 2013 by the Nicolaou group, and in 2014, the structure was revised, and a related active compound was synthesized. Viridicatumtoxin A and B compounds were significantly effective against antimicrobial-resistant *E. faecium, E. faecalis,* and multidrug-resistant strains of bacteria.

Recently, fungi, *Aspergillus nidulans, Plasmodium brasilianum, and Aspergillus* spp*.,* have been discovered to contain biosynthetic gene clusters for Viridicatumtoxin. Viridicatumtoxins A, B, C, D, E, F, and spirohexaline in *Paecilomyces* sp were reported in 2015 by the University of Queensland Capon group. Viridicatumtoxin and spirohexaline are small fungal molecules with a tetracyclic scaffold and spirobicyclic ring in typical.

Antimicrobial activity was 15 to 40 times more pronounced than cell toxicity in the case of Viridicatum toxins B and C. Viridicatumtoxins A, and B are more effective against vancomycin-resistant *E. faecalis* and multidrug-resistant strains. *Paecilomyces* spp. could open the ring structure of regular tetracycline and thus exhibit resistance.

An ACS infectious diseases report in 2020 reported the mechanism for the anti-bacterial activity of these compounds. These agents (Viridicatumtoxins) target the undecaprenyl pyrophosphate synthases of *E. coli, E. faecalis,* and *S. aureus*. These agents bind to this essential component for synthesizing the cell wall with great affinity.

Other agents that have an inhibitory effect on the undecaprenyl pyrophosphate synthases are the two gamboge-derived antimicrobial compounds, Gambogic acid and Neogambogic acid. Gambogic acid is caged prenylated garcinia xanthone and neogambogic acid is C3-C4 hydration form of gambogic acid. Gamboge is a dry resin derived from Garcinia (a traditional Chinese medicine). Modification of biosynthetic gene cluster along with fermentation may lead to more such compounds, which can eliminate Gram-positive ESKAPE bacteria.

Limitations of this chapter

The chapter does not consider studies performed in languages other than English. The chapter has tried to highlight the recent discoveries but may not have been able to include all of them. Also, no human or laboratory experiments have been performed by the researchers of this work while writing the chapter. Our universities do not subscribe to the Web of Science or have no financial support, so we were principally dependent on open-access papers / free downloads from the PubMed database. However, the National Defence University of Malaysia has access to Scopus but only for open-access papers.

Future recommendation

The scientific community, including synthetic chemists, microbiologists, the pharmaceutical industry, and antibiotic discoverers, need to work together to continue to find novel antibiotics. Since the microbes are ever finding ways to escape the grip of the antimicrobials, the researchers should carry on using natural-based products and genomic searches and keep records of their findings.

Conclusion

Chemists can now modify natural product-based antimicrobials that have become ineffective against multi-drug-resistant microbes. Examples of many such modifications and their effectiveness on the resistant microbes have been detailed in this chapter. Polymyxins and colistin, not considered in the 1960s and 1970s, have been modified recently and have proved active against Gram-negative bacteria that had developed resistance. Structural modification to vancomycin has been effective in eliminating resistant Gram-positive bacteria.

Therefore, those discovering or developing antibiotics should work closely with natural products, synthetic chemists, and microbiologists to obtain and create new compounds with clinical significance. Also, the information base regarding genome, emerging compounds, and their functioning should be included while researching and developing novel antimicrobial agents to fight effectively against the ever-rising microbes with drug resistance.

Competing interests

The authors have no competing financial and non-financial interests to declare.

References

1. Katz L, et al. Natural product discovery: past, present, and future. J Ind Microbiol Biotechnol. 2016; 43:155-176.
2. Hutchings MI, et al. Antibiotics: past, present and future. Curr Opin Microbiol. 2019; 51:72-80.
3. Prescott JF. The resistance tsunami, antimicrobial stewardship, and the golden age of microbiology. Vet Microbiol. 2014; 171:273-278.
4. Walsh CT, et al. Prospects for new antibiotics: a molecule-centered perspective. J Antibiot (Tokyo). 2014; 67:7-22.
5. Payne DJ, et al. Drugs for bad bugs: confronting the challenges of anti-bacterial discovery. Nat Rev Drug Discov. 2007; 6:29-40.
6. Haas LF. Papyrus of Ebers and Smith. J Neurol Neurosurg Psychiatry. 1999; 67:578.
7. Harrison F, et al. A 1,000-Year-Old Antimicrobial Remedy with Antistaphylococcal Activity. mBio. 2015;6: e01129.
8. Gelpi A, et al. Magic bullet: Paul Ehrlich, Salvarsan and the birth of venereology. Sex Transm Infect. 2015; 91:68-9.
9. Otten H. Domagk and the development of the sulphonamides. J Antimicrob Chemother. 1986; 17:689-696.
10. Waksman SA, et al. Production of antibiotic substances by actinomycetes. Ann N Y Acad Sci. 2010; 1213:112-124.
11. Newman DJ, et al. Natural Products as Sources of New Drugs from 1981 to 2014. J Nat Prod. 2016; 79:629-661.
12. Muteeb G, et al. Origin of Antibiotics and Antibiotic Resistance, and Their Impacts on Drug Development: A Narrative Review. Pharmaceuticals (Basel). 2023; 16:1615.

13. Miller WR, et al. ESKAPE pathogens: antimicrobial resistance, epidemiology, clinical impact, and therapeutics. Nat Rev Microbiol. 2024 Jun 3.
14. Shafiq N, et al. Shortage of essential antimicrobials: a major challenge to global health security. BMJ Glob Health. 2021;6: e006961.
15. Guo Z. The modification of natural products for medical use. Acta Pharm Sin B. 2017; 7:119-136.
16. Boyd NK, et al. Brief Overview of Approaches and Challenges in New Antibiotic Development: A Focus on Drug Repurposing. Front Cell Infect Microbiol. 2021; 11:684515.
17. Newman DJ. Old and modern antibiotic structures with potential for today's infections. ADMET DMPK. 2022; 10:131-146.
18. Asokan GV, et al. WHO Global Priority Pathogens List: A Bibliometric Analysis of Medline-PubMed for Knowledge Mobilization to Infection Prevention and Control Practices in Bahrain. Oman Med J. 2019; 34:184-193.
19. World Health Organization. Bacterial Priority Pathogens List 2024; Bacterial Pathogens of Public Health Importance to Guide Research, Development and Strategies to Prevent and Control Antimicrobial Resistance; World Health Organization: Geneva, Switzerland, 2024. Available at: https://www.who.int/publications/i/item/9789240093461. Last accessed: 30 August 2024.
20. Butler MS, et al. Glycopeptide antibiotics: back to the future. J Antibiot (Tokyo). 2014; 67:631-644.
21. Harris CM, et al. Structure of the glycopeptide antibiotic vancomycin. Evidence for an asparagine residue in the peptide. J Am Chem Soc. 1982; 104:4293-4295.
22. Mancuso G, et al. Bacterial Antibiotic Resistance: The Most Critical Pathogens. Pathogens. 2021; 10:1310.
23. Wang F, et al. Insights into Key Interactions between Vancomycin and Bacterial Cell Wall Structures. ACS Omega. 2018; 3:37-45.
24. De Vriese AS, et al. Vancomycin: the tale of the vanquisher and the pyrrhic victory. Perit Dial Int. 2014; 34:154-161.
25. Cong Y, et al. Vancomycin-resistant Staphylococcus aureus infections: A review of case updating and clinical features. J Adv Res. 2019; 21:169-176.
26. McGuinness WA, et al. Vancomycin Resistance in Staphylococcus aureus. Yale J Biol Med. 2017; 90:269-281.
27. van Groesen E, et al. Recent Advances in the Development of Semisynthetic Glycopeptide Antibiotics: 2014-2022. ACS Infect Dis. 2022; 8:1381-1407.
28. Okano A, et al. Total Syntheses of Vancomycin-Related Glycopeptide Antibiotics and Key Analogues. Chem Rev. 2017; 117:11952-11993.
29. Okano A, et al. Peripheral modifications of [Ψ[CH2NH]Tpg4]vancomycin with added synergistic mechanisms of action provide durable and potent antibiotics. Proc Natl Acad Sci USA. 2017;114: E5052-E5061.
30. Wu ZC, et al. Vancomycin C-Terminus Guanidine Modifications and Further Insights into an Added Mechanism of Action Imparted by a Peripheral Structural Modification. ACS Infect Dis. 2020; 6:2169-2180.
31. Drott MT, et al. Diversity of Secondary Metabolism in Aspergillus nidulans Clinical Isolates. mSphere. 2020;5: e00156-20.
32. Wu ZC, et al. Maxamycins: Durable Antibiotics Derived by Rational Redesign of Vancomycin. Acc Chem Res. 2020;53:2587-2599.
33. Vaara M. Polymyxin Derivatives that Sensitize Gram-Negative Bacteria to Other Antibiotics. Molecules. 2019; 24:249.
34. Ardebili A, et al. Polymyxin combination therapy for multidrug-resistant, extensively drug-resistant, and difficult-to-treat drug-resistant gram-negative infections: is it superior to polymyxin monotherapy? Expert Rev Anti Infect Ther. 2023;21:387-429.
35. Liu YY, 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; 16:161-168.
36. Cherak Z, et al. Epidemiology of mobile colistin resistance (mcr) genes in aquatic environments. J Glob Antimicrob Resist. 2021;27:51-62.
37. Jiang X, et al. A novel chemical biology and computational approach to expedite the discovery of new generation polymyxins against life-threatening Acinetobacter baumannii. Chem Sci. 2021; 12:12211-12220.

38. Vaara M. Polymyxins and Their Potential Next Generation as Therapeutic Antibiotics. Front Microbiol. 2019; 10:1689.
39. Wang Z, et al. A naturally inspired antibiotic to target multidrug-resistant pathogens. Nature. 2022; 601:606-611.
40. Patel S, et al. Vancomycin. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available at: https://www.ncbi.nlm.nih.gov/books/NBK459263/. Last accessed: 29 August 2024.
41. Shlaes DM, et al. Escherichia coli susceptible to glycopeptide antibiotics. Antimicrob Agents Chemother. 1989; 33:192-7.
42. Antonoplis A, et al. Vancomycin-Arginine Conjugate Inhibits Growth of Carbapenem-Resistant E. coli and Targets Cell-Wall Synthesis. ACS Chem Biol. 2019; 14:2065-2070.
43. Gordon NC, et al. Potent synergy and sustained bactericidal activity of a vancomycin-colistin combination versus multidrug-resistant strains of Acinetobacter baumannii. Antimicrob Agents Chemother. 2010; 54:5316-22.
44. van Groesen E, et al. Vancomyxins: Vancomycin-Polymyxin Nonapeptide Conjugates That Retain Anti-Gram-Positive Activity with Enhanced Potency against Gram-Negative Strains. ACS Infect Dis. 2021; 7:2746-2754.
45. Hotchkiss RD, et al. Fractionation of the bacteriocidal agent from cultures of a soil bacillus. J Biol Chem.1940; 132:791-792.
46. Gause GF. Gramicidin S and its use in the treatment of infected wounds. Nature.1944;154:703.
47. Gause GF, et al. Gramicidin S origin and mode of action. Lancet. 1944; 244:715-716.
48. Gause GF. Gramicidin S review of recent work. Lancet. 1946; 248:46-47.
49. Lazzaro BP, et al. Antimicrobial peptides: Application informed by evolution. Science. 2020;368:eaau5480.
50. Zerweck J, et al. Molecular mechanism of synergy between the antimicrobial peptides PGLa and magainin 2. Sci Rep. 2017;7:13153.
51. Vanzolini T, et al. Multitalented Synthetic Antimicrobial Peptides and Their Antibacterial, Antifungal and Anti-viral Mechanisms. Int J Mol Sci. 2022; 23:545.
52. Klobucar K, et al. New potentiators of ineffective antibiotics: Targeting the Gram-negative outer membrane to overcome intrinsic resistance. Curr Opin Chem Biol. 2022; 66:102099.
53. Rossino G, et al. Peptides as Therapeutic Agents: Challenges and Opportunities in the Green Transition Era. Molecules. 2023;28:7165.
54. Shukla R, et al. Teixobactin kills bacteria by a two-pronged attack on the cell envelope. Nature. 2022; 608:390-396.
55. Gao B, et al. Solution-phase total synthesis of teixobactin. Org Biomol Chem. 2019; 17:1141-1153.
56. Ng V, et al. Rational Design and Synthesis of Modified Teixobactin Analogues: In Vitro Anti-bacterial Activity against Staphylococcus aureus, Propionibacterium acnes, and Pseudomonas aeruginosa. Chemistry. 2018; 24:9136-9147.
57. Charlop-Powers Z, et al. Metagenomic small molecule discovery methods. Curr Opin Microbiol. 2014; 19:70-75.
58. Charlop-Powers Z, et al. Phylogeo: an R package for geographic analysis and visualization of microbiome data. Bioinformatics. 2015; 31:2909-2911.
59. Charlop-Powers Z, et al. Urban Park soil microbiomes are a rich reservoir of natural product biosynthetic diversity. Proc Natl Acad Sci U S A. 2016; 113:14811-14816.
60. Vila-Farres X, et al. An Optimized Synthetic-Bioinformatic Natural Product Antibiotic Sterilizes Multidrug-Resistant Acinetobacter baumannii-Infected Wounds. mSphere. 2018;3: e00528-17.
61. Chu J, et al. Synthetic-Bioinformatic Natural Product Antibiotics with Diverse Modes of Action. J Am Chem Soc. 2020;142:14158-14168.
62. Hover BM, et al. Culture-independent discovery of the malacidins as calcium-dependent antibiotics with activity against multidrug-resistant Gram-positive pathogens. Nat Microbiol. 2018; 3:415-422.
63. Kovalenko N, et al. A Concise Synthetic Strategy Towards the Novel Calcium-dependent Lipopeptide Antibiotic, Malacidin A and Analogues. Front Chem. 2021; 9:687875.
64. Upert G, et al. Emerging peptide antibiotics with therapeutic potential. Med Drug Discov. 2021; 9:100078.
65. Liu Y, et al. The revitalization of antimicrobial peptides in the resistance era. Pharmacol Res. 2021; 163:105276.
66. Zhu Y, et al. Antimicrobial peptides, conventional antibiotics, and their synergistic utility for the treatment of drug-resistant infections. Med Res Rev. 2022; 42:1377-1422.
67. Newman DJ. Natural products and drug discovery. Natl Sci Rev. 2022;9:nwac206.

68. LaPlante KL, et al. Re-establishing the utility of tetracycline-class antibiotics for current challenges with antibiotic resistance. Ann Med. 2022; 54:1686-1700.
69. Rusu A, et al. The Development of Third-Generation Tetracycline Antibiotics and New Perspectives. Pharmaceutics. 2021; 13:2085.
70. Hutchison RD, et al. Viridicatumtoxin, a new mycotoxin from Penicillium viridicatum Westling. Toxicol Appl Pharmacol. 1973; 24:507-509.
71. Zheng CJ, et al. Viridicatum toxin B, a new anti-MRSA agent from Penicillium sp. FR11. J Antibiot (Tokyo). 2008;61:633-7.
72. Nicolaou KC, et al. Total synthesis and structural revision of viridicatum toxin B. Angew Chem Int Ed Engl. 2013;52:8736-8741.
73. Nicolaou KC et al. Total synthesis of viridicatum toxin B and analogs thereof: strategy evolution, structural revision, and biological evaluation. J Am Chem Soc. 2014; 136:12137-60.
74. Li W, et al. Investigations into the Anti-bacterial Mechanism of Action of Viridicatum toxins. ACS Infect Dis. 2020;6:1759-1769.
75. Shang Z, et al. Fungal Biotransformation of Tetracycline Antibiotics. J Org Chem. 2016; 81:6186-6194.
76. Inokoshi J, et al. Inhibition of bacterial undecaprenyl pyrophosphate synthase by small fungal molecules. J Antibiot (Tokyo). 2016; 69:798-805.
77. Grossman TH. Tetracycline Antibiotics and Resistance. Cold Spring Harb Perspect Med. 2016;6: a025387.
78. Deng YX, et al. Cytotoxic alkoxylated xanthones from the resin of Garcinia hanburyi. Fitoterapia. 2012; 83:1548-1552.
79. Li M, et al. Investigations into the anti-bacterial effects and potential mechanism of gambogic acid and neogambogic acid. Front Microbiol. 2022; 13:1045291.
80. Bunduki GK, et al. Antimicrobial resistance in a war-torn country: Lessons learned in the Eastern Democratic Republic of the Congo. One Health. 2019; 9:100120.
81. Dahab R, et al. Barriers to Accessing Maternal Care in Low Income Countries in Africa: A Systematic Review. Int J Environ Res Public Health. 2020; 17:4292.
82. Shafiq Y, et al. Causes of maternal deaths in Sierra Leone from 2016 to 2019: analysis of districts' maternal death surveillance and response data. BMJ Open. 2024;14: e076256.
83. Moyo S, et al. HIV drug resistance profile in South Africa: Findings and implications from the 2017 national HIV household survey. PLoS One. 2020;15: e0241071.
84. Adebisi YA. Antimicrobial resistance and people living with disabilities. Lancet. 2024; 403:2289.
85. Adebisi YA, et al. The global antimicrobial resistance response effort must not exclude marginalized populations. Trop Med Health. 2023; 51:33.
86. Muteeb G, et al. Origin of Antibiotics and Antibiotic Resistance, and Their Impacts on Drug Development: A Narrative Review. Pharmaceuticals (Basel). 2023; 16:1615.
87. Liebenberg D, et al. Drug-resistant tuberculosis: Implications for transmission, diagnosis, and disease management. Front Cell Infect Microbiol. 2022; 12:943545.
88. Adebisi YA, et al. COVID-19 and Antimicrobial Resistance: A Review. Infect Dis (Auckl). 2021; 14:11786337211033870.
89. Worldwide Antimicrobial Resistance National/International Network Group (WARNING) Collaborators. Ten golden rules for optimal antibiotic use in hospital settings: the WARNING call to action. World J Emerg Surg. 2023; 18:50.
90. Okeke IN, et al. The scope of the antimicrobial resistance challenge. Lancet. 2024; 403:2426-2438.

Chapter 75

Principles for appropriate antibiotic therapy

Fabiana Dellai
U.O. Malattie Infettive, Ospedale Universitario Santa Maria della Misericordia, Azienda Sanitaria Universitaria Integrata di Udine, Udine, Italy;
Department of Medicine (DMED), University of Udine, Udine, Italy.

Carlo Tascini
U.O. Malattie Infettive, Ospedale Universitario Santa Maria della Misericordia, Azienda Sanitaria Universitaria Integrata di Udine, Udine, Italy;
Department of Medicine (DMED), University of Udine, Udine, Italy.

Introduction

"With great power comes great responsibility"

Since their discovery, antimicrobial agents have revolutionized medicine, saving millions of lives. Yet, despite their undeniable benefits, they are often not fully recognized for what they truly are: powerful weapons that must be used with caution. Both antimicrobial overuse and misuse are known as major drivers for the rapid selection of multi-resistant pathogens, whose infections can lead to longer hospitalizations, increased morbidity and mortality, and rising healthcare costs, further exacerbating global inequities in access to care.

The World Health Organization (WHO) considers antimicrobial resistance (AMR), alongside the stagnation in the development of novel antibiotics, one of the top ten global health threats. These concerns are well-founded, as demonstrated by the Naghavi *et al.* study where, in 2019 alone, AMR was associated with nearly 5 million deaths worldwide, including approximately 1.27 million deaths directly attributable to resistant infections. Current projections indicate that if left unchecked, AMR could cause 10 million deaths per year by 2050, with an economic toll exceeding USD 1 trillion annually by 2030.

To prevent this catastrophic future, coordinated global efforts focused on antimicrobial stewardship (AMS) combined with infection prevention and control (IPC) are required. A recent study by Kourbeti *et al.* revealed that even if clinicians are generally aware of the ongoing AMR crisis, they often do not perceive it as a pressing issue within their institution. This cognitive dissonance is further supported by the fact that antimicrobial prescription often remains within the purview of a wide range of healthcare professionals, many of whom lack, and may be uninterested in acquiring, a comprehensive understanding of the core principles of antimicrobial pharmacodynamics, pharmacokinetics, microbiology, and stewardship.

Surgeons, who frequently prescribe antibiotics for prophylaxis and treatment, often underestimate their primary role in mitigating AMR. Antimicrobial misuse, driven by diagnostic uncertainty, complex cases, and fear of complications, frequently results in the overuse of broad-spectrum antibiotics and inappropriate dosing. Moreover, several surgeons repute antibiotic management as a marginal activity, delegating this impactful practice to other specialists or unsupervised junior physicians, in order to prioritize time in the surgical theater.

Such misconceptions must be eradicated. We must understand that antimicrobials are "societal drugs" with far-reaching consequences that extend beyond the individual patient, influencing the microbiota of other humans, animals, and the broader environment. Hence, prudent antimicrobial use must become a priority for all healthcare providers rather than being viewed as the sole responsibility of infectious disease specialists or clinical microbiologists.

Principles for appropriate antibiotic therapy

The 6 Ds of antimicrobial stewardship

Appropriate antimicrobial prescribing includes ensuring correct **d**iagnosis, selecting appropriate antimicrobial **d**rugs, determining the optimal **d**ose and **d**uration of treatment, and applying **d**e-escalation strategies when necessary. Whenever feasible, adequate source control should be promptly achieved to reduce bacterial overload (**d**ebridement/**d**rainage).

AMS can be defined as a bundle of actions that must be performed in concert with the objective of improving clinical outcomes while limiting unnecessary healthcare costs and minimizing unintended consequences of antimicrobial use, such as adverse events, selection and spread of AMR. There are three fundamental stages during which the careful use of antimicrobials can help achieve these goals: before, during and at the end of therapy (**Figure 1**).

AMS before antimicrobial therapy: clinical and physical evaluation

Research of clear evidence of infection through a scrupulous clinical assessment is the first step in determining whether a patient is likely to benefit from antimicrobial therapy and therefore if the risk of drug toxicity is justified. Although time-consuming, a meticulous investigation of the syndromic presentation by focusing on symptoms description including their duration, intensity, and evolution over time, along with possible exposure to specific risk factors, can help distinguish not only between infectious and non-infectious conditions but may also suggest its etiopathogenesis (e.g., bacterial *vs.* viral). Grading of individual frailty, including immunodepression factors, severity grade and number of comorbidities, and patient's vaccinal status for vaccine-preventable diseases analysis are other key aspects to identify patients predisposed to a more severe course of illness.

Since infections caused by pathogens with reduced antimicrobial susceptibility are associated with more severe disease progression, prolonged hospital stays, and poorer prognoses, the likelihood of encountering a resistant organism should always be assessed and highly suspected in case of:

- recent infection or colonization with resistant pathogens;
- frequent hospitalization or prolonged stay in healthcare facilities (including rehabilitation centers) within the last 6 to 12 months;
- frequent hospital visits for procedures (e.g. wound care or thrice-weekly hemodialysis);
- diabetes mellitus;
- use of oral or intravenous broad-spectrum antibiotics within the past 6 months;
- recent travel to regions with a high prevalence of resistant pathogens.

Figure 1. Ten Golden Rules for Appropriate Antimicrobial Therapy. Inspired by "The 10 "golden rules" for optimal antibiotic use in hospital settings, which clinicians should always follow in their clinical practice" (Adapted from Worldwide Antimicrobial Resistance National/International Network Group (WARNING) Collaborators, 2023).

Accurate physical examination combined with clinical history evaluation is essential for determining illness severity, which in turn guides the optimal timing (immediate *vs*. delayed), choice (broad *vs.* narrow-spectrum

empirical antimicrobial treatment), and selection of the most appropriate care environment (hospitalization *vs.* dismission at home).

AMS before antimicrobial therapy: investigation for reliable infectious disease diagnosis

Diagnostic stewardship is a concept that refers to ordering the appropriate tests (including specimen collection) for the right patient at the right time with timely reporting of results to promote its accurate interpretation and guide optimal patient treatment.

To confirm or rule out the presumptive diagnosis of infection, clinicians should choose diagnostics - including laboratory, microbiological, and imaging studies - according to the pre-test probability of the disease. The collection of high-quality microbiological specimens can enhance diagnostic accuracy and ensure that treatment decisions are supported by accurate and clinically relevant results while limiting overtesting.

Biomarkers like white blood cell (WBC) counts, C-reactive protein (CRP), and procalcitonin (PCT) may be useful in supporting the possible presence of an infection. Unfortunately, these markers are aspecific and may increase in several non-infectious conditions, such as trauma, severe burns, recent surgery, and impaired renal function, offering limited guidance to clinicians. Also, they can result in false negatives during localized bacterial infections such as abscesses.

When feasible, imaging is an invaluable tool for defining the presence and extension of deep infectious foci, while determining their susceptibility to interventional approaches. Source control refers to the eradication of the infection focus (or, when this is not possible, to the significant reduction of the microbial burden), along with the correction of anatomic derangements to restore physiological homeostasis. Septic focus control can be accomplished through various interventions, including abscess drainage, necrotic tissue debridement, and removal of contaminated medical prosthetic devices. Whenever an intervention for infective management is performed, antimicrobial therapy initiation should be postponed after deep bioptic specimen collection for microbiological analysis, if possible.

If adequately achieved, source control can improve 90-day-overall survival and shorten the duration of antibiotic therapy even in life-threatening conditions like septic shock, complicated intrabdominal infection, and necrotizing soft tissue infections, where rapid resuscitation and adequate antimicrobial therapy alone are often insufficient. In less severe cases, the eradication of the infectious focus may eliminate the need for postoperative antimicrobial treatment (e.g., uncomplicated appendicitis and cholecystitis).

Even in catheter-related bloodstream infections (CR-BSI), rapid source control through device removal is considered an indispensable therapeutic measure that is associated with increased survival, especially when biofilm-producing pathogens such as *Pseudomonas* spp., *Staphylococcus aureus*, or fungi are involved.

If a lack of clinical improvement or persistent signs and symptoms of inflammation are observed days after surgical management, the possibility of incomplete infection control should be promptly evaluated, and a re-intervention procedure should be considered.

Although often undervalued, establishing a microbiological diagnosis is fundamental not only for the patient but also for defining local epidemiological trends and pathogen-specific susceptibility patterns, which guide the adaptation of global guidelines to local contexts. It also enables the early detection of newly emerging outbreaks, facilitating the timely implementation of appropriate containment measures.

Since antimicrobial therapy can suppress the growth of pathogenic organisms, leading to falsely negative cultures, specimens should always be collected prior to treatment initiation and from sites where higher concentrations of organisms are expected. Whenever possible, microbiological samples should be collected during surgery or through direct puncture, since the use of devices that have been in situ for more than 24 hours is biased by the high likelihood of colonization by resident microbiota.

Superficial swabs are inadequate for microbiological analysis because of their high risk of contamination by normal skin microbiota. Therefore, in cases of wound sampling, surgical deep wound cultures should be prioritized and, if this is not feasible, punch biopsy or needle aspiration from the wound edges, should be preferred to minimize contamination.

If sampling from potentially contaminated areas is unavoidable (e.g., wounds or respiratory samples), the site should be meticulously cleaned before sampling. When infections involving bone or synthetic materials are suspected, sonication prior to microbiological investigations can enhance the likelihood of isolating clinically significant pathogens.

Blood culture collection should not be routinely performed in conditions where a low risk of bacteremia exists, such as non-severe community-acquired pneumonia (CAP) or mild skin and soft tissue infections (SSTIs) that affect immunocompetent and clinically stable patients. However, when systemic signs of infection are present is recommended to collect at least 2 sets of blood cultures from different venipuncture sites to detect pathogens while disseminating into the bloodstream. Since endovascular catheters are prone to contamination, relying solely on blood samples drawn from devices frequently leads to false-positive results and unnecessary antimicrobial use. In the absence of a concurrent peripheral venipuncture sample, distinguishing between bloodstream infections (BSI) and device colonization can be challenging, as comparing the differential time to positivity between blood samples obtained from intravenous devices and peripheral veins can assist in diagnosing catheter-related bloodstream infections (CR-BSI), with important implications for management, as previously discussed. If a patient becomes febrile during antimicrobial treatment, blood culture should be repeated following the same protocol to investigate potential treatment failure.

The recent introduction of 'fast microbiology' techniques marked a significant advancement in microbiological diagnostics, enabling the rapid identification of both pathogens and resistance genes within hours, in contrast to the days required by traditional culture-based methods. The ability to provide reliable results within a short turnaround time enables the rapid initiation of quasi-targeted therapy, possibly limiting the necessity of empirical broad-spectrum initiation even in time-sensitive situations.

Thanks to the increased sensitivity, these methods can identify genetic markers of specific pathogens even when traditional cultures may fail. This includes scenarios where antimicrobial therapy has already begun, infections are polymicrobial, or when pathogens are difficult to culture using standard techniques, such as anaerobes and intracellular bacteria.

Despite its considerable advantages, rapid microbiology can both overestimate and underestimate AMR, hence it should maintain for now a supportive role rather than replace traditional methods to ensure accurate diagnosis and optimal treatment. Firstly, these techniques cannot determine pathogen-specific susceptibility profiles, which is essential for planning appropriate de-escalation strategies. Methods such as PCR and FilmArray panels are designed to detect specific pathogens and resistance genotypes potentially overlooking other resistance determinants. On the other hand, the presence of a resistance gene does not always equate to phenotypic resistance.

Finally, by not distinguishing between genetic material from non-viable organisms, colonizing bacteria, and pathogenic microbes, these techniques may generate a large amount of data which can be overwhelming and may hinder the accurate identification of clinically significant microbes, ultimately risking paradoxical inappropriate antimicrobial use.

AMS during antimicrobial therapy: core principles for adequate antimicrobial choice

The "5Ws and the 1H" of antimicrobial selection: **W**ho (patient characteristic), **w**hat (pathogen), **w**hen (appropriate timing of antimicrobial therapy initiation), **w**here (location of the infective focus), and especially **w**hy (rationale of antimicrobial therapy) and **h**ow (correct dosage calculation).

Before prescribing, it should be remembered that antimicrobial use can lead not only to severe adverse effects, like allergic reaction and acute kidney injury (AKI), but can also disrupt the gut microbiota by reducing microbial diversity and selecting resistant strains, thereby increasing susceptibility to opportunistic pathogens such as *Clostridioides difficile*. These changes can persist for up to 12 weeks after the conclusion of antibiotic therapy.

If in clinically stable patients without clear evidence of infection, it may be appropriate to withhold treatment while awaiting diagnostic results, this approach should not be applied to septic, and critically ill patients, as each hour of delay in appropriate antimicrobial therapy administration is associated with an increased risk of mortality.

The selection of the appropriate regimen should be guided by the following core principles:

- **Understand the microorganisms**. Know the nature and classification of the microorganisms commonly causing specific human infections according to the local epidemiology and interpreting preliminary microbiological results (e.g., Gram stain results and time to culture positivization).
- **Follow guidelines**. Select antimicrobial regimens according to established guidelines and adapt them to local epidemiology and resistance patterns, when feasible.
- **Evaluate the spectrum of activity**. Select the drug with the narrowest antimicrobial spectrum according to the local epidemiology, consider its common adverse effects, and the appropriate monitoring strategies.
- **Tailor regimen**. Choose the appropriate drug and dosage based on the suspected infection type, site, and the pharmacokinetic/pharmacodynamic (PK/PD) principles of the antibiotic. These considerations become especially relevant in the case of multidrug-resistant organisms, where attainment of optimal drug penetration into the infection site is crucial to prevent treatment failure.
- **Selection of appropriate antibiotic**. Antimicrobial susceptibility test determines the pathogen's ability to grow in the presence of a specific drug *in vitro* but does not consider the drug's capacity to penetrate the infection site. For example, even if a pathogen appears susceptible to daptomycin, this drug should not be used to treat pulmonary infections as it is inactivated by the surfactant, limiting the possibility of maintaining effective drug concentration.

A commonly used distinction among antibacterial agents is between bactericidal and bacteriostatic agents. Bactericidal drugs cause death and disruption of bacterial cells and include drugs that primarily act on the cell wall (e.g., β-lactams), cell membrane (e.g., daptomycin), or bacterial DNA (e.g., fluoroquinolones). Bacteriostatic agents inhibit bacterial replication without killing the organism, for instance by inhibiting protein synthesis (e.g., sulfonamides, tetracyclines, and macrolides). This distinction is not absolute, and some agents that are bactericidal against certain organisms may only be bacteriostatic against others. In most cases, this distinction is not significant *in vivo*; however, bactericidal agents are preferred in serious infections, such as endocarditis and meningitis to achieve rapid blood culture or cerebrospinal fluid clear.

- **Dosing frequency**. For time-dependent agents like beta-lactams, vancomycin, and clindamycin, optimal bactericidal activity is achieved when serum concentrations remain above the MIC for at least 40% (ideally 70%) of the dosing interval. To ensure this target attainment, time-dependent agents should be administered with an initial loading dose to rapidly reach therapeutic levels, followed by continuous or extended infusions to maintain concentrations above the MIC as long as possible (T>MIC). In contrast, concentration-dependent antibiotics like fluoroquinolones and aminoglycosides rely on peak plasma levels exceeding the MIC (C_{max}/MIC) and the area under the concentration-time curve (AUC) above the MIC (AUC/MIC) for maximal efficacy, with higher values that indicate stronger antimicrobial effect. Therefore, concentration-dependent antibiotics should be administered once daily.

- **Determine the route of administration**. Parenteral administration should be prioritized in patients with sepsis, especially when hemodynamic instability or difficulties with oral intake (e.g., vomiting, gastrointestinal dysfunction, unconsciousness) are associated. Patients hospitalized for reasons other than severe infections and with normal gastrointestinal function may be treated with oral antimicrobial agents, due to their comparable efficacy in many infections.
- **Monitor treatment evolution**. Ensure that appropriate laboratory and imaging studies are performed to monitor the infection's progression if indicated.
- **Consider cost**. Select the most cost-effective option without compromising efficacy.

Although familiarity with a few specific antimicrobials can help clinicians, a “one size fits all” approach is inappropriate for antimicrobial selection due to patient heterogeneity and the dynamic nature of clinical conditions.

To tailor empirical treatment to individual patients, general considerations should be integrated as follows:

- **Specific risk factors**. In planning antimicrobial treatment for immunocompromised patients, the type of treatment received and the severity of immunosuppression must be considered, as these factors may increase the risk of specific bacterial, viral and fungal infections for which antimicrobial prophylaxis may already be administered.
- **Previous microbiological data**. Whenever feasible, reviewing past microbiological results obtained from the last 6 months can help guide antimicrobial selection.
- **Recent antimicrobial exposure**. Antibiotic regimens administered within the last 3 months may promote the selection of resistant subpopulations. This exposure should guide empirical therapy decisions, particularly when clinical failure is noted.
- **Allergy history and de-labeling of spurious allergy**. Beta-lactams are among the most frequently prescribed antibiotics and are, unfortunately, associated with a high incidence of reported allergic reactions. Historically, up to 10% of patients report a penicillin allergy; however, the actual allergy incidence is significantly lower, often less than 1% when evaluated through skin testing. Mislabeling a patient with an antibiotic allergy can profoundly impact clinical decision-making, leading to the unnecessary avoidance of effective, narrow-spectrum, and cost-efficient antibiotics. During an allergology anamnesis should be investigated which drug triggered the reaction, the type of reaction that occurred, and whether symptoms reappeared with the use of a different molecule belonging to the same class. Efforts to clarify antibiotic allergies with or without dedicated skin testing can help distinguish between non-allergic adverse events and true allergic reactions, as well as differentiate between IgE-mediated and delayed reactions since beta-lactams administration should be avoided only in patients with severe IgE-mediated (bronchospasm, angioedema, or anaphylactic shock), or non-IgE-mediated reactions (such as Stevens-Johnson syndrome or toxic epidermal necrolysis). Both clinicians and patients need to understand that a negative skin test does not eliminate the risk of non-IgE-mediated delayed allergic reactions. However, in many cases, the clinical benefits of administering a more appropriate antibiotic outweigh the risks of less severe allergic reactions.
- **Drug-drug interactions** between the proposed antimicrobial regimen and the patient’s chronic medications may influence not only drug selection but also monitoring strategies.

Effective distribution and dosing of antibiotics can be significantly modified by various patient-related factors that need to be recognized to optimize favorable outcomes obtainment while minimizing potential risks associated with antimicrobial therapy.

First, obesity can alter the volume of distribution (VD) of lipophilic antibiotics for multiple reasons like accumulation in the adipose tissue, leading to lower-than-expected plasma antibiotic concentrations. Correct dosing of lipophilic antibiotics should be calculated according to total body weight; conversely, for hydrophilic antibiotics, changes based on adjusted body weight are generally recommended to ensure appropriate dosing.

Also, in septic-shocked patients, the VD may be significantly increased due to elevated microvascular endothelial permeability, which expands the extracellular fluid compartment leading to the strict necessity to administer an initial "loading dose" forbeta-lactams, aminoglycosides, and glycopeptides antibiotics.

Hepatic and renal function play a crucial role in the metabolism and clearance of many antibiotics and their impairment can lead to altered drug metabolism and accumulation, necessitating careful consideration of the dosing regimens.

Although antibiotics loading dose should remain unchanged independently of the renal function, subsequent doses must be adjusted according to the severity of renal impairment using patient-specific estimated glomerular filtration rate (eGFR). Albeit, in sepsis-induced AKI suspicion the appropriate antibiotic dose should be calculated based on the renal function prior to the onset of infection. Also, critically ill patients often experience hyperfiltration (defined as eGFR>120 mL/min), which can justify higher antibiotic doses to maintain adequate plasma drug concentration.

In all these scenarios, daily reassessment of renal and hepatic function associated to close monitoring of antimicrobial serum concentrations via therapeutic drug monitoring (TDM) whenever feasible, is essential to verify that drug posology remains both effective and safe, avoiding potential accumulation-associated risks.

AMS during antimicrobial therapy: regimen review and de-escalation strategy

Empiric therapy should be reviewed within 48-72 hours of initiation, as this is the typical minimum time required to obtain preliminary results from microbiological analyses and to perceive a preliminary favorable clinical (decrease in fever, tachycardia, or confusion) and bio-humoral response (e.g., decreasing WBC, CRP or PCT). On the contrary, instrumental follow-up is not routinely indicated, as radiologic evolution often lags behind clinical improvement.

An “antimicrobial time-out” should be conducted according to both clinical and microbiological data to adjust empiric to definitive antimicrobial treatment. During this process, clinicians should reassess the clinical diagnosis and the ongoing need for antimicrobials based on investigation results, documenting a clear plan of action, including a presumptive date of therapy dismissal or review to ensure clarity and continuity of care. The spectrum of coverage may be narrowed or broadened according to antimicrobial susceptibility test results, dosage may be adjusted, and any unnecessary components of the regimen should be discontinued.

There are five possible outcomes of the antimicrobial review that can be summarized using the acronym "CARES".

- **Cease**. Early discontinuation of unnecessary antibiotics improves survival outcomes, minimize the risk of adverse effects, and decreases the risk of resistance selection. In the absence of evidence of infection, timely antimicrobial therapy cessation should be pursued.
- **Amend**. Narrowing antimicrobial regimens according to the microbiological results improves patient outcomes without increasing risks, hence it is a key goal of antimicrobial stewardship. Broad-spectrum antibiotics should be limited to avoid harm to the commensal flora and the development of resistant strains, such as *Clostridioides difficile*.
- **Refer**. For suitable patients, referral to specialized non-ward-based antimicrobial services like Outpatient Parenteral Antimicrobial Therapy (OPAT) or Complex Outpatient Antimicrobial Therapy (COPAT), can facilitate earlier hospital discharge and reduce the risk of healthcare-associated complications, like

infections (HAI). These services are safe, clinically effective, and highly satisfactory for patients, offering both intravenous and oral antimicrobial options.

- **Extend**. For infections that require prolonged treatment, the duration of antimicrobial therapy should only be extended as long as necessary, with a review or termination date clearly documented.
- **Switch**. Whenever possible, the route of antimicrobial administration should be transitioned from intravenous (IV) to oral. Studies have demonstrated that an early switch to oral therapy is as effective as completing a full IV course and brings additional benefits, including shorter hospital stays, lower risks of device-related infections such as CR-BSI and phlebitis, and reduced healthcare costs.

Indicators to evaluate when performing a safe transition to oral therapy are significant clinical improvement, including afebrile and stable hemodynamical state, good general condition, and favorable trends in inflammatory markers, particularly for C-reactive protein (CRP). Before switching from IV to oral therapy, it is essential to confirm that the gastrointestinal tract is functioning properly, with no signs of malabsorption. Oral drugs with high bioavailability (≥90%) such as fluoroquinolones, triazoles, metronidazole, trimethoprim/sulfamethoxazole, doxycycline, minocycline, rifampin, and linezolid, should be selected.

AMS at the end of antimicrobial therapy: duration of antimicrobial therapy

While a preliminary treatment duration should be estimated when beginning antimicrobial therapy, its length should be adjusted according to diagnosis, microbiologic data, patients' clinical response, and care setting.

Optimizing antimicrobial therapy duration is a critical aspect for effective infection management and AMS, since prolonged courses are associated not only with the adverse effects previously described but also with possible poor adherence that can boost the emergence of resistant organisms.

To avoid excessively long antimicrobial courses and stimulate the adoption of a standardized approach, each hospital should develop personal guidelines based on local epidemiological patterns, with specific recommendations about antimicrobial regimens to choose and their duration. In the absence of local protocols, international guidelines should be followed.

Stewardship proactive educational interventions, such as audits and feedback, are essential tools to mitigate the tendency to over-prolong therapy, due to concerns about undertreatment.

Emerging research supports shorter courses for various common infections, such as 3 days for uncomplicated UTIs in women, 5 days for CAP, and 8 days for ventilator-associated pneumonia (VAP).

In critically ill patients with sepsis or septic shock, several studies have highlighted that antibiotics de-escalation or cessation may be considered in case of PCT levels falling below 0.25–0.5 ng/mL or decreasing by 80–90% from baseline if accompanied by favorable clinical evolution.

When prescribing shorter courses, clinicians must ensure that patients meet the criteria used in these studies and monitor high-risk individuals carefully. For instance, VAP caused by nonfermenting Gram-negative bacilli (e.g. *Pseudomonas aeruginosa*) or affecting immunocompromised patients, may require longer treatment.

Similarly, in conditions requiring extended treatment durations like endocarditis, osteomyelitis, intra-abdominal abscesses, and invasive fungal infections, treatment length should be evaluated by experts in antimicrobial management and individualized based on clinical and radiological response.

Conclusion

Several studies underscore how the long-term success of AMS in empowering appropriate antibiotic use across healthcare institutions can be more sustainable when achieved through persuasive strategies such as education, audit and feedback initiatives.

As is apparent from these brief paragraphs, antimicrobial stewardship programs (ASPs) require the expertise of several healthcare figures to encourage the widespread adoption of transversal, and multidisciplinary best practices.

Infectious disease specialists and clinical microbiologists, supported by pharmacists with advanced training or significant experience in infectious diseases, are pivotal in designing and implementing stewardship interventions. Microbiologists play a vital role in guiding diagnostic test use and interpretation by providing timely reports of antimicrobial identification and susceptibility patterns. Infection control specialists and hospital epidemiologists must collaborate to monitor and prevent HAIs spread. Hospital leadership and administrative support are essential for the development, maintenance and sustainability of these programs.

To optimize the effectiveness of ASPs, representatives from all healthcare categories authorized to prescribe antimicrobials must be included. For instance, defining a surgeon expertized in surgical infections can enhance both therapeutic and prophylactic antimicrobial use within surgical teams. In intensive care units, where infections significantly impact patient outcomes, intensivists play a crucial role in managing antimicrobial treatments, especially for multidrug-resistant organisms. Emergency department practitioners should also be integrated into AMS programs due to the high volume and often inappropriate use of antibiotics in these settings. Moreover, nurses, who continuously monitor patient conditions and facilitate communication within the care team, should be included as vital participants in ASPs.

It is now clear how the designation of a "champion" within each medical specialty can raise awareness of the AMR crisis and emphasize the significance of individual efforts in adhering to stewardship principles within their respective wards, overcoming resistance to behavioral change that often arises from external directives. Each one of us bears the collective responsibility to ensure that antimicrobial agents remain effective tools in the fight against infectious diseases for generations to come. Through active participation, we can appreciate how every effort aimed to address the AMR threat —ranging from the promotion of AMS and IPC principles to adherence— is indispensable.

“The greatest weakness in fighting the AMR crisis is the illusion that someone else will do it. Live as if your actions truly matter, because they do”. Inspired by the thoughts of Robert Swan and William James.

Competing interests

FD has no financial and non-financial competing interests to declare. CT has received funds for speaking at symposia organized on behalf of Pfizer, Novartis, Merck, Gilead, Zambon, Infectopharm, Shionogy, Menarini, Angelini, Hikma, Tillots, Advanz, Diasorin, and Thermofischer.

References

1. A Global Declaration on Appropriate Use of Antimicrobial Agents across the Surgical Pathway. Surg Infect (Larchmt). 2017;18:846-853.
2. Niederman MS. Principles of appropriate antibiotic use. Int J Antimicrob Agents. 2005;26 Suppl 3:S170-5.
3. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022;399:629-655.
4. Poudel AN, et al. The economic burden of antibiotic resistance: A systematic review and meta-analysis. PLoS One. 2023;18:e0285170.
5. Kourbeti I, et al. Antibiotic Stewardship in Surgical Departments. Antibiotics (Basel). 2024;13:329.
6. European Centre for Disease Prevention and Control. Survey of healthcare workers' knowledge, attitudes and behaviours on antibiotics, antibiotic use and antibiotic resistance in the EU/EEA. 2019. Available at: https://www.ecdc.europa.eu/sites/default/files/documents/survey-of-healthcare-workers-knowledge-attitudes-behaviours-on-antibiotics.pdf. Last accessed: 13 October 2024.
7. Owens RC Jr. Antimicrobial stewardship: concepts and strategies in the 21st century. Diagn Microbiol Infect Dis. 2008;61:110-128.
8. Morency-Potvin P, et al. Antimicrobial Stewardship: How the Microbiology Laboratory Can Right the Ship. Clin Microbiol Rev. 2016;30:381-407.
9. UK Health Security Agency. Guidance Start smart then focus: antimicrobial stewardship toolkit for inpatient care settings. Available at: https://www.gov.uk/government/publications/antimicrobial-stewardship-start-smart-then-focus/start-smart-then-focus-antimicrobial-stewardship-toolkit-for-inpatient-care-settings. Last accessed: 22 September 2024.
10. Rodríguez-Villodres Á, et al. Prevalence and Risk Factors for Multidrug-Resistant Organisms Colonization in Long-Term Care Facilities Around the World: A Review. Antibiotics (Basel). 2021;10:680.
11. Fabre V, et al. Principles of diagnostic stewardship: A practical guide from the Society for Healthcare Epidemiology of America Diagnostic Stewardship Task Force. Infect Control Hosp Epidemiol. 2023;44:178-185.
12. World Health Organization. Diagnostic stewardship. A guide to implementation in antimicrobial resistance surveillance sites. Available at: https://iris.who.int/bitstream/handle/10665/251553/WHO-DGO-AMR-2016.3-eng.pdf. Last accessed: 13 October 2024.
13. Worldwide Antimicrobial Resistance National/International Network Group (WARNING) Collaborators. Ten golden rules for optimal antibiotic use in hospital settings: the WARNING call to action. World J Emerg Surg. 2023;18:50.
14. Zakhour J, et al. Diagnostic stewardship in infectious diseases: a continuum of antimicrobial stewardship in the fight against antimicrobial resistance. Int J Antimicrob Agents. 2023;62:106816.
15. Cortegiani A, et al. Rationale and clinical application of antimicrobial stewardship principles in the intensive care unit: a multidisciplinary statement. J Anesth Analg Crit Care. 2023;3:11.
16. Lee CC, et al. Prompt antimicrobial therapy and source control on survival and defervescence of adults with bacteraemia in the emergency department: the faster, the better. Crit Care. 2024;28:176.
17. Talpaert MJ, et al. Impact of guidelines and enhanced antibiotic stewardship on reducing broad-spectrum antibiotic usage and its effect on incidence of Clostridium difficile infection. J Antimicrob Chemother. 2011;66:2168-2174.
18. Leekha S, et al. General principles of antimicrobial therapy. Mayo Clin Proc. 2011;86:156-167.
19. Dyar OJ, et al. ESCMID generic competencies in antimicrobial prescribing and stewardship: towards a European consensus. Clin Microbiol Infect. 2019;25:13-19.
20. Bassetti M, et al. Systematic review of the impact of appropriate versus inappropriate initial antibiotic therapy on outcomes of patients with severe bacterial infections. Int J Antimicrob Agents. 2020;56:106184.
21. Dellit TH, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis. 2007;44:159-177.

22. Campagna JD, et al. The use of cephalosporins in penicillin-allergic patients: a literature review. J Emerg Med. 2012;42:612-620.
23. World Health Organization. Antimicrobial stewardship interventions: a practical guide. 2021. Available at: https://iris.who.int/bitstream/handle/10665/340709/9789289054980-eng.pdf. Last accessed: 13 October 2024.
24. Sager R, et al. Procalcitonin-guided diagnosis and antibiotic stewardship revisited. BMC Med. 2017;15:15.
25. Tian, B.W.C.A, et. al Management of Intra-Abdominal Infections: The Role of Procalcitonin. Antibiotics. 2023;12:1406.
26. Barlam TF, et al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis. 2016;62:e51-e77.
27. European Centre for Disease Prevention and Control. Proposals for EU guidelines on the prudent use of antimicrobials in humans. 2017. Available at: https://www.ecdc.europa.eu/sites/default/files/media/en/publications/Publications/EU-guidelines-prudent-use-antimicrobials.pdf. Last accessed: 13 October 2024.
28. Schoffelen T, et al. European society of clinical microbiology and infectious diseases guidelines for antimicrobial stewardship in emergency departments (endorsed by European association of hospital pharmacists). Clin Microbiol Infect. 2024:S1198-743X(24)00251-9.
29. Anurag N Malani, et al. A Global Call to Action to Fight Antimicrobial Resistance: IDSA and ESCMID Joint White Paper, *Open Forum Infectious Diseases*, 2024;ofae522.

Chapter 76

Antimicrobial stewardship in immunocompromised patients

Emily Wong
Division of Infectious Diseases and Geographic Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, USA.

James Sanders
Pharmacy Department, University of Texas Southwestern Medical Center, Dallas, Texas, USA.

Jonathan Hand
Infectious Diseases, Ochsner Medical Center, New Orleans, Louisiana, USA.

Jeffrey Tessier
Division of Infectious Diseases and Geographic Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, USA.

Introduction

Antimicrobial stewardship programs (ASP) focus on ensuring appropriate antimicrobial use to preserve these essential tools for future generations and minimize adverse outcomes such as selection of antimicrobial resistance, *Clostridioides difficile* infection (CDI), and drug toxicities. Immunocompromised patients are at considerable risk for both surgical site infections (SSIs) due to immunosuppression and pre-existing colonization and infection with multi-drug-resistant organisms (MDROs). Most ASP concentrate interventions on general patient populations, but the elevated infection risks for immunocompromised patients deserve specific ASP efforts that we will discuss in this chapter.

ASPs are important to optimize patient outcomes, especially in the immunocompromised population as they have disproportionally higher rates of multidrug-resistant organism (MDRO) infection and poor outcomes from events such as CDI. The highest-risk populations include solid organ (SOT) and hematopoietic stem cell transplant patients (HSCT). Both these populations account for substantial antimicrobial consumption and are likely to benefit proportionally from ASP interventions.

In most instances, antimicrobials are warranted, especially for empiric therapy when there is a concern for potential infection. However, they are often used for too long, and the agents selected are too broad. This leads to the selection of resistance, adverse drug effects, and CDI. These unintended effects are associated with higher mortality in immunocompromised patients and an increased risk of rejection in SOT recipients related to dysbiosis-induced immune dysregulation.

Several interventions can optimize outcomes for immunocompromised patients requiring surgical care. There is less robust data from SOT and HSCT studies due to smaller sample sizes, but available stewardship data correlates with studies from immunocompetent patients.

Surgical site infections in solid organ transplant recipients

SOT recipients are at high risk for early post-operative infections due to multiple factors: procedure complexity, end-organ disease, recurrent hospitalizations, donor-derived infections, and MDRO colonization. Their elevated net state of immunosuppression also results in higher mortality from infections. SOT infection rates exceed those of the general population, ranging from 3-53% across different organs. The CDC definition of surgical site infection (SSI) includes superficial, deep incisional, and organ space infections that occur within 30 or 90-days from surgery, depending on the procedure. This definition can be challenging in transplant recipients as the allograft can be an infection source.

SSIs in transplant recipients are associated with longer lengths of stay, graft failure, higher healthcare costs, and increased mortality. The highest incidence of SSI is in intestinal or multi-visceral transplants, with risk as high as 100% when mesh closure is implemented, while kidney transplants have the lowest SSI incidence. Risk varies with comorbidities (e.g., diabetes mellitus, prior transplantation, and blood transfusion), organ type, and MDRO colonization status (donor and recipient). Among modifiable risks, appropriate antimicrobial selection and administration timing are crucial.

Agent selection for pre-operative antimicrobial prophylaxis

Antimicrobial allergy assessment and de-labeling

Inaccurate antimicrobial allergies and intolerances result in suboptimal perioperative prophylaxis and an increased SSI rate. Beta-lactam avoidance can increase carbapenem use and non-beta-lactam antimicrobial usage is associated with MDRO selection, CDI, longer length-of-stay (LOS), higher ICU admission rates, and mortality. Antibiotic allergy labels are also associated with delayed empiric antimicrobial therapy.

Approximately 20% of hospitalized patients report a beta-lactam allergy, but 90% tolerate these agents when allergy-tested or rechallenged. Imlay *et al.* identified that 30% of SOT recipients reported ε1 antibiotic allergy, with 10% noting ε2 on the day of transplantation. Only 11% had an allergy evaluation prior to transplantation, but 78% of those patients were de-labeled through history or rechallenge. Another study showed that <5% of SOT recipients saw an allergist during their pre-transplant evaluation, representing a missed opportunity to optimize their perioperative care. There is an abundance of data demonstrating the utility of penicillin skin testing in immunocompromised populations.

Non-beta lactam antibiotics for perioperative prophylaxis are associated with higher SSI risk. In the past 2 decades, robust data have been published confirming low rates of cross-reactivity between cephalosporins and penicillin. Cefazolin, a common agent for perioperative prophylaxis, shares no side chains with penicillin, conferring the lowest cross-reactivity. The most common antimicrobials for beta-lactam allergies were vancomycin and fluoroquinolones, followed by clindamycin, aztreonam, and carbapenems. The use of these alternatives increases risks for CDI, methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant enterococcal (VRE) infections, leading to increased LOS, worse graft outcomes, and increased

mortality. One study in 2013 identified a $3.2 billion annual cost attributed to SSIs as the most common cause of unplanned readmissions after surgery.

Given the high prevalence of inaccurate beta-lactam allergies, de-labeling is a target of ASP to evaluate these allergies as a stewardship strategy. Allergy de-labeling is a benefit to the morbidity and mortality of patients, with significant cost savings from decreased hospital days and improved clinical outcomes.

Perioperative antimicrobial prophylaxis in SOT recipients

Prophylactic agents should be selected according to the organ type, as well as donor/recipient colonization status in certain cases. MRSA status is important to consider as colonization is linked to increased SSI risk and there may be benefits to adding prophylactic vancomycin. Depending on local epidemiology, de-colonization with nasal mupirocin and chlorhexidine baths is recommended, especially in cardiothoracic surgeries to reduce Gram-positive infections. *Staphylococcus aureus* colonization is an independent infection risk in the post-transplant period. Colonization with VRE in liver recipients is also linked to increased infection, and intestinal/multi-visceral transplants have high rates of MDRO infection in the 30-day post-operative period. In **Table 1** the common pathogens causing SSIs by organ transplant type and specific host and surgical risk factors for SSI are illustrated.

Table 1. Common pathogens causing SSIs by organ transplant type and specific host and surgical risk factors for SSI (Adapted and modified from Abbo LM *et al.*, 2019).

Organ type and incidence of SSIs	Most common pathogens causing SSI	Host risk factors for SSI	Surgical risk factors for SSI
Kidney (3-11%)	*Staphylococcus aureus,* Coagulase-negative Staph, *Enterococci.*	DM, obesity, chronic GN, re-operation	Ureteral leak, hematoma, blood transfusion
Pancreas and pancreas-kidney (9-45%)		Re-operation/ transplantation	Prolonged operative or ischemic time, enteric drainage, post-transplant fistula, hand sewn anastomosis (rather than stapled), blood transfusion.
Liver (10-37%)	*Enterobacteriaceae*, *Acinetobacter*, *Pseudomonas* (gram negatives), *Enterococci, Staphylococcus aureus,* Coagulase negative Staph, *Candida* spp.	DM, obesity, hemochromatosis Prolonged ICU or hospital stay Prior liver/renal transplant Prior hepato-biliary surgery High MELD score Ascites	Prolonged operative time, anastomotic leak, Roux en Y biliary anastomosis, entry into GI tract. Other: post-transplant, RRT
Intestinal, multivisceral 14-53% (as high as 100% if mesh used)	Polymicrobial predominant Gram-negative organisms, *Candida* spp., anaerobes, *Enterococci*	Host: hospitalization before transplant	Use of surgical mesh for closure, re-operation in the first 30 days, post-transplant, entero-cutaneous fistulas, skin flaps, staged procedures. Other: post-transplant, RRT

(cont.)

Table 1. Common pathogens causing SSIs by organ transplant type and specific host and surgical risk factors for SSI (Adapted and modified from Abbo LM *et al.*, 2019) *(cont.)*

Organ type and incidence of SSIs	Most common pathogens causing SSI	Host risk factors for SSI	Surgical risk factors for SSI
Heart (4-19%)	Coagulase-negative Staph, *MRSA, Enterococci*	DM, obesity, prior VAD, ECMO, prolonged mechanical ventilation	Prolonged ischemic time, use of bilateral internal mammary arteries
Lung (5-19%)	*Pseudomonas* spp., *Escherichia coli, Klebsiella* spp., *Candida* spp., *Staphylococcus aureus, Enterococci,* Coagulase negative Staph, *Burkholderia* spp.	Renal dysfunction, prior sternotomy, DM	Re-exploration post-transplant due to bleeding, prolonged ischemic time, blood transfusion

Abbreviations. DM: diabetes mellitus, ECMO: extracorporeal membrane oxygenation, GI: gastrointestinal, GN: glomerulonephritis, RRT: renal replacement therapy, ICU: intensive care unit, MELD: model for end-stage liver disease, RRT: renal replacement therapy, SSI: surgical site infection, VAD: ventricular assist devices.

Recommended perioperative antibiotic prophylaxis by organ type

Abbo *et al.* published guidelines in 2019 recommending perioperative antimicrobial prophylaxis for SOT recipients. These guidelines list the most common organisms causing SSI according to organ type, risk factors, and proposed perioperative antibiotic prophylaxis regimens.

Renal

Renal transplant recipients have the lowest rates of SSIs among SOT, ranging from 3-11%. There are specific risks that increase SSI incidence: diabetes mellitus, surgical re-operation, ureteral leak, hematomas, and types of immunosuppression. Complications like delayed graft function, donor-derived infections, and acute rejection are also significant risk factors. The most common pathogens causing SSI are Gram-positive organisms, but Gram-negative bacteria and yeast have also been implicated.

In most cases, a first-generation cephalosporin is adequate for prophylaxis; cefazolin is the agent of choice unless the patient is being treated for an active infection. Recipient/donor colonization should be taken into consideration for prophylaxis if certain MDROs are identified, but further data needs to be compiled for this recommendation.

Heart

SSIs in heart transplantation (HT) can be superficial or deep, resulting in sternal osteomyelitis and/or mediastinitis. SSI incidence ranges from 4-19%, with 1-7% for mediastinitis. HT candidates may have ventricular assist devices (VAD) or other mechanical circulatory support. There are specific SSI risks associated with these devices, especially when vessel repair is required or with circuit colonization. This is also related to a longer LOS, which can predispose to MDRO colonization. Other SSI risk factors in HT recipients include diabetes mellitus, obesity, and re-operation/re-transplantation. Donor colonization can be a significant risk factor and surgical factors such as prolonged cold ischemic time or use of internal mammary arteries can also increase SSI risk.

Perioperative prophylaxis in HT is extrapolated from other cardiac surgeries given the lower number of studies in HT. The most common pathogens implicated are Gram-positives, such as MRSA, and other Staphylococci. A first-generation cephalosporin (e.g., cefazolin) is a clear recommendation, but there is controversy about the benefits of vancomycin over cephalosporins – some studies show no difference while some show vancomycin to be superior; these differences may relate to variances in MRSA colonization. A feasible consideration is the use of vancomycin as an adjunct with a first-generation cephalosporin. In HT candidates with a history of VAD infections or infection/colonization of the ECMO circuit, prophylaxis should also include coverage of the active infection/colonizing organism(s).
The optimal duration of HT antibiotic prophylaxis is unclear, but studies in non-transplant cardiac surgeries demonstrate that prolonging antibiotics beyond 48 hours does not further reduce SSI rates but increases MDRO risk and overall antimicrobial resistance. For HT recipients with an open chest after surgery, an extended antibiotic course may be warranted depending on the timing of closure and the presence of other risk factors.

Lung
SSIs in lung transplant (LT) recipients include superficial infections, mediastinitis and airway anastomosis infection. The incidence ranges from 5-19% and is associated with one-year mortality post-transplant of >30%. If allograft pneumonia are taken into consideration as an SSI, the rates approach 40% post-operatively. Host SSI risks are similar to HT recipients.
In contrast to HT, the typical organisms causing LT SSIs are often Gram-negative bacteria and fungi. Gram-positive bacterial SSIs still occur but are less common. Notably, fungal infections are more common in LT compared to other organ types.
Donor colonization is an important factor for LT recipients. Gram-negative colonization of the donor airways or perfusate liquid is associated with worse outcomes. A study of 115 LT recipients demonstrated longer ICU times, an increase in ventilator days, and overall worse survival when the donor bronchoalveolar lavage (BAL) cultures isolated bacteria. Cystic fibrosis (CF) is the third most common indication for LT and CF patients who have recurrent infections with MDR *Pseudomonas* spp., *Burkholderia* spp., and non-tuberculous mycobacteria. The persistence of these organisms may be due to CF-associated bronchiectasis and altered microbiome. Given the high prevalence of Gram-negative and fungal colonization in LT candidates, there are recommendations to tailor perioperative prophylaxis for any active infections and/or known colonization. In thoracic transplant patients, colonization with GNRs, whether donor or recipient, increases the risk of SSIs and post-operative pneumonia. A 7-day treatment course targeting the donor/recipient organisms is typically done in practice. However, further studies are needed to identify the optimal duration of therapy.
One proposed regimen (if no donor or recipient colonization –including any ECMO circuits) is to administer vancomycin with an anti-pseudomonal beta-lactam. Culture-guided antifungals are also recommended if there is a history of fungal colonization in either the donor or recipient.

