Achromobacter xylosoxidans

Clinical Setting

- Found in soil and water. Cause of bacteremia, meningitis, catheter-related bloodstream infections, pneumonia, urinary tract infections, keratitis, and rarely from respiratory tract secretions from patients with cystic fibrosis.

- Two main intrinsic antibacterial resistance mechanisms: Multidrug efflux pumps Chromosomal OXA-114-like beta-lactamases to include: ESBLactamases, AmpC cephalosporinases Carbapenemases to include metallo-beta-lactamases

- Multidrug efflux pumps

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- ESBLactamases, AmpC cephalosporinases

- Carbapenemases to include metallo-beta-lactamases

- In vitro susceptibility varies with source of the bacteria: Wild type Predictably resistant to: Pen G, first & second generation cephalosporins, Ceftriaxone, Aztreonam , Tetracycline, aminoglycosides, azithromycin Predictably susceptible to : Ceftazidime, cefepime, Piperacillin, Carbapenems, Sulfonamides, Fluoroquinolones, Doxycycline/Tigecycline, Colistin From cystic fibrosis patients: Resistance: As above plus fluoroquinolones Susceptible: Trimethorprim-sulfamethoxazole, Ceftazidime, Carbapenems

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- From cystic fibrosis patients: Resistance: As above plus fluoroquinolones Susceptible: Trimethorprim-sulfamethoxazole, Ceftazidime, Carbapenems

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- Susceptible: Trimethorprim-sulfamethoxazole, Ceftazidime, Carbapenems

- Comprehensive review of treatment: Antimicrob Agents Chemother, doi:10.1128/AAC. 01025-20

Classification

- Gram negative bacilli, glucose non-fermenter

- Nomenclature: Achromobacter xylosoxidans subspecies xylosoxidans is the most common species clinically encountered. Fifteen species isolated from clinical specimens.

Primary Regimens

- Non-cystic fibrosis patients: Cefepime 1-2 gm IV q8-12 h Ceftazidime 1-2 gm IV q8-12 h Imipenem-cilastatin 500 mg IV q6h or Meropenem 1-2 gm IV q8h or Doripenem 500 mg IV q8h (not for pneumonia) Ciprofloxacin 400 mg IV q12h TMP/SMX for UTIs

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- Imipenem-cilastatin 500 mg IV q6h or Meropenem 1-2 gm IV q8h or Doripenem 500 mg IV q8h (not for pneumonia)

- Ciprofloxacin 400 mg IV q12h

- TMP/SMX for UTIs

- Cystic fibrosis patients: There are no standard treatment protocols for cystic fibrosis pulmonary Achromobacter infections. Treatment usually consists of systemic and/or inhaled antibiotics Ceftazidime as above Carbapenem as above Inhaled antibiotics (ceftazidime, colistin and tobramycin). Controlled studies needed Evidence from small observasional studies Refs.: Antimicrob Agents Chemother. 2020; 64: e01025; J Cyst Fibros 2013; 12: 638

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- Ceftazidime as above

- Carbapenem as above

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Alternative Regimens

- Options for salvage therapy: Cefiderocol 2 gm IV over 3hr q8h Eravacycline (not for UTIs): 1 mg/kg IV q12h

- Cefiderocol 2 gm IV over 3hr q8h

- Eravacycline (not for UTIs): 1 mg/kg IV q12h

Antimicrobial Stewardship

- Achromobacter are generally resistant to penicillin G, ceftriaxone, aztreonam, polymyxins and aminoglycosides.

- High frequency of fluoroquinolone resistance

Comments

- Do not treat pneumonia with Doripenem.

- Increasing resistance to carbapenems secondary to activated efflux pumps and production of metallo-carbapenemases

Acinetobacter sp. (baumannii-calcoaceticus complex)

Clinical Setting

- Acinetobacter baumannii-calcoaceticus complex causes a variety of local and systemic infections in both immunocompetent and immunocompromised patients Hospital-acquired opportunistic pathogen, frequent cause of ventilator-associated pneumonia Can cause a variety of other infections: e.g., soft tissue, wounds and bone; UTIs; meningitis; eye infections Any of the above can be associated with bacteremia.

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- Can cause a variety of other infections: e.g., soft tissue, wounds and bone; UTIs; meningitis; eye infections

- Any of the above can be associated with bacteremia.

Classification

- Strictly aerobic non-fermentative coccobacillary gram negative bacillus

- Five Acinetobacter species are associated with human diseases: Acinetobacter baumannii is most important, responsible for 80% of infections A.pittii and A.nosocomialis also considered clinically important A. seifertii and A. dijkshoorniae also isolated from human clinical specimens

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- A.pittii and A.nosocomialis also considered clinically important

- A. seifertii and A. dijkshoorniae also isolated from human clinical specimens

- Acinetobacter calcoaceticus in sensu stricto is considered a nonpathogenic environmental organism, rarely involved in causing disease

- See Future Sci OA. 2019. doi: 10.2144/fsoa-2018-0127 for additional taxonomy.

Primary Regimens

- Treatment options below are for therapy of moderately-severe, or severe infections in patients requiring systemic therapy Complicated UTI Ventilator associated Bacterial Pneumonia/ Hospital acquired bacterial pneumonia Bacteremia Meningitis: see Comments

- Complicated UTI

- Ventilator associated Bacterial Pneumonia/ Hospital acquired bacterial pneumonia

- Bacteremia

- Meningitis: see Comments

Alternative Regimens

- Lab reports susceptibility to multiple antibiotics Some isolates may be susceptible to: Ciprofloxacin 400 mg IV q8h or Levofloxacin 750 mg IV q24h TMP-SMX 10 mg/kg/day (TMP component) IV divided q8h or q12h

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- Lab reports MDR or extensive drug resistance Test for in vitro susceptibility to: Aminoglycosides: Amikacin more frequently active in vitro than gentamicin (Antimicrob Agents Chemother 2019; 63: e01154-19) Plazomicin: Aminoglycoside that is stable in presence of enzymes that inactivate gentamicin, tobramycin, and amikacin. Limited observational reports of success vs MDR pathogens. Eravacycline and Omadacycline: Next generation tetracyclines. Better pharmacokinetics than Tigecycline. Active in vitro vs Acinetobacter. No clinical data.

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- Eravacycline and Omadacycline: Next generation tetracyclines. Better pharmacokinetics than Tigecycline. Active in vitro vs Acinetobacter. No clinical data.

Antimicrobial Stewardship

- Duration of therapy: Regardless of site of infection, duration of therapy is unclear and should be guided by clinical response.

Comments

- In hollow fiber in vitro model, pan-drug resistant strains of Acinetobacter were found susceptible to the combination of high concentrations of Ampicillin-sulbactam + Meropenem + Polymyxin B (Antimicrob Agents Chemother 2017;61:e01268-16).

- Cannot assume in vitro resistance of one carbapenem predicts resistance for another without testing. Acinetobacter is intrinsically resistant to Ertapenem. Susceptibility to Meropenem may not indicate susceptibility to Imipenem and vice versa

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- Susceptibility to Meropenem may not indicate susceptibility to Imipenem and vice versa

- Disease specific treatment considerations: Acinetobacter pneumonia: Based on current data, adjunctive inhaled/nebulized antibiotic therapy not recommended because of failure to show benefit in prospective randomized clinical trials (Chest 2017;151:1239, Crit Care Med 2019;47: 880 and e470) For Meningitis due to Acinetobacter species: If possible, remove CNS devices that may be a source If susceptible, Meropenem is the preferred carbapenem due to CNS penetration and lower risk of

seizures as compared to other carbapenems If resistance to Meropenem, intraventricular or lumbar sac: Colistin; wide range of recommended doses: 0.75 mg to 7.5 mg of Colistin Base Activity per day For UTI: If carbapenem resistant and systemic therapy with a polymyxin is used, Colistin is preferred rather than Polymyxin B, which achieves low concentrations in the urine If possible, remove Foley catheter

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Bacteria: Normal Flora, Non-pathogenic, Contaminants, Rare Pathogens

Introduction

- Rare pathogens

- Normal human flora

- Environmental contaminants

- Often non-pathogenic and of low virulence

- Present in mixed cultures

Organisms

Actinomyces sp.

Clinical Setting

- Actinomycosis typically presents as one of four infection syndromes Abdominal: mass with or without fistula tract after abdominal surgery, e.g., a late complication of a ruptured appendix. Cervicofacial: "lumpy jaw", most common form of actinomycosis with lumps and sinus tracts after dental or jaw trauma. Pelvic: tubo-ovarian abscess, complication of intrauterine device (IUD), which should be removed. Pulmonary: chronic disease, mass lesion, dense infiltrate and can mimic lung cancer, tuberculosis, community-acquired pneumonia.

- Abdominal: mass with or without fistula tract after abdominal surgery, e.g., a late complication of a ruptured appendix.

- Cervicofacial: "lumpy jaw", most common form of actinomycosis with lumps and sinus tracts after dental or jaw trauma.

- Pelvic: tubo-ovarian abscess, complication of intrauterine device (IUD), which should be removed.

- Pulmonary: chronic disease, mass lesion, dense infiltrate and can mimic lung cancer, tuberculosis, community-acquired pneumonia.

- Positive lab result.

- The organism is a slow-growing, anaerobic gram-positive rod.

- Several species cause disease in humans, the most common of which is Actinomyces israelii.

- May grow in clumps in infected tissue, so-called "sulfur granules."

- Majority of infections are polymicrobial (Clin Microbiol Rev 28: 419, 2015)

- For specific diseases or syndromes, see: Actinomycosis

Classification

- Gram positive bacilli

- Numerous species: see J Antimicrob Chemother. 2016;71: 422–427 Actinomyces israelii (most common) Actinomyces meyeri Actinomyces turicensis Actinomyces europaeus Other Actinomyces species (see: J Antimicrob Chemother. 2016;71: 422–427)

- Actinomyces israelii (most common)

- Actinomyces meyeri

- Actinomyces turicensis

- Actinomyces europaeus

- Other Actinomyces species (see: J Antimicrob Chemother. 2016;71: 422–427)

Primary Regimens

- Ampicillin 200 mg/kg/day IV divided in 3-4 doses x 2-6 weeks

- Penicillin G 10-20 million units/day, divided q4-6h, IV x 4-6 weeks, then Penicillin VK 2-4 gm/day po

- Amoxicillin 2 gm po bid x 6-12 months (see Comments).

Alternative Regimens

- Doxycycline 100 mg IV bid for 2-6 weeks and then po for 6-12 months

- Ceftriaxone 2 gm IV once daily for 2-6 weeks and then one of the oral regimens for 6-12 months

- Clindamycin 600-900 mg IV q8h for 2-6 weeks and then 300 mg tid po for 6-12 months

- Amoxicillin 2 gm po bid for 6-12 months

Comments

- Also effective: Clindamycin, Erythromycin Metronidazole is NOT ACTIVE.

- Metronidazole is NOT ACTIVE.

- The recommendations for a 2-6 week run-in with intravenous therapy prior to oral therapy are traditional and empirical. There are case reports of successful treatment with oral therapy preceded by much shorter durations of IV therapy, as little as 3 days, or no IV therapy at all (Chest 2005 Oct;128(4):2211-7), particularly for less severe disease. Durations shorter than 3 months may also be effective in less bulky disease.

- If infection is polymicrobial, choose regimen that covers the other organisms.

- Reference: StatPearls; 2023 Jan. 2023 Feb 19.

Aerococcus urinae, sanguinicola

Clinical Setting

- Cystitis due to Aerococcus urinae is a common cause of cystitis. More common in elderly patients with predisposing conditions.

- Aerococcus sanguinicola is the second most common Aerococcus species causing UTIs.

- Lab note: May be confused with alpha-hemolytic streptococci on culture.

Classification

- Gram-positive bacterium in clusters.

Primary Regimens

- Best regimen and duration of therapy unknown; limited clinical studies Amoxicillin 500 mg po tid x 5 - 10 days Nitrofurantoin 100 mg po bid x 5 days

- Amoxicillin 500 mg po tid x 5 - 10 days

- Nitrofurantoin 100 mg po bid x 5 days

Alternative Regimens

- Best regimen and duration of therapy unknown; limited clinical studies Fosfomycin 3 gm po x 1 (A. urinae only) Ciprofloxacin 500 mg po bid x 3 days (if tests as susceptible)

- Fosfomycin 3 gm po x 1 (A. urinae only)

- Ciprofloxacin 500 mg po bid x 3 days (if tests as susceptible)

Comments

- Penicillin/amoxicillin highly active against both A. urinae and A. sanguincola, although isolates with minimally reduced susceptibility reported.

- MICs of ceftriaxone/cefotaxime generally higher than those of penicillin.

- In vitro susceptibility to fluoroquinolones is variable; resistance occurs, more often in A. sanguinicola.

- In vitro studies demonstrate variable susceptibilities to TMP-SMX and unclear if this would work in vivo; generally avoid this agent unless isolate tests susceptible and no other good options.

- High fosfomycin MICs reported for A. sanguinicola.

- Aerococcus urinae is a rare cause of bacteremia, endocarditis (including PVE and pacer infection), spondylodiscitis and other systemic infections. Best treatment regimens unknown but penicillin ± gentamicin has been used for endocarditis (Clin Microbiol Infect 18:546, 2012)); vancomycin is active in vitro.

- Review of Aerococcus infections: Clin Microbiol Infect 22:22, 2016.

- Susceptibility testing methods and results for several antimicrobials: Open Microbiol Journal 11: 160, 2017.

Bacteria: Normal Flora, Non-pathogenic, Contaminants, Rare Pathogens

Introduction

- Rare pathogens

- Normal human flora

- Environmental contaminants

- Often non-pathogenic and of low virulence

- Present in mixed cultures

Organisms

Aeromonas sp.

Clinical Setting

- An etiology of gastroenteritis or wound infections after exposure to an Aeromonas species in fresh, brackish, or marine water or the oral flora of leeches (Lancet 381:1686, 2013.) Several species with variable antimicrobial susceptibility; Hence, need for culture and susceptibility testing of infected wound, stool, and blood All are aerobic gram-negative bacilli Resistance to beta-lactams and fluoroquinolones recognized in selected areas of the world Uniformly resistant to ampicillin, penicillin, and cefazolin

- Several species with variable antimicrobial susceptibility; Hence, need for culture and susceptibility testing of infected wound, stool, and blood

- All are aerobic gram-negative bacilli

- Resistance to beta-lactams and fluoroquinolones recognized in selected areas of the world

- Uniformly resistant to ampicillin, penicillin, and cefazolin

- Major clinical syndromes:

- Gastroenteritis is the most common. One of the causes of Traveler's diarrhea

- Wounds, Post-trauma and post exposure to leeches (medicinal and otherwise). See Lancet 381:1686, 2013.

- Can cause bacteremic disease.

Classification

- Aeromonas hydrophila (most common) (gram negative bacilli)

- Aeromonas veronii (gram negative bacilli)

- Aeromonas shubertii (gram negative bacilli)

Primary Regimens

- Empiric therapy pending results of culture & susceptibility testing

- For severe wound infection:

- Ciprofloxacin 400 mg IV or 750 mg po bid

- Levofloxacin 750 mg IV once daily (differences in susceptibility by species and by geography).

- Duration varies with wound severity and clinical response

- For gastroenteritis (Traveler's diarrhea):

- Ciprofloxacin 500 mg po bid x 3 days

- Levofloxacin 500 mg po once daily X 3 days

- Remember oral fluoroquinolones are chelated by multi-valent cations: avoid concomitant oral calcium (diary products), iron, magnesium or other multivalent cations an hour before or for one hour after dosing.

Alternative Regimens

- For bacteremia or severe wound infection:

- TMP-SMX 8-10 mg/kg /day IV divided q6h or q8h

- Ceftriaxone 2 gm IV once daily

- Cefepime 2 gm IV q8h

- For gastroenteritis: TMP-SMX DS 1 tab po bid x 3 days

Antimicrobial Stewardship

- If in vitro resistance one or more of the above regimens, another alternative is combining doxycycline with either a fluouroquinolone or an extended-spectrum cephalosporin

Comments

- Ciprofloxacin-resistant Aeromonas reported following leech therapy (J Clin Micro 51:1324, 2013).

- Most strains are also susceptible to antipseudomonal aminoglycosides, carbapenems, and tetracyclines (Antimicrob Agents Chemother 56:1110, 2012).

- Aeromonas species can produce several beta-lactamases that include all Ambler molecular classes: A, B, C, D. As a result, individual isolates may harbor ESBLs , AmpC cephalosporinases, or carbapenemases (to include metallocarbapenemases): Clinics in Lab Med 35:313, 2015.

Aggregatibacter aphrophilus

Clinical Setting

- Small, fastidious gram-negative coccobacilli with colonies that are nonhemolytic, catalase-negative, CO2 dependent, requiring X factor (hemin) but not V factor (nicotinamide adenine dinucleotide) for growth.

- HACEK organisms are slow growing fastidious organisms that can cause endocarditis; rarely causes other infections including dental abscesses, sinusitis, brain abscess, septic arthritis.

- Haemophilus parainfluenzae

- Aggregatibacter (formerly Actinobacillus) actinomycetemcomitans and Aggregatibacter (formerly Haemophilus) aphrophilus

- Cardiobacterium sp.

- Eikenella sp.

- Kingella sp.

Classification

- Gram negative coccobacilli

Primary Regimens

- Ceftriaxone 2 gm IV q24h

Alternative Regimens

- Ciprofloxacin 400 mg IV or 750 mg po q12h or Levofloxacin 750 mg IV/po q24h

- Ampicillin 2 gm IV q4h only if susceptibility confirmed in vitro

Antimicrobial Stewardship

- Gentamicin combination therapy not recommended.

- Recommended duration of therapy for endocarditis is 4 weeks for native valve infection and 6 weeks for prosthetic valve infection (Expert Rev Anti Infect Ther. 2016;14:523).

- Penicillin or Ampicillin may be used provided that growth is sufficient to allow for reliable susceptibility testing and confirmation of in vitro activity.

- Resistant to Vancomycin, Clindamycin, Nafcillin, Oxacillin.

Comments

- Some strains produce beta-lactamase.

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- Comprehensive review of treatment: Antimicrob Agents Chemother, doi:10.1128/AAC. 01025-20

Classification

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- Nomenclature: Achromobacter xylosoxidans subspecies xylosoxidans is the most common species clinically encountered. Fifteen species isolated from clinical specimens.

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- Imipenem-cilastatin 500 mg IV q6h or Meropenem 1-2 gm IV q8h or Doripenem 500 mg IV q8h (not for pneumonia)

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- Cystic fibrosis patients: There are no standard treatment protocols for cystic fibrosis pulmonary Achromobacter infections. Treatment usually consists of systemic and/or inhaled antibiotics Ceftazidime as above Carbapenem as above Inhaled antibiotics (ceftazidime, colistin and tobramycin). Controlled studies needed Evidence from small observasional studies Refs.: Antimicrob Agents Chemother. 2020; 64: e01025; J Cyst Fibros 2013; 12: 638

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- Ceftazidime as above

- Carbapenem as above

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Alternative Regimens

- Options for salvage therapy: Cefiderocol 2 gm IV over 3hr q8h Eravacycline (not for UTIs): 1 mg/kg IV q12h

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Antimicrobial Stewardship

- Achromobacter are generally resistant to penicillin G, ceftriaxone, aztreonam, polymyxins and aminoglycosides.

- High frequency of fluoroquinolone resistance

Comments

- Do not treat pneumonia with Doripenem.

- Increasing resistance to carbapenems secondary to activated efflux pumps and production of metallo-carbapenemases

Bacteria: Normal Flora, Non-pathogenic, Contaminants, Rare Pathogens

Introduction

- Rare pathogens

- Normal human flora

- Environmental contaminants

- Often non-pathogenic and of low virulence

- Present in mixed cultures

Organisms

Arcanobacterium haemolyticum

Clinical Setting

- A cause of pharyngitis in otherwise healthy individuals, frequently adolescents.

- Presents with fever, exudative pharyngitis, scarletiniform rash on extensor surfaces of upper extremities

- Can occasionally cause deep soft tissue infections, pneumonia, bacteremia, meningitis, osteomyelitis and other systemic infections.

Etiologies

- Gram positive or gram variable bacillus

- Formerly Corynebacterium haemolyticum

Primary Regimens

- Azithromycin

Alternative Regimens

- Penicillin G

- Ceftriaxone

- Clindamycin

- Vancomycin

- Erythromycin

Comments

- Sensitive to most drugs, but resistant to TMP-SMX (Antimicrob Agents Chemother 38:142,1994). Isolates resistant to levofloxacin, clindamycin or gentamicin have been encountered (J Med Microbiol 64: 369, 2015).

- Role of antimicrobial therapy unclear for pharyngitis; dose and duration of therapy not established and should be based on disease severity

- Systemic infections may have associated co-pathogens and have been treated with Penicillin G intravenously, Ampicillin-sulbactam, Amoxicillin-clavulanate or Ceftriaxone; some have used combinations of a beta-lactam with gentamicin (Ann Clin Microbiol Antimicrob 10:17, 2011) as some strains appear to be penicillin-tolerant (Eur J Clin Microbiol Infect Dis 17:578, 1998).

Bacillus anthracis

Clinical Setting

- Various clinical settings
- Infections naturally acquired, from animals or from animal hides and other animal products.
- Infection from exposure during laboratory accidents has been reported.
- Agent of bioterrorism.
- Clinical syndromes Systemic infection (includes, inhalational, gastrointestinal, oral) Cutaneous
- Systemic infection (includes, inhalational, gastrointestinal, oral)
- Cutaneous
- Prevention (unique to Anthrax - both vaccine and antibiotic prophylaxis): See Anthrax, Vaccine
- See Anthrax, Vaccine

Classification

- Spore-forming, gram-positive rod

Primary Regimens

- See Systemic or Cutaneous Anthrax

Alternative Regimens

- See above

Comments

- 2023 CDC treatment guidelines: MMWR 2023, 72 (RR-6):1-50.

Bacillus sp.

Clinical Setting

- Species other than Bacillus anthracis.
- Bacillus cereus (Trends Microbiol. 2021;29:458-471) associated with food poisoning; some strains produce enterotoxin that causes diarrhea
- Bacillus subtilis and other Bacillus sp. occasionally cause systemic infections, but often are a culture contaminant.
- Bacillus sp. are etiologic in IV line infections in patients with hematologic malignancies, contamination of the fluid used to transport organs for transplantation, endophthalmitis, toxin-induced fulminant liver failure, soft tissue infection in injection drug users.

Classification

- Spore-forming, gram-positive rods Bacillus subtilis Bacillus cereus and other Bacillus species

- Bacillus subtilis

- Bacillus cereus and other Bacillus species

Primary Regimens

- Vancomycin 15-20 mg/kg IV q8-12h to achieve preferred target AUC 400-600 µg/mL x hr (see vancomycin AUC dosing calculator; alternative is trough level of 15-20 µg/mL) or Clindamycin 600mg IV q8h

Alternative Regimens

- Fluoroquinolone or Imipenem

Comments

- No specific treatment for food poisoning.

- B. cereus often resistant to all beta-lactams other than carbapenems; resistance to imipenem and meropenem has been encountered (J Antimicrob Chemother 60:555, 2007; Intern Med 51:2733, 2012).

- Susceptibility to Clindamycin (or other agents used) should be confirmed, as resistance does occur (J Antimicrob Chemother 60:555, 2007).

- Other agents with in vitro activity: Linezolid, Daptomycin, Tetracycline, macrolides.

Bacteria: Normal Flora, Non-pathogenic, Contaminants, Rare Pathogens

Introduction

- Rare pathogens

- Normal human flora

- Environmental contaminants

- Often non-pathogenic and of low virulence

- Present in mixed cultures

Organisms

Bacteroides sp., Prevotella sp.

Clinical Setting

- Bacteroides, Prevotella and Parabacteroides species cause, or participate in, a variety of infections involving the intestinal tract, peritonitis, gynecologic/obstetric infections, and abscesses in the brain, liver and elsewhere. There are as many as 1011 Bacteroides species per gram of human feces. However, bacteroides species vary in their pathogenic potential.

- Bacteroides fragilis is the most virulent.

- Some bacteria previously classified as Bacteroides species have been reclassified and placed in their own species, i.e.:

- Bacteroides distasonis is now Parabacteroides distasonis

- Bacteroides melaninogenicus is now Prevotella melaninogenica.

- Prevotella nigrescens, Prevotella pleuritidis are oral flora associated with periodontal disease (J Clin Periodontol 2005, 32:1213) and, for P. pleuritidis, rarely, other abscesses (BMJ Case Rep 2020, 13:e235960)

- Fortunately, virtually all Bacteroides, Parabacteroides, and Prevotella remain susceptible to Metronidazole: Clin Infect Dis 59:698, 2014.

- B. fragilis group are predictably susceptible to Piperacillin-tazobactam and the carbapenems

- Cefotetan and Clindamycin are no longer recommended due to resistance.

- Resistance to Moxifloxacin is increasing.

Classification

- Gram negative bacilli, anaerobic Bacteroides fragilis Parabacteroides distasonis Prevotella melaninogenica Prevotella nigrescens Prevotella pleuriditis

- Bacteroides fragilis

- Parabacteroides distasonis

- Prevotella melaninogenica

- Prevotella nigrescens

- Prevotella pleuriditis

Primary Regimens

- See specific pathogen or syndrome: Bacteroides fragilis Peritonitis, Secondary Brain abscess Pelvic inflammatory disease Hepatic abscess Diverticulitis Odontogenic infections

- Bacteroides fragilis

- Peritonitis, Secondary

- Brain abscess

- Pelvic inflammatory disease

- Hepatic abscess

- Diverticulitis

- Odontogenic infections

Alternative Regimens

- See specific pathogen or syndrome

Comments

- None

Bacteroides fragilis

Clinical Setting

- Bacteroides fragilis group (24 species): strict anaerobic bacteria, major component of the intestinal flora.

- Empiric therapy of infections involving fecal flora (e.g., secondary peritonitis due to a ruptured appendicitis, ruptured diverticulits, ischemic bowel, a leaking surgical anastomosis among other conditions, ruptured appendix) includes a drug with activity vs. B. fragilis group bacteria as well as aerobic organisms.

- Blood cultures are rarely positive for Bacteroides or other strictly anaerobic bacterial pathogens. When bacteremia does occur, metastatic seeding of other body sites is documented in the absence of an obvious intestinal portal of entry (Intern Med 47:2183, 2008).

- The bulk of in vitro susceptibility data is generated by, and periodically reported by, a few academic labs (Anaerobe 2017;43:21; Antimicrob Ag Chemother 56:1247, 2012). See Comments.

Classification

- Gram negative bacilli, strict anaerobe

- Other Bacteroides species are occasionally isolated (DOT species = B. distasonis (Now Parabacteroides distasonis), B. ovatus, B. thetaiotaomicron)

Primary Regimens

- Metronidazole 500 mg IV/po q6-8h or 1 gm IV q12h or, in some reports, 1.5 gm IV once daily

- Piperacillin-tazobactam 3.375 gm IV q6h with each dose infused over 30 minutes. However, the same time above the MIC can be achieved with a 3.375 mg loading dose over 15-30 minutes and then, 4 hrs. later, 3.375 mg infused over 4 hrs. and administered q8h

Alternative Regimens

- Imipenem-cilastatin 500 mg IV q6h or Doripenem 500 mg IV q8h or Meropenem 0.5-1 gm or Ertapenem 1 gm IV once daily Prolonged infusion regimens for Doripenem and Meropenem are reported. See Prolonged Infusion.

- Prolonged infusion regimens for Doripenem and Meropenem are reported. See Prolonged Infusion.

- Amoxicillin-clavulanate 875/125 mg po bid for milder disease; e.g., mild diverticulitis treated as an outpatient

Antimicrobial Stewardship

- Due to an increasing prevalence of in vitro resistance, Clindamycin, Cefoxitin and Cefotetan are no longer recommended.

- Resistance to Moxifloxacin is also increasing.

- Virtually no, or very rare, resistance to Metronidazole, Piperacillin-Tazobactam, or the carbapenems

Comments

- Susceptibility testing not routinely performed in most clinical micro labs.

- In vitro antimicrobial activity vs. B. fragilis group: Clin Infect Dis 59: 698, 2014; Anaerobe 2017;43:21.

- Surveys of susceptibility: Anaerobe 2017; 43:21; Antimicrob Agents Chemother 56:1247, 2012.

- Guidance on intra-abdominal infections: Clin Infect Dis 50:133, 2010; Surg Infections 2017; 18: 1-76.

Bartonella sp.

Clinical Setting

- Slow growing fastidious gram-negative bacteria that cause a variety of human infections.

- Hold cultures for 21 days. See links to specific clinical syndromes:

Classification

- Gram negative bacilli

- Three most important Bartonella species are:

- Bartonella bacilliformis

- Bartonella henselae

- Bartonella quintana

Primary Regimens

- Varies with clinical syndrome (see specific topic)

Alternative Regimens

- None

Comments

- See specific topics

Bordetella pertussis

Clinical Setting

- Bordetella pertussis causes pertussis (whooping cough) and occasionally pneumonia (Clin Microbiol Rev 18:326, 2005). For typical case see: N Engl J Med 372:765, 2015.

- 3 stages of illness: First "Catarrhal" 1-2 weeks (rarely recognizable, treatment effective at this stage). Then "paroxysmal coughing" for 2-4 weeks (after 2 weeks of cough, hard to demonstrate any benefit of treatment). Last: 1-2 weeks of "convalesence". Treatment at late stages is used to eradicate the organism from the nose and prevent disease transmission. Suggested case definition, see Clin Infect Dis 54:1756, 2012.

- First "Catarrhal" 1-2 weeks (rarely recognizable, treatment effective at this stage).

- Then "paroxysmal coughing" for 2-4 weeks (after 2 weeks of cough, hard to demonstrate any benefit of treatment).

- Last: 1-2 weeks of "convalesence". Treatment at late stages is used to eradicate the organism from the nose and prevent disease transmission.

- Suggested case definition, see Clin Infect Dis 54:1756, 2012.

- Occasionally Bordetella parapertussis can cause a similar clinical syndrome.

- See also Pneumonia, Infants.

Diagnosis

- PCR or culture on special media.

Classification

- Gram negative coccobacilli

Primary Regimens

- Antibacterial Treatment recommended if within 3 weeks of cough onset;

- Recommend no antibiotic therapy if onset of cough more than 3 weeks ago. There are exceptions: Near term pregnancy with cough onset within 6 weeks to prevent transmission to neonate Up to 6 weeks after cough onset for patients with asthma , COPD, over age 65, or other immunocompromising conditions

- Near term pregnancy with cough onset within 6 weeks to prevent transmission to neonate

- Up to 6 weeks after cough onset for patients with asthma , COPD, over age 65, or other immunocompromising conditions

- Adult: Azithromycin 500 mg po x 1, then 250 mg po once daily x 4 days Clarithromycin 500 mg po bid x 7 days (or 1 gm/day po in two divided doses x 7 days)

- Azithromycin 500 mg po x 1, then 250 mg po once daily x 4 days

- Clarithromycin 500 mg po bid x 7 days (or 1 gm/day po in two divided doses x 7 days)

- Child: Azithromycin 10 mg/kg/day po on day 1 and then 5 mg/kg once daily on days 2 through 5 Clarithromycin 15 mg/kg/day po in 2 divided doses x 7 days Note: there is a small risk of hypertrophic pyloric stenosis associated with Azithromycin in infants less than 1 month old.

- Azithromycin 10 mg/kg/day po on day 1 and then 5 mg/kg once daily on days 2 through 5

- Clarithromycin 15 mg/kg/day po in 2 divided doses x 7 days

- Note: there is a small risk of hypertrophic pyloric stenosis associated with Azithromycin in infants less than 1 month old.

Alternative Regimens

- Adult: TMP-SMX DS, 1 tab po bid x 14 days

- Child: TMP-SMX (TMP component) 8 mg/kg/day po in 2 divided doses x 14 days

Comments

- Azithromycin is the preferred agent due to shorter duration of therapy, less frequent dosing, and better side effects profile. More GI side effects with Clarithromycin than Azithromycin

- TMP-SMX is an alternative for persons older than 2 months who cannot tolerate Azithromycin or Clarithromycin or are infected with a macrolide-resistant strain

- Fluoroquinolones and tetracyclines are active in vitro but clinical efficacy unknown.

- Prophylactic drugs and doses are the same as for treatment.

- Prevention and vaccine: Clin Infect Dis 58:830, 2014. Infection does not result in lifelong immunity; resume recommended immunizations post-recovery from acute disease For history and perspective of Pertussis vaccines: J Pediatric Infect Dis Soc 2019; 8:334

- For history and perspective of Pertussis vaccines: J Pediatric Infect Dis Soc 2019; 8:334

- CDC pertussis treatment and prophylaxis guidelines: MMWR Recomm Rep 67(RR-2):1-44, 2018

- Required immunization of mothers during pregnancy reduced the infant infection rate from 71% to 17% (Clin Infect Dis 60:333, 2015).

Borrelia sp.

Clinical Setting

- Suspected tick bite or documented exposure

-

- Specific therapy. Choice of agent/regimen depends on stage of disease.

- For specifics by syndrome: Lyme Disease, Overview Relapsing Fever: Borrelia recurrentis (louse-borne relapsing fever) and B. hermsii and other Borrrelia species (tick-borne relapsing fever).

- Lyme Disease, Overview

- Relapsing Fever: Borrelia recurrentis (louse-borne relapsing fever) and B. hermsii and other Borrrelia species (tick-borne relapsing fever).

Diagnosis

- Positive lab result could be: Specific serologies for Lyme Disease. Documentation of spirochetes in a blood smear of peripheral blood: e.g., Relapsing Fever.

- Specific serologies for Lyme Disease.

- Documentation of spirochetes in a blood smear of peripheral blood: e.g., Relapsing Fever.

Classification:

- Spirochetes

- Borrelia burgdorferi (Lyme Disease)

- Borrelia afzelii (European Lyme borreliosis)

- Borrelia garinii (European Lyme borreliosis)

- Borrelia recurrentis (Louse-borne relapsing fever)

- Borrelia hermsii, others (Tick-borne relapsing fever)

- Borrelia miyamotoi (related to Borrelia sp. that cause relapsing fever). Harbored by same ticks that carry Lyme Disease. Clinical spectrum of disease not fully characterized: fever, meningoencephalitis described. See N Engl J Med 368:240, 2013; Ann Intern Med 159:21, 2013; Emerg Infect Dis 2019;25: 1965

- Clinical spectrum of disease not fully characterized: fever, meningoencephalitis described. See N Engl J Med 368:240, 2013; Ann Intern Med 159:21, 2013; Emerg Infect Dis 2019;25: 1965

Primary Regimens

- See Lyme Disease, Overview for specific topics.

- See Relapsing Fever.

Alternative Regimens

- See Lyme Disease, Overview for specific topics.

- See Relapsing Fever.

Comments

- Ref.: PLoS Negl Trop Dis 2022;16: e0010212

Tick-borne Illness, Overview

Brucella sp.

Clinical Setting

- Most human disease, Brucellosis, is caused by two species: Brucella melitensis and Brucella abortus. Brucellosis is also known as Malta fever, Mediterranean fever and Undulant fever.

- Zoonotic infection:

- Sheep, goats, and cattle, other mammals (e.g., camels) are reservoirs.

- Transmission occurs by ingestion of unpasteurized dairy products, direct contact with infected animals or animal tissue, blood or secretions.

- Brucellosis may present as a non-specific febrile syndrome or may be associated with bone/joint infections, focal infections at other sites (e.g., genitourinary), and rarely endocarditis.

- Clinical disease: Protean manifestations: febrile illness, osteoarticular disease (20-30%, especially sacroileitis), rare meningitis or endocarditis Can infect any tissue in the body Fever occurs in 90% Malodorous perspiration almost pathognomic but uncommon Relapse rate, post-treatment, is 10%.

- Protean manifestations: febrile illness, osteoarticular disease (20-30%, especially sacroileitis), rare meningitis or endocarditis

- Can infect any tissue in the body

- Fever occurs in 90%

- Malodorous perspiration almost pathognomic but uncommon

- Relapse rate, post-treatment, is 10%.

- Lab findings: Mild hepatitis; leukopenia and relative lymphocytosis.

- General principles governing treatment: Prefer combination therapy to decrease risk of relapse Often need prolonged duration of therapy

- Prefer combination therapy to decrease risk of relapse

- Often need prolonged duration of therapy

Diagnosis

- Serology, bone marrow culture, real-time PCR or 16s rRNA if available.

- Inform lab of possible brucellosis to lower risk of occupational exposure

- Serology remains useful in underdeveloped countries All positive rapid serologies require confirmation with Brucella sp. specific agglutination. False negative can occur due to prozone phenomena

- All positive rapid serologies require confirmation with Brucella sp. specific agglutination.

- False negative can occur due to prozone phenomena

- NAAT (PCR) and 16S rRNA gene sequencing most sensitive and specific if available and certified

- Reference: Clin Micro Rev 2019;33: e00073.

Classification

- Small gram-negative aerobic coccobacilli, slow growing.

- Brucella melitensis

- Brucella abortus

- Brucella suis

- Brucella canis

- Other Brucella species may also cause disease

Primary Regimens

- Adults and children age > 8 years with non-localizing disease: Doxycycline 100 mg po bid x 6 weeks + Gentamicin 5 mg/kg IV once daily x 7 days Doxycycline 100 mg po bid x 6 weeks + Rifampin 600-900 mg po once daily x 6 weeks

- Doxycycline 100 mg po bid x 6 weeks + Gentamicin 5 mg/kg IV once daily x 7 days

- Doxycycline 100 mg po bid x 6 weeks + Rifampin 600-900 mg po once daily x 6 weeks

- Children age < 8 years with non-localizing disease: (TMP-SMX 5 mg/kg (TMP component) po q12h x 6 weeks) + Rifampin 15-20 mg/kg (max 900 mg/day) po divided in one or two doses

- (TMP-SMX 5 mg/kg (TMP component) po q12h x 6 weeks) + Rifampin 15-20 mg/kg (max 900 mg/day) po divided in one or two doses

- Spondylitis/sacroileitis/arthritis: Adult: Doxycycline 100 mg po bid for a minimum of 12 weeks + Rifampin 600 -900 mg po once daily for at least 12 weeks + Gentamicin 5 mg/kg IM/IV once daily for the first 7-14 days Ciprofloxacin 750 mg po bid + Rifampin 600-900 mg po once daily: both for a minimum of 3 months Child age ≥ 8 yrs: Doxycycline 4.4 mg/kg/day (max 200mg/day) in 2 divided doses x 12 or more weeks + Rifampin 15-20 mg/kg/day (max 900 mg/day) po once daily x at least 12 weeks + Gentamicin 5 mg/kg IV/IM once daily for first 7-14 days Child age < 8 yrs: TMP-SMX 10 mg/kg/day TMP (max. 320 mg/day), 50 mg/kg/day SMX (max. 1.6 mg/day) in 2 divided doses x 12 weeks or more + Rifampin 15-20 mg/kg/day (max. 900 mg/day) po once daily x 12 or more weeks + Gentamicin 5 mg/kg IV/IM once daily for the first 7-14 days

- Adult: Doxycycline 100 mg po bid for a minimum of 12 weeks + Rifampin 600 -900 mg po once daily for at least 12 weeks + Gentamicin 5 mg/kg IM/IV once daily for the first 7-14 days Ciprofloxacin 750 mg po bid + Rifampin 600-900 mg po once daily: both for a minimum of 3 months

- Doxycycline 100 mg po bid for a minimum of 12 weeks + Rifampin 600 -900 mg po once daily for at least 12 weeks + Gentamicin 5 mg/kg IM/IV once daily for the first 7-14 days

- Ciprofloxacin 750 mg po bid + Rifampin 600-900 mg po once daily: both for a minimum of 3 months

- Child age ≥ 8 yrs: Doxycycline 4.4 mg/kg/day (max 200mg/day) in 2 divided doses x 12 or more weeks + Rifampin 15-20 mg/kg/day (max 900 mg/day) po once daily x at least 12 weeks + Gentamicin 5 mg/kg IV/IM once daily for first 7-14 days

- Doxycycline 4.4 mg/kg/day (max 200mg/day) in 2 divided doses x 12 or more weeks + Rifampin 15-20 mg/kg/day (max 900 mg/day) po once daily x at least 12 weeks + Gentamicin 5 mg/kg IV/IM once daily for first 7-14 days

- Child age < 8 yrs: TMP-SMX 10 mg/kg/day TMP (max. 320 mg/day), 50 mg/kg/day SMX (max. 1.6 mg/day) in 2 divided doses x 12 weeks or more + Rifampin 15-20 mg/kg/day (max. 900 mg/day) po once daily x 12 or more weeks + Gentamicin 5 mg/kg IV/IM once daily for the first 7-14 days

- TMP-SMX 10 mg/kg/day TMP (max. 320 mg/day), 50 mg/kg/day SMX (max. 1.6 mg/day) in 2 divided doses x 12 weeks or more + Rifampin 15-20 mg/kg/day (max. 900 mg/day) po once daily x 12 or more weeks + Gentamicin 5 mg/kg IV/IM once daily for the first 7-14 days

- Pregnancy (<36 wks gestation): (TMP-SMX 5 mg/kg of TMP component po bid + Rifampin 600–900 mg po q24h) x 4 weeks If ≥ 36 wks gestation, Rifampin monotherapy until delivery

- (TMP-SMX 5 mg/kg of TMP component po bid + Rifampin 600–900 mg po q24h) x 4 weeks

- If ≥ 36 wks gestation, Rifampin monotherapy until delivery

- Neurobrucellosis: Doxycycline 100 mg IV/po bid + Rifampin 600-900 mg po once daily + Ceftriaxone 2 gm IV q12h. Continue until CSF is normal.

- Doxycycline 100 mg IV/po bid + Rifampin 600-900 mg po once daily + Ceftriaxone 2 gm IV q12h. Continue until CSF is normal.

- Endocarditis: Almost always need surgery plus antibiotics. Gentamicin 5 mg/kg IV once daily x 2-4 weeks + combination of Rifampin, Doxycycline and TMP-SMX x 6 weeks to 6 months.

- Almost always need surgery plus antibiotics. Gentamicin 5 mg/kg IV once daily x 2-4 weeks + combination of Rifampin, Doxycycline and TMP-SMX x 6 weeks to 6 months.

- Post-exposure prophylaxis after laboratory exposure. Limited data and regimens often not well-tolerated: Doxycycline 100 mg po bid + Rifampin 600 mg po once daily x 3 weeks If B. abortus strain RB51 (resistant to Rifampin): Doxycycline alone x 3 weeks. If Doxycycline not well-tolerated or in pregnancy, TMP-SMX-DS po bid with or without Rifampin 600 mg po once daily x 3 weeks.

- Doxycycline 100 mg po bid + Rifampin 600 mg po once daily x 3 weeks

- If B. abortus strain RB51 (resistant to Rifampin): Doxycycline alone x 3 weeks.

- If Doxycycline not well-tolerated or in pregnancy, TMP-SMX-DS po bid with or without Rifampin 600 mg po once daily x 3 weeks.

Alternative Regimens

- For non-localizing disease and need to avoid Gentamicin: Ciprofloxacin 500 mg po bid + (Doxycycline or Rifampin) x 6 weeks..

Comments

- CDC guidance on Brucella infections in humans.

- Observational study reports higher frequency (p 0.026) of clearance of Brucella DNA from whole blood with triple therapy: (Gentamicin or Streptomycin) + Doxycycline + Rifampin: Antimicrob Agents Chemother 58:7541, 2014.

- Brucellosis review: N Engl J Med 352:2325, 2005, PLoS One 7:e32090, 2012, Clin Infect Dis 56:1407, 2013.

- Refs for arthritis: MMWR 61:461, 2012;; PLoS One 7:e32090, 2012.

- Antibody testing of exposed personnel via State labs or CDC at 2, 4, 6 and 24 weeks; NOTE: poor antibody response to B. abortus strain RB51.

Burkholderia cepacia

Clinical Setting

- Numerous distinct species within the B. cepacia complex, including B. cepacia, B. cenocepacia, B. multivorans and others (Syst Appl Microbiol 34:87, 2011).

- Multiple mechanisms of antibiotic resistance, variably expressed, complicating recommendations for empiric therapy and resulting in limited treatment options.

- Important pulmonary pathogen in hospital-acquired infection and in individuals with cystic fibrosis. (Clin Microbiol Infect 16:821, 2010).

Classification

- Gram negative bacilli

- Multiple genotypes within Burkholderia cepacia complex

Primary Regimens

- Optimal therapy unknown, susceptibility highly variable; antimicrobial therapy should be selected based on in vitro susceptibility.

- TMP-SMX 8-10 mg/kg/day IV divided q6h or q8h

- Levofloxacin 750 mg IV/po q24h

Alternative Regimens

- Minocycline 200 mg IV loading dose and then 100 mg IV/po bid

- Meropenem 2 gm IV q8h

- Ceftazidime 2 gm IV q8h (see Comments)

Antimicrobial Stewardship

- Drugs listed under Primary and Alternative regimens are more active based on survey of bloodstream isolates from the US Dept of Veterans Affairs (DVA) (Clin Infect Dis 2017;65(8):1253-1259), but in vitro susceptibility can be quite variable: Meropenem 31%, Ceftazidime 28%, Levofloxacin 11%, TMP-SMX 6%

Comments

- If serine-based beta-lactamase, enzyme activity inhibited by avibactam, in vitro data indicate activity of Ceftazidime-avibactam against multiple drug resistant strains, including those resistant to Ceftazidime (ACS Infect Dis 2017;3:502). In patient with persistent B. cepacia complex bacteremia, Cefazidime-avibactam therapy cleared the bacteremia (Antimicrob Agents Chemother

2018;62:e02213-17)

- In patient with persistent B. cepacia complex bacteremia, Cefazidime-avibactam therapy cleared the bacteremia (Antimicrob Agents Chemother 2018;62:e02213-17)

- Imipenem-relebactam active against Ceftazidime-resistant strains (Antimicrob Agents Chemother. 2021 Oct 18;65(11):e0133221).

- Cefiderocol has good in vitro activity (although formal CLSI breakpoints are not established) but clinical data supporting efficacy are lacking; may be a reasonable option, particularly for infections caused by highly drug-resistant strains (Antimicrob Agents Chemother. 2021; 65:e0217120).

- Temocillin (where available), demonstrates potent inhibitory activity vs. MDR Burkholderia species including strains that produce AmpC and ESBLs (Antimicrob Agt Chemother. 2019; 63: e02315-18).

- B. cepacia is usually resistant to aminoglycosides and intrinsically resistant to Colistin and Polymyxin B.

Burkholderia pseudomallei, Melioidosis

Clinical Setting

- The infection caused by Burkholderia pseudomallei is termed melioidosis and can include skin abscess, primary bacteremia, pneumonia (most common), bone and joint infection, central nervous system infection, deep tissue abscess.

- Major cause of fatal pneumonia and sepsis in Southeast Asia, Thailand, Malaysia, Singapore and northern Australia but can also be found in Central and South America.

Classification

- Gram negative bacilli

Primary Regimens

- Initial IV therapy: Ceftazidime 2 gm (child 50 mg/kg) IV q6h Meropenem 1 gm (child 25 mg/kg) (double this dose for CNS disease) IV q8h Duration: 14 days; ≥4–8 weeks in severe disease/clinical deterioration/complicated pneumonia, deep-seated infection, bone/joint infection, neurological disease

- Ceftazidime 2 gm (child 50 mg/kg) IV q6h

- Meropenem 1 gm (child 25 mg/kg) (double this dose for CNS disease) IV q8h

- Duration: 14 days; ≥4–8 weeks in severe disease/clinical deterioration/complicated pneumonia, deep-seated infection, bone/joint infection, neurological disease

- Eradication therapy initiated following initial therapy to prevent relapse and administered for at least 3 months TMP-SMX 6-8 mg/kg po (TMP component) bid

- TMP-SMX 6-8 mg/kg po (TMP component) bid

Alternative Regimens

- Eradication therapy initiated following initial therapy to prevent relapse and administered for at least 3 months (neither of these regimens is as effective as TMP-SMX) Doxycycline 100 mg po bid Pregnancy: Amoxicillin-clavulanate 20 mg/5 mg po tid (note dose, which may be poorly tolerated due to GI intolerance

- Doxycycline 100 mg po bid

- Pregnancy: Amoxicillin-clavulanate 20 mg/5 mg po tid (note dose, which may be poorly tolerated due to GI intolerance

Antimicrobial Stewardship

- In an open label randomized controlled trial, TMP-SMX for 12 weeks was non-inferior to 20 weeks for total mortality and a composite of mortality and disease recurrence (Clin Infect Dis. 2021; 73:e3627)

- Duration of therapy: 3-6 months. Longer duration of IV therapy for certain infections: Septic joint, deep tissue abscess: 4 weeks Osteomyelitis: 6 weeks CNS infection: 8 weeks

- Septic joint, deep tissue abscess: 4 weeks

- Osteomyelitis: 6 weeks

- CNS infection: 8 weeks

- Darwin Melioidosis Treatment Guideline suggestions for duration of therapy for pneumonia/bacteremia: Minimum of 3 weeks of IV antibiotic if bacteremic plus single lobe infiltrate or multi-lobe pneumonia without bacteremia Minimum of 4 weeks of IV antibiotic if bacteremic with multi-lobe pneumonia Reference: PLoS Negl Trop Dis. 2020; 14:e0008659

- Minimum of 3 weeks of IV antibiotic if bacteremic plus single lobe infiltrate or multi-lobe pneumonia without bacteremia

- Minimum of 4 weeks of IV antibiotic if bacteremic with multi-lobe pneumonia

- Reference: PLoS Negl Trop Dis. 2020; 14:e0008659

Comments

- Meta-analysis comparing various treatment regimens: PLoS Negl Trop Dis. 2023; 17:e0011382.

- Reviews: Aust J Gen Pract. 2019; 48:327-332, Clin Microbiol Rev. 2020;33:e00006, Curr Opin Infect Dis. 2022; 35:517.

- Recent US outbreak associated with scented aromatherapy room spray imported from a melioidosis-endemic area (N Engl J Med 2022;386:861). Range may be expanding outside of traditional tropical locations.

- A potential agent of bioterrorism.

Campylobacter fetus

Clinical Setting

- Opportunistic pathogen: systemic disease in debilitated or immunocompromised hosts. Rarely in immunocompetent individuals unless elderly, pregnant, or occupational risk (exposure to live animals or abattoir).

- Recommendations below are for treatment of bacteremia or focal infections, particularly in immuncompromised hosts

- Food-borne illness but diarrhea is uncommon (see Gastroenteritis for treatment recommendations).

- Meningitis, endovascular infections, infections associated with prosthetic material, and other focal infections can occur.

- For review on epidemiology, clinical manifestations, and difficulty culturing, see Clin Infect Dis 58:1579, 2014.

- Outbreaks uncommon, but cluster of intestinal and extraintestinal cases linked to MSM reported. Clin Infect Dis 65:1751, 2017.

Classification

- Gram negative rod (gull-wing appearance)

Primary Regimens

- Imipenem-cilastatin 500 mg IV q6h or Meropenem 1 gm IV q8h

- For meningitis Meropenem 2 gm IV q8h for up to 4-6 weeks (Medicine (Baltimore) 95:e2858, 2016)

Alternative Regimens

- Ampicillin 100 mg/kg/day IV divided q6h

- Gentamicin 5 mg/kg IV q24h

- Ertapenem 1 gm IV q24h

Antimicrobial Stewardship

- Duration of therapy 7-14 days for uncomplicated bacteremia; at least 4 weeks of therapy recommended for endocarditis.

- Do not use macrolides to treat serious infections caused by C. fetus.

- Resistance (Medicine 89:319, 2010) Fluoroquinolones an option for susceptible strains but confirm susceptibility as resistance is common . Resistance to third-generation cephalosporins, found in 10-20% of isolates has been associated with failure in therapy of meningitis.

- Fluoroquinolones an option for susceptible strains but confirm susceptibility as resistance is common .

- Resistance to third-generation cephalosporins, found in 10-20% of isolates has been associated with failure in therapy of meningitis.

Comments

- Consider β-lactam-gentamicin combination for prosthetic valve infection (Tex Heart Inst J 38:584, 2011).

Campylobacter gracilis

Clinical Setting

- Positive lab result

- Oral flora, associated with periodontal, pleuropulmonary disease and, rarely, bacteremia (Emerging Infect Dis 2015 Jun;21(6):1084-5)

Classification

- Anaerobic gram-negative rod

- Formerly Bacteroides gracilis

Primary Regimens

- Optimal treatment unknown; treat as for Bacteroides fragilis

Alternative Regimens

- None

Comments

- None

Campylobacter jejuni, Campylobacter coli

Clinical Setting

- A common cause of acute illness with diarrhea.

- Self-limited illness and modest benefit of antimicrobial therapy which shortens duration of symptoms by about a day (Clin Infect Dis 44:696, 2007)

- Food borne disease; contamination of water or food by Campylobacter in the GI flora of animals, especially poultry (Clin Infect Dis 44:701, 2007; Clin Infect Dis 57: 1600, 2013).

- Campylobacter infection most common infectious agent precipitant of Guillain-Barré syndrome, reactive arthritis, and irritable bowel syndrome (N Engl J Med 366: 2294, 2012).

- Clinical illness caused by C. jejuni and C. coli are identical.

- Abdominal pain can mimic that of appendicitis.

- Diagnosis requires stool culture on selective media.

- Treatment recommended for patients with prolonged or severe disease (e.g., fever and bloody stools) and immunocompromised patients

- Patients 65 years and older, pregnant women, and immunocompromised patients at risk for severe disease

Classification

- Campylobacter jejuni – Gram negative rod (gull-wing appearance) (85% or more of cases)

- Campylobacter coli – Gram negative rod (gull-wing appearance)

Primary Regimens

- Azithromycin 500 mg IV/po q24h x 3 days. If bacteremic (rare), treat x 14 days

- Azithromycin 1000 mg po single dose (for mild, non-bacteremic disease)

Alternative Regimens

- Ciprofloxacin 500 mg po bid x 5 days

- Erythromycin 500 mg po qid x 3 days

- Doxycycline 100 mg po bid x 5 days

Antimicrobial Stewardship

- Note: resistance to fluoroquinolone and doxycycline common, particularly in strains from outside US; confirm susceptibility for treatment of more serious infections. In 5 year observational trial of 592 patients in France, almost half of the strains were resistant to fluoroquinolones and 245 were resistant to macrolides: Clin Infect Dis 2022; 75:702.

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Comments

- For severe life-threatening infection, use an aminoglycoside or carbapenem.

- Azithromycin is the drug of choice for treatment of Campylobacter gastroenteritis in travelers due to high rates of resistance to fluoroquinolones (Antimicrob Agents Chemother 54:1232, 2010 and Clin Infect Dis 48:1500, 2009).

- Implicated as a leading cause of diarrhea in children under 5 in under-resourced settings (Lancet Glob Health 2018:e1309, Lancet 2016 388:1291), associated with resistance to fluoroquinolones and macrolides (Antimicrob Agents Chemother 2018 Nov 12. pii: AAC.01911-18). Consider Amoxicillin-clavulanate as an alternative.

- TMP-SMX, penicillins and cephalosporins are not active against Campylobacter.

- See 2017 IDSA Guidelines (Clin Infect Dis 65: e65, 2017)

Capnocytophaga species

Clinical Setting

- Capnocytophaga canimorsus is an etiology of fulminant septicemia in persons bitten by a dog Greatest risk: patients who have anatomic or functional asplenia, heavy alcohol use, or hepatic cirrhosis Diagnosis of Capnocytophaga species usually by Isolation of the organism in blood culture (slow growing, can take 14 days). Slender, long gram-negative rods (may be seen in peripheral blood or buffy coat stain). Cause of bacteremic shock and/or meningitis after cat or dog bite: Capnocytophaga spp. are divided based on whether they are part of the normal oral flora of humans or dogs and cats. C. canimorsus, C. cynodegmi, and C. stomatis are part of the oral flora of dogs and cats Six other species are part of the normal oral flora of healthy people C. canimorsus is the major pathogen isolated after dog or cat bite in bacteremic asplenic patients

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- C. canimorsus is the major pathogen isolated after dog or cat bite in bacteremic asplenic patients

- Urgent empiric therapy indicated in patients who are asplenic with clinical syndrome of septic shock post dog bite: Mortality is 30-50 % Survivors may suffer DIC and distal peripheral symmetrical gangrene of extremities and ear lobes and perhaps tip of the nose Variables considered in the recommendations for empiric therapy; C. canimorsus isolates are: Considered susceptible to all beta-lactams (Penicillins, cephalosporins, Carbapenems) except aztreonam Susceptible to clindamycin Variable susceptibility to TMP-SMX and aminoglycosides Over 50% of the isolates are resistant to fluoroquinolones Prior to culture confirmation in an asplenic patient, choice of empiric therapy should consider possibility of bacteremia by encapsulated bacteria: e.g., S. pneumoniae, H. influenzae, , N. meningiditis

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- Prior to culture confirmation in an asplenic patient, choice of empiric therapy should consider possibility of bacteremia by encapsulated bacteria: e.g., S. pneumoniae, H. influenzae, , N. meningiditis

- See specific diseases, syndromes:

- Bacteremia, post-splenectomy or functional asplenia

- Shock, post-splenectomy

- Dog Bite

Classification

- Facultative gram negative bacilli Capnocytophaga canimorsus (previously designated DF-2)

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Primary Regimens

- Culture, clean, and debride bite wound

- Assess need for tetanus and/or rabies immunization

- Dog Bite in asplenic patient with no evidence of sepsis. Prophylactic therapy for 3-5 days with one of the following options:

- Amoxicillin-clavulanate 875/125 mg tab, 1 po bid

- Clindamycin 300 mg po qid (S. aureus maybe resistant)

- Septic shock, splenectomized patient:

- Empiric therapy (need predictable activity vs C. canimorsus but also activity vs pneumococci, Neisseria meningitidis., Haemophilus influenzae., and maybe Staph. aureus.

- Piperacillin-tazobactam 4.5 gm IV x 1 dose and then, starting 4 hrs later, 3.375 gm IV over 4 hrs and repeat q8h Add Vancomycin if history of risk factors for MRSA (e.g., illicit drug use) Some add Clindamycin 600-900 mg IV q8h or Metronidazole 500 mg IV q8h for activity vs anaerobic organisms in dog/cat saliva

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- Imipenem-cilastatin 500 mg IV q6h

- Meropenem 1 gm IV q8h Some add Clindamycin 900 mg IV q8h or Metronidazole 500 mg IV q8h

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- Specific therapy for C. canimorus after culture and susceptibility results available

- Piperacillin-tazobactam 4.5 gm IV once; 4 hrs later start 3.375 mg IV over 4 hrs and then repeat q8h

- Imipenem-cilastatin 500 mg IV q6h

- Meropenem 1 gm IV q8h

- If severe beta-lactam allergy: Clindamycin 600 mg IV q8h

Alternative Regimens

- Specific therapy when isolate if positive for production of beta-lactamase and in vitro susceptibility available: Clindamycin 900 mg IV q8h Ceftriaxone 2 gm IV once daily, or other extended spectrum cephalosporin, if susceptible in vitro

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Antimicrobial Stewardship

- In asplenic or alcoholic patients or others at high risk, reasonable to administer antibiotic prophylaxis with Amoxicillin-clavulanate or Clindamycin for 5 days post-dog bite

- Increasing prevalence of beta-lactamase-producing strains in non-canimorsus capnocytophaga species, limiting use of penicillin and cephalosporin unless documented in vitro susceptibility (Int J Antimicrob Agents 29:367, 2007).

Comments

- Unpredictable susceptibility to aminoglycosides and TMP-SMX. Roughly 50% of strains are resistant to fluoroquinolones. Virtually all isolates are resistant to Aztreonam

- Reference: Lancet Infect Dis 9:439, 2009; Eur J Clin Microbiol Infect Dis 34:1271, 2015.

Chlamydia trachomatis

Clinical Setting

- Different serovars of C. trachomatis are associated with different clinical syndromes: Serovars A, B, Ba, & C cause trachoma D-K cause urogenital syndromes (e.g., urethritis/cervicitis) L1-L3 cause Lymphogranuloma venereum (LGV).

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- D-K cause urogenital syndromes (e.g., urethritis/cervicitis)

- L1-L3 cause Lymphogranuloma venereum (LGV).

- Urogenital C. trachomatis syndromes are the most frequent reportable infectious diseases in the U.S.

- Associated with:

- Sexually transmitted infections including nongonococcal cervicitis, urethritis, pelvic inflammatory disease, proctitis

- Lymphogranuloma venereum (LGV)

- Trachoma: a chronic bacterial keratoconjunctivitis that is the most common cause of infectious blindness world-wide. Trachoma is endemic in resource-poor regions of poverty.

- Urethral and cervical infections are commonly asymptomatic.

- Annual screening is recommended in sexually active women age <25 years and older women at risk (N Engl J Med 2017;376:765). Screening of MSM is also advisable. If tests positive and treated with Azithromycin or Doxycycline, need to repeat screening in 3 months If positive screen, suggest testing all sexual contacts that occurred within the the 60 days before the diagnosis or symptoms

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- Neonates who contract infection from their mother can present with Ophthalmia Neonatorum or pneumonia.

Classification

- Intracellular gram negative bacterium

Diagnosis

- Diagnosis of C. trachomatis serovars D-K by NAAT of first-catch urine or swab of involved anatomic site (cervix, urethra).

- NAAT is more sensitive than culture, which, in turn, is more sensitive than direct fluorescent antibody (DFA) testing.

- When NAATs are used, similar sensitivity and specificity with vaginal swab (collected by patient or physician) or swab of endocervical canal

- Can use first voided urine but sensitivity is slightly lower

- NAATs cannot distinguish different serotypes (e.g. D-K vs L1-L3) need further PCR genotyping.

Primary Regimens

- See specific clinical syndrome.

- 2021 CDC STI guidelines MMWR Recomm Rep 70 (RR-4):1 2021 Doxycycline 100 mg bid x 7 preferred regimen

- For most syndromes, Azithromycin and Doxycycline are effective, yet single dose Azithromycin found less effective in patients with rectal infection (Clin Infect Dis 2019;69:1946; Clin Infect Dis 73:824 2021)

- Urethritis or cervicitis

- Proctitis

- Ophthalmia neonatorum

- Neonatal pneumonia

- Trachoma

- LGV

- Pharyngitis (frequency and importance unclear)

Alternative Regimens

- Pregnancy: Amoxicillin can be used in treatment of pregnant women
with Chlamydia trachomatis infection but exposure to penicillin-class antibiotics is reported to induce a persistent state in the organism (J Infect Dis 201:S88, 2010) so amoxicillin is considered an alternative treatment.

Comments

- Recommendations for screening and treatment in 2021 CDC STD guidelines: MMWR Recomm Rep 70 (RR-4):1 2021

- Doxycyline and fluoroquinolones not recommended in pregnancy. Fluoroquinolones usually effective but more expensive.

- For ease of treatment and compliance, single dose azithromycin recommended, but in RCT non inferiority of azithromycin to doxycycline (x 7 days) not established (N Engl J Med 373:2513, 2015).

- Test of cure not routinely recommended for STI except in pregnancy. NOTE: NAAT can remain positive for 2-3 weeks after treatment due to presence of nonviable organisms.

- Retesting to monitor for re-infection recommended every 3-12 months.

- Resistance thought uncommon, but clinical failures are reported. Some studies suggest failure is more common with azithromycin than doxycycline (F1000Prime Rep 6:120, 2014).

- Metaanalysis (J Antimicrob Chemother 70:1290, 2015) and RCT in MSM (CID 73:824 2021) show doxycycline more effective for rectal chlamydia.

- LGV requires longer treatment (3 weeks).

- Treatment of sexual partners recommended (expedited partner therapy or EPT).

- For infants and children, chlamydial infection should prompt consideration of sexual abuse. Remember that perinatally transmitted C. trachromatis can persist in nasopharynx, urogenital tract or rectum of infants for 2-3 years. See MMWR Recomm Rep 70 (RR-4):1 2021

Chlamydia pneumoniae

Clinical Setting

- Agent of atypical, community-acquired pneumonia.

- Relatively mild symptoms; non-productive cough, sore throat are common.

- Serological tests are cross-reactive between C. psittaci and C. pneumoniae.

- Regimens below are for microbiologically confirmed infection.

Diagnosis

- FilmArray Respiratory Panel is FDA-approved diagnostic test.

Etiologies

- Chlamydophila pneumoniae (or Chlamydia pneumoniae)

Primary Regimens

- Doxycycline 100 mg po/IV bid x 14 days

- Azithromycin 500 mg po/IV on day 1, then 250 mg po daily for 4 days

Alternative Regimens

- Levofloxacin 750 mg po/IV x 5-7 days

- Clarithromycin 500 mg bid x 10 days

- Omadacycline 200 mg IV (over 60 min) loading dose and then 100 mg (over 30 min) q24 h OR 100 mg IV over 30 min bid on day one and then 100 mg iv over 30 min q24h OR 450 mg po q24h on days 1 and 2 and then 300 mg po q24h

- 200 mg IV (over 60 min) loading dose and then 100 mg (over 30 min) q24 h OR

- 100 mg IV over 30 min bid on day one and then 100 mg iv over 30 min q24h OR

- 450 mg po q24h on days 1 and 2 and then 300 mg po q24h

Comments

- Reference: N Engl J Med. 2019 Feb 7; 380(6):517-527; StatPearls; 2022 Jan. 2022 Aug 8

Chlamydia psittaci

Clinical Setting

- Agent of atypical pneumonia. See also, Chlamydia pneumoniae.

- Obligate intracellular parasite.

- Zoonotic infection acquired from exposure to birds or bird excrement.

- Fever, non-productive cough, headache are most common symptoms.

- Rare cause of fulminant pneumonia.

Diagnosis

- Diagnosis (note: serological tests are cross-reactive between C. psittaci and C. pneumoniae):

- Isolation of C. psittaci from respiratory secretions

- A fourfold or greater rise in antibody titer between acute and convalescent serum samples collected 2 weeks apart to a titer of greater than or equal to 1:32

- A single IgM titer of 1:16 or greater (by microimmunofluorescence).

- PCR of throat swabs.

Etiologies

- Chlamydia psittaci

Primary Regimens

- Doxycycline 100 mg IV/po q12h x 7-10 days

- Azithromycin 500 mg po on day 1 then 250 mg once daily x 4 days Preferred therapy for children administered as a single 10 mg/kg dose on day 1, then 5 mg/kg once daily on days 2 through 5

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Alternative Regimens

- Clarithromycin 500 mg q12h x 7-10 days

- Minocycline 100 mg IV/po q12h x 7-10 days

Antimicrobial Stewardship

- Duration of therapy not well defined; cough can be persistent and is not a reliable guide to duration of therapy.

Comments

- Tetracycline and erythromycin are also effective, but not considered first line due to more frequent dosing and being less well tolerated.

- Fluoroquinolones active in vitro but limited clinical data.

- Reference: StatPearls Publishing; 2024 Jan.

Citrobacter koseri (formerly diversus)

Clinical Setting

- Citrobacter species cause a variety of infections ranging from uncomplicated urinary tract infections to life-threatening infections of the abdomen, skin and soft tissue, lung, CNS and other sites in both normal and immuno-compromised hosts.

- Suggested treatment regimens vary with the status of cultures and the results of in vitro susceptibility.

- Antibiotic resistance is an increasing problem:

- Major mechanism of resistance is production of beta-lactamases Citrobacter strains can produce extended-spectrum beta-lactamases (ESBLs). ESBLs destroy antibacterial activity of most extended spectrum cephalosporins, penicillins, and aztreonam, though Cefepime may be an exception. Unlike Citrobacter freundii, Citrobacter koseri does not have repressed chromosomal ampC genes. Hence safe to use ceftriaxone if isolate is both speciated and is susceptible in vitro Often concomitant resistance to fluoroquinolones, aminoglycosides and TMP/SMX.

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- Often concomitant resistance to fluoroquinolones, aminoglycosides and TMP/SMX.

- Choice of empiric regimen depends on local resistance pattern, fragility of the patient and the severity of the infection. Specific therapy is directed results of in vitro susceptibility testing.

- For further discussion see Gram Negative Bacilli, Beta-lactam Resistance, Overview.

- For uncomplicated cystitis, see Cystitis, adult female.

- See also Citrobacter freundii

- See Comments for select drug details, emerging data, literature citations and more.

Classification

- Gram negative bacilli that grow aerobically and anaerobically Citrobacter diversus (koseri)

- Citrobacter diversus (koseri)

Primary Regimens

- Strains producing ESBLs and/or AmpC: Ceftolozane-tazobactam 1.5 gm IV over 3h q8h Temocillin 2 gm IV q12h (available in Belgium and United Kingdom) Cystitis: Fosfomycin 3 gm po x 1 dose Pyelonephritis: Fosfomycin 6 gm IV q8h (where available) Cefepime 1-2 gm IV over 3h q8-12h an option for AmpC producer, but not ESBL

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- Strains producing carbapenemases: Strains producing metallo -betalactamase: Ceftazidime-avibactam 2.5 gm IV over 2 hrs q8h + Aztreonam salvage therapy Aztreonam is not hydrolyzed by metallocarbapenemases but is inactivated by ESBLS which are often produced concomitantly with the carbapenemase. Avibactam binds ESBLs. See Antimicrob Agents Chemother

2017 Mar 24; 61(4). pii:e02243-16 Cefiderocol 2 gm IV over 3 hrs q8h (FDA approved for complicated UTI)(See Comments)

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Alternative Regimens

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Antimicrobial Stewardship

- Reserve carbapenems for Citrobacter infections that in addition need anaerobic coverage or for treatment of ESBL producing strains.

- Reserve Meropenem-vaborbactam, Imipenem-cilastatin-relebactam, and Ceftazidime-avibactam for patients with documented KPC infections.

Comments

- Important distinction: C. freundeii frequently houses chromosomal ampC gene. Need to avoid cephalosporins even is susceptible in vitro C. koseri does not house ampC gene and cephalosporins are safe and effective if susceptible in vitro In short, If all you know is the pathogen is Citrobacter species, need to avoid cephalosporins regardless of in vitro susceptibility results. If isolate is Citrobacter koseri (no ampC genes), OK to use cephalosporin if isolate is susceptible in vitro. Reference: IDSA 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections.

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- Cefiderocol: FDA-approved for patients with complicated UTI due to cefiderocol susceptible bacteria and with limited or no alternative treatment options. In an open label randomized trial of cefiderocol vs Best Available Therapy (BAT) in patients with sepsis, pneumoinia, bacteremia or cUTI, mortality at 28 days was 24.8% for cefiderocol pts. vs 18.4% for BAT pts (not statistically significant).

- Plazomicin is approved for complicated UTI. Limited observational experience in combination with Tigecycline or Meropenem for MDR bacteremia or ventilator-associated pneumonia (N Engl J Med 2019; 380: 791).