Liver
SSIs are common in orthotopic liver transplant (OLT) recipients, ranging from 10-37%, including superficial SSIs and peritonitis. These infections increase graft loss and 1-year mortality. Host SSI risks include a high Model for End-stage Liver Disease (MELD) score, ascites, prior transplant or biliary surgery, diabetes mellitus, hemochromatosis, and recent prolonged ICU or hospital stay. Specific surgical complications like contamination from bowel breach, excessive blood loss >2L, and anastomotic leak are also significant SSI risks.
A large proportion of OLT SSIs are caused by enteric Gram-negatives but there are also SSIs caused by *Staphylococci*, *Enterococci*, and *Candida* spp. OLT recipients also have a high prevalence of MDROs, predominantly

VRE, ESBL-producing *Enterobacterales*, and carbapenem-resistant *Enterobacterales* (CRE). Colonization with any MDRO is associated with an increased risk of infection in OLT.
There are no randomized trials of the optimal prophylactic regimen for OLT, but retrospective studies demonstrate that enterococcal coverage may be beneficial over a first-generation cephalosporin. The American Society of Transplantation (AST) guidelines suggest using ampicillin-sulbactam with the addition of *Candida*-directed antifungal prophylaxis if risk factors (e.g., prolonged operation times, excessive blood loss, renal replacement therapy, re-operation) are present.

Pancreas
Pancreas or simultaneous pancreas-kidney (SPK) SSI rates range from 9-45% of transplants. This higher SSI rate compared to renal transplants may be due to a high prevalence of diabetes mellitus in this population.
There are two main surgical anastomosis methods that change the type of flora implicated in SSIs for SPK or pancreas transplants. When bladder drainage is employed, urinary tract infections (UTIs) are more common, as high as 48% in an early study done by Smets *et al.* If enteric drainage is used, then SSIs involving the recipient duodenum occur and are associated with higher SSI rates compared to bladder exocrine drainage. Other surgical SSI risks include prolonged operative time, prolonged ischemic time (>4 hours), fistulas, hand-sewn anastomoses, and excessive blood loss.
Implicated organisms depend on SSI location and on which anastomotic approach is used. Staphylococci and enterococci predominate, but *Enterobacterales* and *Pseudomonas aeruginosa* can also be common. Less common organisms include *Candida* spp., *Streptococci*, and *Mycoplasma hominis*. There is a paucity of prospective data for pancreas transplants but given the variability in SSI site and causative organisms, broad coverage is recommended. In retrospective studies, SSI rates with prophylaxis were moderately decreased. Ampicillin-sulbactam with fluconazole (single dose) is one proposed regimen. Fluconazole can be extended to 7-14 days if there are risk factors for fungal infection such as enteric drainage, anastomotic leaks, or laparotomy after transplantation.

Multi-visceral and intestinal
SSIs occur frequently in multi-visceral and intestinal transplants, ranging from 14-53%, including superficial and deep soft tissue infections and intra-abdominal infections (IAI). SSI rates increase to a range of 27-100% if a mesh closure is used. Other SSI risks include re-operation in the first month after transplant, skin-flap closure, staged procedures, and entero-cutaneous fistulas.
The most common bacteria that cause SSI in intestinal transplants are Gram-negative bacteria (*Pseudomonas* spp., *E. coli*, *Klebsiella* spp.) and anaerobes. Fungal organisms such as *Candida* spp. are also frequent pathogens, but Gram-positive organisms are less common. There is also a high prevalence of MDRO infections in this patient population. Primeggia *et al.* studied 40 patients with small bowel and multi-visceral transplants and found in the 30-day post-transplant period, 57.5% of patients developed infections and half of these were due to MDROs. Professional societies do not provide specific guidelines regarding antimicrobial prophylaxis for these transplant types given the large variety of potential organisms that can cause SSIs.
The AST guidelines propose using antibiotics with activity against enterococci, *Pseudomonas*, anaerobes, and fungi, such as a combination of 1) vancomycin, cefepime, metronidazole, and fluconazole/echinocandin or 2) vancomycin, piperacillin-tazobactam, and fluconazole/echinocandin (**Table 2**).

Table 2. Pre-operative antimicrobial prophylaxis guidelines for different organ transplantation types (Adapted and modified from Abbo LM *et al.*, 2019).

Organ type	2013 guidelines (IDSA, ASHP, SIS, SHEA)	2019 AST ID COP guidelines	Intra-op redosing	Duration post-op	If penicillin- allergic
Kidney	First generation cephalosporin	Cefazolin 2 g IV	Every 4h	24-48h	Vancomycin** OR clindamycin 900 mg IV + IV gentamicin 5 mg/kg
Liver	Third generation cephalosporin *plus* ampicillin OR piperacillin-tazobactam alone	Ampicillin-sulbactam 3 g ± fluconazole 400 mg* OR echinocandin * OR liposomal amphotericin B*	Every 2h (fluconazole not redosed)	24-8h	Ciprofloxacin 500 mg IV q12h + Vancomycin**
Heart without prior VAD	First generation cephalosporin	Vancomycin + cefazolin 2 g	Every 4h	24-48h	Vancomycin** + levofloxacin 750 mg q24h
Heart with prior VAD		Vancomycin + ceftriaxone 1 g OR cefepime 2 g			
Lung		Vancomycin + third-generation cephalosporin or cefepime 2 g		48-72h	Vancomycin + levofloxacin 750 mg q24h
Pancreas, kidney-pancreas		Ampicillin-sulbactam 3 g + fluconazole 400 mg IV	Every 2h (fluconazole not redosed)	24-48h Can be extended if high risk for invasive fungal infection	Vancomycin** OR Clindamycin 900 mg IV + IV gentamicin 5mg/kg +Fluconazole 400 mg IV OR echinocandin or L-Amb *
Intestinal or multivisceral	n/a	Vancomycin** + cefepime 2 g IV + Metronidazole 500 mg + Fluconazole 400 mg IV OR vancomycin + IV piperacillin-tazobactam 4.5 g +fluconazole 400 mg IV	Every 4h (fluconazole not redosed)	48-72h If infection mesh or fistulas, then extend to 7 days	Vancomycin** + levofloxacin 750 mg q24h + Metronidazole 500 mg IV

*If high risk for invasive fungal infection.

** Vancomycin should be renally dosed, with considerations for adjustment to account for weight.

Abbreviations. ASHP: American Society of Health-systems Pharmacists, AST ID COP: American Society of Transplantation Infectious Diseases Community of Practice, IDSA: Infectious Disease Society of America, IV: intravenous, SHEA: The Society for Healthcare Epidemiology of America, SIS: Surgical Infection Society, VAD: ventricular assist device.

Intra-operative repeat dosing for specific clinical scenarios

After selecting the appropriate agent(s) for pre-operative prophylaxis, certain scenarios necessitate repeat dosing of antibiotics. A key principle is to ensure the antibiotics can reach the optimal tissue concentrations before the skin barrier is breached. A 2017 meta-analysis including over 54,000 patients showed that the lowest risk of SSIs occurred when antibiotics were given within 120 minutes of the initial incision. While most infusions should be completed within 60-120 minutes prior to the procedure, each antibiotic has variable pharmacokinetics, so consultation with institutional pharmacy teams is important to ensure optimal concentrations before the initial incision.

In complex surgeries that may take multiple hours, repeat doses of the antimicrobial should be given if the surgery lasts more than 2 half-lives of the drug or if there is excessive blood loss (greater than 1500 mL) during the surgery. Patients with renal/liver failure or morbid obesity may also need loading doses or adjustment of post-operative doses. Pharmacists with ID subspecialty training are especially crucial to ensure that antimicrobial use is optimized.

Duration of antimicrobial perioperative prophylaxis

Generally, antibiotic prophylaxis should be continued 24-72 hours postoperatively. Antibiotics should be extended if there are surgical complications such as anastomotic leak in abdominal/intestinal transplants, fistulas, or mesh infection. In OLT and HT studies, routine extension of prophylaxis beyond 48 hours does not improve the rate of SSIs but increases the rate of antimicrobial resistance. One small trial of short (intraoperative) *versus* extended (72-hour) antimicrobial prophylaxis for liver transplantation demonstrated equivalent SSI rates, suggesting that even shorter durations of perioperative prophylaxis may be considered in this transplant group.

Management of postoperative infectious complications

Post-operative SSIs

There is an abundance of data in the non-transplant population regarding post-operative infection including SSIs, but there are no clear recommendations for treatment in SOT recipients. The standard management of infected surgical wounds includes basic wound care, irrigation and debridement, allowing examination for dehiscence or organ space infection that may require more invasive interventions.

Superficial wound swabs at the bedside are not recommended due to extremely poor sensitivity and specificity related to colonization. Only direct culture, ideally from a sterile aspirate of exudate or tissue, have the best diagnostic utility. If there are organ space infections such as abscesses, empyema, or mediastinitis, then source control is the cornerstone of treatment. While targeted antimicrobial therapy from sterile cultures of these areas is important, antimicrobials alone are insufficient to cure these infections.

Other diagnostic and empiric treatment considerations

The etiology of post-operative fever varies depending on the time elapsed after surgery and there are other aspects to consider for immunocompromised patients. They may not be able to mount an adequate inflammatory response, and fever may be the only sign of infection. Certain factors can also alter temperature control, and masking fevers, such as continuous renal replacement therapy (CRRT), or ECMO.

Cultures of relevant body fluids should be obtained prior to starting antibiotics to maximize diagnostic yield. If the patient has an indwelling urinary catheter, it should be exchanged prior to obtaining urine cultures, to avoid the confounding factors of catheter colonization. Cultures should never be obtained from pre-existing

drainage bags. CDI is also a common cause of hospital-acquired infections and increases mortality in immunocompromised patients. SOT recipients are at high risk for CDI for many reasons, including substantial antibacterial exposure and impaired immune responses. CDI should always be considered if patients have ≥3 episodes of watery diarrhea in the absence of laxatives.

In neutropenic patients receiving cytotoxic chemotherapy, gut mucosal barrier disruption can lead to mucositis and typhlitis (neutropenic enterocolitis). The translocation of microbes and microbial products at these sites can cause fever. In suspected typhlitis, workup should include computed tomography (CT) imaging, blood cultures and initiation of broad enteric, pseudomonal, and anaerobic coverage. In 40-50% of febrile neutropenia, there may not be microbiological evidence of infection, but there is clinical response to antimicrobials.

Non-pharmacologic infection prevention strategies

Intravascular devices are important to administer medications, blood products, and vasoactive medications in the ICU, especially in the post-transplant phase. Many patients with malignancies have implanted ports for chemotherapy. These vascular devices are a risk factor for bacteremia. Over 60% of hospital-acquired bacteremias are linked to intravascular devices and categorized as central line-associated blood stream infections (CLABSIs). CLABSIs have profound effects on mortality, ranging between 12-25%, as well as astounding healthcare costs of an additional $4,000 to $56,000 per episode.

Reducing risk of intravascular device-related bacteremia starts from insertion; effective bundled interventions include barrier precautions, hand hygiene, and removal when the device is obsolete. Similarly, urinary catheter removal when no longer indicated can reduce UTIs.

ID consultation for specific scenarios

ID consultants and ID-trained pharmacy subspecialists can be essential for both antimicrobial stewardship roles and optimizing diagnostic/therapeutic decisions for patients with specific infectious clinical syndromes. Many retrospective studies have shown decreased mortality when ID consultation is obtained. In a high-mortality infection like *Staphylococcus aureus* bacteremia, ID consultation has shown to have mortality benefits from appropriate antibiotic recommendations, device removal, and echocardiography to evaluate for endocarditis. In one single-center study looking at *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Candida* bloodstream infections, lack of ID consultation correlated with a four-fold higher hazard ratio of death at 3 months. Other institutions have published mortality benefits for early ID consultation in Gram-negative infections, especially in cases with multi-drug resistance and polymicrobial infections.

Summary and key points

- MDR infections are a global concern, especially given the increased mortality among immunocompromised patients who are often exposed to prolonged durations of both prophylactic and therapeutic antimicrobials.

- Perioperative prophylaxis can help decrease SSI risk in SOT recipients. The regimens and types of pathogens implicated in SSIs vary depending on the type of transplant.
- Multiple factors (diabetes mellitus, obesity, prolonged hospitalization) contribute to increased SSI risk in SOT recipients. Surgical risks applicable for all organ types include prolonged operative time, blood loss with blood transfusion, and re-operation after transplantation.
- ASP are important to curtail the adverse effects of non-essential antimicrobial usage.
- A multidisciplinary approach is crucial, especially in SOT care, where there are multiple opportunities for collaboration at all phases of pre-surgical and post-surgical care to improve patient outcomes.
- ID consultants and ID-trained pharmacy subspecialists can be essential for both stewardship roles and optimizing diagnostic and therapeutic decisions for patients with specific infectious clinical syndromes.

Competing interests

The authors have no financial and non-financial competing interests to declare.

References

1. Barlam TF, et al. Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis. 2016;62:e51–e77.
2. Tessier J. A work in progress: antimicrobial stewardship in solid organ transplant patient populations. Curr Opin Infect Dis. 2022;35:363-369.
3. Hand JM. The time is now: antimicrobial stewardship in solid organ transplantation. Curr Opin Organ Transplant. 2021;26:405-411.
4. Abbo LM, et al. Surgical site infections: guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33:e13589.
5. Camargo LFA, et al. Nosocomial bloodstream infections in a nationwide study: comparison between solid organ transplant patients and the general population. Transpl Infect Dis. 2015;17:308-313.
6. Surgical site infection (SSI). CDC. Available at: https://www.cdc.gov/nhsn/pdfs/pscmanual/9pscssicurrent.pdf. Last accessed: 28 April 2022.
7. Anesi JA, et al. Perioperative antibiotic prophylaxis to prevent surgical site infections in solid organ transplantation. Transplantation. 2018;102:21-34.
8. Hand, J, et al. Antimicrobial stewardship in transplant patients. Curr Opin Organ Transplant 2019;24:497-503.
9. Conway EL, et al. Impact of penicillin allergy on time to first dose of antimicrobial therapy and clinical outcomes. Clin Ther. 2017;39:2276–2283.
10. del Real GA, et al. Penicillin skin testing in patients with a history of beta-lactam allergy. Ann Allergy Asthma Immunol. 2007;98:355–359.
11. Imlay, H et al. Reported β-lactam and other antibiotic allergies in solid organ and hematopoietic cell transplant recipients. Clin Infect Dis. 2020;71:1587-1594.
12. Zhang HL, et al. The impact of reported β-lactam allergy on clinical outcomes and antibiotic use among solid organ transplant recipients. Open Forum Infect Dis. 2022;9:ofac384.
13. Blumenthal KG, et al. The impact of a reported penicillin allergy on surgical site infection risk. Clin Infect Dis. 2018;66:329-336.
14. Anstey KM, et al. Perioperative use and safety of cephalosporin antibiotics in patients with documented penicillin allergy. J Allergy Clin Immunol Pract. 2021;9:3203-3207.

15. Zimlichman E, et al. Health care-associated infections: a meta-analysis of costs and financial impact on the US health care system. JAMA Intern Med. 2013;173:2039-2046.
16. Sousa-Pinto B, et al. Penicillin allergy testing is cost-saving: an economic evaluation study. Clin Infect Dis. 2021;72:924-938.
17. Dewan KC, et al. Implications of methicillin resistant Staphylococcus aureus carriage on cardiac surgical outcomes. Ann Thorac Surg. 2020;110:776-782.
18. Bert F, et al. Association between nasal carriage of Staphylococcus aureus and infection in liver transplant recipients. Clin Infect Dis. 2000;31:1295-1299.
19. Russell DL, et al. Outcomes of colonization with MRSA and VRE among liver transplant candidates and recipients. Am J Transplant. 2008;8:1737-1743.
20. Primeggia J, et al. Infection among adult small bowel and multivisceral transplant recipients in the 30-day postoperative period. Transpl Infect Dis. 2013;15:441–448.
21. Menezes FG, et al. Risk factors for surgical site infection in kidney transplant recipients. Infect Control Hosp Epidemiol. 2008;29:771-773.
22. Mattner F, et al. Post-operative nosocomial infections after lung and heart transplantation. J Heart Lung Transplant. 2007;26:241-249.
23. Bolon MK, et al. Glycopeptides are no more effective than beta-lactam agents for prevention of surgical site infection after cardiac surgery: a meta-analysis. Clin Infect Dis. 2004;38:1357-1363.
24. O'Neill JM, et al. Nosocomial infections during extracorporeal membrane oxygenation. Intensive Care Med. 2001;27:1247-1253.
25. Shields RK, et al. Epidemiology and outcomes of deep surgical site infections following lung transplantation. Am J Transplant. 2013;13:2137-2145.
26. Avlonitis VS, et al. Bacterial colonization of the donor lower airways is a predictor of poor outcome in lung transplantation. Eur J Cardiothorac Surg. 2003;24:601-607.
27. Vazirani J, et al. Management of multidrug resistant infections in lung transplant recipients with cystic fibrosis. Infect Drug Resist. 2021;14:5293-5301.
28. Husain S, et al. The 2015 International Society for Heart and Lung Transplantation Guidelines for the management of fungal infections in mechanical circulatory support and cardiothoracic organ transplant recipients: executive summary. J Heart Lung Transplant. 2016;35:261-282.
29. Asensio A, et al. Effect of antibiotic prophylaxis on the risk of surgical site infection in orthotopic liver transplant. Liver Transpl. 2008;14:799-805.
30. Garcia Prado ME, et al. Surgical site infection in liver transplant recipients: impact of the type of perioperative prophylaxis. Transplantation. 2008;85:1849-1854.
31. Kawecki D, et al. Bacterial and fungal infections in the early post-transplantation period after liver transplantation: etiologic agents and their susceptibility. Transplant Proc. 2014;46:2777-2781.
32. Freire MP, et al. Carbapenem-resistant enterobacteriaceae acquired before liver transplantation: impact on recipient outcomes. Transplantation. 2017;101:811-820.
33. Smets YF, et al. Infectious disease complications of simultaneous pancreas kidney transplantation. Nephrol Dial Transplant 1997;12:764-771.
34. Natori Y, et al. Risk factors for surgical site infection after kidney and pancreas transplantation. Infect Control Hosp Epidemiol. 2018;39:1042-1048.
35. Freise CE, et al. Low postoperative wound infection rates are possible following simultaneous pancreas kidney transplantation. Transplant Proc. 1995;27:3069-3070.
36. Silveira FP, et al. Candida infections in solid organ transplantation. Am J Transplant. 2013;13:220-227.
37. Silva JT, et al. Infectious complications following small bowel transplantation. Am J Transplant. 2015;16:951-959.
38. Zanfi C, et al. Incidence and management of abdominal closure-related complications in adult intestinal transplantation. Transplantation. 2008;85:1607-1609.
39. De Jonge SW, et al. Timing of preoperative antibiotic prophylaxis in 54,552 patients and the risk of surgical site infection: a systematic review and meta-analysis. Medicine (Baltimore). 2017;96:e6903.

40. Bratzler DW, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm. 2013;70:195-283.
41. Russell DL, et al. Outcomes of colonization with MRSA and VRE among liver transplant candidates and recipients. Am J Transplant. 2008;8:1737-1743.
42. Hamouda K, et al. Different duration strategies of perioperative antibiotic prophylaxis in adult patients undergoing cardiac surgery: an observational study. J Cardiothorac Surg. 2015 Feb 26:10:25.
43. Berry PS, et al. Intraoperative versus extended prophylaxis in liver transplant surgery: a randomized controlled pilot trial. Liver Transpl. 2019;25:1043-1053.
44. Clark ST, et al. Wound swab quality grading is dependent on Gram smear screening approach. Sci Rep. 2023;13:3160.
45. Nohra E., et al. Fever and infections in surgical intensive care: an American Association for the Surgery of Trauma Critical Care Committee clinical consensus document. Trauma Surg Acute Care Open. 2024;9:e001303.
46. Freifeld AG, 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:e56-e93.
47. O'Grady NP, et al. Guidelines for the prevention of intravascular catheter-related infections. Clin Infect Dis. 2011;52:e162-e193.
48. Pittet D, et al. Nosocomial bloodstream infection in critically ill patients. Excess length of stay, extra costs, and attributable mortality. JAMA. 1994;271:1598-601.
49. Vogel M, et al. Infectious disease consultation for Staphylococcus aureus bacteremia - a systematic review and meta-analysis. J Infect. 2016;72:19–28.
50. Chesdachai S, et al. The effect of infectious diseases consultation on mortality in hospitalized patients with methicillin-resistant Staphylococcus aureus, Candida, and Pseudomonas bloodstream infections. Open Forum Infect Dis. 2020;7:ofaa010.
51. Ong SWX, et al. Association between infectious diseases consultation and mortality in hospitalized patients with gram-negative bloodstream infection: a retrospective population-wide cohort study. Clin Infect Dis. 2024:ciae282.

Chapter 77

Antimicrobial stewardship in surgical site infections in oncological patients – a review from the major agents to the treatment strategies

João Paulo Telles
AC Camargo Cancer Center, Department of Infectious Diseases, São Paulo, Brazil.

Diego Feriani da Silva
AC Camargo Cancer Center, Department of Infectious Diseases, São Paulo, Brazil.

Ivan Leonardo França e Silva
AC Camargo Cancer Center, Department of Infectious Diseases, São Paulo, Brazil.

Introduction

Antimicrobial stewardship programs (ASPs) are instrumental in optimizing antibiotic use across various healthcare settings, and their significance is particularly pronounced in the context of cancer surgical patients. Cancer patients often undergo surgical procedures that not only remove tumors but also increase their susceptibility to infections due to compromised immune systems caused by cancer therapies. This is due that innate and adaptative immune response may be impaired in cancer patients. First, the innate immune response, primarily mediated by neutrophils, is crucial for early defense against pathogens. Neutrophils are recruited to the site of surgery, where they phagocytize bacteria and secrete cytokines to orchestrate further immune responses. Impairments in neutrophil function—due to conditions such as chemotherapy and steroids—can lead to an increased susceptibility to infections. Additionally, the adaptive immune response, particularly the role of T lymphocytes, is vital in providing long-term immunity. CD4+ T cells help in coordinating immune responses, while CD8+ T cells can directly kill infected cells. A reduced number of T cells or their impaired activation can diminish the body's ability to combat infections following surgical procedures. Furthermore, factors such as malnutrition, tabagism, advanced age, and metabolic syndrome, which are common factors in oncological scenarios, can affect overall immune function, once again increasing the likelihood of SSIs. Prevention of SSIs in oncological patients should underscore all these fragilities in this special population. ASPs advocate for adherence to evidence-based guidelines for antibiotic prophylaxis, which is particularly vital during surgical procedures in cancer patients. Effective prophylactic strategies can significantly reduce the incidence of SSIs, thereby improving clinical outcomes and reducing overall healthcare costs. The prevention is the first step of a well-structured staircase called ASP.

Inappropriate use of antibiotics, whether through overprescription or inadequate treatment duration, contributes to the development of multidrug-resistant organisms, complicating future treatment options and increasing the burden on healthcare systems. Studies have demonstrated that the emergence of resistant pathogens is often linked to extensive antibiotic use in surgical settings, highlighting the need for targeted stewardship efforts that monitor and evaluate antibiotic prescribing practices.

Furthermore, ASPs play a crucial role in fostering collaboration among multidisciplinary teams, including surgeons, infectious disease specialists, microbiologists, nurses, and pharmacists. Pharmacists, supported by protocols developed in conjunction with infectious disease specialists and surgeons, can adjust doses and suspend prophylactic antibiotics in the given time, helping to reduce costs and especially the emergence of bacterial resistance. By developing communication channels between these stakeholders, ASPs facilitate the timely sharing of information about local resistance patterns, recommending personalized antibiotic therapies that optimize patient care. This collaborative approach ensures that healthcare providers are well-informed about the most effective and appropriate antibiotics to use, ultimately promoting rational antibiotic prescribing.

Here we will describe the major SSIs in cancer patients focusing on their approach (i.e., with and without surgical drainage or debridement) based on the main pathogens and their antimicrobial resistance pattern. Lastly, we will briefly describe the potential and the cautions of biomarkers in ASP to cancer surgical site infections.

Colorectal surgery infections treatments

Colorectal surgery infections in cancer patients present a challenging clinical scenario due to the immunocompromised state of the patients and the polymicrobial flora of the colon. The most common pathogens involved in these infections are *Escherichia coli*, *Enterococcus* spp., and anaerobes such as *Bacteroides fragilis*. These organisms are part of the normal gut flora but can become pathogenic when tissue integrity is compromised during surgery. *E. coli* is a significant concern due to its capability to produce extended-spectrum β-lactamases (ESBLs), which confer resistance to many third-generation cephalosporins and complicate empirical treatment.

The presence of *Enterococcus*, particularly *E. faecalis* and *E. faecium*, adds complexity given their potential for vancomycin resistance (VRE). Treatment options for VRE are limited and often involve the use of linezolid or daptomycin. However, it's important to differentiate *E. faecalis* from *E. faecium*, as *E. faecalis* usually have a high ampicillin susceptibility rate. Lastly, another concern could be anaerobic bacteria like *Bacteroides fragilis*. However, they are generally susceptible to metronidazole.

In managing colorectal surgical site infections, the duration of antibiotic treatment can vary depending on whether surgical drainage is performed. Patients with a surgical approach and adequate source control (i.e., from percutaneous drainage or even major abdominal surgeries) could have their time of antibiotic therapy shortened to 4-5 days after source control. However, the STOP trial included a small number of immunocompromised patients. So, the rigor to follow 4-5 days of therapy may be debatable in cancer patients. Nevertheless, it's interesting to notice that when re-infection occurred patients with a short course of antimicrobial therapy had a sooner diagnosis of it, while patients with 8-10 days of antimicrobial prescription did not change their reinfection outcome and delayed the correct diagnosis. This interpretation follows colon and rectum SSI, but also other gastrointestinal complex infections (e.g., small bowel, biliary tree, liver, esophagus). If source control is not made, patients continue with a high load of bacterial infection, usually impaired of antibiotic action due to acid environment consequence of cellular lysis (e.g. pus). Additionally, microbiological

diagnosis is not made, which makes therapy based on empirical microbiota. Therefore, antibiotic therapy usually lasts at least 7 days depending on several factors and should have an image comparative control before antibiotic cessation. Antimicrobials should aim for broad-spectrum coverage to address both aerobic and anaerobic bacteria. This conservative approach relies heavily on the robust activity of antibiotics against ESBL-producing organisms and enterococci.

This tailored approach to treatment duration, influenced by surgical intervention and guided by antimicrobial susceptibility, is crucial in optimizing clinical outcomes while mitigating the risk of further resistance development. Effective antibiotic stewardship combined with timely surgical management remains key to controlling these challenging infections in cancer patients undergoing colorectal surgery.

Breast surgery infection treatments

The major pathogens associated with surgical site infections (SSIs) in breast cancer patients include *Staphylococcus aureus*, coagulase-negative staphylococci, *Escherichia coli*, and *Pseudomonas aeruginosa*. *Staphylococcus* species, particularly *S. aureus*, are the most frequently isolated pathogens, with methicillin-resistant *S. aureus* (MRSA) being a significant concern.

Resistance patterns show a high prevalence of methicillin resistance among staphylococcal isolates. For instance, *Staphylococcus* spp. accounts for the majority of breast surgery infections in more than 50% in some studies, while MRSA in up to 30%. Additionally, when considering Gram-negative and Gram-positive bacteria, there is a notable resistance to first-generation cephalosporins, such as cefazolin, with resistance rates up to 54.5%. It's important to highlight that metanalysis did not find a difference in prolonging antibiotic prophylaxis prescriptions until drain removal in patients undergoing implant-based breast reconstruction.

Antibiotic treatment is the consensus to try to save the breast expander or prosthesis. However, there is no consensus regarding removing them. Lastly, it's also debatable the time of removing and reimplantation. All these variables impact directly at antimicrobial stewardship program due to the time of treatment, which can induce side effects such as renal injury with vancomycin or increasing bacteria resistance. Therefore, it's important to consider the bacteria biofilm's role and its implication on refractory infection.

Usually, if the expander or prosthesis is not removed, a 10-day antibiotic cycle is tried as a salvage therapy. If surgery is preferred, at least 72 hours of antibiotic is performed before the reimplantation step. Studies have demonstrated that antibiotic salvage therapy to expanders is usually higher when compared to prosthesis group. However, if *Staphylococcus aureus* is a proven infection, a surgical procedure is highly recommended. The duration of treatment is variable. If salvage therapy is tried, a 14-day cycle is usually performed, while in implant-removal strategy a shorter cycle as 7-day therapy could be tried depending upon clinical response.

In conclusion, effective management of breast surgery infections in cancer patients requires a multifaceted approach that includes the identification of pathogens and their resistance patterns, adherence to surgical best practices when possible, and personalized antibiotic regimens. Surgical strategies help optimize outcomes, minimize the time of antibiotic treatment, and combat the development of antibiotic resistance.

Hepatobiliary surgery infection treatments

Hepatobiliary surgery infections in cancer patients encompass a range of postoperative complications due to infections in organs such as the liver, gallbladder, and bile ducts. These infections can arise due to surgical site

contamination by enteric bacteria. Common pathogens include *Enterococcus* spp., *Escherichia coli*, *Klebsiella* spp., and *Enterobacter* spp. Preoperative biliary drainage (PBD) significantly alters the biliary microbiome, increasing the prevalence of multidrug-resistant (MDR) organisms such as *Enterococcus faecium* and *Enterobacter cloacae*.

In this situation, it's important to remember the main patterns of antimicrobial resistance according to each bacterium. *Enterococcus faecium* is highly resistant to vancomycin, so linezolid or daptomycin could be options to treat VRE. However, *E. faecalis* is not commonly resistant to vancomycin. Additionally, *Enterobacteriaceae* is commonly resistant to third cephalosporins generation and/or quinolone.

The treatment duration for hepatobiliary surgery infections varies based on whether drainage is utilized. Metanalysis demonstrated that 72h post biliary tree drainage could be safely used. However, as usual, cancer patients are not often included in these studies. Without drainage procedures, antibiotic therapy generally ranges from 7-10 days to ensure adequate antimicrobial exposure and resolution of the infection. It is also important to consider variables that may impair infection fast resolution such as severe neutropenia. Therefore, clinical and laboratory evaluation is fundamental.

In summary, managing hepatobiliary surgery infections in cancer patients requires a strategic approach that includes biliary tree drainage, identification of pathogens, understanding resistance patterns, and optimizing the duration of antibiotic therapies. Lastly, source control through surgical intervention, when feasible, plays a crucial role in reducing treatment duration and improving patient outcomes while lowering the risk of resistance development.

Head and neck surgery infections

Head and neck surgical site infections (SSIs) are a significant concern in cancer patients, given the complex anatomy of the region and the immunocompromised state of many individuals undergoing cancer treatment. Infections can arise postoperatively or due to tumor-related complications and are associated with increased morbidity, prolonged hospitalizations, and delays in adjuvant therapies.

The major pathogens involved in surgical site infections (SSIs) following head and neck cancer surgery include both Gram-positive and Gram-negative bacteria. *Staphylococcus aureus*, including MRSA, and *Enterococcus* species are the predominant Gram-positive pathogens. Among Gram-negative bacteria, *Klebsiella* species, *Acinetobacter* species, *Pseudomonas aeruginosa*, and *Escherichia coli* are frequently isolated. Resistance patterns among these pathogens are concerning. MRSA is notably prevalent, with resistance rates as high as 64.28% in some studies. Gram-negative pathogens exhibit high levels of resistance to aminopenicillins, third-generation cephalosporins, co-trimoxazole, and fluoroquinolones. Extended-spectrum β-lactamase (ESBL)-producing *E. coli* has shown a significant increase in resistance, with rates rising from 39.5% to 72.5% over a seven-year period.

Given these resistance patterns, empirical antibiotic therapy should be guided by local antibiograms and adjusted based on culture and sensitivity results. The use of anti-MRSA agents such as vancomycin, linezolid, and teicoplanin remains effective against MRSA, with no resistance reported in some studies. For Gram-negative infections, carbapenems are often required due to high resistance rates to other antibiotic classes.

For clean-contaminated head and neck surgery, the optimal duration of antibiotic prophylaxis is 24 to 48 hours. This is supported by multiple systematic reviews and meta-analyses, which indicate that extending prophylaxis beyond 24-48 hours does not further reduce the risk of surgical site infections (SSIs). Lastly, the American Academy of Otolaryngology-Head and Neck Surgery recommends this duration for antibiotic prophylaxis in such cases. American Academy of Otolaryngology-Head and Neck Surgery advises that

antibiotics should only be used if there is clear evidence of bacterial infection. Empiric antibiotic treatment should be avoided in the absence of signs and symptoms of infection, such as warmth, erythema, localized swelling, tenderness, fever, or systemic signs of infection.

However, one important debate in this specific population is if there is any evidence of antibiotic use in tumor-related necrosis. Osteoradionecrosis (ORN) is a serious complication of radiation therapy for head and neck tumors, characterized by non-healing exposed necrotic bone in a previously irradiated site. It can present with pain, infection, and disability, and is often confused with tumor recurrence or infection. ORN is often predisposed to secondary infections due to the exposed necrotic bone. Common pathogens include *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*, including MRSA. Therefore, considering that infection may jeopardize ORN management, empirical antibiotic therapy should be guided by microbial culture and sensitivity testing to ensure appropriate coverage. Conservative management with antibiotics and debridement is often the first line of treatment, but surgical intervention may be necessary for extensive or refractory cases.

Uro-oncologic surgery infections

Uro-oncological surgical infections are a significant concern, particularly following procedures such as radical cystectomy and percutaneous nephrolithotomy (PCNL). The major bacteria involved in these infections include *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, and *Staphylococcus aureus*. These pathogens often exhibit resistance to multiple antibiotics, with high resistance rates noted for quinolones, and first and second-generation cephalosporins.

Commonly, these patients present nephrostomy-related infection. These infections should be interpreted with a high biofilm burden. Therefore, their management includes the removal of the infected device. Once culture and sensitivity results are available, antibiotic therapy should be tailored to the identified pathogens. The duration of antimicrobial therapy depends on whether the infected nephrostomy is removed. If the nephrostomy is removed, a shorter course of antibiotics, 7 days, is typically sufficient. However, if the nephrostomy remains in place, prolonged antibiotic therapy may be necessary to prevent recurrent infections.

It’s important to highlight the correct bacterial agent because in recurrent infections, ensuring concordant antibiotic use and timely catheter exchange (within 4 days of infection) are critical strategies to reduce recurrence.

To improve the microbiological diagnosis of nephrostomy-related infections, incorporating advanced techniques such as sonication and polymerase chain reaction (PCR) can be highly beneficial. Sonication is a method that uses ultrasonic waves to dislodge biofilms from the surfaces of medical devices, such as nephrostomy tubes. This technique has been shown to significantly enhance the detection of microbial colonization. For instance, sonication has been demonstrated to improve the diagnostic yield in ureteral stent colonization, revealing a higher detection rate of microbial ureteral stent colonization (MUSC) compared to conventional urine cultures. Polymerase Chain Reaction (PCR), particularly broad-range 16S rDNA PCR, can complement culture-based methods by identifying a wider spectrum of bacteria, including those that are difficult to culture. PCR techniques have shown higher specificity and can detect bacteria in biofilms that are often missed by standard cultures. Combining these methods, sonication followed by PCR analysis can further enhance diagnostic accuracy. For example, PCR of sonication fluid has been shown to be reliable and valuable in diagnosing periprosthetic joint infections, suggesting its potential applicability in nephrostomy-related infections as well.

In conclusion, the management of uro-oncological surgical infections, particularly those related to nephrostomy procedures, requires a multifaceted approach to address the significant challenges posed by antibiotic resistance and biofilm formation. Recognizing the predominant pathogens involved and their resistance patterns is essential for effective treatment strategies. Timely removal of infected devices, such as nephrostomy tubes, along with tailored antibiotic therapy based on culture and sensitivity results, are crucial aspects of managing these infections. The integration of advanced diagnostic techniques, such as sonication and PCR, represents a promising evolution in the microbiological diagnosis of nephrostomy-related infections, enhancing the detection of pathogens that are often difficult to culture. By prioritizing these methods, clinicians can improve diagnostic accuracy and guide more effective antibiotic use, ultimately reducing recurrence rates and optimizing patient outcomes in this vulnerable population.

Biomarkers in cancer patients

Biomarkers play a debatable role in the management of infections in cancer patients. The debate includes their role, particularly in guiding antimicrobial therapy, risk stratification, and monitoring treatment response. The use of biomarkers could help differentiate between bacterial, viral, and fungal infections, which is essential in immunocompromised cancer patients who are at high risk for severe infections. However, despite the American Society of Clinical Oncology (ASCO) and the Infectious Diseases Society of America (IDSA) highlighted the potential utility of these biomarkers in their guidelines, they also stated that there is a large heterogeneity in clinical studies that jeopardize a systematic use in a daily routine.

The most studied biomarkers used in daily routine practice for managing infections in ASP in cancer patients are (i) procalcitonin (PCT), (ii) C-reactive protein (CRP), (iii) Interleukin-6 (IL-6), (iv) Interleukin-8 (IL-8), and (v) Proadrenomedullin (ProADM). Procalcitonin is widely used to guide antibiotic therapy, particularly in distinguishing bacterial infections from other causes of inflammation. It has been shown to have a fair level of diagnostic accuracy for predicting bacteremia in immunocompromised patients. CRP is a non-specific marker of inflammation that is commonly used to assess the presence and severity of infection. It is useful in monitoring the response to treatment and in guiding decisions about the duration of antibiotic therapy. IL-6 is a cytokine involved in the inflammatory response and has been evaluated as a marker for infection and sepsis. It can provide prognostic information regarding the risk of adverse outcomes in critically ill patients. Additionally, similar to IL-6, IL-8 is another cytokine that plays a role in the inflammatory response. It has been studied for its potential to guide antimicrobial therapy and predict outcomes in patients with infections. Less studied, ProADM is a precursor of adrenomedullin, a peptide involved in the regulation of vascular tone and endothelial function. It has shown promise in guiding antimicrobial therapy and optimizing resource use in cancer patients with febrile neutropenia. Usually, patients with severe neutropenia or immunocompromised status may have false negative biomarker values such as PCT. Therefore, if biomarkers are used in cancer patients to help the ASP decision algorithm, they should not be used alone, but always based along with clinical status.

Competing interests

The authors have no financial and non-financial competing interests to declare.

References

1. Bezu L, et al. Perioperative Immunosuppressive Factors during Cancer Surgery: An Updated Review. Cancers (Basel). 2024;16:2304.
2 Bratzler DW, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm. 2013;70:195-283.
3 Kourbeti I, Kamiliou A, Samarkos M. Antibiotic Stewardship in Surgical Departments. Antibiotics (Basel). 2024;13:329.
4 Dellit TH, et al. Infectious Diseases Society of America; Society for Healthcare Epidemiology of America. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis. 2007;44:159-177.
5 Sartelli M, et al. Intra-abdominal infections survival guide: a position statement by the Global Alliance For Infections In Surgery. World J Emerg Surg. 2024;19:22.
6 Pfaller MA, et al. Temporal and Geographic Variation in Antimicrobial Susceptibility and Resistance Patterns of Enterococci: Results From the SENTRY Antimicrobial Surveillance Program, 1997-2016. Open Forum Infect Dis. 2019;6:S54-S62.
7 Nagy E, et al. Antimicrobial susceptibility of Bacteroides fragilis group isolates in Europe: 20 years of experience. Clin Microbiol Infect. 2011;17:371-379.
8 Sawyer RG, et al. Trial of short-course antimicrobial therapy for intraabdominal infection. N Engl J Med. 2015;372:1996-2005.
9 Montravers P, et al. Short-course antibiotic therapy for critically ill patients treated for postoperative intra-abdominal infection: the DURAPOP randomised clinical trial. Intensive Care Med. 2018;44:300-310.
10 Rolston KV, et al. Current Microbiology of Surgical Site Infections in Patients with Cancer: A Retrospective Review. Infect Dis Ther. 2014;3:245-256.
11 Mukhtar RA, et al. Bacteriologic features of surgical site infections following breast surgery. Am J Surg. 2009;198:529-531.
12 Cohen JB, et al. Breast Implant-Associated Infections: The Role of the National Surgical Quality Improvement Program and the Local Microbiome. Plast Reconstr Surg. 2015;136:921-929.
13 Hernaiz-Leonardo JC, et al. Microbiology of surgical site infections in patients with cancer: A 7-year review. Am J Infect Control. 2017;45:761-766.
14 Banuelos J, et al. Microbiology of Implant-Based Breast Reconstruction Infections: A Systematic Review. Ann Plast Surg. 2020;85:194-201.
15 Lalani T. Breast Implant Infections: An Update. Infect Dis Clin North Am. 2018;32:877-884.
16 McCullough MC, et al. Antibiotic Prophylaxis and Resistance in Surgical Site Infection After Immediate Tissue Expander Reconstruction of the Breast. Ann Plast Surg. 2016;77:501-505.
17 Hsieh HH, et al. Effectiveness of extended antibiotic prophylaxis in implant-based breast reconstruction surgery: A meta-analysis. J Plast Reconstr Aesthet Surg. 2024;95:368-376.
18 Franchelli S, et al. Analysis of clinical management of infected breast implants and of factors associated to successful breast pocket salvage in infections occurring after breast reconstruction. Int J Infect Dis. 2018;71:67-72.
19 Ozturk CN, et al Broad-Spectrum Antibiotics for Breast Expander/Implant Infection: Treatment-Related Adverse Events and Outcomes. Ann Plast Surg. 2021;87:396-401.
20 Scheufele F, et al. Effect of preoperative biliary drainage on bacterial flora in bile of patients with periampullary cancer. Br J Surg. 2017;104:e182-e188.
21 Viehman JA, et al. Surgical Site Infections After Liver Transplantation: Emergence of Multidrug-Resistant Bacteria and Implications for Prophylaxis and Treatment Strategies. Transplantation. 2016;100:2107-2114.
22 Müssle B, et al. Antibiotic resistance patterns of bacterial bile cultures during pancreatic surgery-a single center analysis and systematic review. Langenbecks Arch Surg. 2022;407:2777-2788.
23 Royo-Cebrecos C, et al. Characteristics, aetiology, antimicrobial resistance and outcomes of bacteraemic cholangitis in patients with solid tumours: A prospective cohort study. J Infect. 2017;74:172-178.

24 Chea N, et al. Rates and causative pathogens of surgical site infections attributed to liver transplant procedures and other hepatic, biliary, or pancreatic procedures, 2015-2018. Transpl Infect Dis. 2021;23:e13589.
25 Sugawara G, et al. Preoperative biliary colonization/infection caused by multidrug-resistant (MDR) pathogens in patients undergoing major hepatectomy with extrahepatic bile duct resection. Surgery. 2018;163:1106-1113.
26 Kasparian K, et al. Short vs long-course antibiotic therapy in adults with acute cholangitis: A systematic review, meta-analysis, and evidence quality assessment. World J Gastroenterol. 2023;29:3027-3039.
27 Iwata K, et al. Shortening antibiotic duration in the treatment of acute cholangitis: rationale and study protocol for an open-label randomized controlled trial. Trials. 2020;21:97.
28 Rao SV, et al. Surgical Site Infection in Head and Neck Cancer Patients: Observations from A Tertiary Care Hospital. South Asian J Cancer. 2023;13:110-113.
29 Schuderer JG, et al. Surgical and remote site infections after reconstructive surgery of the head and neck: A risk factor analysis. J Craniomaxillofac Surg. 2022;50:178-187.
30 Yang CH,et al. Surgical site infections among high-risk patients in clean-contaminated head and neck reconstructive surgery: concordance with preoperative oral flora. Ann Plast Surg. 2013 Dec;71 Suppl 1:S55-S60.
31 Hernaiz-Leonardo JC, et al. Microbiology of surgical site infections in patients with cancer: A 7-year review. Am J Infect Control. 2017 ;45:761-766.
32 Belusic-Gobic M, et al. Microbiology of wound infection after oral cancer surgery. J Craniomaxillofac Surg. 2020;48:700-705.
33 Kong W, et al. Mapping the risk factors, pathogens, and antibiotic of pharyngocutaneous fistula in patients after neck open surgery. Eur Arch Otorhinolaryngol. 2024;281:4281-4289.
34 Vila PM, et al. Antibiotic Prophylaxis in Clean-Contaminated Head and Neck Surgery: A Systematic Review and Meta-analysis. Otolaryngol Head Neck Surg. 2017;157:580-588.
35 Haidar YM, et al. Antibiotic prophylaxis in clean-contaminated head and neck cases with microvascular free flap reconstruction: A systematic review and meta-analysis. Head Neck. 2018;40:417-427.
36 Vander Poorten V, et al. Perioperative Antibiotics in Clean-Contaminated Head and Neck Surgery: A Systematic Review and Meta-Analysis. Adv Ther. 2020;37:1360-1380.
37 Patel PN, et al. Evidence-Based Use of Perioperative Antibiotics in Otolaryngology. Otolaryngol Head Neck Surg. 2018;158:783-800.
38 Pynnonen MA, et al. Clinical Practice Guideline: Evaluation of the Neck Mass in Adults. Otolaryngol Head Neck Surg. 2017;157:S1-S30.
39 Peterson DE, et al. Prevention and Management of Osteoradionecrosis in Patients With Head and Neck Cancer Treated With Radiation Therapy: ISOO-MASCC-ASCO Guideline. J Clin Oncol. 2024;42:1975-1996.
40 Zhu Y, et al. Bacterial spectrum analysis and antimicrobial susceptibility study of osteoradionecrosis of the jaw in Southern China. Oral Dis. 2022;28:2015-2025.
41 Kolwijck E, et al. Incidence and microbiology of post-operative infections after radical cystectomy and ureteral stent removal; a retrospective cohort study. BMC Infect Dis. 2019;19:303.
42 Vejlgaard M, et al. Microbial Trends in Infection-related Readmissions Following Radical Cystectomy for Bladder Cancer. Urology. 2024;183:134-140.
43 Jiang G, Li J, et al. Study on risk factors, bacterial species, and drug resistance of acute pyelonephritis associated with ureteral stent after percutaneous nephrolithotomy. Eur J Clin Microbiol Infect Dis. 2021;40:707-713.
44 Mert D, et al. Evaluation of risk factors, causative pathogens, and treatment in recurrent percutaneous nephrostomy catheter-related urinary tract infections in cancer patients. Medicine (Baltimore). 2023;102:e33002.
45 Szvalb AD, et al. Risk factors for recurrent percutaneous nephrostomy catheter-related infections. Infection. 2019;47:239-245.
46 Bonkat G, et al. Improved detection of microbial ureteral stent colonisation by sonication. World J Urol. 2011;29:133-138.
47 Karbysheva S, et al. Comparison of sonication with chemical biofilm dislodgement methods using chelating and reducing agents: Implications for the microbiological diagnosis of implant associated infection. PLoS One. 2020;15:e0231389.

48 Liu K, et al. Meta-analysis of sonication prosthetic fluid PCR for diagnosing periprosthetic joint infection. PLoS One. 2018;13:e0196418.
49 Taplitz RA, et al. Outpatient Management of Fever and Neutropenia in Adults Treated for Malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America Clinical Practice Guideline Update. J Clin Oncol. 2018;36:1443-1453.
50 El Haddad H, et al. Biomarkers of Sepsis and Bloodstream Infections: The Role of Procalcitonin and Proadrenomedullin With Emphasis in Patients With Cancer. Clin Infect Dis. 2018;67:971-977.
51 Póvoa P, et al. How to use biomarkers of infection or sepsis at the bedside: guide to clinicians. Intensive Care Med. 2023;49:142-153.
52 Heilmann E,et al. Biomarkers of Infection: Are They Useful in the ICU? Semin Respir Crit Care Med. 2019;40:465-475.
53 Munsell MK, et al. The utility of procalcitonin for diagnosing bacteremia and bacterial pneumonia in hospitalized oncology patients. J Cancer Res Clin Oncol. 2023;149:5193-5204.

Chapter 78

Principles of antimicrobial stewardship in the intensive care unit

Ryan C. Maves
Sections of Infectious Diseases and Critical Care Medicine, Wake Forest University School of Medicine
Winston-Salem, North Carolina, USA.

Introduction

Antimicrobial resistance (AMR) is one of the great public health challenges of our time. Morbidity and mortality due to infections by multidrug-resistant organisms (MDROs) is high and may be increasing. In 2022, an estimated 14.2 deaths per 100,000 person-years occurred due to bacterial MDRO infections. This has been projected to increase to 20.4 deaths per 100,000 person-years, leading to a cumulative 39.1 million deaths between 2025 and 2050.

The ICU is an antibiotic-rich environment, and pathogens in the ICU have evolved to survive in that environment. At any given time, approximately 70% of all ICU patients are receiving at least one systemic antibiotic. The risk of MDRO infection varies by diagnosis and geographic region, but patients admitted to intensive care units (ICUs) are at markedly increased risks of MDRO acquisition and infection. In the United States and China, 15-20% of ICU patients may be infected with an MDRO; patients hospitalized in European hospitals have been identified as having post-admission MDRO colonization rates of 16.6%. Broad-spectrum agents, including glycopeptides, antipseudomonal beta-lactams, carbapenems, and fluoroquinolones are prescribed at higher rates in ICUs than in other parts of the hospital, partly in response to the aforementioned MDRO rates and partly in response to the severity of patient illness.

The reason for this high rate of empiric antimicrobial drug use is not difficult to understand. Sepsis and septic shock are among the most common causes of ICU admission, with high rates of mortality even with effective therapy. Among the limited modifiable risk factors for death in sepsis is the time to receipt of an active antimicrobial drug, with delays in therapy leading to an approximately 8% increase in mortality risk per hour in patients with shock and with lower but still significant increases in hemodynamically stable patients. Given the high rates of MDRO infections, the limited window for effective intervention, and the high risk of death in septic patients, empiric broad-spectrum antimicrobial use in the ICU is not only understandable but may be in many cases necessary.

Clinicians and health systems alike may struggle with these competing demands. Antibiotics are unique among commonly used drugs, in that how we treat one patient can affect how we treat a future patient. For example, increased carbapenem exposure leads to increased carbapenem resistance, both in the infected patient and in the rest of the hospital. We must balance the public health and ecological imperatives of the AMR crisis, but we almost must care for the patient in front of us. Antimicrobial stewardship programs exist to help us bridge this divide.

Principles of antimicrobial stewardship

The term “antimicrobial stewardship” was described in 1996 by McGowan and Gerding, who encouraged consideration of antibiotics as a scarce and non-renewable resource. The aim of antimicrobial stewardship (AMS) programs is not specifically to reduce antibiotic usage. Rather, the aim of AMS is to *optimize* antibiotic usage, ensuring that each patient receives the appropriate drug, at the appropriate dose, for the appropriate duration. Antimicrobial drugs can be lifesaving, but they are drugs, and drugs have toxicities. These risks go beyond well-known risks such as *Clostridioides difficile* infection and the ecological impact of AMR. Inappropriately broad agents may in fact increase mortality in serious infections compared with narrower, pathogen-targeted approaches, e.g., “double-coverage” of Gram-negative pathogens in the empiric treatment of hospital-acquired and ventilator-associated pneumonia.

An effective AMS program requires a coordinated approach that promotes the appropriate use of antimicrobials, enhances patient outcomes, reduces microbial resistance, and decreases the spread of infections caused by MDROs. The central principles of an AMS program include:

1. *Optimizing antimicrobial prescribing*. A careful review of antibiotic orders by experienced pharmacists, ideally trained in infectious disease pharmacy, can help ensure the correct right drug, dose, duration, and route.
2. *Monitoring and feedback*. AMS programs must track institutional antimicrobial drug use, with continuous evaluation of local usage and resistance patterns. Antimicrobial drug consumption in an institution may be measured using the defined daily dose (DDD) as a unit. For example, a patient who receives a total of seven days of combination therapy with vancomycin and ceftriaxone has received 14 DDDs of antimicrobial therapy. Feedback on total antibiotic prescription can be tracked among clinicians practicing in the same setting and specialty, to identify outliers whose practice may be amenable to improvement. Total antibiotic usage across groups, such as a given ICU or hospital, can be measured using the Standardized Antimicrobial Administration Ratio (SAAR), a metric that normalizes antimicrobial consumption based on location and patient types (e.g., pediatric ICU). A SAAR of 1 indicates that the facility in question uses antibiotics at the same target rate as a “typical” unit of that type.
3. *Education and training*. An effective AMS program requires collaboration with physicians and other prescribers. Education is a critical step in developing this collaborative environment. In settings where physicians view the AMS program as adversarial or where the rationale for antibiotic restrictions may not be apparent, AMS is less likely to be successful. AMS training should be incorporated into the onboarding process for new hospital staff, along with periodic refresher training.
4. *Multidisciplinary collaboration*. While AMS programs are typically led by physicians specializing in infectious diseases, an effective AMS program is multidisciplinary by definition. An AMS program requires representation from medical and surgical specialists (e.g., emergency medicine, pediatrics, hospital medicine, critical care, general surgery, and orthopedics) involved in antimicrobial prescribing, both to ensure institutional collaboration as well as to ensure that the unique concerns of different practices and patient populations are considered in AMS policies. Equally important is the role of pharmacists, microbiologists, and infection prevention professionals, who play a central role in the audit, feedback, and educational functions of the program.

Antimicrobial stewardship in the ICU

As noted above, the ICU is a unique environment for AMS, with unique challenges. These challenges must be taken into consideration for an AMS program to be effective. Indeed, no hospital AMS program is likely to be successful unless it can have an impact in the ICU, given the disproportionate impact of the ICU on antimicrobial usage. The high prevalence of infections in the ICU, the frequency of invasive procedures in critically ill patients, and the increased absolute risk of AMR all lead to high rates of broad-spectrum antimicrobial use. However, critically ill patients, particularly those with sepsis, require rapid decisions regarding empiric antimicrobial use, often with incomplete or imperfect data. Furthermore, intensivists may be reluctant to de-escalate therapy in critically ill patients with ongoing evidence of infection and slow clinical improvement, even when a clear pathogen with narrower-spectrum therapeutic options has been identified. These factors may hinder AMS efforts in the short term.

To implement an AMS program effectively in the ICU, it is useful to address these central concepts:

1. *Initial empiric therapy.* Effective empiric therapy involves the development of quality local guidelines, based on a hospital's antibiogram that permits the selection of appropriate empiric regimens based on common pathogens and resistance patterns. An AMS program's audit and feedback role should address whether clinicians are adhering to these local guidelines for common infections, such as community-acquired pneumonia, and provide education to clinicians regarding the role and importance of these guidelines.
2. *Risk stratification*. International guidelines, such as those of the Surviving Sepsis Campaign, recommend empiric broad-spectrum antimicrobial administration to patients with severe infections. The definition of "broad-spectrum" will vary by patient and location; ceftriaxone, after all, is a broad-spectrum agent with potent Gram-positive and Gram-negative activity. In populations at low risk for MDRO infection, ceftriaxone (or a similar agent) may be the optimal empiric choice. A survey of adults in the United States hospitalized with community-onset sepsis reported that 67% of patients received empiric therapy with agents with activity against ceftriaxone-resistant Gram-negative bacilli, such as *Pseudomonas*, and methicillin-resistant *Staphylococcus aureus* (MRSA), but only around 25% of patients were in fact infected with such an organism. In these cases, both inadequate therapy and unnecessarily broad therapy were associated with increases in mortality of 20% or more. These specific risks will likely vary by region and population. In addition to these demographic and historical features, empiric therapy requires consideration of the severity of a patient's illness, or, alternatively, the potential margin for error. There is no antimicrobial regimen that can account for all conceivable pathogens in a patient's presenting syndrome, but the margin of error for selecting an inactive regimen for a hemodynamically stable, awake patient with uncomplicated pyelonephritis is much wider than it is for a patient requiring mechanical ventilation and two vasopressors. Empiric coverage in the latter patient will be, by necessity, broader. Early and appropriate cultures, obtained before the administration of antibiotics, are necessary to mitigate the risk associated with this empiric broad-spectrum coverage. Delayed cultures obtained after antimicrobial administration will reduce the sensitivity of blood cultures. In a prospective cohort of adult patients with suspected sepsis, blood cultures before antibiotics were positive in 31.4% of patients, but cultures following antibiotics were positive in only 12.0%, indicating a dramatic loss of sensitivity that may impair future efforts at de-escalation and optimizing treatment.
3. *Timely de-escalation.* De-escalation refers to the practice of narrowing antibiotic therapy based on culture results and clinical response. Transitioning a patient with methicillin-susceptible *S. aureus* (MSSA) bacteremia from vancomycin to an anti-staphylococcal beta-lactam, discontinuing a carbapenem in favor of cefazolin for a susceptible *Klebsiella pneumoniae* pyelonephritis, or discontinuing Gram-negative

coverage for a patient with vancomycin-resistant *Enterococcus* endocarditis are all forms of de-escalation. Timely de-escalation (i.e., within 2-3 days of starting therapy) has an ecologic benefit on AMR development; in a retrospective cohort study of 7,742 adult patients with Gram-negative sepsis, de-escalation was associated with a hazard ratio for the patient acquiring a newly resistant infection of 0.59. De-escalation may also lead to decreased mortality, even in settings with high MDRO incidence. De-escalation requires that cultures be reviewed regularly. Newer molecular-based assays may be useful in avoiding some of the intrinsic delays associated with culture-based diagnostics, depending on the pathogen of interest. For patients with pneumonia and meningoencephalitis, for example, multiplex polymerase chain reaction (PCR) assays often have sensitivities that exceed those of culture and may permit discontinuation of Gram-positive or -negative agents even if full susceptibility results are still not available. Nucleic acid detection systems, such as the BioFire BCID 2 panel (bioMérieux, Marcy-l'Étoile, France), permit species identification as well as certain common determinants of drug resistance (e.g., the *mecA* and *mecC* genes in MRSA) from a positive blood culture in minutes to hours. In patients with pneumonia, negative results from a nasal swab PCR are sufficient to exclude an MRSA infection and thus discontinue vancomycin, leading to significant reductions in institutional vancomycin usage without negative impacts on patients. Clinical assessment is also necessary to permit safe de-escalation. In patients who continue to deteriorate despite initial negative cultures and guideline-adherent empiric antibiotics, an "escalation antibiogram" may be a useful tool to permit expanding the spectrum of coverage in a rational manner, thus mitigating the impact of broader therapy.

4. *Duration of therapy.* It is only in recent years that rigorous studies have been conducted evaluating the optimal duration of therapy for common infections. With the slogan of "shorter is better", there has been a recent paradigm shift away from extended courses of antibiotics for bacteremia, pneumonia, pyelonephritis, and other infections. These shorter durations (e.g., 5 days for community-acquired pneumonia as opposed to 10-14 days) have been associated with both fewer complications and decreased emergence of AMR. In the case of community-acquired pneumonia, adult inpatients in a randomized, controlled trial treated with antibiotics for ten days had higher readmission rates than those treated for five days. Similarly, each day of additional exposure to antipseudomonal beta-lactams increases the relative risk of resistance emerging against those agents by 4%.
5. *Infection prevention and control.* Infection control measures are integral to AMS, particularly in the ICU where the risk of healthcare-associated infections is high. Although traditionally separate from AMS programs, infection prevention and control (IPC) programs are closely linked with them. It is intuitive to note that decreases in hospital-acquired infections will lead to less need for antibiotics and, presumably, fewer infections with MDROs. IPC programs can provide useful feedback on the impact of AMS programs, through surveillance for MDROs and assessment of common infectious syndromes in the ICU, such as invasive MRSA infections.

Future directions in antimicrobial stewardship

Just as the threat of AMR advances, so do the advances in diagnostic and therapeutic systems for severe infections. One of the primary limiting factors in AMS is the uncertainty surrounding the presence of a bacterial infection at the time of initial presentation. There is wide divergence and subjectivity associated with the diagnosis of sepsis and septic shock, even among experienced intensivists. Up to one-third of patients receiving broad-spectrum antibiotics for suspected sepsis in emergency departments do not have bacterial

infections; these patients are exposed to the risks of drug toxicity, *C. difficile*, and AMR without receiving any benefit from therapy.

Biomarkers of infection and inflammation, including procalcitonin, have been proposed to differentiate between infected and uninfected patients, or alternatively between patients with bacterial and non-bacterial infections. Procalcitonin has shown limitations in its ability to exclude bacterial infection reliably in the initial phases of illness and is not recommended to be used for decision-making regarding the initiation of antibiotics in patients with sepsis. However, procalcitonin does decline predictably with the resolution of infection during antibiotic therapy and shows promise as a method to personalize durations of treatment, thus potentially reducing antibiotic exposure without increased risks of patient harm.

Rapid pathogen-specific diagnostics may improve AMS by overcoming the time and sensitivity limitations of conventional bacterial culture. The "syndromic" multiplex panels described above for pneumonia, neurologic infections, and bloodstream infections test for a broad but limited list of typical pathogens, i.e., staphylococci and *Pseudomonas*. Emerging investigational systems based on the identification of non-human cell-free DNA (cfDNA) in patients' plasma are pathogen-agnostic (that is, they can identify a wider variety of potential organisms). In an observational study performed with septic patients in a German surgical ICU, a cfDNA-based system identified pathogens in 72% of patients, compared with 33% of patients using blood culture, with 53% of results potentially resulting in changes in therapy. Although still investigational, one could imagine a future where biomarker-guided sepsis identification, combined with cfDNA-based pathogen detection, would prevent the need for broad empiric therapy and instead allow us to initiate more specific therapy at the time of the initial sepsis diagnosis.

Beyond these enhanced diagnostic systems, recent advances in machine learning (ML) and informatics may further improve our ability to select the best therapy and monitor the effectiveness of AMS efforts. The large amounts of data analysis required for evaluating trends in antimicrobial use, including those practices associated with improved outcomes, may be enhanced through the incorporation of ML systems into the electronic medical record. ML systems may enhance antimicrobial drug selection through the analysis of local resistance patterns as well as a patient's risk factors and prior culture data, for example. In the laboratory, matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF) mass spectrometry has become a widespread method for species identification of positive clinical cultures, but ML-enhanced MALDI-TOF systems may permit the identification of AMR as well as speciation, potentially reducing the time to optimum therapy by 24 hours or more.

Conclusion

Few interventions in critical care can improve mortality, reduce complications, improve public health, and lower costs all at the same time. Antimicrobial stewardship is one of those interventions. The principles of antimicrobial stewardship in the ICU are essential for combating the growing threat of antimicrobial resistance. By optimizing antibiotic use through evidence-based practices, fostering a culture of collaboration, and continuously monitoring outcomes, clinicians in the ICU can improve patient care while safeguarding the effectiveness of antimicrobials for future generations. Implementing a robust AMS program in the ICU not only enhances individual patient outcomes but also contributes to the broader goal of controlling antimicrobial resistance in the hospital and beyond.

Competing interests

RCM receives research support paid to his institution from AiCuris, GeoVax, Biotest, and Eagle Pharmaceuticals. He has received honoraria for scientific advisory panel membership from Shionogi and for educational session development from GSK. He is the chair of the Critical Care Medicine Examination Approval Committee of the American Board of Internal Medicine. None of these conflicts relate to the contents of this chapter.

References

1. GBD 2021 Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance 1990-2021: a systematic analysis with forecasts to 2050. Lancet. 2024;404:1199-1226.
2. Vincent JL, et al: Prevalence and Outcomes of Infection Among Patients in Intensive Care Units in 2017. JAMA. 2020;323:1478-1487.
3. Caglayan C, et al. A Data-Driven Framework for Identifying Intensive Care Unit Admissions Colonized With Multidrug-Resistant Organisms. Front Public Health. 2022;10:853757.
4. Wang Y, et al. A deep learning model for predicting multidrug-resistant organism infection in critically ill patients. J Intensive Care. 2023;11:49.
5. Kajova M, et al. European hospitals as source of multidrug-resistant bacteria: analysis of travellers screened in Finland after hospitalization abroad. J Travel Med. 2022;29:taac022.
6. Ghosh S, et al. New Antibiotic Prescription Pattern in Critically Ill Patients ("Ant-critic"): Prospective Observational Study from an Indian Intensive Care Unit. Indian J Crit Care Med. 2022;26:1275-1284.
7. Taylor SP, et al. The Association Between Antibiotic Delay Intervals and Hospital Mortality Among Patients Treated in the Emergency Department for Suspected Sepsis. Crit Care Med. 2021:49:741-747.
8. Kumar A, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006;34:1589-1596.
9. Strich JR, et al. Considerations for Empiric Antimicrobial Therapy in Sepsis and Septic Shock in an Era of Antimicrobial Resistance. J Infect Dis. 2020;222:S119-S131.
10. Righi E, et al. Global prevalence of carbapenem resistance in neutropenic patients and association with mortality and carbapenem use: systematic review and meta-analysis. J Antimicrob Chemother. 2017;72:668-677.
11. McGowan JE Jr, et al. Does antibiotic restriction prevent resistance? New Horiz. 1996;4:370-376.
12. Kett DH, et al: Implementation of guidelines for management of possible multidrug-resistant pneumonia in intensive care: an observational, multicentre cohort study. Lancet Infect Dis. 2011;11:181-189.
13. Ibrahim OM, et al. Antimicrobial use metrics and benchmarking to improve stewardship outcomes: methodology, opportunities, and challenges. Infect Dis Clin North Am. 2014;28:195-214.
14. van Santen KL, et al. The Standardized Antimicrobial Administration Ratio: A New Metric for Measuring and Comparing Antibiotic Use. Clin Infect Dis. 2018;67:179-185.
15. Seemungal IA, et al. Attitudes of housestaff toward a prior-authorization-based antibiotic stewardship program. Infect Control Hosp Epidemiol. 2012;33:429-431.
16. Szymczak JE, et al. Threatened efficiency not autonomy: Prescriber perceptions of an established pediatric antimicrobial stewardship program. Infect Control Hosp Epidemiol. 2019;40:522-527.
17. De Waele JJ, et al. Antimicrobial de-escalation as part of antimicrobial stewardship in intensive care: no simple answers to simple questions-a viewpoint of experts. Intensive Care Med. 2020;46:236-244.
18. Evans L, et al: Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Crit Care Med. 2021;49:e1063-e1143.
19. Rhee C, et al. Prevalence of Antibiotic-Resistant Pathogens in Culture-Proven Sepsis and Outcomes Associated With Inadequate and Broad-Spectrum Empiric Antibiotic Use. Jama Netw Open. 2020;3:e202899.

20. Teshome BF, et al. Preventing New Gram-negative Resistance Through Beta-lactam De-escalation in Hospitalized Patients With Sepsis: A Retrospective Cohort Study. Clin Infect Dis. 2024:ciae253.
21. Garnacho-Montero J, et al. De-escalation of empirical therapy is associated with lower mortality in patients with severe sepsis and septic shock. Intensive Care Med. 2014;40:32-40.
22. Routsi C, et al. De-escalation of antimicrobial therapy in ICU settings with high prevalence of multidrug-resistant bacteria: a multicentre prospective observational cohort study in patients with sepsis or septic shock. J Antimicrob Chemother. 2020;75:3665-3674.
23. Enne VI, et al: Multicentre evaluation of two multiplex PCR platforms for the rapid microbiological investigation of nosocomial pneumonia in UK ICUs: the INHALE WP1 study. Thorax. 2022;77:1220-1228.
24. Liesman RM, et al. Evaluation of a Commercial Multiplex Molecular Panel for Diagnosis of Infectious Meningitis and Encephalitis. J Clin Microbiol. 2018;56:e01927-17.
25. Claeys KC, et al. Day at the Races: Comparing BioFire FilmArray Blood Culture ID Panels With Verigene Blood Culture Panel in Gram-Negative Bloodstream Infections Using DOOR-MAT Analysis. Clin Infect Dis. 2021;73:1103-1106.
26. Baby N, et al. Nasal Methicillin-Resistant Staphylococcus aureus (MRSA) PCR Testing Reduces the Duration of MRSA-Targeted Therapy in Patients with Suspected MRSA Pneumonia. Antimicrob Agents Chemother. 2017;61:e02432-16.
27. Teitelbaum D, et al. Introducing the Escalation Antibiogram: A Simple Tool to Inform Changes in Empiric Antimicrobials in the Nonresponding Patient. Clin Infect Dis. 2022;75:1763-1771.
28. Spellberg B, et al. The Shorter Is Better movement: past, present, future. Clin Microbiol Infect. 2023;29:141-142.
29. Uranga A, et al: Duration of Antibiotic Treatment in Community-Acquired Pneumonia: A Multicenter Randomized Clinical Trial. JAMA Intern Med. 2016;176:1257-1265.
30. Teshome BF, et al. Duration of Exposure to Antipseudomonal beta-Lactam Antibiotics in the Critically Ill and Development of New Resistance. Pharmacotherapy. 2019;39:261-270.
31. Rhee C, et al. Diagnosing sepsis is subjective and highly variable: a survey of intensivists using case vignettes. Crit Care. 2016;20:89.
32. Shappell CN, et al. Likelihood of Bacterial Infection in Patients Treated With Broad-Spectrum IV Antibiotics in the Emergency Department. Crit Care Med. 2021;49:e1144-e1150.
33. Self WH, et al: Procalcitonin as a Marker of Etiology in Adults Hospitalized With Community-Acquired Pneumonia. Clin Infect Dis. 2017;65:183-190.
34. Meier MA, et al: Procalcitonin-guided Antibiotic Treatment in Patients With Positive Blood Cultures: A Patient-level Meta-analysis of Randomized Trials. Clin Infect Dis. 2019;69:388-396.
35. Grumaz S, et al. Enhanced Performance of Next-Generation Sequencing Diagnostics Compared With Standard of Care Microbiological Diagnostics in Patients Suffering From Septic Shock. Crit Care Med. 2019;47:e394-e402.
36. Pinto-de-Sa R, et al. Brave New World of Artificial Intelligence: Its Use in Antimicrobial Stewardship-A Systematic Review. Antibiotics (Basel). 2024;13:307.
37. Moran E, et al. Towards personalized guidelines: using machine-learning algorithms to guide antimicrobial selection. J Antimicrob Chemother. 2020;75:2677-2680.
38. Weis C, et al: Direct antimicrobial resistance prediction from clinical MALDI-TOF mass spectra using machine learning. Nat Med. 2022;28:164-174.

Chapter 79

Antimicrobial stewardship in the emergency department

Hanne Gworek
Department of Emergency Medicine, Hospital Geel, Geel, Belgium;
Department of Emergency Medicine University of Leuven, Leuven, Belgium.

Eline Vanstaen
Department of Emergency Medicine, Hospital Geel, Geel, Belgium;
Department of Emergency Medicine University of Leuven, Leuven, Belgium.

Lore Sypré
Department of Emergency Medicine University Hospital Antwerp, Drie Eikenstraat 655, 2650 Edegem, Belgium.

Francis Somville
Department of Emergency Medicine University Hospital Antwerp, Edegem, Belgium;
Department of Antwerp Surgical Training, Anatomy and Research Centre University of Antwerp, Edegem, Belgium;
Department of Academic Consultants, Faculty of Medicine Medicine Programme Academic Consultants University of Leuven, Leuven, Belgium.

Introduction

Antibiotics are powerful, life-saving medications which treat both hospital- and community-acquired infections, all over the world. They became an indispensable part of modern medicine. However, antibiotics are no harmless intervention. Improper use could lead to unnecessary adverse effects, treatment failure and antimicrobial resistance (AMR). These events may lead to prolonged hospitalization, hospital readmission, need for additional hospital services and increased hospital costs.

The progressive increase in AMR has a significant impact on global healthcare. As known the inappropriate use of antibiotics leads to the generation, acceleration and perpetuation of multi-drug-resistant strains. In the most pessimistic scenario, there will be no more effective antibiotics and now treatable infections will become deadly once again.

To tackle the emergence of resistance regulatory and scientific authorities, such as the World Health Organization (WHO) and the European Center for Disease Prevention and Control (ECDC) recommended the implementation of antimicrobial stewardship programs (ASP) to improve antimicrobial therapy prescriptions including the indication, choice of agent, route of administration and duration of therapy. Several studies have demonstrated a clear benefit on antibiotic consumption, selection of resistance, hospital mortality and costs.

The emergency department (ED) has its own unique challenges and a "one size fits all" approach seems not feasible. Physicians are faced with a high turnover of patients, the care for multiple patients at once, frequent interruptions, a rapid decision-making process and competing priorities. Antimicrobial prescriptions are often empirical due to the lack of microbiological results. Since the ED is at the unique juxtaposition of in- and outpatient care, antibiotic prescribing decisions will impact both in- and outpatient resistance patterns. Nevertheless, antimicrobial stewardship initiatives were frequently focused on hospitalised patients and rarely included the ED. Fortunately, over the last years, there has been a growing number of articles regarding ASP in the emergency services.

Multidrug-resistant microorganisms epidemiology in emergency services

The increase in AMR makes the choice for an appropriate empirical treatment more difficult. This has a direct impact on the morbidity and mortality of patients, especially sepsis patients. Up to 80% of in-patients are admitted through the ED, and empirical treatment initiated in the ED is often continued in the hospital ward. Therefore, it has a significant impact on antimicrobial consumption in-hospital.

A predictive statistical model by Murray *et al.* providing the first assessment of the global burden of AMR, estimated 4.95 million [95% uncertainty interval (UI), 3.62-6.57] deaths globally attributable to bacterial AMR in 2019. The six leading pathogens associated with antibiotic resistance were *Escherichia coli* (*E. coli*), *Staphylococcus aureus* (*S. aureus*), *Klebsiella pneumoniae* (*K. pneumoniae*), *Streptococcus pneumoniae* (*S. pneumoniae*), *Acinetobacter baumannii* (*A. baumannii*) and *Pseudomonas aeruginosa* (*P. aeruginosa*). It is currently estimated that, if no appropriate measures are taken, AMR will cost approximately 10 million lives and 10 trillion US dollars per year by 2050.

Several epidemiological surveillance studies have shown an increased prevalence of multi-drug-resistant strains. A longitudinal surveillance study conducted in several Unites States (US) hospitals from 2012 until 2017 showed a 53.3% increase in the incidence of infections caused by extended-spectrum β-lactamase (ESBL)-producing strains, especially due to a rise in community-acquired infections. There was no change in the incidence of infections caused by carbapenem-resistant *Enterobacteriaceae* (CRE) and a decreased incidence of infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE) spp., carbapenem-resistant *Acinetobacter* (CRA) spp. and multidrug-resistant *P. aeruginosa*. In the ECDC surveillance 2021 report, an increase in the percentage of carbapenem-resistant *E. coli* (CREC) and *K. pneumoniae* strains, VRE and carbapenem-resistant *Acinetobacter* spp., as well as an increase in strains of *S. pneumoniae* with reduced susceptibility to penicillin (14% in 2017 to 16% in 2021) was described.

Furthermore, there has been a dramatic increase in the prevalence of Gram-negative bacteria producing narrow spectrum β-lactamase CTX-M in recent years, hereby dethroning TEM and SHV variants as the most frequent type of ESBL. Although several studies have attempted to develop clinical tools to predict the risk of infection by multidrug-resistant *Enterobacteriaceae* by identifying risk factors of recent antibiotic use (long-term care facility, recent hospitalization, age of 65 years or older), they all lack specificity. In fact, in Ben-Ami *et al.*'s multinational study 34% of ESBL-producing strains isolated (115 out of 336 strains) had no identified contact with the healthcare system.

A multicentre study conducted in healthcare units in the US between 2018 and 2019 found a 17% prevalence of ESBL-producing strains in urinary tract infections. Resistance rates to other antibiotics ranged from 32.3% for fluoroquinolones, 13.7% for gentamicin, 1.3% for amikacine and 0.3% for meropenem. Another retrospective study of all patients presenting with a febrile urinary tract infection in 21 different healthcare centres in the US from 2017 until 2019 found that of the 4107 included patients, 530 (12.9%) had infections caused by *E. coli*, *K. pneumoniae* or *P. mirabilis* that were resistant to third-generation cephalosporin. Empirical

antibiotic treatment was discordant in 63% of the cases in the resistant group, compared to 7% in the non-resistant group (OR 21.0; 95% CI 16.9 to 26.0). Patients in the resistant group also had a longer hospital stay (adjusted mean difference of 29.7 h; 95% CI 19.0 to 40.4) and higher 90-day mortality (12% in patients with resistance *versus* 8% in controls, adjusted OR 1.56; 95% CI 1.07 to 2.28).
Unfortunately, there are limited studies describing variation in the resistance profile specifically in the ED. This is a key element for improvement in the coming years.

Antimicrobial stewardship programs

Implementing ASP in the ED poses significant challenges. The unique characteristics of this unit such as the diversity of treated pathologies and patient profiles and the loss of patient follow-up after discharge hinder their implementation. Research regarding ASP interventions in the ED setting is scarce, only one systematic review has been published thus far. Some ASP activities typically applied in hospitalized patients are difficult to carry out in the ED such as de-escalation of antibiotic treatment or optimisation of duration based on patient evolution. However, some activities have proven to be highly effective.
ASP efforts must be multidisciplinary, collaborative and patient-centred. Therefore, a multidisciplinary ASP team composed of emergency physicians, infectious disease specialists, pharmacists, microbiologists, nurses and ward/ ICU/ primary care physicians is a crucial first step.

Before treatment

Development and knowledge of local resistance rates and guidelines
Antibiotic resistance varies between countries, hospitals and even patient populations. Therefore, it is crucial to conduct national surveillance to determine AMR and develop local guidelines in accordance with local resistance patterns, taking into account patient-specific risk factors. Ideally, guidelines should include the optimal duration of therapy in in- and outpatient settings. ED physicians should frequently be educated to maximize adherence to these local guidelines. Studies examining the effect of provider audit and feedback showed an increase in guideline-based prescribing and a decrease in antimicrobial prescribing overall. Additionally, patient education through brochures or computerized educational programs could contribute to adherence to the prescribed treatment.

Take into account patient-specific factors
Risk factors in specific patients and/ or types of intervention should be taken into account when choosing an antibiotic agent. Immunosuppressed patients are at greater risk in terms of colonisation and infection by resistant microorganisms. Early diagnosis and treatment are even more important, since mortality may be high in this population. Other risk factors include advanced age, comorbidities, earlier antimicrobial treatment and the presence of foreign material such as a central catheter, urinary catheter or mechanical ventilation.
Physicians should decide on the basis of the clinical evaluation of patients which examinations are useful. A positive urine or blood culture requested outside their indications can be a misleading finding which might lead to unnecessary antimicrobial treatment.

Do not use antibiotics to treat fever in the absence of an infection

Fever, or pyrexia, is one of the most common patient complaints in the emergency department. While many fevers represent an infectious source of pathology, other sources of fever including medication, malignancy and drug use may be present.

Serologic testing such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and procalcitonin (PCT) may be utilized to further differentiate between infectious and non-infectious causes. CRP is an acute-phase protein that rises in response to an inflammatory stimulus. Unfortunately, CRP is non-specific and has been found to be elevated in numerous conditions such as malignancy, obstructive sleep apnoea and chronic vascular disease. Therefore, it should not be relied upon alone to exclude or confirm an infectious cause for fever. ESR also lacks specificity, especially in the older population with numerous comorbidities. PCT rises in response to infectious aetiologies and is much more likely to be elevated in bacteria, as opposed to viral infections. The use of PCT in the clinical setting to diagnose and treat acute respiratory infections has been shown to decrease overall antibiotic use, however, there is no difference in mortality.

Frequent re-evaluation of patients for other aetiologies of fever should be conducted and empiric antimicrobials should be discontinued if a non-infectious cause is demonstrated.

Use of rapid molecular testing

Conventional microbiological methods based on culture and antimicrobial susceptibility take up to 24-72 hours to yield results. Rapid diagnostic tests (RDT) enable the acceleration of pathogen identification in the ED and could hereby guide the physician to appropriate antimicrobial therapy. Likewise, the rapid detection of multi-resistant or highly transmissible micro-organisms enables the implementation of control measures to restrict their transmission, something that has been of proven importance with the recent SARS-CoV-2 pandemic.

In bloodstream infections, pathogen identification and antimicrobial susceptibility testing are performed after blood culture positivity. However, at the ED, we will not have these results in time to be useful.

RDT could play a crucial role in the differentiation between viral (Influenza A/ B, Respiratory syncytial virus (RSV), SARS-CoV-2) or bacterial infections (*S. pneumoniae*, *Legionella pneumophila*) when it comes to respiratory tract infections and consequently reduce unnecessary antibiotic prescription for viral infections. A randomized controlled trial of both pediatric and adult patients presenting to the ED with symptoms of an acute respiratory tract infection showed a trend toward decreased antibiotic use with the use of RDT but no difference in length of stay. However, a recent meta-analysis including both patients at the ED and in-hospital found that RDT for respiratory tract infections was associated with reduced length of stay and improved infection control in influenza patients.

For central nervous infections and sexually transmitted infections, the clinical impact of RDT is also well documented. The use of a multiplex polymerase chain reaction (PCR) for meningitis/ encephalitis has been proven to reduce the length of stay and improve antimicrobial therapy. Rapid molecular tests for *Neisseria gonorrhoea* and *Chlamydia trachomatis* have been associated with a significant increase in the appropriateness of antimicrobial treatment, faster results and lower costs.

Various clinical studies have shown a significant reduction in the duration of antimicrobial use when RDT is used in the ED. However, a multidisciplinary approach to guide laboratory testing, patient management and treatment is crucial to optimise patient outcomes and antimicrobial therapy.

During treatment

Consider pharmacokinetic and pharmacodynamics properties

When selecting an antimicrobial agent, the optimal dose is based on pharmacodynamics, pharmacokinetics, patient factors and infection-specific factors. Although a loading dose is needed for both time- and concentration-dependent antibiotics to reach an effective plasma concentration, it is important to differentiate between time- and concentration-dependent activity when determining the further appropriate dose and interval of antimicrobial administration.

The presence of pleural effusion, edema, ascites, hypoalbuminemia, sepsis, burns, co-ingestion of certain medication, and liver- or kidney dysfunction require dosage adjustments since there may be limitations in fluid volume, binding of antibiotics, and increased/ reduced clearance.

The physician should also take into account the penetration rate of an antibiotic especially when treating infections in less vascularized areas or with intracellular pathogens.

Including ED pharmacists in the clinical care team has been shown to reduce the duration of treatment, and cost of care and to have an impact on medication errors. ED pharmacists can also evaluate and document the effects of ASP on surrogate outcomes of antimicrobial resistance such as length of stay, antibiotic use and compliance with guidelines. A recent review article by Bishop *et al.* highlighted the importance of pharmacists to participate in ASP in the ED.

Ensure source control

Drainage, debridement and device removal are considered irreplaceable measurements to gain source control and, if required, will improve outcomes more than early, effective antimicrobial therapy. Since the time-dependent nature of these interventions, appropriate interventions should never be delayed, especially in patients with septic shock.

When an infection is insufficiently controlled despite adequate antimicrobial therapy and resuscitation, inadequate source control should be taken into consideration and urgent re-evaluation is necessary.

Discontinue antibiotics timely and de-escalate when appropriate

Ideally, 48 to 72 hours after antimicrobial treatment is started, the treatment should be reviewed and stopped or de-escalated when possible. This decision will be based on the clinical course as well as the results of cultures and microbial data. The ED is not equipped to review all the outpatient treatments, most patients are advised to consult their general practitioner. Nevertheless, a telephone follow-up could be beneficial both for targeting antimicrobial therapy as well as patient satisfaction. Additionally, it provides an assessment of the patient's adherence to treatment as well as an opportunity to identify adverse events.

The development of phone applications for patients who are treated ambulatory can provide counselling based on some simple parameters such as blood pressure, fever and oxygen saturation. Home follow-up through these apps can detect a deteriorating status and thus advise representation to the ED.

To reduce the additional workload on ED physicians, a culture follow-up program is suggested. Out of experience, it is shown that these programs can improve treatment and reduce ED revisits and costs.

Research on ED pharmacists examined their participation in the follow-up of cultures taken and patients discharged from the ED. An increase in the number of interventions for inadequate therapy as well as more appropriate prescribing was noted. Better effects on other outcomes such as ED revisits and readmissions in comparison to other healthcare providers could not be demonstrated.

After treatment

Utilize automatic early warning systems

ASP for inpatient treatments should encourage the re-evaluation of the implemented antibiotics based on the clinical status and response to therapy. In the intensive care unit (ICU) antibiotic stop-orders encourage healthcare providers to review laboratory results, microbiological reports and imaging. At this point, the decision to continue, stop or de-escalate antimicrobial therapy can be made. These interventions are shown to reduce the rate of invalid and long-term drug use.

Foster cooperation and communication

Patients who are admitted to the hospital with an antibiotic treatment, are cared for by a broad team. The ASP team ideally consists of emergency physicians, infectious disease specialists, pharmacists, microbiologists, nurses and ward/ ICU/ primary care physicians. They should work collaboratively, to review results and to update treatment guidelines. Optimizing antibiotics dosage, overseeing drug interactions, supervising nurse drug administration and investigations of the causal microorganism are further executed by the ward/ ICU physician. After discharge, continued antimicrobial treatment will be supervised by the patient's primary care physician. Adequate communication between both treating physicians at the point of transition is crucial for the correct treatment course.

Implement infection control and provide feedback

The goal of ASP is to reduce antibiotic resistance. In settings where most resistant microorganisms are encountered, vigilance is necessary as well as measures to prevent further spread. In the ED physicians and nurses encounter a significant number of patients with infections every day, the nature and possible resistance patterns of these microorganisms are unknown at the moment of contact. Hygiene measures are thus vital to prevent the contamination of patients with resistant pathogens. Implemented measures in ASP should continuously be reviewed within the healthcare system.

Infection prevention

The prevention of developing an infection is pivotal and continues to be the foundation of reducing AMR. This involves hospital-focused programmes to prevent hospital-acquired infections as well as interventions to prevent community-acquired infections, such as water, sanitation and hygiene. The latter is essential in low-income countries with suboptimal infrastructure where AMR is more severe. Vaccination is another pillar in infection prevention thus lowering the demand for antimicrobial treatment. A vaccine for *S. pneumoniae* is available, one of the six leading pathogens in AMR. Further development of vaccines for the pathogens with high AMR burden is crucial. Prevention of viral fever through vaccines (*Haemophilus Influenza*, rotavirus...) can also reduce the use of inappropriate antibiotic prescriptions.

Conclusion

The rise of antimicrobial resistance represents a formidable challenge to global healthcare, with significant implications for patient outcomes and healthcare costs. As multidrug-resistant strains become more prevalent, particularly in the high-stakes environment of emergency departments, the need for robust antimicrobial stewardship programs becomes critical. The unique pressures and fast-paced nature of the ED necessitate tailored approaches to antimicrobial stewardship that can adapt to the specific demands of this setting.

Implementing ASPs in the ED is challenging due to the wide variety of patient cases, the urgency of clinical decisions, and often limited follow-up opportunities. Despite these hurdles, evidence demonstrates that effective ASPs can substantially reduce inappropriate antibiotic use, thus curbing the development and spread of resistance. Essential strategies include creating and adhering to local guidelines informed by resistance patterns, considering individual patient factors before prescribing antibiotics and utilizing rapid diagnostic tests to distinguish between bacterial and viral infections.

During treatment, it is crucial to consider the pharmacokinetics and pharmacodynamics properties of antibiotics, ensuring appropriate dosing and adjustment based on patient-specific variables such as renal or hepatic function. The role of ED pharmacists in the clinical care team is also pivotal, as they help optimize antibiotic use, reduce treatment duration, and prevent medication errors.

Post-treatment, the emphasis should be on reviewing and de-escalating antibiotic therapy based on clinical and microbiological data within 48 to 72 hours. Follow-up programs, potentially including telephone calls of home follow-up, can ensure adherence to treatment, monitor for adverse events, and adjust therapy as needed. Automatic early warning systems and continuous feedback loops within the healthcare team can further enhance infection control and antimicrobial stewardship efforts.

In conclusion, while the ED presents unique challenges, tailored, multidisciplinary antimicrobial stewardship programs can significantly improve antibiotic use, enhance patient outcomes, and curb antimicrobial resistance. Overcoming barriers requires ongoing research, adaptation, and collaboration. By leveraging advanced diagnostics and monitoring tools, we can ensure antibiotics remain an effective therapeutic option, safeguarding their efficacy for the future.

Competing interests

The authors have no financial and non-financial competing interests to declare.

References

1. Tamma PD, et al. Association of adverse events with antibiotic use in hospitalized patients. JAMA Intern Med. 2017;177:1308–1315
2. Karanika S, et al. Systematic review and meta-analysis of clinical and economic outcomes from the implementation of hospital-based antimicrobial stewardship programs. Antimicrob Agents Chemother. 2016;60:4840-4852.
3. May L, et al. A call to action for antimicrobial stewardship in the emergency department: approaches and strategies. Ann Emerg Med. 2013;62:69-77.
4. Pin M, et al. Antimicrobial resistance control in the emergency department: A need for concrete improvement. Antimicrob. Resist. Infect. Control. 2022;11:94.
5. Murray CJ, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022;399:629-655.
6. O'Neill J, et al. Tackling drug-resistant infections globally: final report and recommendations. The review on antimicrobial resistance. May 2016. Available at: https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf. Last accessed: 27 August 2024.
7. Jernigan JA, et al. Multidrug-Resistant Bacterial Infections in U.S. Hospitalized Patients, 2012–2017. N Engl J Med. 2020;382:1309–1319-
8. European Centre for Disease Prevention and Control Antimicrobial Resistance in the EU/EEA (EARS-Net)—Annual Epidemiological Report 2021. Published November 2022. Available at: https://www.ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-resistance-europe-2021. Last accessed: 27 August 2024.

9. Ben-Ami R, et al. A multinational survey of risk factors for infection with extended-spectrum beta-lactamase-producing enterobacteriaceae in nonhospitalized patients. Clin. Infect. Dis. 2009;49:682–690.
10. Quaegebeur A, et al. Trends and prediction of antimicrobial susceptibility in urinary bacteria isolated in European emergency departments: The EuroUTI 2010–2016 Study. J. Antimicrob. Chemother. 2019;74:3069–3076.
11. González Del Castillo J, et al. A multidrug-resistant microorganism infection risk prediction model: Development and validation in an emergency medicine population. Eur. J. Clin. Microbiol. Infect. Dis. 2020;39:309–323.
12. Talan DA, et al. Emergence of Extended-Spectrum β-Lactamase Urinary Tract Infections among Hospitalized Emergency Department Patients in the United States. Ann. Emerg. Med. 2021;77:32–43.
13. Mark DG, et al. Third-Generation Cephalosporin Resistance and Associated Discordant Antibiotic Treatment in Emergency Department Febrile Urinary Tract Infections. Ann. Emerg. Med. 2021;78:357–369.
14. Losier M, et al. A systematic review of antimicrobial stewardship interventions in the emergency department. Ann Pharmacother. 2017;51:774-790.
15. Zeynep T. et al. Antimicrobial stewardship in the intensive care unit. Journal of Intensive Medicine 2023;3:244-253.
16. Harrison M. Erythrocyte sedimentation rate and C-reactive protein. Aust Prescr. 2015;38:93-94.
17. Pepys MB. et al. C-reactive protein: a critical update. J Clin Invest. 2003;111:1805-1812.
18. Becker KL, et al. Procalcitonin assay in systemic inflammation, infection, and sepsis: clinical utility and limitations. Crit Care Med. 2008;36:941-952.
19. Schuetz P, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. Cochrane Database Syst Rev. 2017;10:CD007498.
20. May L, et al. Rapid Multiplex Testing for Upper Respiratory Pathogens in the Emergency Department: A Randomized Controlled Trial. Open Forum Infect Dis. 2019;6:ofz481.
21. Clark TW, et al. Rapid Multiplex PCR for Respiratory Viruses Reduces Time to Result and Improves Clinical Care: Results of a Systematic Review and Meta-Analysis. J. Infect. 2023;86:462-475.
22. Moffa MA, et al. Impact of a Multiplex Polymerase Chain Reaction Assay on the Clinical Management of Adults Undergoing a Lumbar Puncture for Suspected Community-Onset Central Nervous System Infections. Antibiotics. 2020;9:282.
23. Rivard KR, et al. Impact of Rapid Diagnostic Testing for Chlamydia and Gonorrhea on Appropriate Antimicrobial Utilization in the Emergency Department. Diagn. Microbiol. Infect. Dis. 2017;87:175-179.
24. May L, et al. A randomized controlled trial comparing the treatment of patients tested for chlamydia and gonorrhea after a rapid polymerase chain reaction test versus standard of care testing. Sex Transm Dis. 2016;43:290–295.
25. Evans L, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021;47:1181–1247.
26. Bishop BM. Antimicrobial stewardship in the emergency department: challenges, opportunities, and a call to action for pharmacists. J Pharm Pract. 2016;29:556-563.
27. Martínez ML, et al. Impact of source control in patients with severe sepsis and septic shock. Crit Care Med. 2017;45:11–19.
28. Ruiz-Ramos J, et al. The Interventions and Challenges of Antimicrobial Stewardship in the Emergency Department. Antibiotics. 2023;12:1522.

Chapter 80

Antibiotic stewardship in pediatric patients

Fabrizio Motta
Hospital da Criança Santo Antônio da Santa Casa de Porto Alegre, Porto Alegre, Rio Grande do Sul, Brazil.

Fabio Araujo Motta
Hospital Pequeno Príncipe, Curitiba, Paraná, Brazil.

Introduction

Definition and importance

Antimicrobial stewardship (AMS) is used in hospitals, communities, veterinary care, and globally. However, unclear definitions lead to varied interpretations and confusion. Despite this, AMS is key for responsible antimicrobial use, balancing patient care with long-term treatment effectiveness. Strengthening AMS is vital to combat resistance and preserve therapies.

Since the 2007 IDSA guidelines, AMS programs in pediatric hospitals have significantly increased, addressing both general AMS needs and the specific requirements of pediatric patients.

Epidemiology of antimicrobial resistance

Antimicrobial resistance (AMR) has become a leading global health threat, particularly in low-income regions. A 2022 study found that drug-resistant bacterial infections contributed to nearly 5 million deaths worldwide in 2019, with 1.3 million directly attributed to bacterial AMR. Children are especially affected, with one in five AMR-related deaths occurring in those under five years old.

Multidrug-resistant (MDR) bacteria are a growing concern in pediatric populations. In Europe, 30% of pediatric infections are caused by MDR bacteria, while in the Middle East, 90% of newborns hospitalized with sepsis in ICU have resistant infections. Southeast Asia and Sub-Saharan Africa report high rates of *Escherichia coli* resistance and neonatal sepsis caused by resistant strains. A study from southern Brazil revealed a 46.1% community prevalence of MRSA in children, highlighting a significant public health issue. The WHO's 2024 Bacterial Priority Pathogens List prioritizes resistant pathogens like *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*, which are especially dangerous in resource-limited settings.

AMS in pediatric care is fundamental both in outpatient and inpatient settings, particularly in high-risk groups such as surgical patients, oncology, and transplant cases. Implementing AMS in these contexts ensures the appropriate use of antibiotics, reducing resistance and improving patient outcomes.

Objectives of the stewardship program

- Improvement of clinical outcomes.
- Reduction of antimicrobial resistance.

- Minimization of adverse effects.

The primary goal of AMS is to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, such as toxicity, secondary infections, and the emergence of resistance. This includes reducing mortality, morbidity, and hospital stay durations, decreasing selective pressure on bacteria to reduce antimicrobial resistance, and avoiding adverse drug reactions, *Clostridioides difficile* infection (CDI), and disruptions to the microbiota. Although many antibiotics have been developed since penicillin's discovery, they quickly became resistant once introduced into clinical practice. The rise of MDR infections has outpaced the development of new antibiotics to treat them.
Additionally, CDI is a potential consequence, with a large surveillance study showing that 71% of CDI cases in children were community-associated, often following antibiotic use for otitis media, sinus infections, or respiratory tract infections. Research on antibiotic exposure and the gut microbiome suggests that frequent, early exposure can promote intestinal dysbiosis and may contribute to conditions like juvenile idiopathic arthritis, inflammatory bowel disease, asthma, and diabetes.
Implementing a successful AMS is challenging, and identifying the right resources is vital. Professionals should set goals, measure outcomes, and secure support from hospital administrators. A multidisciplinary approach is key to meeting these objectives effectively.

Program structure and implementation

Multidisciplinary team
An effective AMS team should include pediatricians, pharmacists, microbiologists, nurses, and infection control specialists. This multidisciplinary approach ensures comprehensive patient care and management of antimicrobial use.

Policies and protocols
The development of evidence-based guidelines for antimicrobial use is essential. These policies ensure consistency and adherence to best practices in antimicrobial prescribing across healthcare facilities.

Decision support tools
The use of algorithms, prescribing software, and continuous education for healthcare professionals are critical in supporting decision-making and optimizing antimicrobial use.

AMS team composition
According to IDSA/SHEA guidelines, AMS teams should include:
- Infectious diseases (ID) specialist: leads the team and oversees program implementation and evaluation.
- Clinical pharmacist: manages daily tasks and supports the team leader.
- Clinical microbiologists, infection control experts, and information technology specialists: provide essential support in areas such as microbiology, infection control, and data management.
- Nurses: regularly review patient prescriptions and administer antimicrobial treatments.

AMS programs should include all professionals recommended by IDSA/SHEA, but incorporating a pediatric surgeon and a pediatric intensivist into the group can greatly enhance effectiveness, especially in high-risk pediatric surgical and critical care settings.

While AMS programs are most effective when led by ID specialists with AMS training, many hospitals in resource-limited areas lack the staff for a full team. In these cases, hospitals can use available resources, such as having a clinician from another specialty or a clinical pharmacist lead. At minimum, the AMS team should include a clinician, a pharmacist, and a collaborating microbiologist.

Management and policy review

AMS professionals must engage in reviewing hospital policies to ensure comprehensive program implementation. Internal orders and guidelines, based on scientific literature, are essential for ensuring the program's effectiveness. Collaboration with clinical microbiology laboratories is crucial for providing antibiogram data to guide decision-making. Specific recommendations, such as advisory notes on respiratory cultures that identify yeast growth (e.g., "*Candida* species are common colonizers/contaminants in respiratory cultures"), can guide clinicians in making more informed and appropriate antimicrobial decisions. Other strategies include withholding the antibiogram for coagulase-negative Staphylococci when it is isolated from only one blood culture, assuming multiple samples were collected, and refraining from reporting carbapenem susceptibility for bacteria susceptible to cephalosporins.

Additionally, AMS teams should support the adoption of advanced technologies, such as:

- MALDI-TOF Mass Spectrometry: for rapid bacterial and yeast identification.
- Multiplex PCR: for testing positive blood culture samples.

These technologies shorten microbiological result turnaround times, helping to reduce broad-spectrum antimicrobial use, though their high cost remains a barrier to widespread implementation. Molecular panels designed for syndromic testing can detect multiple agents, including viruses, helping to avoid unnecessary antibiotic use and reducing further diagnostic testing. These panels are applied in various clinical syndromes, such as gastrointestinal infections, meningitis/encephalitis, osteoarticular infections, and hospital-acquired pneumonia. They are especially valuable in identifying bacterial pathogens in complex cases, enabling more targeted and effective treatments. All of these advancements fall under the emerging concept of diagnostic stewardship, which emphasizes the optimal use of diagnostic testing to guide antimicrobial therapy and improve patient outcomes.

Dissemination of AMS tools

One of the key challenges for AMS programs is ensuring the effective dissemination and awareness of decision-making algorithms based on local antibiograms. Studies have shown that many healthcare professionals are unaware of these resources or find them difficult to access.

Smartphone integration

Smartphones present a modern solution for medical education. A 2014 study found that 80-85% of healthcare professionals were using smartphones, making them ideal platforms for providing real-time clinical data. A smartphone app offering localized antibiotic resistance patterns and treatment guidelines could be an innovative tool for healthcare trainees. In 2017, Fralick *et al.* demonstrated that increasing access to antibiogram data through a smartphone app significantly improved healthcare professionals' knowledge of antibiotic prescribing.

Pediatric-specific challenges

In pediatric care, the lack of guidance on antibiotic dosage, intervals, and duration remains a significant hurdle. No tool currently considers the demographics, pathogen susceptibility, and pharmacokinetic-pharmacodynamic (PK-PD) targets for efficacy.

Recent publications on PK-PD in pediatric and neonatal populations have expanded our understanding of how these parameters differ from adults. These studies emphasize the impact of both maturational changes, such as renal and hepatic development, and non-maturational factors, such as disease states and critical interventions like extracorporeal membrane oxygenation (ECMO) or augmented renal clearance (ARC). The variability in drug absorption, distribution, metabolism, and excretion in critically ill neonates and children requires precise, individualized dosing. The challenge is optimizing antibiotic exposure while avoiding under- or over-dosing in these vulnerable populations, underscoring the need for further research to tailor antibiotic therapy for pediatric patients.

Intervention strategies

Prospective prescription review

- Objective: analyze antimicrobial prescriptions and intervene when necessary.
- Action: regular review of prescribed antibiotics ensures that therapy aligns with best practices and adjusts as needed. Additionally, implementing active restrictions that require justification for extending surgical prophylaxis beyond a single dose helps reinforce adherence to recommended guidelines and prevents unnecessary prolonged antibiotic use.

Optimization of doses and duration

- Objective: tailor antimicrobial doses based on patient and pathogen characteristics.
- Action: adjust doses and determine appropriate treatment durations to optimize efficacy and minimize toxicity. Additionally, review doses of hydrophilic antimicrobials in cases of ARC or renal impairment to maintain therapeutic levels, especially in critical infection sites like the central nervous system (CNS), where drug penetration may be limited. For antimicrobials with high plasma protein binding, such as those bound to albumin, dosage adjustments should be made based on albumin levels to ensure effective free drug concentrations and prevent subtherapeutic exposure.

Therapeutic de-escalation

- Objective: narrow the spectrum of antimicrobial treatment as pathogen identification occurs.
- Action: implement a third-day time-out to review culture results and adjust therapy accordingly. At this point, the pathogen and its susceptibility profile should be available, allowing clinicians to de-escalate from broad-spectrum antibiotics to targeted therapies, thereby reducing unnecessary antimicrobial exposure and optimizing treatment.

Ongoing education and training

- Objective: ensure the healthcare team stays informed on best AMS practices.
- Action: implement continuous training programs tailored for all healthcare team members, including clinicians, pharmacists, and microbiologists. These programs should focus on key areas such as appropriate antibiotic selection, dosing, and de-escalation strategies. Utilize virtual training platforms and interactive case-based learning through virtual classrooms to enhance engagement. Workshops, simulations, and

real-time feedback sessions can further strengthen antimicrobial stewardship skills, ensuring the team consistently applies evidence-based practices in patient care.

AMS program strategies in hospitals

Pre-prescription strategy

- Definition: restricts certain antimicrobials and requires pre-authorization before use.
- Advantages: effective in controlling antimicrobial use, shown to reduce inappropriate prescribing.
- Challenges:
  - Requires a trained, readily available AMS team.
  - May face resistance from prescribers.
  - Potential for increased resistance to essential medications. For example, cephalosporin restriction led to a 44% reduction in ceftazidime-resistant *Klebsiella i*nfections but a 68.7% rise in imipenem-resistant *P. aeruginosa*.

Post-prescription strategy

- Definition: involves prospective audits and feedback to adjust antimicrobial therapy after prescription.
- Advantages: more collaborative and less restrictive than pre-authorization, focusing on education and adjustment.
- Key components:
  - No restrictions or pre-authorizations.
  - Review of all antimicrobials by a team (pharmacist and physician).
  - In-person feedback during clinical rounds (handshake stewardship).

This strategy has been highly effective in improving antimicrobial use and outcomes, including in pediatric settings.

Dose optimization and therapeutic drug monitoring (TDM)

- Objective: adjust antimicrobial doses based on patient-specific factors and drug concentrations.
- Action: use TDM to optimize antibiotic therapy, especially in critically ill children, who often have altered pharmacokinetics (PK). For instance, in intensive care unit (ICU) settings, nearly 50% of adult patients and up to 95% of pediatric ICU (PICU) patients have antibiotic concentrations outside the therapeutic window.

Extended infusion of antibiotics in pediatrics

Extended infusion of beta-lactams and glycopeptides has become a key strategy in pediatric care, especially for critically ill patients, to optimize PK/PD parameters. This approach prolongs drug exposure, crucial for time-dependent antibiotics, improving efficacy and reducing treatment failure. It is increasingly used to meet target PK/PD ratios for more effective bacterial eradication. Studies show a 52% reduction in mortality compared to traditional dosing. However, the high costs and infrastructure needs present challenges, especially in resource-limited settings.

For specific beta-lactams, the infusion duration in pediatrics is typically adjusted to enhance time above the minimum inhibitory concentration (T>MIC). Meropenem is commonly infused over 3 hours, while piperacillin-tazobactam and cefepime are also administered over 4 hours. These extended infusions optimize drug efficacy, especially in critically ill pediatric patients, by maximizing bacterial kill rates and improving outcomes

for multidrug-resistant infections. Other techniques to enhance antibiotic exposure include loading doses, reducing dosing intervals, or increasing the dose.

Key antimicrobials in PICU and NICU

- Vancomycin and aminoglycosides: these are among the most frequently used antibiotics in pediatric and neonatal ICUs, where dose adjustments based on TDM are crucial to achieving the right balance between efficacy and safety.

Vancomycin use in pediatrics

Vancomycin is a concentration-independent antibiotic, meaning its efficacy does not rely on achieving high peak concentrations. Instead, its pharmacodynamics predict 97% efficacy based on achieving the therapeutic target, calculated as the area under the curve to the minimum inhibitory concentration (AUC/MIC). Vancomycin also follows time-dependent pharmacokinetics, where the drug's effectiveness is linked to the duration of bacterial exposure and serum concentrations, making continuous infusion a potential option.
Monitoring serum levels is crucial, especially in newborns, as bioavailability varies. Premature infants often have higher free drug concentrations, increasing the risk of adverse effects like nephrotoxicity, ototoxicity, and hypersensitivity reactions.

New dosing guidelines

Recent vancomycin guidelines recommend shifting from trough serum levels to calculating the AUC/MIC24 (target range: 400-600) for better efficacy and reduced toxicity. This approach, using Bayesian methods, provides a more individualized dosing strategy. Studies show that relying solely on trough levels often misses the necessary pharmacokinetic profile, while Bayesian calculations improve clinical outcomes, particularly in pediatric patients.

Aminoglycoside use in pediatrics

TDM of aminoglycosides, like gentamicin and amikacin, is crucial in neonatology and pediatrics to optimize efficacy and minimize toxicity. In neonates, gentamicin is dosed at 4–5 mg/kg once daily, while in older children, it ranges from 5–7.5 mg/kg/day, divided every 8 hours. However, once-daily dosing is generally preferred for its lower nephrotoxicity risk. Target trough concentrations are ≤1 mg/L for neonates and ≤0.5 mg/L for older children, with peak concentrations between 8–12 mg/L for neonates and 15–20 mg/L for children. For amikacin, the recommended dose is 15–20 mg/kg once daily, with peak concentrations aimed at 25–40 mg/L and trough levels ≤5 mg/L. Similar to gentamicin, a once-daily dosing of amikacin is associated with lower toxicity, making it a safer option in pediatric populations. TDM helps individualize therapy by adjusting doses based on renal function and infection severity, ensuring optimal therapeutic outcomes while minimizing adverse effects.
Summarizing the strategies, a recent publication from the WARNING Collaborators outlines 10 golden rules to improve antibiotic use in hospitals. These include: 1) prescribing antibiotics only when clearly necessary to treat bacterial infections; 2) selecting the most appropriate antibiotic based on infection source and local resistance patterns; 3) ensuring the correct dose and administration route for effectiveness; 4) starting antibiotics promptly, particularly in critical infections like sepsis; 5) tailoring therapy based on culture results to narrow the spectrum; 6) monitoring the patient's clinical response daily and adjusting treatment as needed; 7) using the shortest effective therapy duration to limit resistance risk; 8) avoiding prophylactic antibiotics unless clearly indicated; 9) prioritizing infection prevention strategies such as hand hygiene and aseptic techniques to prevent healthcare-associated infections; and 10) engaging in AMS programs to promote

responsible antibiotic use and combat antimicrobial resistance. These steps aim to optimize antibiotic use and curb the growing threat of antimicrobial resistance.

Monitoring and evaluation

Effective monitoring and evaluation of an AMS program involve key components, including performance indicators, audits, and feedback mechanisms. These elements are essential for assessing the program's impact and ensuring continuous improvement.

Performance indicators

Defining metrics to evaluate the program's effectiveness is critical. Key performance indicators include:

- Antimicrobial usage rates: measured in days of therapy per 1,000 patient-days and total antimicrobial days.
- Clinical outcomes: 30-day readmission rates for specific clinical conditions.
- Process adherence: compliance with AMS recommendations.

These consensus metrics for pediatric AMS programs help track the effectiveness and areas needing improvement. Monitoring these indicators provides insight into antimicrobial consumption, clinical outcomes, and adherence to best practices.

Audits and feedback

As the AMS team conducts prospective audits, various antimicrobial therapy-related problems arise. In 2021, Ricieri *et al.* proposed the Problem Related Antimicrobial Therapy (PRAT) tool (**Figure 1**), which categorizes 17 primary domains and 67 subcategories of problems. These categories include:

- prescribed dose, frequency, and administration route;
- drug interactions (drug-drug or drug-food);
- inappropriate or unnecessary medications;
- therapeutic inefficacy or adverse reactions.

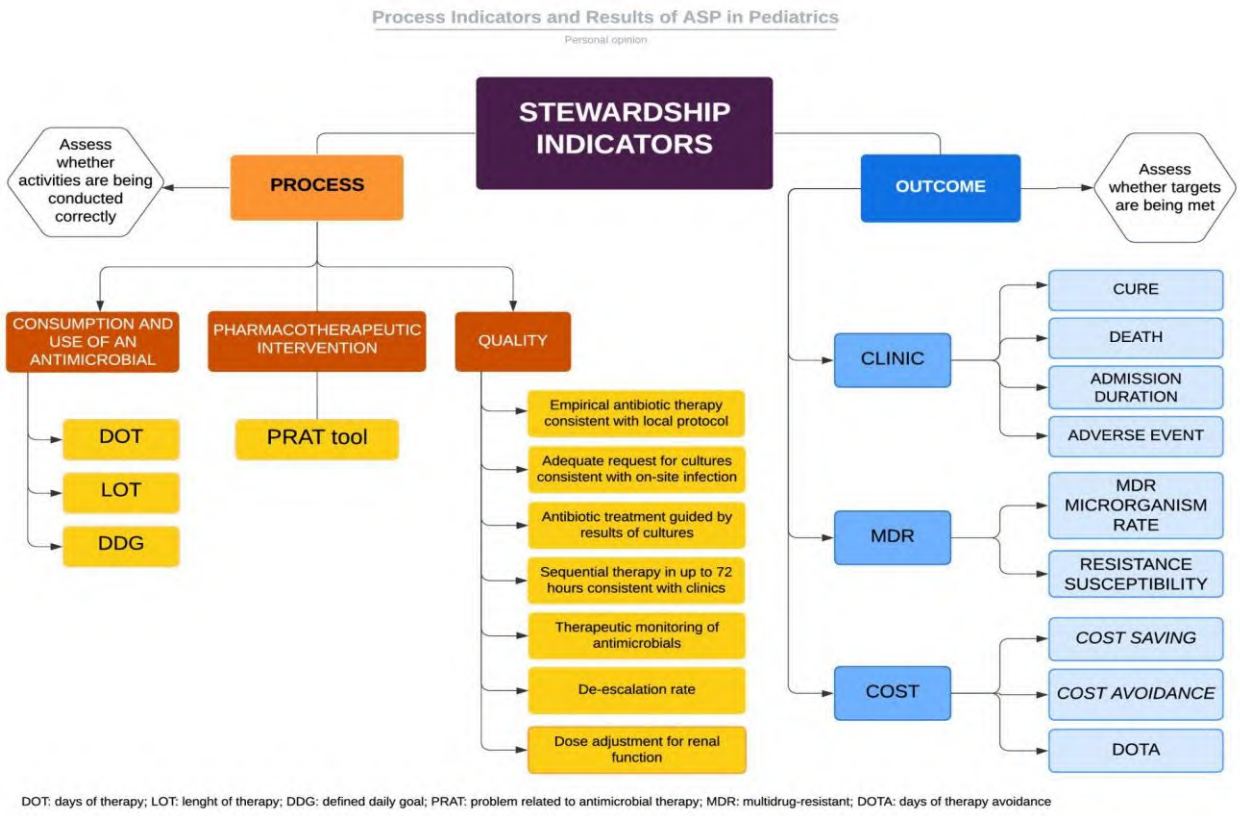

Figure 1. Process indicators and results of ASP in pediatrics (Adapted from: Ricieri M, et al. 2021).

The PRAT tool offers a standardized approach to identifying antimicrobial therapy issues, allowing for targeted interventions. It also helps establish an epidemiological profile of common issues, enabling focused educational and quality improvement efforts.

Additional metrics

Other metrics include:

- antimicrobial resistance rates;
- length of hospital stay;
- hospital mortality rates.

These indicators provide a broader view of AMS programs' impact on patient outcomes and hospital performance. By tracking these metrics, hospitals can better assess the overall effectiveness of AMS initiatives and make necessary adjustments to optimize patient care.

Antibiotic stewardship in pediatric surgery

In pediatric surgery, surgical site infections (SSI) remain a significant concern, especially given the vulnerability of neonates and children. The rate of SSIs varies by the type of surgical procedure and can lead to complications, extended hospital stays, and an increased burden on healthcare systems. Although limited data exist

specifically for pediatric surgical prophylaxis, the principles of antimicrobial selection and site exposure are the same for children as for adults. Surgical procedures are commonly categorized into four types based on the potential for infection: clean, clean-contaminated, contaminated, and dirty.

- Clean surgeries. These are non-invasive procedures where there is no inflammation or infection, such as elective orthopedic surgeries.
- Clean-contaminated surgeries. Procedures that involve opening a cavity that may harbor bacteria, such as gastrointestinal surgeries.
- Contaminated surgeries. These are operations where there is significant exposure to bacteria, such as surgeries involving traumatic wounds.
- Dirty surgeries. Procedures that involve active infection or devitalized tissue, such as emergency procedures to manage perforated organs.

Risk factors for SSI in pediatrics include prolonged hospital stays, immunosuppression, malnutrition, and colonization with resistant pathogens such as MRSA or other multidrug-resistant organisms. Specific high-risk conditions are identified in neonates and children, including recent surgery, colonization with multidrug-resistant organisms, or comorbidities that may increase their susceptibility to infection.

Non-pharmacological measures

Effective non-pharmacological measures are essential to prevent SSIs and include:

- Preoperative bathing. Using chlorhexidine baths before surgery is strongly recommended. In neonates and infants under 2 months, chlorhexidine baths before surgery are generally not recommended due to the risk of skin irritation and systemic absorption through their delicate skin. Additionally, the lack of robust evidence in NICU subpopulations highlights the need for well-designed multicenter trials to better assess the risk/benefit ratio, particularly in neonates and infants below certain ages or birth weights
- Intraoperative sterility. Maintaining strict sterile procedures, limiting operating room traffic, and minimizing operative time are critical strategies to prevent infection.
- Postoperative care. Ensuring wound care is performed using sterile techniques and monitoring for early signs of infection during recovery.
- Surveillance programs. Monitoring SSI rates and implementing standardized checklists such as the WHO Surgical Safety Checklist ensures better compliance and reduces postoperative infection.

Pharmacological measures

For pharmacological interventions, antimicrobial prophylaxis is crucial, with the timing, selection, and duration playing key roles. Common choices include cefazolin for clean surgeries and cefazolin combined with vancomycin for patients at higher risk of MRSA colonization.

A single dose of cefazolin should be administered within 60 minutes before incision. Broader-spectrum antibiotics, such as piperacillin-tazobactam, may be indicated for contaminated or dirty surgeries, with longer courses of up to 72 hours for therapeutic purposes in the latter. Maintaining adequate antimicrobial levels during surgery is essential, and redosing is required if the procedure exceeds twice the antibiotic's half-life or involves significant blood loss, with cefazolin redosed every 4 hours. Postoperative prophylaxis should not

exceed 24 hours, even if drains are placed, except in specific cases like high-risk neurosurgeries, where prophylaxis may extend up to 24 hours. For cardiac surgeries or transplants, antibiotics may be used for up to 48 hours, although evidence suggests no additional benefit beyond this period and an increased risk of resistance.

Penicillin allergy

Patients with a penicillin allergy pose a unique challenge. For patients allergic to penicillin, alternatives such as clindamycin or vancomycin are recommended. In cases of MRSA colonization, vancomycin should be included, and testing for antibiotic allergies should be part of the preoperative assessment.

High-risk patient data

Patients with the following high-risk factors may require tailored prophylactic strategies:

- Colonization by MRSA or other multidrug-resistant organisms.
- Recent surgery or prolonged hospitalization (greater than two weeks) increases the risk of colonization and infection.
- Immunocompromised patients or those on immunosuppressive therapy.

These patients may benefit from preoperative screening for MRSA and other multidrug-resistant bacteria, decolonization strategies (such as mupirocin nasal ointment and chlorhexidine bathing), and the use of broader-spectrum antibiotics to cover resistant organisms.

Challenges and solutions

One of the major challenges in implementing AMS programs is the resistance from healthcare professionals to adopt new prescribing guidelines, particularly in environments with limited resources. Physicians may feel restricted by pre-authorization policies or hesitant to shift from established practices, especially when dealing with critically ill patients. To overcome this, AMS teams must focus on continuous education and training, emphasizing the benefits of evidence-based antimicrobial prescribing and fostering collaboration between healthcare providers. Establishing clear communication channels between AMS team members and prescribers, along with promoting the use of decision-support tools, can help reduce resistance and ensure more consistent application of stewardship principles.

Another significant challenge is the high cost associated with advanced diagnostic technologies, such as MALDI-TOF and multiplex PCR. While these tools dramatically reduce turnaround time for microbiological results, enabling more targeted therapy, their implementation in resource-limited settings is often hindered by financial constraints. Hospitals can address this challenge by seeking external funding, collaborating with government and non-governmental organizations, or leveraging public health initiatives to acquire these technologies. Moreover, investing in the training of AMS team members and prioritizing cost-effective interventions can improve the overall program's impact while staying within budgetary limits.

Another challenge in pediatric antimicrobial stewardship regarding SSIs is the lack of robust, pediatric-specific data to guide prophylaxis protocols. Many current guidelines are extrapolated from adult data, which may not fully account for the unique physiological considerations in children and neonates. Furthermore, the ongoing challenge is balancing the need to prevent SSIs while minimizing antibiotic overuse and the risk of developing resistance.

Future perspectives

Looking ahead, the future of AMS programs includes integrating advanced technologies like artificial intelligence (AI) and big data analytics to optimize antimicrobial use. AI-powered systems can analyze large datasets in real-time, providing patient-specific recommendations for therapy. These tools could improve AMS efficiency, especially in high-volume settings, by identifying resistance patterns and predicting the most effective treatments.

There is also a growing need for research in pediatric antimicrobial stewardship, especially in refining dosing strategies through PK/PD modeling and validating pediatric-specific tools, including in surgical settings. As accurate PK/PD models and Bayesian dosing methods develop, personalized medicine may become the norm in pediatric antimicrobial therapy and surgical prophylaxis. These advancements will help reduce resistance and improve outcomes, ensuring a more sustainable future in combating antimicrobial resistance.

Conclusion

Implementing a robust Antimicrobial Stewardship Program (AMS) in pediatrics is essential for improving outcomes and preserving antibiotic efficacy. ASPs play a vital role in reducing mortality, morbidity, and antimicrobial resistance, particularly in vulnerable pediatric populations. By optimizing antibiotic use through dose adjustments, TDM, and de-escalation of broad-spectrum antibiotics, ASPs ensure that therapies remain both effective and safe.

The benefits of a well-structured ASP extend beyond individual care, helping preserve the long-term efficacy of antimicrobials and prevent the rise of multidrug-resistant infections. Regular audits, feedback, decision-support tools, and evidence-based guidelines promote informed, responsible antibiotic use. In surgical settings, ASPs are equally critical for optimizing prophylaxis and postoperative care. Integrating technologies like rapid diagnostics enhances tailored therapies, improving outcomes and reducing unnecessary antibiotic exposure.

ASP success relies on a multidisciplinary team including pediatricians, surgeons, intensivists, pharmacists, microbiologists, nurses, and infection control specialists. This approach ensures all aspects of antimicrobial management are addressed, from diagnosis to evaluation. Continuous education is crucial to keep professionals updated on best practices. Given the growing threat of antimicrobial resistance, prioritizing ASPs is essential. These programs not only preserve antibiotic effectiveness for future generations but also improve overall care quality. Engaging all stakeholders is key to supporting global health efforts and ensuring safer, more effective treatments for pediatric infections.

Competing interests

The authors have no financial and non-financial competing interests to declare.

References

1. Dellit TH, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America

Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship. Clin Infect Dis. 2007;44:159–177.
2. Murray CJL, Iet al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. The Lancet. 2022;399:629–655.
3. Romandini A, et al. Antibiotic Resistance in Pediatric Infections: Global Emerging Threats, Predicting the Near Future. Antibiotics. 2021;10:393.
4. Fassbind DA, et al. Community-acquired and healthcare-associated Staphylococcus aureus infections in a pediatric hospital in southern Brazil over 8 years: how common is MRSA? Front Pediatr. 2023;11:1212239.
5. Jesudason T. WHO publishes updated list of bacterial priority pathogens. Lancet Microbe. 2024;5:100940.
6. Barlam TF, Cet al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis. 2016;62:e51–e77.
7. Wendt JM, et al. *Clostridium difficile* Infection Among Children Across Diverse US Geographic Locations. Pediatrics. 2014;133:651–658.
8. Vangay P, et al. Antibiotics, Pediatric Dysbiosis, and Disease. Cell Host Microbe. 2015;17:553–64.
9. Levy Hara G. Antimicrobial stewardship in hospitals: Does it work and can we do it? J Glob Antimicrob Resist. 2014;2:1–6.
10. Kim J, et al. Building an Antimicrobial Stewardship Program: Cooperative Roles for Pharmacists, Infectious Diseases Specialists, and Clinical Microbiologists: Table 1. Lab Med. 2015;46:e65–e71.
11. Ventola CL. Mobile Devices and Apps for Health Care Professionals: Uses and Benefits. Pharmacy and Therapeutics. 2014;39:356-364.
12. Fralick M, et al. Can a smartphone app improve medical trainees' knowledge of antibiotics? Int J Med Educ. 2017;8:416–420.
13. Gijsen M, et al. Pharmacokinetics of Antibiotics in Pediatric Intensive Care: Fostering Variability to Attain Precision Medicine. Antibiotics. 2021;10:1182.
14. Smits A, et al. Antibiotic PK/PD Research in Critically Ill Neonates and Children: How do we Proceed? Int J Pharmacokinet. 2018;3:1–3.
15. Rahal JJ. Class Restriction of Cephalosporin Use to Control Total Cephalosporin Resistance in Nosocomial Klebsiella. JAMA. 1998;280:1233.
16. Hurst AL, et al. Handshake Stewardship: A Highly Effective Rounding-based Antimicrobial Optimization Service. Pediatr Infect Dis J. 2016;35:1104–1110.
17. McCreary ML, et al. Physician experiences implementing antimicrobial stewardship rounds in pediatric hospital medicine: An exploratory, qualitative study. Antimicrob Steward Healthc Epidemiol. 2021;1:e11.
18. Hartman SJF, et al. Pharmacokinetics and Target Attainment of Antibiotics in Critically Ill Children: A Systematic Review of Current Literature. Clin Pharmacokinet. 2020;59:173–205.
19. Burch AR, Vet al. Extended Infusion of Beta-Lactams and Glycopeptides: A New Era in Pediatric Care? A Systematic Review and Meta-Analysis. Antibiotics. 2024;13:164.
20. Rybak MJ, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: A revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm. 2020;77:835–864.
21. Hollander EM, et al. Evaluation of Dosing Guidelines for Gentamicin in Neonates and Children. Antibiotics. 2023;12:810.
22. Worldwide Antimicrobial Resistance National/International Network Group (WARNING) Collaborators. Ten golden rules for optimal antibiotic use in hospital settings: the WARNING call to action. World J Emerg Surg. 2023;18:50.
23. Science M, et al. Quality Metrics for Antimicrobial Stewardship Programs. Pediatrics. 2019;143:e20182372.
24. Ricieri MC, et al. PRAT tool: a harmonization of antimicrobial stewardship program interventions. Rev Ciênc Farm Básica E Apl - RCFBA. 2021;42:e735.
25. Zaffagnini A, et al. Enforcing surveillance of antimicrobial resistance and antibiotic use to drive stewardship: experience in a paediatric setting. J Hosp Infect. 2024;144:14–19.

26. Bianchini S, et al. Surgical Antimicrobial Prophylaxis in Neonates and Children with Special High-Risk Conditions: A RAND/UCLA Appropriateness Method Consensus Study. Antibiotics. 2022;11:246.
27. Kimberlin DW, et al. Antimicrobial Prophylaxis in Pediatric Surgical Patients. In: Red Book: 2021–2024 Report of the Committee on Infectious Diseases. p. 1010–1021.
28. Bratzler DW, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm. 2013;70:195–283.
29. Meoli A, et al. Prevention of Surgical Site Infections in Neonates and Children: Non-Pharmacological Measures of Prevention. Antibiotics. 2022;11:863.
30. Burzyńska J, et al. Perioperative Antibiotic Prophylaxis in Pediatric Cardiac Surgery—Simple Is Better. Antibiotics. 2022;12:66.