- Investigational drug in late development with activity vs MDR GNB: Aztreonam-avibactam

- Aztreonam-avibactam

Citrobacter freundii

Clinical Setting

- Citrobacter species cause a variety of infections ranging from uncomplicated urinary tract infections to life-threatening infections of the abdomen, skin and soft tissue, lung, CNS and other sites in both normal and immuno-compromised hosts. Citrobacter freundii encodes an inducible ampC gene that when over-expressed can cause clinical failures with Ceftriaxone, Cefotaxime, Ceftazidime, Aztreonam, or Piperacillin-tazobactam Notably, Citrobacter koseri (formerly diversus) does not possess genes that encode production of AmpC

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- Suggested treatment regimens vary with the status of cultures and the results of in vitro susceptibility.

- Antibiotic resistance is an increasing problem:

- Major mechanism of resistance is production of beta-lactamases ampC gene maybe present but repressed and the isolate may appear susceptible to cephalosporins. Administration of a cephalosporin derepresses the gene with then production of AmpC enzymes that hydrolyse the cephalosporin. Warning: Until a citrobacter isolate is speciated, have to assume it could be C. freundii and hence the need to avoid empiric cephalosporin therapy regardless of the in vitro susceptibility results. Citrobacter strains can produce extended-spectrum beta-lactamases (ESBLs). ESBLs destroy antibacterial activity of most extended spectrum cephalosporins, penicillins, and aztreonam, though Cefepime may be an exception. Often concomitant resistance to fluoroquinolones, aminoglycosides and TMP/SMX. Other potential mechanisms of resistance: porin closure with reduced cell wall permeability, change in cell wall binding protein, and efflux pumps

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- Other potential mechanisms of resistance: porin closure with reduced cell wall permeability, change in cell wall binding protein, and efflux pumps

- Choice of empiric regimen depends on local resistance pattern, fragility of the patient and the severity of the infection. Specific therapy is directed by the results of in vitro susceptibility testing.

- For further discussion see Gram Negative Bacilli, Beta-lactam Resistance, Overview.

- For uncomplicated cystitis, see Cystitis, adult female.

- See also Citrobacter diversus, koseri

- See Comments for select drug details, emerging data, literature citations and more.

Classification

- Gram negative bacilli that grow aerobically and anaerobically Citrobacter freundii

- Citrobacter freundii

Primary Regimens

- Strains producing ESBLs and/or AmpC: Ceftolozane-tazobactam 1.5 gm IV over 3h q8h (de-repressed AmpC producers may be resistant) Temocillin 2 gm IV q12h (available in Belgium and United Kingdom) Cystitis: Fosfomycin 3 gm po x 1 dose Pyelonephritis: Fosfomycin 6 gm IV q8h (where available) Cefepime 1-2 gm IV over 3h q8-12h an option for AmpC producer, but not ESBL Cefepime-enmetazobactam recently FDA approved for treatment of complicated UTIs, including ESBL

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Alternative Regimens

- Strains producing ESBLs and/or AmpC: Ceftolozane-tazobactam 1.5 gm IV over 3h q8h (de-repressed AmpC producers may be resistant) Temocillin 2 gm IV q12h (available in Belgium and United Kingdom) Cystitis: Fosfomycin 3 gm po x 1 dose Pyelonephritis: Fosfomycin 6 gm IV q8h (where available) Cefepime 1-2 gm IV over 3h q8-12h an option for AmpC producer, but not ESBL Cefepime-enmetazobactam recently FDA approved for treatment of complicated UTIs, including ESBL producers

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Antimicrobial Stewardship

- Reserve carbapenems for Citrobacter infections that in addition need anaerobic coverage or for treatment of ESBL producing strains.

- Reserve Meropenem-vaborbactam and Ceftazidime-avibactam for patients with documented KPC infections.

Comments

- The rationale for the Ceftazidime-avibactam/Aztreonam combination for metallo-beta-lactamase (MBL) producers is that Aztreonam is not hydrolyzed by MBLs and Ceftazidime is. However, MBL-producers commonly produce ESBLs or serine-carbapenemases, which can degrade Aztreonam. Although avibactam does not inhibit MBLs, it does inhibit serine beta-lactamases (i.e., ESBLs, AmpC, and serine-carbapenemases) such that the Aztreonam which would otherwise be degraded by the serine beta-lactamases remains active. See Antimicrob Agents Chemother 2017 Mar 24; 61(4). pii:e02243-16

- Cefiderocol: FDA-approved for patients with complicated UTI due to cefiderocol susceptible bacteria and with limited or no alternative treatment options. In an open label randomized trial of cefiderocol vs Best Available Therapy (BAT) in patients with sepsis, pneumoinia, bacteremia or cUTI, mortality at 28 days was 24.8% for cefiderocol pts. vs 18.4% for BAT pts (not statistically significant).

- High percentage of Citrobacter freundii, Enterobacter cloacae, and Klebsiella aerogenes have chromosomal repressed amp-C genes. Citrobacter koseri isolates are ampC negative. The ampC gene is de-repressed during exposure to a variety of antibiotics: e.g., piperacillin-tazobactam and virtually all parenteral cephalosporins except Cefepime which is a weak inducer. Note: strains with Cefepime MICs of 4-8 mcg/ml have dose-dependent susceptibility and may co-produce ESBL, therefore caution is advised when used to treat C. freundii infections caused by strains with MICs in this range.

- Plazomicin is approved for complicated UTI. Limited observational experience in combination with Tigecycline or Meropenem for MDR bacteremia or ventilator-associated pneumonia (N Engl J Med 2019; 380: 791).

- Investigational drug in late development with activity vs MDR GNB: Aztreonam-avibactam

- Aztreonam-avibactam

- IDSA Guideline on treatment of ESBL, AmpC, and carbapenemase producers: Clin Infect Dis. 2023 Jul 18:ciad428.

Clostridium bifermentans

Clinical Setting

- Anaerobic infection caused by Clostridium bifermentans

Classification

- Anaerobic spore-forming Gram-positive bacillus

Primary Regimens

- Optimal regimen not defined, case reports only: in vitro susceptibilities similar to other Clostridium spp. (see Comments)

Alternative Regimens

- Not defined

Comments

- Case report of isolate susceptible to Amoxicillin-clavulanate, Cefoxitin, Clindamycin, Meropenem, Metronidiazole, Penicillin (Can J Infect Dis Med Microbiol. 2015; 26: 105–107).

Clostridioides difficile, C. diff

Clinical Setting

- Clostridioides difficile associated diarrhea (CDAD), C. difficile infection (CDI) and abbreviated as C diff. Inflammation almost always limited to colonic mucosa: C. diff. toxin-mediated colitis Rarely, post-colectomy, C. diff. toxin can cause inflammation of small intestine: C.diff. toxin-mediated enteritis (Open Forum Inf Dis 6:ofz409, 2019)

- Inflammation almost always limited to colonic mucosa: C. diff. toxin-mediated colitis

- Rarely, post-colectomy, C. diff. toxin can cause inflammation of small intestine: C.diff. toxin-mediated enteritis (Open Forum Inf Dis 6:ofz409, 2019)

- Risk factors include advanced age, hospitalization, prior or concomitant systemic antibacterial therapy, cancer chemotherapy, gastrointestinal surgery.

- Suspect if new onset of diarrhea with > 3 unformed stools per day.

- See summary of approach in IDSA / SHEA 2018 guidelines Clin Infect Dis 66:987, 2018.

- IDSA / SHEA 2021 focused guidelines recommend fidaxomicin and bezlotoxumab: Clin Inf Dis 73:755, 2021

- Because fidaxomicin is more efficacious (though very expensive) latest guidelines recommend as first line therapy, if feasible (Clin Inf Dis 73:755, 2021, Med Lett 2021, 63:137)

- Asymptomatic carriage There is a substantial rate of C. difficile asymptomatic carriage particularly in children <2, so NAAT testing may be positive without clinical diarrhea. Although associated with transmission of CDI (Microbiol Spectr 10:e0132221, 2022), screening and treatment of carriage is not currently recommended. (Clin Infect Dis 66:987, 2018)

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- Although associated with transmission of CDI (Microbiol Spectr 10:e0132221, 2022), screening and treatment of carriage is not currently recommended. (Clin Infect Dis 66:987, 2018)

- Repeat testing to document cure of CDI or during same episode of diarrhea is not recommended. For recurrence, see Comments.

- Clinical stages of CDI Mild to moderate disease WBC <15,000 No increase in serum creatinine Fulminant (Severe) disease WBC >15,000 ≥50% increase in serum creatinine Zar score > 2 (see Clin Infect Dis 45:302, 2007)

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- ≥50% increase in serum creatinine

- Zar score > 2 (see Clin Infect Dis 45:302, 2007)

Classification

- Gram positive anaerobic bacilli, spore former

Diagnosis

- Optimal diagnostic algorithms are still the subject of studies and not all centers offer the same panel of diagnostic tests. For a summary see: Clin Infect Dis 67:e1 2018

- NAAT tests will be positive for asymptomatic carriers

- Testing recommended only in cases of diarrhea (> 3 unformed stools per day), no laxatives for 48 hrs, or where there is a high suspicion of disease (e.g. megacolon, severe ileus).

- For patients with symptoms consistent with C. difficile-associated infection (CDI) diagnosis made with nucleic acid amplification test (NAAT) alone or 2- or 3-step testing (e.g., glutamate dehydrogenase

[GDH] immunoassay + toxin assay followed by NAAT only if either the GDH assay and toxin assay, but not both, are negative).

- Automated clinical testing criteria for appropriate testing can enforce appropriate testing and treatment (Infect Control Hosp Epidemiol 39:625-627, 2018)

Primary Regimens

- Treatment considerations If possible, stop the inciting antibiotic Up to 20-25% patients relapse though less frequent with fidaxomicin In general, avoid antiperistaltic medicine during acute phase Generally 10 days recommended, but course can be extended to 14 days if improving but not resolved.

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- Up to 20-25% patients relapse though less frequent with fidaxomicin

- In general, avoid antiperistaltic medicine during acute phase

- Generally 10 days recommended, but course can be extended to 14 days if improving but not resolved.

- Mild Disease or Moderate disease, initial episode: Fidaxomicin 200 mg po bid x 10 days (significantly more expensive than vancomycin). Vancomycin 125 mg po qid x 10 days (see Comments)

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- Vancomycin 125 mg po qid x 10 days (see Comments)

- Fulminant (Severe) disease, initial episode: Vancomycin 500 mg q6h po or via nasogastric tube +/- Metronidazole 500 mg IV every 8h, particularly if ileus is present For patients with ileus, administer Vancomycin 500 mg in 100 mL normal saline per rectum as a retention enema q6h. In retrospective study of ICU patients, Vancomycin + Metronidazole combination associated with decrease in mortality from 36 to 16% (Clin Infect Dis 61:934, 2015).

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- Severe disease with toxic megacolon: treatment as above PLUS Sometimes only option is colectomy Alternative: loop ileostomy coupled with antegrade colonic irrigation with Vancomycin + intravenous Metronidazole (Ann Surg 254:423, 2011) No data on the efficacy of Fidaxomicin in patients with severe life-threatening disease. Fecal microbiota transplant is promising; supportive evidence in one retrospective cohort study (Open Forum Infect Dis 6:ofz398, 2019)

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- Fecal microbiota transplant is promising; supportive evidence in one retrospective cohort study (Open Forum Infect Dis 6:ofz398, 2019)

- Recurrent CDI

- First Recurrence (use a regimen different from original, if possible) Fidaxomicin 200 mg po bid x 10 days Fidaxomicin (extended regimen) 200 mg po bid x 5 days, 200mg po every other day for 20 days Vancomycin 125 mg po qid x 10 days, Vancomycin taper as follows: 125 mg po qid x 10 days, followed by 125 mg tid x 1 week, then 125 mg bid x 1 week, then 125 mg q24h x 1 week, then 125 mg q48h x 1 week, then 125 mg once every third day x 1 week

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- Recurrence following treatment with Metronidazole as primary regimen Vancomycin 125 mg po qid x 10 days Fidaxomicin 200 mg po bid x 10 days

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- Fidaxomicin 200 mg po bid x 10 days

- Multiple recurrences: Fecal microbiota transplantation (FMT) emerging as a treatment of choice for recurrent infections (J Hosp Med 11:56, 2016). For details of donor screening used for commercial product from Open Biome see N Engl J Med 2019; 381:2070. Vancomycin 125 mg po qid x 10 days followed by Rifaximin 400 po tid x 20 days FMT is becoming more logistically difficult due to emergence MDR fecal contents, increased regulations (see comments)

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- Vancomycin 125 mg po qid x 10 days followed by Rifaximin 400 po tid x 20 days

- FMT is becoming more logistically difficult due to emergence MDR fecal contents, increased regulations (see comments)

- Prophylaxis (recurrence within 6 mo) Treatment as above PLUS Bezlotoxumab single intravenous 10 mg/kg dose of the anti-toxin monoclonal antibody (see Comments)

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- Prophylaxis to prevent recurrent CDI in patients requiring on-going systemic antimicrobial therapy for another indication: retrospective study of treatment doses of oral Vancomycin while patient was receiving systemic antibiotics found reduced incidence of recurrent CDI to 4.2% versus 26.6% in patients not treated with concurrent vancomycin (Clin Infect Dis 63:651, 2016).

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Alternative Regimens

- Mild disease only: Metronidazole 500 mg po tid in resource constrained settings if limited access to Vancomycin or Fidaxomicin.

- More severe disease: Avoid Metronidazole which is associated with higher mortality than Vancomycin (JAMA Intern Med 177:546, 2017).

Antimicrobial Stewardship

- Limit the number of systemic antibiotics used and duration of antibiotic therapy.

- Avoid unnecessary antibiotics and discontinue suspected offending antibiotics as soon as possible.

- Consider restriction of higher risk antibiotics such as fluoroquinolones, clindamycin, cephalosporins, carbapenems, particularly in outbreaks and high infection rates.

- Consider discontinuation of proton-pump inhibitor therapy.

- Infection Control Handwashing with soap and water is more effective for removal of spores than alcohol-based hand hygiene agents.

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- Reference: Ann Int Med 2019; 171 (suppl 7): S45

- Emergence of strains with reduced susceptibility (Clin Inf Dis 74:120, 2022) to both vancomycin and metronidazole is reported but susceptibility testing not routinely available.

- FMT now requires screening of donors for MDRO as per FDA guidelines (see Comments)

Comments

- Specific virulent ribotypes (NAP1/BI/ribotype 027) are associated with epidemics and more severe disease.

- Salvage therapy for CDI: Summarized in N Engl J Med 372:1539, 2015. Antibiotics with poorly documented efficacy are rifaximin, nitazoxanide, ramoplanin, teicoplanin, and tigecycline. Use of these agents is not recommended but may be considered for salvage therapy when other options have failed.

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- Use of these agents is not recommended but may be considered for salvage therapy when other options have failed.

- Probiotics: Guidelines state insufficient data to recommend use for primary prevention of CDI Clin Infect Dis 2018;66:987 In studies with high risk patients (CDAD >5%) moderate evidence that probiotics are effective (Cochrane Database Syst Rev 2017 Dec 19;12:CD006095).

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- Antimotility agents: Can be used cautiously in certain patients with mild disease who are receiving treatment (Clin Infect Dis 48:598, 2009).

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- Recurrence: Recurrence rates appear to be similar for Metronidazole and Vancomycin (although others have found higher cure rates with Vancomycin: Ann Intern Med 165:JC4, 2016) but mortality less in Vancomycin-treated patients with more severe disease (JAMA Intern Med 177:546, 2017). Fidaxomicin had lower rate of recurrence than Vancomycin for diarrhea with non-NAP1/BI strains (N Engl J Med 364:422, 2011 & Lancet Inf Dis 12:281, 2012) and for patients who required concomitant antibiotics during treatment of CDI (Clin Infect Dis 53:440, 2011); cure rates and recurrence rates similar for Vancomycin and Fidaxomicin for NAP1/BI/027 strains (Clin Infect Dis 55:351, 2012) Addition of a single intravenous 10 mg/kg dose of the anti-toxin monoclonal antibody Bezlotoxamab to standard of care (SOC) therapy (primarily Metronidazole or Vancomycin) did not improve initial cure rates but did reduce recurrence rates by 11% and 14 % in two controlled trials vs placebo (N Engl J Med 376:305, 2017; Clin Infect Dis 68:699, 2019). IV Vancomycin is not effective as insufficient drug reaches lumen of the colon.(Med Lett 63:137, 2021).

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- IV Vancomycin is not effective as insufficient drug reaches lumen of the colon.(Med Lett 63:137, 2021).

- FMT is an investigational treatment governed by enforcement discretion by the FDA. Most practitioners do not get an IND, raising concerns that adverse outcomes are not consistently reported. Due to these concerns, FMT has become logistically difficult in many centers. After reports of transmission of MDRO organisms, FDA has issued regulatory requirements including extensive donor screening and MDRO testing prior to issue of IND and administration (Cell Host Microbe 27:173, 2020, FDA/CBER 2019a, FDA/CBER2019b) or alternatively, using donor feces collected prior to 2019. A FMT national registry tracks outcomes. Results for the first 259 patients from 20 centers (Gastroent 160:183, 2021): 30-day follow-up for 222 participants, 90% were cured; among them, 98% required only a single FMT. Synthetic alternatives to fecal transfer for FMT are being explored but are investigational.

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Clostridium perfringens

Clinical Setting

- Specific therapy

- For related topics, see Necrotizing fasciitis, Clostridium sp. Gangrene, Muscle Shock, Toxic, Clostridia

- Necrotizing fasciitis, Clostridium sp.

- Gangrene, Muscle

- Shock, Toxic, Clostridia

Classification

- Anaerobic, spore-forming Gram positive bacilli

Primary Regimens

- Prompt surgical debridment for gas gangrene

- Penicillin G ± Clindamycin (see Comments)

- Hyperbaric oxygen is not recommended for treatment of clostridial gas gangrene and myonecrosis, as no proven benefit and arrangements for HBO may delay needed surgical debridement.

- Rehydration for C. perfringens food poisoning; antibiotics not indicated.

Alternative Regimens

- Doxycycline

Comments

- Penicillin is the drug of choice with the addition of Clindamycin for the theoretical benefit of inhibition of toxin production.

- Remains susceptible to most front-line antibiotics: Erythromycin, Chloramphenicol, Cefazolin, Cefoxitin, Ceftriaxone, Piperacillin, Carbapenem, Metronidazole, Vancomycin, Linezolid.

- Clinical practice guideline: Clin Infect Dis 59:147, 2014.

- Review: N Engl J Med 377(23): 2253, 2017

Clostridium tetani

Clinical Setting

- Cause of tetanus, a toxin mediated disease.

- The diagnosis is usually clinical based on the typical features of persistent tonic muscle spasms, trismus ("lockjaw") in the setting of inadequate or absent vaccination.

- Cultures, which are frequently negative, are not useful in confirming or excluding the diagnosis.

- Serum and urine should be submitted for toxin assay in suspected cases.

- Preventable by immunzation. Survivors are not immune: Vaccinate. See www.immunize:org/askexperts

- Review of maternal and neonatal tetanus: Lancet 385:362, 2015; Ped in Review 2018; 39:430

Classification

- Anaerobic Gram positive spore forming bacilli

Primary Regimens

- Steps in management and treatment of tetanus:

- Urgent endotracheal intubation to protect the airway. Laryngeal spasm is common. Early tracheostomy.

- Eliminate reflex spasms with diazepam, 20 mg/kg/day IV or midazolam. Reports of benefit combining diazepam with magnesium sulfate (Lancet 368:1436, 2006). Worst cases: need neuromuscular blockade with vecuronium.

- Neutralize toxin: Human hyperimmune globulin 500 units IM at a different site than tetanus toxoid with part of the dose infiltrated around the wound; start tetanus toxoid immunization–no immunity from clinical tetanus.

- Surgically debride infected source tissue.

- Start antibiotic and treat for 7-10 days (See Comment) Metronidazole 500 mg IV q6h or 1000 mg IV q12h Aqueous Penicillin G 3 million units IV q4h

- Metronidazole 500 mg IV q6h or 1000 mg IV q12h

- Aqueous Penicillin G 3 million units IV q4h

- Avoid light as may precipitate muscle spasms.

- Use beta blockers, e.g., short acting esmolol, to control sympathetic hyperactivity.

Alternative Regimens

- Doxycycline 100 mg IV q12h x 7-10 days

Comments

- Review: Lancet 393; 1657; 2019

- Metronidazole for 10-14 days (Ann Intern Med 154:329, 2011)

- Note: Clinical tetanus does not confer immunity; an immunization series should be completed in all cases of tetanus.

- Penicillin, metronidazole, tetracyclines, macrolides, are all active but the role of, or whether there is benefit from, antimicrobial therapy is controversial.

Bacteria: Normal Flora, Non-pathogenic, Contaminants, Rare Pathogens

Introduction

- Rare pathogens
- Normal human flora
- Environmental contaminants
- Often non-pathogenic and of low virulence
- Present in mixed cultures

Organisms

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Organisms

Corynebacterium diphtheriae

Clinical Setting

- Cause of respiratory tract infections (anterior nasal, pharyngeal, laryngeal, tracheal) but can also cause cutaneous infection and invasive disease.
- See Pharyngitis, Diphtheria

Diagnosis

- Definitive diagnosis made by isolation of the organism in culture on tellurite-selective medium (e.g., Tinsdale agar).

Classification

- Gram positive bacilli - Corynebacterium diphtheriae

Primary Regimens

- See Pharyngitis, Diphtheria

Alternative Regimens

- See Pharyngitis, Diphtheria

Prevention

- See Tetanus, Diphtheria, Pertussis, Vaccines for indications, available products, dosing, and vaccine characteristics for pre-exposure prevention.

Comments

- Toxigenic strains of Corynebacterium ulcerans; acquired from animals. Clinical disease mimics diphtheria. No human to human transmission.

Corynebacterium jeikeium

Clinical Setting

- Positive lab result: isolation in culture.

- Hospital-acquired or healthcare-associated infection.

- Multiple-drug resistant corynebacterium species (not a contaminant).

- Cause of bacteremia, endocarditis, intravascular and dialysis catheter-associated infections, prosthetic device infections, CSF shunt infections.

- Patients are often immunocompromised; risk factors as follows:

- Hematologic malignancy

- AIDS

- Neutropenia

- Prior antibiotic exposure

Classification

- Gram positive bacilli

- Corynebacterium jeikeium

Primary Regimens

- Vancomycin

Alternative Regimens

- Daptomycin

Antimicrobial Stewardship

- High-level daptomycin resistance reported (J Clin Microbiol 47:2328, 2009)

- Many, if not most strains are resistant to penicillin (Clin Micro Infect 2:209, 1996), therefore confirm in vitro susceptibility before using a penicillin.

Comments

- Some have used combinations of vancomycin with gentamicin for endocarditis (IDCases 11: 26–30, 2018; Eur J Clin Micro Infect Dis 25:349, 2006); not clear if this provides a benefit over vancomycin

alone.

- Linezolid, Teicoplanin, and Tigecycline are active in vitro (Antimicrob Agents Chemother 47:337, 2003, Int J Antimicrob Agents 33:453, 2009).

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- Present in mixed cultures

Organisms

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Organisms

Corynebacterium urealyticum

Clinical Setting

- Rare cause of urinary tract infection; generates struvite stones that manifest as "encrusted" pyelitis and cystitis.
- Occurs in renal transplant patients and associated with obstruction and graft loss.

Classification

- Gram positive bacilli

Primary Regimens

- Vancomycin 15-20 mg/kg IV q8-12h to achieve preferred target AUC 400-600 µg/mL x hr (see vancomycin AUC dosing calculator; alternative is trough level of 15-20 µg/mL)

- Surgical removal of stones causing obstruction or encrusted pyelitis

Alternative Regimens

- Teicoplanin (where available) 100-400 mg IM once daily x 14 days

Comments

- Linezolid, Daptomycin, and Tigecycline active in vitro (Int J Antimicrob Agents 33:453, 2009).

- Reference: Clin Infect Dis 46:825, 2008; review Infect Drug Res 8: 129, 2015.

Coxiella burnetii, Q Fever

Clinical Setting

- Zoonotic infection caused by Coxiella burnetii. Cattle, sheep and goats are common reservoirs.

- Spread to humans by aerosolization of infected animal birth products or excreta.

- Can cause acute or chronic illness.

- Acute infection: Acute infection is a flu-like illness with fever, chills, night sweats, myalgia, headache, and perhaps a non-productive cough. Usually mild and resolves spontaneously within 2 weeks. Can progress to chronic infection to include endocarditis which is associated with abnormal cardiac valves or other vascular involvement, other signs of chronic infection (fever, night sweats, weight loss, hepatosplenomegaly) (Clin Infect Dis 57:836, 2013). Positive whole blood or serum PCR or positive culture or immunohistochemistry for C. burnetii Four-fold increase in IFA phase II IgG in paired sera In prospective study of 1797 patients with acute Q fever, 48 had evidence of acute Q fever endocarditis, most identified by TTE; associated risk factors were presence of anticardiolipin antibodies and older age (Clin Infect Dis 2019; 69:1987-1995).

- Acute infection is a flu-like illness with fever, chills, night sweats, myalgia, headache, and perhaps a non-productive cough.

- Usually mild and resolves spontaneously within 2 weeks. Can progress to chronic infection to include endocarditis which is associated with abnormal cardiac valves or other vascular involvement, other signs of chronic infection (fever, night sweats, weight loss, hepatosplenomegaly) (Clin Infect Dis 57:836, 2013).

- Can progress to chronic infection to include endocarditis which is associated with abnormal cardiac valves or other vascular involvement, other signs of chronic infection (fever, night sweats, weight loss, hepatosplenomegaly) (Clin Infect Dis 57:836, 2013).

- Positive whole blood or serum PCR or positive culture or immunohistochemistry for C. burnetii

- Four-fold increase in IFA phase II IgG in paired sera

- In prospective study of 1797 patients with acute Q fever, 48 had evidence of acute Q fever endocarditis, most identified by TTE; associated risk factors were presence of anticardiolipin antibodies and older age (Clin Infect Dis 2019; 69:1987-1995).

- Clinical evidence of an atypical pneumonia and/or an anicteric hepatitis is common

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- C. burnetii demonstrated in a clinical specimen by immunohistopchemistry or culture

- Positive blood or tissue PCR in absence of acute infection

- IFA (immunofluorescent assay) ≥1: 800 for phase I IgG is consistent with diagnosis.

- Increased interest in value of PET scans to detect a variety of persistent focal infections: JAMA Network Open 2018; 1(4): e181580

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Classification

- Pleomorphic gram negative bacilli or coccobacilli, obligate intracellular organism

Primary Regimens

- Acute disease (initiate therapy as soon as the diagnosis suspected):

- Adults:

- Doxycycline 100 mg po bid x 2 weeks

- Pregnancy: TMP-SMX DS tab 1 po bid for duration of pregnancy to prevent premature labor. Discontinue prior to delivery so as to lessen risk of hyperbilirubinemia in the infant. Doxycycline and fluoroquinolones are contraindicated in pregnancy.

- If known cardiac valvulopathy (history of rheumatic fever, bicuspid aortic valve, prosthetic valve, valvular stenosis or regurgitation), can lower risk of progression to endocarditis by prescribing Doxycycline 100 mg po bid + hydroxychloroquine 200 mg po tid x 12 months

- Children:

- Immunosuppressed and/or valvular heart disease: Doxycycline 2.2 mg/kg/dose IV/po bid x 14 days (max 100 mg/dose)(safe for duration up to 21 days: J Pediatr 166:1246, 2015)

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- Chronic persistent focal disease: Endocarditis or infected aneursym/graft: Doxycycline 100 mg IV/po bid + hydroxychloroquine 200 mg po tid x minimum of 18 months Infected bone, joint, or liver: as per endocarditis until fall in antibody titer is demonstrated Post-partum: as per endocarditis, but perhaps only for 12 months

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- Children: Consultation is recommended.

Alternative Regimens

- Acute disease:

- Fluoroquinolone (e.g., Moxifloxacin 400 mg po once daily x 2-3 weeks)

- Erythromycin, Clarithromycin, or Azithromycin); some concern about the risk of prolongation of the QTc interval with macrolides.

- Chronic disease: In large retrospective observational cohort study, doxycycline + fluoroquinolone (ciprofloxacin or moxifloxacin) was as efficacious as doxycycline + hydroxychloroquine (Clin Infect Dis 2018;66:719). May be useful in patients unable to tolerate hydroxychloroquine Anecdotal reports of efficacy of TMP-SMX and Chloramphenicol

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Comments

Coxiella burnetii, Q Fever

Clinical Setting

- Zoonotic infection caused by Coxiella burnetii. Cattle, sheep and goats are common reservoirs.

- Spread to humans by aerosolization of infected animal birth products or excreta.

- Can cause acute or chronic illness.

- Acute infection: Acute infection is a flu-like illness with fever, chills, night sweats, myalgia, headache, and perhaps a non-productive cough. Usually mild and resolves spontaneously within 2 weeks. Can progress to chronic infection to include endocarditis which is associated with abnormal cardiac valves or other vascular involvement, other signs of chronic infection (fever, night sweats, weight loss, hepatosplenomegaly) (Clin Infect Dis 57:836, 2013). Positive whole blood or serum PCR or positive culture or immunohistochemistry for C. burnetii Four-fold increase in IFA phase II IgG in paired sera In prospective study of 1797 patients with acute Q fever, 48 had evidence of acute Q fever endocarditis, most identified by TTE; associated risk factors were presence of anticardiolipin antibodies and older age (Clin Infect Dis 2019; 69:1987-1995).

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- Positive whole blood or serum PCR or positive culture or immunohistochemistry for C. burnetii

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Comments

Dialister pneumosintes

Clinical Setting

- Positive lab result

- Oral flora associated with periodontal and other oral infections. Rarely intra-abdominal and soft tissue abscesses.

Classification

- Anaerobic gram-negative rod

Primary Regimens

- Amoxicillin or Piperacillin

Alternative Regimens

- Metronidazole

- Carbapenems

Comments

- Limited data on susceptibility: see Antimicrob Agents Chemother 2007; 51:4498

Ehrlichiosis: Ehrlichia sp., Anaplasma sp.

Clinical Setting

- Ehrlichiae are obligate intracellular bacteria that multiply in the cytoplasm of human and animal white blood cells

- See also, Tick-borne Illness, Overview

- Pathogenic Ehrlichia, epidemiology, and incidence of rash:

Etiologies

- Ehrlichia chaffeensis: etiology of HME

- Ehrlichia ewingii: dog variant etiology of HGE

- Anaplasma phagocytophilum: etiology of HGE

Diagnosis

- Diagnostic methods: PCR is preferred and now available from CDC, some State Public Health labs and commercial labs. Indirect fluorescent antibody assay. Need separate assays for each Ehrlichia species. Definitive diagnosis requires documentation of a 4-fold rise in antibody titer. Microscopy of peripheral blood for presence of organisms (morulae) in the cytoplasm. Present in 20-80 % of HGA and 1-20% of HME.

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- For summary of lab methods to diagnose Tick-Borne Diseases in the USA see: Clinical Chemistry. 2020; 66:537

Primary Regimens

- Adult: Doxycycline IV/po 100 mg bid x 10 days Pregnancy: see Alternative Regimens

- Pregnancy: see Alternative Regimens

- Child (wt < 45 kg): Doxycycline 2.2 mg/kg bid (max dose 100 mg) x 10 days

Alternative Regimens

- Rifampin 10 mg/kg po bid (max dose 300 mg bid) x 10 days

- Levofloxacin active in vitro but no clinical experience (Antimicrob Agents Chemother 47:413, 2003).

- Children:

- Doxycycline (wt > 45 kg) 100 mg IV/po bid x 7-10 days (wt < 45 kg) 4 mg/kg/day IV/po in two divided doses (max dose 100 mg) x 4-5 days

- Rifampin 10 mg/kg po bid (max dose 300 mg) x 7-10 days

- Pregnancy: Usually avoid Doxycycline. However, if life-threatening infection, doxycycline is probably warranted. (Expert Opinion Drug Saf 2016;15:367). Possible alternative is Rifampin

Comments

- Ciprofloxacin, Ofloxacin and Chloramphenicol are active in vitro but clinical efficacy not proven.

- Resistant to Clindamycin, TMP-SMX, Imipenem-cilastatin, Ampicillin, Erythromycin and Azithromycin (Antimicrob Agents Chemother 47:413, 2003).

- Review: JAMA 315:1767, 2016.

Enteroaggregative E. coli

Clinical Setting

- Enteroaggregative E. coli (EAEC or EaggEC) is a cause of acute diarrhea in children and adults in less-developed countries, travelers to less-developed countries and in children in developed countries. May also cause persistent diarrhea in infants

- On recent study detected EAEC frequently in Minnesota patients of all ages with acute diarrhea Clin Infect Dis 2019;69:473

- EAEC has been associated with diarrhea in HIV infected patients which may be prolonged

- Generally watery diarrhea, abdominal pain, low grade fever. Occasional mucous or blood

Diagnosis

- Gold standard is HEp-2 adherence which is not generally available. May be diagnosed by PCR detection of virulence genes aatA and aggR in some commercial and research assays.

Classification

- Enteroaggregative E. coli

Primary Regimens

- Hydration

- Ciprofloxacin 750 mg once daily x 3 days

- Ciprofloxacin 500 mg bid x 7 days used in AIDS patients with EAEC

- Rifaximin 200 mg po tid x 3 days

Alternative Regimens

- None

Antimicrobial Stewardship

- Often self limited, so antibiotics not always necessary.

- Treatment probably indicated in immunocompromised patients and prolonged illness.

- One small study showed response to antibiotics (Clin Infect Dis 29:335, 1999) and antibiotics were effective in HIV infected patients with EAEC (J Infect Dis 178:1369, 1998). Rifaximin appeared to improve duration of symptoms Clin Gastroenterol Hepatol 2004;2(2):135.

Comments

- While EAEC is consistently detected more frequently in patients with diarrhea than controls in children and adults in developing countries, travelers, and children in developed countries, EAEC can be detected in asymptomatic persons

- Molecular detection may not always correlate with symptomatic infection

- General reviews Clin Microbiol Rev 2014;27(3):614; Current Opinion Gastroenterol 25:8, 2009; Lancet Infect Dis 1:304, 2001.

- Review of persistent diarrhea, including EAEC JAMA 2016 28;315(24):2712

Eikenella corrodens

Clinical Setting

- Part of the normal flora of the human mouth.

- Potential etiology of wound infections after human bite or closed fist injury.

- One of the HACEK/HABCEK organisms that cause culture negative or hard to culture and slow growing etiologies of infective endocarditis.

Classification

- Gram negative coccobacilli, ~50% of strains pit ("corrode") agar

Primary Regimens

- Infected human bite wound:

- Amoxicillin-clavulanate: 875/125 mg tab 1 po bid

- Infective endocarditis:

- Recommendations are distillate of activity vs. Eikenella corrodens plus guideline-based suggested treatment for HACEK microorganisms.

- Ceftriaxone 2 gm IV once daily for 4 weeks

- Ampicillin-sulbactam 3 gm IV q6h for 4 weeks

Alternative Regimens

- Infected human bite wound:

- If penicillin allergic, Levofloxacin 750 mg po once daily

- Infective endocarditis:

- Ciprofloxacin 400 mg IV q12h for 4 weeks

- Ceftriaxone 2 gm IV once daily for 4 weeks

Comments

- Basis of treatment recommendations:

- Usually susceptible to penicillin but rare beta-lactamase producers are resistant; combination of a penicillin with a beta-lactamase inhibitor has near uniform in vitro susceptibility.

- Ceftriaxone active but Eikenella sp. usually resistant to cephalexin and cefazolin.

- Fluoroquinolones are active in vitro.

Elizabethkingia meningoseptica

Clinical Setting

- Isolation of Elizabethkingae meningoseptica in culture.

- Nosocomial pathogen, intrinsic resistance to multiple antibiotics.

- Associated with outbreaks of meningitis in premature newborns in neonatal ICUs.

- Rarely, nosocomial pneumonia, endocarditis meningitis and bacteremia in immunocompromised adults; soft tissue infections and bacteremia reported in immunocompetent hosts.

- Review: Clin Infect Dis 2018; 67:144

Classification

- Gram negative bacilli

Primary Regimens

- Piperacillin-tazobactam 4.5 mg q6h IV or initial dose of 4.5 gm IV over 30 minutes, followed four hours later by 3.375 gm IV (infused over 4 hours) q8h

- Ciprofloxacin 400 mg IV q12h or Levofloxacin 750 mg IV/po once daily

Alternative Regimens

- Minocycline 100 mg q12h po/IV

- TMP-SMX 8-10 mg/kg/day IV divided q6-8h

Antimicrobial Stewardship

- Choice of definitive therapy based on antimicrobial susceptibility.

- This organism and other Elizabethkingae spp. are typically resistant to cephalosporins, carbapenems, aminoglycosides, polymixins, tetracycline, chhloramphenicol (Microorganisms. 2019; 7:295; Infect Drug Resist. 2020; 13:247-256).

Comments

- Consider combination therapy in severely ill patients.

- Review: Infect Drug Resist. 2023;16:531.

Bacteria: Normal Flora, Non-pathogenic, Contaminants, Rare Pathogens

Introduction

- Rare pathogens
- Normal human flora
- Environmental contaminants
- Often non-pathogenic and of low virulence
- Present in mixed cultures

Organisms

Erysipelothrix rhusiopathiae

Clinical Setting

- Positive lab result: recovery of the organism in culture.
- Causes localized (without systemic symptoms) or diffuse (systemic symptoms present) skin lesions, bacteremia, or endocarditis.
- Zoonotic infection of fishermen, fish handlers, butchers acquired by direct animal contact, most commonly with fish, but also with other animals (e.g., swine).

Classification

- Gram-positive, pleomorphic rod non-sporulating

Primary Regimens

- Localized skin infection. Usual treatment is for 7 days.
- Penicillin VK 500 mg po qid or Amoxicillin 500 mg po tid
- Cephalexin 500mg po q6h
- Ciprofloxacin 250 mg po bid or Levofloxacin 750 mg po once daily
- Clindamycin 300 mg po q8h
- Widespread skin infection or bacteremia. Often requires 4 weeks or more of therapy.
- Penicillin G 2-4 million units IV q4h
- Ceftriaxone 2 gm IV q24h
- Imipenem-cilastatin 500 mg IV q6h (other carbapenems also active)
- Ciprofloxacin 400 mg IV q12h or Levofloxacin 750 mg IV q24h

Alternative Regimens

- None

Comments

- Resistant to Vancomycin, antipseudomonal aminoglycosides, TMP-SMX.

- Not consistently active vs macrolides, chloramphenicol and tetracyclines.

Enterococcus faecalis

Clinical Setting

- Enterococcus faecalis is less often resistant to Vancomycin than E. faecium, but is increasingly resistant to Streptomycin (MIC >2000 ug/ml) and/or Gentamicin (MIC > 500 μg/mL), in which case there is no synergy with penicillin.

- Penicillin resistance is uncommon, but when it occurs the mechanism is either: 1) production of a penicillinase (very rare) or 2) a change in the penicillin binding protein drug target (usual mechanism).

Classification

- Gram positive cocci in pairs, chains

Primary Regimens

- See Enterococcal Endocarditis for specific treatment recommendations

- Penicillin-susceptible strains

- For systemic infections: Penicillin G 3 million units IV q4h or Ampicillin 2 gm IV q4h.

- For cystitis (only): Nitrofurantoin 100 mg po q6h or Fosfomycin 3 gm po x 1 dose or Amoxicillin 1 gm po q12h

- Penicillin-resistant strains

- For systemic infections: Vancomycin 15-20 mg/kg IV q8-12h

- If isolate is beta-lactamase positive, Ampicillin-Sulbactam 3 gm IV q6h

- For cystitis: Nitrofurantoin 100 mg po bid or Fosfomycin 3 gm po x 1 dose

- Vancomycin-resistant strains (VRE)

- Consultation recommended

- For severe systemic infections (e.g., endocarditis): Daptomycin 8-12 mg/kg IV q24h + (Ampicillin 2 gm IV q4h OR Ceftriaxone 2 gm IV q12h OR Ceftaroline 600 mg IV q8h)

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- For cystitis: Nitrofurantoin 100 mg po q6h or Fosfomycin 3 gm po x 1 dose

Alternative Regimens

- VRE bacteremia: Linezolid 600 mg IV/po bid as an alternative to Daptomycin (see Comments)

Comments

- 3 meta-analyses comparing Linezolid alone to Daptomycin alone for VRE bloodstream infections suggested a survival benefit with the use of Linezolid. However, a VA cohort study of VRE bacteremia

comparing Linezolid alone vs Daptomycin alone found that Linezolid was associated with greater 30-day mortality and microbiologic failure (Clin Infect Dis 2015; 61:871). Linezolid is bacteriostatic, a theoretical disadvantage in endocarditis, and long term use carries a risk of bone marrow toxicity and neurotoxicity.

- Review of VRE: Infect Dis Clin North Am. 2016; 30:953.

- Oritavancin has in vitro activity against vancomycin-resistant enterococci (Antimicrob Agents Chemother. 2022; 66:e0166721)

Enterococcus faecium

Clinical Setting

- Enterococcus faecium is often resistant to penicillin, aminoglycosides and vancomycin (VRE). Infectious disease consultation is imperative!

- Resistance to beta-lactams is almost universal among strains of E. faecium and there is frequent concomitant resistance to aminoglycosides and vancomycin.

Classification

- Gram positive cocci in pairs, chains

Primary Regimens

- See Entercoccal Endocarditis for recommendations for treatment of this infection.

- Penicillin-susceptible strains

- For systemic infections: Penicillin G 3 million units IV q4h or Ampicillin 3-4 gm IV q6h

- For cystitis (only): Nitrofurantoin 100 mg po q6h or Fosfomycin 3 gm po x 1 dose or Amoxicillin 1 gm po q12h

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- Vancomycin-resistant strains (VRE)

- Consultation strongly recommended.

- For systemic infections, bacteremia: Daptomycin 10-12 mg/kg IV q24h + (Ampicillin 2 gm IV q4h OR Ceftaroline 600 mg IV q8h)

- Linezolid 600 mg IV/PO q12h

- For cystitis: Nitrofurantoin 100 mg po q6h or Fosfomycin 3 gm po x 1 dose

- Infections due to VRE:

- Linezolid 600 mg IV/po bid Alternative to Daptomycin for the treatment of VRE bacteremia, but data are conflicting as to which is better (Crit Care Med 2018; 46:1634 & editorial 1700)

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Alternative Regimens

- Infections due to VRE:

- Linezolid 600 mg IV/po bid Alternative to Daptomycin for the treatment of VRE bacteremia, but data are conflicting as to which is better (Crit Care Med 2018; 46:1634 & editorial 1700)

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Antimicrobial Stewardship

- Daptomycin dose > 9 mg/kg is associated with lower mortality in treatment of bacteremia due to VRE (Clin Infect Dis 2017;64:605).

- Linezolid should be used for treatment of VRE infections if the Daptomycin MIC > 4 µg/mL.

Comment

- Best to use daptomycin in combination therapy. Concomitant beta-lactam impedes development of resistance and can reverse resistance if daptomycin resistance is already evident.

- Oritavancin has in vitro activity against vancomycin-resistant enterococci (Antimicrob Agents Chemother. 2022; 66:e0166721).

- For review of VRE treatment: Infect Dis Clin North Am 2016 Jun;30(2):415-43.

- Quinupristin-dalfopristin was an alternative for VRE, but the drug has been discontinued by the manufacturer and is no longer available.

Escherichia coli

Clinical Setting

- Escherichia coli causes a variety of infections ranging from uncomplicated urinary tract infections to life-threatening infections of the abdomen, skin and soft tissue, lung, CNS and other sites in both normal and immunocompromised hosts.

- Suggested treatment regimens are for parenteral therapy of more serious infections and based on status of pathogen detection and results of in vitro susceptibility. The clinical settings: Empiric therapy: Pathogen detected but in vitro susceptibility pending/unavailable Specific therapy: Pathogen detected and in vitro susceptibility reported For detailed discussion of beta-lactam drug resistance classes and mechanisms Gram Negative Bacilli, Resistance to Beta-lactams, Overview.

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- Specific therapy: Pathogen detected and in vitro susceptibility reported

- For detailed discussion of beta-lactam drug resistance classes and mechanisms Gram Negative Bacilli, Resistance to Beta-lactams, Overview.

- For treatment of uncomplicated urinary tract infections, see Cystitis (adult female) or Cystitis (adult male)

- See Comments for selected drug details, emerging data, literature citations and more

Classification

- E. coli, susceptible and antibiotic-resistant strains

Primary Regimens

- Treatment options below are for therapy of moderately-severe, or severe infections in patients requiring systemic therapy

Alternative Regimens

- ESBL-negative strain and susceptibility confirmed to the specific agent Cefazolin 2 gm IV q8h TMP-SMX administered as 10 mg/kg/d of TMP component in 2-3 divided doses Amoxicillin-clavulanate 1.2-2.4 gm IV q8h (where available; not available in US) Ampicillin-sulbactam 3 gm IV q6h (Gentamicin or Tobramycin) 5-7 mg/kg q24h, dose adjusted for renal function

- Cefazolin 2 gm IV q8h

- TMP-SMX administered as 10 mg/kg/d of TMP component in 2-3 divided doses

- Amoxicillin-clavulanate 1.2-2.4 gm IV q8h (where available; not available in US)

- Ampicillin-sulbactam 3 gm IV q6h

- (Gentamicin or Tobramycin) 5-7 mg/kg q24h, dose adjusted for renal function

- Other alternatives for ESBL-positive strains: Ceftolozane-tazobactam 1.5 gm IV q8h Cefepime-enmetazobactam recently FDA approved for treatment of complicated UTIs Ceftazidime-avibactam 2.5 gm IV over 2 hrs q8h Temocillin 2 gm IV q12h (available in Belgium and United Kingdom but not the US) (Gentamicin or Tobramycin) 5-7 mg/kg q24h, if susceptible Plazomicin 15 mg/kg once daily x 4-7 days (if available)(FDA-approved for complicated UTI only) For UTI, another option: Cystitis: Fosfomycin 3 gm po x one dose Pyelonephritis and where IV formulation is available: Fosfomycin 6 gm IV q8h NOTE: Piperacillin-tazobactam is not recommended due to treatment failures perhaps due to inoculum effect

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- Cefepime-enmetazobactam recently FDA approved for treatment of complicated UTIs

- Ceftazidime-avibactam 2.5 gm IV over 2 hrs q8h

- Temocillin 2 gm IV q12h (available in Belgium and United Kingdom but not the US)

- (Gentamicin or Tobramycin) 5-7 mg/kg q24h, if susceptible

- Plazomicin 15 mg/kg once daily x 4-7 days (if available)(FDA-approved for complicated UTI only)

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- Pyelonephritis and where IV formulation is available: Fosfomycin 6 gm IV q8h

- NOTE: Piperacillin-tazobactam is not recommended due to treatment failures perhaps due to inoculum effect

- Carbapenemase resistant strain, suspected metallo-beta-lactamase phenotype (resistant to Ceftazidime-avibactam and Meropenem-vaborbactam) Infectious Diseases consultation recommended Plazomicin 15 mg/kg once daily x 4-7 days (if available)(FDA-approved for complicated UTI only) Ceftazidime-avibactam 2.5 gm IV over 3 hrs q8h + Aztreonam 2 gm IV over 3 hrs q6h. A last resort recommendation based entirely on in vitro data and case reports: Antimicrob Agents Chemother 2017 Mar 24;61(4). pii: e02243-16) Based on the resistance of aztreonam to hydrolysis by metallo-beta-lactamases; use the ceftazidime-avibactam to protect the aztreonam from hydrolysis by concomitant ESBLs. See J Antimicrob Chemother 2018; 73:1104. Meropenem-vaborbactam 4 gm IV

infused over 3h q8h + Aztreonam 2 gm IV over 3 hrs q8h. Similar in vitro activity to aztreonam plus ceftazidime-avibactam against Enterobactales producing NDM and other non-OXA serine β-lactamases but no clinical data (Antimicrob Agents Chemother 2019; 63: e01426-19). Cefiderocol 2 gm IV over 3 hrs q8h (see Comments)

- Infectious Diseases consultation recommended

- Plazomicin 15 mg/kg once daily x 4-7 days (if available)(FDA-approved for complicated UTI only)

- Ceftazidime-avibactam 2.5 gm IV over 3 hrs q8h + Aztreonam 2 gm IV over 3 hrs q6h. A last resort recommendation based entirely on in vitro data and case reports: Antimicrob Agents Chemother 2017 Mar 24;61(4). pii: e02243-16) Based on the resistance of aztreonam to hydrolysis by metallo-beta-lactamases; use the ceftazidime-avibactam to protect the aztreonam from hydrolysis by concomitant ESBLs. See J Antimicrob Chemother 2018; 73:1104.

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- Cefiderocol 2 gm IV over 3 hrs q8h (see Comments)

Antimicrobial Stewardship

- Carbapenems should be reserved for polymicrobial infections for which anaerobic coverage is required or for treatment of infections due to ESBL-producing strains

- Although active against ESBLs and related beta-lactamases, use of Ceftazidime-avibactam, Imipenem-relebactam, and Meropenem-vaborbactam should be reserved for patients with documented carbapenemase mechanism of resistance.

Comments

- Aztreonam is not hydrolyzed by metallocarbapenemases (ceftazidime is) but is inactivated by ESBLS which are often produced concomitantly with the carbapenemase. Avibactam inactivates ESBLs. See Antimicrob Agents Chemother 2017 Mar 24; 61(4). pii:e02243-16

- Cefiderocol: FDA-approved for patients with complicated UTI due to cefiderocol susceptible bacteria and with limited or no alternative treatment options. In an open label randomized trial of cefiderocol vs Best Available Therapy (BAT) in patients with sepsis, pneumoinia, bacteremia or cUTI, mortality at 28 days was 24.8% for cefiderocol pts. vs 18.4% for BAT pts (not statistically significant). Reference: Clin Infect Dis 2019; 69 (suppl.7): S519-S575

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- Reference: Clin Infect Dis 2019; 69 (suppl.7): S519-S575

- If Ertapenem resistance, check for susceptibility to Meropenem or Imipenem; if the isolate is susceptible to both of the latter either may be used.

- Combination of Meropenem + Polymyxin (either Polymyxin B or Colistin) for therapy of MDR gram-negative bacillii is not recommended based on treatment failures in controlled clinical trial : Failures occurred in a randomized controlled trial (Lancet Infect Dis 2018 ; 18:391): 77% of enrolled patients had infections due to Acinetobacter baumannii Study was underpowered to assess comparative efficacy vs other carbapenemase producing gram-negative bacteria.

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- Suspected metall0-beta-lactamase producer: Meropenem-vaborbactam 4 gm IV infused over 3h q8h + Aztreonam 2 gm IV over 3 hrs q8h. Similar in vitro activity to aztreonam plus ceftazidime-avibactam against Enterobacterales producing NDM and other non-OXA serine β-lactamases but no clinical data (Antimicrob Agents Chemother 2019; 63: e01426-19).

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- Plazomicin FDA approved for the treatment of complicated UTI and pyelonephritis (N Engl J Med 2019;380:729); Limited observational experience with Plazomicin in combination with Tigecycline or Meropenem for treatment of MDR bloodstream infections or hospital-acquired or ventilator-associated pneumonia (N Engl J Med 2019; 380:791).

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- Limited observational experience with Plazomicin in combination with Tigecycline or Meropenem for treatment of MDR bloodstream infections or hospital-acquired or ventilator-associated pneumonia (N Engl J Med 2019; 380:791).

- Investigative agents in late clinical development with activity vs MDR gram-negative bacilli Aztreonam-avibactam

- Aztreonam-avibactam

- IDSA Guideline on treatment of ESBL, AmpC, and carbapenemase producers: Clin Infect Dis. 2023 Jul 18:ciad428.

Francisella tularensis, Tularemia

Clinical Setting

- Francisella tularensis causes a variety of infections as a consequence of:

- Direct contact with infected tissues of infected animals (hunters, farmers, veterinarians, landscapers, and meat handlers)

- Inhalation of infected aerosol (hazard to clinical microbiologists)

- Exposure to an infected biting insect (ticks, mosquitoes, deer and horse flies, and fleas)

- Tularemia: Clinical illness can vary from asymptomatic to septic shock and death; in aerosol form, a potential agent of bioterrorism.

- F. tularensis can cause one or more of several clinical syndromes:

- Ulceroglandular

- Oculoglandular

- Glandular

- Pharyngeal (oropharyngeal)

- Pneumonic: Infect Dis Clin North Am 24:43, 2010

- Typhoidal (fever and hypotension)

- Meningtis

- For complications, see Comments.

- Tularemia: CDC-sponsored review: Clin Infect Dis 2024; 78:S1

Diagnosis

- Laboratory diagnosis is difficult: Rarely see on gram-stain; fastidious, may need special media, notify lab for both the special media and to prevent infection of lab technologists Four-fold rise in antibody confirms diagnosis but not timely for clinical use PCR best; check for availability with commercial and State Public Health Dept. Labs

- Rarely see on gram-stain; fastidious, may need special media, notify lab for both the special media and to prevent infection of lab technologists

- Four-fold rise in antibody confirms diagnosis but not timely for clinical use

- PCR best; check for availability with commercial and State Public Health Dept. Labs

Classification

- Gram-negative coccobacilli

Primary Regimens

- Ciprofloxacin Adult: 400 mg IV q12h (or 750 mg po) bid x 14-21 days Children: 20-40 mg/kg/day po (max 1.5 gm/day) divided bid (child) Treat for 14-21 days NOTE: Levofloxacin should work but only limited observational data

- Adult: 400 mg IV q12h (or 750 mg po) bid x 14-21 days

- Children: 20-40 mg/kg/day po (max 1.5 gm/day) divided bid (child) Treat for 14-21 days

- NOTE: Levofloxacin should work but only limited observational data

- IF Critically ill and not responding to monotherapy with ciprofloxacin, reasonable to add an aminoglycoside: Gentamicin or Tobramycin 5.1 mg/kg/day IV divided q8h or Streptomycin 10 mg/kg IV q12h Adult: Treat for 10 days Child: Treat for 5-7 days

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- Child: Treat for 5-7 days

- Meningitis is a rare complication: Reported empiric therapy Aminoglycoside + Doxycycline 100 mg IV/po bid (adult) / 4 mg/kg/d divided q12h IV/po (max dose 200 mg/day)(child) Aminoglycoside

+ Ciprofloxacin 400 mg IV (or 750 mg po) q12h (adult) / 20-40 mg/kg/day po (max 1.5 gm/day) divided bid (child) Treat for 14-21 days

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- Aminoglycoside + Doxycycline 100 mg IV/po bid (adult) / 4 mg/kg/d divided q12h IV/po (max dose 200 mg/day)(child)

- Aminoglycoside + Ciprofloxacin 400 mg IV (or 750 mg po) q12h (adult) / 20-40 mg/kg/day po (max 1.5 gm/day) divided bid (child)

- Treat for 14-21 days

Alternative Regimens

- Less severe illness: Adult: Doxycycline 100 mg IV/po bid x 14-21 days OR Ciprofloxacin 400 mg IV q12h (or 750 mg po) bid x 14-21 days Child: Ciprofloxacin 20-40 mg/kg/day po (max 1.5 gm/day) divided bid x 10-14 days

- Adult: Doxycycline 100 mg IV/po bid x 14-21 days OR Ciprofloxacin 400 mg IV q12h (or 750 mg po) bid x 14-21 days

- Child: Ciprofloxacin 20-40 mg/kg/day po (max 1.5 gm/day) divided bid x 10-14 days

- Pregnancy: treatment recommendation is uncertain, but suggest Streptomycin or Chloramphenicol: 15 mg/kg qid for at least 14 days

- Prophylaxis for aerosol exposures (not for natural exposures): Doxycycline 100 mg po bid x 14 days or Ciprofloxacin 500 mg po bid x 14 days

Comments

- There are no controlled clinical trials: Suggested therapy is based on combination of in vitro activity, infected animal models, and systematic reviews of observational data. Monotherapy reported effective for mild illness and outpatient therapy; Hospital patients may need combination therapy. Recommended therapies are Fluoroquinolones, Aminoclycosides, and Doxycycline as monotherapy or, for severe illness, combination therapy. Beta-lactam antibiotics are not efficacious. Doxycycline and Chloramphenicol are bacteriostatic, may result in relapses.

- Suggested therapy is based on combination of in vitro activity, infected animal models, and systematic reviews of observational data.

- Monotherapy reported effective for mild illness and outpatient therapy; Hospital patients may need combination therapy.

- Recommended therapies are Fluoroquinolones, Aminoclycosides, and Doxycycline as monotherapy or, for severe illness, combination therapy.

- Beta-lactam antibiotics are not efficacious.

- Doxycycline and Chloramphenicol are bacteriostatic, may result in relapses.

- Large variety of potential complications:

- Suppuration of infected lymph nodes

- Acute renal injury

- Rhabdomyolysis

- Hepatitis

- Empyema

- Others: pericarditis, meningitis, osteomyelitis, prosthetic joint infection, and even endocarditis.

- Tularemia bioterrorism reference: N Engl J Med 372:954, 2015.

Fusobacterium necrophorum

Clinical Setting

Classification

- Gram negative bacillus, anaerobic

Primary Regimens

- Often need surgical drainage and debridement

- Metronidazole 500 mg IV/po q8h + Ceftriaxone 2 gm IV once daily

- Piperacillin-tazobactam 3.375 gm IV over 30 minutes and then starting 4 hrs later 3.375 gm iv over 4 hrs and repeat q8h

Alternative Regimens

- Imipenem-cilastatin 500 mg IV q6h or Meropenem 0.5-1.0 gm IV q8h

- Clindamycin 600-900 mg IV q8h

Comments

- Fusobacterium sp. are part of normal flora of mouth (primarily), GI tract, female GU tract. Found (often with other mouth flora) in dental abscesses, peritonsillar abscesses and other forms of oro-pharyngeal sepsis. Striking propensity (usually as complication of peritonsillar abscess) to cause septic jugular thrombosis with bacteremia and metastatic abscesses (Lemierre's syndrome) (Lancet Infect Dis 12:808, 2012). 4-23% produce β-lactamase (Ped Infect Dis J 12:532, 1993).

- Found (often with other mouth flora) in dental abscesses, peritonsillar abscesses and other forms of oro-pharyngeal sepsis.

- Striking propensity (usually as complication of peritonsillar abscess) to cause septic jugular thrombosis with bacteremia and metastatic abscesses (Lemierre's syndrome) (Lancet Infect Dis 12:808, 2012).

- 4-23% produce β-lactamase (Ped Infect Dis J 12:532, 1993).

- Pharyngitis/tonsillitis: in one study, infection with F. necrophorum was twice as common as Group A strep.; clinically resembles streptococcal pharyngitis (Ann Intern Med 162:241, 2015). Detected by PCR but, at present, no commercial assay available Like GpA streptococcus, can be present in asymptomatic carriage state Re: potential role as a pathogen, see Ann Intern Med 162:876, 2015; PLoS ONE 13:e0189423. 2018; J Clin Micro 2017;55:1147

- Detected by PCR but, at present, no commercial assay available

- Like GpA streptococcus, can be present in asymptomatic carriage state

- Re: potential role as a pathogen, see Ann Intern Med 162:876, 2015; PLoS ONE 13:e0189423. 2018; J Clin Micro 2017;55:1147

- Treatment for patient with severe IgE mediated anaphylaxis to beta-lactams: metronidazole OR clindamycin; in vitro resistance to either is very rare (Perry, M et al. Anaerobe.2023 Apr; 80: 102717)

- Review: Anaerobe 2016; 42:89

Fusobacterium nucleatum

Clinical Setting

- Positive lab result

- Oral and gastrointestinal flora. Rare cause of liver and other abscesses. Often polymicrobial; linked to gastrointestinal cancers.

Classification

- Anaerobic gram-negative rod

Primary Regimens

- Typically susceptible to Penicillin, Clindamycin, Metronidazole

Alternative Regimens

- A carbapenem

Comments

- See Eur J Clin Microbiol Infect Dis. 2024;43:423 for typical antimicrobial susceptibilities.

Gardnerella vaginalis

Clinical Setting

- Sexually active female (typically) with complaints of malodorous vaginal discharge (see bacterial vaginosis).

- Mild to moderate grayish vaginal discharge with a fishy odor. pH >4.5

- Absence of vaginal inflammation on exam.

- Itching and irritation are minimal or absent.

- Wet mount of vaginal discharge shows "clue" cells, vaginal epithelial cells with numerous adherent coccobacilli; presence of numerous polys suggestive of coexisting infection.

Classification

- Gram variable coccobacilli, facultative anaerobe

Primary Regimens

- Metronidazole 0.5 gm po bid x 7 days (Do NOT use 2 gm po x one dose)

- Metronidazole 0.75% gel one full applicator (5 gm) intravaginally daily x 5 days

- Clindamycin 2% cream one full applicator (5 gm) intravaginally at bedtime x 7 days

Alternative Regimens

- Tinidazole 2 gm po once daily x 2 days

- Tinidazole 1 gm po once daily x 5 days (see Bacterial vaginosis)

- Clindamycin 300 mg po bid x 7 days (see Bacterial vaginosis)

- Clindamycin ovules 100 mg intravaginally once at bedtime x 3 days

- Ovules use an oleaginous base that might weaken latex or rubber products (e.g., condoms and vaginal contraceptive diaphragms).

Comments

- 50% of asymptomatic sexually active women harbor G. vaginalis

- G. vaginalis, although associated with bacterial vaginosis, does not by itself cause this infection, which is a synergistic infection with other microorganisms, including Mobiluncus spp.

- CDC STD Guidelines:MMWR 70 (RR-4); 1, 2021

Gemella mobillorum

Clinical Setting

- Positive lab result

- Oral flora. Cause of endocarditis, abscesses

Classification

- Catalase-negative facultative anaerobic gram-positive coccus

Primary Regimens

- (Penicillin or Ampicillin or Ceftriaxone) + Gentamicin (addition of Gentamicin recommended for treatment of infective endocarditis but no proven benefit over monotherapy (Anaerobe. 2022; 75:102573) OR

- Vancomycin

- See Endocarditis, Streptococcal

Alternative Regimens

- None

Comments

- Formerly considered as a viridans group streptococcus

- See Antibiotics. 2023;12:1538 and for typical antimicrobial susceptibilities

Gram Negative Bacilli, Resistance to Beta-lactams, Overview

Overview

- See Antibacterial Drug Resistance Genotypes

- Guidelines from IDSA for treatment of AmpC beta-lactamases Treatment of ESBL producing enterobacterales, carbapenem-resistant enterobacterales, and resistant Pseudomonas aeruginosa. Clin Infect Dis 2022;75:1887 Treatment of Amp C beta-lactamase-positive positive enterobacterales, carbapenem-resistant Acinetobacter baumannii, and Stenotrophomonas maltophilia infections. IDSA Guideline: Clin Infect Dis 2022; 74:2089.

- Treatment of ESBL producing enterobacterales, carbapenem-resistant enterobacterales, and resistant Pseudomonas aeruginosa. Clin Infect Dis 2022;75:1887

- Treatment of Amp C beta-lactamase-positive positive enterobacterales, carbapenem-resistant Acinetobacter baumannii, and Stenotrophomonas maltophilia infections. IDSA Guideline: Clin Infect Dis 2022; 74:2089.

- Note: Treatment options below are for therapy of moderately-severe, or severe infections in patients requiring systemic therapy

- Mechanisms of resistance to beta-lactams, i.e., penicillins, cephalosporins, monobactam (aztreonam) and carbapenems, can occur via several mechanisms, often present in combination: Production of beta-lactamases that hydrolyze the beta-lactam ring Decreased permeability of the bacterial cell wall (e.g., porin protein mutations) Drug efflux pumps Modified penicillin binding protein targets

- Production of beta-lactamases that hydrolyze the beta-lactam ring

- Decreased permeability of the bacterial cell wall (e.g., porin protein mutations)

- Drug efflux pumps

- Modified penicillin binding protein targets

- Concomitant resistance to fluoroquinolones, tetracyclines, trimethoprim-sulfamethoxazole and aminoglycosides is commonly associated with resistance to beta-lactams

- Beta-lactamases are divided into four Ambler classes based on their amino acid homology. See Antibacterial Drug Resistance Genotypes. Reference: Cold Spring Harb Perspect Med 2017 Jan 3;7(1). pii: a025239 Class A beta-lactamases: narrow spectrum penicillinases and extended spectrum beta-lactamases (ESBLs) and serine carbapenemases (KPCs, Klebsiella pneumoniae carbapenemases) that hydrolyze selected advanced generation cephalosporins and carbapenems, respectively ESBLs (Curr Opin Infect Dis. 2020;33:78) Confer resistance to advanced generation cephalosporins (e.g., ceftriaxone, ceftazidime, cefepime) and aztreonam Carbapenems, meropenem, imipenem-cilastatin, ertapenem are uneffected by ESBLs and are treatment options Serine carbapenemases Confer resistance to all beta-lactams Treatment options Ceftazidime-avibactam, Meropenem-vaborbactam, and Imipenem-cilastatin-relebactam (which owe their activity to their respective companion beta-lactamase inhibitors that inhibit KPCs and ESBLs). Non-beta-lactam options: Plazomicin (Clin Infect Dis 2020; 70:704) Fosfomycin Eravacycline/Omadacycline (active in vitro; limited clinical data) Polymyxin B (or Polymyxin E for UTIs only). Infectious Diseases consultation recommended Class B: metallo-beta-lactamases, zinc metallo-enzymes, e.g., New Dehli Metallo, VIM-1, IMP-1 Hydrolyze all penicillins, cephalosporins, and carbapenems, but not Aztreonam. However, since most metallo-beta-lactamase producing strains also produce ESBLs, aztreonam, which is inactivated by ESBLs, is not active against the vast majority of these strains. Aztreonam in

combination Ceftazidime-avibactam may be active because the avibactam inactivates the ESBL and other serine carbapenemases, and thereby protecting the antibacterial activity of the aztreonam Treatment options Aztreonam + Ceftazidime-avibactam Aztreonam in combination Meropenem-vaborbactam also may be active in vitro by similar mechanisms, but efficacy data are lacking Cefiderocol (Clin Infect Dis 2019; 69 (suppl 7): S519 ; Clin Infect Dis 2022; 75: 1981 and editorial 2022; 75:1085) Polymyxin B (in combination therapy) for non- UTI; Polymyxin E (Colistin) for UTI only If susceptible, an aminoglycoside (e.g. Plazomicin has variable activity) If susceptible, Fosfomycin Often susceptible in vitro to Eravacycline and Omadacycline; little clinical data Infectious Diseases consultation recommended Class C: AmpC beta-lactamase (Clin Infect Dis 2019;69:1446). When expressed confers resistance to ceftriaxone and ceftazidime especially in Enterobacter cloacae, Klebsiella aerogenes and Citrobacter freundii. Avoid empiric cephalosporins (Ceftriaxone, Cefotaxime, Ceftazidime) therapy for latter three organisms even if initial in vitro susceptibility testing indicates susceptibility. Treatment options: Meropenem or Ertapenem, Cefepime (dose-dependent) Fluoroquinolone (if susceptible), Ceftolozane-tazobactam Class D: oxacillinases (e.g., OXA-23-like, OXA-48, OXA-48-like, OXA-58, others) A large heterogeneous group of beta-lactamase enzymes, which are often accompanied by other beta-lactamase classes (e.g., co-express ESBLs and AmpC) Of most concern are Enterobacterales, mainly Klebsiella species, that are plasmid based, endemic in Turkey and Middle East with increasing reports from the US. OXA-48 and OXA-48-like: Hydrolyze penicillins efficiently, carbapenems slowly, and extended cephalosporins poorly OXA-48 and some others are inactivated by avibactam (e.g., ceftazidime-avibactam); In contrast vaborbactam and relebactam are poor inhibitors of OXA-48 and other OXA enzymes and Meropenem-vaborbactam and Imipenem-relebactam have unreliable activity (Antimicrob Agents Chemother. 2017; 61: e01443-17; Antimicrob Agents Chemother 2019; 63: e00029-19) Treatment options are extremely limited (Antimicrob Agts Chemother 2018;62: e01195-18) High likelihood that Ceftazidime-avibactam will have in vitro activity against OXA-48 producers (Clin Infect Dis 2019; 68:519). Cefiderocol Fosfomycin and Eravacycline often active in vitro Polymyxin B (or Polymyxin E for UTIs only) Infectious Diseases consultation recommended

- Class A beta-lactamases: narrow spectrum penicillinases and extended spectrum beta-lactamases (ESBLs) and serine carbapenemases (KPCs, Klebsiella pneumoniae carbapenemases) that hydrolyze selected advanced generation cephalosporins and carbapenems, respectively ESBLs (Curr Opin Infect Dis. 2020;33:78) Confer resistance to advanced generation cephalosporins (e.g., ceftriaxone, ceftazidime, cefepime) and aztreonam Carbapenems, meropenem, imipenem-cilastatin, ertapenem are uneffected by ESBLs and are treatment options Serine carbapenemases Confer resistance to all beta-lactams Treatment options Ceftazidime-avibactam, Meropenem-vaborbactam, and Imipenem-cilastatin-relebactam (which owe their activity to their respective companion beta-lactamase inhibitors that inhibit KPCs and ESBLs). Non-beta-lactam options: Plazomicin (Clin Infect Dis 2020; 70:704) Fosfomycin Eravacycline/Omadacycline (active in vitro; limited clinical data) Polymyxin B (or Polymyxin E for UTIs only). Infectious Diseases consultation recommended

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- Cefiderocol

- Fosfomycin and Eravacycline often active in vitro

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- Infectious Diseases consultation recommended

- Pan-resistant to multiple antibiotic classes in addition to beta-lactams in Enterobacterales, P. aeruginosa, and Acinetobacter sp. Treatment options limited: Infectious Diseases consultation necessary Cefiderocol has a broad range of in vitro antibacterial activity, including carbapenemase-producing strains and is FDA-approved for complicated UTI in patients with limited or no alternative treatment option However, in randomized open label study of cefiderocol vs best available therapy (BAT) for pneumonia, bloodstream infection/sepsis or complicated UTI due to carbapenemase-producing bacteria, all cause mortality in the Cefiderocol-treated patients at 14 days, 28 days, and end of study was higher, 19/101 (18.8%), 25/101 (24.8%), and 34/101 (33.7%), respectively versus 6/49 (12.2%), 9/49 (18.4%), and 9/49 (18.4%) for BAT-treated patients, although these differences are not statistically significant. Investigational drugs in late stage development: Aztreonam-avibactam Review of carbapenemase-producing organisms (Current infect Dis Rep 2020; 22:6; Clin Micro Rev 2020; 33: e001181-19) Summary of phenotypic methods to detect carbapenemase-producing bacteria (J Clin Micro 2018; 56:e01140-18).

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Links to Organisms

- Acinetobacter sp.

- Citrobacter sp.

- Enterobacter sp.

- Escherichia coli

- Klebsiella sp.

- Morganella morganii

- Proteus sp.

- Providencia sp.

- Pseudomonas aeruginosa

- Serratia marcescens

- Stenotrophomonas maltophilia

Bacteria: Normal Flora, Non-pathogenic, Contaminants, Rare Pathogens

Introduction

- Rare pathogens

- Normal human flora

- Environmental contaminants

- Often non-pathogenic and of low virulence

- Present in mixed cultures

Organisms

Haemophilus ducreyi (Chancroid)

Clinical Setting

- Cause of Chancroid, an infection characterized by a painful genital ulcer with ragged edges and associated inguinal adenopathy.