Chapter 81

The value of global access to microbiology diagnostics

Selma Souf
Institut Pasteur d'Algérie, Annexe de Constantine, Algeria.

Meriem Benkhemissa
CHU de Constantine, Laboratoire de Bactériologie, Algeria.

Penelope Bryant
Hospital-in-the-Home and Infectious Diseases Departments, The Royal Children's Hospital Melbourne, Murdoch Children's Research Institute, Department of Paediatrics, University of Melbourne, Australia.

Introduction

Infectious diseases are a leading cause of morbidity and mortality worldwide, and the emergence of resistance to existing antimicrobial treatments will make the situation even worse, posing further significant challenges to global health. Access to microbiology diagnostics that enable the identification of infectious pathogens and their optimal treatment is therefore a cornerstone of effective healthcare, yet it remains unevenly distributed across the globe.

Accurate and timely diagnostics are essential for the detection and management of infectious diseases, informing appropriate treatment decisions, and curbing the spread of antimicrobial resistance (AMR). However, disparities in access to these crucial tools are stark, particularly between high-income and low- and middle-income countries (LMICs). In high-resource settings, advanced diagnostic technologies enable precise identification of pathogens, guiding targeted therapies and optimizing patient outcomes. Conversely, many LMICs struggle with limited access to even basic diagnostic facilities, leading to delayed or inaccurate diagnoses, inappropriate treatments, and ultimately, poorer health outcomes.

The global health community recognizes the urgent need to improve access to microbiology diagnostics as part of a broader strategy to combat infectious diseases and AMR. Initiatives such as the World Health Organization's (WHO) Global Antimicrobial Resistance Surveillance System (GLASS) and the Diagnostics Access Initiative underscore the critical role of diagnostics in global health security. Despite these efforts, significant barriers remain, including inadequate infrastructure, lack of trained personnel, high costs, and logistical challenges in remote and underserved areas.

This chapter explores the multifaceted importance of global access to microbiology diagnostics, highlighting their significance in improving patient care, enhancing public health outcomes, and promoting global health equity. It examines the current state of diagnostic access across different regions, the challenges faced in expanding this access, and the strategies and innovations that can help bridge the gap. By understanding and

addressing the value and challenges of global access to microbiology diagnostics, we can work towards a more equitable and effective approach to infection prevention and management.

What do we mean by microbiology diagnostics?

Microbiology diagnostics are the range of techniques and tools used to detect, identify, and characterize microorganisms responsible for infectious diseases. These diagnostics are crucial for determining the presence of bacteria, viruses, fungi, and parasites in clinical samples, providing essential information for the diagnosis, treatment, and management of infections. They encompass a wide array of methodologies, from traditional culture techniques to cutting-edge molecular technologies, each offering unique advantages and applications, but also with some disadvantages.

Traditional microbiological techniques

Traditional methods in microbiology diagnostics, such as microscopy, Gram stain and culture-based techniques have been the cornerstone of clinical microbiology for decades. These methods involve isolating and growing microorganisms from clinical specimens, allowing for the identification of pathogens and testing for antimicrobial susceptibility. While highly reliable, these techniques often require specialized laboratory facilities and skilled personnel that are not always available, and the techniques take time, which risks delaying diagnosis and treatment.

Molecular diagnostics

The advent of molecular diagnostics has revolutionized the field of microbiology by enabling the rapid and precise detection of pathogens, along with the detection of resistance genes, virulence factors, and genotype determination. Techniques such as polymerase chain reaction (PCR), next-generation sequencing (NGS), and nucleic acid amplification tests (NAATs) can identify microorganisms at the genetic level, even when they are present in low numbers. Multiplex PCR can detect several microorganisms in a single clinical sample (bacteria and viruses) with the additional possibility of detecting resistance genes at the same time eg mecA, vanA, extended-spectrum beta-lactamase-producing genes, and carbapenemase genes. Several syndromic panels are available: respiratory, gastrointestinal, blood culture, and meningitis/encephalitis. They have strong performance characteristics, and results are available in 1 to 2.5 hours. The mass spectrometry technique MALDI-TOF can rapidly identify microorganisms (in as little as a few minutes) and reduce the time to appropriate therapy. These methods offer high sensitivity and specificity and significantly reduce the turnaround time for diagnosis. Molecular diagnostics can detect antimicrobial resistance genes, which can provide critical information for tailoring appropriate treatment regimens. However, these molecular techniques do not solve every diagnostic problem and have several shortcomings. First, investment into the technology and initial training of staff is expensive and not accessible in all settings. Second, there are relatively few AMR genes routinely tested in clinical practice via molecular techniques, so compared to traditional culture and susceptibility techniques, they are weaker at identifying resistance. Third, because they can detect at low numbers, identification of a microorganism can create clinical confusion about whether it is the pathogen causing the symptoms, so clinical correlation is critical.

Point-of-care testing

Point-of-care testing (POCT) refers to diagnostic tests performed at or near the site of patient care, providing immediate results. Examples include rapid diagnostic tests (RDTs) for malaria, HIV, and tuberculosis (TB).

POCT is particularly valuable in resource-limited settings in improving accessibility to microbiology diagnostics where access to centralized laboratories may be challenging. However, there are only a limited number of microorganisms that can be identified via POCT, and the sensitivity and specificity are often lower than with other techniques.

Automated and high-throughput systems

Automation and high-throughput technologies in molecular microbiology diagnostics have enhanced the efficiency and accuracy of this testing. As automated systems can process large volumes of samples with minimal human intervention, they reduce the potential for errors and increase the speed of diagnosis. These systems are especially beneficial in outbreak situations where rapid identification of pathogens is crucial for effective response and containment. The downsides are that such systems are expensive to set up initially, and may not show cost benefits for small healthcare settings with relatively few samples. They also have the same weaknesses as simple molecular diagnostic techniques.

Emerging technologies and innovations

Emerging technologies, such as metagenomics, nanotechnology-based and CRISPR-based diagnostics, biosensors, artificial intelligence and machine learning are expanding what is possible with microbiology diagnostics. These innovations hold the promise of providing faster, more accurate and more comprehensive diagnoses, addressing some of the limitations of current methodologies. Many of these technologies currently remain financially out of reach for lower-income settings, but as costs reduce and they become more accessible, they have the potential to revolutionize health diagnostics globally, particularly in underserved regions.

The role of microbiology diagnostics in clinical care

The ability to quickly and accurately diagnose infectious diseases is essential for effective patient clinical care, infection prevention and control, public health surveillance, and stewardship of antimicrobials in the fight against AMR.

Patient clinical care

The effective management of patients with infectious diseases relies heavily on microbiology diagnostics. Improved microbiological testing strategies are associated with improvements in antimicrobial prescribing, ongoing monitoring of infections and treatment efficacy.

First, the identification of a pathogen guides management down a specific pathway and can avoid the need for further investigations and treatment while a diagnosis is being elucidated. This is good for the patient as it avoids unnecessary risks associated with some investigations, such as radiation from imaging. It is also good for healthcare sustainability as it saves additional unwarranted costs. Identification of a pathogen additionally allows treatment to be targeted, both to manage the infection effectively and to decrease the coverage of the antimicrobial(s) used, for example, identification of Mycobacterium tuberculosis or malaria means empiric antibacterials can often be ceased. The reverse is also true in resource-limited settings. The absence of microbiological testing, or delays caused by traditional bacterial culture and susceptibility testing taking up to several days to obtain, remain major barriers to providing optimal therapy; this is especially important for severe infections such as sepsis and septic shock.

Beyond pathogen identification, antimicrobial susceptibility testing (AST) determines the susceptibility of pathogens to specific antibiotics, and although it exists for other pathogens (e.g., fungi, viruses); it is the cornerstone of targeted antibiotic prescribing for bacteria. Where AST is available, antimicrobials can be further narrowed, to decrease the ecological impacts of broader-spectrum antibiotics.

In an ideal world, a lack of identification of a pathogen should lead to the ceasing of antimicrobials, but this relies on very sensitive tests with high negative predictive values. This was the promise of molecular diagnostics over traditional microscopy and culture techniques. In reality, even with the advent of even more sensitive tests, studies have shown that if there is a high index of suspicion of infection, clinicians will usually continue treatment with antimicrobials despite negative tests. However, if a virus is detected, for example in meningitis, this will usually lead to cessation of antibiotics.

Microbiological diagnostics do not represent a single point in time and are a dynamic part of ongoing monitoring of infection. Ongoing positive microbiological tests suggest that the infection is not being adequately treated and often lead to clinician concern that an ineffective antibiotic is being used. This has several caveats. Ongoing positive molecular testing may simply reflect the nuclear material of dead pathogens so this finding alone does not necessarily need any change in management. Ongoing positive cultures represent live bacterial replication, but is often due lack of source control (e.g., a retained foreign body or an abscess) rather than antibiotic failure. This shows the importance of AST as this will confirm whether the treatment antibiotic is likely to be effective. Without AST, clinicians cannot determine this, antibiotic coverage is frequently broadened (eg flucloxacillin to vancomycin). While this is reasonable for empiric treatment in an unwell patient, long courses of 'just in case' broad-spectrum antibiotics contribute to antimicrobial resistance. Determining a negative result after a previous positive result confirms that the treatment is effective, for example, an end-of-treatment negative cerebrospinal fluid culture can reassure about stopping treatment in severe bacterial meningitis. It may also allow clinicians to shorten the duration of treatment or switch from intravenous to oral antibiotics earlier, for example, the duration of antibiotics for *Staphylococcus aureus* bacteraemia is based on the first negative blood culture. By shortening courses, or switching earlier to oral antibiotics, patients can be treated at home, which improves outcomes.

Infection prevention and control

Microbiology diagnostics play a critical role in infection prevention and control, particularly in hospital settings. They allow the rapid identification of outbreaks in wards, and interventions such as renewed hand hygiene education, wearing of personal protective equipment and cohorting of patients can prevent widespread transmission. AST and/or molecular testing allows even more accurate identification of outbreaks in areas where some pathogens may be more common – such as intensive care units – by allowing differentiation between strains of the same organism. Hospital-acquired infections have an associated morbidity and mortality, and microbiological investigations are critical to limit their occurrence. Accurate microbiology also assists in infection prevention through preoperative screening and informing decisions about perioperative surgical prophylaxis. Ongoing microbiological surveillance allows the auditing of the effectiveness of infection control strategies and the impact of special interventions to keep healthcare facilities safe.

It is worth noting in the context of infection control, that the results of microbiology investigations can also serve as educational tools for both healthcare providers and patients, reinforcing the importance of appropriate antibiotic use and infection control.

Public health surveillance

Microbiology is a critical component of public health surveillance for pathogens. Surveillance is the ongoing and systematic collection, analysis, and interpretation of health data essential to the planning,

implementation, and evaluation of public health practice. Surveillance can be passive (with detection via normal laboratory pathways or workflow and alerting on an individual basis) or active (when specific targets are pursued and followed by informatics models and processes). Pathogen surveillance allows the identification of certain pathogens, in particular notifiable diseases such as legionella infection, measles and salmonellosis. This allows public health authorities to take steps to control the spread of infectious diseases and to protect the health of the community. Early accurate diagnosis enables interventions to take place that are specific to the pathogen identified; in the examples above, these may include cleaning out a cooling tower, vaccination and closing down a restaurant kitchen respectively. The most recent example of the role of microbiology diagnostics in public health surveillance on a global scale was with the rapid sequencing and identification of SARS-CoV-2 causing the COVID-19 outbreak and then the pandemic. It was rapidly developed into a molecular test which had a huge impact on the ability of public health authorities to control spread by quarantining patients both with and exposed to the virus. It also enabled the development of effective vaccines.

Antimicrobial stewardship

In severe acute infections, broad-spectrum empirical antibiotics are started. While these are likely to be effective, high and prolonged use of broad-spectrum antibiotics is associated with the emergence of antimicrobial resistance (AMR). AMR is a global health crisis threatening the utility of antibiotics, and with it, both our ability to fight even simple infections and our ability to undertake routine treatments such as surgery and cancer care. To address this, the concept of antimicrobial stewardship (AMS) arose, referring to the optimization of antimicrobial use aiming to be judicious with prescribing, while not decreasing efficacy.

The goals of using microbiology diagnostics in AMS are to optimize antibiotic use to improve patient outcomes and limit the development of AMR. The integration of microbiology diagnostics into AMS is pivotal and synergistic in the global effort to combat AMR.

To achieve these goals, AMS programs are ideally administered by multidisciplinary teams; while infectious diseases physicians, with clinical pharmacists, are considered the main leaders, clinical microbiologists with the resources of a microbiology laboratory play a key role. This role can be exemplified by the '6 Ds of antimicrobial stewardship' (**Table 1**).

Patient-level AMS to improve clinical outcomes

The microbiology laboratory plays a critical role in AMS by providing timely patient-specific data to optimize individual antimicrobial management. Optimizing antibiotics to improve patient care involves choosing the right antibiotic for the treatment of the infection, and diagnostics aid this by identifying the pathogen and providing antibiotic susceptibility information. Empiric broad antibiotics are often started when a patient is severely unwell, but as soon as more information is available, this can be targeted. Timeliness of the administering the right antibiotic also improves patient outcomes, and newer microbiological techniques have greatly shortened the time to accurate identification of pathogens. Optimal prescribing for effective infection management also involves selecting the appropriate antibiotic dose, and the minimum inhibitory concentration can guide this. Regarding limiting AMR in individual patients, choosing a narrow-spectrum antibiotic is ideally guided by AST where available. This limits broader unwanted effects on other microbiota in the gastrointestinal tract and other ecological niches that set up the development of AMR. Shortening antibiotic duration and/or switching from IV to oral antibiotics as early as possible can be supported by ongoing microbiological investigations showing improvement in infection. These have the combined effect of limiting antibiotic pressure on the development of AMR and potentially allowing a patient to be treated at home instead of hospital, limiting the spread of AMR.

Table 1. The 6 Ds of antimicrobial stewardship, showing the role of microbiology diagnostics. (Adapted with permission from: Morency-Potvin P, *et al.* 2017).

The 6 Ds of antimicrobial stewardship	Description	Examples of the key roles of microbiology laboratories
Diagnosis	Make and document the right diagnosis.	Perform rapid identification testing of critical specimens (e.g., rapid molecular testing of positive blood cultures).
Debridement/drainage	Drainage of abscesses and removal of necrotic tissue or foreign material when required.	Provide guidance for obtaining adequate and significant specimens.
Drug	Use the right drug empirically according to suspected or confirmed diagnosis, risk factors for resistant pathogens, allergy, or major side effects.	Provide, revise, and publicize annual cumulative susceptibility reports to clinicians. Participate in creating local guidelines for common infectious syndromes. Perform surveillance for emerging pathogens and resistance patterns and inform clinicians and public health authorities as appropriate.
Dose	Use the right dose according to diagnosis, site of infection, or renal or hepatic dysfunction.	Collaborate with pharmacists and ID physicians to improve reporting of MICs for dosing based on pharmacokinetic targets.
Duration	Use drugs for an appropriate duration.	Perform biomarker testing and develop protocols to optimize their use for informing therapy duration as indicated.
De-escalation	Re-evaluate diagnosis and therapy routinely and de-escalate therapy to narrow-spectrum and/or oral agents when appropriate.	Leverage opportunities to append clinical guidance to microbiological reports.

Institution-level AMS to limit AMR

Pathogen identification and antibiotic susceptibility testing provide data for institutional surveillance. This can be used in two main ways: surveillance to alert to individual results and the broader gathering of information for planning. Surveillance and alert systems can provide relevant microbiology information to the AMS team, including positive results (e.g., stain, detection, culture) in critical specimens such as normally sterile sites (e.g., blood, cerebrospinal fluid), identification of specific pathogens that require rapid intervention, such as *Clostridium difficile* or *Mycobacterium tuberculosis*, and specific resistance patterns, such as carbapenem-resistant *Enterobacteriaceae* or vancomycin-resistant *Enterococcus* spp.

Surveillance systems are important for gathering broader information to understand the institutional, regional and national epidemiology of certain pathogens. Such surveillance allows for antibiograms (summary antimicrobial susceptibility data) to be developed at the institutional level, to inform empirical guidelines for accurate presumptive management of infections. This can also be done at a regional level in areas of the world where laboratory testing has not yet been established, to give a basis for empirical prescribing. Understanding of the current state of AMR in a country is important for defining national objectives and implementing AMS policy.

Several regional surveillance programmes provide surveillance of AMR in specific geographical areas, for example, the Central Asian and Eastern European Antimicrobial Resistance Surveillance Network (CAESAR), the European Antimicrobial Resistance Surveillance Network (EARSNet) and the Latin American Antimicrobial Resistance Surveillance Network (ReLAVRA). Despite the success of these programmes, there are still gaps in

the surveillance of many pathogenic bacteria, as well as a lack of common standards for methodology, data sharing and coordination at local, national, regional and global levels. These hamper efforts to collect meaningful data on a global scale and these are needed to ensure comprehensive monitoring and analysis of the occurrence and evolution of AMR worldwide. Reducing the overuse of unnecessary antibiotics globally, particularly those with broad coverage, and being able to measure the impact on AMR is the best hope we have of preserving the use of current antibiotics into the future.

Development and research

The development of new antibiotics is one of the solutions to the emergence of multi-resistant bacteria. Microbiological investigations play an important role in research activities targeting new antibiotics, by confirming the diagnosis in patients who are candidates for clinical trials before the new antibiotics are administered.

Microbiology laboratories should stay abreast of new drug development and assess the laboratory's capacity to test the activity of new agents against appropriate pathogens.

Economic and healthcare sustainability impact

Microbiological diagnosis has the potential for major economic impact, especially with the emergence of RDTs. The rapid management of patients using these techniques means that hospital stays can be reduced which has a major cost benefit to healthcare institutions and patients. In addition, inappropriate treatment can be avoided which in turn limits AMR development (see above). AMR has a significant cost associated with it, due to its impact not only on the requirement for broader, newer, more expensive antibiotics, but also due to the financial impact of AMR on hospital length of stay and mortality. Preserving the use of narrow-spectrum, low-cost oral antibiotics to the best of our abilities provides optimal healthcare sustainability.

Global access to microbiology diagnostics and the risks of disparity

The global landscape of healthcare is marked by stark inequalities, particularly in access to microbiology diagnostics.

The Lancet Commission on Diagnostics, which aims to develop a comprehensive strategy for improving access to diagnostic services worldwide, reported in 2021 that 47% of the world's population has little or no access to diagnostics, and only about 19% of LMIC populations have access to the most basic diagnostic tests.

In wealthier nations, cutting-edge diagnostics tools allow for fast and precise identification of pathogens, supporting effective interventions and optimal clinical outcomes. However, in many LMICs, these critical resources remain out of reach. The geographical remoteness of many communities within LMICs, and the consequent distance to healthcare, create vulnerable underserved populations with limited capacity to manage acute conditions. Facilities serving these populations generally have inadequate infrastructure, limited funding, and a shortage of skilled professionals (**Figure 1**).

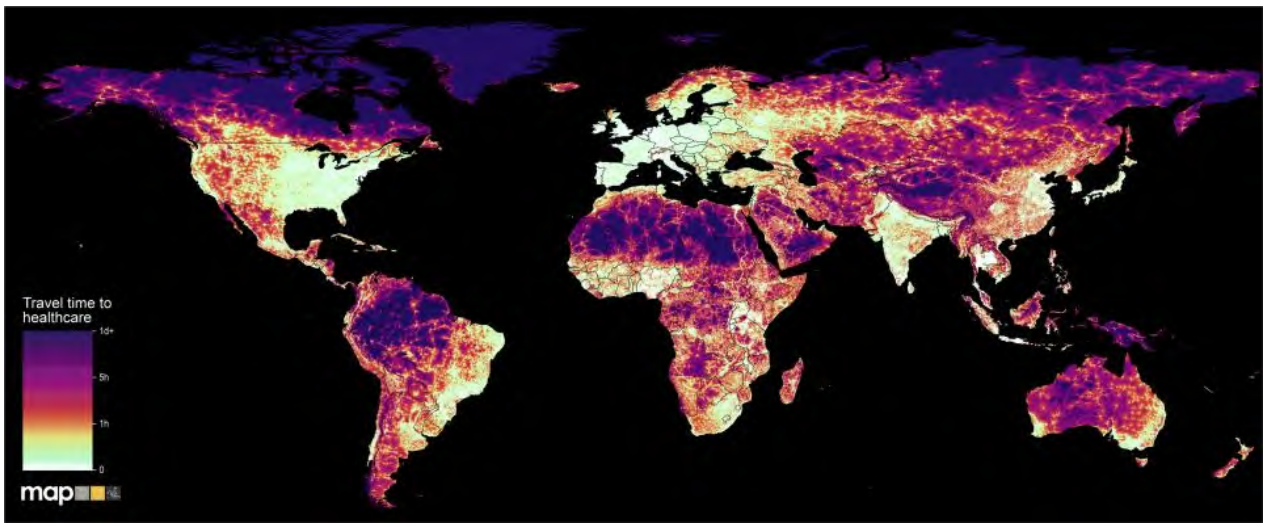

Figure 1. The map shows the best travel time to reach healthcare facilities with access to motorized transportation on a global scale. Color-coded logarithmic timescale from minutes (yellow) to 24 h (dark purple). From "Global maps of travel time to healthcare facilities" by Weiss DJ, et al. 2020. Reprinted with permission

Despite the efforts deployed since the early 2000s in Africa to strengthen clinical laboratories, local capacity within the 11 African countries that constitute the Economic Community of Central African States (ECCAS) are still insufficient; only 7 laboratories are accredited ISO 15189 for human health, and only 6 countries have whole genome sequencing equipment. The majority of microbiology laboratories with high biosafety levels (BSL 3 and 4) for safe pathogen containment are in Europe and North America, with only 5 in Africa, despite it being a high-risk region for dangerous diseases like Ebola.

These disparities result in delayed diagnoses and improper treatments in LMICs. They also fuel the global crisis of AMR, as unchecked infections, empirical treatments and the misuse of antibiotics drive the evolution of drug-resistant strains. We are also perpetuating a global healthcare system where those most in need often have the least access to optimal diagnosis and treatment.

Bridging this diagnostic divide is imperative to advancing global health equity and executing sustainable global and national action plans to control AMR. However, implementing proper access to microbiology diagnostics faces several significant barriers and challenges, which vary across regions and healthcare systems. These challenges are interconnected and will require coordinated efforts to overcome.

Challenges and barriers to global access to microbiology diagnostics

Economic constraints

High costs of advanced equipment and reagents in LMICs lead to limited diagnostic capacity. In many LMICs, healthcare budgets are stretched thin, with priority often given to immediate care needs rather than investment in diagnostic facilities. This underfunding hampers the ability to establish and sustain diagnostic services.

Infrastructure deficiencies

There is a lack of appropriate microbiology laboratory facilities, particularly in rural or remote areas. Even existing labs in urban areas may be outdated or poorly equipped, limiting their diagnostic capabilities. Added

to this are inadequate supply chains that are essential for maintaining a steady supply of reagents, consumables, and other necessary materials for diagnostics. In many regions, supply chain disruptions due to political instability, logistical and geographic challenges, or economic sanctions can severely impact the availability of essential diagnostic tools.

Human resource shortages

The shortage of trained microbiologists, laboratory technicians, and other skilled healthcare workers is a major barrier. Many countries face difficulties in training, recruiting, and retaining skilled personnel, which limits the capacity to perform and interpret complex diagnostic tests. In some LMICs, skilled professionals often migrate to high-income countries in search of better opportunities, leaving a critical gap in expertise

Technological challenges

While high-income countries benefit from cutting-edge diagnostic technologies, many LMICs are limited to unreliable basic utilities. In addition, some advanced diagnostic technologies are not designed for low-resource settings, where electricity, water, and other basic utilities necessary for running high-tech equipment may be unreliable. The lack of appropriate, context-specific technology hinders effective implementation in these regions.

Cultural and social barriers

Limited awareness of the importance of diagnostics in some communities leads to underutilization of available services. Patients and even healthcare providers may not fully understand the role of diagnostics in guiding treatment, resulting in delayed or inappropriate care. In certain cultures, there may be stigma associated with seeking medical care or undergoing diagnostic tests, particularly for infectious diseases like HIV or TB. Misconceptions about the purpose and safety of diagnostics can also deter people from seeking testing.

Regulatory and policy challenges

Many countries lack robust regulatory frameworks for diagnostic testing, leading to variations in the quality and availability of diagnostic services. In some regions, there is also a lack of standardization in diagnostic practices, which can lead to inconsistent results and difficulties in data comparison. Poor governance, including corruption and mismanagement, can undermine efforts to improve diagnostic access. In some cases, resources intended for healthcare infrastructure and diagnostics may be misallocated or siphoned off, further hindering progress.

Sustainability issues

Many initiatives to improve diagnostic access rely on short-term funding from international donors, research collaborators or non-governmental organizations (NGOs). While these initiatives can provide immediate improvements, they often lack sustainability once external funding ends.

In regions where technical support is limited once external funding ends, maintenance of the existing diagnostic systems becomes challenging and equipment deteriorates with time.

Data and surveillance limitations

In many regions, public health surveillance systems are underdeveloped or non-existent, making it difficult to monitor disease trends, track outbreaks, and respond to emerging threats. Even when diagnostics are available, the lack of robust data management systems can hinder the effective use of diagnostic information.

Poor data collection, reporting, and analysis can lead to missed opportunities for public health interventions and policy development.

Political and economic instability

In regions affected by conflict, natural disasters, or economic crises, healthcare infrastructure, including diagnostic services, often collapse. The displacement of populations, destruction of facilities, and disruption of supply chains exacerbate the challenges of providing consistent diagnostic services.

Global disparities in innovation and research

Much of the research and development in microbiology diagnostics is focused on diseases prevalent in high-income countries. Diseases that disproportionately affect LMICs may receive less attention, leading to a lack of appropriate diagnostic tools for these regions. The cost of proprietary diagnostic technologies and the complexities of intellectual property rights can also limit the ability of LMICs to access new and innovative diagnostic tools.

As the burden of infectious diseases is highest in LMICs along with the existing challenges, the pressure on governments, healthcare systems and international organizations increases every year. Overcoming these barriers requires coordinated global efforts to ensure that high-quality microbiology diagnostics are accessible to all, regardless of geographic or economic context.

Strategies for better implementation of microbiology diagnostics

To achieve adequate and equitable access to microbiology diagnostics worldwide, especially in resource-limited settings, and tackle the interconnected challenges and barriers, several strategic directions are essential. These strategies must address both the immediate challenges of access in LMICs and the long-term goals of strengthening healthcare systems to sustain diagnostic capacity.

Developing low-cost, portable diagnostics

The development of low-cost, portable diagnostic tools is essential for reaching populations in remote and resource-limited areas, and implementation of innovative technologies tailored to the challenges of LMICs. The WHO Diagnostic Stewardship, The Lancet Commission on Diagnostics and organizations like Médecins Sans Frontières (MSF) emphasize the need for diagnostic tools that are not only technically advanced, but also designed with the specific needs of these regions in mind. A prime example of this strategy is the Xpert MTB/RIF assay, which is used for the rapid diagnosis of TB and the immediate detection of rifampicin resistance. This has had a profound impact on TB control efforts in resource-constrained settings. Smartphone ownership and use is widespread globally, including in LMICs, and this technology can be used to bridge the gap in diagnostic capacity where expert microbiologists are scarce and reduce inequity. An example initiative is the MSF's Antibiogo application, which allows non-expert technicians to interpret ASTs using a smartphone.

Promoting local manufacturing and innovation

Encouraging local manufacturing and innovation in LMICs is a key strategy to reduce the costs associated with importing diagnostic tools and to improve their availability. By building local capacity, governments can foster innovation that is tailored to the specific needs and conditions of their regions. For example, Biovac is a biopharmaceutical company based in South Africa that is the result of a partnership formed with the South African government in 2003. Its establishment demonstrates the benefits of local production of vaccines and

diagnostics in reducing reliance on imports and ensuring a more consistent supply of critical healthcare products. This approach not only makes diagnostics more affordable but also stimulates the local economy and builds regional expertise and capacity.

Strengthening public-private partnerships

Public-private partnerships (PPPs) can play a vital role in the funding, development, and distribution of diagnostic tools. These collaborations leverage the strengths of both sectors, with public organizations providing regulatory support and funding, and private companies contributing expertise in product development and distribution. The Global Fund's collaboration with private companies like Abbott to improve HIV diagnostics in Africa illustrates the power of PPPs. Through these partnerships, essential diagnostic tools have become more accessible, leading to improved testing and treatment coverage.

Implementing point-of-care testing

As already highlighted, POCTs are affordable, reliable, rapid and easy to use. They are particularly valuable in low-resource settings where access to centralized laboratories is limited and traditional or molecular diagnostics may be out of reach. One of the best examples is the m-PIMA HIV-1/2 VL from Abbott, a POCT viral load assay that has significantly improved the management of HIV patients in sub-Saharan Africa. By enabling healthcare providers to make immediate decisions regarding treatment adjustments, this POCT has enhanced patient outcomes and reduced the time between diagnosis and treatment initiation.

Improving laboratory infrastructure

A significant focus should be placed on enhancing the infrastructure and capacity for diagnostics in LMICs. This involves not only the physical establishment of laboratories but also ensuring that these facilities are equipped with the necessary tools, reagents, technology, and support systems for maintaining and upgrading the technology, that is suitable for the local context. In the example of POCT above, to make the most of this diagnostic capability, it is crucial to ensure the infrastructure is in place for the use of these tools in low-resource and rural areas where they have the greatest impact. International initiatives such as the UK Fleming Fund support infrastructure development in up to 25 countries in Africa and Asia, by providing technical assistance to develop AMR governance systems, and to improve existing capacity for bacteriology diagnostics, AMR reporting and data analysis.

Improving supply chain and distribution networks

Strengthening supply chains and distribution networks is essential for getting tools and reagents to where they are most needed. Efficient supply chains reduce delays in testing and treatment, which is critical during outbreaks of infectious diseases. In the POCT example above, there is no point in having a stock of tests waiting in a central warehouse – they need to be distributed to the low-resource and rural areas where they have the most impact. This is frequently a challenging logistical feat and may be hindered by geography, weather, political systems and war. The WHO Logistics Support System (LSS) has been successfully implemented in various countries to improve the distribution of diagnostics and medicines during outbreaks and has played a key role in controlling the spread of infections during public health emergencies.

Workforce expansion and training

Investing in the training of healthcare workers and laboratory technicians is crucial for ensuring that diagnostic tools are used effectively. Capacity-building initiatives help to improve the accuracy of results, reduce the risk of errors, and enhance the overall quality of healthcare services. The African Society for Laboratory

Medicine (ASLM) provides a model for successful capacity building. Through its training programs across the continent, ASLM has improved the skills of laboratory professionals, building capacity and leading to more reliable diagnostics.

Using artificial intelligence and machine learning

The integration of AI and machine learning in diagnostics has the potential to greatly enhance the speed, accuracy, and accessibility of microbiology diagnostics. AI-driven tools can assist in the analysis of complex data and provide decision support in settings where trained professionals may be scarce. For example, in Rwanda, AI algorithms are being used to analyze digital images of blood samples for the detection of malaria, a technology that provides rapid and accurate diagnostics in rural clinics. By reducing the reliance on human expertise, AI-driven diagnostics can help bridge the gap in healthcare delivery in resource-constrained settings.

Improving data management

The need for improving the surveillance and data collection systems related to microbiology diagnostics and AMR requires collaborative global efforts in building robust data systems. By creating centralized, interoperable databases, countries can share real-time data, and track the spread of infectious diseases and the emergence of resistant strains, which in turn facilitates early detection and response. The Global Antimicrobial Resistance Surveillance System (GLASS) established by WHO is the most extensive example of this. By working with countries to improve data collection and use of AMR, GLASS influences policy decisions and funding allocations for diagnostics. This system has raised awareness about the importance of robust diagnostics in the fight against AMR, leading to increased investment in this area.

Advocating for global health policies

Advocacy for global health policies that prioritize the funding and distribution of microbiology diagnostics is necessary to secure the resources needed for sustained improvements. Policy advocacy and international cooperation are essential to ensure that diagnostics are prioritized within national and international health agendas. This includes advocating for the inclusion of diagnostics in universal health coverage frameworks, thereby making diagnostics more accessible and affordable to all populations, particularly in LMICs. Governments, non-governmental organizations, and international bodies must work together to create policies that support the sustainable development of diagnostic services, including funding mechanisms that ensure continuous access to necessary diagnostic tools and supplies.

Conclusion

Global access to microbiology diagnostics remains a critical challenge, deeply intertwined with broader issues of health equity and social justice. The disparities in access to these essential diagnostic tools reflect and exacerbate existing health inequities, particularly in low- and middle-income countries (LMICs) where infectious diseases impose a heavy burden on public health systems. As this chapter highlights, the barriers to equitable access are multifaceted, encompassing economic, technological, infrastructural, and policy-related dimensions.

Efforts to bridge these gaps require a comprehensive and coordinated approach that addresses both the supply and demand sides of diagnostic services, as well as health policies and strategies.

By addressing the challenges and leveraging the opportunities identified, the global health community can make significant headway toward reducing the disparities in microbiology diagnostics. Such progress will not only improve health outcomes for millions of people, but also contribute to the broader goals of universal health coverage and global health security.

Competing interests

The authors have no financial and non-financial competing interests to declare.

References

1. Santos M, et al. A review on urinary tract infections diagnostic methods: Laboratory-based and point-of-care approaches. J Pharm Biomed Anal. 2022;219:114889.
2. Zengin Canalp H, et al. Direct Rapid Identification from Positive Blood Cultures by MALDI-TOF MS: Specific Focus on Turnaround Times. Microbiol Spectrum. 2021;9:e01103- e01121.
3. Brookes-Howell L, et al. Challenges in managing urinary tract infection and the potential of a point-of-care test guided care in primary care: an international qualitative study. BJGP Open. 2019;3:bjgpopen18X101630.
4. Tai-Han L, et al. Innovative strategies against superbugs: Developing an AI-CDSS for precise Stenotrophomonas maltophilia treatment. J Glob Antimicrob Resist. 2024;38:173-180.
5. Vieceli T, et al. Optimization of antimicrobial prescription in the hospital. Eur J Intern Med. 2022;106:39-44.
6. Abelenda-Alonso G, et al. Multiplex real-time PCR in non-invasive respiratory samples to reduce antibiotic use in community-acquired pneumonia: a randomised trial. Nat Commun. 2024;15:7098.
7. Bryant PA, et al. Prospective study of a real-time PCR that is highly sensitive, specific, and clinically useful for diagnosis of meningococcal disease in children. J Clin Microbiol. 2004;42:2919-2925.
8. Mo Y, et al. Implications of reducing antibiotic treatment duration for antimicrobial resistance in hospital settings: A modelling study and meta-analysis. PLOS Med. 2023;20:e1004013.
9. McMullan BJ, 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:e139-e152.
10. Ierano C, et al. Factors associated with antimicrobial choice for surgical prophylaxis in Australia. JAC Antimicrob Resist. 2020;2:dlaa036.
11. Ibrahim LF, et al. Intravenous ceftriaxone at home versus intravenous flucloxacillin in hospital for children with cellulitis: a cost-effectiveness analysis. Lancet Infect Dis. 2019;19:1101-1108.
12. Australian Commission on Safety and Quality in Health Care. Antimicrobial Stewardship in Australian Health Care. Sydney: ACSQHC; 2023.
13. Shrestha J, et al. Antimicrobial Stewardship. StatPearls Publishing LLC; 2024.
14. Morency-Potvin P, et al. Antimicrobial Stewardship: How the Microbiology Laboratory Can Right the Ship. Clin Microbiol Rev. 2017;30:381-407.
15. Żukowska ME. Advanced methods of bacteriological identification in a clinical microbiology laboratory. Journal of Pre-Clinical and Clinical Research. 2021;15:68-72.
16. Peeling RW, et al. The value of diagnostics in the fight against antimicrobial resistance. GARDP Antimicrobial Viewpoints. 2024. Available at: https://revive.gardp.org/the-value-of-diagnostics-in-the-fight-against-antimicrobial-resistance/. Last accessed: 1 October 2024.
17. Bouza E, et al. Role of the Clinical Microbiology Laboratory in Antimicrobial Stewardship. Med Clin N Am. 2018;102:883-898.
18. World Health Organization. GLASS Manual for Early Implementation. 2016. Available at: https://iris.who.int/bitstream/handle/10665/188783/9789241549400_eng.pdf?sequence=1. Last accessed: 1 October 2024.

19. Fleming KA, et al. The Lancet Commission on diagnostics: transforming access to diagnostics. Lancet. 2021;398:1997-2050.
20. Weiss DJ, et al. Global maps of travel time to healthcare facilities. Nat Med. 2020;26:1835-1838.
21. Vounba P, et al. Microbiology laboratories involved in disease and antimicrobial resistance surveillance: Strengths and challenges of the central African states. Afr J Lab Med. 2022;11:1570.
22. Villalva-Serra K, et al. Impact of Xpert MTB/RIF implementation in tuberculosis case detection and control in Brazil: a nationwide intervention time-series analysis (2011–2022). The Lancet Regional Health – Americas. 2024;36:100804.
23. Diop-Ndiaye H, et al. m-PIMA™ HIV1/2 VL: A suitable tool for HIV-1 and HIV-2 viral load quantification in West Africa. J Virological Methods. 2024;324:114872.
24. Gordon N, et al. The UK Fleming Fund: Developing microbiology laboratory capacity for AMR surveillance. Int J Infect Dis. 2021;101:86.

Chapter 82

The role of microbiologists in tackling antimicrobial resistance

Bih Awazi
Ekoumdoum Baptist Hospital Yaoundé, Cameroon.

Introduction

Antimicrobial resistance (AMR) is one of the most serious global public health threats in this century. Years of unregulated use of antibiotics and other anti-microbial medicines have led to the emergence and rapid spread of AMR. WHO report for 2022-2023 states that AMR is directly responsible for 1.3 million deaths and contributes to 5 million deaths every year. AMR also threatens our economic future, with an estimated global annual cost of up to US$ 3.4 trillion by 2030 and 28 million people pushed into poverty by 2050. It doesn't matter where you live everybody can be affected whether you are in good health or not. AMR is invisible, but its victims are not. AMR occurs when bacteria, viruses, fungi and parasites change over time and no longer respond to medicines making infections harder to treat. AMR is threatening not only our ability to treat infectious diseases but also the entire practice of modern medicine. Unless the emergence and spread of AMR are controlled, it will mean returning to the pre-antibiotic era. It is widely acknowledged that there is a linear relationship between antimicrobial prescribing and the development of AMR. Right now, resistant infections are killing patients at the rate of one every 45 seconds, by 2050; AMR will kill a patient every three seconds.

AMR is so widespread, that clinicians can no longer automatically reach for antibiotics without microbiological investigation or discussion with clinical microbiologists. For this to happen the clinicians must be confident of the quality of clinical microbiology service. Clinicians and microbiologists need to work closely to improve patient care and control antimicrobial resistance. Microbiologists in academic, industrial and clinical settings worldwide are at the forefront of developing innovative solutions to tackle AMR. Constant surveillance of drug-resistant pathogens, supported by good quality diagnostics, is therefore of utmost importance in identifying the prevalence of drug-resistant organisms and forecasting future outbreaks. Surveillance data is also crucial for planning better treatment strategies with an available arsenal of antibiotics and informing R and D requirements for future Antibiotics. Good quality data is only possible through quality diagnostics.

Antimicrobial resistance

Antimicrobial resistance, or AMR, also referred to as drug resistance, is the ability of microbes to grow in the presence of a chemical substance, such as a drug, that would normally kill them or limit their growth. Microbes are constantly evolving or mutating, enabling them to efficiently adapt to new environments. Some of these mutations can confer a survival advantage to the microbe, allowing them to grow in the presence of

a substance that normally kills them. Antibiotic resistance is a form of antimicrobial resistance. Antibiotics are chemical substances that are produced by bacteria or fungi to kill or inhibit the growth of other bacteria in their natural environment.

Antimicrobial medicines including antibiotics, antifungals, antivirals and antiparasites, save millions of lives. However, when bacteria, viruses, fungi and parasites develop the capacity to defeat antimicrobial medicines, these drugs become ineffective, making infections harder or impossible to treat and increasing the risk of disease spread, severe illness and death. Antimicrobial resistance refers to resistance to bacteria, viruses, fungi and parasites. Antibiotic resistance refers specifically to bacteria and is a form of antimicrobial resistance. Antimicrobial-resistant microbes are found in people, animals, food and the environment (in water, soil and air). Overuse and misuse of anti-microbial medicines are among the major factors that have contributed to the development of drug-resistant microbes. Most bacteria multiply every 20 minutes. And every time a person takes antibiotics, sensitive bacteria - that is, bacteria that antibiotics can still attack - are killed, but resistant bacteria are left to grow and multiply. This is how repeated use of antibiotics can increase the number of resistant bacteria.

The development of antimicrobial resistance usually occurs through four major stages as follows:

- STEP 1 - In a population of bacteria, one bacterium acquires resistance mechanisms and becomes resistant.
- STEP 2 - Antibiotic kills off all bacteria except for the antibiotic-resistant bacterium.
- STEP 3 - The antibiotic-resistant bacterium proliferates forming a population of resistant bacteria.
- STEP 4 - The antibiotic-resistant bacterium can transfer resistance genes to other bacteria.

Mechanisms of antimicrobial resistance

The mechanism through which bacteria cells develop resistance can be through any of these ways. The first is a modified cell wall. Some bacteria can modify their cell wall to make it impermeable to antibiotics, such as beta-lactams and vancomycin. Other bacteria can actively pump out antibiotics which have entered the bacteria cell, such as beta-lactams, macrolides, fluoroquinolones, tetracyclines, and aminoglycosides. Another mechanism is that mutations of some bacteria modify molecules used by antibiotics for nucleic acid - for example, fluoroquinolone - or protein synthesis; examples are macrolides, tetracyclines, aminoglycosides, and chloramphenicols. The last common mechanism of antibiotic resistance is antibiotic inactivation. Some bacteria can produce proteins, such as enzymes, that inactivate antibiotics, such as beta-lactams, macrolides, and aminoglycosides before they can act.

The emergence of antibiotic-resistant organisms is a major public health concern, particularly in hospitals and other healthcare settings. Antibiotic-resistant organisms appear to be biologically fit and are capable of causing serious, life-threatening infections that are difficult to manage because treatment options are limited. This increase in the prevalence of drug-resistant pathogens is occurring at a time when the discovery and development of new anti-infective agents is slowing down dramatically. Consequently, there is concern that in the not-too-distant future, we may be faced with a growing number of potentially untreatable infections

Antimicrobial resistance in healthcare settings

Patients in healthcare facilities are commonly exposed to antibiotics and receive lots of hands-on care. Asymptomatic and symptomatic carriers can bring resistant bacteria into healthcare settings and healthcare workers' hands are the most consistent source of transmission, these are factors which can lead to the spread of resistant germs. Good hand hygiene practice is one of the most important things anyone can do to help prevent and control the spread of many illnesses. In the hospital setting, the intensive and prolonged use of antimicrobial drugs is probably the main contributor to the emergence and spread of highly antibiotic-resistant nosocomial infections; but other factors can play an important role: presence of highly susceptible immunosuppressed patients (e.g. AIDS patients, cancer patients, or transplant recipients) and fragile elderly patients, invasive surgical procedures and intensity of clinical therapy, length of stay in hospital, failure to control infections spread from patient to patient.

Below are AMR bacteria that pose a challenge in hospital settings and are responsible for most hospital-acquired infections (HAIs) or healthcare infections. They have been classified on the WHO global priority pathogens list of antibiotic-resistant bacteria. *Enterococcus faecium*, methicillin-resistant *Staphylococcus aureus*, *Enterobacteriaceae* (including *Escherichia coli*, *Serratia*, *Proteus* and *Klebsiella*), Carbapenem-resistant ESBL producing carbapenem resistance, (ESBL - Extended Spectrum Beta-Lactamases), *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, Multidrug-resistant tuberculosis and *Neisseria gonorrhoeae* are currently among the most prevalent bacterial pathogens affected by AMR issues. Some of these microorganisms have become resistant to most antimicrobials and they are referred to as 'SUPER BUGS'.

There are three common clinical syndromes for which antibiotics are commonly given in hospital settings, respiratory infections, urinary tract infections and sepsis. In the syndrome approach to patient management, a patient comes with a syndrome; it might be a fever or a fever and cough or a urethral discharge. A syndrome is a collection of symptoms and signs. The syndromic approach to managing that patient is you try and treat them for all the possible causes of that syndrome. A man came complaining of pain passing urine and urethral discharge. Is it gonorrhoea, is it chlamydia, or is it something else? We don't know. So, we'll treat all of them, we'll give at least two different antibiotics. So clearly, the more antibiotics you give, the more you're promoting antimicrobial resistance. You see a child with a fever; he is most likely to have a viral infection, which doesn't need antibiotics. But you don't know that. The clinical team during this time is trying to determine why the patient is sick and what the patient is sick with, to determine the appropriate treatment. So, could you have a diagnostic test that will say this child probably has a viral infection whereas this child probably has a bacterial infection? It doesn't give you the exact cause, but it helps you decide whether to give an antibiotic, which again will limit the prescription of antibiotics, which is a good thing.

In the lab, once a blood culture turns positive, it will take at least 18 to 24 more hours to determine the pathogen's identification and antimicrobial susceptibility results to tell the clinical team which antibiotics should be used against which bacteria. Before this data is available, the clinical team will often treat empirically, or give broad-spectrum antibiotics that are effective against a wide variety of bacteria. And then once they have data from the lab indicating which bacteria are present, if any and what antibiotics would work best for them, they can then narrow down the antibiotic treatment and tailor treatment to the patient. What the doctors need is better diagnostics to say which infection the patients have. This brings us to these questions; what are diagnostics? And what is the role of the microbiologist in tackling AMR?

Diagnosis

What are diagnostics? A diagnostic test for an infectious disease can be used to demonstrate the presence or absence of infection or to detect evidence of a previous infection - for example, the presence of antibodies. Basic diagnostic methods for infectious diseases typically fall into two different categories. The first category is pathogen detection. One example of this is microscopy, where a sample is put on a slide and someone looks at that sample through a microscope to try and identify it. Another example is culturing organisms on solid or liquid media. This is where the microbiology lab tries to grow organisms in the lab to be able to identify them. Another example is molecular assays that can detect the DNA or RNA of an infectious organism to be able to identify it. And fourth, antigen detection assays can detect proteins present in an infectious organism. The second category of diagnostic methods are host biomarker detection tests. The most common example of this is an antibody detection test that can detect, for example, an IgG antibody or an IgM antibody, which are two types of antibodies that the body produces in response to an infection. Another example of such a test is a test that can identify other biomarkers of infection, such as C reactive protein, which is a protein that the body produces in response to an infection. In terms of characteristics of diagnostic tests, to be useful, diagnostic methods must be accurate and fit for use in the population for which they are intended. In the microbiology laboratory, resistance or susceptibility of bacteria to antimicrobial medicines is usually detected through a two-step process. In the first step, the bacteria of interest have to be identified through culture or molecular methods. Then, in the second step, there are two different ways to detect bacterial resistance. One, bacteria can be cultured in the presence of antibiotics to determine which antibiotics inhibit their growth. This is called Antimicrobial Susceptibility Testing, or AST. The second way is that molecular methods can be used to determine if the bacteria carry any resistance genes. This is called Antimicrobial Resistance Testing, or ART. The MIC, the lowest antimicrobial agent concentration that inhibits microbial growth, can be determined by different methods, such as broth or agar dilution, and disk or gradient diffusion. The MIC value, expressed as mcg/ mL, is often translated by clinical microbiology laboratories as “susceptible,” “intermediate,” or “resistant” according to defined “breakpoints” established by the Clinical and Laboratory Standards Institute (CLSI, Wayne, PA, USA) or “susceptible,” “susceptible, increased exposure,” or “resistant” according to the criteria of the European Committee on Antimicrobial Susceptibility Testing.

Rapid diagnostic testing for possible pathogens is considered indispensable in healthcare settings. Coupled with prompt action and results using rapid diagnostic testing, appropriate therapy and antibiotic use is decreased, mortality is reduced, hospital stays are shortened, and cost is lowered. The lack of availability of modern diagnostic tests represents an important barrier in low-resource settings. Rapid diagnostics may contribute in furtherance by limiting unnecessary initiation of broad-spectrum therapy, thus decreasing the need for subsequent de-escalation. Ideally, the role of a diagnostic test is, you have a diagnostic test that says this patient has pneumonia due to strep pneumonia that is sensitive to Penicillin, and then you administer treatment to the patient. It’s important to select the right diagnostic tests for the right patient and at the right time. We encourage the use of rapid molecular diagnostics to initiate targeted antibiotic therapy. However, equally important is accurate interpretation of test results to prevent overdiagnosis and unnecessary costs.

There are three major ways diagnostics can be used to combat AMR. First, diagnostics are critical in reducing the overuse of antibiotics in clinical medicine. Second, diagnostics can be used to screen for resistant bacteria to prevent their spread in healthcare settings. Finally, diagnostics is the only way to gather data on resistance trends and be alerted to outbreaks.

The role of microbiologists in tackling antimicrobial resistance

The role of the microbiologist is to demonstrate the presence of the infecting organism or a surrogate marker of infection in the patient's sample in the laboratory. This is vital for effective management and for guiding the treatment of infectious diseases. Microbiologists carry out diagnosis in the laboratory using different diagnostic methods for pathogen identification. Clinicians and microbiologists need to work closely to improve patient care and control antimicrobial resistance and for this to be possible, the clinicians should be confident of the quality of clinical microbiology service.

In the microbiology laboratory, accurate diagnosis starts with the proper collection, transportation and handling of specimens together with the provision of relevant clinical information. This means that appropriate specimens are collected, and transported promptly, and relevant clinical information is provided to assist the laboratory. Clinicians frequently provide sparse clinical details when sending the specimens, not realizing that adequate clinical information including previous antibiotic treatment is crucial to laboratory interpretation of the culture results. The role of timely transportation of specimens to the laboratory is often not appreciated. For example, a delay in the transportation of urine specimens may lead to the multiplication of bacteria ex vivo, leading to misleading results and unnecessary antibiotic treatment. Nurses and doctors need to be instructed in how to collect specimens.

The laboratory practice which consists mainly of carrying out diagnosis using any of the test procedures mentioned earlier, must assure the clinicians that the tests will accurately detect most common pathogens that may cause the infection. This means that the laboratory has appropriate processes and, importantly, suitably trained staff (both technical and medical) to provide the service. Presently, more than 70% of medical decisions in hospitals rely on pathology (including microbiology) results; therefore, the laboratory results must be accurate and reliable. The most challenging aspect of microbiology is interpreting the laboratory results. The human body is colonized with, at least, as many bacterial cells (37 trillion cells) as human cells to as many as more than 100 trillion microorganisms according to earlier estimates. Most of the time, these bacteria are harmless when they remain in their natural habitat in the body. At other times, they can cause infection. The clinical microbiologist plays a key role in deciding the clinical significance of the culture result. To do so, the microbiologist should not only have wide clinical knowledge but also work closely with clinicians. For example, *Staphylococcus epidermidis* isolated from the blood culture or tissues is usually a contaminant, but in the context of a patient having a central line, prosthetic vascular grafts or joint replacements, *S. epidermidis* may be significant. Similarly, the culture of *Enterobacteriaceae* from open wounds is not usually significant but may indeed be significant if the specimen was collected appropriately (after irrigation of the wound) and there are local or systemic signs of infection such as spreading cellulitis or fever. Clinical microbiologists are expected to review all serious infections in the wards and discuss the management with clinical colleagues. This gives the opportunity to find out more about the patient understand clinical concerns and advise accordingly. Clinical microbiologists can also discuss the results in daily intensive care, clinical multidisciplinary, and morbidity and mortality meetings. These meetings are particularly useful not only for reviewing infection-related issues in individual patients but also for discussing antimicrobial stewardship and infection control. Clinical microbiologists can advise clinicians on evidence-based antimicrobial prophylaxis for a variety of surgical procedures or infection control measures to prevent the emergence and transmission of healthcare-associated infections.

Discussion

All countries today are grappling with the challenge of anti-microbial resistance. AMR is here in a big way, and we need to focus people on that. The problem is bigger in low-middle-income countries, as we still don't know how big the demon that we are fighting with is. Due to the absence of systematic surveillance systems in low-resource settings, the extent of anti-microbial resistance in LMICs is largely unknown. The true burden of AMR in low- and middle-income countries (LMICs) would remain unknown unless surveillance is resourced adequately. In particular, bacterial identification and susceptibility testing are not performed routinely in LMICs, owing to a lack of personnel, equipment, and supplies; moreover, testing may represent an out-of-pocket expense for patients in some healthcare systems. As a result, antibiotic therapy is mostly empiric and broad-spectrum antibiotics may be misdirected. The resultant suboptimal care of infections can lead to clinical failure, higher mortality, and increased AMR. In many developing countries, excessive use is also due to the easy availability of antimicrobial drugs that can be purchased without the prescription of a physician or other qualified health professional. Some progress has been made in LMICs over the last decade regarding data collection to inform AMR and monitoring of antibiotic use. However, more must be done. The poorest people are particularly vulnerable to the threat of AMR, as poverty increases the risk of contracting infectious diseases and being exposed to antibiotics. A 2018 systematic review by Alividza *et al.* highlighted the complex relationship between AMR and various dimensions of poverty, including education level, income, and housing and water quality. Addressing these disparities will be crucial for reducing the burden of AMR and improving public health outcomes in vulnerable communities. In the community of affluent countries, excessive prescription by general practitioners, even in the absence of appropriate indications, plays an important role in the inappropriate use of antibiotics. Diagnostic uncertainty often fosters over-prescription especially when the clinical picture of viral or bacterial etiology is similar. The inappropriate use of antibiotics is also associated with other common behavior patterns, such as failure to complete the recommended treatment and self-medication also plays an important part. Self-medication with antimicrobials almost always involves unnecessary, inadequate, and ill-timed dosing, creating an ideal environment for microbes to adapt rather than be eliminated.

Conclusion

The clinical microbiologist has a key role to play in tackling AMR, and their responsibilities are as follows; they screen to identify patients who are colonized with healthcare-associated (HAIs) infections so that they can be placed under strict infection prevention and control measures. Identifying infected patients to guide their treatment, and for surveillance. Also, determining the prevalence of HAIs to facilitate IPC strategies related to outbreaks and to assess the impact of interventions. They generate AMR surveillance data which are needed for the development of treatment guidelines and the AMR control strategies.

Clinical microbiologists are unique among hospital-based clinicians because without the laboratory results the doctor is guessing when administering empiric treatment to the patient, which might have a negative effect on the patient's health and lead to AMR. The microbiologist should work very closely with the doctors and nurses in the fight against AMR, which if not handled properly might lead to the next pandemic. The future is in our hands.

WITHOUT THE MICROBIOLOGIST WE ARE BLIND!

Competing interests

The author has no financial and non-financial competing interests to declare.

References

1. Marimuthu K, et al. A meta-analysis of the effect of combinations of immune modulating nutrients on outcome in patients undergoing major open gastrointestinal surgery. Ann Surg. 2012;255:1060-1068.
2. Goltsman D, et al. The Association between Smoking and Plastic Surgery Outcomes in 40,465 Patients: An Analysis of the American College of Surgeons National Surgical Quality Improvement Program Data Sets. Plast Reconstr Surg. 2017;139:503-511.
3. Lefebvre A, et al. Preoperative hair removal and surgical site infections: network meta-analysis of randomized controlled trials. J Hosp Infect. 2015;91:100-108.
4. Seropian R, Reynolds BM. Wound infections after preoperative depilatory versus razor preparation. Am J Surg. 1971;121:251-254.
5. Andersson AE, et al. Traffic flow in the operating room: an explorative and descriptive study on air quality during orthopedic trauma implant surgery. Am J Infect Control. 2012;40:750-755.
6. Smith EB, et al. The effect of laminar air flow and door openings on operating room contamination. J Arthroplasty. 2013;28:1482-1485.
7. Roth JA, et al. Frequent Door Openings During Cardiac Surgery Are Associated With Increased Risk for Surgical Site Infection: A Prospective Observational Study. Clin Infect Dis. 2019;69:290-294.
8. Darouiche RO, et al. Association of Airborne Microorganisms in the Operating Room With Implant Infections: A Randomized Controlled Trial. Infect Control Hosp Epidemiol. 2017;38:3-10.
9. Kang SI, et al. Systematic review and meta-analysis of randomized controlled trials of the clinical effectiveness of impervious plastic wound protectors in reducing surgical site infections in patients undergoing abdominal surgery. Surgery. 2018;164:939-945.
10. Sartelli M, et al. Surgical Antibiotic Prophylaxis: A Proposal for a Global Evidence-Based Bundle. Antibiotics (Basel). 2024 Jan;13:100.
11. Sartelli M, et al. Six Long-Standing Questions about Antibiotic Prophylaxis in Surgery. Antibiotics (Basel). 2023;12:908.

Chapter 83

How rapid diagnostics can influence antibiotic-decision making

Mohammad Tahir Siddiqui
Department of Biochemical Engineering and Biotechnology, Indian Institute of Technology Delhi, New Delhi, India.

Sidra Ghazali Rizvi
Department of Biochemical Engineering and Biotechnology, Indian Institute of Technology Delhi, New Delhi, India.

Qazi Mohammad Rizwanul Haq
Department of Biosciences, Jamia Millia Islamia (A Central University), New Delhi, India.

T.R. Sreekrishnan
Department of Biochemical Engineering and Biotechnology, Indian Institute of Technology Delhi, New Delhi, India.

Shaikh Ziauddin Ahammad
Department of Biochemical Engineering and Biotechnology, Indian Institute of Technology Delhi, New Delhi, India.

Introduction

Antimicrobial resistance (AMR) is a pressing global health crisis with far-reaching effects on public health, clinical outcomes, and economic stability. The overuse and misuse of antibiotics are key contributors to AMR, particularly when infections are treated empirically without sufficient diagnostic information. Many infections, including viral and fungal respiratory conditions, often present similarities to bacterial infections, complicating accurate diagnosis and leading to inappropriate antibiotic use. For example, viral respiratory infections can mimic symptoms of bacterial infection, and fungal infections like invasive aspergillosis or *Candida* sepsis can also be mistaken for the same infection. This misdiagnosis can result in unnecessary broad-spectrum antibiotic use, thereby increasing resistance and negatively impacting patient outcomes.

Timely and precise diagnosis is essential for effective antimicrobial stewardship, a strategy focused on optimizing antibiotic use to combat resistance while ensuring the best patient outcomes. However, traditional microbiology methods, which can take up to 96 hours for pathogen identification and additional days for drug susceptibility testing, often necessitate empirical treatment, particularly in critical cases such as sepsis. This reliance on empirical therapy promotes AMR by compelling unnecessary antibiotic use. Rapid diagnostic

tests (RDTs) address this issue by reducing the time to appropriate therapy, minimizing broad-spectrum antibiotic use, and guiding de-escalation or treatment discontinuation.

RDTs are central to policies aimed at tackling AMR. The U.S. National Action Plan for Combating Antibiotic-Resistant Bacteria stresses the need for rapid diagnostics to distinguish bacterial from viral infections and detect resistant pathogens. Similarly, the WHO's Global Action Plan on Antimicrobial Resistance calls for integrating cost-effective rapid diagnostics into clinical and veterinary practices to guide optimal antibiotic use. While RDTs offer significant benefits, their global integration into antimicrobial stewardship programs (ASPs) remains limited. The COVID-19 pandemic has highlighted the crucial role of rapid diagnostics in managing infectious disease outbreaks, but further advancements and broader adoption are needed to fully leverage RDTs in the fight against AMR.

This chapter explores the transformative impact of RDTs on antibiotic usage decision-making and antimicrobial stewardship, examining how they enhance diagnostic accuracy, reduce unnecessary antibiotic use, and improve patient outcomes. Additionally, it discusses the challenges and future directions for integrating RDTs into healthcare systems to better address AMR.

Rapid diagnostic tests for infections

Bloodstream infections

Bloodstream infections (BSIs), caused by bacteria (bacteremia) or fungi (fungemia), are systemic in nature and can arise from various sources such as infections elsewhere in the body, catheter use, contaminated procedures, or skin breaches. BSIs are severe, with high global morbidity and mortality. Blood cultures, the standard diagnostic tool, have limitations including slow turnaround and reduced sensitivity, with estimates as low as 50%.

RDTs enhance pathogen detection sensitivity and reduce result reporting times. Molecular RDTs address issues like infection from coagulase-negative staphylococci and provide actionable insights earlier than traditional methods. They are associated with faster effective therapy, reduced hospital length of stay (LOS), and decreased mortality when used with antimicrobial stewardship programs (ASPs). Cost-effectiveness analysis supports their benefits, showing an 80% chance of cost-effectiveness with ASPs, compared to 41.1% without. Automated phenotypic systems like the Accelerate PhenoTest can identify organisms and determine susceptibility within 7 hours after a positive blood culture.

Various RDT technologies for BSIs include PCR-based methods (e.g., BioFire FilmArray BCID, GenMark ePlex BCID), nanoparticle probes (e.g., VERIGENE BC-GP, BC-GN), MALDI-TOF (e.g., BioMérieux, BD Bruker), magnetic resonance (e.g., T2Candida, T2Bacteria), and morphokinetic analysis (e.g., Accelerate PhenoTest BC Kit). The T2 panels, FDA-approved for direct whole blood processing, are crucial for rapid result reporting in severe infections but detect fewer pathogens than larger panels like ePlex. Among RDTs processing positive blood cultures, detection time differences are minimal, with BioFire BCID2 offering the fastest turnaround (1 hour). Some RDTs are not FDA-cleared for all pathogens or may have limitations in distinguishing certain bacteria. For instance, the VERIGENE Bloodstream Infections Testing Panel does not identify *Serratia marcescens* or *Micrococcus* species and cannot differentiate *Escherichia coli* from *Shigella*. Only BioFire BCID2 and ePlex BCID can identify *Stenotrophomonas maltophilia*. New developments like the FAST-ID BSI Panel (Qvella) aim to further reduce result times to under 1 hour, potentially improving outcomes, especially in critically ill patients. Additionally, RDTs can aid in early discontinuation of empirical therapy, as seen with the T2Candida panel reducing antifungal days compared to beta-D-glucan testing. The Fungitell STAT assay provides rapid invasive candidiasis screening through beta-D-glucan detection.

Retrospective studies have demonstrated the effectiveness of various RDTs. The VERIGENE BC-GN panel identified 87% of Gram-negative cultures accurately and reduced identification time compared to traditional methods. The BioFire and VERIGENE panels showed faster pathogen identification and better outcomes than traditional cultures. The ePlex BCID panels also performed well, with a high percentage of agreement for Gram-positive and Gram-negative bacteria. The T2Candida and T2Bacteria panels offered quicker pathogen identification than traditional methods. The Accelerate PhenoTest system provides organism identification and susceptibility testing within 7 hours, significantly improving antibiotic decision-making.

Respiratory tract infections (RTIs)

Respiratory tract infections (RTIs) are a major global health concern, causing significant morbidity and mortality. Their incidence varies based on factors such as socioeconomic status, population density, and geographic location, with denser populations and cold, dry climates posing higher risks. Additional factors, including age, chronic lung disease, smoking, and immunocompromised conditions, also increase susceptibility to RTIs. RTIs are classified into upper respiratory tract infections (URTIs), such as influenza and pharyngitis, and lower respiratory tract infections (LRTIs), including pneumonia and bronchitis.

Historically, RTI diagnosis relied on traditional culture methods, which took 24 to 48 hours for microorganism identification and another 24 to 48 hours for antimicrobial susceptibility testing. During this period, patients often received empiric antibiotics, which are suboptimal or overly broad-spectrum, contributing to antimicrobial resistance (AMR) and adverse effects like *Clostridioides difficile* infections. The introduction of novel molecular testing methods, such as multiplex PCR assays, has significantly improved diagnostic accuracy and reduced inappropriate antibiotic use.

URTIs are predominantly viral, with bacterial infections accounting for fewer than 10% of cases. Despite this, the over-prescription of antibiotics for URTIs has been persistent, partly due to the slow turnaround times of traditional diagnostics. The increased availability of RDTs has enhanced the appropriateness of antibiotic use for URTIs by quickly distinguishing viral from bacterial infections.

Several RDT panels for URTIs, such as the VERIGENE Respiratory Pathogens Flex Test, NxTAG Respiratory Pathogen Panel, BioFire Respiratory 2.1 (RP2.1) Panel, and others, are crucial in reducing unnecessary antibiotic use. These panels detect viral pathogens like influenza A and B, respiratory syncytial virus (RSV), and human parainfluenza viruses (HPIV). However, the panels differ in technology, turnaround times, and pathogen detection capabilities. For instance, the BioFire RP2.1 Panel was the first FDA-cleared RDT to identify SARS-CoV-2, while the NxTAG Respiratory Pathogen Panel can identify bocavirus, which other panels may not. The turnaround time for these RDTs ranges from 15 minutes to several hours, much faster than traditional diagnostic methods.

These RDTs demonstrate high sensitivity and specificity. For example, the BioFire RP2.1 Panel has a sensitivity of 97.1% and a specificity of 99.3%, while the NxTAG Respiratory Pathogen Panel achieves similar accuracy. Studies have confirmed the diagnostic accuracy of the ePlex Respiratory Pathogen Panel, which showed 97.4% agreement with real-time PCR assays and detected 17 more pathogens than traditional methods. Another study compared the ePlex Respiratory Pathogen Panel with the BioFire RP2.1 for detecting viral and bacterial respiratory pathogens, showing over 95% agreement for all targets.

Other infections

RDTs are also used for diagnosing infections beyond bloodstream and respiratory tract infections.

Meningitis. The BioFire FilmArray Meningitis/Encephalitis (ME) Panel detects 14 pathogens from cerebrospinal fluid (CSF) with 90% sensitivity and 97% specificity.

Group B *Streptococcus* (GBS). The ARIES GBS assay detects GBS from vaginal-rectal swabs in about 18-24 hours, with high sensitivity (96.1%) and specificity (91.4%).
Gastrointestinal and joint infections. RDTs such as the VERIGENE Enteric Pathogens Test and BioFire Joint Infection Panel are used for rapid diagnosis.
***Clostridioides difficile*.** Tests like the VERIGENE *C. difficile* Test and Xpert *C. difficile* BT offer rapid detection.
In summary, RDTs enhance the rapid identification of bacterial, viral and other infections, offering significant improvements in diagnostic speed and accuracy compared to traditional methods. These advancements have the potential to guide timely treatment decisions, optimize antimicrobial use, and improve patient outcomes.

Rapid diagnosis in antimicrobial resistance

Antimicrobial resistance (AMR) arises through several mechanisms, including enzymatic inactivation (e.g., TEM, SHV, CTX-M, NDM, IMP, VIM, AmpC, OXA), alterations in membrane permeability (e.g., porin loss), efflux pump overexpression, target site modification, and bypass of inhibition. These mechanisms contribute to increased healthcare costs, morbidity, and mortality. Traditionally, antimicrobial susceptibility testing (AST) is performed using methods such as the broth microdilution (BMD) method, which determines the minimum inhibitory concentration (MIC) and guides treatment decisions. The BMD method is considered the gold standard due to its quantitative MIC values, but it can be time-consuming, taking 2-3 days for results. The Kirby-Bauer disk diffusion method, developed in 1940, is also widely used but provides qualitative results based on zones of inhibition and similarly requires 2-3 days for results. RDTs have emerged as a solution to expedite the detection of antimicrobial resistance, significantly shortening the turnaround time from days to hours.

Molecular testing
Molecular RDTs detect resistance-associated genes or mutations through technologies such as PCR and probes. These methods provide rapid results but cannot confirm antimicrobial susceptibility and are limited to detecting predefined resistance markers. Notable examples include:
PCR-based RDTs: BioFire FilmArray Pneumonia Panel, BioFire BCID2 Panel, ePlex Blood Culture Identification panels.
Nanoparticle probe-based RDTs: VERIGENE Bloodstream Infections Testing panels.

Phenotypic testing
Phenotypic RDTs assess microbial growth in the presence of antimicrobial agents, providing both susceptibility and resistance information. These tests offer a more comprehensive assessment compared to molecular tests. The Next Generation Phenotyping (NGP) System and the Accelerate PhenoTest BC Kit provide AST results within 5-7 hours. The Accelerate PhenoTest BC Kit also identifies pathogens, making it a versatile tool for rapid diagnosis. Phenotypic methods are particularly useful for detecting resistance in organisms with multiple resistance mechanisms.

Mass spectrometry
MALDI-TOF mass spectrometry identifies microorganisms and detects resistance patterns based on their unique protein profiles. Despite its ability to identify organisms quickly, its turnaround time is relatively slow compared to other RDTs. MALDI-TOF methods are commonly used for pathogen identification but are less effective for direct susceptibility testing.

DNA-sequencing technologies

Next-generation sequencing (NGS) provides detailed information on pathogen resistance by analyzing whole genomes. Although NGS offers comprehensive insights, it is costly and has a slower turnaround time. The Karius test and Clear Dx Surveillance are examples of NGS platforms. The Karius test identifies over 100 pathogens from blood samples, while Clear Dx Surveillance provides complete bacterial isolate characterization in about 27 hours. However, neither method confirms antimicrobial susceptibility.

Immunochromatographic assays

These lateral flow tests use antibodies to detect specific resistance-associated antigens. They are simple to perform, with a fast turnaround time. For example, the NG-Test CARBA 5 detects carbapenemase-producing bacteria and is straightforward to use, requiring minimal training and equipment.

Bacteriophage technology

The cobas vivoDx MRSA test utilizes bacteriophage technology to detect MRSA in nasal swabs. It involves inserting a plasmid into *S. aureus* that produces bioluminescence upon substrate addition. While this method is innovative and offers unique applications, its turnaround time of about 5 hours is slower compared to other RDTs, and it does not provide susceptibility information.

Impact of RDTs on antimicrobial stewardship

Antimicrobial stewardship (AMS) encompasses coordinated efforts to enhance the appropriate use of antibiotics, aiming to optimize drug regimens, including dosing, duration, and route of administration. The primary objectives of AMS programs are to improve patient outcomes, reduce adverse drug events, limit infections, and mitigate the emergence of antibiotic resistance. RDTs align with these AMS goals by accelerating the identification of pathogens and resistance markers, ultimately contributing to improved patient management.

Literature highlights the advantages of molecular RDTs in blood cultures, showing significant improvements in time to optimal antibiotic therapy, recurrent infection rates, mortality, hospital length of stay, and costs. Recent IDSA AMS guidelines recommend using RDTs on blood specimens to enhance antibiotic therapy and patient outcomes. Below, we review evidence on the impact of RDTs with and without AMS interventions, focusing on blood specimens.

Studies have explored various combinations of RDTs and AMS interventions. Bauer *et al.* found that rapid PCR testing for methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-susceptible *Staphylococcus aureus* (MSSA) from blood cultures, combined with AMS pharmacist intervention, significantly reduced time to therapy and hospital costs. Similarly, evaluations of MALDI/TOF plus AMS interventions in patients with bacteremia or candidemia revealed reduced times to organism identification and effective therapy, alongside decreased hospital stays and costs.

In resource-limited settings, RDTs still offer benefits, even without direct AMS intervention. Turner *et al.* demonstrated that PCR for *S. aureus* bacteremia led to a significant reduction in time to optimal therapy, though the effect was modest without AMS support. Bhowmick *et al.* compared PCR alone with PCR plus AMS intervention and found the most substantial reduction in time to directed therapy with the combined approach. Another study assessing various intervention sequences showed that RDT plus AMS led to the fastest time to effective therapy and higher rates of antimicrobial de-escalation.

Despite these benefits, observational studies have limitations. Banerjee *et al.* conducted a randomized trial comparing standard culture processing, rapid multiplex PCR with templated comments, and rapid PCR with real-time AMS feedback. This study found that while RDTs improved outcomes and reduced broad-spectrum antibiotic use, the addition of AMS further enhanced the time to antimicrobial de-escalation. A meta-analysis corroborated these findings, showing decreased mortality risk with RDTs used in conjunction with AMS programs, whereas RDTs alone did not significantly impact mortality compared to traditional methods.

Recent research has explored the impact of new technologies such as Accelerate Pheno™. Henig *et al.* assessed its potential effect on time to effective therapy in drug-resistant Gram-negative bacteremia, noting improvements even when combined with other RDTs. However, its impact on time to effective therapy was minimal when considering the use of existing molecular RDTs. Another study found that Accelerate Pheno™ implementation led to reduced time to optimal therapy, hospital length of stay, and antibiotic duration compared to conventional methods.

Overall, while RDTs alone can modestly improve time to optimal therapy, combining them with AMS interventions provides the most substantial benefits, enhancing patient outcomes and optimizing antimicrobial use.

The future state of RDT and AMS integration

Future advancements in clinical care for infectious diseases will hinge on the progress of RDTs and clinicians' ability to act on rapid results. Traditionally, RDTs follow positive blood culture signals, leading to delays in pathogen identification and resistance information. This delay can be critical, as each hour without appropriate antibiotics increases the mortality risk in septic shock. Faster microbiological results are essential for targeted therapy, rather than relying solely on broad-spectrum antibiotics.

Recent innovations include the FDA-approved GenMark ePlex® panels for blood cultures, which cover a wide range of bacterial and fungal targets. These panels offer comprehensive PCR-based assays but still depend on positive blood culture signals. The T2Candida® and T2Bacteria® panels represent a significant advancement, providing direct pathogen identification from blood without waiting for blood cultures to signal positivity. T2Candida® has shown promise in detecting candidemia and monitoring treatment response.

While these technologies are promising, their cost-effectiveness and integration into clinical practice need further evaluation. Administrators require robust data to justify the expense, and more research is needed to determine the best way to incorporate RDT results into clinical decision-making and AMS support. For instance, studies suggest that T2Candida® may improve antifungal therapy timing when combined with AMS support, but large-scale clinical studies are needed.

Ideally, future RDTs will provide rapid, accurate pathogen identification and antimicrobial susceptibility testing directly from clinical specimens. Such advancements could reduce both under-treatment and over-treatment by offering timely, precise diagnostic information. The integration of RDTs with AMS programs will require collaboration between AMS experts and clinical microbiologists for effective implementation and interpretation of results.

In summary, as RDT technology evolves, its integration into AMS programs will likely become standard practice across various healthcare settings. This shift promises significant improvements in patient outcomes and cost savings, but more evidence is needed to confirm the benefits and guide implementation strategies.

Conclusion

The rapid advancement of RDTs represents a transformative leap in the realm of infectious disease management. By significantly reducing the time between specimen collection and the availability of results, RDTs offer a critical advantage over traditional culture methods. Unlike conventional approaches that require extended incubation periods, non-culture-based RDTs provide near-instantaneous insights into causative pathogens, susceptibility profiles, and resistance markers. This swift turnaround not only accelerates the initiation of targeted therapies but also curtails the reliance on inappropriate antimicrobial agents, thereby mitigating the risks associated with delayed or incorrect treatment (**Table 1** and **Table 2**).

Furthermore, RDTs are instrumental in reducing the unnecessary use of empirical antimicrobial therapy, thus supporting more precise and effective treatment regimens. The accuracy and rapidity demonstrated by these tests underscore their potential to enhance patient outcomes and optimize antimicrobial stewardship. Moving forward, the challenge lies in developing and implementing cost-effective RDT solutions that can be seamlessly integrated into clinical microbiology laboratories. By focusing on these advancements, we can leverage RDTs to drive significant improvements in patient care and infection management.

Competing interests

The authors have no financial and non-financial competing interests to declare.

Acknowledgments

SGR would like to acknowledge the Ministry of Human Resources and Development for financial assistance in the form of a fellowship.

Table 1. Diagnostic platforms and turnaround time for infectious diseases and gastrointestinal infections.

Diagnostic platform	Pathogen type	Turnaround time
Accelerate Pheno™ by Accelerate Diagnostics	Bacteria, Fungi	1.5 - 7 hrs
BacT/ALERT® VIRTUO® by bioMérieux®	Initial detection of bacteremia and fungemia	6 – 48 hrs
Determine™ HBsAg 2 by Abbott	Hepatitis B Virus	15 mins
Enterococcus QuickFISH by OpGen®	Gram-positive bacteria	20 mins
ePlex® BCID panel by GenMark Diagnostics, Inc.	Bacteria, Fungi, Resistance Genes	1.5 hr
FilmArray® Blood Culture Identification Panel 2 (BCID2) by BioFire® Diagnostics	Bacteria, Fungi, Resistance Genes	1 hr
FilmArray® Blood Cultures Identification (BCID) by BioFire® Diagnostics	Bacteria, Fungi, Resistance Genes	1 hr
Gram-Negative QuickFISH by OpGen®	Gram-Negative Bacteria	20 mins
HTLV-I/II ELISA by Abbott	Human T-lymphotropic Virus type I and II	3-4 hrs
MagicPlex™ Sepsis Real-time Test by Seegene	Bacteria, Fungi, Resistance Genes	6-7 hrs
MALDI/TOF by Biomerieux, Bruker	Bacteria, Fungi	>30 mins
NG-Test® CARBA 5 by NG Biotech	*Enterobacterales* and *P. aeruginosa* having Carbapenemase enzymes	15 mins
OraQuick® HCV Rapid Antibody Test by OraSure Technologies	Hepatitis C Virus	20-40 mins
Prove-it™ Sepsis by Mobidiag® Ltd.	Bacteria, Fungi, Resistance Genes	3-5 hrs
Verigene® Gram-Positive Blood Culture (BC-GP) by Luminex®	Gram Positive Bacteria, Resistance Genes	2-2.5 hrs
Verigene® BC-GP2 and BC-GN2 Panels by Luminex®	Gram Positive Bacteria, Resistance Genes	2-2.5 hrs
VITEK® MS by bioMérieux®	Bacteria, Fungi	<1hr
Xpert® MRSA/SA BC by Cepheid	*S. aureus* (MSSA and MRSA)	1 hr
ARIES C. difficile assay by Luminex®	*C. difficile*	2 hrs
ARIES® GI panel assay by Luminex®	Viruses, Bacteria, Bacterial Toxins, Parasites	2 hrs
BDMAX™ Cdiff by Becton, Dickinson (BD)	*C. difficile* toxin B gene (tcdB)	3 hrs
BDMax™ Enteric Bacterial Panel by Becton, Dickinson	Bacteria	2-3 hrs
BD MAX™ Enteric Parasite Panel by Becton, Dickinson	Parasites	2-3 hrs
BD MAX™ Enteric Viral Panel by Becton, Dickinson	Viruses	2-3 hrs
FilmArray® Gastrointestinal (GI) Panel by bioMérieux	Bacteria, Viruses, Parasites	1 hr
Illumigene® by Meridian Bioscience®, Inc.	*C. difficile* (*c. difficile* toxin A and B genes)	1 hr
Solana® C. difficile Assay by Quidel Corporation	*C. difficile* (*C. difficile* toxin genes tcdB)	40 mins
Verigene® C. difficile Test by Luminex®	*C difficile* (*C. difficile* toxin genes tcdB)	1.5 hrs
Xpert® C. difficile by Cepheid®	*C. difficile* toxin B gene (tcdB), Binary toxin genes (cdtA and cdtB)	1 hr
Xpert® EV by Cepheid®	Norovirus (Genogroups I and II), Rotavirus, Astrovirus, and Sapovirus	1 hr
Xpert® Norovirus by Cepheid®	NOROVIRUS (Genogroups I and II).	1 hr
xTAG® by Luminex®	Bacterial toxins, Viruses, Parasites	6 hrs

Table 2. Diagnostic platforms and turnaround time for respiratory, central nervous system, sexually transmitted, and vector-borne diseases.

Diagnostic platforms	Pathogen type	Turnaround time
ARIES® by Luminex®	Bacteria, Viruses	2 hrs
BD Veritor™ Plus System for Group A Streptococcus by Becton Dickinson (BD)	*S. pyogenes*	15 mins
BD Veritor™ Plus System for SARS-CoV-2, Influenza A & Influenza B by Becton Dickinson (BD)	SARS-CoV-2, Influenza A, Influenza B	15 mins
BinaxNOW™ COVID-19 Ag Card 2 by Abbott	SARS-CoV-2 virus	15 mins
BioCode® Respiratory Pathogen Panel by Applied Bio-Code®	Bacteria, Viruses	5 hrs
Cobas® SARS-CoV-2, Influenza A/B & RSV by Roche	SARS-CoV-2, Influenza A, Influenza B, Respiratory Syncytial Virus (RSV)	1.5 hrs
FilmArray® Respiratory Panel 2.1 by Biofire®	Bacteria, Viruses	1 hr
GenMark ePlex® by GenMark Diagnostics, Inc.	Bacteria, Viruses	1 hr
Liat™ Influenza A/B & RSV Assay by Roche	Influenza A/B and RSV	20 mins
NxTAG® By Luminex®	Bacteria, Viruses	1 to 3 hrs
Simplexa™ Flu A/B & RSV Direct by DiaSorin Molecular	Influenza A/B and RSV	1 hr
Solana® RSV Assay by Quidel Corporation	Influenza A/B, RSV and hMPV	45 mins
Verigene® RP Flex Test by Luminex®	Bacteria, Viruses	1-2 hrs
Xpress Flu by Cepheid®	Influenza A and Influenza B viruses	30 mins
Xpert Xpress Flu/RSV by Cepheid®	SARS-CoV-2, Influenza A/B, RSV	30 mins
xTAG® Respiratory Pathogen Panel by Luminex®	Bacteria, Viruses	5-6 hrs
xTAG® RVP Respiratory Viral Panel by Luminex®	Viruses	4-5 hrs
FilmArray® by BioFire Diagnostics	Bacteria, Viruses, Fungi, Parasites	1 hr
Xpert® EV by Cepheid®	Enterovirus RNA in CSF	2 hrs
Xpert® HSV-1/2 by Cepheid	*HSV-1, HSV-2*	2 hrs
GeneXpert® MTB/RIF Assay by Cepheid®	M. TUBERCULOSIS rpoB	2 hrs
Alere Determine™ HIV-1/2 Ag/Ab Combo by Abbott	HIV-1, HIV-2	20 mins
Aptima® Combo 2 Assay by Hologic®	*C. trachomatis* and *N. gonorrhoeae*	3 hrs
APTIMA® HIV-1 Quant Dx Assay by Hologic®	HIV-1	3 hrs
APTIMA® Trichomonas vaginalis Assay by Hologic®	*T. vaginalis*	3 hrs
BD MAX™ CT/GC/TV by Becton, Dickinson (BD)	*C. trachomatis*, *N. gonorrhoeae*, *T. vaginalis*	2 hrs
BinaxNOW® HIV-1/2 Ag/Ab Combo by Abbott	HIV-1, HIV-2	20 mins
BioPlex 2200 Syphilis Total & RPR by Bio-Rad	*T. pallidum*	1 hr
GeneXpert® HPV by Cepheid®	HPV16, 18/45, and other high-risk types	1 hr
Illumigene® Chlamydia by Meridian Bioscience®	*C. trachomatis*	45 mins
Illumigene® Group B Streptococcus (GBS) by Meridian Bioscience®	*S. agalactiae*	45 mins
Illumigene® Mycoplasma genitalium by Meridian Bioscience®	*M. genitalium*	45 mins
OraQuick® HIV Self-Test by OraSure Technologies®	HIV-1, HIV-2	20 mins
VERSANT® HIV-1 RNA 1.0 Assay by Siemens Healthineers	HIV-1	2-3 hrs
Xpert® CT/NG by Cepheid®	*C. trachomatis* and *N. gonorrhoeae*	90 mins
BinaxNOW™ Malaria Test by Abbott	*P. falciparum, P. vivax*	15 mins
Chikungunya IgM Combo Rapid Test by SD Biosensor	Chikungunya Virus	15 mins
SD BIOLINE Dengue Duo by Abbott	Dengue Virus (serotypes 1-4)	15 mins
Sofia 2 Lyme FIA by Quidel	*B. burgdorferi*	15 mins
Zika Detect™ Test by InBios International, Inc.	Zika Virus	15 mins

References

1. Denning DW, et al. Delivering on Antimicrobial Resistance Agenda Not Possible without Improving Fungal Diagnostic Capabilities. Emerg Infect Dis. 2017;23:177-183.
2. Zumla A, et al. Rapid point of care diagnostic tests for viral and bacterial respiratory tract infections--needs, advances, and future prospects. Lancet Infect Dis. 2014;14:1123-1135.
3. Benedict K, et al. Emerging issues, challenges, and changing epidemiology of fungal disease outbreaks. Lancet Infect Dis. 2017;17:e403-e411.
4. Mehrotra A, et al. Tipping the Balance Toward Fewer Antibiotics. JAMA Intern Med. 2016;176:1649-1650.
5. Bauer KA, et al. Review of rapid diagnostic tests used by antimicrobial stewardship programs. Clin Infect Dis. 2014;59 Suppl 3:S134-S145.
6. Doernberg SB, et al. Antimicrobial Stewardship Approaches in the Intensive Care Unit. Infect Dis Clin North Am. 2017;31:513-534.
7. Daniel Markley J, et al. De-escalating Antibiotic Use in the Inpatient Setting: Strategies, Controversies, and Challenges. Curr Infect Dis Rep. 2017;19:17.
8. Goff DA, et al. Eight Habits of Highly Effective Antimicrobial Stewardship Programs to Meet the Joint Commission Standards for Hospitals. Clin Infect Dis. 2017;64:1134-1139.
9. Moore LSP, et al. Rapid Diagnostic Test Value and Implementation in Antimicrobial Stewardship Across Low-to-Middle and High-Income Countries: A Mixed-Methods Review. Infect Dis Ther. 2023;12:1445-1463.
10. World Health Organization. Antimicrobial stewardship programmes in health-care facilities in low- and middle-income countries: a WHO practical toolkit. Geneva: World Health Organization; 2019.
11. Willemsen A, et al. A review of national action plans on antimicrobial resistance: strengths and weaknesses. Antimicrob Res Infect Control. 2022;11:90.
12. Rizvi SG, et al. COVID-19 and antimicrobial resistance: A cross-study. Sci Tot Environ. 2022;807:150873.
13. Tan CCS, et al. No evidence for a common blood microbiome based on a population study of 9,770 healthy humans. Nat Microbiol. 2023;8:973-985.
14. Viscoli C. Bloodstream Infections: The peak of the iceberg. Virulence. 2016;7:248-251.
15. Santella B, et al. Sepsis—A Retrospective Cohort Study of Bloodstream Infections. Antibiotics (Basel). 2020;9:851.
16. Timsit J-F, et al. Bloodstream infections in critically ill patients: an expert statement. Intens Care Med. 2020;46:266-284.
17. Murray PR, et al. Current approaches to the diagnosis of bacterial and fungal bloodstream infections in the intensive care unit. Crit Care Med. 2012;40:3277-3282.
18. Brun-Buisson C, et al. Incidence, Risk Factors, and Outcome of Severe Sepsis and Septic Shock in Adults: A Multicenter Prospective Study in Intensive Care Units. JAMA. 1995;274:968-974.
19. Timbrook TT, et al. The Effect of Molecular Rapid Diagnostic Testing on Clinical Outcomes in Bloodstream Infections: A Systematic Review and Meta-analysis. Clin Infect Dis. 2016;64:15-23.
20. Pliakos EE, et al. The Cost-Effectiveness of Rapid Diagnostic Testing for the Diagnosis of Bloodstream Infections with or without Antimicrobial Stewardship. Clinic Microb Rev. 2018;31:10.1128/cmr.00095-17.
21. Brosh-Nissimov T, et al. Clinical impact of the accelerate PhenoTest® BC system on patients with gram-negative bacteremia and high risk of antimicrobial resistance: a prospective before-after implementation study. Ann Clin Microbiol Antimicrobi. 2023;22:62.
22. Kumar A. Early Antimicrobial Therapy in Severe Sepsis and Septic Shock. Curr Infect Dis Rep. 2010;12:336-344.
23. Claeys KC, et al. Day at the Races: Comparing BioFire FilmArray Blood Culture ID Panels With Verigene Blood Culture Panel in Gram-Negative Bloodstream Infections Using DOOR-MAT Analysis. Clin Infect Dis. 2021;73:1103-1106.
24. Gill CM, et al. T2 Candida versus beta-D-glucan to facilitate antifungal discontinuation in the intensive care unit. Diagn Microbiol Infect Dis. 2019 Oct;95(2):162-165.

25. Bassetti M, et al. A multicenter multinational study of abdominal candidiasis: epidemiology, outcomes and predictors of mortality. Int Care Med. 2015;41:1601-1610.
26. Lamoth F, et al. Assessment of the Role of 1,3-β-d-Glucan Testing for the Diagnosis of Invasive Fungal Infections in Adults. Clinical Infectious Diseases. 2021;72:S102-S108.
27. Walker T, et al. Clinical Impact of Laboratory Implementation of Verigene BC-GN Microarray-Based Assay for Detection of Gram-Negative Bacteria in Positive Blood Cultures. J Clinic Microbiol. 2016;54:1789-1796.
28. Ward C, et al. Performance evaluation of the Verigene® (Nanosphere) and FilmArray® (BioFire®) molecular assays for identification of causative organisms in bacterial bloodstream infections. Eur J Clin Microbiol Infect Dis. 2015;34:487-496.
29. Huang T-D, et al. Evaluation of the ePlex Blood Culture Identification Panels for Detection of Pathogens in Bloodstream Infections. J Clin Microbiol. 2019;57:10.1128/jcm.01597-18.
30. Nguyen MH, et al. Performance of the T2Bacteria Panel for Diagnosing Bloodstream Infections: A Diagnostic Accuracy Study. Ann Intern Med. 2019;170:845-852.
31. Krifors A, et al. T2Candida Assay in the Diagnosis of Intraabdominal Candidiasis: A Prospective Multicenter Study. J Fungi. 2022;8:86.
32. Banerjee R, et al. Randomized Trial Evaluating Clinical Impact of RAPid IDentification and Susceptibility Testing for Gram-negative Bacteremia: RAPIDS-GN. Clin Infect Dis. 2020;73:e39-e46.
33. MacVane SH, et al. Time to Result for Pathogen Identification and Antimicrobial Susceptibility Testing of Bronchoalveolar Lavage and Endotracheal Aspirate Specimens in U.S. Acute Care Hospitals. J Clin Microbiol. 2020;58:10.1128/jcm.01468-20.
34. Kuti EL, et al. Impact of inappropriate antibiotic therapy on mortality in patients with ventilator-associated pneumonia and blood stream infection: A meta-analysis. J Crit Care. 2008;23:91-100.
35. Buchan BW, et al. Multiplex Identification of Gram-Positive Bacteria and Resistance Determinants Directly from Positive Blood Culture Broths: Evaluation of an Automated Microarray-Based Nucleic Acid Test. PLOS Med. 2013;10:e1001478.
36. Althubyani A, et al. Rapid Diagnostic Testing: Changing the Game for Antimicrobial Stewardship. IDSE Infectious Disease Special Edition. 2023;2023:58-71.
37. Nijhuis RHT, et al. Comparison of ePlex Respiratory Pathogen Panel with Laboratory-Developed Real-Time PCR Assays for Detection of Respiratory Pathogens. J Clin Microbiol. 2017;55:1938-1945.
38. Babady NE, et al. Multicenter Evaluation of the ePlex Respiratory Pathogen Panel for the Detection of Viral and Bacterial Respiratory Tract Pathogens in Nasopharyngeal Swabs. J Clinic Microbiol. 2018;56:10.1128/jcm.01658-17.
39. Tansarli GS, Chapin KC. Diagnostic test accuracy of the BioFire® FilmArray® meningitis/encephalitis panel: a systematic review and meta-analysis. Clin Microbiol Infect. 2020;26:281-290.
40. Hernandez DR, et al. Multicenter Diagnostic Accuracy Evaluation of the Luminex Aries Real-Time PCR Assay for Group B Streptococcus Detection in Lim Broth-Enriched Samples. J Clin Microbiol. 2018;56:10.1128/jcm.01768-17.
41. Kakoullis L, et al. Mechanisms of Antibiotic Resistance in Important Gram-Positive and Gram-Negative Pathogens and Novel Antibiotic Solutions. Antibiotics. 2021;10:415.
42. Dadgostar P. Antimicrobial Resistance: Implications and Costs. Infect Drug Resist. 2019;12:3903-3910.
43. Kowalska-Krochmal B, et al. The Minimum Inhibitory Concentration of Antibiotics: Methods, Interpretation, Clinical Relevance. Pathogens. 2021;10:165.
44. Burnham CD, et al. Diagnosing antimicrobial resistance. Nat Rev Microbiol. 2017;15:697-703.
45. Idelevich EA, et al. Matrix-Assisted Laser Desorption Ionization–Time of Flight Mass Spectrometry for Antimicrobial Susceptibility Testing. J Clin Microbiol. 2021;59:10.1128/jcm.01814-19.
46. Vasala A, et al. Modern Tools for Rapid Diagnostics of Antimicrobial Resistance. Front Cell Infect Microbiol. 2020;10:308.
47. Motro Y, et al. Next-generation sequencing applications in clinical bacteriology. Biomol Detect Quantif. 2017;14:1-6.

48. Hogan CA, et al. Clinical Impact of Metagenomic Next-Generation Sequencing of Plasma Cell-Free DNA for the Diagnosis of Infectious Diseases: A Multicenter Retrospective Cohort Study. Clin Infect Dis. 2021;72:239-245.
49. Kon H, et al. Multiplex lateral flow immunochromatographic assay is an effective method to detect carbapenemases without risk of OXA-48-like cross reactivity. Ann Clin Microbiol Antimicrob. 2021;20:61.
50. Barlam TF, et al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis. 2016;62:e51-e77.
51. Bauer KA, et al. An Antimicrobial Stewardship Program's Impact. Clin Infect Dis. 2010;51:1074-1080.
52. Perez KK, et al. Integrating Rapid Pathogen Identification and Antimicrobial Stewardship Significantly Decreases Hospital Costs. Arch Pathol Lab Med. 2013;137:1247-1254.
53. Huang AM, et al. Impact of Rapid Organism Identification via Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Combined With Antimicrobial Stewardship Team Intervention in Adult Patients With Bacteremia and Candidemia. Clin Infect Dis. 2013;57:1237-1245.
54. Turner RB, et al. Impact of rapid identification of Staphylococcus aureus bloodstream infection without antimicrobial stewardship intervention on antibiotic optimization and clinical outcomes. Diagn Microbiol Infect Dis. 2017;89:125-130.
55. Bhowmick T, et al. Collaboration between an antimicrobial stewardship team and the microbiology laboratory can shorten time to directed antibiotic therapy for methicillin-susceptible staphylococcal bacteremia and to discontinuation of antibiotics for coagulase-negative staphylococcal contaminants. Diagn Microbiol Infect Dis. 2018;92:214-219.
56. MacVane SH, et al. Benefits of Adding a Rapid PCR-Based Blood Culture Identification Panel to an Established Antimicrobial Stewardship Program. J Clin Microbiol. 2016;54:2455-2463.
57. Banerjee R, et al. Randomized Trial of Rapid Multiplex Polymerase Chain Reaction–Based Blood Culture Identification and Susceptibility Testing. Clin Infect Dis. 2015;61:1071-1080.
58. Henig O, et al. The Hypothetical Impact of Accelerate Pheno on Time to Effective Therapy and Time to Definitive Therapy for Bloodstream Infections Due to Drug-Resistant Gram-Negative Bacilli. Antimicrob Ag Chemother. 2019;63:10.1128/aac.01477-18.
59. Dare RK, et al. Clinical Impact of Accelerate Pheno Rapid Blood Culture Detection System in Bacteremic Patients. Clin Infect Dis. 2021;73:e4616-e26.
60. Kumar A, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006;34:1589-1596.
61. Clancy CJ, et al. Detecting Infections Rapidly and Easily for Candidemia Trial, Part 2 (DIRECT2): A Prospective, Multicenter Study of the T2Candida Panel. Clinical Infectious Diseases. 2018;66:1678-1686.
62. Mylonakis E, et al. Efficacy of T2 Magnetic Resonance Assay in Monitoring Candidemia after Initiation of Antifungal Therapy: the Serial Therapeutic and Antifungal Monitoring Protocol (STAMP) Trial. J Clin Microbiol. 2018;56:10.1128/jcm.01756-17.
63. Wilson N, et al. T2 Magnetic Resonance Improves Timely Management of Candidemia. Open Forum Infect Dis. 2016;3:1569.

Chapter 84

Advances in antimicrobial resistance testing

Wadha Ahmed Alfouzan
Department of Microbiology, Farwaniya Hospital, Kuwait City, Kuwait;
Department of Microbiology, College of Medicine, Kuwait University, Kuwait City, Kuwait.

Manaf AlQahtani
National Task Force for Combating the Corona Virus (COVID-19), Riffa, Bahrain;
Royal Medical Services, Military Hospital, Riffa, Bahrain; Royal College of Surgeons in Ireland, Muharraq, Bahrain.

Faryal Khamis
Infectious Diseases Unit, Department of Medicine, The Royal Hospital, Muscat, Oman.

Ali S. Omrani
Communicable Disease Center, Hamad Medical Corporation, Doha, Qatar;
Division of Infectious Diseases, Department of Medicine, Hamad Medical Corporation, Doha, Qatar;
Qatar University College of Medicine, Doha, Qatar.

Introduction

The improper use of antibiotics has a significant impact on healthcare systems, causing an increase in healthcare costs and a decrease in the quality of care. According to previous research, over 50% of antibiotic prescriptions are unnecessary or unsuitable, which contributes to antimicrobial resistance (AMR). According to World Health Organization (WHO) data, 700,000 people die each year due to drug-resistant infections. WHO is pressing countries to help with the fight by fostering antimicrobial stewardship in humans, animals, and agriculture as well as investing in research and development to combat AMR. AMR makes infections more difficult to treat and increases complications and mortality.

Globally, there are currently insufficient methods to reverse antibiotic tolerance. Overuse of conventional antibiotics in the clinical, parturient, agricultural, and aquaculture industries contributes to the development of antibiotic-resistant microorganisms. These risks exacerbate antibiotic-resistance genetics in hospital and household microbial ecosystems. Another challenge is the use of traditional diagnostic procedures for infectious diseases. Clinicians frequently misdiagnose infectious infections, which results in wasteful treatment. Classical microbiological antimicrobial susceptibility testing (AST) may require time and delay treatment decisions. Consequently, numerous techniques for the rapid identification and detection of antimicrobial resistance have been developed. These include conventional, non-conventional, and Microfluidic Systems methods.

AMR surveillance relies on rapid and accurate identification and characterization of antimicrobial-resistant bacteria. To understand its spread, numerous AMR monitoring systems exist, with the WHO Global

Antimicrobial Resistance and Use Monitoring System (GLASS) being the most prevalent. GLASS launched global AMR surveillance in 2015. GLASS initially gathered AMR data for common human ailments but was later expanded to cover antimicrobial consumption (AMC), invasive fungal infections, and other disorders.
In 2017, the WHO published a list of bacteria for which new antibiotics were urgently required, including extended-spectrum beta-lactamase (ESBL) and carbapenemase-producing *Enterobacterales*, carbapenem-resistant *Acinetobacter baumannii* (CRAB), and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA). Methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium* (VRE) are the most common Gram-positive pathogens. Here, we discuss various approaches to AST and the detection of microbial resistance.

Overview of antimicrobial susceptibility testing methods

Several methods are available for determining antimicrobial susceptibility, each with its own advantages and limitations.

Conventional methods

Phenotypic Methods

The choice of the best therapeutic option for the treatment of bacterial infections is supported by the results of AST, a part of the routine work of all clinical microbiological laboratories. Conventional methods rely on phenotypic resistance detection, as many still depend on bacterial growth to determine if resistance is present. The speed at which growth is detected is an important factor in determining the speed and sensitivity of a test. Numerous techniques have demonstrated utility in clinical microbiology laboratories for identifying antimicrobial resistance. The comments are based on direct assessments of susceptibility using methods such as disk diffusion (Kirby-Bauer test), gradient methods (Etest), dilution methods, or automated systems.
Although these techniques are sensitive and specific, they generally suffer from long turnaround times. An additional challenge of current culture-based methods is their dependency on cultured isolates for the detection and identification of infections.

Disk Diffusion Method (Kirby-Bauer Test)

This method involves placing antibiotic disks on an agar plate inoculated with bacteria of interest. The zones of inhibition around the disks indicate the susceptibility or resistance of the bacteria to antibiotics. This method is simple and inexpensive but lacks precision and may not accurately predict the resistance mechanisms.

Gradient Method (Etest)

Etest relies on Minimum Inhibitory Concentration (MIC) testing, which determines the lowest concentration of an antibiotic that inhibits bacterial growth. A manufactured gradient strip was used to read the MIC, which provided quantitative results, allowing for precise determination of antibiotic susceptibility. Etest is simple and easy to use, but relatively expensive. It is considered a “gold standard” recommended by both the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and The Clinical and Laboratory Standards Institute (CLSI).

Broth and Agar Dilution Method

Broth and agar dilution methods are standard reference methods, especially when new drugs are launched. This method allows a more accurate MIC reading in addition to providing the minimum bactericidal concentration (MBC) reading, which is not consistent with the previous two methods. MBC is the lowest concentration of antibacterial agent required to kill a particular bacterium. This method has the advantage of providing both MIC and MBC; however, it is labor-intensive and requires significant training. Furthermore, the broth dilution method may not be suitable for all antibiotics and bacterial strains, as demonstrated by the poor performance of polymyxin B compared with other methods. Both the CLSI and EUCAST have separate guidelines for broth testing that are regularly revised.

Automated Systems

VITEK 2, BD Phoenix systems, and Microscan are automated systems widely used in microbiology laboratories. These systems use biochemical and/or turbidimetric methods to establish the rapid identification and antimicrobial susceptibility testing of bacterial isolates. They provided AST results for multiple antibiotics in a single run, depending on the bacterial isolates. Automated systems provide rapid turnaround results, high throughput, practicality, and simplicity, with increased accuracy compared to traditional methods.

Molecular based methods

DNA microarrays

A DNA microarray is an instrument used to evaluate the diversity of bacterial genomes and is operated by identifying the presence or absence of genes in a target organism compared to a reference strain or genome. A convenient and rapid DNA labelling system utilizing biotinylated primers designed for disposable microarrays was developed. Additionally, a DNA microarray was developed for the simultaneous detection of ARGs in *Staphylococcus* clinical isolates using fluorescently labelled PCR products and a multiplex asymmetric PCR amplification method.

Nonconventional methods

Mass Spectrometry

Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry

All major matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) platforms operate on the same basic principle: they detect and measure the mass/charge ratio of ionized molecules from a bacterial colony or pellet. In doing so, they generate unique spectra that represent the entire cell or cell extract of a specific microorganism. Provided that there are no shared ions between the proteomic fingerprints of different species, and the mass range covered by the measurement includes the entire spectrum, the technology can accurately differentiate mass differences between species and the ionization of both proteinic and non-proteinic components within the given limits, which can be used for taxonomic purposes.

MALDI-TOF is one of the most advanced mass spectrometry techniques. This permits the identification of microorganisms by mass profile analysis. The technique displays a high level of sensitivity and specificity, and because the equipment is relatively inexpensive to purchase and maintain, it is now frequently used in clinical microbiology laboratories.

MALDI-TOF MS has also enabled the identification of antibiotic resistance mechanisms such as carbapenemases. MALDI-TOF MS is widely regarded as a reliable and efficient method that provides rapid and accurate results within minutes. It is also user-friendly, cost-effective, and environmentally friendly. However, the high cost of purchasing and maintaining these systems, along with their large size, presents significant challenges for their implementation in low-resource settings or as a point-of-care testing platform for antibiotic resistance or antimicrobial susceptibility. It is important to establish a standardized procedure to ensure consistent and reliable results. Additionally, MALDI-TOF MS is not suitable for analyzing mixed samples because prior purification, cultivation, and sample preparation are required. The execution of these tests also necessitates the use of additional chemicals, such as matrices. It is crucial to have databases containing spectra that can differentiate between susceptible and resistant strains. The two commercially available MALDI-TOF MS systems were MALDI Biotyper (Bruker Daltonik, Germany) and VITEK MS (bioMérieux, France). Comparative studies on the performance of these platforms have been reported in the literature.

Genome sequencing and metagenomics

Next-generation sequencing (NGS) technologies

Recent scientific analyses have shown that NGS is widely considered a de facto standard for transmitting data and sharing the results of clinical microbiology investigations. NGS includes whole genome sequencing (WGS), targeted metagenomic sequencing, and shotgun metagenomics sequencing, where the former is the most common. Several public health organizations use WGS for diagnostic DNA-resistant gene detection. WGS predicts the emergence of resistant strains, informs taxonomy, tracks resistance spread in the environment, monitors gene movement channels investigate fitness costs, and describes plasmids/transposons to monitor their spread within bacterial hosts or as mobile genetic elements (MGEs). WGS eliminates bias from gene scanning techniques, reducing signal-to-noise artefacts and selective bias caused by mutational changes.

WGS has been applied for the identification of bacteria; speciation is determined from 16 and/or 23S rRNA gene sequence data, where defining species boundaries is critical. WGS is useful for typing bacteria, such as characterizing the genotypic and phenotypic attributes of strains, to delineate causative strains from others in an outbreak investigation. At the ultimate level for comparison of strains, WGS provides strain-resolved microbiology, without the need for other relatively expensive and time-consuming methods such as pulsed-field gel electrophoresis (PFGE) or multilocus sequence typing (MLST). By combining information on the genetic background and genetic makeup of the causative agents, the ability to minimize the matrix and other confounding environmental sources and the key genetic and sporadic sources are identified, helping to prevent future cases of disease. In forensic epidemiology, using genomic data to identify contaminating sources of organisms is an increasingly important effort; the natural, which can be especially important where the stability in the environment of a pathogenic agent such as *Clostridium difficile* over time, in the absence of additional evidence, would make a definitive source improbable to determine.

Rapid methods

Rapid AST is crucial for guiding appropriate antibiotic prescriptions and for combating the dissemination of antimicrobial resistance. Innovative and rapid antimicrobial susceptibility testing systems are essential in addressing the spread and emergence of AMR, highlighting the importance of rapid detection and quantification of resistance alongside antimicrobial stewardship practices.

Microfluidic methods

Microfluidics involves the handling of small volumes of liquids using microfluidic chips or lab-on-a-chip. It integrates fluidics and detection with a single substrate. This technology is seen as the future of biology and offers affordable chip-based assays for point-of-care diagnostics. These assays can identify and quantify bacteria, determine their resistance status, and provide quick results for patient management.

Multiplex PCR

Polymerase chain reaction (PCR) is a molecular-based method used to detect specific gene sequences. PCR is widely used in research because it is simple, accurate, rapid, and highly sensitive. It outperforms traditional culture and serological methods for detecting single-pathogen cells. The disadvantages of these methods can be overcome using predetermined statistical values, such as the limit of detection (LOD) and/or limit of quantification (LOQ) with an interpolation model.

Currently, a microfluidic chip for rapid phenotypic AST has been developed that is capable of processing eight samples simultaneously. The chip consisted of an array of microchambers containing a mixture of bacterial isolates and agarose. To observe the growth rate of bacterial colonies when exposed to antibiotic gradients, a custom dark-field microscope connected to a motorized camera was used to capture snapshots every 10 min. These images were then automatically analyzed. The total analysis time was 5 h, and the results obtained from this method exhibited stable MIC values, demonstrating 100% agreement with the reference MIC values determined using the broth microdilution technique. The main advantage of this proposed system is its ability to analyze multiple samples in parallel on a single chip, enabling the simultaneous testing of multiple antibiotics.

Many different single-plex PCR for the detection and identification of various pathogenic bacteria, viruses, and parasites have been used for a long period. Applying these techniques in a microbiology clinical laboratory is impractical because of limitations in sample volume and quality, as well as economic and time resources. Depending on the panel used, multiplex PCR assays offer advantages in terms of time, cost, and sample volume reduction for detecting multiple pathogens with multiple resistance genes in a single assay. However, carrying resistance genes may not translate into actual resistance. This potentially raises concerns about the overuse of broad-spectrum antibiotics and their inappropriate use.

Point-of-care (POC) tests

A proof-of-concept (POC) system that focuses on the diagnosis of AMR and phenotypic AST for bacteriuria and urinary tract infections (UTIs) has been developed by Toosky *et al.* and colleagues. The system has a turnaround time (TAT) of 2 h and can detect and quantify bacterial concentrations ranging from 50 to 105 CFU/mL. It utilizes a portable particle-counting instrument that includes a miniature confocal microscope and real-time data analysis software. This instrument enables the measurement of growth curves for fluorescently stained bacterial cells in both the control and antibiotic-treated samples. The proposed POC system offers several advantages, including the elimination of pre-processing steps (such as pre-culture, enrichment, and centrifugation) for urine samples as well as its high sensitivity. However, it is important to note that only preliminary data are currently available for this method; therefore, further studies are necessary. Similar to other AST methods, one limitation of this approach is the potential impact of mixed cultures on the specificity and sensitivity of results.

Conclusion

Many innovative technologies were developed in the late twentieth century, including POCT, multiplex PCR, genomics, and proteomics. Even though such breakthroughs have resulted in the discovery of several novel medications, including those for bacterial infections, there has been no growth in the production of antibiotics for many years owing to a lack of business incentives for pharmaceutical corporations. Bacteria, on the other hand, have rapidly evolved resistance to new medications by passing on genes picked up by new antibiotics. The misuse of antibiotics has also significantly contributed to this process. These threats have prompted academic and industrial researchers to devise alternative antibiotic discovery methodologies including artificial intelligence. Furthermore, there is an urgent need for "rapid detection" and "informed decision-making tools to monitor the spread of AMR and prescribe timely and effective antimicrobials.

Rapid AST supports antimicrobial stewardship efforts by providing timely information on bacterial susceptibility, guiding clinicians on the prudent use of antibiotics, and encouraging the use of narrower-spectrum agents whenever possible, thereby reducing inappropriate use, saving lives, and contributing to global AMR efforts.

Continuous breakthroughs in microbiology and molecular biology have enabled the development of quick and high-throughput benchtop methods for identifying resistance directly from clinical samples, as shown in **Table 1**. However, owing to resource constraints and demands, laboratories may not always be able to meet the diversity of clinical specimens, infections, resistance genes, and related mandatory recommended criteria. Furthermore, issues exist with quality assurance requirements even when implementing the simplest diagnostic tools at the point of care. Collaboration between the government, pharmaceutical industry, researchers, and healthcare practitioners is critical for financing projects and accessible tools.

Competing interests

Alfouzan WA has received speaker grants and honorariums from BioMérieux, Cephid, Pfizer, Sanofi, Merck, Gilead, and Hikma. Alqahtani MM has received grants and honorariums from Pfizer, Cephid, Abbott and BioMérieux. Khamis F has no competing interest. Omrani AS has received speaker and/or advisory board honoraria from Pfizer, MSD, Gilead, BioMérieux, and Cephid.

Table 1. Available methods for determining antimicrobial susceptibility.

Method	Method	Advantages	Disadvantages
Conventional	1. Phenotypic		
	A. Disk Diffusion (Kirby-Bauer Test)	Simple and inexpensive	Lacks precision, long TAT
	B. Gradient Method (Etest)	Simple and easy to use	Relatively expensive, long TAT
	C. Broth and Agar dilution	Provide MIC and MBC	Labor-intensive, requires significant training, long TAT, not suitable for all antibiotics or bacterial strain
	D. Automated system	Rapid results, high throughput, practical, simple, increased accuracy than A and B	Relatively expensive, software update for cutoff value is slow.
	2. Molecular *DNA microarrays*	Convenient and rapid	Expensive, significant training
Non-conventional	1. Mass Spectrometry	Rapid results, simple, high throughput	Expensive, identification rely on databases spectra, still investigated for AST
	2. Genome sequencing and metagenomics *Next-generation sequencing (NGS) technologies*	Convenient and rapid	Expensive, significant training, data base needs to be expanded
Microfluidic	1. Multiplex PCR	Rapid results, simple, small sample	Expensive, detect genes not phenotypic resistance, contains certain gene pool
	2. Point of Care (POCT)	No culture required, Rapid results, simple, small sample	Expensive, identification rely on databases spectra, still investigated for AST, issues with of mixed cultures affecting sensitivity and specificity

Abbreviations. TAT: turn-around-time, MIC: Minimum inhibitory concentration, MBC: minimum bactericidal concentration.

References

1. World Health Organization. Antibiotic Resistance. Available at: https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance. Last accessed: 4 May 2024.
2. World Health Organization. New Report Calls for Urgent Action to Avert Antimicrobial Resistance Crisis. Available at: https://www. who.int/news/item/29-04-2019-new-report-calls-for-urgent-action-to-avert-antimicrobial-resistance-crisis. Last accessed: 4 May 2024.
3. Salam MA, et al. Antimicrobial Resistance: A Growing Serious Threat for Global Public Health. Healthcare (Basel). 2023;11:1946.
4. McAdams D, et al. Resistance diagnostics as a public health tool to combat antibiotic resistance: A model-based evaluation. PLoS Biol. 2019;17:e3000250.
5. Kaprou GD, et al. Rapid Methods for Antimicrobial Resistance Diagnostics. Antibiotics (Basel). 2021;10:209.

6. World Health Organization. 2023. GLASS manual for antimicrobial resistance surveillance in common bacteria causing human infection. Available at: https://www.who.int/publications/i/item/9789240076600. Last accessed: 9 July 2024.
7. World Health Organization. WHO publishes list of bacteria for which new antibiotics are urgently needed. Available at: https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed. Last accessed: 9 July 2024.
8. Gajic I, et al. Antimicrobial Susceptibility Testing: A Comprehensive Review of Currently Used Methods. Antibiotics (Basel). 2022;11:427.
9. Clinical and Laboratory Standards Institute. M07: Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically, 11th ed.; Clinical and Laboratory Standards Institute: Wayne, PA, USA, 2018; ISBN 1562388363.
10. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint Tables for Interpretation of MICs and Zone Diameters, Version 12.0. Available at: http://www.eucast.org/clinical_breakpoints/. Last accessed: 23 February 2022.
11. Zhu LX, et al. Use of a DNA microarray for simultaneous detection of antibiotic resistance genes among staphylococcal clinical isolates. J Clin Microbiol. 2007;45:3514-3521.
12. Hoyos-Mallecot Y, et al. Rapid detection and identification of strains carrying carbapenemases directly from positive blood cultures using MALDI-TOF MS. J Microbiol Methods. 2014;105:98-101.
13. Vrioni G, et al. MALDI-TOF mass spectrometry technology for detecting biomarkers of antimicrobial resistance: current achievements and future perspectives. Ann Transl Med. 2018;6:240.
14. Chen XF, et al. Matrix-Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry (MALDI-TOF MS) Analysis for the Identification of Pathogenic Microorganisms: A Review. Microorganisms. 2021;9:1536.
15. Hilt EE, et al. Next Generation and Other Sequencing Technologies in Diagnostic Microbiology and Infectious Diseases. Genes (Basel). 2022;13:1566.
16. van Belkum A, et al. Innovative and rapid antimicrobial susceptibility testing systems. Nat Rev Microbiol. 2020;18:299-311.
17. Uelze L, et al. Typing methods based on whole genome sequencing data. One Health Outlook. 2020 Feb 18;2:3.
18. Yang, Q., et al. Emerging rapid detection technologies for multidrug-resistant bacteria. Journal of Global Antimicrobial Resistance, vol. 28, 2021, pp. 17-29.
19. Wistrand-Yuen P, et al. A Multiplex Fluidic Chip for Rapid Phenotypic Antibiotic Susceptibility Testing. mBio. 2020;11:e03109-19.
20. Toosky MN, et al. A rapid, point-of-care antibiotic susceptibility test for urinary tract infections. J Med Microbiol. 2020;69:52-62.

Chapter 85

New frontiers in diagnostic clinical microbiology

Fabio Arena
Department of Clinical and Experimental Medicine, University of Foggia, Foggia, Italy.

Gian Maria Rossolini
Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy;
Microbiology and Virology Unit, Careggi University Hospital, Florence, Italy.

Introduction

The advancements in the field of clinical microbiology, over the past decades, have significantly improved the diagnosis and management of infectious diseases. With the integration of innovative technologies, enhanced laboratory practices, and interaction with antimicrobial stewardship programs, clinical microbiology is better equipped to address the challenges posed by emerging pathogens and antimicrobial resistance in the context of a "patient centered" approach. This chapter aims to explore the new frontiers in diagnostic clinical microbiology, focusing on the latest technological advancements and their implications for patient care by examining key innovations, their applications, and the challenges they present.

Laboratory automation: Automation in clinical microbiology laboratories, exemplified by systems for automated sample inoculum, has improved efficiency in specimen processing, biosafety, reduced manual errors, and streamlined workflows. The most advanced technologies, incorporating instruments for identification and susceptibility testing steps, have reached the goal of a fully automated process and are currently known as systems for "total laboratory automation" (TLA). TLA systems provide consistent and standardized procedures, which minimize variability and enhance the reliability of results compared to conventional approaches. Automation also decreases the technicians' workload, reducing repetitive and time-consuming actions, allowing personnel to focus on more complex tasks while also potentially lowering overall staffing costs. By automating repetitive and hazardous tasks, laboratories can reduce the risk of injuries and exposure to biohazards for laboratory operators.

Furthermore, automated systems often incorporate quality control procedures that ensure accurate tracking and documentation of processes, enhancing overall laboratory quality. Finally, automation allows for more efficient use of resources, including reagents and equipment, leading to cost savings and improved throughput.

MALDI-TOF mass spectrometry

Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) is a game-changing technique in clinical microbiology for the rapid identification of microorganisms. The method involves the ionization of proteins, directly from microbial isolate or, in some cases from a clinical sample (e.g.

positive blood culture broth). Ions are then accelerated in an electric field and sorted based on their mass-to-charge ratio, generating typical mass spectra. The generated mass spectrum serves as a unique fingerprint for each microorganism, allowing for comparison against a reference database of known spectra. MALDI-TOF can identify microorganisms in a few minutes, significantly faster than traditional biochemical methods, which can take days. MALDI-TOF MS can identify a wide range of pathogens, including bacteria and fungi. Despite the initial costs for MALDI-TOF MS instruments can be high, its adoption can lead to long-term savings by reducing labor costs and turnaround times.
Among limitations of the method, it should be noted that the accuracy of MALDI-TOF MS relies on the quality of the reference database. If a microorganism is not present in the database, it may not be identified correctly.

Molecular diagnostics

The integration of molecular techniques, such as polymerase chain reaction (PCR) has revolutionized pathogens detection. These methods offer the opportunity of rapid identification and deeper characterization of pathogens directly from clinical specimens, significantly reducing turnaround times for diagnostic results. Molecular methods are generally more sensitive and specific compared to conventional culture-based techniques, allowing for the detection of pathogens that may be present in low microbial load. Furthermore, many molecular tests can provide results within hours, which is essential for timely diagnosis and treatment. Further developments have led to the introduction of multiplex PCR assays that can simultaneously detect multiple pathogens from a single specimen, providing a more comprehensive overview of a sample.

Rapid diagnostic testing (RDT) refers to a variety of molecular laboratory methods that provide quick results for the identification of pathogens or the detection of specific traits associated with infections. The primary aim of RDTs is to accelerate the time to diagnosis and treatment, ultimately improving patient outcomes and facilitating appropriate antimicrobial use. In fact, RDTs are characterized by an extremely low hands-on time (need of operator interventions) and can provide results in a matter of hours, allowing for timely clinical decisions and initiation of appropriate therapy. There are several commercially available RDTs capable of identifying pathogens and detecting antibiotic resistance from various specimen sources, such as blood, sputum, urine, and cerebrospinal fluid in a highly automated process. Same RTDs can be adapted to the use outside the laboratory enabling diagnostics to be performed bedside, at the site of patient care. This approach enhances access to testing and facilitates immediate clinical decision.

Syndromic testing is a diagnostic approach that employs multiplex molecular panels to detect a large set of pathogens associated with specific clinical syndromes, such as genital, respiratory, gastrointestinal, or bloodstream infections. Syndromic tests can detect a broad range of pathogens (bacteria, viruses, fungi and some antimicrobial resistance determinants) in a single test. These tests streamline the diagnostic process by allowing healthcare providers to order one test instead of multiple individual tests for suspected pathogens. Syndromic panels usually provide results faster than traditional methods, reducing turnaround times from several days to just a few hours. Furthermore, these tests can identify pathogens that may not be routinely searched by traditional microbiology, including those that are rare or emerging. Syndromic panels are generally more expensive than traditional diagnostic methods, which may limit their adoption in some healthcare settings. Furthermore, the interpretation of results can be challenging in some cases. For example, the detection of non-pathogenic organisms or colonizers may lead to unnecessary treatments.

Next-Generation Sequencing (NGS) is increasingly becoming a useful tool in clinical microbiology, particularly for the detection and identification of pathogens, as well as for understanding antimicrobial resistance. In some cases, NGS allows the identification of pathogens directly from clinical specimens, even in cases where traditional culture methods fail (e.g. in cases of recent antibiotic exposure). It can provide high-resolution identification of organisms, including those that are rare or fastidious. Furthermore, metagenomic NGS enables the simultaneous analysis of all microbial DNA present in a sample, being particularly useful for the study of the composition of the human microbiome.

NGS can be used for tracking the spread of infectious agents and provides insights into outbreak dynamics giving an idea of clonal relationships and transmission pathways. Furthermore, NGS can facilitate a deeper understanding of the genetic basis of antimicrobial resistance by identifying known and potentially new resistance genes. However, the analysis of NGS data often requires sophisticated bioinformatics tools to analyze complex data sets, which can include millions of reads. This has led to the development of various software solutions to streamline data analysis and visualization.

Data Analytics, Machine Learning and Artificial Intelligence

The application of machine learning and data analytics in clinical microbiology is on the rise. The current application of artificial intelligence (AI) in clinical microbiology is transforming the field through various innovative technologies and methods aimed at improving diagnostic accuracy, efficiency, and patient outcomes. AI, particularly through machine learning algorithms, is being used for automated interpretation of digital images in microbiology. For instance, systems have been developed to analyze Gram stain results, where AI can recognize pathogen morphologies with high accuracy. Deep learning AI-based methods have been developed for automated detection of malaria parasites in blood smear, while other AI-based computer vision techniques are being implemented to improve the identification of pathogens from culture plates. These systems can classify media as “negative” or “non-negative” and provide presumptive identification, which enhances the workflow and reduces the burden on laboratory staff. With the availability of digital images from automated systems, AI is facilitating telemicrobiology, which allows microbiologists to read and interpret results remotely. This can lead to faster clinical decisions and better collaboration between laboratory staff and clinicians.

AI can be also utilized to automate the process of determining antimicrobial susceptibility. Through machine learning approaches, algorithms can analyze growth patterns and predict minimum inhibitory concentrations (MIC) for various pathogens, enhancing the speed and accuracy of susceptibility results. Furthermore, AI systems can predict whether certain samples require further testing based on various parameters, including patient demographics and clinical data.

Conclusion

The future of clinical microbiology is poised for transformative advancements, significantly reshaping the scenario of infectious disease diagnosis and management. As the field is in continuous evolution, it is anticipated that automation and digitalization will play pivotal roles in enhancing the efficiency and accuracy of laboratory procedures. TLA systems are expected to streamline workflows, minimize human error, and

improve turnaround times for test results, which is critical for timely clinical decision-making in managing infections and resource optimization. Moreover, the integration of AI and machine learning (ML) into clinical microbiology practices represents a promising frontier. For instance, AI algorithms can enhance the accuracy of pathogens identification and of determination of the antimicrobial resistance pattern, thus optimizing treatment strategies. Furthermore, the advent of metagenomic next-generation sequencing offers a revolutionary approach to pathogen detection, allowing for the identification of a broad spectrum of microorganisms directly from clinical specimens without the need for culture. This capability is particularly useful in cases of polymicrobial infections where traditional culture methods may fail. Metagenomic next-generation sequencing can also facilitate the detection of rare or emerging pathogens (or non-culturable microbes), which is increasingly important given the rise of newly recognized infectious agents.

The incorporation of point-of-care (POC) testing is another significant advancement, providing rapid diagnostic results at or near the site of patient care. POC could enhance patient outcomes by enabling immediate clinical decisions but also reduce the burden on centralized laboratory facilities. As the healthcare landscape evolves, POC testing technologies will need to become more sophisticated, with the capability to detect multiple pathogens and resistance markers simultaneously.