- Higher prevalence in developing countries. Associated with contact with sex workers. Cause of sporadic outbreaks in US, Western Europe.

- Overall incidence declining. Curr Opin Infect Dis 29:52, 2016

- Now recognized as a cause of skin ulcers in children Emerg Infect Dis. 2016 Jan;22(1):1-8

Diagnosis

- Require special growth medium.

- Positive PCR assay (not FDA approved but available in some clinical labs).

- Diagnosis often empiric after excluding other causes of genital ulcers.

Classification

- Gram negative coccobacilli

Primary Regimens

- Azithromycin 1 gm single dose

- Ceftriaxone 250 mg IM single dose

Alternative Regimens

- Erythromycin 500 mg tid x 7 days

- Ciprofloxacin 500 mg bid x 3 days

Comments

- Most strains are resistant to Tetracycline, Amoxicillin, TMP-SMX.

- Intermediate resistance to Ciprofloxacin or Erythromycin reported.

- Relatively little high quality data as to most efficacious treatment (Cochrane Database Syst Rev 2017 12:CD012492).

- CDC 2021 STD Guidelines: MMWR Recomm Rep 70 (RR-4):1 2021

Haemophilus influenzae

Clinical Setting

- Isolation of Haemophilus influenzae in culture of CSF, blood, sputum, respiratory tract secretions or tissue.

- Encapsulated type B strains (HiB), as well as other typable strains A, C, E, F, typically cause more invasive disease, but HiB preventable by vaccination.

- Nontypeable strains cause most disease in adults and vaccinated children.

Classification

- Gram negative coccobacilli

Primary Regimens

- Empiric therapy should cover for β-lactamase positive strains until susceptibility is confirmed

- Meningitis, epiglottitis, other life-threatening illness (in Adults):

- Ceftriaxone 2 gm IV q12h

- Cefotaxime 2 gm IV q4-6h (where available outside the US)

- Pediatric Ceftriaxone 100 mg/kg/day div q12h

- Non life-threatening illness (in Adults):

- Amoxicillin-clavulanate 875/125 mg tab 1 po bid

- Cefprozil 500 mg po q12h

- Cefuroxime axetil 500 mg po q12h

- Cefdinir 600 mg po q24h

- See Antimicrobial Stewardship for duration of therapy

- Confirmed β-lactamase negative non life-threatening: Ampicillin 2 gm IV q6h Amoxicillin 1 gm po q8h

- Ampicillin 2 gm IV q6h

- Amoxicillin 1 gm po q8h

Alternative Regimens

- Levofloxacin 750 mg IV/po once daily

- Moxifloxacin 400 mg IV/po once daily

- Clarithromycin 500 mg po bid or Azithromycin 500 mg po x 1 dose and then next day 250 mg po once daily

- Doxycycline 100 mg po bid

Antimicrobial Stewardship (pneumonia, sinusitis)

- Duration of therapy: 5-7 days (N Engl J Med 370:543, 2014)

- Patient can be switched to po therapy when improving clinically and able to take oral medications.

- Antibiotics can be safely discontinued after 5 days in patients who are afebrile for 48 hours or more and have no more than one of the following (JAMA Intern Med 2016;176:1257): Systolic BP < 90 mm Hg Heart rate > 100/min Respiratory rate > 24/min Arterial oxygen saturation < 90% or room-air PaO_2 less than 60 mm Hg

- Systolic BP < 90 mm Hg

- Heart rate > 100/min

- Respiratory rate > 24/min

- Arterial oxygen saturation < 90% or room-air PaO2 less than 60 mm Hg

Prevention

- Ampicillin 100 mg/kg IV q4-6h or Amoxicillin 500 mg po tid are alternatives if the organism is susceptible.

- Up to 40% of nontypeable strains are Ampicillin-resistant beta-lactamase producing strains.

- TMP-SMX resistance in up to 25% of strains U.S.

- Reference: StatPearls;Jan 2023.

Comments

- Ampicillin 100 mg/kg IV q4-6h or Amoxicillin 500 mg po tid are alternatives if the organism is susceptible.

- Up to 40% of nontypeable strains are Ampicillin-resistant beta-lactamase producing strains.

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Helicobacter cinaedi

Clinical Setting

- Cause of recurrent multifocal cellulitis, osteomyelitis, bacteremia primarily in immunocompromised individuals (esp HIV or hematological malignancies)

- Bacteremia may be recurrent

- Infections of aortic aneurysms described

- Also associated with diarrhea or proctitis in MSM

- Chemotherapy, steroids thought to be independent risk factors.

- Can have asymptomatic colonization of the colon; disease due to translocation across the bowel.

- Cultures may require prolonged incubation

Classification

- Gram negative spiral bacterium

- Formerly considered member of Campylobacter sp.

Primary Regimens

- Carbapenems including Meropenem

- Aminoglycosides

Alternative Regimens

- None

Antimicrobial Stewardship

- Duration of therapy: May need to treat 14 days as recurrent bacteremia described with <10 days rx (Helicobacter 25:e12675. 2020)

- Typically intermediate beta lactam susceptibilities

- Fluoroquinolone and macrolide resistant

Comments

- References: Helicobacter Suppl 1:e12744.2020; Helicobacter 25:e12675. 2020

Helicobacter pylori

Clinical Setting

- Humans only natural host Common infection (>50% world-wide, 20-40% US) Often asymptomatic but majority will have chronic active gastritis

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- Often asymptomatic but majority will have chronic active gastritis

- Testing for Helicobacter pylori infection should be performed for patients with any of the following: Active peptic ulcer disease (duodenal or gastric) Past history of peptic ulcer disease (not previously treated for H. pylori) Atrophic gastritis Gastric mucosa-associated lymphoid tissue (MALT) lymphoma Following endoscopic resection of early gastric cancer idiopathic thrombocytic purpura (ITP) Age < 55 years and un-investigated dyspepsia, low suspicion for malignancy

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- Past history of peptic ulcer disease (not previously treated for H. pylori)

- Atrophic gastritis

- Gastric mucosa-associated lymphoid tissue (MALT) lymphoma

- Following endoscopic resection of early gastric cancer

- idiopathic thrombocytic purpura (ITP)

- Age < 55 years and un-investigated dyspepsia, low suspicion for malignancy

Classification

- Gram negative bacteria (curved or helical)

Primary Regimens

- See Gastric/Duodenal Ulcer

Alternative Regimens

- See Gastric/Duodenal Ulcer

Antibiotic Stewardship

- Susceptibility testing should be performed where available. PCR typing of clarithromycin resistance now available in some centers; J Clin Micro.59:e03040 2021.

- Emerging resistance (especially to macrolides), contributes to treatment failures.

- Treatment regimens should be guided by prior history of antibiotic usage (AGA guidelines: Am J Gastroenterol 112:212 2017; Maastricht Consensus Report Gut 66:6 2017; Toronto Guidelines Gastroenterology 151:51, 2016)

- Triple therapy recommended only in regions where resistance rate <15%.

Comments

- Response rates with primary regimens in the range of 70-85% with response falling due to increasing resistance, especially to macrolides (Antimicrob Agents Chemother 2017 Mar 24;61(4). pii: e02530-16. doi: 10.1128/AAC.02530-16).

- Review of comparative effectiveness and tolerance of many treatment options: Med Lett 2017;59:113. Am J Gastroenterol 112:212 2017; Gut 66:6 2017; Gastroenterology 151:51, 2016

- Movement from triple therapy to quadruple therapy with sequential therapy no longer recommended (AGA guidelines: Am J Gastroenterol 112:212 2017; Maastricht Consensus Report Gut 66:6 2017; Toronto Guidelines Gastroenterology 151:51, 2016)

- Recent PPI, H2 Receptor blockers, Antibiotics, Bismuth, Bleeding may interfere with H. pylori testing

- Test for cure 4-8 weeks after completion of therapy.

Enterobacter cloacae complex

Clinical Setting

- Enterobacter cloacae complex causes a variety of infections in both normal and immunocompromised hosts.

- Enterobacter species carry the ampC cephalosporinase gene in one of two forms: ampC chromosomal gene (carried by virtually all isolates) Inducible and normally repressed such that ampC gene may not be detected by routine in vitro antibiotic susceptibility testing AmpC is not inhibited by beta-lactam beta-lactamase inhibitors, clavulanate, sulbactam, tazobactam; it is inhibited by avibactam. Exposure to a 3rd-generation cephalsporins can select for de-repressed mutants that over-express AmpC, with emergence of resistance during therapy in 5-20% of treatment courses, greatest risk in patients with a large burden of organisms, e.g., bacteremia and/or pneumonia; avoid Ceftriaxone, Cefotaxime, and Ceftazidime for treatment of infections caused by this species even if in vitro testing indicates susceptible. Plasmid AmpC gene (Rare) Constitutive, high-level production of AmpC Resistance is evident in initial in vitro susceptibility testing Primer on AmpC beta-lactamases: Clin Infect Dis 2019;69:1446

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- Resistance is evident in initial in vitro susceptibility testing

- Primer on AmpC beta-lactamases: Clin Infect Dis 2019;69:1446

- Enterobacter spp. can be multi-drug resistant (MDR) due to other mechanisms: Plasmid-encoded genes that confer resistance to carbapenems, aminoglycosides and fluoroquinolones ESBLs detected by broad resistance of such isolates to 3rd generation cephalosporins, but not readily distinguishable phenotypically from de-repressed or plasmid-encoded ampC. Over-expression of drug efflux pumps Target alterations Outer membrane protein mutations affecting drug permeability

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- Over-expression of drug efflux pumps

- Target alterations

- Outer membrane protein mutations affecting drug permeability

- For further discussion of resistance mechanisms, issues and treatment considerations, see Resistant Gram Negative Bacilli, Resistance to Beta-lactams, Overview

- IDSA Guidelines on treatment of ESBLs , carbapenemases, and AmpC production (Clin Infect Dis 2022;75:187), (Clin Infect Dis 2022;74:2089).

Classification

- Aerobic facultative gram negative bacilli

- Enterobacter cloacae complex includes: Enterobacter cloacae Enterobacter hormaechei

- Enterobacter cloacae

- Enterobacter hormaechei

Primary Regimens

- Treatment options below are for therapy of moderately-severe, or severe infections in patients requiring systemic therapy

- Recommendations based on status of pathogen detection and in vitro susceptibility

Alternative Regimens

- Lab reports susceptibility to aztreonam, ceftriaxone, cefotaxime, ceftazidime (strain should be assumed to carry repressed chromosomal AmpC gene). (Gentamicin or Tobramycin) 7 mg/kg q24h (adjust dose based on renal function) Note: Avoid cephalosporins other than Cefepime

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- Lab reports ESBL isolate with in vitro resistance to extended spectrum cephalosporins, aztreonam, fluoroquinolones, Non-urinary tract source: Ceftazidime-avibactam 2.5 gm IV infused over 3h q8h Ceftolozane-tazobactam 1.5 gm over 3h IV q8h Urinary tract source: Cefepime-enmetazobactam recently FDA approved for treatment of complicated UTIs, including ESBL producers Temocillin 2 gm IV q12h (where available) Plazomicin 15 mg/kg IV q24h X 4-7 days: An aminoglycoside stable in the presence of aminoglycoside-modifying enzymes. FDA approved for complicated UTIs Complicated UTI: Fosfomycin 6 gm IV over 60 minutes q8h (where available)(See Comments for US emergency IND) Uncomplicated cystitis: Fosfomycin 3 gm po x 1 dose

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- Uncomplicated cystitis: Fosfomycin 3 gm po x 1 dose

- Resistant to all carbapenems due to production of metallo-carbapenemase Infectious Disease consultation suggested Cefiderocol 2 gm IV over 3h q8h (See Comments)

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Antimicrobial Stewardship

- Carbapenems should be reserved for Enterobacter infections for which mixed aerobic and anaerobic coverage is required or for treatment of infections due to ESBL producing strains.

- Although active against ESBLs and related beta-lactamases, use of Ceftazidime-avibactam and Meropenem-vaborbactam should be reserved for patients with documented carbapenemase mechanism of resistance.

Comments

- The rationale for the Ceftazidime-avibactam/Aztreonam combination for metallo-beta-lactamase (MBL) producers is that Aztreonam is not hydrolyzed by MBLs and Ceftazidime is. However, MBL-producers commonly produce ESBLs or serine-carbapenemases, which can degrade Aztreonam. Although avibactam does not inhibit MBLs, it does inhibit serine beta-lactamases (i.e., ESBLs, AmpC, and serine-carbapenemases) such that the Aztreonam which would otherwise be degraded by the serine beta-lactamases remains active. See Antimicrob Agents Chemother 2017 Mar 24; 61(4). pii:e02243-16.

- Polymyxin B: Combination of Meropenem + a polymyxin (either Polymyxin B or Colistin) is not recommended Based on a failed randomized controlled trial (Lancet Infect Dis 2018 ;18:391) 77%, of the infections were due to Acinetobacter baumannii Trial underpowered to address efficacy of combination vs KPCs and P.aeruginosa

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- Cefepime compared to other extended spectrum cephalosporins Penetrates bacterial outer membrane faster than other cephalosporins Weak inducer of chromosomal AmpC gene and resistant to hydrolysis by AmpC Tends not to select for resistant mutants Note: strains with Cefepime MICs of 4-8 mcg/ml have dose-dependent susceptibility and may co-produce ESBL, therefore caution is advised when used to treat E. cloacae infections caused by strains with MICs in this range. AmpC overproducers may produce sufficiently high levels of AmpC to inactivate cefepime if other mutations (e.g., porin, efflux pumps) are present.

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- Other approved or investigational agents with activity vs MDR GNB: Aztreonam-avibactam (late stage development) Fosfomycin (IV formulation where available) In US it is possible to obtain Fosfomycin IV as a single patient emergency IND from the Division of Anti-infective Products at the FDA. Phone: 1-888-6332 or +1-301-796-1400; or Emergency Operations: +1-301-796-8240 or 1-866-300-4374.

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- IDSA Guideline on treatment of ESBL, AmpC, and carbapenemase producers: Clin Infect Dis. 2023 Jul 18:ciad428.

Kingella kingae

Clinical Setting

- Consider Kingella in the differential diagnosis of:

- Septic arthritis, especially in young children (Clin Infect Dis 2018; 67:1951). In Europe, Kingella reported as the most common cause of septic arthritis/osteomyelitis in children between age 6 and 48 months (Pediatrics 2019;144: e20191509; Ped Infect Dis J 2021; 40:623)

- Hematogenous osteomyelitis

- Bacteremia

- Infective endocarditis; one of the HACEK acronym; slow growing fastidious gram -negative organisms that cause endocarditis (Microorganisms. 2024;12:164)

- Treatment considerations:

- Susceptible in vitro to cephalosporins, aminoglycosides, TMP/SMX, tetracyclines, and fluoroquinolones

- In children, cephalosporin therapy is preferred

- Predictably resistant to vancomycin, clindamycin, oxacillin and nafcillin.

Diagnosis

- Culture on blood or chocolate agar. Grows slowly.

Classification

- Gram negative coccobacilli

Primary Regimens

- Because of its rarity, activity vs. Kingella species is not usually considered in selection of empiric therapy for children with septic arthritis or osteomyelitis.

- If child with haematogenous osteomyelitis does not respond to empiric therapy targeting possible Staph. aureus (e.g., Vancomycin), it would be reasonable to add Cefazolin or Ceftriaxone empirically or while awaiting culture results. Avoid tetracyclines and fluoroquinolones in children under age 8 years. Doxycycline is now considered safe by the American Academy of Pediatrics for up to 21 days of therapy.

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- In adults with endocarditis, treatment is with Ceftriaxone ± low dose aminoglycoside (only theoretic data for the combination).

Alternative Regimens

- In children under age 4 years allergic to beta-lactam antibiotics, could consider TMP-SMX.

- In adults with endocarditis and allergic to beta-lactams, could consider therapy with Levofloxacin based on in vitro susceptibility. No clinical data.

Comments

- Hematogenous osteomyelitis (children)(N Engl J Med 370:352, 2014).

- Treatment review (Pharmacotherapy 2018;38:947).

Klebsiella aerogenes

Clinical Setting

- Klebsiella sp. cause a variety of infections ranging from uncomplicated urinary tract infections to life-threatening infections of the abdomen, skin and soft tissue, lung, CNS and other sites in both normal and immunocompromised hosts.

- Klebsiella aerogenes is unique among Klebsiella spp. in that it encodes an inducible ampC gene.

- Suggested treatment regimens based on status of pathogen detection and results of in vitro susceptibility. Clinical settings: Pathogen detected but no reported in vitro susceptibility, empiric therapy Pathogen detected and in vitro susceptibility reported, specific/directed therapy Specific therapy based on the pattern of in vitro susceptibility which can provide hints as to the mechanism(s) of antibiotic resistance For detailed discussion of drug resistance classes and mechanisms among gram negative bacilli see Gram Negative Bacilli, Beta-lactam Resistance, Overview.

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- Virulent, highly mucoid (hypermucoviscous) strains can cause severe infection, often metastatic (e.g., liver abscess), in otherwise healthy hosts. See Clin Infect Dis 58:225, 2014.

- For treatment of uncomplicated urinary tract infections, see Cystitis (adult female) or Cystitis (adult male)

- For other species, see Klebsiella sp. (oxytoca, pneumoniae, variicola)

- See Comments for selected drug details, emerging data, literature citations and more.

Classification

- Klebsiella aerogenes

Primary Regimens

- Lab reports that strain does not produce an ESBL and susceptibility confirmed to the selected agent TMP-SMX administered as 10 mg/kg/day (TMP component) in 2-3 divided doses (Gentamicin or Tobramycin) 7 mg/kg q24h, dose adjusted for renal function

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- Strain is an ESBL-producer Non-urinary tract source: Ceftolozane-tazobactam 1.5 gm over 3 hrs IV q8h Ceftazidime-avibactam 2.5 gm IV infused over 3 hrs q8h Urinary tract source Pyelonephritis and other complicated UTIs Temocillin 2 gm IV q12h (where available) Fosfomycin IV 6 gm IV over 60 minutes q8h (where available) In US, see Comments for emergency access from FDA Use of other agents, if confirmed active in vitro, may be considered (Clin Infect Dis 2017;64:972)

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- Carbapenemase resistant strain, suspected metallo-beta-lactamase producer Plazomicin 15 mg/kg once daily may be an option (FDA-approved for complicated UTI only and recommended duration is 4-7 days)

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Antimicrobial Stewardship

- Carbapenems should be reserved for treatment of infections due to ESBL producing strains or for treatment of mixed anaerobic/aerobic infections.

- Although active against ESBLs and related beta-lactamases, use of Ceftazidime-avibactam, Imipenem-relebactam, and Meropenem-vaborbactam should be reserved for patients with documented carbapenemase mechanism of resistance.

Comments

- See IDSA 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections.

- Aztreonam is not hydrolyzed by metallocarbapenemases (ceftazidime is) but is inactivated by ESBLS which are often produced concomitantly with the carbapenemase. Avibactam inactivates ESBLs. See Antimicrob Agents Chemother 2017 Mar 24; 61(4). pii:e02243-16

- Cefiderocol: FDA-approved for patients with complicated UTI due to cefiderocol susceptible bacteria and with limited or no alternative treatment options. In an open label randomized trial of cefiderocol vs best available therapy (BAT) in patients with sepsis, pneumonia, bacteremia or complicated UTI, mortality at 28 days was 24.8% for cefiderocol pts. vs 18.4% for BAT pts (not statistically significant).

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Granuloma inguinale (Donovanosis)

Clinical Setting

- Granuloma inguinale or Donovanosis

- Painless, progressive ulcerative disease without regional lymphadenopathy.

- Highly vascular (beefy red) lesions that bleed easily.

- Rare in US; common in Southeast Asia (India), South America & Southern Africa. Was endemic in Australia, but now relatively rare.

Etiologies

- Klebsiella granulomatis (formerly Calymmatobacterium granulomatis)

Diagnosis

- Culture of causative organism is difficult and unreliable.

- Darkfield microscopy; Donovan Bodies organisms visible in macrophages using Wright-Giemsa on biopsy.

- PCR techniques for diagnosis also available in some labs.

Primary Regimens

- Azithromycin 1 gm po once weekly (or 500 mg daily) x at least 3 weeks (or until resolved)

- If no evident improvement in the first few days, some experts add Gentamicin 1 mg/kg IV q8h.

Alternative Regimens

- Doxycycline 100 mg po bid x 3 weeks

- TMP-SMX DS po q12h x 3 weeks

- Ciprofloxacin 750 mg po bid x 3 weeks

- Erythromycin 500 mg po qid x 3 weeks

Antimicrobial Stewardship

- Duration: clinical response is usually seen in 1 week. Treat until all lesions are healed. This may take 4 weeks.

- Treatment failures and recurrence seen with Doxycycline and TMP-SMX.

Comments

- Sexual partners within 60 days should be evaluated. Role of empiric therapy in asymptomatic contacts unclear.

- Screen all patients for HIV.

- Treatment is no different for HIV patients with Granuloma inguinale.

- Relapse can occur 6–18 months after apparently effective therapy.

- See 2021 CDC STD Guidelines: MMWR Recomm Rep 70 (RR-4):1 2021 or 2016 European Guideline on Donovanosis Int J STD AIDS 27:605, 2016.

- Review non syphilis non HSV genital ulcers: Infect Dis Clin North Am 37:369 2023.

Klebsiella sp. (oxytoca, pneumoniae, variicola)

Clinical Setting

- Klebsiella sp. cause a variety of infections ranging from uncomplicated urinary tract infections to life-threatening infections of the abdomen, skin and soft tissue, lung, CNS and other sites in both normal and immunocompromised hosts. Klebsiella pneumoniae complex encompasses the group of organisms which includes K. pneumoniae and K. variicola.

- Suggested treatment regimens based on status of pathogen detection and results of in vitro susceptibility. Clinical settings: Pathogen detected but no reported in vitro susceptibility, empiric therapy Pathogen detected and in vitro susceptibility reported, specific/directed therapy Specific therapy based on the pattern of in vitro susceptibility which can provide hints as to the mechanism(s) of antibiotic resistance For detailed discussion of drug resistance classes and mechanisms among gram negative bacilli see Gram Negative Bacilli, Beta-lactam Resistance, Overview.

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- Increasing recognition of highly virulent, highly mucoid (hypermucoviscous) strains. Can cause infection, often metastatic (e.g., liver abscess), in otherwise healthy hosts. See Clin Infect Dis 58:225, 2014.

- For treatment of uncomplicated urinary tract infections, see Cystitis (adult female) or Cystitis (adult male)

- See also Klebsiella aerogenes

- See Comments for selected drug details, emerging data, literature citations and more.

Classification

- Facultative anaerobic fermentative Gram negative bacilli Klebsiella oxytoca Klebsiella pneumoniae Klebsiella variicola

- Klebsiella oxytoca

- Klebsiella pneumoniae

- Klebsiella variicola

Primary Regimens

- Treatment options below are for therapy of moderately-severe, or severe infections in patients requiring systemic therapy

Alternative Regimens

- Lab reports that strain does not produce an ESBL and susceptibility confirmed to the selected agent Cefazolin 1 gm IV q8h TMP-SMX administered as 10 mg/kg/day (TMP component) in 2-3 divided doses Amoxicillin-clavulanate 1.2 -2.4 gm IV q8h (where available)

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Klebsiella sp. (rhinoscleromatis, ozaenae)

Clinical Setting

- Rhinoscleroma (also termed respiratory scleroma): a chronic granulomatous infection of nasal passages and the respiratory tract caused by K. rhinoscleromatis and typically seen in immigrants from, or residents of, developing countries.

- Purulent nasal discharge

- Nodule formation with obstruction

- Characteristic histological findings of Mikulicz cells, which are foamy macrophages containing intracellular organisms

- Diagnosis: Isolation of organism in culture

- Ozena

- Chronic atrophic rhinitis or sinusitis frequently accompanied by a persistent fetid odor, often in elderly patients; classic triad: fetid nasal discharge, crusting, and atrophy

- Associated with isolation of K. ozaenae in culture.

Classification

- Gram negative bacilli Klebsiella rhinoscleromatis Klebsiella ozaenae

- Klebsiella rhinoscleromatis

- Klebsiella ozaenae

Primary Regimens

- For rhinoscleroma: Ciprofloxacin 750 mg po bid or Levofloxacin 750 mg po once daily for 2-3 months

- For ozena: Ciprofloxacin 750 mg po bid or Levofloxacin 750 mg po once daily for 8 weeks

Alternative Regimens

- None

Comments

- Rhinoscleroma

- Relapses can occur.

- Reference: Acta Otolaryngol 131:440, 2011.

- Ozena

- Role of infection in ozena controversial: topical moistening agents recommended as initial therapy with antibiotics reserved for superinfection.

- Ozena in immigrants: Am J Trop Med Hyg 2016;35:7.

Legionella sp.

Clinical Setting

- Community or hospital-acquired pneumonia, extrapulmonary infections (e.g., endocarditis) occur but are rare

- Despite cough, patients with pneumonia may produce small amounts of mucoid non-purulent sputum

- Risk factors: Immunocompromised patient, smoking, co-morbidities.

- Associated clinical findings with pneumonia (although nonspecific): Diarrhea, other gastrointestinal symptoms Confusion Relative bradycardia Hyponatremia Elevated hepatic enzymes Elevated BUN and creatinine Elevated ferritin levels. Range of peak levels: 591-5990 (Clin Infect Dis 46:1789, 2008)

- Diarrhea, other gastrointestinal symptoms

- Confusion

- Relative bradycardia

- Hyponatremia

- Elevated hepatic enzymes

- Elevated BUN and creatinine

- Elevated ferritin levels. Range of peak levels: 591-5990 (Clin Infect Dis 46:1789, 2008)

Diagnosis

- Culture (requires selective media) or PCR: detects multiple serotypes.

- Antigen assay, direct fluorescent antibody, or serology detects L. pneumophila serotype 1 strains only (for review of diagnostics see Clin Microbiol Rev 28:95, 2015).

Classification

- Gram negative bacilli

- Legionella pneumophila (60-80% of cases)

- Legionella (tatlockia) micdadei

- Legionella wadsworthii

- ~40 species identified, most rarely associated with human disease

Primary Regimens

- Pneumonia Levofloxacin 750 mg IV/po q24h or Moxifloxacin 400 mg IV/po q24 Azithromycin 500 mg IV/po q24h No proven benefit of Rifampin combination therapy (and drug interactions are a major issue in many patients) or combination of Azithromycin + fluoroquinolone

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- No proven benefit of Rifampin combination therapy (and drug interactions are a major issue in many patients) or combination of Azithromycin + fluoroquinolone

- Endocarditis: above (see Comments)

Alternative Regimens

- Pneumonia Clarithromycin 500 mg IV/po q12h or Erythromycin 500 mg to 1 gm q6h IV/po q6h (less well tolerated and may be less effective than primary regimens) Doxycycline 100 mg IV/po q12h

- Clarithromycin 500 mg IV/po q12h or Erythromycin 500 mg to 1 gm q6h IV/po q6h (less well tolerated and may be less effective than primary regimens)

- Doxycycline 100 mg IV/po q12h

- Endocarditis (see Comments) Doxycycline 200 mg bid po/IV Erythromycin 500 mg po/IV q6h + Rifampin 600-1200 mg po in 2 or more divided doses Ciprofloxacin at 400 mg IV q12h or 500 mg po bid

- Doxycycline 200 mg bid po/IV

- Erythromycin 500 mg po/IV q6h + Rifampin 600-1200 mg po in 2 or more divided doses

- Ciprofloxacin at 400 mg IV q12h or 500 mg po bid

Antimicrobial Stewardship

- Duration of therapy. 7-10 days of IV/po therapy depending on clinical response is appropriate for immunocompetent patients with legionella pneumonia. 14-21 days of therapy with IV/po therapy depending on clinical response is recommended for immunocompromised patients. Duration of therapy not well defined, but prolonged therapy, up to 5 months, has been used

- 7-10 days of IV/po therapy depending on clinical response is appropriate for immunocompetent patients with legionella pneumonia.

- 14-21 days of therapy with IV/po therapy depending on clinical response is recommended for immunocompromised patients.

- Duration of therapy not well defined, but prolonged therapy, up to 5 months, has been used

Comments

- For endocarditis Advise microbiology laboratory when considering the diagnosis of Legionella spp. endocarditis as it is possible to isolate the organism in blood culture media with special handling.. Infectious Diseases consultation recommended Several Legionella spp have been reported as causes of endocarditis. Most patients reported in the literature have undergone valve replacement in addition to medical therapy. Treatment recommendations based on anecdotal case reports. References: J Infect 51:e256, 2005, Clin Micro Rev 2001; 14:177, Circulation. 2015;132:1435-1486.

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- Infectious Diseases consultation recommended

- Several Legionella spp have been reported as causes of endocarditis.

- Most patients reported in the literature have undergone valve replacement in addition to medical therapy.

- Treatment recommendations based on anecdotal case reports.

- References: J Infect 51:e256, 2005, Clin Micro Rev 2001; 14:177, Circulation. 2015;132:1435-1486.

- Macrolides and fluoroquinolones are probably equally effective (Clin Infect Dis 2021;72:1979). Most fluoroquinolones are active in vitro (Gemifloxacin, Moxifloxacin).

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- TMP-SMP also probably effective but less data to support its efficacy

- Reference on diagnosis and treatment: Infect Dis Ther. 2022; 11:973-986.

Lactobacillus sp.

Clinical Setting

- Positive blood culture in patient with an IV line.

- Immunocompromised hosts.

- Specific therapy.

- Removal of infected IV line is primary therapy.

Classification

- Gram positive bacilli, microaerophilic

Primary Regimens

- Penicillin G 2 million units IV q4h

- Ampicillin 2 gm IV q4h

Alternative Regimens

- Clindamycin 600 mg IV q8h

Comments

- May be resistant to Vancomycin.

- Combination often used, at least initially; see Clin Infect Dis 38: 62, 2004.

- For species-specific susceptibility to various antimicrobials see Clin Infect Dis 42: e35, 2006.

Leptospira sp.

Clinical Setting

- History helps if exposure to fresh water contaminated by lepto-infected rodent urine

- Acute onset of systemic febrile illness with a highly variable clinical presentations: Headache and myalgia in 75-100% Conjunctival suffusion in 55% Some patients have aseptic meningitis; some hepatitis with renal failure (Weil's disease)

- Headache and myalgia in 75-100%

- Conjunctival suffusion in 55%

- Some patients have aseptic meningitis; some hepatitis with renal failure (Weil's disease)

- A zoonotic infection with multisystem manifestations that is caused by the spirochete Leptospira interrogans. Leptospira is found in urine of a large variety of domestic and wild animals: livestock (cattle, swine, sheep, horses, and goats), dogs, small rodents. Ask about exposure to potentially conmtaminated fresh water (streams, rivers, creeks) or lepto-infected rodent urine

- Leptospira is found in urine of a large variety of domestic and wild animals: livestock (cattle, swine, sheep, horses, and goats), dogs, small rodents.

- Ask about exposure to potentially conmtaminated fresh water (streams, rivers, creeks) or lepto-infected rodent urine

- Spirochete can enter host through skin, mucous membranes or conjunctiva.

- Acute onset of systemic febrile illness with a highly variable clinical presentations from mild to severe Headache and myalgia in 75-100% Conjunctival suffusion in 55% Some patients have aseptic meningitis; some hepatitis with renal failure (Weil's disease)

- Headache and myalgia in 75-100%

- Conjunctival suffusion in 55%

- Some patients have aseptic meningitis; some hepatitis with renal failure (Weil's disease)

- Often dramatic increases in bilirubin but AST/ALT increases to no more than 5 times normal.

Diagnosis

- Previous gold standard: serology done by CDC (4-fold rise in antibody titer); variety of commercial antibody tests; good for epidemiology but not much help clinically due to delayed increase in antibody

- Isolation of the organism from blood or CSF, generally during the first 10 days of illness and prior to initiation of antibiotic. Requires high index of suspicion and special media. Not practical.

- Increasing availability of PCR testing on blood, urine, and CSF. Check with State public health labs and commercial diagnostic laboratories

- Increasing use of metagenomic next generation sequencing methods: J Pediatric Infect Dis Soc 2021; 10 (supplement-4):S78; N Engl J Med 2014; 370:2408

Classification

- Spirochete Leptospira interrogans Other Leptospira spp. (Clin Med (Lond). 2022; 22:14-17)

- Leptospira interrogans

- Other Leptospira spp. (Clin Med (Lond). 2022; 22:14-17)

Primary Regimens

- Mild disease (outpatient) Doxycycline 100 mg po bid x 5-7 days Amoxicillin 500 mg po tid x 7 days Azithromycin 1 gm po x one dose and then 500 mg po daily x 2 days Pregnancy or children age <8 years: Amoxicillin 25-50 mg/kg/day po in 3 divided doses x 7 days

- Doxycycline 100 mg po bid x 5-7 days

- Amoxicillin 500 mg po tid x 7 days

- Azithromycin 1 gm po x one dose and then 500 mg po daily x 2 days

- Pregnancy or children age <8 years: Amoxicillin 25-50 mg/kg/day po in 3 divided doses x 7 days

- Severe disease (inpatient) Penicillin G 1.5 million units IV q6h Ceftriaxone 2 gm IV once daily x 7 days Children: Penicillin G 250,000-400,000 units per kg IV per day in 4-6 divided doses x 7 days.

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- Ceftriaxone 2 gm IV once daily x 7 days

- Children: Penicillin G 250,000-400,000 units per kg IV per day in 4-6 divided doses x 7 days.

Alternative Regimens

- Mild disease (outpatient) Adult: Azithromycin 500 mg po once daily x 3 days Children age < 8 years or pregnancy: Azithromycin 10 mg/kg (max 500 mg) on day one and then 5 mg/kg /day (max 250 mgs) x 3 days

- Adult: Azithromycin 500 mg po once daily x 3 days

- Children age < 8 years or pregnancy: Azithromycin 10 mg/kg (max 500 mg) on day one and then 5 mg/kg /day (max 250 mgs) x 3 days

- Severe disease (inpatient) Adults: Doxycycline 100 mg IV x 7 days Children Ceftriaxone 80-100 mg/kg IV once daily x 7 days Doxycycline 2-4 mg/kg/day IV divided q12h

- Adults: Doxycycline 100 mg IV x 7 days

- Children Ceftriaxone 80-100 mg/kg IV once daily x 7 days Doxycycline 2-4 mg/kg/day IV divided q12h

- Ceftriaxone 80-100 mg/kg IV once daily x 7 days

- Doxycycline 2-4 mg/kg/day IV divided q12h

Comments

- Patients treated, especially with penicillin, may experience Jarisch-Herxheimer reactions, which may be severe.

- Use of tetracyclines in children has historically been limited because of reports of permanent tooth discoloration in children age <8 years The American Academy of Pediatrics acknowledges that doxycycline can safely be administered for short durations (≤21 days) regardless of patient age (AAP Red Book 2018, Section 4; J Pediatr 166:1246, 2015)

- The American Academy of Pediatrics acknowledges that doxycycline can safely be administered for short durations (≤21 days) regardless of patient age (AAP Red Book 2018, Section 4; J Pediatr 166:1246, 2015)

- No clear role for corticosteroids which are not routinely recommended.

- If not possible to exclude infection due to Rickettsiae species, use Doxycycline and avoid penicillins and cephalosporins as beta-lactams have no activity vs rickettsiae.

Leuconostoc sp.

Clinical Setting

- Isolation of vancomycin-resistant, catalase-negative Gram-positive cocci in blood or other culture.