In this context, the role of clinical microbiologists will expand beyond traditional diagnostics to encompass a more integrated approach to patient care, emphasizing collaboration with clinicians, pharmacists, and infection control specialists. A multidisciplinary approach, for example, is essential for the implementation of antimicrobial stewardship programs that aim to optimize the use of antibiotics and combat the rising threat of antimicrobial resistance while improving the patient outcome. As healthcare systems increasingly recognize the importance of data-driven decision-making, clinical microbiologists will need to engage actively in the interpretation of laboratory data, guiding clinical teams in tailoring antibiotic treatment schemes based on real-time diagnostic information. Furthermore, the evolution of personalized medicine will influence clinical microbiology by enabling more tailored therapeutic approaches based on individual patient features (including gender) and pathogen profiles. This shift will also necessitate the discovery of new biomarkers and novel diagnostic tools that can provide insights into the host-pathogen interaction, aiding in the stratification of patients (e.g. based on probability of rapid clinical progression). The future also holds the potential for enhanced public health surveillance programs through the integration of genomic epidemiology into clinical microbiology. By utilizing genomic sequencing data, healthcare providers will be able to track the transmission dynamics of pathogens within populations, thereby informing outbreak investigations and control measures. This capability will be particularly crucial in the context of global health threats, such as pandemics, where rapid identification and containment of infectious diseases are paramount. However, the advancement of clinical microbiology will not be without challenges. Ethical considerations about data privacy, especially with the increasing reliance on digital health technologies and data-sharing platforms, will need to be addressed. Additionally, the implementation of new technologies must be accompanied by robust validation studies to ensure their reliability and clinical utility. Training and education for laboratory personnel will also be essential to keep pace with technological advancements and ensure the effective integration of novel diagnostic methods into clinical practice. Ultimately, the future of clinical microbiology is bright, characterized by a commitment to innovation and excellence in the pursuit of improved patient care. As the discipline continues to adapt to the ever-changing landscape of infectious diseases, its role will become increasingly central in preserving global health, responding to emerging threats, and guiding the responsible use of antimicrobial agents.

Competing interests

The authors have no financial and non-financial competing interests to declare, relevant to this article.

References

1. Alizadeh M, et al. MALDI-TOF Mass Spectroscopy Applications in Clinical Microbiology. Adv Pharmacol Pharm Sci. 2021;2021:9928238.
2. Arena F, et al. Editorial: Clinical impact of fast platforms and laboratory automation for the rapid diagnosis of infectious diseases and detection of antimicrobial resistance determinants. Front Cell Infect Microbiol. 2023;13:1321663.
3. Leo S, et al. Mini Review: Clinical Routine Microbiology in the Era of Automation and Digital Health. Front Cell Infect Microbiol. 2020;10:582028.
4. Mencacci A, et al. Laboratory automation, informatics, and artificial intelligence: current and future perspectives in clinical microbiology. Front Cell Infect Microbiol. 2023;13:1188684.
5. Novak SM, et al. Automation in the clinical microbiology laboratory. Clin Lab Med. 2013;33:567-588.
6. Özenci V, et al. Rapid microbial identification and antimicrobial susceptibility testing to drive better patient care: an evolving scenario. J Antimicrob Chemother 2019;74.
7. Trotter AJ, et al. Recent and emerging technologies for the rapid diagnosis of infection and antimicrobial resistance. Curr Opin Microbiol. 2019;51:39-45.
8. Signoroni A, et al. Hierarchical AI enables global interpretation of culture plates in the era of digital microbiology. Nat Commun. 2023;14:6874.
9. Sinha M, et al. Emerging Technologies for Molecular Diagnosis of Sepsis. Clin Microbiol Rev. 2018;31:e00089-17.
10. Wang H, et al. Clinical microbiology in detection and identification of emerging microbial pathogens: past, present and future. Emerg Microbes Infect. 2022;11:2579-2589.
11. Wenzler E, et al. Antimicrobial susceptibility testing: An updated primer for clinicians in the era of antimicrobial resistance: Insights from the Society of Infectious Diseases Pharmacists. Pharmacotherapy. 2023;43:264-278.

Chapter 86

Pharmacists' role in antimicrobial stewardship

Katia Iskandar
Faculty of Public Health-Section 2 (CERIPH), Lebanese University, Fanar, Lebanon;
Faculty of Pharmacy, Lebanese International University, Beirut, Lebanon;
Institut National de Santé Publique d'Épidémiologie Clinique et de Toxicologie-Liban (INSPECT-LB), Beirut, Lebanon.

Introduction

Antimicrobial Stewardship (AMS) programs are coordinated and structured interventions implemented within different healthcare settings to optimize the use of antimicrobial agents. The primary objective is to enhance patient and medication safety by selecting the appropriate drug regimens, including the choice of antimicrobial agent, dose, dosage form, route of administration, de-escalation, and duration of therapy. The ultimate goal is to decrease the selection pressure and the emergence and spread of antimicrobial resistance to preserve these medications for future generations. AMS interventions must consider patient needs and local microbiological trends to enhance clinical outcomes, reduce adverse drug reactions and toxicity, decrease relapse and recurrence of infections, and lower mortality rates. The efficient implementation of this program depends on the concerted efforts of a multidisciplinary, interprofessional team that includes predominantly a physician, pharmacist, infectious disease expert, and microbiologist. Numerous studies highlighted the forefront role of the pharmacist, particularly those with expertise in infectious disease management. However, the pharmacists' training, expertise, and role vary among countries. While the pharmacist contribution is well-defined in high-income countries, it is still ambiguous and less supported in Low and Low-middle-income countries. This review examines the pharmacists' role and the impact of their contribution to the AMS program.

Pharmacist role and impact in Antimicrobial Stewardship programs

Fostering appropriate use of antimicrobial agents

Pharmacists' contribution is pivotal in AMS programs to translate antimicrobial use policy into practice. The predominant responsibility of the pharmacist is supervising and managing the AMS programs' clinical and operational aspects. The pharmacist coordination and collaboration with a multidisciplinary team enhances the implementation and monitoring of evidence-based protocols and the development of institutional algorithms and guidelines to optimize the prophylactic, empirical, and therapeutic use of antimicrobial agents and minimize antimicrobial resistance. As a result, pharmacists' active interventions in AMS enhance prescribing behaviors, reduce unnecessary antimicrobial prescribing, and improve adherence to guidelines. Their expertise in drug pharmacokinetics and pharmacodynamics principles makes them uniquely positioned to implement targeted therapy based on special population considerations (e.g., Children, elderly, oncology

patients), patient-specific factors (e.g., renal failure, hepatic failure), and underlying conditions. Pharmacists' role includes suggesting dosage adjustments or antimicrobials switch according to antimicrobial susceptibility testing results, ensuring appropriate therapeutic monitoring, including initiation and follow-up doses, intervals, and ongoing monitoring of medication regimen based on therapeutic antimicrobial levels and patient factors and comprehensive medication reviews.

Pharmacists are integral to establishing protocols for restricted antimicrobial use, therapeutic interchange, and treatment guideline development. They contribute to the pharmacy and therapeutics comity (P&T) in formulary and drug shortage management by suggesting alternative therapies to align antimicrobial agent availability with established institutional policies and guidelines to enhance therapeutic outcomes while minimizing the risk of antimicrobial resistance. A systematic review of the clinical pharmacists' role in AMS programs in hospital settings described the effectiveness of pharmacist-led stewardship programs. The results indicated clinical and economic benefits, including a decrease in antibiotic use and readmissions, enhancement of timeliness and appropriateness of antibiotic use in the emergency department, an improvement in prescribing practice and compliance and adherence to guidelines. Another systematic review conducted in the community pharmacy showed that a pharmacist-led AMS contributed to lower use of unnecessary antibiotics in cases of urinary tract infection and acute pharyngitis, in addition to high clinical improvement rates and enhanced patient satisfaction.

Optimizing patient outcomes

Pharmacist-led AMS programs significantly enhance patient outcomes by reducing the incidence of healthcare-associated infections, increasing cure rates, and lowering recurrence and mortality rates. Shrestha (2023) reported that the pharmacist-led AMS decreased the incidence of *Clostridium difficile* infections. Uda (2019) reported similar findings in addition to an improvement in clinical outcomes. Other studies indicated a decrease in the duration of therapy for uncomplicated Gram-negative bacteremia and a lowered length of hospital stay (LOS) as a result of the collaboration between the AMS pharmacist and infectious disease (ID) specialist. Other studies reported that pharmacists' involvement in AMS lowered the adverse events due to antimicrobial use by 38%.

Reducing healthcare costs

Pharmacist-led AMS programs significantly lowered healthcare costs by decreasing antibiotic use, eliminating unnecessary antibiotic use, switching when appropriate from intravenous to oral forms, and minimizing the length of stay and readmission rates. Cantudo-Cuenca (2022) reported € 164,953 in cost-savings when comparing pre-and post-pharmacist-led AMS intervention. Similarly, Xu (2022) indicated a lower antibiotic use markedly decreased costs. Polidori (2022) found that the pharmacist AMS interventions led to cost containment, improved conversion from IV to oral antibiotic therapy, a 5% dosing improvement, a 4% decrease in allergy reports, and 275% in reporting adverse drug reactions. In other terms, the pharmacist's contribution to AMS programs enhanced the quality of care and the efficiency of resource use and increased healthcare professionals' awareness. Sawada (2023) noted a decrease in LOS length of therapy and the number of days to de-escalation, in addition to an approximately 30% reduction in antibiotic costs per hospitalization post-implementation of the pharmacist-led AMS program.

Enhancing infection prevention and control

Pharmacists' involvement in AMS programs minimizes the infection rate through the continuum of care. In healthcare settings, their involvement includes participation in infection prevention and control comity and fostering institutional policies to maintain sterility and prevent contamination and cross-contamination,

particularly in sterile product preparation. They apply strict quality control measures to ensure proper cleaning and sterilization of pharmaceutical equipment. Pharmacists promote best practices in labeling, dating, and sterile product storage and encourage adherence to standard infection prevention protocols. Pharmacists support routine immunization programs for healthcare staff, including influenza vaccination and tuberculosis screening. Their leadership is crucial in developing guidelines for managing exposures to infectious pathogens and preventing various healthcare-associated infections, such as surgical site infections and catheter-associated bloodstream infections. Through these comprehensive efforts, pharmacists help ensure a safer hospital environment for patients and staff.

Educating, counseling, and training patients and healthcare professionals

Pharmacists have important leadership in educating the public, patients, staff, and healthcare professionals about appropriate antimicrobial use, stewardship principles, and infection prevention and control. The ultimate goal is engaging patients and enhancing vaccination and adherence to prescribed medication regimens, improving awareness about risks of antimicrobial misuse, and their knowledge about antimicrobial resistance. Pharmacists also counsel the public on appropriate storage and handling of antimicrobials. In inpatient care, pharmacists serve as accessible resources about potential adverse events and hygiene practices. While also addressing the knowledge gaps and educating healthcare professionals and students about adequate antimicrobial prescribing, providing regular updates on antimicrobial prescribing trends and local and national resistance patterns, and enhancing their knowledge about antimicrobial resistance. Education is most effective when coupled with interventions and outcomes measurements, including formulary restrictions and preauthorization to enforce the impact of educational interventions in clinical settings.

Pharmacists required skills in AMS programs

Pharmacists leading AMS must exhibit a comprehensive set of skills, including a good understanding of antimicrobial stewardship principles, an in-depth knowledge of antimicrobials and microbiology, expertise in managing infectious diseases, an ability to measure and analyze stewardship outcomes and leverage informatics and diagnostics to support stewardship initiative. They must show leadership and communication skills. In microbiology and laboratory diagnostics, pharmacists should be able to interpret cultures and other diagnostic tests and understand microbiological principles and resistance trends. Knowledge of common infectious syndromes requires knowledge about interpreting national guidelines and incorporating based on evidence-based practices. Pharmacists must stay updated on infectious disease trends and understand the link between antimicrobial use and resistance patterns. They should apply pharmacokinetic and pharmacodynamic principles to optimize dosing strategies, manage drug allergies and interactions, and handle antimicrobial shortages. Measurement and analysis skills are essential for assessing antimicrobial use data, applying metrics like Defined Daily Dose (DDD) and Days of Therapy (DOT), benchmarking practices, and measuring the impact of stewardship interventions on patient outcomes and resistance trends. Pharmacists should also be capable of leveraging resources to track antimicrobial use, develop alerts, and assess external software. Additionally, pharmacists must be able to adapt stewardship approaches for special populations and non-acute hospital settings and apply infection control principles, including implementing guidelines for surgical prophylaxis and understanding definitions for healthcare-associated infections (HAIs).

Challenges and barriers to pharmacists' engagement in AMS programs

Pharmacists face numerous barriers in their involvement with AMS programs across diverse healthcare settings, including limited resources, lack of support, and inadequate staffing emerge as primary constraints, often leaving pharmacists with insufficient time dedicated to AMS activities. The lack of comprehensive training and educational opportunities, predominantly in resource-limited settings, significantly influences the pharmacists' ability to lead AMS initiatives. Insufficient support from other healthcare professionals, especially physicians, further complicates pharmacists' roles in AMS. IN LIC and LMICs, integration challenges persist, with unclear role definitions and collaboration difficulties jeopardizing effective multidisciplinary teamwork. Technological barriers, including suboptimal electronic prescribing systems and complex data integration processes, are additional barriers. In developing regions, insufficient laboratory support, inadequate documentation practices, and a lack of standardized guidelines exacerbate these issues. The scarcity of high-quality evidence demonstrating the impact of pharmacist-led interventions on patient outcomes and antimicrobial use patterns undermines support for AMS initiatives. Limited enrollment capacity in specialized courses and training programs discontinuation further impedes progress. Addressing these multifaceted challenges requires concerted efforts to enhance resource allocation, expand training opportunities, improve interdisciplinary collaboration, and foster a supportive environment for pharmacists' crucial contributions to combating antimicrobial resistance. Nampoothiri (2024) conducted a comparative analysis of pharmacists' roles in AMS programs throughout multiple counties, including across India, South Africa (SA), and the United Kingdom (UK). The results showed significant disparities in AMS implementation and challenges. In the UK, pharmacists lead AMS programs, supported by a robust professional curriculum developed by the Clinical Pharmacy Association Infection Committee network, which has become a model for effective AMS leadership. While Indian pharmacists, particularly in the private sector, collaborate with clinicians to drive AMS initiatives, they face challenges such as limited advanced training programs and insufficient acceptance from medical professionals. South African pharmacists experience a dichotomy between active involvement in the private sector and participation in clinician-led programs in the public sector. Across all three countries, insufficient training emerges as a significant barrier, impacting pharmacists' effectiveness and acceptance within AMS programs. India's 'Fellowship in Antimicrobial Stewardship for Pharmacists' at Christian Medical College faces limitations due to restricted enrollment capacity, further exacerbating the training deficit. Time constraints, shortage of trained AMS pharmacists, and inadequate support from physicians are common challenges reported not only in these countries but also in Malaysia and Nigeria, underscoring the global nature of these obstacles. Addressing country-specific challenges while leveraging successful models like the UK's curriculum is crucial to improving training, interdisciplinary acceptance, and resource allocation globally.

Conclusion

The pharmacists' role in AMS programs is integral, and their contributions encompass clinical, educational, and operational domains. The literature review showed a substantial impact of pharmacist-led interventions on optimizing antimicrobial use, improving patient outcomes, and reducing healthcare costs. However, the global landscape of pharmacist involvement in AMS reveals significant disparities and persistent challenges, particularly in resource-limited settings.

These findings highlight several areas for future focus:

a. Global standardization and localization. Developing internationally recognized standards for pharmacist involvement in AMS adapted to local contexts could enhance consistency and effectiveness across diverse healthcare systems.
b. Interdisciplinary collaboration. Strengthening partnerships, communication, and leadership between pharmacists and other healthcare professionals is essential for overcoming barriers to AMS implementation and maximizing program impact.
c. Education and training. Expanding specialized training opportunities and integrating AMS principles into pharmacy curricula worldwide could address the skills gap identified in multiple countries. A pharmacist with expertise in infectious diseases is required.
d. Evidence generation. Conducting robust, long-term studies to quantify the impact of pharmacist-led AMS interventions on antimicrobial resistance patterns and patient outcomes is crucial to attracting broader support and resources.
e. Technology integration. Leveraging advanced informatics and diagnostic tools could enhance pharmacists' capacity to drive data-driven AMS initiatives effectively.
f. Sustainable funding for AMS implementation and adequate training support the pharmacists' contribution through the continuum of care.
g. Expanding AMS programs to ambulatory care, nursing homes, surgery facilities, and dentistry is highly needed.
h. Enhancing pharmacist prescribing authority in community settings.

As the AMR crisis spreads globally, it is crucial to expand the role of pharmacists in AMS. By addressing current challenges and capitalizing on emerging opportunities, the pharmacy profession can consolidate its position as a cornerstone of global efforts to preserve antimicrobial efficacy for future generations. This strategic focus enhances patient care and contributes significantly to global public health by mitigating the spread of antimicrobial resistance.

Competing interests

The author has no financial and non-financial competing interests to declare.

References

1. Ponto JA. ASHP statement on the pharmacist's role in antimicrobial stewardship and infection prevention and control. Am J Health Syst. Pharm. 2010;67:575-577.
2. Barlam TF, et al. Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis. 2016;62:e51-77.
3. Fishman N, et al. Policy statement on antimicrobial stewardship by the society for healthcare epidemiology of America (SHEA), the infectious diseases society of America (IDSA), and the pediatric infectious diseases society (PIDS). Infect Control Hosp Epidemiol. 2012;33:322-327.
4. Cosgrove SE, et al. Guidance for the knowledge and skills required for antimicrobial stewardship leaders. Infect Control Hosp Epidemiol. 2014;35:1444-1451.

5. CDC. Core Elements of Hospital Antibiotic Stewardship Programs. Atlanta, GA: US Department of Health and Human Services, CDC. 2014. Available at: http://www.cdc.gov/getsmart/healthcare/ implementation/core-elements.html. Last accessed: 23 September 2024.
6. Shrestha J, et al. Antimicrobial stewardship. StatPearls. Available at: https://www.ncbi.nlm.nih.gov/books/NBK572068/. Last accessed: 23 September 2024.
7. Nampoothiri V, et al. Pharmacist roles in antimicrobial stewardship: a qualitative study from India, South Africa and the United Kingdom. J Antimicrob Resist. 2024;6:dlae047.
8. Ha DR, et al. The role of antibiotic stewardship in promoting appropriate antibiotic use. Am J Lifestyle Med. 2019;13:376-383.
9. Wang H, et al. Impact of antimicrobial stewardship managed by clinical pharmacists on antibiotic use and drug resistance in a Chinese hospital, 2010–2016: a retrospective observational study. BMJ Open. 2019;9:e026072.
10. Dustin Waters C. Pharmacist-driven antimicrobial stewardship program in an institution without infectious diseases physician support. Am J Health Syst Pharm. 2015;72:466-468.
11. Wu JH, et al. Community pharmacist prescribing of antimicrobials: A systematic review from an antimicrobial stewardship perspective. Can Pharm J (Ott). 2021;154:179-192.
12. Mas-Morey P, et al. A systematic review of inpatient antimicrobial stewardship programmes involving clinical pharmacists in small-to-medium-sized hospitals. Eur J Hospl Pharm. 2018;25:e69-e73.
13. Otieno PA, et al. A Systematic Review of Pharmacist-Led Antimicrobial Stewardship Programs in Sub-Saharan Africa. Int J Clin Pract. 2022;2022:3639943.
14. Cantudo-Cuenca MR, et al. Pharmacist-led antimicrobial stewardship programme in a small hospital without infectious diseases physicians. Sci Rep. 2022;12:9501.
15. Gilchrist M, et al. Antimicrobial stewardship from policy to practice: experiences from UK antimicrobial pharmacists. Infect Dis Ther. 2015;4:51-64.
16. Garau J, et al. Role of pharmacists in antimicrobial stewardship programmes. International journal of clinical pharmacy. 2018;40:948-952.
17. World Health Organization. Antimicrobial stewardship interventions: a practical guide. 2021. Available at: https://iris.who.int/bitstream/handle/10665/340709/9789289054980-eng.pdf?sequence=1. Last accessed: 23 September 2024.
18. Dighriri IM, et al. The role of clinical pharmacists in Antimicrobial Stewardship Programs (ASPs): a systematic review. Cureus. 2023;15:e50151.
19. Dubrovskaya Y, et al. Multilayer model of pharmacy participation in the antimicrobial stewardship program at a large academic medical center. Hosp Pharm. 2017;52:628-634.
20. Giruzzi ME, et al. Evaluation of antibiotic utilization in an emergency department after implementation of an antimicrobial stewardship pharmacist culture review service. Hosp Pharm. 2020;55:261-267.
21. Fay LN, et al. Pharmacist-led antimicrobial stewardship program in an urgent care setting. Am J Health Syst Pharm. 2019;76:175-181.
22. Xu J, et al. The impact of a multifaceted pharmacist-led antimicrobial stewardship program on antibiotic use: evidence from a quasi-experimental study in the department of vascular and interventional radiology in a Chinese tertiary hospital. Front Pharmacol. 2022;13:832078.
23. Uda A, et al. Sustained improvements in antimicrobial therapy and clinical outcomes following a pharmacist-led antimicrobial stewardship intervention: uncontrolled before–after study. J Clin Med. 2022;11:566.
24. Fukuda T, et al. Impact of a pharmacist-led antimicrobial stewardship program on the number of days of antimicrobial therapy for uncomplicated gram-negative bacteremia in a community hospital. Cureus. 2021;13:e14635.
25. Jantarathaneewat K, et al. The role of the clinical pharmacist in antimicrobial stewardship in Asia: A review. Antimicrob Steward Healthc Epidemiol. 2022;2:e176.
26. Sawada K, et al. Effectiveness of Noncertified Pharmacist–Led Antimicrobial Stewardship Programs in a Medium-Sized Hospital Without an Infectious Disease Specialist: A Retrospective Pre–Post Study. Open Forum Infect Dis. 2023;10:ofad116.

27. Suh Y, et al. Potential impact of the involvement of clinical pharmacists in antimicrobial stewardship programs on the incidence of antimicrobial-related adverse events in hospitalized patients: A multicenter retrospective study. Antibiotics. 2021;10:853.
28. Imaura M, et al. [Evaluation of the Effects of Pharmacist Intervention for Adverse Drug Reaction Detection and Exacerbation Avoidance]. Yakugaku Zasshi. 2017;137:767-774.
29. Harmon S, et al. The clinical and financial impact of a pharmacist-driven penicillin skin testing program on antimicrobial stewardship practices. Hosp Pharm. 2020;55:58-63.
30. Polidori P, et al. Role of the hospital pharmacist in an Italian antimicrobial stewardship programme. Eur J Hosp Pharm. 2022;29:95-100.

Chapter 87

Monitoring of antibiotic use, consumption, and the quality of prescribing

Joseph O. Fadare
Department of Pharmacology and Therapeutics, Ekiti State University College of Medicine, Ado-Ekiti, Nigeria;
Department of Medicine, Ekiti State University Teaching Hospital, Ado-Ekiti, Nigeria;
Department of Clinical Pharmacology and Therapeutics/ Medicine, Gombe State University / Federal Teaching Hospital Gombe, Nigeria.

Mohammed M. Manga
Department of Medical Microbiology and Immunology, Gombe State University /Federal Teaching Hospital Gombe Nigeria.

Olayinka O. Ogunleye
Department of Pharmacology, Therapeutics and Toxicology, Lagos State University College of Medicine, Ikeja, Lagos, Nigeria.

Steward Mudenda
Department of Pharmacy, School of Health Sciences, University of Zambia, Lusaka, Zambia.

Introduction

Antibiotics are one of the most-prescribed classes of medicines worldwide; the United States Centre for Disease Control (CDC) reported that a total of 236.4 million prescriptions for antibiotics were issued for outpatients in 2022. Studies have also shown an increase in the quantity of antibiotics utilized worldwide, especially since the year 2000. Although antibiotics are useful for prophylaxis and treatment of infections when used rationally, evidence abound regarding the inappropriate and unnecessary prescribing and use of antibiotics globally. The burden of inappropriate use of antibiotics is more in low- and middle-income countries in comparison to higher-income countries; established drivers for this include poor regulatory policies, poor access to healthcare facilities and lack of stewardship activities within the healthcare facilities. Antibiotic consumption has been particularly recognized as one of the major drivers of antimicrobial resistance (AMR) with higher volume of antibiotic consumption proportionally linked to increased levels of AMR.
A systematic review and analysis of the literature reported mortality attributable to AMR in 2019 at about 4.95 million deaths globally with Sub-Sahara Africa having the largest proportion. This increase in AMR has also been associated with other unwanted consequences such as increased healthcare costs and over-burdening of an already fragile healthcare system. One of the objectives of the Global Action Plan of the World Health Organization (WHO) is the promotion of rational use of antibiotics across the entire world. The monitoring of antibiotic use, volume of consumption and quality of prescribing is the first step towards its rational

use. This evaluation of antibiotic utilisation can be done at various levels: prescribing, dispensing and procurement (facility/central) using mainly quantitative methods.
This chapter describes narratively various indicators (quantitative and qualitative) used in assessing antibiotic utilization with emphasis on their strengths and inadequacies. Articles relating to monitoring of antibiotic use, consumption and quality of prescribing were explored. No time limitation was employed because of the chronological nature of the review.

Monitoring of antibiotic use, consumption, and the quality of prescribing

The monitoring of antibiotic use and quality of prescription is best carried out in drug utilization or pharmacoepidemiologic studies with quality indicators being employed. Data used for such studies include prescription and dispensing data, information from hospital charts, sales or procurement data, health insurance reimbursement claims and other healthcare databases (electronic health records, pharmacy claims).
Some of the quality indicators used in evaluating antibiotic use/consumption are World Health Organisation/International Network of Rational Use of Drugs (WHO/INRUD) Prescribing Indicators, Anatomical Therapeutic Chemical / Defined Daily Dose ATC/DDD Classification and the recently introduced AWaRe class of indicators. These indicators are discussed in greater detail below:

WHO/INRUD prescribing indicators
This set of indicators was introduced by the WHO and International Network for the Rational Use of Drugs in 1993 and consisted of prescribing, facility and dispensing components. The prescribing component, which is still used widely in DUR is descriptive and not specific for antibiotics. One of the main indicators is the percentage of prescribed drugs that are antibiotics with 20-26.8% being the accepted normal values. Medical literature is awash with DU studies from many countries, especially in LMICs using this indicator. While this indicator may be valuable in collecting data from primary healthcare centres, there are challenges when using it in the inpatient settings of secondary and tertiary healthcare facilities. One major deficiency of this indicator is that being mainly descriptive, it does not take into consideration the context of the study. In addition, it does not give room for quantification and classification of prescribed antibiotics, thus, not giving room for objective comparison of studies.

Anatomical therapeutic chemical / defined daily dose (ATC/DDD) classification
The ATC is a broad-based classification of medicines based on the active ingredient of the said drug and the organ system on which they exert their actions, and chemical and pharmacological properties. It was developed by the WHO in 1981 and is being coordinated by its Collaborating Centre for Drug Statistics Methodology. It enables the identification of medicines (including antibiotics) using the same nomenclature worldwide; for example, Amoxicillin is classified as (J01C BETA-LACTAM ANTIBACTERIALS, PENICILLINS) using the ATC. This standardization of nomenclature has enabled seamless data sharing among practitioners and researchers with a positive impact on international collaboration.
The Defined Daily Dose (DDD) is “the assumed average maintenance dose per day for a drug used for its main indication in adults”. The assigned DDD for Amoxicillin is 1g and that for Ceftriaxone is 2g. Antibiotic use is often measured as DDDs per 1,000 patient days; however, other units of measurement also exist such as DDDs per 100 bed days for inpatients (DBDs), Days of therapy per 1000 inhabitants/day (DOTID), DDDs per 1000 inhabitants per day for outpatients (DIDs) and DDDs per inhabitant per year depending on the study population and time frame. The DDDs are particularly useful in point prevalent studies (PPS) for assessing

antimicrobial utilization in healthcare facilities. This indicator is also used in the quantification of antibiotics procured and utilized by regions/countries. It is an objective quantification of drug consumption and enables for comparison of drug consumption between countries, regions, and other healthcare settings. For example, a pan-European study on antibiotic utilization identified countries with high and low consumption levels. This type of information is vital to stakeholders in healthcare for planning and intervention purposes. In addition, it allows for the analysis of trends in antibiotic consumption within facilities and countries.

The Drug Utilization 90% (DU 90%) index

This is an indicator showing drugs responsible for 90% of the total quantity of prescribed drugs using the DDD to rank them. Though used in assessing drug utilization generally, it can be applied with antibiotics to identify the frequently prescribed ones based on quantity and can act as an adjunct indicator for its monitoring.

AWaRe Classification

This classification which was developed in 2017 (and reviewed in 2019 &2021) by the WHO Expert Committee on Selection and Use of Essential Medicines into Access, Watch and Reserve antibiotics takes into consideration the resistance potential of the prescribed antibiotics thus enhancing antibiotic stewardship efforts globally. This new classification is seen as more “practical” as it has more impact on developing practice and policy guidelines. Components of this classification include Percentage of Access antibiotics, Access to Watch Index and Amoxicillin Index which have become very useful in describing antimicrobial use based on resistance potential. According to the WHO, Access class antibiotics should constitute at least 60% of the total consumption of antibiotics at the national level. These indicators have the potential to forewarn healthcare authorities about the trend toward irrational use of antibiotics and the potential for the development of AMR. Recently, the WHO AWaRe (Access, Watch and Reserve) antibiotic book was released with evidence-based recommendations for the treatment of about 30 common infections in clinical settings (both primary healthcare and hospital). **Table 1** shows a summary of the strengths and limitations of the above-listed indicators for assessing antibiotic utilization.

Point prevalence survey of antibiotic Use

This is used to gather information regarding antibiotic prescribing practices in hospitalized patients. It employs some of the above-mentioned indicators (ATC/DDD and AWaRe classification) in addition to gathering other relevant qualitative and contextual data regarding the prescribed antibiotics. Some of the key qualitative indicators included in PPS are adherence to guidelines (especially regarding surgical prophylaxis), indications for antibiotic use, presence of culture-guided prescriptions and parenteral-oral conversion of antibiotics. One of the advantages of PPS is the ability to identify potential gaps where interventions to improve on antimicrobial use within the study settings exist. Additionally, the PPS method is increasingly being employed to develop new quality indicators for different disease entities and population groups.

Table 1. Strengths and limitations of some of the indicators.

Indicators	Strengths	Limitations
WHO/INRUD prescribing indicators	● One of the oldest indicators. ● May be valuable in collecting data from primary healthcare centres.	● Mainly descriptive and lacking relevant contextual information. ● Not specific for antibiotics. ● Does not give room for quantification and classification of prescribed antibiotics.
Anatomical Therapeutic Chemical / Defined Daily Dose (ATC/DDD) Classification	● Enables the identification of medicines (including antibiotics) using same nomenclature worldwide. ● This standardization of nomenclature has enabled seamless data sharing and comparison worldwide. ● DDD is an objective quantification of drug consumption and enables for comparison of drug consumption in and between healthcare facilities.	● Mainly descriptive and lacking relevant contextual information. ● Lacks relevant information regarding resistance potential of prescribed antibiotics.
The Drug Utilization 90% (DU 90%) index	● Useful in assessing most commonly prescribed medicines (including antibiotics) in relation to all prescribed medicines.	● Mainly descriptive and lacking relevant contextual information. ● Does not give room for quantification. ● Lacks relevant information regarding resistance potential of prescribed antibiotics.
AWaRe classification	● Takes into consideration the resistance potential of the prescribed antibiotics. ● Combines both quantitative and qualitative aspect of antibiotic utilisation. Can be used in combination with the ATC/DDD classification in PPS to enrich the antibiotic utilisation data and compare between facilities and countries. ● New AWaRe book has incorporated recommendations for the treatment of common infections in clinical settings. ● Easy to use at almost no cost to researchers.	● Not all antibiotics are listed yet under this classification, hence, may be left out when drug utilisation data is being analysed.

Abbreviations. WHO/INRUD: World Health Organization/International Network of Rational Use of Drugs.

Disease-specific quality indicators of antibiotic use

There are ongoing efforts by different stakeholders to develop disease-specific quality indicators. Examples of such include the percentage of adult patients with bronchitis who receive an antibiotic, antibiotic prescription for acute/chronic sinusitis, tonsillitis and the proportion of patients with pneumonia receiving antibiotics. While it may be easier for these new indicators to be assessed in high-income countries, this may not be the case for LMIC where access to quality healthcare remains a challenge. There may be a need to develop context-specific indicators for these regions.

Conclusion

The monitoring of antibiotic utilisation and quality of prescribing are important components of antimicrobial stewardship. The field is ever-evolving with the development of measurable quantifiable and quality indicators with the overall goal of improving the rational use of antimicrobials and reducing the scourge of AMR. The AWaRe classification of antibiotics and related quality indicators are very accessible and easy-to-use tools in all settings. In addition, the incorporation of multiple indicators in PPS tools has the potential to enrich antibiotic utilisation data and provide key information necessary for more rational use of antibiotics and reducing the scourge of AMR.

Competing interests

The authors have no financial and non-financial competing interests to declare.

References

1. Centers for Disease Control and Prevention. Outpatient antibiotic prescriptions—United States, 2020. Available at: archive.cdc.gov. Last accessed: 20 August 2024.
2. Browne AJ, et al., Global antibiotic consumption and usage in humans, 2000-18: a spatial modelling study. Lancet Planet Health. 2021;5:e893-e904.
3. World Health Organization. WHO report on surveillance of antibiotic consumption: 2016-2018 early implementation. 2018. Available at: https://www.who.int/publications/i/item/9789241514880. Last accessed: 20 August 2024.
4. Tangcharoensathien V, et al. Complex determinants of inappropriate use of antibiotics. Bull World Health Organ. 2018;96:141-144.
5. Otaigbe II, et al. Drivers of inappropriate antibiotic use in low- and middle-income countries. JAC Antimicrob Resist. 2023;5:dlad062.
6. Machowska A, et al. Drivers of Irrational Use of Antibiotics in Europe. Int J Environ Res Public Health. 2018;16:27.
7. Klein EY, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proc Natl Acad Sci U S A. 2018;115:E3463-e3470.
8. Hou J, et al. Global trend of antimicrobial resistance in common bacterial pathogens in response to antibiotic consumption. J Hazard Mater. 2023;442:130042.
9. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022;399:629-655.
10. Founou RC, et al. Clinical and economic impact of antibiotic resistance in developing countries: A systematic review and meta-analysis. PLoS One. 2017;12:e0189621.
11. World Health Organization. Monitoring and evaluation of the global action plan on antimicrobial resistance: framework and recommended indicators. 2019. Available at: apps.who.int. Last accessed: 20 August 2024.
12. Wettermark B, et al. Studies of drug utilization. Pharmacoepidemiology. 2019:373-410.
13. Hogerzeil HV, et al. Field tests for rational drug use in twelve developing countries. Lancet. 1993;342:1408-1410.
14. World Health Organization. How to investigate drug use in health facilities: selected drug use indicators. 1993. Available at: apps.who.int. Last accessed: 20 August 2024.
15. Galappatthy P, et al. WHO/INRUD Core drug use indicators and commonly prescribed medicines: a National Survey from Sri Lanka. BMC Pharmacol Toxicol. 2021;22:67.

16. Goruntla N, et al. Evaluation of Rational Drug Use Based on WHO/INRUD Core Drug Use Indicators in a Secondary Care Hospital: A Cross-Sectional Study in Western Uganda. Drug Healthc Patient Saf. 2023;15:125-135.
17. Ofori-Asenso R, et al. Prescribing indicators at primary health care centers within the WHO African region: a systematic analysis (1995-2015). BMC Public Health. 2016;16:724.
18. Hollingworth S, et al. Measuring medicine use: Applying ATC/DDD methodology to real-world data. Pharmacy. 2021;9:60.
19. Stanic Benic M, et al. Metrics for quantifying antibiotic use in the hospital setting: results from a systematic review and international multidisciplinary consensus procedure. J Antimicrob Chemother. 2018;73:vi50-vi58.
20. Adriaenssens N, et al. Quality appraisal of antibiotic consumption in the community, European Union/European Economic Area, 2009 and 2017. J Antimicrob Chemother. 2021;76:ii60-ii67.
21. Wettermark B, et al. Drug utilisation 90% profiles--a useful tool for quality assessment of prescribing in primary health care in Stockholm. Pharmacoepidemiol Drug Saf. 2003;12:499-510.
22. Uçar EA, et al. ANTIBACDUS-PAN: Antibacterial Utilization among Adult Patients Before and During COVID-19 Pandemic within 12-Months Period: A Tertiary Hospital Pharmacoepidemiology Study. Infect Dis Clin Microbiol. 2022;4:30-39.
23. World Health Organization. The WHO AWaRe (access, watch, reserve) antibiotic book. 2022.
24. Zanichelli V, et al. The WHO AWaRe (Access, Watch, Reserve) antibiotic book and prevention of antimicrobial resistance. Bull World Health Organ. 2023;101:290–296.
25. Mudenda S, et al. World Health Organization AWaRe framework for antibiotic stewardship: Where are we now and where do we need to go? An expert viewpoint. Antimicrob Steward Healthc Epidemiol. 2023 ;3(1):e84.
26. Boltena MT, et al. Point prevalence of evidence-based antimicrobial use among hospitalized patients in sub-Saharan Africa: a systematic review and meta-analysis. Sci Rep. 2024;14:12652.
27. Versporten A, 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:e619-e629.
28. Akintan P, et al. Point prevalence surveys of antibiotic prescribing in children at a tertiary hospital in a resource constraint, low-income sub-Saharan African country-the impact of an antimicrobial stewardship program. BMC Pediatr. 2024;24:383.
29. Versporten A, et al. The Worldwide Antibiotic Resistance and Prescribing in European Children (ARPEC) point prevalence survey: developing hospital-quality indicators of antibiotic prescribing for children. J Antimicrob Chemother. 2016;71:1106-1117.
30. Vellinga A, et al. Disease-Specific Quality Indicators for Outpatient Antibiotic Prescribing for Respiratory Infections (ESAC Quality Indicators) Applied to Point Prevalence Audit Surveys in General Practices in 13 European Countries. Antibiotics. 2023;12:572.

Chapter 88

The core concepts of antimicrobial stewardship

Cornelius C. Dodoo
School of Pharmacy, University of Health and Allied Sciences, Ghana.

Ebo Hanson-Yamoah
School of Pharmacy, University of Health and Allied Sciences, Ghana.

Rita Sewornu
Laboratory Department, Ho Teaching Hospital, Ghana.

Helena Owusu
Korle-Bu Teaching Hospital, Ghana.

Introduction

Antimicrobial stewardship (AMS) is a coordinated programme that promotes the appropriate use of antimicrobials (including antibiotics), improves patient outcomes, reduces microbial resistance, and decreases the spread of infections caused by multidrug-resistant pathogens. The emergence of antimicrobial resistance as a health issue has been linked to high economic costs, prolonged hospitalizations, increased morbidity and occasionally, death. The continuous and unguided use of antimicrobials has resulted in the development of resistant microbes implicated in hospital-associated infections; this has resulted in treatment failures, particularly in intensive care units. Several pathogens have been linked to hospital-associated infections with high resistance to standard antibacterials. These include *Clostridium difficile* infections, methicillin-resistant *Staphylococcus aureus* (MRSA), *Acinetobacter baumannii* and extended-spectrum beta-lactamases (ESBL) producing bacteria such as *Escherichia coli*.

According to the Centers for Disease Control and Prevention (CDC), implementing hospital-based AMS programmes can improve infection cure rates while reducing treatment failures, adverse effects, antimicrobial resistance, hospital costs and duration of stay. Despite the concept of AMS being conceived in the 1990s, many staff and facilities have struggled to implement such programmes. AMS initiatives are crucial for ensuring better patient care, reduced dependency on antimicrobials, and accessibility to care. The World Health Organization (WHO) released a Global Action Plan to fight antimicrobial resistance (AMR) in 2015. This served as the basis for the development of National Action Plans around the world. In 2017, Ghana developed its policy on antimicrobial use and resistance and the National Action Plan to reduce AMR with ongoing monitoring activities.

Currently, AMS is one of the pillars of strengthening healthcare systems. Integrating AMS with AMR monitoring and ensuring a steady supply of quality medicines can enhance equitable healthcare and aid in achieving universal health coverage.

The focus of AMS revolves around the 5 ‘D’s of antimicrobial therapy, which are, the right Drug, the correct Dose, the right drug route, suitable Duration and timely De-escalation to pathogen-directed therapy. These principles promote interventions when multiple antibiotics with similar activity are prescribed, as well as when the prescribed antimicrobial is ineffective against the resistant microorganism being targeted. Another focus is on recommending a change from intravenous to oral dosage forms.

Core concepts

To establish a successful AMS programme at a healthcare institution, some core elements are generally recommended by the Centers for Disease Control, World Health Organization and the Commonwealth Pharmacists Association. The core elements outline the details of the structures and procedures needed for successful stewardship programmes.

Leadership commitment

The progress and success of an AMS programme are dependent on leadership support. Regular updates on strategies and activities are important to engage the leadership team, helping them to fully appreciate the fundamentals of the AMS initiative and how they are linked to the overall provision of care. By encouraging and fostering this understanding, the leadership is better equipped to make informed decisions regarding the allocation and distribution of budgetary and material needs. Cooperation between management and the AMS team is crucial for ensuring that the goals of the programme are aligned with the broader objectives of the institution. This alignment not only strengthens the programme’s importance, but it further ensures its integration into the operating procedures of the institution. Moreover, for an AMS programme to thrive, it must go beyond the required substantial and sustained institutional support. This includes not just the provision of financial resources and materials, but also active involvement in developing a professional workplace culture that prioritizes the appropriate use of antimicrobials. By promoting a culture that highlights the appropriate use of antimicrobials consistent with existing national or international guidelines, the leadership can make the AMS programme a central part of providing efficient outcomes.

Accountability

A formal AMS committee must be established, guided by a clear and concise written policy. This policy must outline the objectives, protocols, and accountability measures necessary to ensure the appropriate use of antimicrobials. Remuneration, hierarchical structure, roles and responsibilities and frequency of meetings must be included in the policy guide. AMS committees are unique and may vary from one institution to another. In some facilities, they may either be standing committees or sub-committees. In cases where they are sub-committees, they are usually embedded into other committees such as the Drugs and Therapeutic Committee, Infection Prevention and Control Committee, or Patient Safety Committee. The AMS committee must liaise with other committees in facilities where they are independent, especially with the Infection Prevention and Control Committee. A leader with sufficient knowledge in infection management and practices may be selected as the leader of the committee. In certain facilities, an infectious diseases specialist pharmacist or physician may be the lead for the implementation of the programme. This key figure in leadership provides oversight and is responsible for tracking and documenting the achievement of measures. It is imperative to have a diverse team of health professionals with different competencies to perform assigned duties and deliver on the aims and objectives of the programme. However, the makeup of the team can be

adjusted based on facility type (quaternary, tertiary, secondary or primary care facility) and tailored to fit the specific needs of the facility.

In understaffed facilities, members of the committee may be limited. In smaller facilities, an AMS champion, usually a nurse practitioner, may be identified to handle the programme. The nominated members must dedicate time to hold regular meetings to discuss issues of concern and then provide regular detailed reports to management and fellow staff. These may include reports on antimicrobial use data analysis and prescription improvement efforts. The report must include both short-term and long-term measurable goals or targets, with specific timeframes to optimize antimicrobial usage. Input from non-members must be encouraged and incorporated into discussions and reports.

Pharmacy expertise

To strengthen an AMS programme, there must be good engagement with pharmacists qualified in infection management practices. Pharmacists can be empowered through formal training and certificate programmes in infectious disease management to enhance their contribution toward AMS in hospitals. The skills of infectious disease specialists are central to infection management practices. The infectious disease pharmacist will identify the appropriate medication, dose and route of the antimicrobial agent. The presence and collaboration of infectious disease experts are vital in diagnosing, treating and preventing infections. This approach is important in ensuring smoother patient care.

Action

The healthcare facility must maintain a current set of protocols for diagnosing, treating, managing and preventing infections consistent with national and international guidelines and based on local and national susceptibility patterns. The facility-endorsed protocols must include procedures for hand hygiene and sanitation, a restricted antimicrobial list that limits the use of antimicrobials for specific conditions and a policy on switching from intravenous medications to oral. Antimicrobial prescribing guidelines must be incorporated into the facility formulary. These guidelines must conform to the WHO Access, Watch and Reserve groups. Regular patient medication reviews and audits, through ward rounds and bedside consultations, must be conducted on critical wards such as intensive care units and surgical wards, as patients in these areas are at higher risk of contracting new infections and experiencing exacerbations of existing ones. Focusing on these departments allows for close monitoring, ensures adherence to the stated protocols and helps to identify areas for improvement. Mandatory documentation of processes is required to ensure continuity of care. This requirement ensures that all healthcare providers regardless of shift, have access to detailed information about the treatment plan, thereby reducing the risk of errors and omissions.

Tracking

This involves the routine monitoring of prescription and resistance trends. Point prevalence surveys can be conducted by the AMS team at the unit and/or facility level to evaluate the suitability of antimicrobial prescribing practices and infection management. The antimicrobial agent, dose and frequency should be examined to determine the appropriateness. The AMS team, in partnership with the pharmacy department, can track and analyze the consumption rate of antimicrobials by monitoring how they are purchased, prescribed and dispensed - that is the Defined Daily Doses (DDD) approach. Other metrics such as Days of Therapy (DOT) can be employed to observe the frequency of antimicrobial use. This enables the identification of areas in need of development and improvement as well as tracking the programme's performance over time.

Reporting

Antimicrobial stewardship thrives on transparent communication. There must be frequent sharing of facility data on antimicrobial use and resistance. To guide practice, findings from analyses of antimicrobials purchased, prescribed and dispensed must be shared with prescribers with specific action points. Reports on antimicrobial susceptibility rates must be shared to inform clinicians about resistance patterns such that the most effective antimicrobials can be selected for use. The results of audits must be shared directly with prescribers. This feedback must include recommendations and suggestions to improve prescribing practices helping to ensure that antimicrobials are appropriately used. This feedback loop fosters informed decision-making and ultimately improves programme outcomes.

Education

This includes the dissemination of current information to staff and management through lectures, poster presentations and grand rounds. Continuous education and training on antimicrobial stewardship to healthcare providers improves prescribing practices and enhances programme effectiveness.

The national agency in charge of health must make available materials such as guidelines, best practice protocols, training modules to enhance understanding, capacity and support training of staff on antimicrobial prescribing. Facilities can assist by conducting internal workshops and seminars to make sure staff are well informed about best practices. Larger facilities with large workforces can employ online lectureships to keep their staff and other smaller facilities updated. Recruits and older staff must regularly undergo mandatory training on antimicrobial use, infection prevention, control and management. This is to ensure that staff always have updated knowledge on such themes. Training sessions should be conducted at least biannually if not quarterly to reinforce practices.

The stewardship team

Despite the unique organizational structure of each health facility, every facility must strive to have several essential members as contact persons to initiate and sustain the AMS programmes. An infectious disease physician, a clinical pharmacist with specialized training in infectious diseases, a laboratory microbiologist, a nurse, an information technology expert/data analyst, a quality assurance and improvement manager, a hospital administrator, an infection prevention and control specialist and a hospital epidemiologist are some of the key members needed. This may be challenging for some facilities due to facility type, therefore as many as can be included is ideal.

The role of the infectious disease physician is to provide clinical guidance to assist in running the programme. Having a physician on the team will ensure engagement and cooperation from other physicians. Antimicrobial education, pre- and post-prescription review and development of guidelines are duties to be performed by the pharmacist. Even in the absence of an infectious disease physician, significant cost savings and a notable reduction in the length of hospital stay for patients have been recorded during the implementation of AMS programmes. Facilities with infectious diseases pharmacists tend to have more successful patient outcomes compared to general pharmacists as their recommendations are more patient-specific. Whereas the infectious disease pharmacist may be proficient in pharmacology and pathophysiology, he/she may still require the help of an infectious disease physician to make decisions based on the patient's history, laboratory and imaging findings.

Reports from culture and sensitivity tests are needed for the optimization of therapy. An antibiogram must be drafted and updated yearly to generate susceptibility data to help in the development of guidelines for

use. This will help tailor antimicrobial treatment based on susceptibility profiles and promote prudent antimicrobial use by discouraging unnecessary broad-spectrum therapy. In addition to retrieving records for use and analysis, the information technology/data analyst will be vital in generating reports and statistics.

Antimicrobial stewardship strategies

There are several strategies needed for AMS, including pre-prescription and post-prescription approaches, diagnostic stewardship and education. The pre-prescription or front-end approach and the post-prescription or back-end approach to stewardship are two major approaches to antimicrobial stewardship in the hospital setting. The pre-prescription approach involves restrictive prescribing authority, where some antimicrobials are classified as restricted. These antimicrobials require pre-approval for use, except for a select group of clinicians. Physicians and support staff without prescribing authority must contact the designated antimicrobial steward to request approval. This allows for targeted use of antimicrobials based on local resistance patterns and hospital formulary preferences. The drawback of this approach is that as authorization is required, it may cause a delay in the onset of therapy.

The post-prescription approach relies on prospective review and feedback. This includes suggestions/recommendations to continue, adjust, change, or discontinue therapy, ensuring appropriate treatment decisions are made. In this approach, an antimicrobial steward reviews current antimicrobial orders and provides prescribers with recommendations based on available microbiology results and clinical features of the case. A key benefit of this approach is de-escalation. This involves the discontinuation of one or more components of combination empirical therapy, and/or the substitution of a broad-spectrum antimicrobial with a narrow-spectrum antimicrobial based on culture and sensitivity testing, general laboratory findings, and the patient's clinical status. This is particularly preferred in intensive care unit settings for patients on broad-spectrum antimicrobials. The aim is to ensure more targeted control. However, this approach's prolonged nature, due to the alterations in antimicrobial therapy, can be expensive and resource-intensive. Resource-constrained facilities may lack the adequate capacity needed to establish active surveillance.

Exposure of patients to several antimicrobials may adversely affect the microbiome. Despite its demerits, an examination of these strategies has revealed that back-end approaches, though requiring more effort, are more commonly used, readily accepted by clinicians, and offer greater education opportunities. This review assesses the appropriateness of antibiotic use, and feedback is provided directly to the healthcare provider responsible for the patient. The goal is to enhance antimicrobial use while reducing the risk of bacterial resistance and adverse effects. Prospective audit and feedback can be adapted to various healthcare environments, whether inpatient or outpatient, depending on the available resources and can be used to target a range of interventions.

Diagnostic stewardship involves the process of modifying the ordering, performing, or reporting of diagnostic tests to guide clinical management by ensuring the accuracy of diagnosis and treatment of infections and other conditions. It also helps to curb costs, unnecessary testing, invasiveness and harm. These pre-analytic, analytic and post-analytic workflow interventions are to reduce the incidence of false positives. A key objective of diagnostic stewardship is to prevent diagnostic errors.

Also, education is a key strategy and is integral in establishing AMS programmes. This may come in the form of didactic training, lectures, tutorials, conferences, or even guidelines. The emphasis of such programmes should be on the threat of antimicrobial resistance and the consequences of the inappropriate use of antimicrobials. AMS should be included in the curriculum of health programmes. It can also be made available to healthcare providers as a form of continuous professional development or on-the-job training. This ensures

that they can receive current evidence-based information on AMS to make informed decisions. After an AMS training in England, it was noted that there was an improvement in knowledge as test scores had risen from 67.7% pre-training to 81.1% post-training. However, education alone without the incorporation and integration with other strategies, is ineffective.
Kpokiri *et al.* also noted that through AMR-focused training, AMS skills and practice among healthcare providers could be improved. This improvement was observed after an AMS educational intervention was introduced in Ho Teaching Hospital in Ghana.

Challenges and barriers

Implementing AMS is inherently difficult and is further worsened when resources are scarce such as human resources, capital, laboratory support, drugs, policies, and the implementation of formal programmes. The limited availability of these essential resources makes AMS particularly demanding. A global survey of health facilities among African countries revealed that the most common barriers to establishing an AMS programme are the lack of IT infrastructure, lack of resources and funding and lack of awareness on the part of the hospital administration. High staff turnover and poor communication between the laboratory, pharmacists and clinicians are also identified as potential challenges in implementing AMS. In Low- and Middle-Income Countries (LMIC), unique challenges such as densely populated areas can lead to the spread of resistant strains when there is an outbreak of disease and a high incidence of infectious diseases which places pressure on the already limited capacity of available laboratories and uneven and often inadequate healthcare infrastructure. Coupled with high provider-to-patient ratios and restricted or poorly regulated access to essential antimicrobials, these factors can impair AMS programmes. The impaired capacity of laboratories complicates the ability to generate antibiograms to aid clinicians in making sound clinical decisions. Despite the numerous problems, significant progress has been made in achieving AMS goals in LMICs.
Further, behavioural and cultural barriers significantly hinder AMS programmes. Altering key behaviours across multiple levels, including individual, team, organizational, and policy levels, is essential for the success of an AMS programme. This complex change requires multiple healthcare providers to adapt to various behaviours at different stages within the patient care pathway. Implementing such changes necessitates coordinated efforts across diverse levels of the healthcare system.
The majority of AMS initiatives focus on prescribing behaviours and practices., However, in the hierarchical organizational culture in most hospitals, the lack of acceptance of questioning or recommendations, as well as the demur nature of staff to question prescribers, can pose significant barriers to implementing AMS.
Time constraints are a major problem hampering the adoption of AMS programmes in several facilities. The high provider-to-patient ratio restricts the ability of healthcare providers, especially in Ghana, to join such programmes due to their demanding nature. Even in instances when time is allocated for the programme, it is insufficient to cover the entire scope. Some facilities in High-Income Countries have had to abandon their programmes due to busy schedules and the unavailability of staff.
Effective AMS programmes in LMICs are also hindered by high costs and a lack of regulation and quality assurance resulting in widespread availability of counterfeit and substandard medicines which leads to low confidence in generic medications. Delayed or inadequate access to antimicrobials is another major issue in LMICs, which inadvertently leads to increased mortality. Access to quality antibiotics in LMIC is therefore essential to ensure a successful AMS programme due to its impact on treatment.

Conclusion

AMS must be championed by all cadres of healthcare professionals. In the clinical space, positive reinforcement must be given to healthcare providers who adhere to AMS practices to enrich participation. Regulatory and enforcement mechanisms must be instituted to restrict the over-the-counter sales of antimicrobials to prevent misuse. Increased funding, support and mentorship by developed countries must be increased to guide policies aimed at combatting AMR and lowering the associated morbidity and mortality. A country can have the best practices, but all it takes is for an individual carrying resistant microbes to travel to that country to introduce the resistant strain. Collective and supportive action is needed by all countries to address AMR effectively.

Furthermore, antimicrobial resistance represents a grave threat to public health and security. As resistant strains emerge, there is a pressing need for efforts to either curtail or slow down the spread of resistance. Active surveillance must be conducted to isolate and identify pathogenic bacteria of concern that pose a chance of being resistant to current medications in the near future.

Finally, frequently consumed antimicrobials must be cautiously used to avoid rendering them ineffective. Definitive therapy, personalized treatment and combination therapy should be prioritized over monotherapy to prevent the development of resistance, enhance treatment success rates, and allow the use of lower drug concentrations for shorter treatment periods. Additionally, the development of costly new antimicrobials is necessary to meet growing demands, as treatment options for resistant bacteria are becoming increasingly limited.

Competing interests

The authors have no financial and non-financial competing interests to declare.

References

1. Alajmi SM, et al. Effective antibiotic stewardship program: controlling antibiotic resistance and optimizing drug use in Ahmadi Hospital. Journal of Analytical Sciences, Methods and Instrumentation. 2020:10:1-11.
2. Centers for Disease Control. The core elements of hospital antibiotic stewardship programs. 2019. Available at: https://www.cdc.gov/antibiotic-use/healthcare/pdfs/hospital-core-elements-H.pdf. Last accessed: 28 September 2024.
3. Commonwealth Pharmacists Association. Commonwealth Partnerships for Antimicrobial Stewardship. 2020. Available at: https://commonwealthpharmacy.org/cwpams/. Last accessed: 28 September 2024.
4. Cox JA, et al. Antibiotic stewardship in low- and middle-income countries: the same but different? Clin Microbiol Infect. 2017;23:812-818.
5. D'Arcy N, et al. Antibiotic Prescribing Patterns in Ghana, Uganda, Zambia and Tanzania Hospitals: Results from the Global Point Prevalence Survey (G-PPS) on Antimicrobial Use and Stewardship Interventions Implemented. Antibiotics (Basel). 2021;10:1122.
6. Daneman N, et al. The association of hospital prevention processes and patient risk factors with the risk of Clostridium difficile infection: a population-based cohort study. BMJ Qual Saf. 2015;24:435-443.
7. De Waele JJ, et al. Antimicrobial de-escalation as part of antimicrobial stewardship in intensive care: no simple answers to simple questions-a viewpoint of experts. Intensive Care Med. 2020;46:236-244.

8. Dodoo CC, et al. Development of a local antibiogram for a teaching hospital in Ghana. JAC Antimicrob Resist. 2023;5:dlad024.
9. Dodoo CC, et al. Antimicrobial Prescription Pattern in Ho Teaching Hospital, Ghana: Seasonal Determination Using a Point Prevalence Survey. Antibiotics (Basel). 2021;10:199.
10. Dorobisz MJ, et al. Antimicrobial Stewardship Metrics: Prospective Audit with Intervention and Feedback. R I Med J (2013). 2018;101:28-25.
11. Doron S, et al. Antimicrobial stewardship. Mayo Clin Proc. 2011;86:1113-1123.
12. Dyar OJ, et al. What is antimicrobial stewardship? Clin Microbiol Infect. 2017;23:793-798.
13. Elshenawy RA, et al. Antimicrobial stewardship implementation before and during the COVID-19 pandemic in the acute care settings: a systematic review. BMC Public Health. 2023;23:309.
14. Fabre V, et al. Principles of diagnostic stewardship: A practical guide from the Society for Healthcare Epidemiology of America Diagnostic Stewardship Task Force. Infect Control Hosp Epidemiol. 2023;44:178-185.
15. Gebretekle GB, et al. Opportunities and barriers to implementing antibiotic stewardship in low and middle-income countries: Lessons from a mixed-methods study in a tertiary care hospital in Ethiopia. PLoS One. 2018;13:e0208447.
16. Gilchrist M, et al. Antimicrobial Stewardship from Policy to Practice: Experiences from UK Antimicrobial Pharmacists. Infect Dis Ther. 2015;4:51-64.
17. Goff DA, et al. Impact of a national antimicrobial stewardship mentoring program: Insights and lessons learned. Am J Health Syst Pharm. 2017;74:224-231.
18. Howard P, et al. An international cross-sectional survey of antimicrobial stewardship programmes in hospitals. J Antimicrob Chemother. 2015;70:1245-1255.
19. Indian Council of Medical Research. Antimicrobial Stewardship Program Guideline. 2018. Available at: https://main.icmr.nic.in/sites/default/files/guidelines/AMSP_0.pdf. Last accessed: 28 September 2024.
20. Jang W, et al. Effect of discontinuation of an antimicrobial stewardship programme on the antibiotic usage pattern. Clin Microbiol Infect. 2021;27:1860.e1-1860.e5.
21. Kpokiri EE, et al. Knowledge, Awareness and Practice with Antimicrobial Stewardship Programmes among Healthcare Providers in a Ghanaian Tertiary Hospital. Antibiotics (Basel). 2021;11:6.
22. Kumar A, et al. Nosocomial infections-related antimicrobial resistance in a multidisciplinary intensive care unit. MGM J Med Sci. 2022;9:12-18.
23. Lam TT, et al. What are the most effective community-based antimicrobial stewardship interventions in low- and middle-income countries? A narrative review. J Antimicrob Chemother. 2021;76:1117-1129.
24. Laxminarayan R, et al. Access to effective antimicrobials: a worldwide challenge. Lancet. 2016;387:168-175.
25. Madden GR, et al. Diagnostic Stewardship for Healthcare-Associated Infections: Opportunities and Challenges to Safely Reduce Test Use. Infect Control Hosp Epidemiol. 2018;39:214-218.
26. Majumder MAA, et al. Antimicrobial Stewardship: Fighting Antimicrobial Resistance and Protecting Global Public Health. Infect Drug Resist. 2020;13:4713-4738.
27. Morgan DJ, et al. Diagnostic Stewardship-Leveraging the Laboratory to Improve Antimicrobial Use. JAMA. 2017;318:607-608.
28. Mzumara GW, et al. Protocols, policies and practices for antimicrobial stewardship in hospitalized patients in least-developed and low-income countries: a systematic review. Antimicrob Resist Infect Control. 2023;12:131.
29. Ng V, et al. Outcomes of a National, Cross-Sector Antimicrobial Stewardship Training Initiative for Pharmacists in England. Pharmacy (Basel). 2021;9:165.
30. Otieno PA, et l. A Systematic Review of Pharmacist-Led Antimicrobial Stewardship Programs in Sub-Saharan Africa. Int J Clin Pract. 2022;2022:3639943.
31. Rzewuska M, et al. Prioritizing research areas for antibiotic stewardship programmes in hospitals: a behavioural perspective consensus paper. Clin Microbiol Infect. 2019;25:163-168.
32. Sefah IA, et al. An Assessment of the Current Level of Implementation of the Core Elements of Antimicrobial Stewardship Programs in Public Hospitals in Ghana. Hosp Pharm. 2024;59:367-377.
33. Shrestha J, et al. Antimicrobial Stewardship. 2023 Jun 20. In: StatPearls. Treasure Island (FL): StatPearls Publishing;

2024 Jan–.
34. Sneddon J, et al. Supporting antimicrobial stewardship in Ghana: evaluation of the impact of training on knowledge and attitudes of healthcare professionals in two hospitals. JAC Antimicrob Resist. 2020;2:dlaa092.
35. Steinmann B, et al. The Path Is the Goal: How Transformational Leaders Enhance Followers' Job Attitudes and Proactive Behavior. Front Psychol. 2018;9:2338.
36. Tamma PD, et al. Antimicrobial stewardship. Infect Dis Clin North Am. 2011;25:245-60.
37. Umemura T, et al. Efficacy of Combination Therapies for the Treatment of Multi-Drug Resistant Gram-Negative Bacterial Infections Based on Meta-Analyses. Antibiotics (Basel). 2022;11:524.
38. World Health Organization. Antimicrobial stewardship programmes in health-care facilities in low-and middle-income countries: a WHO practical toolkit. 2019. Available at: https://iris.who.int/handle/10665/329404. Last accessed: 28 September 2024.
39. World Health Organization. Health workers' education and training on antimicrobial resistance: curricula guide. 2019. Available at: https://iris.who.int/bitstream/handle/10665/329380/9789241516358-eng.pdf?sequence=1. Last accessed: 28 September 2024.
40. Zimbwe KB, et al. Surveillance of antibiotics use in inpatients at Benjamin Mkapa Zonal Referral Hospital in Dodoma, Tanzania: a point prevalence survey. BMJ Open. 2024;14:e083444.

Chapter 89

Challenges of antimicrobial stewardship in hospital settings

Majdi N. Al-Hasan
University of South Carolina School of Medicine, Columbia, South Carolina, USA;
Prisma Health Midlands, Columbia, South Carolina, USA.

Hana R. Winders
Prisma Health Midlands, Columbia, South Carolina, USA.

P. Brandon Bookstaver
University of South Carolina College of Pharmacy, Columbia, South Carolina, USA;
Prisma Health Midlands, Columbia, South Carolina, USA.