- Generally non-pathogenic organism found in plants, food, and GI tract, but rarely may cause infection: e.g., infected IV lines., prosthetic joint infection.

Classification

- Leuconostoc spp.

Primary Regimens

- Penicillin G 2 million units IV q4h

- Ampicillin 2 gm IV q4h

Alternative Regimens

- Clindamycin 600 mg IV q8h

Comments

- Intrinsic resistance to Vancomycin.

- Other susceptibilities in vitro (Antimicrob Agents Chemother 34: 543, 1990) MICs for cephalosporins can be quite high; for some isolates, elevated MICs for imipenem and ciprofloxacin were noted Erythromycin, clindamycin, daptomycin, gentamicin and tobramycin were highly active

- MICs for cephalosporins can be quite high; for some isolates, elevated MICs for imipenem and ciprofloxacin were noted

- Erythromycin, clindamycin, daptomycin, gentamicin and tobramycin were highly active

- Report of Leuconostoc mesenteroides periprosthetic knee infection (BMC Infectious Diseases 17:227, 2017)

Listeria monocytogenes

Clinical Setting

- Range of clinical syndromes that vary from mild self-limited disease to life-threatening meningitis. Neonatal sepsis, bacteremia, meningitis, encephalitis (brainstem encephalitis--termed rhombencephalitis), endocarditis, febrile gastroenteritis More severe disease in pregnancy, neonates, and in immunocompromised patients (if possible, decrease dose of immunosuppressive medications). Incidence of Listeriosis in infants has been low and stable; almost all occur in first 7 days of life (Hosp Pediatrics 6(4):196, 2016; Clin Infect Dis 74(1):8;2022) Review of all facets of Listeriosis in pregnancy: Obst & Gynecology 2019;74:362 For prognosis, see comment below

- Neonatal sepsis, bacteremia, meningitis, encephalitis (brainstem encephalitis--termed rhombencephalitis), endocarditis, febrile gastroenteritis

- More severe disease in pregnancy, neonates, and in immunocompromised patients (if possible, decrease dose of immunosuppressive medications).

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- Review of all facets of Listeriosis in pregnancy: Obst & Gynecology 2019;74:362

- For prognosis, see comment below

- Use of proton pump inhibitors associated with an increased risk of listeriosis. Presumed mechanism is marked reduction in killing of listeria by gastric acid (Clin Infect Dis 2017; 64: 845)

- Susceptible to ampicillin, penicillin, gentamicin and TMP-SMX.

Classification

- Gram positive bacilli

Primary Regimens

- Meningitis, meningoencephalitis: TMP-SMX 20 mg/kg/day divided q6-12h x 21 days

- Bacteremia during pregnancy (but not first or last trimester): TMP-SMX 10-20 mg/kg IV divided q6-12h x 2 weeks

- Allergy to Penicillin and not IgE mediated, Meropenem 1-2 gm IV q8h x 2 weeks (See Comment)

Alternative Regimens

- Meningitis, meningoencephalitis: TMP-SMX 20 mg/kg/day divided q6-12h x 21 days

- Bacteremia during pregnancy (but not first or last trimester): TMP-SMX 10-20 mg/kg IV divided q6-12h x 2 weeks

- Allergy to Penicillin and not IgE mediated, Meropenem 1-2 gm IV q8h x 2 weeks (See Comment)

Antimicrobial Stewardship

- Antimicrobial drug choice considerations: Vancomycin is active in vitro but clinical failures reported; vancomycin resistant strains also identified. A few case reports describe treatment with Linezolid (J Infect 52:e73, 2006); hematologic toxicity with prolonged use. Erythromycin and tetracyclines not recommended because they are bacteriostatic and resistance reported (Lancet 335:1422, 1990); some fluoroquinolones (e.g, Levofloxacin, Moxifloxacin) active in vitro but limited clinical data on efficacy. Chloramphenicol not effective. Cephalosporins are not active vs. Listeria sp.

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- Chloramphenicol not effective.

- Cephalosporins are not active vs. Listeria sp.

Comments

- Clinical microbiology may mistakingly identify organisms detected in CSF as "diphtheroids"

- Most infants with Listeria are born prematurely, suggesting maternal infection leads to pre-term labor

- Infant mortality is decreased if mother started therapy ≥ 24 hours before delivery Clin Infect Dis 74(1):8;2022

- Meropenem. Both success (J Chemother 18:331, 2006) and failure (Eur J Clin Micro Inf Dis 23:484, 2004) reported for treatment of meningitis with Meropenem. Recommend use in only special circumstances where first line drugs cannot be used.

- For clinical features and prognostic factors, see MONALISA prospective cohort study: Neurolisteriosis higher in bacteremic patients (OR 3.67, p 0.002) and in those given adjunctive dexamethamethasone (OR 4.58, p 0.008) Lancet Infect Dis 2017; 17: 510

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- Lancet Infect Dis 2017; 17: 510

- Review: Clin Microbiol Rev. 2023; 36: e0006019

Bacteria: Normal Flora, Non-pathogenic, Contaminants, Rare Pathogens

Introduction

- Rare pathogens

- Normal human flora

- Environmental contaminants

- Often non-pathogenic and of low virulence

- Present in mixed cultures

Organisms

Moraxella catarrhalis

Clinical Setting

- Sinusitis, otitis media, and pneumonia.

- May be seen on gram-stain of sputum of smoker with an acute exacerbation of chronic bronchitis.

- See also, Moraxella pneumonia.

Classification

- Gram negative diplococci

Primary Regimens

- Amoxicillin-clavulanate 875/125 mg tab 1 po bid x 5-7 days

- Cefuroxime axetil 500 mg po q12h x 5-7 days

Alternative Regimens

- TMP-SMX-DS tab 1 po bid x 5-7 days

- Azithromycin 500 mg po x 1, then next day 250 mg po once daily x 4 days

- Cefprozil 500 mg po q12h x 5-7 days

- Cefdinir 600 mg po once daily x 5-7 days

Comments

- Vast majority of strains produce beta-lactamase.

- Also effective: Erythromycin, Doxycycline, Fluoroquinolones.

Morganella morganii

Clinical Setting

- Morganella morganii can cause a variety of infections but most often identified as the etiology of urinary tract and post-operative wound infections.

- Typically a nosocomial pathogen.

- Resistance and susceptibility: Isolates are intrinsically resistant to polymyxins (Colistin and Polymyxin B), penicillin, ampicillin, ampicillin/sulbactam, amoxicillin-clavulanate, 1st and 2nd generation cephalosporins, nitrofurantoin and fosfomycin. Strains are generally sensitive to aztreonam, aminoglycosides, antipseudomonal penicillins (cefepime, ceftazidime) , extended spectrum cephalosporins, carbapenems, fluoroquinolones and sometimes TMP-SMX Isolates may produce a carbapenemase Strains may have other plasmid-mediated resistance to aminoglycosides and fluoroquinolones as a result of enzyme modifications, target changes, efflux pumps and /or decreased cell-wall permeability

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- Isolates may produce a carbapenemase

- Strains may have other plasmid-mediated resistance to aminoglycosides and fluoroquinolones as a result of enzyme modifications, target changes, efflux pumps and /or decreased cell-wall permeability

- For further discussion of resistance mechanisms, issues and treatment considerations, see Gram Negative Bacilli, Beta-lactam Resistance, Overview. See Comments for IDSA Guideline references.

Classification

- Facultative anaerobic gram negative enteric bacterium

Primary Regimens

- Treatment options below are for therapy of moderately-severe, or severe infections in patients requiring systemic therapy

Alternative Regimens

- For patients with severe IgE-mediated allergy to beta-lactams (anaphylaxis, angioneurotic edema + susceptible in vitro):

- Aztreonam 1gm IV q8h to 2 gm IV q6h

- Ciprofloxacin 400 mg IV q12h or 750 mg po bid

- Levofloxacin 750 mg IV/po once daily

- Alternative options for ESBL producing strains: Ceftolozane-tazobactam 1.5 gm IV over 3 hr q8h Temocillin 2 gm IV q12h (where available)

- Ceftolozane-tazobactam 1.5 gm IV over 3 hr q8h

- Temocillin 2 gm IV q12h (where available)

- Carbapenemase resistant strain, suspected metallo-beta-lactamase phenotype (resistant to Ceftazidime-avibactam and Meropenem-vaborbactam) Ceftazidime-avibactam 2.5 gm IV over 2 hrs q8h + Aztreonam 2 gm IV q8h A last resort recommendation based entirely on in vitro data and case reports: Antimicrob Agents Chemother 2017 Mar 24;61(4). pii: e02243-16) Based on the resistance of aztreonam to hydrolysis by metallo-carbapenemases; use the ceftazidime-avibactam to protect the aztreonam from hydrolysis by concomitant ESBLs Cefiderocol 2 gm IV over 3 hrs q8h

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- Based on the resistance of aztreonam to hydrolysis by metallo-carbapenemases; use the ceftazidime-avibactam to protect the aztreonam from hydrolysis by concomitant ESBLs

- Cefiderocol 2 gm IV over 3 hrs q8h

Antimicrobial Stewardship

- Considerations in antimicrobial selection: For ESBL-producing strains avoid Pieracillin-tazobactam even if reported susceptible in vitro (JAMA 2018; 320:979) Check susceptibility of all carbapenems. Cannot assume resistance to meropenem if lab indicates resistance to imipenem ((J Glob Antimicrob

Resist 2020;21:223). For MDR and XDR strains: Tigecycline may have in vitro activity but clinical efficacy questionable due to low serum levels. Laboratory reports evidence of metallo-beta-lactamase production: If susceptible, a fluoroquinolone or aminoglycoside Metallo-beta-lactamases cannot hydrolyze Aztreonam. However, there often is concomitant production of serine-beta-lactamases (KPCs, ESBLs or AmpC) which do hydrolyze Aztreonam. Case reports of success by combining Ceftazidime-avibactam, which inhibits co-existing serine-beta-lactamases that would otherwise hydrolyze Aztreonam (Antimicrob Agents Chemother 2019; 63:e02463-18).

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Comments

- Cefiderocol: FDA-approved for patients with complicated UTI due to cefiderocol susceptible bacteria and with limited or no alternative treatment options. In an open label randomized trial of cefiderocol vs Best Available Therapy (BAT) in patients with sepsis, pneumoinia, bacteremia or cUTI, mortality at 28 days was 24.8% for cefiderocol pts. vs 18.4% for BAT pts (not statistically significant).

- For UTIs: Remove indwelling Foley catheter if possible and ensure no urinary obstruction. Note the absence of activity of nitrofurantoin and fosfomycin

- Remove indwelling Foley catheter if possible and ensure no urinary obstruction.

- Note the absence of activity of nitrofurantoin and fosfomycin

- References: See 2023 IDSA Guidance on the treatment of multidrug resistant isolates

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Mycoplasma genitalium

Clinical Setting

- Detected in 40% of men with persistent and/or recurrent non-gonococcal urethritis (NGU). Prevalence of 19.7% in report from China (Clin Infect. Dis 2020;70: 805)

- Symptomatic and asymptomatic urethritis among men 15%–20% of NGU, 20%–25% of nonchlamydial NGU, and 40% of persistent or recurrent urethritis.

- Associated with cervicitis (10-30% of clinical cervicitis), PID, preterm delivery, spontaneous abortion, and infertility.

- Documented as etiology of pelvic inflammatory disease in women.

- Also frequently asymptomatic.

- Rectal and pharyngeal sites can be positive, but usually asymptomatic.

- NGU treatment guidelines from Britain, Europe, Australia and US now recommend doxycycline as primary therapy with azithromycin as an alternative.

- Resistance is a major problem (Clin Infect Dis 2020; 70:811) Molecular marker for macrolide resistance, which correlates with clinical failure, ranges from 44-90% Concomitantly, resistance to fluoroquinolones ranges from 5-15% (Emerg Infect Dis 2017;23: 809). Fluoroquinolone resistance often coexists with macrolide resistance.

- Molecular marker for macrolide resistance, which correlates with clinical failure, ranges from 44-90%

- Concomitantly, resistance to fluoroquinolones ranges from 5-15% (Emerg Infect Dis 2017;23: 809).

- Fluoroquinolone resistance often coexists with macrolide resistance.

- Not all FDA approved NAAT for detection of M. genitalium test for antibiotic resistance, but testing for macrolide resistance more common.

- Culture available only in research settings

- Tests for antibiotic resistance in development, but not generally available.

- 2021 CDC STI guidelines MMWR Recomm Rep 70 (RR-4):1 2021

Diagnosis

- If NAAT available: can test urine or urethral, penile meatal, endocervical, and vaginal swab samples

- Testing of asymptomatic individuals not recommended

- If resistance testing available, use results to guide treatment

- M. genitalium should be suspected in cases of persistent or recurrent urethritis or cervicitis and considered for PID.

Primary Regimens

- Two stage therapy now recommended: Doxycycline to reduce organism load followed by high dose azithromycin or moxifloxacin

- If macrolide sensitive: Doxycycline 100 mg orally 2 times/day for 7 days, followed by azithromycin 1 g orally initial dose, followed by 500 mg orally once daily for 3 additional days (2.5 g total)

- If macrolide resistant: Doxycycline 100 mg orally 2 times/day for 7 days followed by moxifloxacin 400 mg orally once daily for 7 days

- If resistance testing unavailable, treat as for macrolide resistant. If unable to use moxifloxacin, test of cure recommended. If symptomatic treatment failure or positive test of cure occurs, expert consultation recommended.

Alternative Regimens

- Limited data with minocycline in instances of treatment failure

- Pristinamycin 1 gm po qid x 10 days (where available)(a streptogramin antibiotic highly active vs M. genitalium but not marketed in the US)

Antibiotic Stewardship

- Significant concerns that azithromycin used in dual STI regimens is responsible for increasing resistance of N. gonorrhoeae, M. genitalium, enteric and respiratory pathogens.

- Monitoring emergence of resistance, antibiotic use is critical

Comments

- Pristinamycin is reported effective in treating macrolide and FQ-resistant strains but not widely available (Emerg Infect Dis 24:328, 2018).

- M genitalium has no cell wall so beta lactams are NOT effective.

- In systematic review and meta-analysis, the cure rate was only 67% with Azithromycin 1 gm single dose (Clin Infect Dis 61:1389, 2015).

- Doxycycline 100 mg po bid x 7 days gives microbiologic cure in only 22-45%: Nat Rev Urol 2017;14:139

- A common pathogen in MSM, including in rectal specimens from patients with proctitis.

Mycoplasma hominis

Clinical Setting

- Adhere to epithelial cells of urogenital tract so may represent colonization rather than infection

- Colonization correlated with sexual maturity

- Associated with urogenital infection in adults including urethritis, urinary tract infection, PID, chorioamnionitis

- Can disseminate, particularly in settings of disruption of mucosal barriers, especially in neonates and immunocompromised individuals (particularly with antibody deficiencies)

- Neonates (especially preterm): meningoencephalitis, bacteremia, pneumonia

- Extragenital infections are usually in immunocompromised (wound, joint, lung, CNS).

Diagnosis

- Culture very difficult so diagnosis usually by NAAT, if available (culture and NAAT typically only in reference labs).

- NAAT in a joint, valve, CSF should be considered diagnostic, but from genital or urinary tract may represent colonization.

- Diagnosis in sterile sites (CSF, blood) improved with metagenomics/next generation sequencing techniques

Classification

- Small free-living bacteria with no cell wall (don't stain with gram stain) so all beta-lactam drugs are ineffective.

Primary Regimens

- Doxycycline 100 mg po/IV bid x 7-14 days (duration depending on clinical syndrome)

Alternative Regimens

- (Levofloxacin 500 mg po/IV daily or Moxifloxacin 400 mg po/IV daily) x 10-14 days

- Clindamycin 900 mg q8 po/IV x 10-14 days (safe in pregnancy)

Antimicrobial Stewardship

- Usually resistant to macrolides, aminoglycosides, TMP/SMX, beta-lactams

- Resistance emerges readily

Comments

- Clinical syndromes overlap considerably with Ureaplasma

- Linked to nonhepatic hyperammonemia syndromes in the immunocompromised, particularly lung transplant recipients (Curr Op Inf Dis 35:262 2022). Presentation includes high ammonia, neurological symptoms (encephalopathy, seizures, brain edema). Because diagnosis may be difficult or delayed, empiric treatment is often required.

- Due to variable susceptibilities, in serious infections, often double coverage with doxycycline plus fluoroquinolone is administered, though little definitive data.

- Source of organism in lung transplant recipients is probably the donor (Open Forum Inf Dis 9:ofac607 2022; Clin Infect Dis 73:e2531 2021). Prophylaxis of positive recipients has been proposed with variable success (Open Forum Inf Dis 9:ofac607 2022; Clin Infect Dis 73:e2531 2021)

Mycoplasma pneumoniae

Clinical Setting

- Young or older (age > 60 years) patient with minimally productive cough (atypical) with, or without, pulmonary infiltrates. Diagnosis: Clinical syndrome plus sputum or throat swab for PCR (now the gold standard: Ped Infect Dis J 2018;37:1192) Four-fold rise in specific antibody titer was the former gold standard Clinical picture: Patient with minimally productive cough for up to 2 weeks; Cough of sufficient severity to cause syncope, urinary incontinence, and even rib fractures.

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- Four-fold rise in specific antibody titer was the former gold standard

- Clinical picture: Patient with minimally productive cough for up to 2 weeks; Cough of sufficient severity to cause syncope, urinary incontinence, and even rib fractures.

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- Cough of sufficient severity to cause syncope, urinary incontinence, and even rib fractures.

- Fever often leads to chest X-ray that demonstrates infiltrates. Pneumonia usually mild and self-limited but severe disease with ARDS can occur.

- Extra-pulmonary manifestations: Skin manifestations in 25%: urticaria, erythema nodosum, erythema multiforme, Stephens-Johnson syndrome Serious neurologic manifestations: encephalitis, transverse myelitis, Guillain-Barre Other: cold-agglutinin positive hemolytic anemia, arthritis, glomerulonephritis, encephalitis (rare),

- Skin manifestations in 25%: urticaria, erythema nodosum, erythema multiforme, Stephens-Johnson syndrome

- Serious neurologic manifestations: encephalitis, transverse myelitis, Guillain-Barre

- Other: cold-agglutinin positive hemolytic anemia, arthritis, glomerulonephritis, encephalitis (rare),

Etiologies

- Mycoplasma (Mycoplasmoides) pneumoniae

Primary Regimens

- Doxycycline 100 mg IV/po bid x 7 days

Alternative Regimens

- Azithromycin 500 mg po on day 1 and then 250 mg po once daily x 4 days (see Comments re macrolide resistance)

- Levofloxacin 750 mg po/IV x 5 days. Not approved for children age < 16 yrs.

Comments

- Use of tetracyclines in pediatric patients has historically been limited because of reports of permanent tooth discoloration in children <8 years of age caused by incorporation of the drugs and their colored degradation products in enamel. Doxycycline can safely be administered for durations (≤21 days) regardless of patient age (AAP Red Book 2018, Section 4; J Pediatr 166:1246, 2015). Doxycycline binds less readily to calcium compared with other members of the tetracycline class, and recent comparative data suggest that doxycycline is not likely to cause visible teeth staining or enamel hypoplasia in children <8 years of age.

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- Doxycycline preferred over Azithromycin (or other currently available macrolides) because of increasing reports of macrolide-resistant strains of mycoplasma and better outcomes with tetracyclines Macrolide resistance: First recognized in SE Asian countries but now documented in the U.S.: With some geographic variability, overall resistance in US as of 2018 is 7.5% (geographic range 1.9 to 21.7%) Global prevalence of resistance to macrolides (J Antimicrob Chemother. 2022;77:2353). Efficacy of tetracyclines and fluoroquinolones for treartment of macrolide-refractory M. pneumoniae pneumonia in children (BMC Infect Dis. 2021; 21:1003). Clinical disease from resistant strains, at least in China, maybe intrinsically more severe. Because infections are mainly in children, treatment with a fluoroquinolone is not an option

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- Clinical disease from resistant strains, at least in China, maybe intrinsically more severe. Because infections are mainly in children, treatment with a fluoroquinolone is not an option

- NOTE: Beta-lactams and clindamycin not effective.

Neisseria gonorrhoeae

Clinical Setting

- Sexually transmitted infection.

- Isolation of the organism in culture of urethra, cervix, blood, pharynx, or joint fluid or by nucleic acid amplification test of urine, urethral, or cervical discharge.

- Differentiated from meningococcus by fermentation of glucose but not maltose

- See also, gonorrhea overview for links to specific clinical settings. See 2020 CDC Guidelines at MMWR 69:1911 2020 or updated CDC 2021 STD guidelines MMWR Recomm Rep 70 (RR-4):1 2021 European guidelines Int J. STD & AIDS, 2020

- Fluoroquinolones not recommended. Oral cephalosporins generally less effective.

- Resistance emerging: 2015 CDC recommendations were for 2 effective drugs (Ceftriaxone + Azithromycin), but revised in 2020 to Ceftriaxone 500 IM in light of increasing azithromycin resistance and stable patterns of resistance to Ceftriaxone.

- See CDC report on STD surveillance in 2018

Classification

- Gram negative diplococci

Primary Regimens

- Gonococcal infection of urethra, cervix, rectum, or pharynx: Ceftriaxone 500 mg IM x one dose

- Wt ≥ 150 kg (300 lb) Ceftriaxone 1gm IM x one dose

- In Europe: Ceftriaxone 1gm IM x one dose + Azithromycin 2 gm po

- Higher doses of Ceftriaxone (1 gm) recommended for disseminated infection, conjunctival disease and endocarditis.

- If chlamydial infection cannot be ruled out or concomitant C. trachomatis, recommend treating empirically with Doxycycline 100 mg po bid x 7 days

Alternative Regimens

- Uncomplicated gonococcal urethritis, cervicitis, or rectal infection (For each of the regimens listed below, Test of Cure is recommended one week after treatment):

- Azithromycin 2 gm po x 1 + Gentamicin 240 mg IM x 1

- Cefixime 800 mg po if Ceftriaxone IM not available, but this regimen has lower levels and is of limited efficacy for pharyngeal infection

- Note: Azithromycin 2 gm po as a single dose, Spectinomycin 2 gm IM x one dose are no longer recommended

- If chlamydial infection cannot be ruled out, recommend treating empirically with Doxycycline 100 mg po bid x 7 days

- In locations where allowed, partner should be treated with Cefixime 800 mg po ± Doxycycline 100 mg po bid x 7 days

- European recommendations (IntJ STD and AIDS, 2020): First line: Ceftriaxone 1gm IM x 1 + Azithromycin 2 gm po x 1 Alternative: Ceftriaxone 1gm IM ×1 (recommend Doxycycline 100 bid x 7 days if Chlamydia not excluded by NAAT) Spectinomycin 2 gm IM ×1 + Azithromycin 2 gm po x 1 Treatment failure: Ceftriaxone 1 gm IM ×1 + Azithromycin 2 gm ×1 Gentamicin 240 mg IM ×1 + Azithromycin 2 gm po ×1

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- Alternative: Ceftriaxone 1gm IM ×1 (recommend Doxycycline 100 bid x 7 days if Chlamydia not excluded by NAAT) Spectinomycin 2 gm IM ×1 + Azithromycin 2 gm po x 1

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- Spectinomycin 2 gm IM ×1 + Azithromycin 2 gm po x 1

- Treatment failure: Ceftriaxone 1 gm IM ×1 + Azithromycin 2 gm ×1 Gentamicin 240 mg IM ×1 + Azithromycin 2 gm po ×1

- Ceftriaxone 1 gm IM ×1 + Azithromycin 2 gm ×1

- Gentamicin 240 mg IM ×1 + Azithromycin 2 gm po ×1

- For severely cephalosporin allergic patients, recommended alternative regimens include:

Antimicrobial Stewardship

- Development of gonococcal resistance has been inexorable Clin Infect Dis. 2018 Apr 5. doi: 10.1093/cid/ciy271.

- Multiple drug resistance is increasing with reports of gonococcus resistant to both ceftriaxone and azithromycin. Treatment was successful in one MDR case in the UK with resistance to Ceftriaxone and high-level resistance to Azithromycin with ertapenem (Euro Surveill. 2018 Jul;23(27))

- National and international guidelines have been formulated to slow the selection and spread of resistant organisms Nat Rev Urol. 2017 Mar;14(3):139-152.

- Double coverage of gonorrhea had been recommended since 1985, but increasing effects of macrolides on microbiome and emergence of other macrolide resistant organisms, azithromycin is no longer recommended with Ceftriaxone in the US as of 2020 recommendations (MMWR 69:1911 2020)

Comments

- High dose Azithromycin (2 gm) associated with frequent GI side effects, high cost, and concern regarding increasing resistance on pathogenic organisms.

- High risk patients (e.g. MSM) should have multiple sites tested (rectum, urethra, pharynx).

- Spectinomycin is available outside the U.S. It is not efficacious for pharyngeal infections.

- Pharyngeal infection is usually asymptomatic and more difficult to eradicate. Do not use oral cephalosporins to treat pharyngeal gonorrhea.

- Test of cure not required for urogenital or rectal infections, but is recommended for pharyngeal infection.

- If Ceftriaxone IM is not available, US guidelines suggest Cefixime, 800 mg po x 1 dose while European guidelines suggest Cefixime, 400 mg po x 1 dose + Azithromycin but need test of cure (NAAT or culture) one week post treatment.

- Note: 2020 US CDC Guidelines MMWR 69:1911 2020 and 2020 European guidelines Int J. STD & AIDS, 2020 are similar but not the same. European Guidelines recommend test of cure whereas US guidelines do not (except pharyngeal GC). European Guidelines still recommend Ceftriaxone plus single dose treatment for Chlamydia with 2 gm Azithromycin (or doxycycline). European Guidelines recommend 1 gm Ceftriaxone IM.

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- European Guidelines recommend 1 gm Ceftriaxone IM.

- For a summary of the evidence contributing to revised 2020/2021 CDC guidelines Clin Inf Dis 74:S95 2022

Neisseria meningitidis

Clinical Setting

- Isolation of N. meningitidis in CSF, blood, and occasionally other sterile sites (joint fluid, pericardium).

- See also, Meningitis Overview for specific clinical settings.

- Regimens listed below are for the treatment of bacterial meningitis.

Classification

- Gram negative diplococci

Primary Regimens

- Ceftriaxone 2 gm IV q12-24h (q12h for suspected or documented meningitis) or Cefotaxime 2 gm IV q4-6h (where available outside the US)

Alternative Regimens

- Aqueous Penicillin G 3-4 million units IV q4h (max dose of 24 million units/day recommended for meningitis)

- Ampicillin 2 gm IV q3-4h (higher dose for meningitis)

- Chloramphenicol 100 mg/kg/day in 4 divided doses up to a maximum dose of 4 gm/day.

- Ciprofloxacin listed as a treatment option in meningitis by ESCMID guidelines (Clin Microbiol Infect 2016 May;22 Suppl 3:S37), but efficacy not well established. It should be reserved for use in patients who have severe penicillin and beta-lactam allergy. Recommended dose: 400 mg iv q8h for 7 days.

Ciprofloxacin is a first-line agent for meningitis prophylaxis; dose is 20 mg/kg po x1 (max dose 500 mg)

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Antimicrobial Stewardship

- Susceptibility testing recommended before switching from empiric ceftriaxone or cefotaxime to penicillin or ampicillin due to reported increase in U.S. incidence of penicillin (and/or ciprofloxacin) resistance (MMWR 69:735, June 19, 2020; Clin Infect Dis. 2021; 73:1185).

- See also Comments

Prevention

- See Meningococcal ACWY, Vaccines and Meningococcal B, Vaccines for indications, available products, dosing, and vaccine characteristics for pre-exposure prevention. Regimens for MenB vaccines may vary during outbreak situations.

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Comments

- A penicillin or third-generation cephalosporin remains the treatment of choice.

- Chloramphenicol: Increasing worldwide resistance to chloramphenicol. Note: other regimens preferred due to higher mortality rates with chloramphenicol (J Antimicrob Chemother 70: 979, 2015)

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Nocardia sp.

Clinical Setting

- Roughly two thirds of infected patients are immunocompromised and one third are immunocompetent.

- Specific therapy differs depending on the clinical syndrome.

- See specific settings: lymphadenitis, brain abscess, pneumonia.

Classification

- Gram positive, filamentous, beaded bacteria; aerobic and weakly acid fast; slow growing

- Over 40 species of Nocardia have been identified in human infections (Clin Microbiol Rev. 2006; 19:259; Clin Microbiol Rev. 2022; 35:e0002721). The more common are listed below. Nocardia nova complex Nocardia farcinica Nocardia cyriacigeorgica Nocardia brasiliensis Nocardia abscessus

- Nocardia nova complex

- Nocardia farcinica

- Nocardia cyriacigeorgica

- Nocardia brasiliensis

- Nocardia abscessus

Primary Regimens

- Brain abscess or pneumonia: TMP-SMX 15 mg/kg/day (TMP component) IV in 2-4 divided doses + Imipenem-cilastatin 500 mg IV q6h

- Lymphadenitis and/or skin abscess: TMP-SMX 5-10 mg/kg/day (TMP component) IV/po divided in 2-4 doses

Alternative Regimens

- Brain abscess: Linezolid 600 mg IV/po q12h + Meropenem 2 gm IV q8h

- Pneumonia: Imipenem-cilastatin 500 mg IV q6h + Amikacin 7.5 mg/kg IV q12h x 3-4 weeks, then po TMP-SMX

- Lymphadenitis and/or skin abscess: Minocycline 100-200 mg po bid

Comments

- Increasing number of Nocardia species recognized: susceptibility of 1299 isolates representing 39 different species (Antimicrob Agents Chemother 58:795, 2014). All isolates susceptible to Linezolid. Resistance to TMP/SMX in only 2 % overall but as high as 31% in some rarely encountered species. Variable suscept. of rare species to Imipenem, Amikacin, Ceftriaxone. In short, susceptibility testing appears desirable with less frequently encountered species or in patients allergic/intolerant to TMP-SMX.

- For in vitro susceptibility testing: Wallace lab (+1) 903-877-7680 or CDC (+1) 404-639-3158 or some commercial labs.

- For brain abscess: If the organism is sulfonamide resistant or patient is sulfonamide allergic, possible therapies are Amikacin IV plus one of the following: Imipenem, Meropenem, Ceftriaxone, or Cefotaxime (where available outside the US).

- Moxifloxacin active in vitro but clinical experience is limited (Antimicrob Agents Chemother 55:2084, 2011).

Bacteria: Normal Flora, Non-pathogenic, Contaminants, Rare Pathogens

Introduction

- Rare pathogens

- Normal human flora

- Environmental contaminants

- Often non-pathogenic and of low virulence

- Present in mixed cultures

Organisms

Parvimonas micra

Clinical Setting

- Positive lab result

- Oral and gastrointestinal flora. Associated with odontogenic infections and, rarely, bacteremia, abscess (Anaerobe 2018, 54:136)

Classification

- Anerobic gram-positive coccus

Primary Regimens

- Typically susceptible to Penicillin, Clindamycin, Metronidazole

Alternative Regimens

- A carbapenem

Comments

- See Eur J Clin Microbiol Infect Dis. 2023;42:903 and Microorganisms. 2021;9:1665 for cases series and antimicrobial susceptibilities

Bacteria: Normal Flora, Non-pathogenic, Contaminants, Rare Pathogens

Introduction

- Rare pathogens

- Normal human flora

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Organisms

Pasteurella multocida

Clinical Setting

- Management of cat and dog bites Pasteurella is normal flora of the mouth of cats and dogs. Soft tissue infection, or even bacteremia, occurs in humans as a result of the bite or sometimes the lick of the cat or dog. Prophylactic (anticipatory) antibiotic therapy indicated due to high frequency of infection

- Pasteurella is normal flora of the mouth of cats and dogs.

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- Wound culture, wound cleansing and debridement are needed.

- See Cat bites and Dog bites.

- Can occur in the absence of animal contact (Front Cell Infect Microbiol. 2023; 13: 1267941).

- Evaluate for need of tetanus toxoid immunization and rabies prophylaxis.

Classification

- Gram-negative coccobacilli

Primary Regimens

- Desired spectrum: Predictable activity against 1) Pasteurella species isolated from the mouth of the animal, 2) Staph. aureus, and 3) Streptococcal species isolated from the patient's skin:

- Amoxicillin-clavulanate 875/125 mg tab, 1 po bid x 7-10 days (not defined, but seems reasonable)

Alternative Regimens

- IgE-mediated severe penicillin allergy; positive cultures for Pasteurella species; negative for Staph. aureus: Cefuroxime 500 mg po q12h

- Cefuroxime 500 mg po q12h

Antimicrobial Stewardship

- Pasteurella species are susceptible to some, but not all, beta-lactams.

- If penicillin allergic, do not use cephalexin, clindamycin, or an erythromycin due to frequent in vitro resistance.

Comments

- For parenteral use: Ceftriaxone, Penicillin G, Ciprofloxacin, Levofloxacin or Moxifloxacin.

- High level resistance to Erythromycin, Clindamycin, and Vancomycin.

- Only moderate susceptibility to Cephalexin, Cefazolin, Azithromycin, Nafcillin, and aminoglycosides.

Peptoniphilus sp., Finegoldia sp.

Clinical Setting

- Peptoniphilus species (includes 15 or more species), Finegoldia magna. Formerly: Peptostreptococcus species

- Formerly: Peptostreptococcus species

- Anaerobic streptococci that are part of the normal flora of the upper respiratory tract, pharynx, GI tract and vagina.

- Local infections can occur, e.g., periodontal, endometritis, or bacteremia can ensue.

- Bacteremia can be complicated by brain abscess, endocarditis, or a variety of other focal infections.

Classification

- Anaerobic streptococcus, includes P. anaerobius P. stomatis Two species might vary somewhat in in vitro susceptibility (Antimicrob Agents Chemother 51: 2205, 2007) Finegoldia magna (Anaerobe 61:102111, 2020)

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- Finegoldia magna (Anaerobe 61:102111, 2020)

Primary Regimens

- Penicillin G dose depends on the site of infection. High dose for meningitis/brain abscess: 18-24 million units per day.

- One reported patient with anaerobic endocarditis was cured with a 4-week course of aqueous Penicillin G 3 million units IV q4h (Am J Med Sci 342:174, 2011).

Alternative Regimens

- Metronidazole 500 mg IV q8h

- Clindamycin dose depends on site of infection. IV dose ranges from 600-900 mg IV q8h (see Comment)

Comments

- One French study reported 28% Clindamycin resistance (Int J Antimicrob Agents 10:229, 1998); in another in vitro study, the majority (but not all) of isolates were susceptible to Clindamycin, Moxifloxacin, Metronidazole, and Penicillins (Antimicrob Agents Chemother 51: 2205, 2007).

- One case report of successful treatment of a brain abscess with Linezolid (Scand J Infect Dis 38: 203, 2006).

- Series of 15 cases of Peptoniphilus sp bloodstream infection (Clin Microbiol Infect 20(11): O857, 2014).

Plesiomonas shigelloides

Clinical Setting

- Found in water and soil. Causes intestinal disease after eating raw seafood; found in fresh or brackish water especially in warmer waters.

- Called "shigelloides" because of antigenic cross reactions with Shigella sp., particularly S. sonnei

- Clinically varies from watery secretory diarrhea to dysentery and fever.

- Can cause extra-intestinal infection, especially in immunocompromised patients and those with hepatobiliary disease.