Introduction

Antimicrobial stewardship teams have essential roles in serving the hospital population, supporting the healthcare providers, and facilitating antimicrobial management. This includes improving the appropriateness of both empirical and targeted antimicrobial therapy, minimizing antimicrobial-associated adverse effects such as *Clostridioides difficile* infection (CDI), reducing the development and selection of antimicrobial resistance, and providing cost-effective antimicrobial management. However, in pursuit of these major tasks, antimicrobial stewardship teams face significant challenges in hospitals. In this chapter, the major challenges and potential, practical and evidence-based solutions are proposed.

Excessive use of broad-spectrum antibiotics

Receipt of appropriate empirical antimicrobial therapy is the most important modifiable variable in the management of patients with serious infections. It has been associated with improved survival and shorter hospital length of stay in patients with sepsis and bloodstream infection (BSI). In a noble and genuine effort to improve patient outcomes, healthcare providers tend to use excessive amounts of broad-spectrum antimicrobials in fear of rising antimicrobial resistance rates. This is particularly common in critically ill patients, those with major comorbid medical conditions, and immune compromised hosts. The excessive use of broad-spectrum antibiotics is, by far, the most important challenge that faces antimicrobial stewards in hospitals. The art of antimicrobial management is to achieve a near-perfect balance between prescribing appropriate empirical antibiotic regimens before the availability of microbiology results and avoiding excessive broad-spectrum antibiotic use as much as possible. This section summarizes the rationale and proposes solutions for the excessive use of five major classes of antibiotics in hospitals.

Antipseudomonal beta-lactams (APBL)

Despite the relative infrequency of infections due to *Pseudomonas aeruginosa* in immune-competent patients, APBL are commonly prescribed in hospitals for the empirical therapy of many community-acquired infections. Piperacillin/tazobactam, ceftazidime, and cefepime are among the most frequently used antibiotics in hospitals worldwide. These antibiotics are often used as first-line agents for empirical therapy of hospitalized patients with sepsis, intraabdominal infections, and diabetic foot infections, among other common infections. While the empirical use of these antibiotics may be appropriate in patients with hospital-acquired infections and severely immune compromised hosts, APBLs are often used without risk stratification. The empirical use of APBL in the general population is often not justified due to the relative infrequency of *P. aeruginosa* infections in patients without specific risk factors. These risk factors include prolonged hospitalization for five or more days, severely immune compromised status (e.g., chemotherapy-induced neutropenia, hematogenous and solid organ transplantation, prolonged use of high-dose glucocorticoids, and other immune suppressive medications), and recent use of beta-lactam antibiotics (i.e., penicillins and cephalosporins). The routine use of APBL for empirical therapy of community-acquired respiratory, urinary tract, intra-abdominal, and diabetic foot infections is discouraged in international management guidelines.

Once initiated, most often APBLs are continued for the majority of the antibiotic course. The inability to establish the microbiological etiology of infection due to negative blood cultures and difficulty collecting clinical samples for culture from the site of infection, as in many patients with pneumonia and intraabdominal infections, contribute to the lack of de-escalation of APBL therapy. In addition, delayed collection of clinical cultures after initiation of antibiotic therapy is common in many patients with urinary tract and soft tissue infections. This limits antimicrobial stewardship efforts in the de-escalation of APBL to narrower spectrum agents. Even when a microbiological etiology is established as in patients with BSI, de-escalation of APBL is often not carried out or delayed for several days after the culture results are available. The reliance on traditional culture methods rather than rapid diagnostics for microbial identification in most of the world contributes further to the delay in the de-escalation of antibiotic therapy.

The prolonged use of APBL is associated with an increased risk of hospital-onset CDI and the selection of antimicrobial resistance in hospitals, which further fuels the excessive use of broad-spectrum antibiotics. In many hospitalized patients with a low-predicted risk of infections due to *P. aeruginosa*, the potential risks of these major complications in association with APBL use exceed the potential benefits from empirical APBL therapy, if any at all.

Carbapenems

The increasing incidence of community- and hospital-onset infections due to extended-spectrum beta-lactamase (ESBL)-producing bacteria has driven the excessive use of carbapenems in hospitals. Carbapenems are considered first-line antimicrobial agents for the treatment of BSI and other serious infections due to ESBL-producing bacteria. In patients with BSI due to ESBL-producing *Escherichia coli* and *Klebsiella* species, meropenem is associated with lower mortality as compared to piperacillin/tazobactam or cephalosporins. The fear of missing ESBL-producing bacteria in a critically ill patient has fueled the excessive use of meropenem and other carbapenems in hospitals even in settings with less than 10% overall incidence of ESBL production among *E. coli* and other *Enterobacterales*. In addition, this practice has been extrapolated without evidence to non-critically ill patients, including those with urinary tract infections. Penicillin allergy also seems to drive unnecessary carbapenem use in hospitals.

The excessive use of carbapenems in hospitals and skilled nursing facilities is associated with the development and selection of carbapenem-resistant *Enterobacterales* (CRE) and other carbapenem-resistant bacteria. The potential of subsequent transmission of CRE to other patients in the hospital and skilled nursing

facilities constitutes a major challenge not only to antimicrobial stewards but also to infection prevention and control programs. Treatment of infections due to CRE and other carbapenem-resistant bacteria often requires either new and very expensive or old and highly toxic antibiotics. This constitutes an additional major challenge to hospitals. Moreover, the prognosis of many patients with serious infections due to CRE and carbapenem-resistant *P. aeruginosa* and *Acinetobacter baumannii* remains poor. Carbapenem use is also associated with a high risk of CDI infection in hospitals and skilled nursing facilities.

Clindamycin

In hospital settings, clindamycin overuse becomes a problem often due to allergies to penicillin or vancomycin. Often patients with allergy labels do not have true allergies to these antibiotics. With vancomycin, the reaction is often infusion-related. In the United States, it is estimated that 10% of the population has a reported allergy to penicillin. However, often these patients have very low-risk reactions such as gastrointestinal upset, a childhood rash after a possible viral illness, or a family history of penicillin allergy. Even in truly allergic patients, at least 80% of people with penicillin-allergic reactions will "lose" their allergy after 10 years. Unfortunately, even though there is low cross-reactivity between penicillin and cefazolin, it is reported that patients with penicillin allergy labels are significantly more likely to receive clindamycin as pre-operative prophylaxis than those without penicillin allergies. Due to the increased use of cefazolin alternatives, patients with penicillin allergy labels have a 50% increased odds of surgical site infections. Clindamycin use in suspected or proven necrotizing skin and soft tissue infections is also common. Emerging data on the effectiveness of linezolid for this indication may provide stewards with an evidence-based alternative. Clindamycin is associated with a high risk of CDI in hospitals and the community.

Fluoroquinolones

Another class of antibiotics that can be overused in hospitals are fluoroquinolones. While fluoroquinolones are considered first-line agents for certain indications such as oral treatment of acute pyelonephritis and transition from intravenous to oral therapy for Gram-negative BSI, the overuse may lead to unnecessary toxicities. Fluoroquinolones are associated with significant adverse events including tendinopathy and tendon rupture, peripheral neuropathy, aortic aneurysm, dysglycemia, and central nervous system effects. Fluoroquinolone use in hospitals is also associated with a high risk of CDI. Studies have shown that decreasing fluoroquinolone use in hospitals can lead to a corresponding decrease in healthcare facility-associated CDI. In addition, fluoroquinolones are associated with the development of antibiotic resistance, including selection of ESBLs.

Anti-methicillin-resistant *Staphylococcus aureus* (MRSA) agents

Although declining in the United States, the proportion of methicillin resistance among *Staphylococcus aureus* clinical isolates was slightly below 40% in 2019, necessitating empirical antibiotic coverage for MRSA in many hospitalized patients when *S. aureus* is considered a potential pathogen. Vancomycin has been the longstanding option for MRSA treatment, however use of other agents including daptomycin and linezolid presents potentially cost-effective and safe options. Antimicrobial stewardship programs may seek vancomycin alternatives to optimize effectiveness, minimize the risk of nephrotoxicity, and reduce the need for therapeutic drug monitoring and personnel time to calculate and adjust dosing. Transitioning to these alternatives may prove challenging to some institutions due to a lack of updated local protocols or guidelines recommending vancomycin alternatives and/or the concern with antibiotic access upon discharge. Much like when direct oral anticoagulants were coming on the market, there was concern about replacing the job

responsibilities of some clinicians who specialized in international normalized ratio (INR) follow-up for warfarin, a similar concern may be present for those doing lots of daily vancomycin consults.

Proposed solutions for excessive use of broad-spectrum antimicrobial agents

Risk stratification using clinical tools for the prediction of antimicrobial resistance

Stratification of patients based on the predicted risk of infection due to resistant bacteria is a useful strategy to stem the tide of excessive broad-spectrum antibiotic use in hospitals. Based on this strategy, APBL would be started empirically only in patients with specific risk factors for infections due to *P. aeruginosa* (severely immune compromised, prolonged hospitalization, prior infections or colonization with *P. aeruginosa*, or recent use of beta-lactams). This would spare most hospitalized patients with suspected infections, particularly at community hospitals, from unnecessary use of APBL for empirical therapy.

Similarly, carbapenems would be started empirically in patients with serious infections if they had major risk factors for ESBLs such as prior infections or colonization with ESBLs or multiple recent courses of beta-lactams and/or fluoroquinolones in the past 90 days. Acute severity of illness should be taken into consideration in this risk stratification as well since there is smaller room for error in critically ill patients. Carbapenems may be considered in critically ill patients with minor risk factors for infections due to ESBL-producing bacteria such as recent genitourinary or gastrointestinal procedures or one prior course of beta-lactams or fluoroquinolones in the past 90 days.

Stratification of patients based on fluoroquinolone resistance risk factors (prior fluoroquinolone use, residence at a skilled nursing facility, etc.) may also improve the management of acute pyelonephritis and reduce excessive use of broad-spectrum antimicrobial agents in this population.

Early de-escalation of broad-spectrum antibiotics using rapid diagnostics

The availability of rapid diagnostic tests for the identification of microbes and common antimicrobial resistance genes opened the horizon for the de-escalation of antibiotic therapy within as early as 48 hours. BSI is considered the prime example of the evolution of rapid diagnostics. The identification of *E. coli* in a blood culture using multiplex polymerase chain reaction (PCR) and lack of detection of CTX-M (the most common ESBL gene in North America and Europe) should be considered enough information to discontinue APBL or carbapenems and de-escalate to ceftriaxone therapy. The use of rapid phenotypic susceptibility tests may allow de-escalation to even narrower-spectrum agents such as ampicillin/sulbactam or cefazolin within 48 hours.

The availability of MRSA nasal PCR technology has also allowed many institutions to implement a stewardship intervention for streamlining anti-MRSA agents in respiratory tract infections due to the high negative predictive values (NPV). Emerging data has suggested high NPV for non-pulmonary sources of infection as well. Despite these data, there remain concerns that NPV at or below 90% may not be sufficient for such pathogenic bacteria without a randomized, controlled trial.

Syndrome-specific antimicrobial stewardship interventions using live alerts

Prior authorization and prospective audit and feedback are the most commonly used antimicrobial stewardship interventions in hospitals. However, syndrome-specific interventions using live antimicrobial stewardship alerts and antimicrobial recommendations have been very successful in reducing the use of broad-spectrum antibiotics and hospital-onset CDI.

Antimicrobial-specific alerts are often considered easy, low-hanging targets for antimicrobial stewardship programs. Unfortunately, in many cases, while a reduction in the days of therapy of said targeted antibiotic will result, it may not reach the ultimate goal of an overall reduction in unnecessary antibiotics due to a "squeezing balloon" effect where one antibiotic simply replaces another. The use of syndrome-specific alerts targeting a particular infection type (e.g. BSI) can assist antimicrobial stewards in not only reducing unnecessary broad-spectrum antibiotic use but also optimizing therapy in patients with a high risk of morbidity and mortality. Many electronic health records will offer automatic alerts to triage workload for a stewardship team, allowing for potentially multiple syndrome-specific interventions to be ongoing at any one time. In the absence of electronic health records capabilities, partnerships with microbiology and/or the use of a third-party clinical decision support software may offer a solution.

Penicillin allergy reconciliation and skin testing

Other methods of decreasing broad-spectrum antibiotic use including carbapenems, fluoroquinolones, and clindamycin are penicillin allergy reconciliation, skin testing, and antibiotic challenges. Often broad-spectrum antibiotics are used instead of first-line therapy with penicillins or cephalosporins in patients with penicillin allergy labels. Allergy reconciliation and knowledge of cephalosporin cross-reactivity alone can improve antibiotic prescribing. Additional steps such as penicillin allergy skin testing can be used for patients with a history of higher-risk penicillin allergies to de-label patients, improve prescribing, and improve patient outcomes. The oral amoxicillin challenge may be useful in some patients with penicillin allergy.

Transitions of care

While there are many challenges in antimicrobial stewardship in hospitals, one area that has recently become a topic of interest is antimicrobial stewardship during transitions of care. In hospitals, transitions of care can include the transition from an inpatient unit or the emergency department to home, long-term acute care, or skilled nursing facilities. There are unique challenges that affect the transition at hospital discharge and from the emergency department.

Transition at hospital discharge

While historically hospital antimicrobial stewardship programs do not have interventions in place to monitor and intervene on discharge antibiotic orders, there has been shown to be significant room for improvement among these antibiotic discharge prescriptions. Studies demonstrate that durations of antibiotic therapy are longer than necessary for common infectious diseases such as urinary tract infections and community-acquired pneumonia at hospital discharge. Studies have also found an excess of unnecessary fluoroquinolones prescribed at discharge. Excess prescribing of antibiotics at discharge has also been linked to increases in adverse drug events such as CDI.

Few studies have examined interventions to improve antibiotic prescribing at hospital discharge. The majority of these involved some component of antimicrobial stewardship or pharmacist audit and feedback on discharge antibiotic prescriptions. Improvements were seen in antibiotic appropriateness including choice and durations. When examined, no differences were seen in 30-day readmission or mortality. In one study, a decrease in severe adverse drug events in the post-intervention group was demonstrated.

For more complex disease states, implementing multidisciplinary outpatient parenteral antimicrobial therapy (OPAT) programs can help improve antibiotic management at hospital discharge. The use of structured OPAT programs has been associated with improved clinical cure and decreased hospital readmissions. Complex

outpatient antimicrobial therapy (COpAT) can also be a component of the OPAT team, as these patients are on oral antimicrobials that often require frequent laboratory work and/or monitoring for adverse events. One of the main challenges with the implementation of successful programs is a lack of funding and institutional support.

Transition from the emergency care department

Another point of transition into the community is directly from the emergency department. Some of the unique challenges in this setting are that many of the clinical cultures that were performed during the emergency department visit are still pending upon discharge. Because of this, traditional culture-driven syndrome-specific interventions for improving antibiotic use do not work. Often follow-up on these test results can be delayed leading to poor outcomes for patients. However, studies have shown that pharmacist-driven culture call-back programs in the emergency department can lead to positive outcomes including decreased emergency department readmission, decreased treatment failure, shortened time to patient contact, fewer missed interventions, more optimal antimicrobial therapy, and improved guideline-concordant antimicrobial prescribing.

Drug shortages

According to the U.S. Department of Health and Human Services report in 2024, 123 drugs were considered to be in shortage, with 12% of these being antimicrobials. The majority of infectious diseases clinicians surveyed in 2016 indicated that antimicrobial shortages have impacted patient outcomes which may lead to delays in optimal therapy or use of alternative agents with higher cost or greater toxicity. Shortages, including those of recent (e.g., intravenous clindamycin, intramuscular penicillin, intravenous acyclovir), have required significant stewardship personnel time to develop alternative guidance, implement restriction policies, and/or field clinician inquiries. Drug shortages are often unpredictable and include critical antimicrobials, adding to the potential concerns shared across many antimicrobial stewards.

While most would agree the negative impact significantly outweighs the potential positives presented by drug shortages, opportunistic research has also resulted. Dating back to 2011, Lee *et al.* published the comparative outcomes of cefazolin *versus* nafcillin for methicillin-susceptible *S. aureus* BSI during a nationwide anti-staphylococcal penicillin shortage in South Korea. More recently, efforts during intravenous clindamycin shortage have resulted in practice-changing publications for necrotizing skin and soft tissue infections, intra-amniotic infections, and endometritis.

Designing and evaluating the impact of antimicrobial stewardship interventions

Responsibilities of antimicrobial stewardship programs focus on patient-centered outcomes. However, there is a collective need to measure the impact of newly implemented interventions, diagnostic tools, and other resources at the institutional level. Much data come from resource-rich institutions, which may not reflect most hospitals across the world. Foster *et al.* reported that only a minority of antimicrobial stewards evaluate the impact of rapid diagnostics on patient outcomes. The concern is that other institutions don't learn from either the successes or failures of other stewardship programs. While infectious diseases organizations and noted journals have shown a commitment to antimicrobial stewardship-related scholarship, the quality of

stewardship intervention publications has declined in recent years according to some experts. Although some stewardship personnel may lack training or even time to complete large-scale research, opportunities to partner with larger parent organizations or research networks (e.g., Southeastern Research Group Endeavor, SERGE-45), can assist in producing meaningful results. Recent publications have offered some insight to clinicians to aid in designing methods for evaluating novel antimicrobial stewardship interventions.

Competing interests

The authors have no financial and non-financial competing interests to declare.

References

1. Cain SE, et al. Stratification of the impact of inappropriate empirical antimicrobial therapy for Gram-negative bloodstream infections by predicted prognosis. Antimicrob Agents Chemother. 2015;59:245-50.
2. Battle SE, et al. Association between inappropriate empirical antimicrobial therapy and hospital length of stay in Gram-negative bloodstream infections: stratification by prognosis. J Antimicrob Chemother. 2017;72:299-304.
3. Hammer KL, et al. Differential effect of prior β-lactams and fluoroquinolones on risk of bloodstream infections secondary to *Pseudomonas aeruginosa*. Diagn Microbiol Infect Dis. 2017;87:87-91.
4. Senneville É, et al. IWGDF/IDSA guidelines on the diagnosis and treatment of diabetes-related foot infections (IWGDF/IDSA 2023). Clin Infect Dis. 2023:ciad527.
5. Bookstaver PB, et al. Cumulative effect of an antimicrobial stewardship and rapid diagnostic testing bundle on early streamlining of antimicrobial therapy in Gram-negative bloodstream infections. Antimicrob Agents Chemother. 2017;61:e00189-17.
6. Seddon MM, et al. Role of early de-escalation of antimicrobial therapy on risk of *Clostridioides difficile* infection following Enterobacteriaceae bloodstream infections. Clin Infect Dis. 2019;69:414-420.
7. Harris PNA, et al. Effect of piperacillin-tazobactam vs meropenem on 30-day mortality for patients with *E. coli* or *Klebsiella pneumoniae* bloodstream infection and ceftriaxone resistance: a randomized clinical trial. JAMA. 2018;320:984-994.
8. Al-Hasan MN, et al. Impact of penicillin allergy on empirical carbapenem use in Gram-negative bloodstream infections: An antimicrobial stewardship opportunity. Pharmacotherapy. 2018;38:42-50.
9. Blumethal KG, et al. The impact of a reported penicillin allergy on surgical site infection risk. Clin Infect Dis. 2018;66:329-36.
10. Dorazio J, et al. Clindamycin plus vancomycin versus linezolid for treatment of necrotizing soft tissue infection. Open Forum Infect Dis. 2023;10:ofad258.
11. Pizzuti M, et al. Application of precision medicine concepts in ambulatory antibiotic management of acute pyelonephritis. Pharmacy (Basel). 2023;11:169.
12. Silva SY, et al. Inpatient fluoroquinolone use in Veterans' Affairs hospital is a predictor of *Clostridioides difficile* infection due to fluoroquinolone-resistant ribotype 027 strains. Infect Control Hosp Epidemiol. 2021;42:57-62.
13. Augustine MR, et al. Clinical risk score for prediction of extended-spectrum β-lactamase-producing Enterobacteriaceae in bloodstream isolates. Infect Control Hosp Epidemiol. 2017;38:266-272.
14. Carrel M, et al. Antimicrobial resistance patterns of outpatient *Staphylococcus aureus* isolates. JAMA Netw Open. 2024;7:e2417199.
15. Shah A, et al. Application of fluoroquinolone resistance score in management of complicated urinary tract infections. Antimicrob Agents Chemother. 2017;61:e02313-16.
16. Liu C, et al. Should a MRSA nasal swab guide empiric antibiotic treatment? NEJM Evid. 2022;1:EVIDccon2200124.

17. Mediwala KN, et al. Syndrome-specific versus prospective audit and feedback interventions for reducing use of broad-spectrum antimicrobial agents. Am J Infect Control. 2019;47:1284-1289.
18. Mabilat C, et al. Improving antimicrobial stewardship with penicillin allergy testing: A review of current practices and unmet needs. JAC Antimicrob Resist. 2022;4:dlac116.
19. Dumkow LE, et al. Antimicrobial stewardship at transitions of care. Infect Dis Clin North Am. 2023;37:769-791.
20. Smith J, et al. Optimizing transitions of care antimicrobial prescribing at a community teaching hospital. Antimicrob Steward Healthc Epidemiol. 2023;3:e228.
21. Belza-Mai AC, et al. Optimizing discharge antimicrobial therapy: Evaluation of a transitions of care process and electronic scoring system for patients with community-acquired pneumonia or chronic obstructive pulmonary disease. Am J Health Syst Pharm. 2024:zxae174.
22. Mercuro NJ, et al. Pharmacist-driven transitions of care practice model for prescribing oral antimicrobials at hospital discharge. JAMA Netw Open 2022;5:e2211331.
23. U.S Department of Health and Human Services. Policy considerations to prevent drug shortages and mitigate supply chain vulnerabilities in the United States. Available at: https://aspe.hhs.gov/sites/default/files/documents/3a9df8acf50e7fda2e443f025d51d038/HHS-White-Paper-Preventing-Shortages-Supply-Chain-Vulnerabilities.pdf. Last accessed: 16 September 2024.
24. Gundlapalli AV, et al. Antimicrobial agent shortages: The new norm for infectious diseases physicians. Open Forum Infect Dis. 2018;5:ofy068.
25. Lee S, et al. Is cefazolin inferior to nafcillin for treatment of methicillin-susceptible *Staphylococcus aureus* bacteremia? Antimicrob Agents Chemother. 2011;55:5122-5126.
26. Bailey P, et al. Cefoxitin for intra-amniotic infections and endometritis: A retrospective comparison to traditional antimicrobial therapy regimens within a healthcare system. Clin Infect Dis. 2024;79:247-254.
27. Foster RA, et al. Pharmacists' familiarity with and institutional utilization of rapid diagnostic technologies for antimicrobial stewardship. Infect Control Hosp Epidemiol. 2017;38:863-866.
28. Barfield RK, et al. A baker's dozen of top antimicrobial stewardship intervention publications in 2022. Open Forum Infect Dis. 2024;11:ofad687.
29. Langford BJ, et al. Five steps to high quality antimicrobial stewardship research. Antimicrob Steward Healthc Epidemiol. 2024;4:e82.
30. Courtney M, et al. Designing antimicrobial stewardship initiatives to enhance scientific dissemination. J Am Coll Clin Pharm. 2020;3:109–115.

Chapter 90

Antimicrobial stewardship: who are the stakeholders and how to engage them?

Helen Giamarellou
1st Department of Internal Medicine-Infectious Diseases, Hygeia General Hospital, Marousi, Athens, Greece.

Ilias Karaiskos
1st Department of Internal Medicine-Infectious Diseases, Hygeia General Hospital, Marousi, Athens, Greece.

Introduction

There is no doubt that nowadays resistance to antibiotics is a leading public health threat. It was President Barack Obama who in 2015 proposed a National Action Plan to limit the rise of bacteria resistant to last-resort antibiotics, the so-called "superbugs", by demanding the reduction of the inappropriate use of antibiotics to 50% in the community and 20% in the hospital. Nevertheless, it is astonishing that in the USA at least in 2011, 842 prescriptions of antibiotics were written per 1000 people. The Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) in March 2023 declared the new silent pandemic of antimicrobial resistance in the shadow of the COVID-19 pandemic, whereas a report of the preparation of the next pandemic in the era of antimicrobial resistance with current national pandemic preparedness policies is already illustrated. In the meantime, several hospital Leaders all over the world have already accepted the necessity of the application of Antibiotic Stewardship (AS) programs. It is therefore a priority that Infectious Diseases Physicians should create specific plans to force hospitals' Leadership to fund their "lifesaving" schedules and plans to combat resistance. How and why?

The global burden of resistance

In 2019 a systemic analysis of the global burden of antibiotic resistance revealed 4,95 million deaths associated with bacterial antimicrobial resistance (AMR), whereas 1,27 million deaths were directly attributable to AMR, with respective numbers for the EU/EEA in 2019 of 865,767 and 38,710 cases. Within the USA, the CDC has estimated that 2,868,700 people were infected with antimicrobial-resistant (AR) bacteria and fungi, resulting in 35,900 deaths annually. In the meantime, AMR to carbapenems regarding *Klebsiella pneumoniae* according to the last ECDC end EU/EEA Net report, amounted to 10.9% in 2022 with an incidence of increase by almost 50%. On the other hand, the geographical distribution of the consumption of carbapenems in the hospital sector in Europe for 2022 revealed in Greece a priority of 0.11074 to 0.13506 DDDs per 1.000 inhabitants per day, to be followed by Bulgaria, Romania, Spain, Slovenia and Austria with 0.008642 to 0.11674 DDDs per 1.000 inhabitants, indicating the slow progress towards the EU target reduction of carbapenem

resistance by 20% in 2030. It is therefore evident that efforts to apply rational antibiotic consumption in hospitals should be continuous and multifactorial.
At least in the USA, starting in January 2017, all hospitals accredited by the Joint Commission had to meet the new standards about AS including also small hospitals. These refer to the following items: (i) establishing AS as an organizational priority, (ii) educating staff, patients and students on the appropriate use of antibiotics, and (iii) creating a multidisciplinary AS Team.

The AS team

Since 2007 both Deresinki and Dellit *et al.* suggested that in each hospital an AS interdisciplinary team should be established, composed of an Infectious Diseases Specialist as a Leader who should be dedicated to AS, a Clinical Pharmacist with infectious diseases training, a Clinical Microbiologist, an Information System Specialist, an Infection Control Professional, a Hospital Epidemiologist, and a Skilled Nurse well trained in epidemiology of Infectious Diseases. The addition of a Surgeon and an Intensivist, as well as a haematologist/solid tumour specialist, seem to be indispensable. However, the latter specialists could be rather invited than being permanent members, whenever topics of their interest will be handled by the AS Team.
It is self-understood that the AS Team members should cooperate with the Hospital Infection Control Committee and all other Hospital Therapeutic Committees with emphasis on Surgery and Hematology/Oncology Committees, as well as with the C-suite members among whom a top Administrator should become an official member of the AS Team. The updated seven CDC core elements of hospital AS programs in which the Administrator should play a major role and therefore should be constantly engaged in the AS Team, are the following:

- *Leadership Commitment*: Dedicating necessary human, financial, and information technology resources.
- *Accountability*: Appointing a single dedicated Leader responsible for program outcomes. Experience with successful programs shows that an Infectious Diseases physician as a Leader is effective.
- *Drug Expertise*: Appointing a single Pharmacist Leader responsible for working to improve antibiotic use.
- *Action*: Implementing interventions focusing on “Restrictive Antibiotic Formulary and Preauthorization”, as well as in “Prospective Audit and Feedback”.
- *Tracking*: Monitoring the antibiotic prescribing impact of interventions and side effects, through continuous assessment including resistance patterns.
- *Reporting*: Communicating at regular time intervals information on antibiotic use, consumption and resistance to doctors, nurses and relevant hospital staff including Administrators.
- *Education*: Targeting prescribers, pharmacists and nurses regarding antibiotic resistance, optimal prescribing and adverse reactions.

It should be pointed out that the Joint Commission has added two more core elements: (i) the establishment of AS in every hospital as an organizational priority through support of its AS program and (ii) the allocation of financial resources for staffing and information technology to support the AS program.

The C-Suite: what is required from the hospital leadership commitment?

It is obvious that for the hospital Leadership Commitment, the following are required: (i) Dedicated, human, financial and information technology resources with emphasis on "the necessity of AS Team Leaders having dedicated time" to operate the program effectively. (ii) Support from the Senior Leadership of the hospital, particularly the Chief Medical Officer, the Chief Nursing Officer, and the Director of Pharmacy, which is considered critical for the success of AS programs. (iii) Obtaining the resources required to accomplish AS targets, a goal in which hospital Leadership and Administrators play critical roles. The Infectious Diseases Leader should submit a business plan to Hospital Leadership justifying the cost and structure of the AS program and explaining what benefits the hospital will gain in return, engaging the hospital Leadership to fund it. On the other hand, the appropriate officers should be addressed to support the AS program. The C-suite of the hospital, as for any business organization, comprises Chief Officers of Administrative Departments, such as the Chief Operations Officer, Chief Financial Officer, and Chief Medical Officer, whereas any of these Officers may be the recipient of the business proposal supporting the AS program. There is no doubt that an effective AS program will require people and money. It has been estimated that one full-time equivalent (FTE) ID physician and one 0.5 FTE ID-trained clinical pharmacist should be required and proposed for every 500 acute care hospital beds.

Which are the major roles and the plans of an AS program?

If funded, the AS program is expected to achieve the following objectives: (i) Reduce antibiotic days of therapy, length of therapy, and associated antibiotic expenses. (ii) Attenuate and/or reverse the rate of emergence of resistant bacteria, namely replacing older with newer β-lactamase inhibitors, i.e. ceftazidime/avibactam, meropenem/vaborbactam and imipenem/cilastatin/relabactam), which are active against most of the extensively drug-resistant Gram (-) negative bacteria is not the solution, since they are expensive, whereas resistance development is always a pending fear. (iii) Increase access to state-of-the-art molecular diagnostics and biomarkers to ensure that patients get individualized specific therapy rather than a clinician's having to guess the microbial etiology of the patient's infection leading to overuse of empiric therapy. Typically, the business plans agree to support funding because (i) the plan is critical to patient care; (ii) the result will include a decrease in AMR and fewer expenses to the medical center; (iii) the plan will help to reduce costs for the hospital by shortening the length of stay (or reducing readmissions) and thus will pay for itself; and (iv) the plan is cost-effective based on published medical literature and analysis. An optimized credible plan that addresses costs and revenue should be written. The advantages of shortening lengths of stay and reducing readmissions, include improved patient flow, reduced hospital-acquired adverse events, avoiding insurance financial penalties for readmissions, and, most importantly, increasing revenue by enabling more paying admissions to the hospital. The choice is whether any of the new proposals are more important than existing programs, such that redirected expenditures that support an existing program will be redirected to fund the new program, and, if so, how can this be accomplished in a way that minimizes the damage to existing programs: e.g., how the costs of the new program could be kept down?

The 10 pieces of evidence indicating increased funding

Spellberg *et al.* tried to define which are the increasing chances of funding by the identification of 10 Evidence the most important of which are the following:

1. Reductions of the modifiable costs, including pharmacy (days of therapy), supplies (e.g. catheters, IV tubing), laboratory testing (e.g. blood culture bottles, reagents, etc), as well as pharmacy savings from reducing antibiotic use, particularly from the more expensive ones.
2. Conversion from parenteral to oral therapy with antimicrobials possessing enhanced oral bioavailability resulting in reduced hospital stay, healthcare costs and complications from the IV access.
3. A stepwise implementation of the AS program initially with passive strategies, i.e. education and order forms, to be followed by an active strategy with "Prospective Audit and Feedback" plus "Handshake AS" interventions.
4. Development and cost-effectiveness of more rapid and sensitive diagnostic tests, to identify patients with bacterial *versus* viral infections and to identify resistant bacterial organisms earlier, like the Accelerate Pheno® system (Accelerate Diagnostics, Tucson, Arizona, United States) and the VITEK® REVEAL™ (Bio-Merieux, Marcy l'Étoile, France, Europe), that provide the antibiotic susceptibility testing in approximately 6 and 4.5 h respectively). The latter tests are particularly beneficial in cases of bloodstream infections, as well as in nosocomial sepsis and septic shock, where immediate initiation of active and not empirical antimicrobial therapy is critical, whereas a big amount of money will be saved whenever cheaper but "appropriate" antibiotics are administered instead of the expensive newer β-lactamase inhibitors.
5. Decrease in antimicrobial use (22%–36%), with annual savings of $200,000–$900,000 in both larger academic hospitals and smaller community hospitals after applying for comprehensive AS programs. Therefore, Health Care Facilities Administrators should be encouraged to implement AS programs.
6. Presentation of antimicrobial use and outcomes to the hospital medical staff and Pharmacy Administration on an annual or semi-annual basis.

Conclusion

In inclusion how the AS program could be optimized to increase the possibilities of funding? The following should be seriously considered: (i) job descriptions for each type of personnel, e.g. physicians, pharmacists, nursing staff, in order for the C-suite to understand clearly the day-to-day functions, for which they are asked and pressed to pay; (ii) clarification of the clinical importance that antibiotics are used correctly, therefore, obtaining lower resistance rates, or even lower rates of *Clostridioides difficile* colitis in alignment with professional societies goals, i.e. the IDSA; (iii) the necessity of the leadership commitment to be strong, i.e. the Infectious Diseases Leader of the AS program to be implemented by the AS Team, except for education and specific knowledge, requires leadership skills, such as trust and confidence. The appointment of a person as a Leader does not qualify him. He should be able to influence others, to engage, inspire and motivate without fearing confrontations and negotiations. As a Leader he should emphasize to the Administrator that the AS program has the potential to improve antibiotic use while reducing costs without any adverse impact on the quality of care; (iv) the administrator should be well aware and persuaded that two core strategies should be obligatory in their implementation, i.e. "Formulary Restrictions with Preauthorization" and "Prospective Audit with Intervention and Feedback" to be followed by "Handshake Stewardship".

There is no doubt that the Healthcare Administrator, as a member of the AS Team, should play a major role in tackling antimicrobial resistance in hospital settings. His/her engagement is a key factor for developing, implementing, and sustaining the AS program in order to fight antibiotic resistance, regarding both its prevention and reduction, while simultaneously improving the therapeutic approach and reducing death rates.

Competing interests

The authors have no financial and non-financial competing interests to declare.

References

1. Office of the Press Secretary. Fact Sheet: Obama Administration Releases National Action Plan to Combat Antibiotic-Resistant Bacteria. Washington, DC; 2015. Available at: https://whitehouse.gov/the-press-office/2015/12/22/fact-sheet-obama-administration-releases-national-action-plan-combating. Last accessed: 6 February 2016.
2. Hicks LA, et al. US outpatient antibiotic prescribing variation according to geography, patient population, and provider specialty in 2011. Clin Infect Dis. 2015;60:1308-1316.
3. The Presidential Advisory Council on Combating Antimicrobial-Resistant Bacteria. March 2023. Available at: https://www.hhs.gov/sites/default/files/paccarb-pandemic-preparedness-report.pdf. Last accessed: 6 September 2024.
4. Giamarellou H, et al. Antimicrobial stewardship in the hospital setting: a narrative review. Antibiotics (Basel). 2023;12:1557.
5. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022;399:629-655.
6. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States. 2019. Available at: https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf Last accessed: 12 September 2023.
7. European Centre for Disease Prevention and Control. Assessing the health burden of infections with antibiotic-resistant bacteria in the EU/EEA, 2016-2020. https://www.ecdc.europa.eu/en/publications-data/health-burden-infections-antibiotic-resistant-bacteria-2016-2020. Last accessed: 6 September 2024.
8. European Centre for Disease Prevention and Control. Antimicrobial resistance in the EU/EEA (EARS-Net)-Annual Epidemiological Report 2022. Stockholm: ECDC; November 2023. Available at: https://www.ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-resistance-europe-2022. Last accessed: 6 September 2024.
9. Centers for Disease Control and Prevention. Core elements of hospital antibiotic stewardship programs. Atlanta, GA: US Department of Health and Human Services, CDC; 2019. Available at: https://www.cdc.gov/antibiotic-use/healthcare/pdfs/hospital-core-elements-H.pdf Last accessed: 12 September 2023.
10. Centers for Disease Control and Prevention. Antimicrobial stewardship programmes in health-care facilities in low-and middle-income countries: a WHO practical toolkit. 2019. Available at: https://www.who.int/publications/i/item/9789241515481. Last accessed: 12 September 2023.
11. Deresinki S. Principles of antibiotic therapy in severe infections: optimizing the therapeutic approach by use of laboratory and clinical data. Clin Infect Dis. 2007;45 Suppl 3:S177-S183.

12. Dellit TH, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis. 2007;44:159-177.

13. Barlam TF, et al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis. 2016;62:e51-77.

14. Martinez-Sobalvarro JV, et al. Antimicrobial stewardship for surgical antibiotic prophylaxis and surgical site infections: a systematic review. Int J Clin Pharm. 2022;44:301-319.

15. The Joint Commission. R3 Report Issue 35: New and revised requirements for antibiotic stewardship. June 20, 2022. Available at: https://www.jointcommission.org/standards/r3-report/r3-report-issue-35-new-and-revised-requirements-for-antibiotic-stewardship/. Last accessed: 30 August 2024.

16. Spellberg B, et al. How to pitch an antibiotic stewardship program to the hospital C-suite. Open Forum Infect Dis. 2016;3:ofw210.

17. Giamarellou H, et al. Current and potential therapeutic options for infections caused by difficult-to-treat and pandrug resistant gram-negative bacteria in critically ill patients. Antibiotics (Basel). 2022;11:1009.

18. Nordmann P, et al. Epidemiology and diagnostics of carbapenem resistance in gram-negative bacteria. Clin Infect Dis. 2019;69:S521-S528.

19. Magiorakos AP, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012;18:268-281.

20. Gelfer G, et al. The clinical impact of the detection of potential etiologic pathogens of community-acquired pneumonia. Diagn Microbiol Infect Dis. 2015;83:400-406.

21. Gilbert D, et al. The potential of molecular diagnostics and serum procalcitonin levels to change the antibiotic management of community-acquired pneumonia. Diagn Microbiol Infect Dis. 2016;86:102-107.

22. Pancholi P, et al. Multicenter evaluation of the Accelerate PhenoTest BC kit for rapid identification and phenotypic antimicrobial susceptibility testing using morphokinetic cellular analysis. J Clin Microbiol. 2018;56:e01329-17.

23. Tibbetts R, et al. Performance of the Reveal Rapid Antibiotic Susceptibility Testing System on gram-negative blood cultures at a large urban hospital. J Clin Microbiol. 2022;60:e0009822.

24. Goff DA, et al. Eight habits of highly effective antimicrobial stewardship programs to meet the joint commission standards for hospitals. Clin Infect Dis. 2017;64:1134-1139.

25. MacBrayne CE, et al. Sustainability of handshake stewardship: extending a hand is effective years later. Clin Infect Dis. 2020;70:2325-2332.

26. Moghnieh R, et al. Effect of a "handshake" stewardship program versus a formulary restriction policy on High-End antibiotic use, expenditure, antibiotic resistance, and patient outcome. J Chemother. 2020;32:368-384.

27. Antoniadou A, et al. Impact of a hospital-wide antibiotic restriction policy program on the resistance rates of nosocomial Gram-negative bacteria. Scand J Infect Dis. 2013;45:438-445.

28. Chrysou K, et al. Impact of a 4-year antimicrobial stewardship program implemented in a Greek tertiary hospital. Eur J Clin Microbiol Infect Dis. 2022;41:127-132.

Chapter 91

Measurement of performance in antimicrobial stewardship programmes

Alfredo Ponce-de-Leon
Department of Infectious Diseases, Antimicrobial Stewardship Programme, Laboratory of Clinical Microbiology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico.

María Dolores Niembro-Ortega
Department of Infectious Diseases, Antimicrobial Stewardship Programme, Laboratory of Clinical Microbiology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico.

María Fernanda Gonzalez-Lara
Department of Infectious Diseases, Antimicrobial Stewardship Programme, Laboratory of Clinical Microbiology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico.

Bernardo Martínez Guerra
Department of Infectious Diseases, Antimicrobial Stewardship Programme, Laboratory of Clinical Microbiology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico;
Department of Internal Medicine, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico.

Introduction

There is no doubt that antimicrobial resistance has emerged as one of the most important health problems in the last three decades. The WHO and other national agencies have issued a much-needed action plan whose main emphasis is the control of the spread of resistance. The Global Burden of Disease Initiative published the burden of Antimicrobial Resistance for 2019 two years ago, and *"highlighted the importance of developing policies … through expansion of infection prevention and control programmes".* Recently, the same initiative has published a forecast for 2050, underscoring the need to minimize the inappropriate use of antimicrobials. To meet this need, one of the most important strategies employed thus far has been the implementation of antimicrobial stewardship programmes (ASPs). In ASPs, a combination of strategies is used to monitor antimicrobial use within healthcare facilities. These strategies frequently incorporate different medical specialties, pharmacists, administrators, and computational experts. As different ASP strategies evolve, different background focuses have been incorporated, such as animal health, ecosystems, clinical practice, social health and governance. Most, if not all, ASPs focus on the responsible or judicious use of antimicrobials by healthcare professionals to prevent the emergence of resistance. This means that the purpose of the programmes is rather specific. Generally, a good antimicrobial stewardship program (ASP) emphasizes, as Fishman suggests, the use of an *appropriate drug and optimal dose and duration to cure an*

infection while minimizing toxicity and conditions for the selection of resistant bacterial strains. The objectives of AMS are quite straightforward:

a) to achieve optimum clinical outcomes;
b) to keep at a minimum the unintended consequences of antimicrobial use;
c) to avoid toxic effects, selection of pathogenic organisms, and resistance emergence;
d) to ensure the cost-effectiveness of therapy.

However, even if these objectives are clear and easily understandable, measuring the different strategies, under very different conditions (type of patient, institution, country, etc), is a rather difficult task. In this chapter, our intention is to incorporate some ideas as to how to achieve these measurements. Also, we want to emphasize the fact that these are suggestions that by no means intend to be comprehensive, but rather open to discussion in each centre trying to implement an ASP.

Evaluation of antimicrobial stewardship

Some 20 years ago, Harbarth and Samore, described some of the most important factors that influence the dissemination and control of antimicrobial resistance: from the pathogen itself and its biology to healthcare policies. However, most of the attention to these factors has been allocated to the prescription practices. Monitoring the process of the prescription and measuring its outcome is of the utmost importance. This process requires that each institution where an ASP is instituted develops a strategic plan that involves:

a) evaluation of ancillary activities (e.g. hand washing, correct use of protection equipment and respiratory isolation);
b) continuous generation of solid evidence of current and past data (e.g. local antimicrobial susceptibility patterns, evolution of local regulatory adaptations);
c) execution (e.g. multidisciplinary approach, regular meetings of all parties involved within the health-care centre);
d) development of local clinical management guidelines based on the most common diseases and antimicrobial resistance patterns at each centre;
e) smart thinking (e.g. individualized antimicrobial regime and dosage);
f) setting outcome goals (e.g. when to de-escalate the antimicrobial, when to stop antibiotics).

This strategic plan has to be tailored to the institution, and although following it up should be strict, it has to be flexible enough so that the primary goal of medical care is accomplished: optimal patient care. Now, the evaluation of ASPs must take into consideration that different interventions depending on the institution, region, and specific patient population, as different interventions lead to different effects, and adequate evaluations are crucial from programmatic and financial perspectives.

Unfortunately, and derived from these differences, it should be emphasized that the methods employed to evaluate ASPs are not straightforward. These methods have to be progressive and inclusive, taking into account that one important part of every ASP has to be accountability and continuous feedback for all partners involved.

The very first step in the evaluation of the programmes is the conformation of a “core group”, as we have called it in our Institution. This particular group includes healthcare professionals (e. g. nurses, microbiologists, internal medicine and infectious diseases specialists, surgeons, urologists, pharmacists), and administrators (informatics specialists, financial administrators). This group foresees all activities of the program,

and, as we found out during the course of this adventure (18 years so far), a group leader has to be fully devoted to the tasks involved.

Methods to evaluate ASPs

As Marris states**,** "*Antimicrobial stewardship is a new field that struggles to find the right balance between meaningful and useful metrics to study the impact of antimicrobial stewardship programs".* It is inherently difficult to find this balance, not only because the primary goal is the optimal care of each case, but also because the effect of the quality of prescription practices on antimicrobial susceptibility will not be tangible in the short term. Also, as stated before, most ASPs are applied in a complex, real-world setting, where bias and random time effects can jeopardize the validity of causal inference. Therefore, metrics used to assess an ASP may seem an easy task when in reality is still an exploratory endeavour.

Most programs focus on antimicrobial use, prescription practices and outcome indicators. As Looke and Duguid describe very adequately in their program for Australian hospitals, "*Performance measurement is an integral part of the quality improvement cycle, and a number of indicators for appropriate antimicrobial prescribing have been reported in the literature. These are predominately process indicators such as rates of adherence to guidelines, appropriateness and timeliness of therapy for a given infection, advice acceptance rates and rates of concordance with susceptibility"*.

Measuring the impact of ASPs

As stated above, and mentioned by Tamma and Cosgrove, ASPs have multiple goals. Measurement of each of these goals is important. It is quite straightforward that the focus of these measurements is antimicrobial use, since its "*inappropriate usage" contributes to the increasing costs of health care, the emergence of multidrug-resistant organisms (MDROs), and unnecessary adverse drug reactions*, and more importantly, to suboptimal patient care. The main key points to measure include:

a) Antimicrobial resistance prevalence:
   - Tracking selected pathogens.
   - Aggregates of resistance patterns.
   - Sentinel organisms (i.e. *Clostridoides difficile* infection, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus faecium,* carbapenem-resistant *Enterobacteriaceae*).

b) Antimicrobial consumption:
   - Defined daily dose (DDD) and/or Days of therapy (DOT).
   - Specific Antibiotic use targeting.
   - Antimicrobials costs.
   - Consumption by specific disease.

c) Process measures:
   - Compliance to guidelines
   - Adequacy of written indications for antibiotic use
   - Appropriateness of antibiotic use

d) Clinical outcomes:
   - Clinical and microbiologic cure.

- Length of stay.
- Treatment failures.
- Adverse reactions.
- De-escalation (adequacy) rates by syndrome or clinical isolate.
- Intravenous-to-oral antibiotic switch therapy.
- Mortality.

It is important to understand that these measures need to be considered as a whole, since using them separately may lead to some important conclusions and actions but neglection of other important needs. Not only is it necessary to assess them systematically and dynamically, but also to interpret and communicate them to the healthcare authorities and ultimately to clinicians and those in charge of individual patients. At the same, the programme is expected to receive and analyse feedback from the end users. Only through a conscious assessment of all the ASP-related processes may we identify whether improvements have been achieved.

What have we done

At the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, a tertiary care centre that attends extremely complex internal medicine and surgical patients in Mexico City, we instituted an ASP more than 15 years ago. As can be seen in **Figure 1**, a multi-professional network has been implemented. Not long after we temporarily converted into a solely COVID-19 facility, we decided to polish the programme and incorporate prospective data into a more simplistic and accessible format (**Figures 1** and **Figure 2A, B,** and **C**).

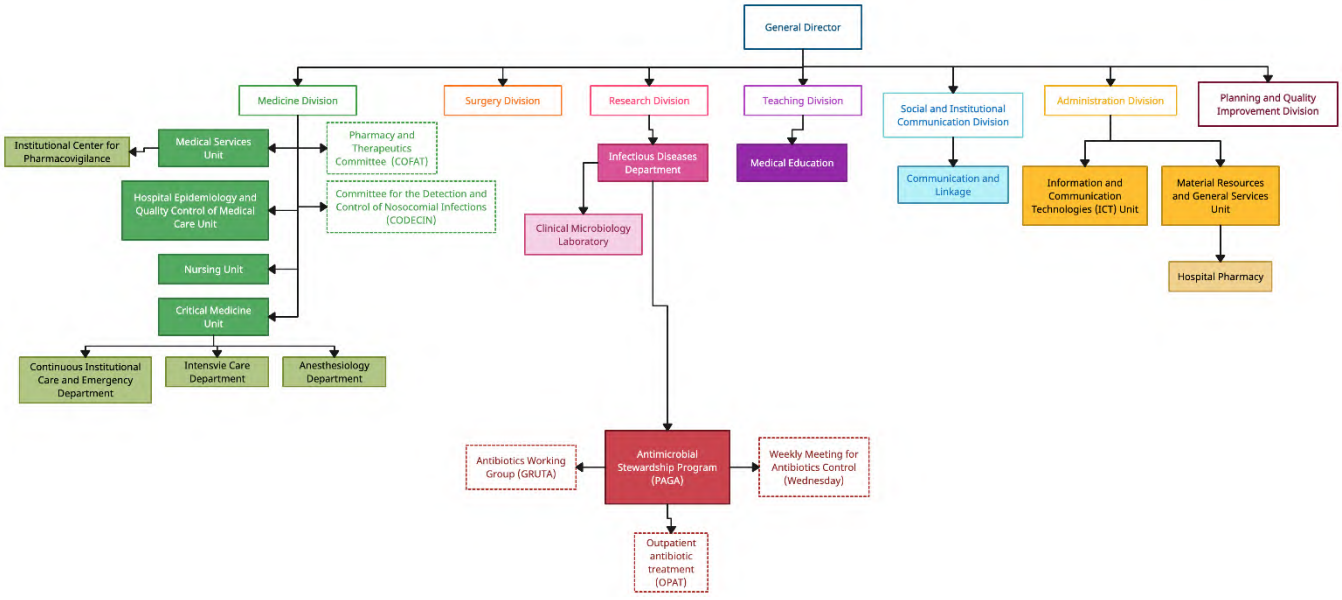

Figure 1. Organization chart at Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubiran. Although our ASP depends directly on the Infectious Diseases Department, we have working experiences and relation with almost every area mentioned in this figure.

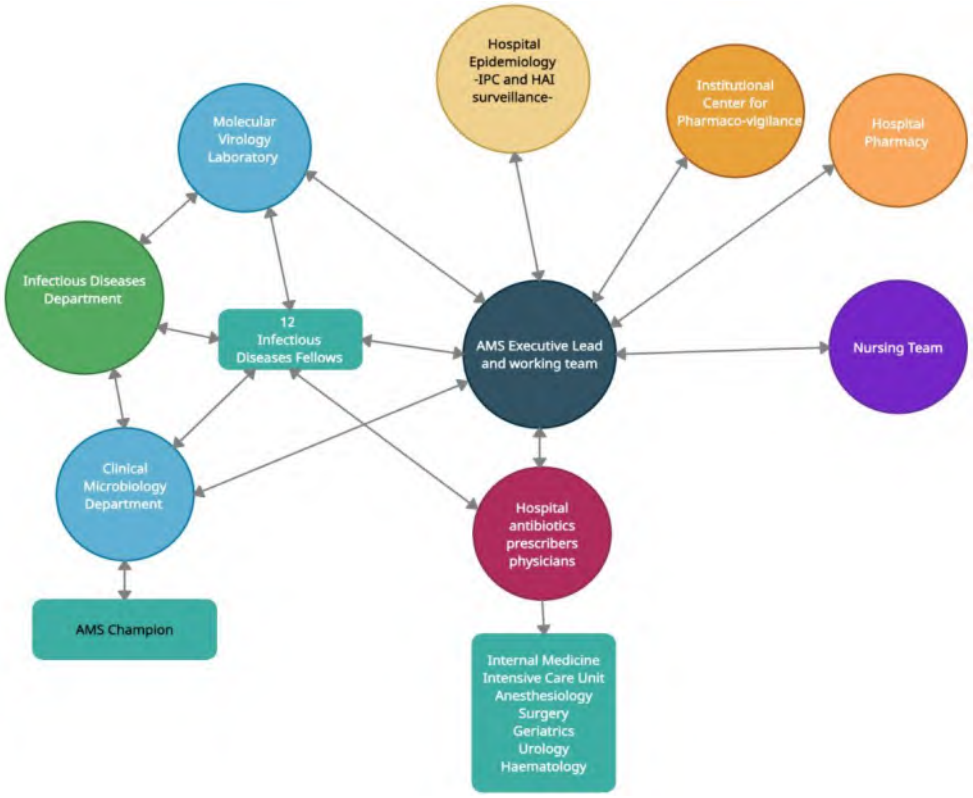

Figure 2A. Conformation of the ASP and activities.

Figure 2B. Conformation of the ASP and activities.

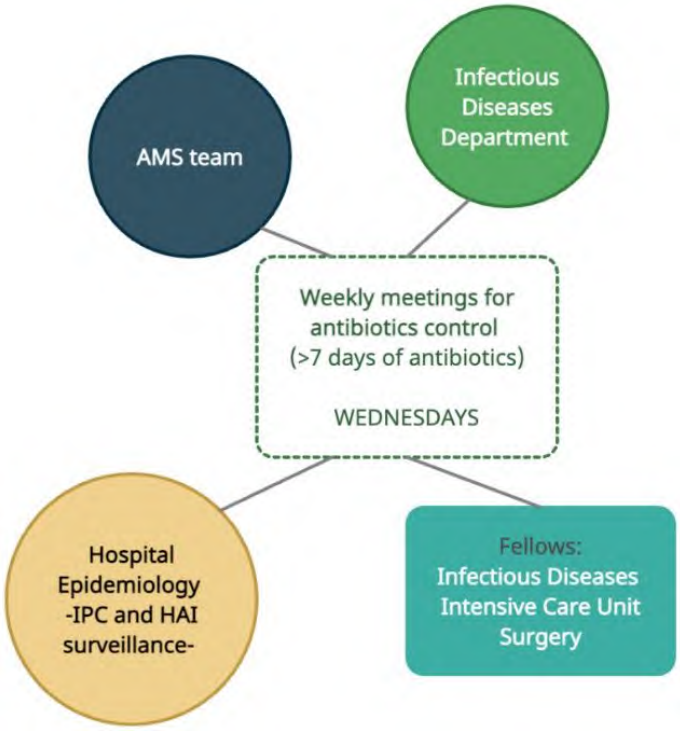

Figure 2C. Conformation of the ASP and activities.

As part of the ASP, we incorporated aims to evaluate its performance in real-time through the following:

a) Measure adherence to local clinical management guidelines.
b) Standardize traceability of antibiotic prescription and administration by implementing real-time electronic registration.
c) Monthly report of antibiotic use and susceptibility patterns.
d) Monthly report of adverse reactions.
e) Assisting in treatment selection decisions.

All these actions are quantified and supervised in an orderly fashion, and activities are calendarized in advance for members of the group according to specified needs (**Figure 3, and Figure 4**).

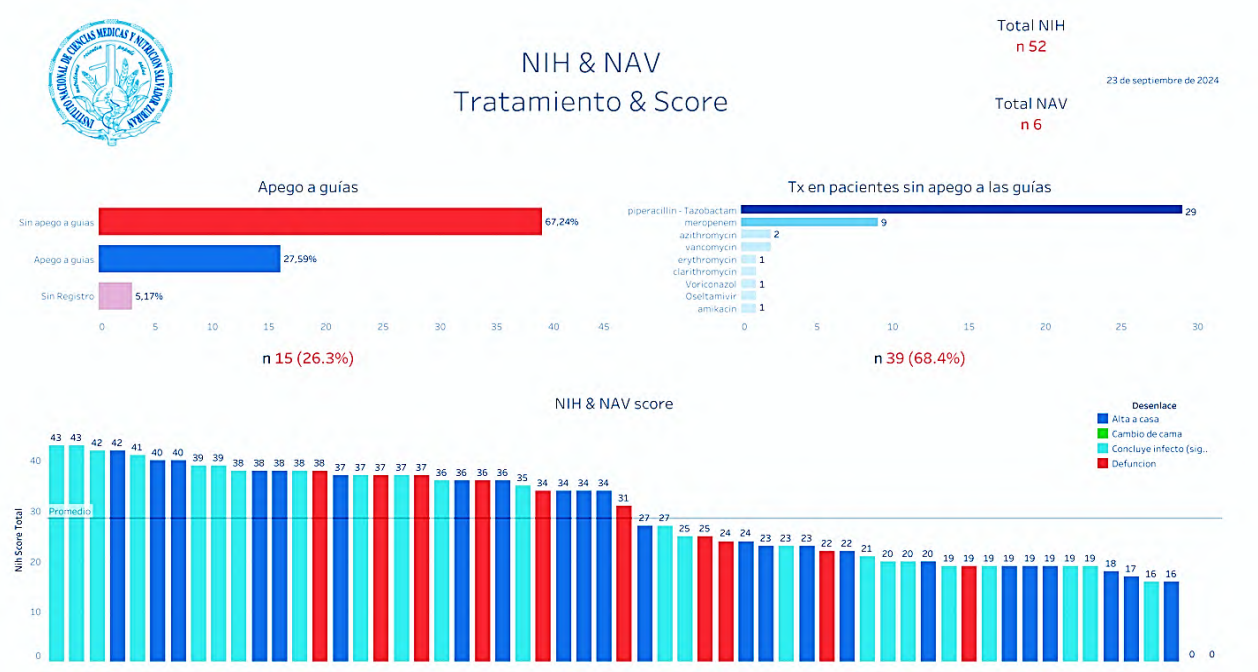

Figure 3. Activities and annual planning of the ASP in Mexico City.

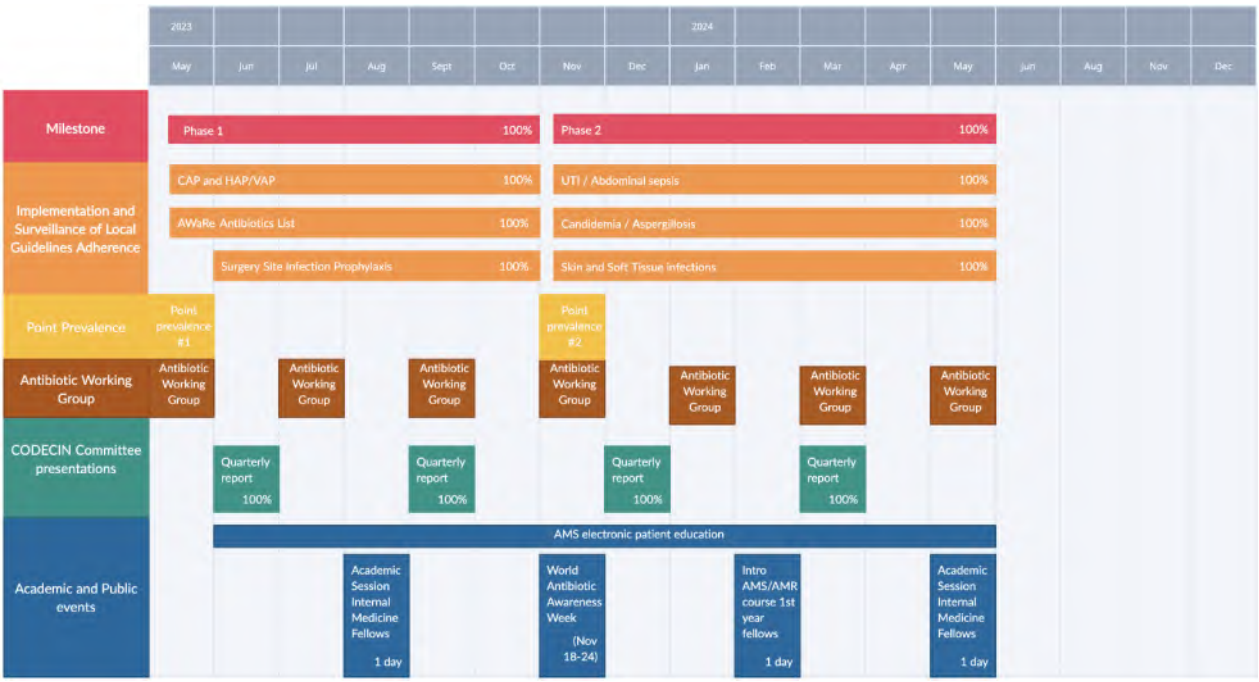

Figure 4. Adherence measurement to HAP and VAP guidelines.

Conclusion

Measurements of ASPs are still a difficult task, not only because of the diversity of methods that can be used but also because of the diversity of the clinical venues in which the programs are instituted. However, the common goal of all ASPs should be, firstly, improving the quality of care for each individual patient. Only through a progressive and assertive manner in which the different parameters of the programmes are assessed, proper and opportune decisions may be taken.

Competing interests

The authors have no financial and non-financial competing interests to declare.

References

1. Tanuma M, et al. Evaluation of antimicrobial stewardship activities using antibiotic spectrum coverage. Sci Rep. 2024;14:13998.
2. Morris AM. Antimicrobial Stewardship Programs: Appropriate Measures and Metrics to Study their Impact. Curr Treat Options Infect Dis. 2014;6:101-112.
3. Dyar OJ, et al. What is antimicrobial stewardship? Clin Microbiol Infect. 2017;23:793-798.
4. Tamma PD, et al. Antimicrobial stewardship. Infect Dis Clin North Am. 2011;25:245-60.
5. Barlam TF, et al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis. 2016;62:e51-77.
6. Harbarth S, et al. Antimicrobial resistance determinants and future control. Emerg Infect Dis. 2005;11:794-801.
7. De Waele JJ, et al. Antimicrobial resistance and antibiotic stewardship programs in the ICU: insistence and persistence in the fight against resistance. A position statement from ESICM/ESCMID/WAAAR round table on multi-drug resistance. Intensive Care Med. 2018;44:189-196.
8. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022;399:629-655.
9. World Health Organization. Antimicrobial resistance. 2021. Available at: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance. Last accessed: 23 February 2021.
10. World Health Organization. Global action plan on antimicrobial resistance. 2015. Available at: https://iris.who.int/bitstream/handle/10665/193736/9789241509763_eng.pdf?sequence=1. Last accessed: 30 September 2024.
11. Fishman N. Antimicrobial stewardship. Am J Infect Control. 2006;34:S55-63-73.
12. GBD 2021 Lower Respiratory Infections and Antimicrobial Resistance Collaborators. Global, regional, and national incidence and mortality burden of non-COVID-19 lower respiratory infections and aetiologies, 1990-2021: a systematic analysis from the Global Burden of Disease Study 2021. Lancet Infect Dis. 2024;24:974-1002.
13. Looke D, et al. Measuring the performance of antimicrobial stewardship programs. Antimicrobial Stewardship in Australian Hopsitals, eds M. Duguid and M. Cruickshank (Australian Commission on Safety and Quality in Healthcare). 2011. Available at: http://www.safetyandquality.gov.au/wp-content/uploads/2012/02/chapter5_measuring_performance_anti microbial_stewardship_programs. pdf. Last accessed: 30 September 2024.
14. Brotherton AL. Metrics of Antimicrobial Stewardship Programs. Med Clin North Am. 2018;102:965-976.
15. GBD 2021 Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance 1990-2021: a systematic analysis with forecasts to 2050. Lancet. 2024:S0140-6736(24)01867-1.

Chapter 92

The role of nurses in antimicrobial stewardship

Enrique Castro-Sánchez
Brunel University London, Antimicrobial Innovations Research Centre & College of Social and Political Science, Uxbridge, England;
Imperial College London, National Institute for Health Research Health Protection Research Unit in Healthcare-Associated Infection and Antimicrobial Resistance, London, England;
University of Balearic Islands, Global Health Unit, Palma, Spain;
Valencia International University, Valencia, Spain.

Introduction

The threat of antibiotic-resistant infections demands urgent attention from health and social care services worldwide because of its significant clinical, economic, human, and environmental costs. The efforts implemented to combat these infections, known as antimicrobial stewardship (AMS) programs, require a multifaceted approach and close collaboration among all health and social care professionals involved in decisions about the use of antimicrobials. Historically, nurses have largely been absent from such initiatives, which represents a missed opportunity to profit from the most abundant workforce cadre to strengthen existing and future AMS initiatives.
This chapter explores existing evidence supporting the need and impact of nursing engagement and leadership in AMS, discussing four key obstacles to increased nursing participation in AMS: fundamental issues, ownership concerns, educational gaps, and leadership challenges. This chapter also includes potential solutions and implications for addressing these barriers.

The nursing workforce: a potential AMS powerhouse

Antibiotic-resistant infections are planetary challenges to human, animal, and environmental well-being. Their global impact requires comprehensive and coordinated responses, with commitment from governments, healthcare system leaders, and private stakeholders. These organizations and agencies should increase funding and promote mechanisms which encourage the involvement of all essential health and social care workers in tackling antibiotic resistance. This approach appears to be logical and desirable, yet its implementation faces a challenge likely to be as difficult as the resistant infections themselves– the current worldwide shortage of 15 million health workers. More concerningly, the deficit in human health resources is projected to remain at 10 million by 2030, and given that this workforce shortage is unlikely to be resolved quickly, from a health systems perspective it would be crucial to leveraging all existing workforce cadres as optimally as possible. This optimization should be supported by innovative reassessments of clinical pathways, clinical skills, and competencies, and always focus on value-based, person-centered care.

The O'Neill report highlighted nurses, as the largest health professional group, as a crucial frontline workforce for tackling the escalating AMR crisis. Worldwide, additionally, health systems are sustained by nursing professionals and other roles allied to nursing such as community health workers. Nurses, although in a chronic limited supply, are still much more available than other health care workers such as physicians and pharmacists, in particular in low-and-middle-income countries, where they often support and sometimes lead AMS efforts.

However, nearly a decade later, there are still concerns that the largest cadre of healthcare professionals remains significantly underutilized in AMS efforts and faces multiple barriers to greater AMS engagement, including lack of role clarity, inadequate education, hierarchical cultures limiting their autonomy, and failure to meaningfully involve them in stewardship leadership and decision-making.

The "all-hands-on-deck" approach still requires a much clearer delineation of concrete nursing roles, responsibilities, and activities within the AMS framework. Adding ad hoc tasks to nurses' already overwhelming workload is unlikely to be sustainable or impactful. Evidence of the long-term effectiveness of one-off, decentralized, nurse-driven AMS interventions remains limited. More coordinated programs that systematically integrate nursing involvement and leadership at all levels, from bedside to board, may be required to achieve the full benefits of interprofessional antimicrobial management in both inpatient and ambulatory settings.

The need to broaden participation in AMS programs is not a new concept, with questions about the fit of the traditional physician-pharmacist-microbiologist triad in AMS programs to adequately reflect the realities of current interprofessional care models that embrace shared decision-making and flattened hierarchies. Maximizing the full potential of the nursing profession may require a paradigm shift, rethinking entrenched power dynamics, dismantling outdated hierarchies, and authentically empowering nurses as equal partners in antimicrobial management. With their ubiquitous presence across all care settings, nurses appear uniquely positioned to help operationalize and reinforce core stewardship principles at the point of care.

Activities such as promoting IV-to-oral switch of antimicrobial therapy, ensuring appropriate dosing, and monitoring patients' allergies or clinical responses naturally align with routine and essential nursing work. Initial ideas about the involvement of nurses in AMS focused primarily on clinical areas, perhaps aligning with views on antimicrobial stewardship as a technical task. These clinical activities, including collection of samples for microscopy or culture, patient education and information to relatives, or documentation of allergies, remain a cornerstone of nursing practice and would be universally agreed upon. However, there is much less clarity and certainty about competency frameworks, nursing profiles, and specific posts in AMS for nurses.

However, these reviews offer a useful starting point for ideas on AMS nursing, later updated by other perspectives on nonclinical roles for nurses in stewardship. These other domains would include leadership and contribution to research, not only in their own AMS nursing role but also in evaluating AMS programs, as well as policy development and implementation. It is very likely that the sustained progress in nurse prescribing seen in health systems globally, particularly in LMICs, has also contributed to the greater interest and participation of nurses in AMS. Considering the increasing volume of antimicrobials prescribed by nurses, which in some settings may soon surpass the units prescribed by hospitalists, it is reassuring to see the high quality of this prescribing.

Barriers to nursing engagement in AMS

Health systems interested in promoting the participation of nurses in AMS would usually have to consider and address four crucial barriers. These barriers are not unsurmountable, and could be resolved by framing AMS as a fundamental dimension of high-quality, safety-focused, patient-centered care; reframing AMS as

core nursing practice through the motto "good stewardship is good nursing care, and good nursing care is good stewardship"; developing nurse-specific educational resources; and fostering grassroots networking opportunities.

Foundational barrier. A pre-requisite for nursing engagement in AMS activities is the acknowledgement and recognition among nurses of these activities as legitimate and appropriate for nurses. Such recognition is yet to be universal, although current studies as well as policy developments and professional debates reflect much more willingness of nurses to take part in antibiotic improvement interventions, compared with just a few years ago. As mentioned before, activities such as ensuring appropriate antimicrobial dosing, monitoring the therapeutic response, and discussing whether to discontinue treatment when no longer needed align closely with core nursing responsibilities around medication management, patient assessment, and care co-ordination.

Why, then, is there apparent reluctance? Part of this collective nursing behavior may be due to the cultural milieu and professional dynamics in certain clinical practice environments. The earlier emphasis on decision-making aspects of antimicrobials –diagnosis, therapeutics, etc.–, hierarchical structures, and rigid demarcations of prescribing authority (especially in hospitals) may have made nurses feel less empowered to engage in roles perceived as "prescribing" territory, and overall deterring nurses from accepting AMS as a central nursing role.

Ownership and branding barriers. There seems to be a disconnect between nurses' reluctance to collaborate in optimal antimicrobial management when asked about it explicitly, particularly when using the stewardship concept, and their actual leadership and involvement in many typical and essential AMS activities. This dichotomy was elegantly highlighted in a 2016 survey of nurses across Africa regarding their involvement in AMS. The depth and breadth of AMS-related activities reported by the participants were striking, ranging from clinical to managerial outputs, participating in policy formation, prescribing antimicrobials, and educating peers and other professionals about AMS.

In many ways, as ensuring optimal antimicrobial use through rigorous clinical assessment, therapeutic monitoring, and effective communication embodies the very essence of excellence in nursing practice, framing AMS as a fundamental dimension of high-quality, safety-focused, patient-centered care should resonate well with how nurses perceive their professional identity and duties (**Table 1**). From this viewpoint, the lack of engagement in key AMS activities such as timely IV-to-oral switch would not simply be an issue of "poor antimicrobial stewardship", but one instead of “poor nursing care” which would fail to uphold the essential principles of evidence-informed practice.

Table 1. Examples of essential clinical nursing actions in antimicrobial stewardship.

Minimize unnecessary prescribing of antimicrobials *(by influencing decisions).*
Ensure adequate timing of antimicrobial administration.
Adopt necessary infection prevention and control measures.
Obtain biological samples for microscopy, culture, and sensitivity.
Therapeutic drug monitoring, following adequate and/or adjusted dosing.
IV administration only in severely ill, unable to tolerate oral treatment.
Review micro results daily, *(to help)* de-escalate to narrow-spectrum.
Review intravenous treatment daily, *(engage in discussion to)* and switch to oral route promptly.
Require single-dose surgical prophylaxis regimens as appropriate.

Educational barrier. The observed reluctance or perceived unwillingness of nurses to engage in AMS activities may be more reflective of education gaps in essential areas than a fundamental resistance to participate in AMS. This distinction is critical, as it shifts the focus from a perceived lack of interest or motivation among nurses to a more structural issue concerning their preparation and training for this role.

Evidence suggests that these gaps are widespread and may hinder the effective participation of nurses in AMS. Surprisingly, the earliest data in the UK on AMS-related education within undergraduate programs revealed significant deficiencies, particularly within nursing education. This research, conducted by Castro-Sánchez *et al.*, highlighted opportunities for improvement across several core domains critical to AMS. These areas include but are not limited to, microbiology, antimicrobial prescribing principles, interpretation of laboratory diagnostics, and general AMS best practices.

Each of these domains is fundamental for understanding the dynamics of infections, the mechanisms and optimal use of antimicrobials, and the interpretation of diagnostic results that guide therapeutic decisions. However, these topics are often inadequately covered in current nursing curricula. The implications of these educational gaps are important. When educational deficits prevent nurses from fully understanding or effectively participating in AMS activities, there is a significant missed opportunity for optimizing antimicrobial use and combating AMR.

Leadership barriers. Finally, there is a clear need for more professional and institutional leadership in AMS nursing. The gap between aspirational statements affirming the role of nurses in AMS found in some institutional policies and programs *versus* the actual limited engagement seen in practice is quite concerning. The nursing voice has historically been marginalized in antimicrobial policy and decision-making arenas at regional, national, and global levels, despite the front-line role of nursing in treatment delivery and infection care, and the presence of nurses across health service levels, settings, and services.

Strategies for improvement

Several initiatives and approaches have been developed to overcome these barriers and optimize nursing presence in AMS, although the adoption and implementation of these and similar initiatives is gradual and uneven across health systems and professional nursing cultures.

Educational Initiatives: Addressing these educational deficits presents both a challenge and an opportunity. The diversity and size of the global nursing workforce mean that any attempt to standardize and enhance AMS-related education must be both adaptable and scalable. Targeted interventions to address the gaps in education identified include several learning resources already developed, including textbooks and manuals commissioned by nursing and transdisciplinary scientific societies (https://www.esno.org/assets/files/AMR_Module_3.pdf), tools such as serious games addressing AMS and prescribing behaviors, and e-learning modules. These resources generally emphasize AMS principles, are interdisciplinary to bring together nursing, pharmacy, and medical students, and incorporate AMS into continuous professional development and training.

To effectively integrate nurses into AMS activities, educational strategies must also be multi-dimensional. This means not only incorporating the essential scientific knowledge of microbiology and pharmacology but also fostering a culture of critical thinking, decision-making, and inter-professional collaboration. Active learning approaches –such as problem-based learning, simulation training, and case-based discussions– may be more effective in teaching complex topics like AMS than traditional didactic methods. These innovative methods can help nurses develop the competencies needed to critically assess clinical situations, interpret diagnostic results accurately, and make informed decisions about antimicrobial use.

Moreover, efforts to enhance nursing education in AMS should also consider ongoing professional development. Continuous education programs, workshops, and e-learning platforms could provide accessible, flexible, and up-to-date resources for practicing nurses. Such initiatives would not only keep nurses informed about the latest AMS guidelines and evidence-based practices but also empower them to take on leadership roles in AMS, advocating for prudent antimicrobial use and driving quality improvement initiatives within their healthcare settings.

Education programs must however consider the local contexts and resources available, particularly in low- and middle-income countries where the burden of AMR is often highest, yet the resources for education and training may be even more limited. When these educational interventions are implemented, their effect is robust and sustainable. For example, several studies have demonstrated the effectiveness of education interventions in changing nursing practice and improving outcomes related to AMS. The systematic review by Olans *et al.* found that educational programs increased nurses' knowledge, confidence, and engagement in AMS activities. Specifically, interventions that combined didactic teaching with interactive components like case studies and role-playing were most effective, with multimodal education programs including online modules, in-person workshops, and clinical mentoring significantly improving nurses' adherence to AMS best practices like timely IV-to-oral antibiotic switches and appropriate specimen collection. This led to reductions in unnecessary antibiotic use. Additionally, tailored AMS education for nurse prescribers can enhance their antibiotic prescribing behaviors and decision-making.

In terms of technology, the "On Call: Antibiotics" serious game developed by Castro-Sánchez *et al.* (**Figure 1, Figure 2**) presents several clinical scenarios with increasing difficulty and uncertainty, where decisions to prescribe antibiotics or not, and continue their use, are then balanced with the consequences of such use such as antibiotic-related colitis or peripheral vascular access inflammation. The impact of ‘nudges’ by nurses on the decisions made by the game user is explored, together with the effect of uncertainty imposed by late results from biological samples. Approaches based on serious games or software ‘apps’ may be increasingly common but are likely to still appeal more to younger, more technologically inclined nurses, and they may focus on the diagnostic and therapeutic steps of infection management, which are least likely to involve nurses.

Figure 1, Figure 2. Selected behavioral nudges in 'On call: antibiotics' game (Adapted from Castro-Sánchez *et al.* 2014).

Other interventions have focused on strengthening nurses' communication with prescribers and decision-makers, developing conversational 'scripts' to reduce anxiety in the interactions about IV-to-oral switch and continuation of antibiotic courses, aiming to understand optimal points for intervention during clinical conversations, with brief standardized sentences which encourage open communication about prescribing decisions.

While novel educational strategies, such as serious games and dialogue support, hold promise for building nursing's AMS capabilities, the overall impact and practicality of such approaches remain unclear based on existing evidence. The dialogue support model of providing structured guidance for therapeutic decisions could potentially assist novice nurses but faces philosophical concerns about oversimplifying inherently complex diagnostic and treatment decisions. There may be fears that this approach could promote "cookbook" clinical care and end up undermining nursing critical thinking over time. More robust trials evaluating the real-world clinical utility, cost-effectiveness, and sustainability of such interventions are needed to justify scaling these models and secure institutional investment, particularly in low- and middle-income settings. Moreover, both games and dialogue tools fundamentally adopt an individual-focused educational approach when AMS is a profound social and collective undertaking which requires sustainable system-level solutions. While more research is still needed, the existing evidence suggests that well-designed education interventions can positively impact nursing practice and patient outcomes in AMS. However, stand-alone

knowledge/skill boosters are unlikely to overcome entrenched cultural and structural barriers, such as hierarchies, staffing deficits, lack of peer support, and organizational prioritization of AMS. Ultimately, a multipronged approach integrating AMS training across nursing curricula from undergraduate to postgraduate and continued professional education will likely be required to build sustainable competencies.

Leadership development. Fostering grassroots networking opportunities for knowledge mobilization and seeding communities of practice, such as international nursing summits in AMS nursing organized in the UK, or national and international networks in AMS nursing, such as the Brazilian Nurses Network Tackling the Antimicrobial Resistance (REBRAN) in Brazil, should be encouraged. Other examples include the online community of practice on AMS nursing hosted by the British Society of Antimicrobial Chemotherapy, connecting nurses internationally, and building clinical and leadership capacity.

The emergence of "nurse leaders in stewardship" through such forums is helping advocate for clearer nursing role delineation and decision-making power to be formalized within national action plans. However, high-level policy endorsements and commitments alone are unlikely to be sufficient for widespread transformation. Substantive institutional support, sustainable funding models, and the accompanying scope of practice modernization will ultimately be required to operationalize nursing stewardship roles and antimicrobial management responsibilities at scale. Efforts such as those by US Centers for Disease Control and Prevention to develop comprehensive nurse-specific AMS competencies could help to codify minimum practice standards.

Organizational approaches. A final hurdle to clear for organizations interested in implementing nurse roles in AMS would be to decide which model to adopt. Institutions may choose 'vertical' roles, where highly visible, consultant-type roles, are introduced (which on the other hand may not translate into a true transformational impact), or increase the skills of all nurses via 'horizontal' programs. This call to systematically "scan the landscape" for existing nursing stewardship roles, collaborations, and research is prudent given the relative paucity of published literature and data in this area compared to other disciplines. Identifying and disseminating exemplar nurse-led AMS models that are successfully operationalized could help build a stronger evidence base to advocate for wider role adoption across regions and care settings.

However, this bottom-up approach, driven by grassroots nursing advocacy, has clear limitations without corresponding top-down commitments from organizational leadership, policymakers, and professional governing bodies. Pioneering nurses pushing the envelope on expanded antimicrobial management may be doing so, in contrast to the existing professional regulations in many jurisdictions. A symbiotic cycle of nursing initiatives demonstrating their stewardship value proposition, followed by formal policy/regulatory updates to license such activities in an accountable manner, may be required for widespread scale-up.

Conclusion

The challenge presented by drug-resistant infections deserves the full focus of health systems and their clinical workforce. Nurses, where available, are educated and eager to increase their involvement and leadership in AMS programs. However, to profit from their skills and compassion, health services and professional organizations must strengthen emerging and design new nursing roles, address educational shortcomings, and agree upon metrics of success. While nursing work and expertise in the clinical arena are vital and valuable, anchoring nurses in such a role runs the risk of underusing their full potential, limiting professional growth, and ultimately fueling dissatisfaction.

Increased educational content on AMS included in undergraduate and postgraduate nursing courses worldwide could foster the involvement of future nurses in AMS efforts. It is particularly important to develop educational interventions aimed at improving the communication, confidence, and assertiveness of nursing students and qualified nurses to participate in multidisciplinary decisions about antibiotic management.
The call for nurses to increase their involvement in stewardship must integrate with local professional nursing culture, tradition, and legislative framework. Similarly, increased competencies and responsibilities must be carefully aligned with existing expectations from other professions to minimize friction and foster interprofessional collaborative practice.

Competing interests

The author has no financial and non-financial competing interests to declare.

References

1. Boniol M, et al. The global health workforce stock and distribution in 2020 and 2030: a threat to equity and universal health coverage? BMJ Global Health 2022;7:e009316.
2. Bos M, et al. Nurses' contribution to antimicrobial stewardship: business as usual? Antimicrob Resist Infect Control. 2024;13:93.
3. Bowler S, et al. Diagnostic stewardship: establishing the role of the hospital nurse to inform local engagement strategies. Infect Prev Pract. 2024;6:100381.
4. Broom A, et al. Nurses as Antibiotic Brokers: Institutionalized Praxis in the Hospital. Qual Health Res. 2017;27:1924-1935.
5. Bulabula AN, et al. Education and management of antimicrobials amongst nurses in Africa—a situation analysis: an infection control Africa network (ICAN)/BSAC online survey. J Antimicrob Chemother. 2018;73:1408-1415.
6. Castro-Sánchez E, et al. "On call: antibiotics"- development and evaluation of a serious antimicrobial prescribing game for hospital care. In: Schouten B, et al, Eds. Games for Health 2014: Proceedings of the 4th conference on gaming and playful interaction in healthcare. Wiesbaden, Germany: Springer Vieweg 2014; 1–8.
7. Castro-Sánchez E, et al. Mapping Antimicrobial Stewardship in Undergraduate Medical, Dental, Pharmacy, Nursing and Veterinary Education in the United Kingdom. PLoS One. 2016;11:e0150056.
8. Cotta M, et al. Attitudes towards antimicrobial stewardship: results from a large private hospital in Australia. Healthcare Infect. 2014;19:89 -94.
9. Courtenay M, et al. Patterns of GP and nurse independent prescriber prescriptions for antibiotics dispensed in the community in England: a retrospective analysis. J Antimicrob Chemother. 2023;78:2544-2553.
10. Courtenay M, et al. Applying an antimicrobial stewardship competency framework in nurse education and practice. Nurs Stand. 2020;35:41-46.
11. Gotterson F, et al. Nurse role and contribution to antimicrobial stewardship: An integrative review. Int J Nurs Stud. 2021;117:103787.
12. Hamdy RF, et al. The Key to Antibiotic Stewardship Is Combining Interventions. Pediatrics. 2020;146:e2020012922.
13. Lim SH, et al. Evaluating knowledge and perception of antimicrobial stewardship among nurses in an acute care hospital. Infect Dis Health. 2021;26:228-232.
14. Manning ML, et al. Health care system leaders' perspectives on infection preventionist and registered nurse engagement in antibiotic stewardship. Am J Infect Control. 2018;46:498-502.
15. Nowbuth AA, et al. Gamification as an educational tool to address antimicrobial resistance: a systematic review. JAC Antimicrob Resist. 2023;5:dlad130.

16. Olans RD, et al. Nurses and Antimicrobial Stewardship: Past, Present, and Future. Infect Dis Clin North Am. 2020;34:67-82.
17. OlansOlans RN, et al. The Critical Role of the Staff Nurse in Antimicrobial Stewardship--Unrecognized, but Already There. Clin Infect Dis. 2016;62:84-89.
18. O'Neill J. Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. Review on Antimicrobial Resistance. 2016. Wellcome Trust and HM Government.
19. Rzewuska M, et al. Barriers and Facilitators to Implementation of Antibiotic Stewardship Programmes in Hospitals in Developed Countries: Insights From Transnational Studies. Front Sociol. 2020;5:41.
20. Sumner S, et al. Antibiotic stewardship: The role of clinical nurses and nurse educators. Nurse Educ Today. 2018;60:157-160.
21. Tan W, et al. Outline of nurse prescribing education programs: A scoping review. Nurse Educ Today. 2023;131:105941.
22. Tartari E, et al. World Health Organization SAVE LIVES: Clean Your Hands global campaign-'Fight antibiotic resistance-it's in your hands'. Clin Microbiol Infect. 2017;23:596-598.
23. van Gulik N, et al. Perceived roles and barriers to nurses' engagement in antimicrobial stewardship: A Thai qualitative case study. Infect Dis Health. 2021;26:218-227.
24. World Health Organization. WHO competency framework for health workers' education and training on antimicrobial resistance. 2018. Available at: https://iris.who.int/bitstream/handle/10665/272766/WHO-HIS-HWF-AMR-2018.1-eng.pdf?sequence=1. Last accessed: 25 September 2024.
25. Zhao W, et al. Bedside nurses' antimicrobial stewardship practice scope and competencies in acute hospital settings: A scoping review. J Clin Nurs. 2023;32:6061-6088.

Chapter 93

Strengthening and expanding quality research efforts to improve the impact of antimicrobial stewardship in hospital settings

Dena van den Bergh
Division of Infectious Diseases and HIV Medicine, Department of Medicine, Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa.

Introduction

Despite the urgent calls for an increasing focus on antimicrobial stewardship (AMS) in hospital settings as part of global efforts to tackle antimicrobial resistance (AMR), there are substantial gaps in effective implementation at the scale and pace to make the impact needed.
Available estimates indicate the rate of inappropriate and overuse of antibiotics remains at between 30% and 50%. In addition, there is a significant disparity in the implementation of hospital antibiotic stewardship programs (ASPs) within countries, across continents and many low-middle income countries (LMIC) continue to face substantial obstacles that impede AMS implementation in hospitals. Strengthening and expanding quality research efforts to improve the impact of AMS in hospital settings is essential to enable context-specific implementation and to facilitate the spread and sustainability of hospital-based stewardship programs.

Defining AMS and rationale for expanding and strengthening the impact of hospital ASPs

The concept of antimicrobial stewardship (AMS) has become an essential part of international efforts to optimise antimicrobial use (AMU) including appropriate drug selection, dosing, route and duration of therapy and limiting or avoiding unintended consequences, such as the emergence of antimicrobial resistance (AMR), adverse drug events and the selection of pathogenic organisms. It entails diverse activities related to the use of antimicrobials aimed at ensuring antimicrobial effectiveness as well as their ongoing availability for those who need them.
While AMS efforts have expanded to include human, animal and environmental contexts under the umbrella of One Health, the day-to-day clinical reality of antimicrobial resistance is still most experienced in hospitals, with infections caused by multidrug-resistant organisms (MDROs) becoming even more prevalent all over the world and the added risk in hospitals of harbouring and spreading healthcare-associated infections (HAIs) and MDROs.

Hospital antibiotic stewardship programs (ASPs) require a combination of system-based interventions with distinct professional and organisational responsibilities as well as a coherent set of collective strategies to manage the appropriate use of antimicrobial agents.
Given the huge differences in resources across health systems internationally, it is not surprising that there is substantial global variability in the development and implementation of hospital ASPs.
In many LMICs, additional challenges especially the lack of a robust healthcare infrastructure such as staff workforce, access to clinical microbiology laboratory facilities, and other health system and organisational constraints hinder the implementation and research of ASP. At the same time, there are valuable lessons that can be learnt across all systems from the innovations and resilience that low-resource hospital settings have shown through the implementation of successful ASPs in the face of these challenges.

Foundational structures, standards and guidelines.

The dramatic growth and improved quality of hospital ASPs over the past 20 plus years has been boosted by the development of standards, guidelines and implementation of “best practices” led by global and local healthcare agencies, hospital organisations as well as various government departments.
The Center for Disease Control and Prevention (CDC) developed and released the Core Elements for Hospital Antibiotic Stewardship Programs in 2014 to help outline structural and procedural components associated with successful ASPs. In 2015, the World Health Organization (WHO) published a Global Action Plan on AMR that led to the development of AMR National Action Plans (NAPs) and raised expectations of political and financial support for ASPs to enable alignment.
Further global expansions of standards and structures for hospital ASPs have been developed using expert consensus approaches that added to the core elements and checklists, for hospitals to develop, implement, and track the impact of hospital AMS programs.
In some countries, these standards have been widely adopted to monitor and benchmark performance across hospitals in different geographies and have in some cases become mandated for hospital accreditation.
In the United States (US), one study reported that 76% of hospitals had all seven of the core elements in place in 2021, compared to just 41% in 2014. A survey of 660 hospitals across 67 countries highlighted disparities about the foundational structures and standards with only 52% of respondents reporting that National AMS standards are in place and 62% had hospital AMS standards, with a range from 21% in Africa and 73% in Europe.
It is acknowledged that ASPs in LMICs face significant barriers to implementation such as a shortage of human resources, limited laboratory infrastructure, a lack of national guidelines and inadequate governmental support. A systematic review of ASPs in African countries showed the majority of countries were not yet aligned with global efforts to combat increasing antibiotic resistance and reported that hospital ASPs remain limited.
The applicability of recommended core elements, checklists, standards and structures for ASPs in hospitals have not been tested for contextual relevance and value in different geographies, cultures, and resource settings. Furthermore, the unintended consequences of mandatory standards for hospital ASPs have not been sufficiently explored including the risks of hospitals “ticking the box” of having AMS structures in place without sufficient attention to driving ASPs aligned to local and global needs.
It has also been noted that the term LMIC itself is applied to a wide range of countries that may have very different characteristics, challenges and capacities, and may overgeneralize understanding of how AMS tools for LMICs can be “lifted and shifted”, even within the LMIC setting.

Further work is needed to address and understand the organizational structures, range of interventions and impact of AMS programs in hospitals across different geographies and contexts.

Strengthening evidence on IMPACT

Strengthening evidence on the impact of hospital ASPs is important to direct AMS strategies and enable more targeted use of resources.

There is an increased call on healthcare organizations to develop quality measures or indicators to monitor and evaluate the impact of ASPs on antimicrobial use, resistance patterns and patient outcomes.

Systematic reviews have described common outcomes reported in hospital ASP studies including changes in antimicrobial drug utilization and costs, appropriate antimicrobial choice, duration of treatment, adverse effects of antimicrobials, hospital-associated infection rates, antimicrobial resistance, length of stay, readmission rates and mortality.

Other process measures recommended for use in assessing hospital ASPs include documentation of indication for prescribed antimicrobials, indicating stop/review dates on prescription charts, time to administration of antibiotics, adherence to hospital-specific or national guidelines, level of acceptance of AMS recommendations, oral to intravenous switch, and rate of de-escalation of initial therapy.

Additional outcome measures include microbiological outcomes such as the percentage of difficult-to-treat organisms e.g. MRSA, ESBL-producing *Enterobacteriaceae*, and the rate of isolation of resistant organisms.

While many studies assess the impact of antimicrobial stewardship on antibiotic utilisation, the measurements used vary between studies, making it difficult to compare the impact of interventions across systems.

Data from published studies indicates that hospital ASPs have significant value with beneficial clinical and economic impacts, however more robust data is required in terms of the impact of ASP implementation on length of stay (LOS), and overall costs so that decision-makers can make a stronger case for investing in ASPs. Such data on ASPs in LMICs is even more limited and requires urgent attention.

Improving and expanding the QUALITY of research

AMS strategies in hospital settings are usually implemented in complex, 'real-world', clinical situations making it difficult to use the quality research reference standard of randomized clinical trials (RCTs) to evaluate interventions. The methodological quality of AMS studies remains a concern and most reviews report that the quality of research in hospital ASPs is poor and has not sufficiently improved over time.

Most ASP studies assessed in systematic reviews are quasi-experimental, and few used interrupted time-series analysis or external controls. In addition, many exclusively used process measures and clinical outcomes reported were most often limited to mortality and length of hospital stay which are commonly available in hospital information systems.

To ensure a more robust design, it is suggested that implementation and reporting of ASP studies in hospital settings should use randomized allocation of stewardship interventions to different units or hospitals or adopt a stepped-wedge design, in which all units eventually receive the intervention, but the timing of implementation is staggered. Where randomization or control units are not possible, the use of interrupted time series (ITS) analysis with multiple measurements in the intervention and non-intervention time periods, is recommended. Before-after quasi-experimental studies without an ITS analysis and sufficient data points

to control for time-dependent bias are discouraged: A sufficiently long duration of follow-up is also important to demonstrate AMS sustainability and to rule out negative consequences such as difficulty in sustaining interventions, decline in compliance or emergence of other confounding factors.

Given that AMS interventions in hospitals are inherently multifaceted, often involving significantly varying local structures as well as interpersonal and system dynamics, a key limitation is that too few ASP studies integrate qualitative research into the design, evaluation and reporting of interventions.

Further improvements to hospital AMS initiatives can be made by ensuring they are contextually designed and/or implemented with end-users of different specialties in mind. More research is needed on what behaviour change strategies work in hospitals, how to implement them and what refinements are needed to tailor the interventions to local contexts.

Quality research in hospital ASPs in different environmental and cultural contexts will provide an understanding of how effective interventions can be adapted and sustained across diverse settings.

EXPANDING research to improve the impact of ASPs in hospital setting

Capacity-building is one of the key components for expanding ASPs in hospital settings. Most research in AMS in hospitals has been initiated by specialist members of AMS teams such as ID physicians, clinical microbiologists and ID-trained pharmacists. A shortage of these resources in many developing countries and in hospitals outside of large centres makes it difficult to replicate this approach, necessitating AMS intervention led by non-specialised health professionals in collaboration with different members of the multidisciplinary teams (MDT).

For example, AMS multi-hospital studies across as many as 47 public and private hospitals in South Africa using non-ID-trained pharmacists, nurses and IPC professionals, have demonstrated the feasibility of expanding successful ASP research beyond AMS specialists.

Expanding AMS research programs to include multiple hospitals was made possible by using a collaborative research approach and constituting a team comprising a core study faculty of academic specialists in AMS and hospital-based AMS leaders who worked with frontline health professionals to co-design and implement AMS research.

Partnerships between academic researchers, health professionals and health systems leaders working together in ASP research in hospitals help address gaps in specialist knowledge and support better quality ASP research through the co-design of AMS studies with standardised rigorous measurement. Partnerships with academic researchers also facilitates the required ethics approval for ASP studies including for different hospitals involved in multisite research studies, which is a barrier to publishing ASP initiatives in non-academic hospitals.

These and other collaborative muti-hospital studies have demonstrated the value of accelerated and enriched learnings as a result of incorporating academic and non-academic centres from private and public sector hospitals as well as a broader community of specialised and non-specialised healthcare professionals. Expansion of ASP research to include national and international collaborations and extend beyond can also support capacity building across geographic boundaries as well as within and outside of disciplines.

Collaborative multi-hospital ASP research methods can also be used to scale qualitative research efforts and to further understand the critical features for success in ASP research collaboratives.

Integrating qualitative research into hospital ASP collaborative interventions offers the prospect of exploring and addressing contextual factors that impact outcomes and inform future research. For example, to expand the method of AMS collaboratives to the more specialised environments of neonatal AMS, a train-the-trainer

program together with a neonatal multidisciplinary team (MDT) approach was used with expert support faculty from academic centres. In addition, a nested qualitative component was included in the study design to understand the barriers and enablers and to describe the contextual factors for MDT-led neonatal AMS implementation across a diverse group of fourteen public and private hospitals in South Africa.

There is growing evidence that patient safety programs (including hospital ASPs) could benefit from more blended implementation science (IS) and quality improvement (QI) research strategies where IS provides the principles to inform implementation, evaluate efforts to produce generalizable knowledge and QI is the mechanism by which these principles are operationalized to support local practice change. Used together researchers and ASP leaders can determine what works, when, and why and thereby enhance the potential of successful implementation and sustainability of ASP research in practice.

Other focus areas for expanding the field of hospital AMS include involving patient and family representatives, exploring ways to integrate AMS interventions into existing health system structures, more studies to investigate the sustainability of ASP over longer periods and understanding how to bring together diverse stakeholders to co-produce quality research in hospital ASP in different contexts.

STRENGTHENING efforts to improve the impact of AMS in hospitals

The fragmentation of patient care pathways that involve multiple medical and surgical specialties, pharmacists, nurses, infection prevention practitioners and healthcare managers remains a significant constraint to AMS implementation in hospital settings.

Organisational culture in healthcare has the power to influence behaviour and shape ASP intervention outcomes. To strengthen AMS research efforts in hospital settings a better understanding of organisational culture is needed to ensure interventions are successful and sustainable.

Consideration of the contextual drivers of antibiotic decision-making provides a valuable opportunity to design and implement unique AMS interventions that can be adapted to different hospital settings and specialty levels within hospitals and address local culture and professional behaviours.

Insufficient attention has been given to how healthcare administration, clinical leadership and organisational design and culture in hospitals impact ASPs through the allocation of resources and determining the priorities and activities for hospitals to achieve their goals.

To strengthen the impact of ASPs it is important to understand how leaders at different levels of hospital organisations influence the agenda, institutional buy-in and priorities for ASP implementation and to more directly engage with leaders in the design of interventions to address barriers in hospital organisational design and culture that impact ASPs.

Developing ASP research leadership capability across a wider spectrum of healthcare professional disciplines can significantly strengthen efforts to improve the impact of AMS in hospitals. Expanding leadership roles for ASP initiatives to nursing, pharmacy and non-ID specialists such as surgeons, intensive care physicians and paediatricians has the potential to enable a broader distribution of hospital ASP initiatives and more sustainability.

Using health technology and Artificial Intelligence

Health information systems globally are expanding, maturing and converging, and as a result, offer significant opportunities to strengthen efforts to improve the scale and impact of hospital ASPs.

The large volumes of routine clinical data generated in health systems globally can be used to increase understanding of the epidemiology of infectious diseases and the levels, patterns and trends of antimicrobial usage and resistance. However, more work is needed to investigate how to effectively use facility-level and/or national-level data to understand antimicrobial use and resistance to inform antimicrobial stewardship programs and treatment guidelines.

Integration of information technology (IT) systems to enable real-time interventions to optimize antimicrobial therapy and patient management has advanced significantly in recent years but is hindered by limited resources for data analysis and poor interoperability between software systems.

Electronic health records (EHRs), clinical decision support systems (CDSSs) and electronic prescribing systems can draw together information from different hospital systems enabling efficient targeting of AMS opportunities as well as to provide data to support diagnosis, treatment decisions and review of ASPs and strategies in hospitals but are largely limited to high-income settings due to prohibitive costs.

Smartphone apps can provide stewardship guidelines, antibiograms, and other information which can potentially reach thousands of prescribers and healthcare professionals. Apps can also support easy data collection for ASP research across hospitals including in resource-limited countries. The use of social media platforms has also increased the visibility of AMS research and can support connections to networks of health professionals engaged in ASP globally.

While the speed of technology adoption in healthcare is advancing rapidly, evidence of the impact of health information technology on outcomes for ASP remains limited with few randomised studies and several weaknesses in study design which require attention. In addition, technology-enabled antimicrobial stewardship interventions need to strengthen stakeholder engagement and participation in the investigation of behavioural changes related to technology-enabled interventions.

Undoubtedly, the proliferation of various forms of artificial intelligence (AI) will bring many opportunities to strengthen ASP strategies including in hospitals.

While AI models can bring together complex evolving data and provide insights for large-scale optimisation of antimicrobial use and wider infection care, there is still a significant implementation gap between the promise of AI models and how they can be used to improve antimicrobial use and infection care which will require further research.

Conclusion

AMR affects countries in all regions and at all income levels. For hospital systems increased resistance not only makes infections harder to treat, it makes other medical procedures and treatments such as caesarean sections, hip replacements, organ transplantation, other surgeries and cancer chemotherapy much riskier.

Strengthening and expanding quality research efforts to improve the impact of ASPs in hospitals should be prioritised across all hospital settings, regardless of their size or academic affiliation. There are significant opportunities to improve ASP research in individual hospitals and collectively across hospitals globally to leverage efforts and amplify the impact.

Competing interests

The author has no financial and non-financial competing interests to declare.

References

1. Bertagnolio S, et al. WHO global research priorities for antimicrobial resistance in human health. Lancet Microbe. 2024:100902.
2. Del Fabro G, et al. Time is running out. No excuses to delay implementation of antimicrobial stewardship programmes: impact, sustainability, resilience and efficiency through an interrupted time series analysis (2017-2022). JAC Antimicrob Resist. 2024;6:dlae072.
3. Giamarellou H, et al. Antimicrobial Stewardship in the Hospital Setting: A Narrative Review. Antibiotics. 2023;12: 1557.
4. Akpan MR, et al. Implementation of antimicrobial stewardship programmes in African countries: a systematic literature review. J Glob Antimicrob Res. 2020;22:317-324.
5. Nathwani D, et al. Value of hospital antimicrobial stewardship programs [ASPs]: a systematic review. Antimicrob Resist Infect Control. 2019;8:35.
6. Davey P, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev. 2013;4:CD003543.
7. Vijay S, et al. Hospital-based antimicrobial stewardship, India. Bull World Health Organ. 2023;101:20-27A.
8. Thursky KA, et al. Antimicrobial stewardship in Australia: the role of qualitative research in programme development. JAC Antimicrob Resist. 2021;3:dlab166.
9. O'Leary EN, et al. An Update From the National Healthcare Safety Network on Hospital Antibiotic Stewardship Programs in the United States, 2014-2021. Open Forum Infect Dis. 2024;11:ofad684.
10. Veepanattu P, et al. Building resilient and responsive research collaborations to tackle antimicrobial resistance—Lessons learnt from India, South Africa, and UK. Int J Infect Dis. 2020;100:278-282.
11. Restrepo-Arbeláez N, et al. Antimicrobial Stewardship Programs in Latin America and the Caribbean: A Story of Perseverance, Challenges, and Goals. Antibiotics. 2023;12:1342.
12. Charani E, et al. Antibiotic Stewardship—Twenty Years in the Making. Antibiotics. 2019;8:7.
13. Charani E, et al. Investigating the cultural and contextual determinants of antimicrobial stewardship programmes across low-, middle- and high-income countries—A qualitative study. PLOS One. 2019;14:e0209847.
14. Pulcini C, et al. Developing core elements and checklist items for global hospital antimicrobial stewardship programmes: a consensus approach. Clin Microbiol Infect. 2019;25:20-25.
15. Harun MGD, et al. Barriers, facilitators, perceptions and impact of interventions in implementing antimicrobial stewardship programs in hospitals of low-middle and middle countries: a scoping review. Antimicrob Resist Infect Control. 2024;13:8.
16. Schuts EC, et al. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. Lancet Infect Dis. 2016;16:847-856.
17. Hulscher MEJL, et al. Antibiotic stewardship: does it work in hospital practice? A review of the evidence base. Clin Microbiol Infect. 2017;23:799-805.
18. Cox JA, et al. Antibiotic stewardship in low- and middle-income countries: the same but different? Clin Microbiol Infect. 2017;23:812-818.
19. Hibbard R, et al. Antimicrobial stewardship: a definition with a One Health perspective. npj Antimicrobials and Resistance 2024;2:15.

20. Kaki R, et al. Impact of antimicrobial stewardship in critical care: a systematic review. J Antimicrob Chemother. 2011; 66:1223-1230.
21. Rzewuska M, et al. Prioritizing research areas for antibiotic stewardship programmes in hospitals: a behavioural perspective consensus paper. Clin Microbiol Infect. 2019;25:163-168.
22. Godman B, et al. Strategies to Improve Antimicrobial Utilization with a Special Focus on Developing Countries. Life. 2021;11:528.
23. Shamas N, et al. Challenges of implementing antimicrobial stewardship tools in Low to Middle Income Countries (LMICs). Infect Prev Pract. 2023;5:100315.
24. Cosgrove SE, et al. Antibiotic Stewardship. Infect Dis Clin N Am. 2023;37:659-667.
25. Willemsen A, et al. A review of national action plans on antimicrobial resistance: strengths and weaknesses. Antimicrob Resist Infect Control. 2022;11:90.
26. Howard P, et al. An international cross-sectional survey of antimicrobial stewardship programmes in hospitals. J Antimicrob Chemother. 2015;70:1245-1255.
27. Cairns KA, et al. Antimicrobial Stewardship in Australian Hospitals and Other Settings. Infect Dis Ther. 2015;4:27-38.
28. Broom A, et al. The modern hospital executive, micro improvements, and the rise of antimicrobial resistance. Soc Sci Med. 2021;285:114298.
29. Wojcik G, et al. Understanding the complexities of antibiotic prescribing behaviour in acute hospitals: a systematic review and meta-ethnography. Arch Public Health. 2021;79:134.
30. Schweitzer VA, et al. The quality of studies evaluating antimicrobial stewardship interventions: a systematic review. Clin Microbiol Infect. 2019;25:555-561.
31. De Kraker MEA, et al. Good epidemiological practice: a narrative review of appropriate scientific methods to evaluate the impact of antimicrobial stewardship interventions. Clin Microbiol Infect. 2017;23:819-825.
32. Pulcini C, et al. CMI policy on antimicrobial stewardship research. Clin Microbiol Infect. 2018;24:91-92.
33. Van Den Bergh D, et al. A commitment and call to strengthen and expand qualitative research efforts to improve the impact of antimicrobial stewardship. JAC Antimicrob Resist. 2021;3:dlab151.
34. Brink AJ, et al. Antimicrobial stewardship across 47 South African hospitals: an implementation study. Lancet Infect Dis. 2016;16:1017-1025.
35. Brink AJ, et al. From guidelines to practice: a pharmacist-driven prospective audit and feedback improvement model for peri-operative antibiotic prophylaxis in 34 South African hospitals. J Antimicrob Chemother. 2017;72:1227-1234.
36. Brink A, et al. Passing the baton to pharmacists and nurses: New models of antibiotic stewardship for South Africa? S Afr Med J. 2016;106:947-948.
37. Schellack N, et al. 'Esprit de Corps':Towards collaborative integration of pharmacists and nurses into antomicrobial stewardship programs in South Africa. S Afr Med J. 2016;106:973-974.
38. Dramowski A, et al. Prospective antimicrobial stewardship interventions by multidisciplinary teams to reduce neonatal antibiotic use in South Africa: The Neonatal Antimicrobial Stewardship (NeoAMS) study. Int J Infect Dis. 2024;146:107158.
39. McGowan JG, et al. What are the features of high-performing quality improvement collaboratives? A qualitative case study of a state-wide collaboratives programme. BMJ Open. 2023;13:e076648.
40. Ashiru-Oredope D, et al. Global collaborations in antimicrobial stewardship: All hands on deck. Antimicrob Steward Healthc Epidemiol. 2023;3:e66.
41. Goff DA, et al. International train the trainer neonatal antibiotic stewardship program for South African pharmacists. J Am Coll Clin Pharm 2021;4:1572-1582.
42. Dramowski A, et al. Prospective antimicrobial stewardship interventions by multidisciplinary teams to reduce neonatal antibiotic use in South Africa: The Neonatal Antimicrobial Stewardship (NeoAMS) study. Int J Infect Dis. 2024;146:107158.
43. Davis MM, et al. Integration of Improvement and Implementation Science in Practice-Based Research Networks: a Longitudinal, Comparative Case Study. J General Int Med. 2021;36:1503-1513.

44. Kapadia SN, et al. The Expanding Role of Antimicrobial Stewardship Programs in Hospitals in the United States: Lessons Learned from a Multisite Qualitative Study. Jt Comm J Qual Patient Saf. 2018;44:68-74.
45. Cowman K, et al. Using Technology to Enhance Antimicrobial Stewardship Impact in the Acute Care Setting. Curr Treat Options Infect Dis. 2020;12:145-157.
46. King A, et al. Investigating the ways in which health information technology can promote antimicrobial stewardship: a conceptual overview. J R Soc Med. 2017;110:320-329.
47. Howard A, et al. Antimicrobial learning systems: an implementation blueprint for artificial intelligence to tackle antimicrobial resistance. Lancet Digital Health. 2024;6:e79-e86.
48. Rawson TM, et al. A systematic review of clinical decision support systems for antimicrobial management: are we failing to investigate these interventions appropriately? Clin Microbiol Infect. 2017;23:524-532.

Chapter 94

Role of telemedicine in managing infectious diseases

Juan Pablo Escalera-Antezana
Instituto de Investigaciones Biomédicas e Investigación Social, IIBISMED. Associate Researcher, Cochabamba, Bolivia;
CIES Cochabamba Clinic, General Manager, Cochabamba, Bolivia.

Introduction

The World Health Organization defines Telemedicine as the provision of health care by health professionals who use information and communication technologies to exchange data to establish diagnoses, propose treatments and prevent illnesses and accidents, as well as the ongoing training of health personnel and clinical, research and evaluation activities, to improve the health of the population.
The use of Telemedicine in medical specialties began in the 1950s, with radiology being the first medical specialty to use it reliably, since then the expansion to other clinical branches has generated the opportunity to ensure diagnosis, interpretation of laboratory tests and images, treatment and even the monitoring of patients, thus guaranteeing better care and evolution of patients with different known pathologies.
Infectology or the care of infectious diseases through Telemedicine can generate a great benefit in the management of these types of pathologies, because several studies have substantially demonstrated correct and adequate use of antibiotic therapy, as well as improvement in hospitalization, reducing the patient's stay, giving a faster improvement, with fewer transfers or referrals to other clinical units or higher-level health establishments respectively.
In Bolivia, the National Telehealth Program was born as a project with international collaboration to a) use internet connections between regional and national health institutions; b) develop teleconsultations, teleconferences and telemedicine; c) implement tele-teaching, and d) evaluate long-distance collaboration for clinical consultation and continuing medical training, which at that time practically the national medical professional was not aware of the potential that would be reflected years later, during its peak in the COVID-19 pandemic.

Telemedicine and infectious diseases

Telemedicine, as part of the new information and communication technologies in the medical field, has been a fundamental tool in recent years to treat patients, helping to develop clinical care and ensuring the safety of health personnel.

Information and Communication Technologies (ICTs) had already evolved and developed in many countries, especially in developed ones, prior to the COVID-19 pandemic, but this technology in its medical use was undervalued, and even despised by the health professional component.

According to the experiences of colleagues, the use of WhatsApp since its inception in 2009 has been a platform in which patients take advantage of direct contact with their treating physician, however, many of them even refused to respond, because it was practically an economic loss, but everything changed in a decade from the incursion of WhatsApp in our lives.

Telemedicine or telehealth, as it is known in other countries, has had an impact on the management of infectious diseases since the 1990s, especially on the treatment, monitoring and follow-up of patients with HIV/AIDS, hepatitis C and tuberculosis.

Another important field of action, which has a great opportunity and challenge, is the monitoring of postoperative wounds. Patients take photographs with their smartphones, and they are sent to platforms remotely and asynchronously, so that health personnel can review them, which would help in a remote assessment. However, on the other side of the coin, there is the difficulty that older adults, with obesity in different degrees, and wounds in limiting areas, are unable to use this alternative properly.

On December 31, 2019, a new virus emerged in the world, which has been a milestone of a before and after in public health, and especially in the management of infectious pathologies, and even more so in one that no one knew anything about its management at that time.

On July 23, 2022, the World Health Organization (WHO) declared the monkeypox outbreak a public health emergency of global importance, with the countries with the highest number of confirmed cases being the United States, Brazil, Spain, France, Colombia, the United Kingdom, Germany, Peru, Mexico and Canada.

Regular infectious diseases, the latest pandemic and the global health emergency, respectively, have marked a new milestone in the strengthening of ICTs in the health field, making it clear that they have been in force for many years, but today they are already an essential tool in our medical practice.

Consultation management through telemedicine

Due to the incursion of the COVID-19 pandemic in our lives 5 years ago, and still living with new cases, and consequences that the population manifests, at the time manuscripts, protocols, and algorithms for patient care were made, which were a strong pillar for monitoring and follow-up of them.

Within one of the largest telemedicine networks in Latin America, Bolivia, in its National Telehealth Program, has 340 points in 338 municipalities, at the three levels of health care, during the pandemic the National Call Center was installed, with a free line that carried out the capture, geographic identification, follow-up, monitoring, treatment, referral and/or guidance of suspected cases, which in coordination with rapid response services and health facilities, allowed the timely care of patients (**Figure 1**)

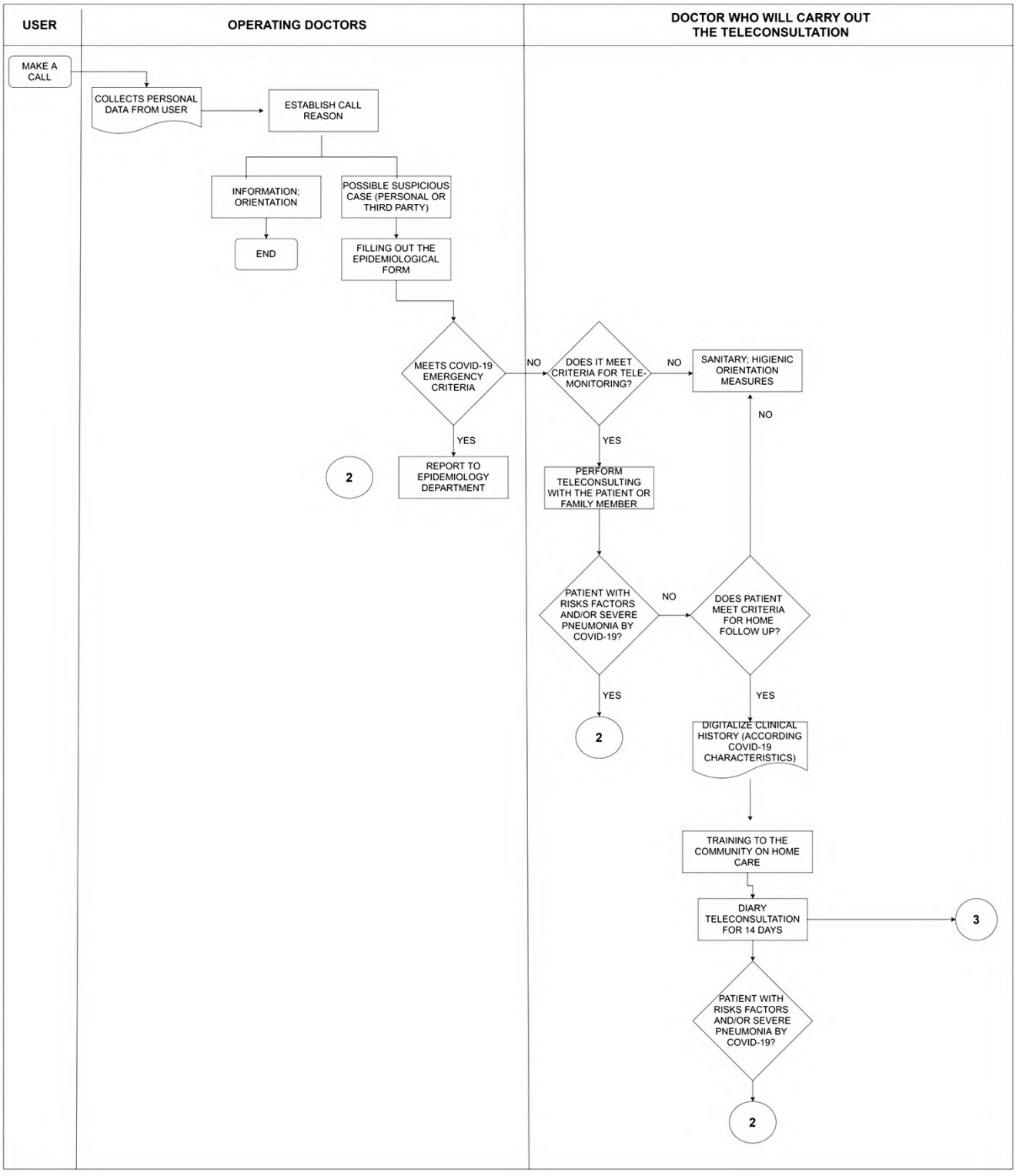

Figure 1. Call Center COVID-19 - Teleconsulting attention flowchart - Programa Nacional de Telesalud Bolivia (Adapted from Nina-Mollinedo JM, *et al.* 2022).

The transfer of service or referral to another health facility was also done through the National Telehealth Program platform, proposing an algorithm for this (**Figure 2**).

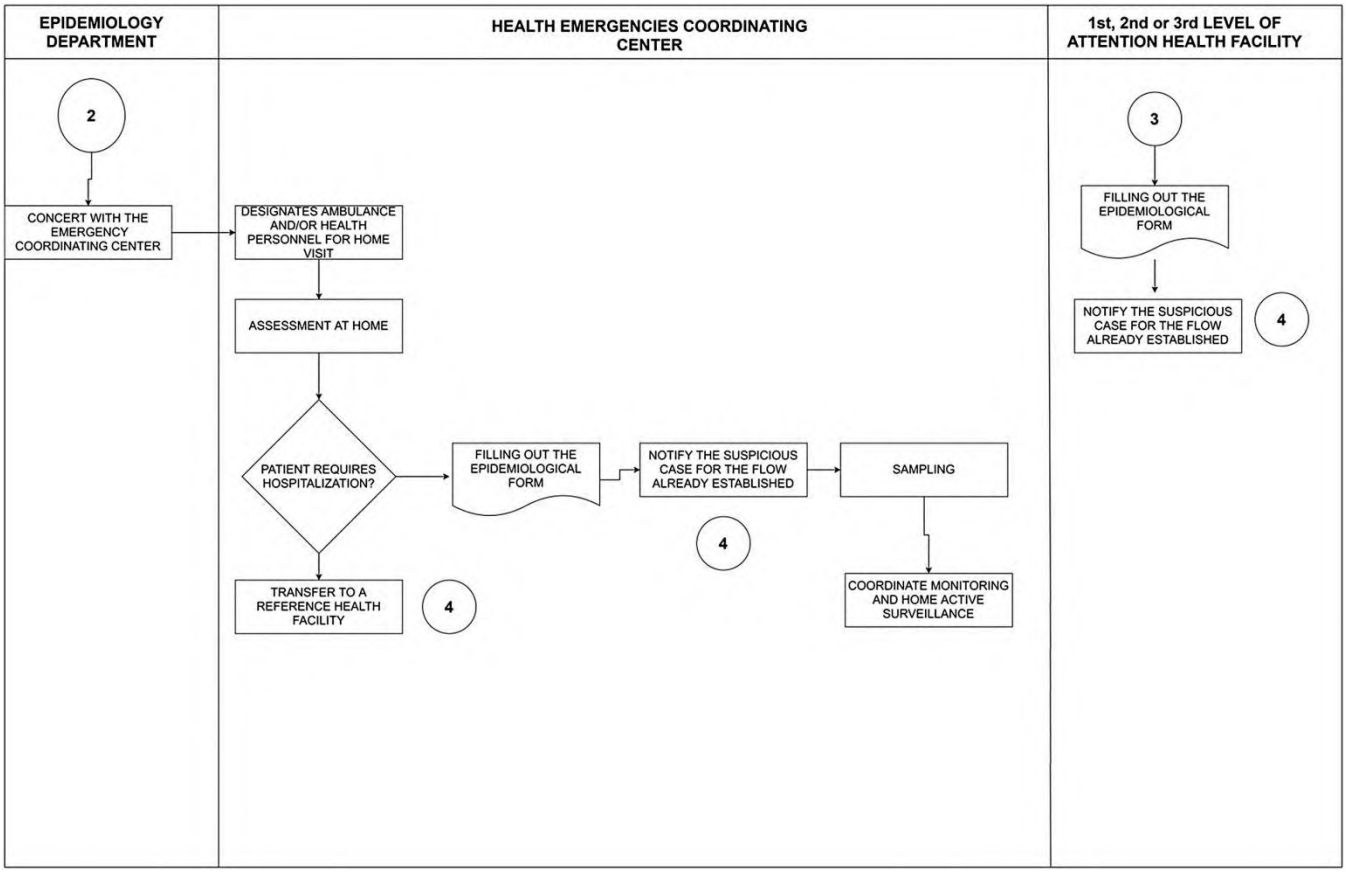

Figure 2. Transfer flowchart for serious and critical patients (Adapted from Nina-Mollinedo JM, *et al.* 2022).

Siciliano *et al.* in their study on the implementation and use of telemedicine in healthcare delivery of the monkeypox outbreak in the Health Area of Ibiza and Formentera, Spain, also proposes a simplified diagram of the care circuit showing the flow of information, sample collection, administrative and epidemiological coordination, and telephone assistance provided from patient recruitment to notification of discharge and closure of the infectious episode, based and focused on the same way as that proposed by Bolivia, thus showing that the same hermeneutics and logic of use of ICTs in health follow a similar pattern to develop the necessary tool and with the same variables of care for the population.

Conclusion

Telemedicine has been developed for many years, however, it has only been since the beginning of the COVID-19 pandemic that it has gained strength, boosted the service in many countries, and positioned itself in some others as a tool, unit or program that executes the fundamental purpose for which it was developed, which is to shorten distances, facilitate access to treatment and monitor the evolution of the infectious disease, taking care of or maintaining the necessary distance to avoid the unnecessary spread of the pathology. Public health has taken a new direction with a new tool, which must be regulated and made compatible according to common regions, such as South America, Asia, and Europe, essentially, due to their own cultural, demographic, and social factors, in addition to a regulated normative establishment with everything that

entails, such as the use of digital medical records, electronic signature of health personnel, which, for example in Bolivia, is still lacking.

With all these aspects, telemedicine or telehealth is a tool that has proven to be effective in all its forms, developed at a high, medium, or low level, allowing in all cases epidemiological control, in addition to clinical control, providing substantial information that allows improving health policies that are in force in the country where it is used.

Competing interests

The author has no financial and non-financial competing interests to declare.

References

1. World Health Organization Global Observatory for eHealth. Telemedicine: Opportunities and developments in Member States. Observatory. Available at: https://iris.who.int/bitstream/handle/10665/44497/9789241564144_eng.pdf?sequence=1. Last accessed 25 October 2024
2. G. Gras. Use of telemedicine in the management of infectious diseases. Med Mal Infect, 2018;48:231-237.
3. E. Palau. Telemedicina, e-Salud y enfermedades infecciosas. Enferm Infecc Microbiol Clin. 2001;19:145-147.
4. L. Eron, et al. Treating acute infections by telemedicine in the home. Clin Infect Dis. 2004;39:1175-1181.
5. Assimacopoulos A, et al. A brief retrospective review of medical records comparing outcomes for inpatients treated via telehealth versus in-person protocols: Is telehealth equally effective as in-person visits for treating neutropenic fever, bacterial pneumonia, and infected bacterial wounds? Telemed J E Health. 2008;14762-768.
6. Vargas A, et al. Telemedicina en Bolivia: proyecto RAFT- Altiplano, experiencias, perspectivas y recomendaciones. Rev Panam Salud Publica. 2014;35:359–364.
7. Zhu N, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382:727–733.
8. Fundación Carlos Slim. La evolución de la telesalud en Bolivia durante la pandemia. 2020. Available at https://saluddigital.com/comunidadesconectadas/la-evolucion-de-la-telesalud-en-bolivia-durante-la-pandemia/. Last accessed: 1 October 2024.
9. Becker C. High-tech treatment: federal grant allows HIV/AIDS patients to receive treatment through telemedicine. Mod Healthc. 2002;32:18–19.
10. Makulowich JS. AIDS and telemedicine. AIDS Patient Care STDs.1996;10:387–388.
11. Rossaro L, et al. The evaluation of patients with hepatitis C living in rural California via telemedicine. Telemed J E Health. 2008;14:1127–1129.
12. DeMaio J, et al. The application of telemedicine technology to a directly observed therapy program for tuberculosis: a pilot project. Clin Infect Dis. 2001;33:2082–2084.
13. DeMaio J, et al. Tuberculosis therapy and telemedicine. Expert Opin Pharmacother. 2002;3:1283–1288.
14. Gunter R, et al. Evaluating patient usability of an image-based mobile health platform for postoperative wound monitoring. JMIR Mhealth Uhealth. 2016;4:e113.
15. Totty JP, et al. Use of photograph-based telemedicine in postoperative wound assessment to diagnose or exclude surgical site infection. J Wound Care. 2018;27:128–135.
16. Wiseman JT, et al. Inter-rater agreement and checklist validation for postoperative wound assessment using smartphone images in vascular surgery. J Vasc Surg Venous Lymphat Disord. 2016;4:320–8.e2.
17. Wiseman JT, et al. Conceptualizing smartphone use in outpatient wound assessment: patients' and caregivers' willingness to use technology. J Surg Res. 2015;198:245–251.
18. World Health Organization. WHO Director-General declares the ongoing monkeypox outbreak a Public Health Emergency of International Concern. Available at: https://www.who.int/europe/news/item/23-07-2022-who-

director-general-declares-the-ongoing-monkeypox-outbreak-a-public-health-event-of-international-concern. Last accessed: 1 October 2024.
19. Mpox (Monkeypox) Outbreak: Global Trends World Health Organization. Available at: https://worldhealthorg.shinyapps./mpx global/.
20. Situación epidemiológica de los casos de viruela del mono en España. Sistema para la Vigilancia en España. Centro Nacional de Epidemiología.
21. Siciliano B, et al. Implantación y uso de la telemedicina en la asistencia sanitaria del brote de viruela símica en el Área de Salud de Ibiza y Formentera [Implementation and use of telemedicine in health care during the outbreak of monkeypox in the health area of Ibiza and Formentera]. Aten Primaria. 2024;56:102742.
22. Peek N, et al. Digital health and care inpandemic times: Impact of COVID-19. BMJ Health Care Inform. 2020;27:e100166.
23. Leão CF, et al. El uso del WhatsApp en la relación médico-paciente. Revista Bioética. 2018;26:412-419.
24. Nina-Mollinedo JM, et al. Hundred Days of Teleconsultations and Their Usefulness in the Management of COVID-19: Experience of the COVID-19 National Call Center in Bolivia. Telemed J E Health. 2022;28:654-665.