Classification

- Gram negative bacilli, facultative anaerobe, nonlactose fermenter

- Formerly Aeromonas shigelloides

Primary Regimens

- Hydration

- Ciprofloxacin (400 mg IV or 750 mg po) bid. Duration to depend on disease severity. As few as 3 days may work for mild diarrhea

Alternative Regimens

- Hydration

- For severe disease: Ceftriaxone 2 gm IV qd or carbapenem based on susceptibility testing

- For less severe disease: Amoxicillin-clavulanate 875/125 mg po bid

- Duration of treatment based on clinical response

Antimicrobial Stewardship

- Susceptibility testing should be done for all treated with antibiotic therapy

- Most strains are resistant to Ampicillin, Piperacillin, aminoglycosides and Tetracycline.

Comments

- Resistance to TMP-SMX, erythromycin has been reported

- Avoid raw or undercooked shell fish, especially during warmer summer months.

Porphyromonas endodontalis

Clinical Setting

- Positive lab result

- Oral flora. Associated with odontogenic infections, rarely, other abscesses (J Endod 1992, 18:431)

Classification

- Anaerobic gram-negative rod

- Formerly Bacteroides endodontalis

Primary Regimens

- Typically susceptible to Penicillin, Clindamycin, Metronidazole, Tetracyclines

Alternative Regimens

- None

Comments

- None

Cutibacterium acnes

Clinical Setting

- Slow growing anaerobic gram-positive anaerobic bacilli that are part of the normal flora of the human skin, hair follicles, and sebaceous glands.

- Prosthetic hip joint infections from related C. acnes and other Propionibacterium (now Cutibacterium) species (Clin Infect Dis 2018; 66:54).

- Infects orthopedic hardware, endovascular devices (including prosthetic heart valves), ventricular CSF shunts. Grow slowly and often overlooked unless cultures held for 5 or more days. Key part of management is to remove, if possible, the infected device.

- Implicated as a cause of acne infection. See specific topics: Acne vulgaris, Acne rosacea.

- Rare cause of endocarditis: Clin Microbiol Infect 15:387, 2009.

Classification

- Gram positive bacilli

- Cutibacterium acnes (formerly Propionibacterium acnes)

Primary Regimens

- Penicillin G 12-18 (higher doses if CSF infected) million units/day divided q4-6h

- Ceftriaxone 2 gm IV q12h if CSF infected

Alternative Regimens

- Vancomycin 15 mg/kg q12h; increase to 15 mg/kg q8h if CSF infected

- Daptomycin may be effective for endocarditis; active in vitro; limited clinical data

- Linezolid static in vitro but high concentrations in bone.

Antimicrobial Stewardship

- Often resistant to Metronidazole.

Comments

- Review: Future Microbiol. 2023;18:235

- Treatment of infected prosthetic joints: Clin Infect Dis 49:1083, 2009.

- In vitro activity of Daptomycin and Vancomycin: Antimicrob Agents Chemother 50:2728, 2006.

- Sonication of shoulder joint prostheses (J Clin Microbiol 47:1878, 2009) and inoculation of homogenized tissue and bone samples into aerobic thioglycolate broth and incubation for 10 days

followed by blind subculture onto chocolate and Brucella agar plates improves yield (J Clin Microbiol 543043, 2016).

Proteus sp., mirabilis, penneri, vulgaris

Clinical Setting

- Proteus sp. cause a variety of infections that range from uncomplicated UTIs to life-threatening infections of the abdomen, skin and soft tissue, lung and other sites in both normal and immunocompromised hosts. Urinary tract infections are the most common and are often catheter associated. Proteus species are known for biofilm formation and the production of a potent urease enzyme which in turn stimulates stone (struvite) formation in the urinary tract. Urease converts urea into CO2 and ammonia. Result is alkaline urine that fosters precipitation of crystals of magnesium ammonium phosphate and stone formation 10-15% of ureteral stones composed of ammonium magnesium phosphate (called struvite stones)

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- Specific therapy depends on antimicrobial susceptibility, site and severity of infection.

- For discussion of antibiotic resistance mechanisms, issues and treatment considerations, see Antimicrobial Stewardship and Gram Negative Bacilli, Resistance to Beta-lactams, Overview.

Classification

- Gram negative bacilli, motile (swarming on culture plate)

- Proteus mirabilis (indole negative)

- Proteus penneri (indole negative)

- Proteus vulgaris (indole positive)

Primary Regimens

- Treatment options below are for therapy of moderately-severe, or severe infections in patients requiring systemic therapy

Alternative Regimens

- No evidence that infecting strain is producing either an ESBL or plasmid based AmpC: Cefixime or Cefpodoxime or Cefdinir (all po) Fosfomycin 3 gm po x 1 dose (UTI only) Severe beta-lactam allergy: Aztreonam

- Cefixime or Cefpodoxime or Cefdinir (all po)

- Fosfomycin 3 gm po x 1 dose (UTI only)

- Severe beta-lactam allergy: Aztreonam

- If in vitro susceptibility consistent with ESBL production and patient cannot be given a carbapenem, other options: An aminoglycoside or a fluoroquinolone if susceptibile Ceftolozane-tazobactam 1.5 gm over 3h IV q8h or Ceftazidime-avibactam 2.5 gm IV over 3 hrs q8h Both are stable in the presence of ESBLs and are approved for the treatment of complicated UTIs and intra-abdominal infections (with Metronidazole) Cefepime-enmetazobactam recently FDA approved for treatment of complicated UTIs, including ESBL producers Temocillin 2 gm IV q12h (where available) Uncomplicated cystitis: Fosfomycin 3 gm po x 1 dose Complicated UTI: Fosfomycin 6 gm IV q8h (where available)

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- Both are stable in the presence of ESBLs and are approved for the treatment of complicated UTIs and intra-abdominal infections (with Metronidazole)

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- Temocillin 2 gm IV q12h (where available)

- Uncomplicated cystitis: Fosfomycin 3 gm po x 1 dose

- Complicated UTI: Fosfomycin 6 gm IV q8h (where available)

Antimicrobial Stewardship

- Reserve carbapenems for mixed anaerobia/aerobic infections or for treatment of infections due to ESBL-producing strains

- Reserve ceftazidime-avibactam and Meropenem-vaborbactam for infections caused by bacteria documented to produce carbapenemases

- Antibiotic resistance: Proteus species are intrinsically resistant to polymyxins Check susceptibility of all carbapenems. Cannot assume resistance to meropenem if lab indicates resistance to imipenem.

- Proteus species are intrinsically resistant to polymyxins

- Check susceptibility of all carbapenems. Cannot assume resistance to meropenem if lab indicates resistance to imipenem.

Comments

- Do not use Piperacillin-tazobactam for suspected or proven ESBL production even if in vitro susceptibility is present; clinical failures reported: Antimicrob Agents Chemother 57:3402, 2013.

- The rationale for the Ceftazidime-avibactam/Aztreonam combination for metallo-beta-lactamase (MBL) producers is that Aztreonam is not hydrolyzed by MBLs and Ceftazidime is. However, MBL-producers commonly produce ESBLs or serine-carbapenemases, which can degrade Aztreonam. Although avibactam does not inhibit MBLs, it does inhibit serine beta-lactamases (i.e., ESBLs, AmpC, and serine-carbapenemases) such that the Aztreonam which would otherwise be degraded by the serine beta-lactamases remains active. See Antimicrob Agents Chemother 2017 Mar 24; 61(4). pii:e02243-16.

- Cefiderocol: FDA-approved for patients with complicated UTI due to cefiderocol susceptible bacteria and with limited or no alternative treatment options. In an open label randomized trial of cefiderocol vs Best Available Therapy (BAT) in patients with sepsis, pneumoinia, bacteremia or cUTI, mortality at 28 days was 24.8% for cefiderocol pts. vs 18.4% for BAT pts (not statistically significant).

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- Investigational drug in late stages of development Aztreonam-avibactam

- Aztreonam-avibactam

- IDSA Guideline on treatment of ESBL and carbapenemase producers: Clin Infect Dis. 2023 Jul 18:ciad428.

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Clinical Setting

- Proteus sp. cause a variety of infections that range from uncomplicated UTIs to life-threatening infections of the abdomen, skin and soft tissue, lung and other sites in both normal and immunocompromised hosts. Urinary tract infections are the most common and are often catheter associated. Proteus species are known for biofilm formation and the production of a potent urease enzyme which in turn stimulates stone (struvite) formation in the urinary tract. Urease converts urea into CO2 and ammonia. Result is alkaline urine that fosters precipitation of crystals of magnesium ammonium phosphate and stone formation 10-15% of ureteral stones composed of ammonium magnesium phosphate (called struvite stones)

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- Specific therapy depends on antimicrobial susceptibility, site and severity of infection.

- For discussion of antibiotic resistance mechanisms, issues and treatment considerations, see Antimicrobial Stewardship and Gram Negative Bacilli, Resistance to Beta-lactams, Overview.

Classification

- Gram negative bacilli, motile (swarming on culture plate)

- Proteus mirabilis (indole negative)

- Proteus penneri (indole negative)

- Proteus vulgaris (indole positive)

Primary Regimens

- Treatment options below are for therapy of moderately-severe, or severe infections in patients requiring systemic therapy

Alternative Regimens

- No evidence that infecting strain is producing either an ESBL or plasmid based AmpC: Cefixime or Cefpodoxime or Cefdinir (all po) Fosfomycin 3 gm po x 1 dose (UTI only) Severe beta-lactam allergy: Aztreonam

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- Fosfomycin 3 gm po x 1 dose (UTI only)

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- If in vitro susceptibility consistent with ESBL production and patient cannot be given a carbapenem, other options: An aminoglycoside or a fluoroquinolone if susceptibile Ceftolozane-tazobactam 1.5 gm over 3h IV q8h or Ceftazidime-avibactam 2.5 gm IV over 3 hrs q8h Both are stable in the presence of ESBLs and are approved for the treatment of complicated UTIs and intra-abdominal infections (with Metronidazole) Cefepime-enmetazobactam recently FDA approved for treatment of complicated UTIs, including ESBL producers Temocillin 2 gm IV q12h (where available) Uncomplicated cystitis: Fosfomycin 3 gm po x 1 dose Complicated UTI: Fosfomycin 6 gm IV q8h (where available)

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- Uncomplicated cystitis: Fosfomycin 3 gm po x 1 dose

- Complicated UTI: Fosfomycin 6 gm IV q8h (where available)

Antimicrobial Stewardship

- Reserve carbapenems for mixed anaerobia/aerobic infections or for treatment of infections due to ESBL-producing strains

- Reserve ceftazidime-avibactam and Meropenem-vaborbactam for infections caused by bacteria documented to produce carbapenemases

- Antibiotic resistance: Proteus species are intrinsically resistant to polymyxins Check susceptibility of all carbapenems. Cannot assume resistance to meropenem if lab indicates resistance to imipenem.

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Comments

- Do not use Piperacillin-tazobactam for suspected or proven ESBL production even if in vitro susceptibility is present; clinical failures reported: Antimicrob Agents Chemother 57:3402, 2013.

- The rationale for the Ceftazidime-avibactam/Aztreonam combination for metallo-beta-lactamase (MBL) producers is that Aztreonam is not hydrolyzed by MBLs and Ceftazidime is. However, MBL-producers commonly produce ESBLs or serine-carbapenemases, which can degrade Aztreonam. Although avibactam does not inhibit MBLs, it does inhibit serine beta-lactamases (i.e., ESBLs, AmpC, and serine-carbapenemases) such that the Aztreonam which would otherwise be degraded by the serine beta-lactamases remains active. See Antimicrob Agents Chemother 2017 Mar 24; 61(4).

pii:e02243-16.

- Cefiderocol: FDA-approved for patients with complicated UTI due to cefiderocol susceptible bacteria and with limited or no alternative treatment options. In an open label randomized trial of cefiderocol vs Best Available Therapy (BAT) in patients with sepsis, pneumoinia, bacteremia or cUTI, mortality at 28 days was 24.8% for cefiderocol pts. vs 18.4% for BAT pts (not statistically significant).

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- Investigational drug in late stages of development Aztreonam-avibactam

- Aztreonam-avibactam

- IDSA Guideline on treatment of ESBL and carbapenemase producers: Clin Infect Dis. 2023 Jul 18:ciad428.

Providencia sp. (stuartii, rettgeri, alcalificiens)

Clinical Setting

- Isolation, in culture from urine, blood, or wound, of: Providencia stuartii Providencia rettgeri Providencia alcalifaciens

- Providencia stuartii

- Providencia rettgeri

- Providencia alcalifaciens

- Typically a nosocomial pathogen with several resistance mechanisms. Resistance varies with species; P. stuartii is generally the most resistant, frequently produces ESBLs, and 50% or more of isolates are resistant to aminoglycosides and fluoroquinolones. P. alcalifaciens and P. rustigianii are more often susceptible to penicillins and older cephalosporins P. rettgeri susceptibility falls between that of P. stuartii and P. alcalifaciens Providencia species are intrinsically resistant to polymyxins

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- P. rettgeri susceptibility falls between that of P. stuartii and P. alcalifaciens

- Providencia species are intrinsically resistant to polymyxins

- Specific therapy depends on the location and severity of the infection, the fragility of the patient, and the result of in vitro antibiotic susceptibility testing.

- For further discussion of resistance mechanisms, issues and treatment considerations, see Gram Negative Bacilli, Beta-lactam Resistance, Overview.

Classification

- Facultative anaerobic gram negative bacilli

Primary Regimens

- Treatment: Recommendations for systemic treatment of moderately-severe, or severe, infection. For details see IDSA Guieance on the treatment of Antimicrobial Resistant Gram-Negative Infections

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Alternative Regimens

- For patients with severe IgE-mediated allergy to beta-lactams (e.g., anaphylaxis, angioneurotic edema) and if susceptible in vitro:

- Aztreonam 2 gm IV q6-8h

- Ciprofloxacin 400 mg IV q12h or 750 mg po bid

- Levofloxacin 750 mg IV/po once daily

- ESBL and/or AmpC producing strains: Ceftolozane-tazobactam 1.5 gm IV over 3h q8h or Temocillin 2 gm IV q12h (where available)

- In vitro resistance of Providencia species to all carbapenems including meropenem-vaborbactam with concomitant resistance to ceftazidime-avibactam, fluoroquinolones, TMP/SMX, and aminoglycosides Infectious Diseases consultation suggested

- Infectious Diseases consultation suggested

- Possible salvage regimens: Ceftazidime-avibactam + Aztreonam combination (Antimicrob Agents Chemother 2017; 61: e02243-16). Regimen based on resistance of aztreonam to hydrolysis by metallo-carbapenemases with avibactam protecting the aztreonam from destruction by concomitant ESBLs. Fosfomycin IV (where available) US: Emergency single patient IND from the FDA: Call 1-888-6332 OR +1-301-796-1400; Emergency operations at +1-301-796-8240 or 1-866-300-4374 Plazomicin 15 mg/kg IV q24h (complicated UTIs)

- Ceftazidime-avibactam + Aztreonam combination (Antimicrob Agents Chemother 2017; 61: e02243-16). Regimen based on resistance of aztreonam to hydrolysis by metallo-carbapenemases with avibactam protecting the aztreonam from destruction by concomitant ESBLs.

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Antimicrobial Stewardship

- Considerations in antimicrobial selection: ESBL: Avoid piperacillin-tazobactam, even if susceptible in vitro, due to documented clinical failures: JAMA 2018;320:979. There is often concomitant in vitro resistance to fluoroquinolones and aminoglycosides. Due to risk of toxicity, avoid aminoglycosides unless no other option is available Providencia sp. are intrinsically resistant to Polymyxins (Colistin and Polymyxin B). Providencia sp. usually resistant to nitrofurantoin Tigecycline may have in vitro activity but clinical efficacy questionable due to low serum levels. If urinary tract source, Providencia sp. are usually multidrug resistant.

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Comments

- Cefiderocol: FDA-approved for complicated UTI due to cefiderocol susceptible bacteria and with limited or no alternative treatment options. In an open label randomized trial of cefiderocol vs Best Available Therapy (BAT) in patients with sepsis, pneumoinia, bacteremia or cUTI, mortality at 28 days was 24.8% for cefiderocol pts. vs 18.4% for BAT pts (not statistically significant).

- References: See IDSA 2023 Guidance on the treatment of multidrug resistant isolates

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Pseudomonas aeruginosa

Clinical Setting

- Recommendations below are for therapy of moderately severe or severe infections in patients requiring systemic therapy.

- Pseudomonas aeruginosa causes a variety of local and systemic infections in both normal and immunocompromised hosts: e.g., Ventilator-associated pneumonia Haematogenous seeding of the skin evolving to deep ulcers, termed ecthyma gangrenosum in neutropenic patients

- Ventilator-associated pneumonia

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- P. aeruginosa has a wide variety of antibacterial resistance mechanisms which may occur in combination including:

- Permeability mutants due to multi-drug efflux pumps and/or loss of outer membrane porins most commonly, particularly for carbapenem resistance

- Beta-lactamase mediated AmpC (most common) due to production and/or overexpression of chromosomal AmpC which hydrolyses penicillins, monobactams, cephalosporins (cefepime is a possible exceptioin), and not inhibited by serine-beta-lactamse inhibitors (e.g., tazobactam) Extended-spectrum beta-lactamases (ESBL) (uncommon) hydrolyze anti-pseudomonal cephalosporins (e.g., Cefepime, Ceftazidime) Production of serine carbapenemases is rare but metallo-beta-lactamases may be present

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- Production of serine carbapenemases is rare but metallo-beta-lactamases may be present

- Mutation of drug target: e.g., fluoroquinoline resistance due to selection of gyrase mutants

- For further discussion of resistance mechanisms, issues and treatment considerations, see Gram Negative Bacilli, Beta-lactam Resistance, Overview. See Comments for IDSA Guidelines reference.

Classification

- Aerobic gram negative bacilli, glucose non-fermenter

Primary Regimens

- No detected in vitro resistance Aztreonam 2 gm IV q6h (for patients with IgE-mediated beta-lactam allergy) Levofloxacin 750 mg IV q24h or Ciprofloxacin 400 mg IV q8h (see Comment for septic shock patients) Cefoperazone 2 gm IV q12h (where available) Imipenem-cilastatin 0.5-1 gm IV q6h

- Aztreonam 2 gm IV q6h (for patients with IgE-mediated beta-lactam allergy)

- Levofloxacin 750 mg IV q24h or Ciprofloxacin 400 mg IV q8h (see Comment for septic shock patients)

- Cefoperazone 2 gm IV q12h (where available)

- Imipenem-cilastatin 0.5-1 gm IV q6h

- Critical illness, combination therapy pending in vitro susceptibility: Piperacillin-tazobactam or Ceftazidime or Meropenem plus Tobramycin 7 mg/kg IV q24h OR Ciprofloxacin 400 mg IV q8h or Levofloxacin 750 mg IV q24h

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Antimicrobial Stewardship

- No value to continued combination therapy once in vitro susceptibility is known

- Encourage use, if available, of pathogen detection with multiplex PCR platforms, gene sequencing to identify resistance mechanisms and other modalities that improve targeted therapy.

Comments

- NOTE: recommendations are for therapy of moderately severe or severe infections for patients requiring systemic therapy

- Cefiderocol. FDA-approved for patients with complicated UTI due to cefiderocol susceptible bacteria and with limited or no alternative treatment options. Comment: In an open label randomized trial of cefiderocol vs Best Available Therapy (BAT) in patients with sepsis, pneumoinia, bacteremia or cUTI, mortality at 28 days was 24.8% for cefiderocol pts. vs 18.4% for BAT patients (not statistically significant)

- Carbapenem resistance is usually due to impaired permeability and/or efflux pump activity and not a carbapenemase (Antimicrob Agents Chemother 2015; 59:1020) The variability in the in vitro susceptibility to the combination of Ceftazidime-avibactam plus Aztreonam is likely due to non-enzymatic mechanisms of resistance (Diag Microbiol & Infect Dis 2017; 88: 352; Antimicrob Agents Chemother. 2017;61: e01008-17) Combination of (Meropenem or Imipenem) + Polymyxin B is not recommended as result of failure of a prospective randomized clinical trial to show benefit: Lancet Infect Dis 2018;18:391 Pending results of ongoing controlled clinical trials, prudent to avoid the polymyxin-carbapenem combination Possible carbapenem-aminoglycoside salvage regimen for extensively resistant strains needs clinical validation. Ertapenem is not active in vitro vs. P. aeruginosa.

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- Combination therapy Potential benefits of a combination for empiric therapy, especially in patient at high risk of infection with multi-drug resistant strain: Increased likelihood that at least one of the two drugs will be active Decreased risk of selection of resistant subpopulations (unproven clinically but demonstrated in animal models) Additive or synergistic antibacterial activity if both drugs active (unproven clinically but demonstrated in animal models)

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- Beta-lactams. Ceftolozane-tazobactam Of 3,851 isolates, 97% susceptible in vitro. 87.6% of 699 meropenem-resistant isolates were susceptible. Ref: Antimicrob Agents Chemother 2017;61:e00465-17 Report of emergence of resistance in 15% of patients after 7 to 53 days of therapy due to ampC mutations Mutations lead to cross resistance to ceftazidme-avibactam but restored susceptibility to imipenem-cilastatin-relebactam Ref.: Antimicrob Agents Chemother 2021; 65: e00084-21

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- Reference: IDSA Guidance on the treatment of multidrug resistant isolates (Clin Infect Dis 2022; 75: 187)

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Rhodococcus hoagii

Clinical Setting

- Zoonotic organism, initially isolated from foals but can cause infection in a variety of animal species. Isolation of the organism in culture of sputum, respiratory tract specimens, lung, blood, other tissues.

- Intracellular pathogen.

- Subacute pneumonia, often mimicking tuberculosis, in immunocompromised patient: e.g., HIV with CD4 < 200.

- Cavitary pneumonia with hemoptysis in 1/3 of patients.

- Extrapulmonary complications include brain and/or skin abscesses.

Classification

- Aerobic gram positive coccobacilli, pleomorphic, may be weakly acid fast

- Nomenclature change: Rhodococcus hoagii (formerly Rhodococcus equi, Corynebacterium equi)

- Rhodococcus hoagii (formerly Rhodococcus equi, Corynebacterium equi)

Primary Regimens

- Combine two from the following:

- Moxifloxacin 400mg po daily or Levofloxacin 750 mg IV/po once daily OR Ciprofloxacin 500 mg po bid

- Rifampin 600 mg IV/po once daily

- Azithromycin 250 mg IV/po once daily

Comments

- Because of ability to survive within macrophages, usually need combination therapy that includes use of a drug with adequate intracellular concentrations: e.g., macrolide with either rifampin or doxycycline.

- Due to resistance or uncertain susceptibility avoid Clindamycin, Chloramphenicol, tetracyclines (usually sensitive to doxycycline), penicillins, cephalosporins, and TMP-SMX.

- Duration of therapy uncertain but 10-14 days may be sufficient with longer courses, 2 months, in patients who are immunocompromised or for those with cavitary disease (Clin Microbiol Infect 2018 May 16. pii: S1198-743X(18)30400-2).

- Careful monitoring of drug-drug interactions and for toxicity with longer duration combination therapy (e.g., ECG for QTc with macrolides, quinolones)

- HIV/AIDS Treat for 2 months Secondary prophylaxis until CD4 > 200: Azithromycin 250 mg po once daily + Levofloxacin 750 mg po once daily.

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- Linezolid active in vitro and is another option, although prolonged use is accompanied by bone marrow suppression and neurotoxicity (peripheral neuropathy, optic neuritis)

- Review: Lancet Infect Dis 10:350, 2010.

Bacteria: Normal Flora, Non-pathogenic, Contaminants, Rare Pathogens

Introduction

- Rare pathogens
- Normal human flora
- Environmental contaminants
- Often non-pathogenic and of low virulence
- Present in mixed cultures

Organisms

Bacteria: Normal Flora, Non-pathogenic, Contaminants, Rare Pathogens

Introduction

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- Often non-pathogenic and of low virulence
- Present in mixed cultures

Organisms

Salmonella sp.

Clinical Setting

- Foodborne (or waterborne) illness, often in an outbreak setting.

- Treatment not recommended for mild-to-moderate gastroenteritis in immunocompetent patients as infection is self-limited.

- Recommendations below are for patients with severe illness, immunocompromised patients, others at risk of complication or invasive disease (young children, elderly).

- CLSI has established interpretive breakpoints for susceptibility to Ciprofloxacin (Clin Infect Dis 55:1107, 2012)

- Susceptible strains: MIC < 0.06 ■g/mL

- Higher MICs (0.12-1.0, intermediate and > 2.0, resistant) correlate with presence of mutations in gyrA, gyrB, or plasmid-mediated fluoroquinolone resistance

- For commercial antimicrobial susceptibility test systems that have not incorporated lower dilutions into test panels either Ciprofloxacin Etest or disk diffusion testing with both ciprofloxacin (zone diameter > 31 mm indicates susceptible) and nalidixic acid are recommended to detect decreased ciprofloxacin susceptibility and high level resistance

- Ampicillin, TMP-SMX, and Chloramphenicol should not be used empirically due to high frequency of resistance (Clin Infect Dis 50:241, 2010).

- Treatment, if needed, should be guided by region of the world where the isolate was acquired.

- Emerging MDR and XDR isolates described especially in South Asia.

- Clinical syndromes: Salmonella, overview Typhoid Fever or Enteric Fever Salmonella Typhi Salmonella Parathyphi Salmonella bacteremia Salmonella gastroenteritis

- Salmonella, overview

- Typhoid Fever or Enteric Fever Salmonella Typhi Salmonella Parathyphi

- Salmonella Typhi

- Salmonella Parathyphi

- Salmonella bacteremia

- Salmonella gastroenteritis

Etiologies

- Salmonella enterica serovars Salmonella Typhi Salmonella Parathyphi Salmonella Choleraesuis Salmonella Typhimurium

- Salmonella Typhi

- Salmonella Parathyphi

- Salmonella Choleraesuis

- Salmonella Typhimurium

Primary Regimens

- Ciprofloxacin 400 mg IV or 500 mg po bid OR Levofloxacin 750 mg IV/po once daily for 7-14 days. (not if Salmonella Typhi aka Typhoid fever suspected due to extensive XDR)

- Ceftriaxone 2 gm IV once daily for 7-14 days (preferred if there is history of travel to Asia or other regions where fluoroquinolone resistance is prevalent)

- If severely ill or XDR suspected: Meropenem 1-2 gm IV q8h (or other carbapenem)

Alternative Regimens

- Azithromycin 1 gm IV/po for 1 dose and then 500 mg IV/po once daily for 5-7 days

- If above not available: Chloramphenicol 2-3 gm IV/po in 4 divided doses for 14 days

- Cefixime 20-30 mg/kg/day po in two divided doses for 7-14 days (experience more mixed in trials, may not perform as well as other agents)

- TMP-SMX 8-10 mg/kg of TMP component IV/po in 2-3 divided doses if confirmed susceptibility in vitro

- Severe illness: add Dexamethasone as above.

Antimicrobial Stewardship

- Antimicrobial therapy of uncomplicated gastroenteritis may prolong carriage.

Comments

- In severe illness caused by S. Typhi (i.e., typhoid fever) consider concomitant Dexamethasone 3 mg/kg IV loading dose and then 1 mg/kg IV q6h for 48 hrs (N Engl J Med 310:82, 1984).

- The longer duration of therapy, e.g., 14 days or more, is recommended for patients who are immunocompromised.

- Relapse can occur: 10-20% with Chloramphenicol; with fluoroquinolones and Ceftriaxone estimated at 1-6%.

- Chronic carriage in 1-6%, especially in patients with cholelithiasis.

- Molecular epidemiology and resistance patterns will differ for Non Typhoid Salmonella (NTS; Clin Infect Dis 75:732 2022) compared to Salmonella typhi with Salmonella typhi more frequently XDR (Open Forum Infect Dis 10:S26 2023)

Serratia marcescens

Clinical Setting

- Serratia marcescens causes a variety of local and systemic infections in both normal and immunocompromized hosts.

- Treatment regimens vary based on culture and in vitro susceptibility results.

- Prevalence of multi-drug resistant (MDR) strains is increasing. Serratia sp. isolates can express one, or more, mechanisms of antibiotic resistance: Extended spectrum beta-lactamases (ESBL) or AmpC (uncommon). Carbapenemases, serine and metalloenzymes Resistance to other classes of antibiotics can occur: Reduced susceptibility of aminoglycosides may be due to production of drug-modifying enzymes, reduced cell wall permeability and/or efflux pumps, altered the targeted antibiotic ribosomal binding site Serratia are intrinsically resistant to polymyxins (Polymyxin B and Colistin), ampicillin, ampicillin-sulbactam, amoxicillin clavulanate, cefazolin, cephamycins and nitrofurantoin

- Extended spectrum beta-lactamases (ESBL) or AmpC (uncommon).

- Carbapenemases, serine and metalloenzymes

- Resistance to other classes of antibiotics can occur:

- Reduced susceptibility of aminoglycosides may be due to production of drug-modifying enzymes, reduced cell wall permeability and/or efflux pumps, altered the targeted antibiotic ribosomal binding site

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- For further discussion of resistance mechanisms, issues and treatment considerations, see Gram Negative Bacilli, Beta-lactam Resistance, Overview.

Classification

- Aerobic facultative gram negative bacilli

Primary Regimens

- Treatment options below are for therapy of moderately-severe, or severe infections in patients requiring systemic therapy

Alternative Regimens

- If no in vitro resistance but severe IgE-mediated beta-lactam allergy (anaphylactic shock, urticaria):

- Ciprofloxacin 400 mg IV q12h or 750 mg po bid or Levofloxacin 750 mg IV/po once daily

- Aztreonam 2 gm IV q6h

- Gentamicin or Tobramycin 7 mg/kg IV loading dose and then 5.1 mg/kg IV q24h

Antimicrobial Stewardship

- Do not use polymyxins as Serratia sp. are intrinsically resistant.

- Reserve carbapenems for mixed anaerobic/aerobic infections or for the treatment of infections due to ESBL producing strains

- Reserve Meropenem-vaborbactam and ceftazidime-avibactam for documented KPC infections

Comments

- Aztreonam is not hydrolyzed by metallocarbapenemases (ceftazidime is) but is inactivated by ESBLS which are often produced concomitantly with the carbapenemase. Avibactam inactivates ESBLs. See Antimicrob Agents Chemother 2017 Mar 24; 61(4). pii:e02243-16

- Cefiderocol: FDA-approved for complicated UTI due to cefiderocol susceptible bacteria and with limited or no alternative treatment options. In an open label randomized trial of cefiderocol vs Best Available Therapy (BAT) in patients with sepsis, pneumoinia, bacteremia or cUTI, mortality at 28 days was 24.8% for cefiderocol pts. vs 18.4% for BAT pts (not statistically significant).

- Other drug in late development with activity vs MDR GNB: Aztreonam-avibactam

- Aztreonam-avibactam

- IDSA Guideline on treatment of ESBL, AmpC, and carbapenemase producers: Clin Infect Dis. 2023 Jul 18:ciad428.

Shigella sp.

Clinical Setting

- Acute self-limited febrile diarrhea (Shigellosis) that usually lasts 7 days if untreated.

- Stool culture and in vitro susceptibility should be performed; specific therapy dictated by in vitro susceptibility results.

- Important cause of morbidity and mortality globally from infectious intestinal disease in young children in low-income and middle-income countries

- Outbreaks linked to international travel caused by ciprofloxacin-resistant S. sonnei (Emerg Infect Dis 21:1246, 2015 and Emerg Infect Dis 22:1640, 2016).

- Local outbreaks of strains resistant to ciprofloxacin, ampicillin, and TMP/SMX: MMWR 64:318, 2015

- Now also a frequent cause of sexually transmitted infection in men have sex with men

- Increased risk of antibiotic resistance to ceftriaxone, azithromycin, or fluoroquinolones for Shigella infection especially in MSM: Emerg Infect Dis, 22:1613, 2016.Lancet Infect Dis. 15:913, 2015.Lancet ID 2022 S1473-3099(22)00370-X.

- See also, Gastroenteritis, Shigella, Specific Therapy.

Classification

- Gram negative bacilli Shigella dysenteriae (serogroup A) Shigella flexneri (serogroup B) Shigella boydii (serogroup C) Shigella sonnei (serogroup D)

- Shigella dysenteriae (serogroup A)

- Shigella flexneri (serogroup B)

- Shigella boydii (serogroup C)

- Shigella sonnei (serogroup D)

Primary Regimens

- Routine therapy for uncomplicated gastroenteritis not recommended as treatment shortens duration of illness by only 1-2 days.

- Antibiotic treatment recommended for immunocompromised patients or those with severe illness (e.g., hospitalization, invasive disease, or other complications) or to prevent outbreaks (e.g., treatment of food handlers).

- Empiric therapy: Ciprofloxacin 500 mg po bid or 750 mg po once daily x 3 days Levofloxacin 500 mg po once daily x 3 days

- Ciprofloxacin 500 mg po bid or 750 mg po once daily x 3 days

- Levofloxacin 500 mg po once daily x 3 days

- If infection acquired in Asia or other locales with known high frequency of antibiotic resistance: Ceftriaxone 1-2 gm IV once daily x 5 days

- For traveler's diarrhea, usually the causative organism is not known. Single dose treatment (continuing up to 3 days if symptoms continue) often sufficient.

- Specific therapy is based on in vitro susceptibility results. If sensitive in vitro:

- Ciprofloxacin or Levofloxacin (as above)

- Ceftriaxone (as above)

- Azithromycin 500 mg po once daily x 3 days

- TMP-SMX-DS 1 tab po bid x 5 days

Alternative Regimens

- None

Antimicrobial Stewardship

- Shigellosis is a self-limited infection, lasting 5-7 days. Treatment shortens course of illness by only a day or two, promotes resistance, and may prolong shedding. Reserve therapy for more severely ill patients or for use in an outbreak setting if so advised by public health officials.

- Isolates with ciprofloxacin MICs of 0.12 µg/mL to 1.0 µg/mL may be reported as susceptible but these concentrations are associated with presence of fluoroquinolone resistance genes. Confirm MIC and avoid fluoroquinolones if the ciprofloxacin MIC is > 0.12 µg/mL even if the laboratory reports the isolate as susceptible.

- Outbreaks of MDR/XDR Shigella flexneri and Shigelli sonnei resistant to multiple antibiotics have been reported increasingly frequently, including in retirement facilities Clin Inf Dis 74:455 2022 and amongst MSM Lancet ID 2022, S1473-3099(22)00370-X.

Comments

- CDC advisory about resistance breakpoints: https://emergency.cdc.gov/han/han00401.asp and CDC resistance threat report.

- Avoid Ampicillin and Amoxicillin due to high frequency of resistance; TMP-SMX only if sensitivity is confirmed.

- Resistance to nalidixic acid associated with treatment failure or relapse with a fluoroquinolone.

- With respect to food handlers, stool cultures become culture negative after a minimum of 48 hrs of effective therapy.

- Emergence and expansion of an extensively drug resistant (XDR) ESBL Shigella sonnei has been associated with an outbreak in MSM in the UK (sensitive to pivmecillinam, fosfomycin, chloramphenicol, colistin or carbapenems). Lancet ID 2022, S1473-3099(22)00370-X.

Staphylococcus aureus, MSSA

Clinical Setting

- Isolation of a methicillin-susceptible strain of Staph. aureus (MSSA) in culture.

- Definitive therapy depends on severity and site of infection.

- For specific recommendations see the following:

- Bacteremia

- Endocarditis

- Furuncules, skin abscess, boils

- Osteomyelitis

- Pneumonia

- Prosthetic joint infection

- Septic arthritis

Classification

- Methicillin-susceptible Staphylococcus aureus (MSSA)

Primary Regimens

- First-line agents: Nafcillin, Oxacillin, Flucloxacillin, Cefazolin

- Bacteremia, other invasive infection Nafcillin or Oxacillin 1-2 gm IV q4-6h Cefazolin 1-2 gm IV q8h

- Nafcillin or Oxacillin 1-2 gm IV q4-6h

- Cefazolin 1-2 gm IV q8h

- Oral options for mild to moderate infections Dicloxacillin 500 mg po qid Cephalexin 500 mg po qid

- Dicloxacillin 500 mg po qid

- Cephalexin 500 mg po qid

Alternative Regimens

- Bacteremia, other invasive infection and severe allergy to beta-lactams or other treatment-limiting adverse effect Vancomycin 15-20 mg/kg IV q8-12h to achieve preferred target AUC24 400-600 μg/mL x hr (see vancomycin AUC dosing calculator; alternative is trough of 15-20 μg/mL)(see Comments) Daptomcyin 6 mg/kg IV q24h (consider use of 8-10 mg/kg dose for bacteremia) Linezolid 600 mg po/IV q12h: for patients without bacteremia or for selected patients with uncomplicated bacteremia (good source control, no metastatic foci of infection, prompt conversion of blood cultures to negative), uncomplicated intravascular catheter-related bacteremia, or bacteremia accompanying acute bacterial skin and skin structure infections or pneumonia; not recommended as a first- or second-line agent for endocarditis or other endovascular infection (Int J Antimicrob Agents. 2021;57:106329, Clin Infect Dis. 2019;69:381, J Antimicrob Chemother. 2005; 56:923).

- Vancomycin 15-20 mg/kg IV q8-12h to achieve preferred target AUC24 400-600 μg/mL x hr (see vancomycin AUC dosing calculator; alternative is trough of 15-20 μg/mL)(see Comments)

- Daptomcyin 6 mg/kg IV q24h (consider use of 8-10 mg/kg dose for bacteremia)

- Linezolid 600 mg po/IV q12h: for patients without bacteremia or for selected patients with uncomplicated bacteremia (good source control, no metastatic foci of infection, prompt conversion of blood cultures to negative), uncomplicated intravascular catheter-related bacteremia, or bacteremia accompanying acute bacterial skin and skin structure infections or pneumonia; not recommended as a first- or second-line agent for endocarditis or other endovascular infection (Int J Antimicrob Agents. 2021;57:106329, Clin Infect Dis. 2019;69:381, J Antimicrob Chemother. 2005; 56:923).

- Oral options for mild or moderate infections

- Clindamycin 300-450 mg po tid

- TMP-SMX 160-800 mg 1-2 tabs po bid

- Linezolid 600 mg po q12h

Antimicrobial Stewardship

- Empiric vancomycin for suspected or proven S. aureus bacteremia pending in vitro susceptibility results appears to be comparable to empiric use of a beta-lactam provided a beta-lactam is used for definitive therapy.

- No evidence that empiric beta-lactam-vancomcyin combination therapy improves outcome and is not recommended.

- Beta-lactams (e.g., Ceftriaxone) other than Cefazolin, Nafcillin, or Oxacillin for parenteral therapy of bacteremia or other invasive S. aureus infections are of unproven efficacy and generally not recommended.

- See Comments

Comment

- A beta-lactam is the preferred agent for treatment of staphylococcal infections. Vancomycin is less effective than nafcillin or cefazolin and should be reserved for patients unable to tolerate a beta-lactam because of allergy or adverse effect (Clin Infect Dis 2015; 61:361-7). Nafcillin and cefazolin appear to be equally effective clinically and cefazolin is better tolerated (Clin Microbiol Infect 2018; 24:125-132) and (Clin Microbiol Infect 2018; 24:152-158). Cefazolin inoculum effect (CzIE), likely due to beta-lactamase mediated hydrolysis of cefazolin in which the Cefazolin MIC is increased several-fold by use of a 100-fold higher than the standard inoculum, may be associated with clinical failure (Open Forum Infect Dis 2018; 5:ofy123). Whether treatment failure is a direct result of hydrolysis of Cefazolin or due to some other factor was not determined in this study. A study of osteoarticular infections in children (Antimicrob Agents Chemother 2020;64:e00703-20) found that the CzIE was independently associated with worse outcome and treatment failure irrespective of which antibiotic was used, suggesting that the CzIE phenotype may be a marker for strain-dependent virulence factors and not true, cefazolin-specific treatment failure.

- Nafcillin and cefazolin appear to be equally effective clinically and cefazolin is better tolerated (Clin Microbiol Infect 2018; 24:125-132) and (Clin Microbiol Infect 2018; 24:152-158).

- Cefazolin inoculum effect (CzIE), likely due to beta-lactamase mediated hydrolysis of cefazolin in which the Cefazolin MIC is increased several-fold by use of a 100-fold higher than the standard inoculum, may be associated with clinical failure (Open Forum Infect Dis 2018; 5:ofy123). Whether treatment failure is a direct result of hydrolysis of Cefazolin or due to some other factor was not determined in this study. A study of osteoarticular infections in children (Antimicrob Agents Chemother 2020;64:e00703-20) found that the CzIE was independently associated with worse outcome and treatment failure irrespective of which antibiotic was used, suggesting that the CzIE phenotype may be a marker for strain-dependent virulence factors and not true, cefazolin-specific treatment failure.

Staphylococcus aureus, MRSA

Clinical Setting

- Clinical isolate of Staphylococcus aureus that is resistant to nafcillin and other semi-synthetic anti-staphylococcal penicillins.

- For IDSA Guidelines for treatment of MRSA in adults and children see Clin Infect Dis 52(3):e18, 2011.

- For specific recommendations see the following topics:

Classification

- Methicillin-resistant (MRSA)

- Gram positive cocci in clusters

Primary Regimens

- Staph. aureus resistant to methicillin (MRSA, Vancomycin MIC <4 μg/mL):

- Vancomycin 15-20 mg/kg IV q8-12h to achieve preferred target AUC24 400-600 μg/mL x hr (see vancomycin AUC dosing calculator); alternative is trough of 15-20 μg/mL

- Linezolid 600 mg po/IV q12h for pneumonia or acute bacterial skin and skin structure infections (see Comments):

- Daptomycin 4-6 mg/kg once daily IV (consider higher dose of 8-12 mg/kg q24h for bacteremia, see Comments) Daptomycin should not be used to treat primary MRSA pneumonia (but is effective for tricuspid valve endocarditis with septic pulmonary emboli).

- Daptomycin should not be used to treat primary MRSA pneumonia (but is effective for tricuspid valve endocarditis with septic pulmonary emboli).

- Staph. aureus resistant to methicillin and intermediate (VISA, MIC 4-8 μg/mL) or resistant (VRSA, MIC >8 μg/mL) to Vancomycin:

- Linezolid

- Daptomycin (confirm susceptibility, see bacteremia if used for salvage therapy or treatment failures for MRSA)

- TelavancinNAI: Active in vitro and in vivo against VISA only but not VRSA

- CeftarolineNAI 600 mg q8-12h IV (q8h for treatment of bacteremia) (Open Forum Infect Dis. 2021; 23:ofab606)

Alternatives

- MRSA and Vancomycin MIC <4 μg/mL: Staphylococci with inducible MLSB resistance may appear susceptible to clindamycin in vitro but are associated with treatment failure; test for inducible resistance [double-disc (“D test”)] before treating with clindamycin). TMP-SMX but not an agent of first choice as a randomized controlled trial that failed to show non-inferiority to vancomycin (BMJ 14:350, 2015).

- Staphylococci with inducible MLSB resistance may appear susceptible to clindamycin in vitro but are associated with treatment failure; test for inducible resistance [double-disc (“D test”)] before treating with clindamycin).

- TMP-SMX but not an agent of first choice as a randomized controlled trial that failed to show non-inferiority to vancomycin (BMJ 14:350, 2015).

- Possible alternatives, based on in vitro susceptibility and severity of infection: TeicoplaninNUS, Telavancin, TMP-SMX, Minocycline, Doxycycline, Ceftaroline, or Clindamycin

- Fusidic acidNUS, Fosfomycin, Rifampin may be active; use only in combination to prevent in vivo emergence of resistance.

- Ceftaroline 600 mg q8h IV appears to be an effective salvage therapy for bacteremia, either as a single agent (Am J Health Syst Pharm. 74:201, 2017). (Antimicrob Agents Chemother. 2017; 61(2). pii: e02015-16) or in combination with vancomycin or daptomycin (Pharmacotherapy. 2023; 43:15-23, Int J Antimicrob Agents. 2021;57:106310)

- See also Staph. aureus bacteremia.

- VISA/VRSA (MIC ≥4 μg/mL): Rifampin must be combined with another active agent to prevent emergence of resistance during therapy.

- Rifampin must be combined with another active agent to prevent emergence of resistance during therapy.

- VISA: most susceptible to Daptomycin (some strains are cross-resistant so confirm susceptibility), Linezolid, TMP-SMX, Minocycline, Doxycycline, Rifampin, Ceftaroline, and Telavancin.

- VRSA: fewer than 20 clinical isolates of truly vancomycin-resistant strains reported worldwide (MIC ≥16 μg/mL); organisms susceptible to TMP-SMX, Linezolid, Minocycline, Quinupristin-dalfopristin, Daptomycin, Ceftaroline.

- Currently recommended only for treatment of acute bacterial skin and skin structure infections: MRSA with Vancomycin MIC <4 μg/mL: Dalbavancin, Oritavancin, Tedizolid VISA/VRSA (MIC ≥4 μg/mL): Unknown but Tedizolid is active

- MRSA with Vancomycin MIC <4 μg/mL: Dalbavancin, Oritavancin, Tedizolid

- Dalbavancin, Oritavancin, Tedizolid

- VISA/VRSA (MIC ≥4 μg/mL): Unknown but Tedizolid is active

- Unknown but Tedizolid is active

Comments

- Linezolid may be an option for oral step-down for selected patients with uncomplicated bacteremia due to intravascular catheter-related infections, or accompanying acute bacterial skin and skin structure infections or pneumonia; not recommended as a first- or second-line agent for endocarditis or other endovascular infection (Int J Antimicrob Agents. 2021;57:106329, Clin Infect Dis. 2019;69:381, J Antimicrob Chemother. 2005; 56:923).

- Methicillin resistance is encoded by either of two genes, mecA and mecC, which code for a low-affinity penicillin-binding protein, PBP2a and PBP2c, respectively. Tests designed to detect PBP2a (e.g., MRSA latex agglutination assay) will not reliably detect PBP2c and tests designed to detect mecA (nucleic acid amplification tests such as BD MAX MRSA or Cepheid Xpert MRSA) will not detect mecC. The Cepheid Xpert MRSA NxG and BD MAX MRSA XT, in vitro tests for detection of MRSA DNA from nasal swabs of MRSA colonized patients, are able to detect both mecA and mecC.

- Some authorities recommend higher then the 6 mg/kg FDA-approved dose of Daptomycin (8-12 mg/kg/day) for MRSA bacteremia, particularly for salvage therapy or treatment failures as this may improve efficacy and appears to have acceptable rates of toxicity (Pharmacotherapy 31:527, 2011).

- Infectious Disease consultation advised when treating MRSA infections not responding to primary regimens or caused by strains intermediate or resistant to vancomycin.

- Best treatment for infections caused by MRSA strains with Vancomycin MIC = 2 μg/mL unclear.

- Treatment failure has been associated with isolates Vancomycin MIC = 2 μg/mL (Clin Infect Dis 52:975, 2011), but meta-analysis of 38 studies found no association (JAMA 312:1552, 2014).

- If clinical or microbiological response to Vancomcyin therapy is unsatisfactory, alternative therapy should be considered regardless of MIC.

- An alternative to Vancomycin should always be used for infections caused by MRSA strains with Vancomycin MICs > 2 μg/mL.

Staphylococcus epidermidis

Clinical Setting

- Isolation of S. epidermidis in sterile-site culture. Most common species among coagulase-negative staphylococcal pathogens and a frequent contaminant.

- Important cause of prosthetic or implantable device infections, vascular catheters, peritoneal dialysis catheters.

- Strains are often methicillin-resistant.

- Agents and doses listed below are for more serious infections, such as bacteremia or prosthetic device infections.

Classification

- Gram positive cocci in clusters

Primary Regimens

- Methicillin-susceptible

- Nafcillin or Oxacillin 2 gm q4-6h

- Cefazolin 2 gm q8h

- Methicillin-resistant:

- Vancomycin 15-20 mg/kg IV q8-12h to achieve preferred target AUC24 400-600 μg/mL x hr (see vancomycin AUC dosing calculator; alternative is trough of 15-20 μg/mL)

- Daptomycin 6 mg/kg IV q24h

- Methicillin and intermediate glycopeptide resistance:

- Linezolid 600 mg po/IV q12h

- Daptomycin 6 mg/kg IV q24h (confirm susceptibility)

Alternative Regimens

- Oral therapy for prosthetic device infections, implants sue to susceptible organism: Rifampin + (TMP-SMX or Fluoroquinolone)

Comments

- Infections due to other coagulase-negative species are treated similar to those caused by Staph. epidermidis.

- Rifampin 300-450 mg q12h often added in combination with one of the above for prosthetic device infections.

Staphylococcus sp., Coagulase-negative

Clinical Setting

- Coagulase-negative Staphylococcus species.

- Skin flora and a frequent contaminant of blood and other cultures, but can cause serious infections, usually involving implanted devices. Prosthetic or implanted device infections, peritoneal dialysis catheter infections, vascular device infections

- Prosthetic or implanted device infections, peritoneal dialysis catheter infections, vascular device infections

- Frequently methicillin resistant.

Classification

- Gram positive cocci in clusters Staphylococcus capitis Staphylococcus epidermidis Staphylococcus hominis Staphylococcus lugdunensis (severity and spectrum of disease similar to S. aureus) Staphylococcus caprae Staphylococcus haemolyticus

- Staphylococcus capitis

- Staphylococcus epidermidis

- Staphylococcus hominis

- Staphylococcus lugdunensis (severity and spectrum of disease similar to S. aureus)

- Staphylococcus caprae

- Staphylococcus haemolyticus

Primary Regimens

- Vancomycin for empiric therapy, see Staphylococcus epidermidis for details

Alternative Regimens

- Infections due to methicillin-susceptible strains can be treated with Nafcillin, Oxacillin, or Cefazolin

- Linezolid or Daptomycin are alternatives for methicillin-resistant strains

Comments

- None

Staphylococcus haemolyticus

Clinical Setting

- Isolation of the organism in culture.

- A coagulase-negative species that is a common cause of intravascular catheter infections, but may cause other infections similar to those caused by Staph. epidermidis.

- Usually resistant to methicillin and may be glycopeptide resistant.

Classification

- Gram positive cocci in clusters

Primary Regimens

- Glycopeptide-susceptible strain:

- Vancomycin 15-20 mg/kg IV q8-12h to achieve preferred target AUC24 400-600 μg/mL x hr (see vancomycin AUC dosing calculator; alternative is trough of 15-20 μg/mL)

- Glycopeptide-non-susceptible strain:

- Daptomycin 6 mg/kg IV q24h

- Linezolid 600 mg po/IV q12h

Alternative Regimens

- Methicillin-susceptible strains: Nafcillin, Oxacillin, or Cefazolin

- Other options, once susceptibility is confirmed: TMP/SMX, Doxycycline

Comments

- Review: Microbiol Res. 2024; 282:127652.

Staphylococcus lugdunensis

Clinical Setting

- Isolation of the organism in culture.

- May be confused with Staph. aureus because Staph. lugdunensis clumping factor reacts with the latex agglutination test used to identify Staph. aureus.

- Coagulase-negative species, but severity of infection resembles Staph. aureus: may cause endocarditis, vascular catheter-related bloodstream infections, bone and joint, skin and soft-tissue infections.

Classification

- Gram positive cocci in clusters

Primary Regimens

- Methicillin-susceptible strain Oxacillin 2 gm IV q4-6h or Nafcillin 2 gm IV q4-6h If beta-lactamase negative strain: Penicillin G 2 million units IV q4h (if beta-lactamase negative)

- Oxacillin 2 gm IV q4-6h or Nafcillin 2 gm IV q4-6h

- If beta-lactamase negative strain: Penicillin G 2 million units IV q4h (if beta-lactamase negative)

- Methicillin-resistant strain or severe beta-lactam allergy Vancomycin 15-20 mg/kg IV q8-12h to achieve preferred target AUC24 400-600 μg/mL x hr (see vancomycin AUC dosing calculator; alternative is trough of 15-20 μg/mL) Daptomycin 10 mg/kg IV q24h

- Vancomycin 15-20 mg/kg IV q8-12h to achieve preferred target AUC24 400-600 μg/mL x hr (see vancomycin AUC dosing calculator; alternative is trough of 15-20 μg/mL)

- Daptomycin 10 mg/kg IV q24h

Alternative Regimens

- Cefazolin 2 gm IV q8h (Methicillin-susceptible strain)

Comments

- Add Rifampin and Gentamicin if prosthetic valve infection (See Endocarditis, Coagulase-Negative Staphylococci)

- Treatment similar as for S. aureus infections; duration of therapy determined by severity and site of infection.

- Approximately 75% are penicillin-susceptible; prevalence of methicillin resistance is low historically, ~5%, but may be increasing.

- Review: J Clin Microbiol. 2017 Feb;55(2):585-595.

Staphylococcus saprophyticus

Clinical Setting

- Uncomplicated urinary tract infection (and less frequently upper tract infection) with isolation of the organism in urine culture.

- After E. coli, S. saprophyticus is the second most common cause of uncomplicated UTI.

- Novobiocin resistant, differentiating it from other coagulase-negative species.

Classification

- Gram positive cocci in clusters

Primary Regimens

- TMP-SMX 160/800 mg po bid x 3 days

Alternative Regimens

- Nitrofurantoin 100 mg po bid x 5 days (lower tract infection only)

- Levofloxacin 500 mg po once daily x 3 days (see comments)

- Cephalexin 500 mg po qid or Amoxicillin-clavulanate 875/125 mg po bid x 7 days

Antimicrobial Stewardship

- Longer durations, e.g., 7-10 days indicated for upper tract infection.

- Resistant to Fosfomycin.

Comments

- Susceptible to most agents used for treatment of urinary tract infections.

Stenotrophomonas maltophilia

Clinical Setting

- Stenotrophomonas maltophilia causes pneumonia, bacteremia, and other infections. Immunocompromised and/or debilitated patients are predisposed. Can be an etiology of acute exacerbations, with or without P. aeruginosa, in patients with cystic fibrosis

- Immunocompromised and/or debilitated patients are predisposed.

- Can be an etiology of acute exacerbations, with or without P. aeruginosa, in patients with cystic fibrosis

- Stenotrophomonas is intrinsically resistant to: Beta-lactams (penicillins, cephalosporins, aztreonam, and carbapenems) due to chromosomal: Zinc-dependent metallo-beta lactamase Production of extended-spectrum beta lactamases (ESBLs) OXA-type beta-lactamase In vitro susceptibility of 1,839 clinical isolates (Antimicrob Agents Chemother 2020;64: e01433-20): Trimethoprim-sulfamethoxazole 95.4 Levofloxacin 78.0 Minocycline 99.5 Ceftazidime 20.9 (not recommended as monotherapy) Omadacycline, Eravacycline, and Cefiderocol active in vitro but limited or no clinical data

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- Zinc-dependent metallo-beta lactamase

- Production of extended-spectrum beta lactamases (ESBLs)

- OXA-type beta-lactamase

- In vitro susceptibility of 1,839 clinical isolates (Antimicrob Agents Chemother 2020;64: e01433-20): Trimethoprim-sulfamethoxazole 95.4 Levofloxacin 78.0 Minocycline 99.5 Ceftazidime 20.9 (not recommended as monotherapy) Omadacycline, Eravacycline, and Cefiderocol active in vitro but limited or no clinical data

- Trimethoprim-sulfamethoxazole 95.4

- Levofloxacin 78.0

- Minocycline 99.5

- Ceftazidime 20.9 (not recommended as monotherapy)

- Omadacycline, Eravacycline, and Cefiderocol active in vitro but limited or no clinical data

- Therapy is almost always in response to a positive culture and is guided by in vitro susceptibility results.

- See also, Stenotrophomonas pneumonia.

Classification

- Gram negative bacilli

Primary Regimens

- Combination therapy is recommended for treatment of moderately-severe or severe infections: see Stenotrophomonas pneumonia for recommended regimens

- For mild infections and polymicrobial infections where the role of S. maltophilia as a pathogen is unclear: TMP-SMX 8-12 mg/kg/day IV/po based on TMP component divided q8h or q12h is a preferred regimen

Alternative Regimens

- For moderately severe or severe infections: Combination therapy with two of the following agents: TMP-SMX (8-12 mg/kg/d IV/po divided q8h or q12h), Levofloxacin (750 mg Iv/po q24h), Minocycline (200 mg IV/po q12h), Tigecycline (200 mg IV x1, then 100 mg IV q12h), or Cefiderocol 2 g IV q8h infused over 3 hours) (Clin Infecf Dis 2022; 74:2089) Ceftazidime-avibactam 2.5 gm IV over 3h q8h + Aztreonam 2 gm IV over 2h q8h

- Combination therapy with two of the following agents: TMP-SMX (8-12 mg/kg/d IV/po divided q8h or q12h), Levofloxacin (750 mg Iv/po q24h), Minocycline (200 mg IV/po q12h), Tigecycline (200 mg IV x1, then 100 mg IV q12h), or Cefiderocol 2 g IV q8h infused over 3 hours) (Clin Infecf Dis 2022; 74:2089)

- Ceftazidime-avibactam 2.5 gm IV over 3h q8h + Aztreonam 2 gm IV over 2h q8h

- For mild infections and polymicrobial infections where the role of S. maltophilia is unclear: monotherapy with TMP-SMX, Levofloxacin, Minocycline, Tigecycline, or Cefiderocol

Antimicrobial Stewardship

- Depending on severity of illness and with source control plus in vitro susceptibility and clinical response to combination therapy can consider de-escalating to oral TMP-SMX IV or Minocycline.

Comments

- There is no standard of care regimen. IDSA guidance (Clin Infecf Dis 2022; 74:2089) is to use combination therapy in a effort to prevent emergence of resistance on therapy, which is common, with the agents listed above.

- Based on observational evidence levofloxacin is a reasonable alternative to TMP-SMX for the treatment of bloodstream and lower respiratory tract infections caused by S. maltophilia (Open Forum Infect Dis. 2022; 9:ofab644).

- Cefiderocol: FDA-approved for complicated UTI due to cefiderocol susceptible bacteria and with limited or no alternative treatment options. In an open label randomized trial of cefiderocol vs Best Available Therapy (BAT) in patients with sepsis, pneumoinia, bacteremia or cUTI, mortality at 28 days was 24.8% for cefiderocol pts. vs 18.4% for BAT pts (not statistically significant). Cefiderocol active in vitro and in animal pneumonia model against both TMP/SMX susceptible and TMP/SMX resistant strains (Antimicrob Agents Chemother 2021; 65: e01436-20) Cefiderocol more efficacious than TMP/SMX in experimental Stenotrophomonas pneumonia in neutropenic rabbits (Antimicrob Agents Chemother 2022 May 17;66(5):e0006522)

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- Cefiderocol active in vitro and in animal pneumonia model against both TMP/SMX susceptible and TMP/SMX resistant strains (Antimicrob Agents Chemother 2021; 65: e01436-20)

- Cefiderocol more efficacious than TMP/SMX in experimental Stenotrophomonas pneumonia in neutropenic rabbits (Antimicrob Agents Chemother 2022 May 17;66(5):e0006522)

- Most strains are susceptible to polymyxins (Polymyxin B, Colistin) in vitro but they are rarely used due to toxicity. Polymyxin B: easier to dose than Colistin. Do not use for UTIs due to low concentrations in urine. Colistin: reserve for UTIs

- Polymyxin B: easier to dose than Colistin. Do not use for UTIs due to low concentrations in urine.

- Colistin: reserve for UTIs

- Tigecycline: FDA cites higher risk of death among patients given tigecycline compared to other antibacterials and recommends use only in situations where alternative therapy is not suitable.

Streptobacillus moniliformis

Clinical Setting

- Most common cause of rat bite fever in the U.S. Spirillum minus is most common cause in Asia and elsewhere. See also Bites, Rat

- Presents with fever, myalgia, arthralgia and headache; suspect when history of rat bite and maculopapular rash on extremities; polyarthralgia in 50%.

- Diagnosis: culture of blood and/or synovial fluid.

- Management: debridement of wound and tetanus prophylaxis.

- No need for rabies prophylaxis after rodent bite.

Classification

- Slender Gram negative bacilli

Primary Regimens

- Aqueous Penicillin G 200,000 units IV q4h to 2 million units IV q4h; can follow, once improving, with Penicillin V-K 500 mg po qid before meals and hs

Alternative Regimens

- Doxycycline 100 mg IV/po bid

Comments

- Other alternatives but experience is limited: Erythromycin, Chloramphenicol, Clindamycin and Ceftriaxone.

- Streptomycin effective but seldom used due to potential for ototoxicity.

- For endocarditis, recommendation has been for penicillin plus aminoglycoside (Clin Microbiol Rev 20: 13, 2007)

Streptococcus agalactiae, Group B Strep

Clinical Setting

- Important cause of neonatal meningitis and bacteremia and peripartum infections.

- See also prophylaxis for intrapartum Group B streptococcal infection in pregnancy.

- Reference for infants at risk for Group B Streptococcal Disease (Pediatrics 2019; 144: e20191881)

- May also cause infection in non-pregnant adult women and men; risk factors include older age, diabetes, obesity, liver disease, malignancy, HIV.

- Types of infections include post-partum endometritis, bacteremia, puerperal sepsis, and wound infection; primary bacteremia, endocarditis, meningitis, pneumonia, septic arthritis, skin and soft tissue infections and urinary tract infection. Toxic shock-like syndrome reported; Clin Infect Dis. 1993 Jul;17(1):26-31.

- Diagnosis is made by isolation of the organism from blood, CSF, sputum, urine, or other site of infection.

Classification

- Gram positive cocci in chains

Primary Regimens

- Adult

- Meningitis: Penicillin G 4 million units IV q4h

- Endocarditis: Penicillin G 4 million units IV q4h + Gentamicin 1 mg/kg IV q8h

- Bacteremia, skin and soft tissue, other infections: Penicillin G 2 million units IV q4h

- Neonate and infant (Ampicillin 100-150 mg/kg/d in 3-4 divided doses + Gentamicin 2.5 mg/kg q8h-q24h depending on weight and age) (may be discontinued once infection is under control) Penicillin G 200,000-400,000 units/kg/day

- (Ampicillin 100-150 mg/kg/d in 3-4 divided doses + Gentamicin 2.5 mg/kg q8h-q24h depending on weight and age) (may be discontinued once infection is under control)

- Penicillin G 200,000-400,000 units/kg/day

- Meningitis or endocarditis: (Ampicillin 100 mg/kg IV q6h or Penicillin G 400,000 units/kg/day)+ Gentamicin 2.5 mg/kg q8h-q24h depending on weight and age (gentamicin may be discontinued once infection is under control)

- Bacteremia, soft tissue, other infections:

Alternative Regimens

- Penicillin allergic patient Vancomycin 15-20 mg/kg IV q8-12h (Check trough levels, target 15-20 μg/mL) Ceftriaxone 2g IV q24h Clindamycin 600 mg IV 8h (must confirm susceptibility; see comment below)

- Vancomycin 15-20 mg/kg IV q8-12h (Check trough levels, target 15-20 μg/mL)

- Ceftriaxone 2g IV q24h

- Clindamycin 600 mg IV 8h (must confirm susceptibility; see comment below)

- Adult:

- Child: see Vancomycin for dosing schedules

Antimicrobial Stewardship

- Duration of therapy 10-14 days except for endocarditis or osteomyelitis which should be treated for 4-6 weeks.

Comments

- Ampicillin and penicillin are equally effective and interchangeable.

- Oral therapy with Amoxicillin 500 mg po tid for 10 days is an option for treatment of urinary tract infection; these infections, which tend to occur in middle aged and older women, may be associated with urinary tract abnormalities (e.g., stones).

- If possible avoid Vancomycin in combination with Gentamicin because of enhanced nephrotoxicity.

- Gentamicin for synergy and may be discontinued once the infection is controlled or after 2 weeks in patients with endocarditis.

- In infants with meningitis, lumbar puncture should be repeated in 48-72 hours to determine sterility. If cultures negative, gentamicin can be stopped.

- Caution if Clindamycin is considered as an alternative in patients with severe beta-lactam allergy and severe infection; Failures with Clindamycin monotherapy due to inducible resistance reported in animal model and retrospective detection in 8 patients (Antimicrob Agents Chemother 58:1327, 2014) In vitro resistance over 45% per CDC acute bacterial core surveillance data.

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- In vitro resistance over 45% per CDC acute bacterial core surveillance data.

Streptococcus anginosus group

Clinical Setting

- Streptococus anginosus group, formerly the Streptococcus milleri group, consists of three distinct species of viridans streptococci: S. anginosus, S. intermedius and S. constellatus (Clin Infect Dis 32:1511, 2001).

- Can be normal flora of mouth and GI tract but also capable of causing bacteremia and abscess formation; it is the propensity to produce abscesses that clinically distinguishes the anginosus group from other viridans streptococci.

- Gram-positive cocci with variable patterns of hemolysis on blood agar: alpha, beta, or gamma.

- Of interest, colonies often produce a butterscotch or caramel odor.

Classification

- Gram positive coccus in chains

- Streptococcus anginosus group (formerly Strep. milleri group) consists of three species:

- Streptococcus intermedius

- Streptococcus anginosus

- Streptococcus constellatus

Primary Regimens

- Susceptible to the beta-lactams: penicillins, cephalosporins, and carbapenems (Antimicrob Agents Chemother 45:1511, 2001)

- Dose and selection depends on site and severity of infection: e.g.,

- Dental abscess should respond to surgical drainage and Pen VK 500 mg po qid before meals and h.s.

- Brain abscess would require high dose Penicillin G, 18-24 million units divided q4-6h IV or Ceftriaxone 2 gm IV q12h

Alternative Regimens

- Vancomycin is active and a reasonable alternative

- Emergence of resistance, see Comments

Comments

- Because of ease of development of resistance, fluoroquinolones are not considered first line therapy (J Antimicrob Chemother 2000;45:771. Note: FQs studied were ciprofloxacin, norfloxacin, and ofloxacin).

- Evidence of emerging macrolide resistance (J Med Microbiol 58:222, 2009).

- Many strains are resistant to aminoglycosides.

- Sulfonamides are not active.

Streptococcus pneumoniae

Clinical Setting

- Isolation of Streptococcus pneumoniae; may display in vitro resistance to penicillin, macrolides, and/or TMP-SMX.

- Criteria for resistance varies depending on whether the in vivo target is effective concentrations in the CSF or non-CSF sites of infection.

Classification

- Gram positive cocci in pairs, chains

Primary Regimens

- Non-meningeal infections

Alternative Regimens

- None

Prevention

- See Pneumococcal, Vaccines, Adult for indications, available products, dosing, and vaccine characteristics for pre-exposure prevention. Single dose Prevnar 20 (PCV20) has de facto replaced all previous vaccines (PCV13, PPSV23). Less cumbersome than sequential dosing with PCV15/PPSV23 spaced by 1 year.

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Comments

- Resistance to Penicillin G (MIC > 4.0 μg/mL):

- Meningeal isolates: < 0.1= Susceptible; 0.1-1.0 = Intermediate; ≥ 2.0 = Resistant.

- Non-meningeal isolates: ≤ 2.0 = Susceptible; 4.0 = Intermediate; ≥ 8.0 = Resistant.

- Resistance to Ceftriaxone Meningeal isolates: < 0.5 = Susceptible; > 0.5 and < 1.0 = Intermediate; > 1.0 = Resistant. Non-meningeal isolates: ≤ 1.0 = Susceptible; > 1 and < 2.0 = Intermediate; > 2.0 = Resistant.

- Meningeal isolates: < 0.5 = Susceptible; > 0.5 and < 1.0 = Intermediate; > 1.0 = Resistant.

- Non-meningeal isolates: ≤ 1.0 = Susceptible; > 1 and < 2.0 = Intermediate; > 2.0 = Resistant.

Streptococcus pyogenes, Beta hemolytic, Group A, B, C, F, G Strep

Clinical Setting

- Identification of Streptococcus pyogenes (Group A streptococcus) in culture of tissue or blood or positive rapid test in patient with pharyngitis

- Positive tissue or blood culture of other beta-hemolytic streptococci

- Causes pharyngitis, variety of cutaneous infections generally referred to as "cellulitis" (e.g., erysipelas, impetigo, necrotizing fasciitis), bacteremia, and toxic shock syndrome. Other species of

beta-hemolytic streptococci cause similar infections.

- Post-infectious immune complications include acute rheumatic fever and acute glomerulonephritis.

Classification

- Beta-hemolytic streptococci include the following Groups: A - S. pyogenes B - S. agalactiae C - S. equi F, G - S. dysgalactiae

- A - S. pyogenes

- B - S. agalactiae

- C - S. equi

- F, G - S. dysgalactiae

Primary Regimens

- For Group A streptococcal pharyngitis: Adult: Penicillin G benzathine (Bicillin L-A) 1.2 million units IM x one dose Cephalexin 500 mg po bid x 10 days Azithromycin 500 mg po on day one, then 250 mg po daily on days 2 through 5 Clindamycin 300 mg po tid x 10 days Pen VK 500 mg po bid x 10 days Child: Wt < 27 kg: To lessen pain of injection, Penicillin G benzathine combined with procaine penicillin G: (900,000 units of benzathine Pen G combined with 300,000 units of procaine penicillin G) IM X one dose Some substitute Amoxicillin suspension 50 mg/kg/day divided bid. Amoxicillin suspension is more palatable and, due to better absorption, may be more efficacious Cephalexin 25-50 mg/kg/day po in 2 equally divided doses x 10 days Azithromycin 12 m/kg po once daily for 5 days Clindamycin (Wt < 70 kg) 7 mg/kg/dose po tid for 10 days Pen VK 25-50 mg/kg/day div q6h x 10 days Other considerations: Other later generation cephalosporins also efficacious and perhaps offer less risk of cross hypersensitivity. Of interest, Cefdinir and Cefpodoxime are FDA approved for 5 days of therapy NOTE: Sulfonamides (to include trimethoprim/sulfamethoxazole), doxycycline and other tetracyclines, and fluoroquinolones are NOT indicated due to either high rates of resistance and/or clinical failure to eradicate in vitro susceptible organisms from the pharynx Pockets of resistance. Check local antibiograms If compliance is an issue, can use IM repository Penicillin G: If history of penicillin allergy manifest as a skin rash (non-IgE-mediated allergy), could use a cephalosporin If history of IgE-mediated allergic reaction to penicillins, cephalosporins, or carbapenems:

- Adult: Penicillin G benzathine (Bicillin L-A) 1.2 million units IM x one dose Cephalexin 500 mg po bid x 10 days Azithromycin 500 mg po on day one, then 250 mg po daily on days 2 through 5 Clindamycin 300 mg po tid x 10 days Pen VK 500 mg po bid x 10 days

- Penicillin G benzathine (Bicillin L-A) 1.2 million units IM x one dose

- Cephalexin 500 mg po bid x 10 days

- Azithromycin 500 mg po on day one, then 250 mg po daily on days 2 through 5

- Clindamycin 300 mg po tid x 10 days

- Pen VK 500 mg po bid x 10 days

- Child: Wt < 27 kg: To lessen pain of injection, Penicillin G benzathine combined with procaine penicillin G: (900,000 units of benzathine Pen G combined with 300,000 units of procaine penicillin G) IM X one dose Some substitute Amoxicillin suspension 50 mg/kg/day divided bid. Amoxicillin suspension is more palatable and, due to better absorption, may be more efficacious Cephalexin 25-50 mg/kg/day po in 2 equally divided doses x 10 days Azithromycin 12 m/kg po once daily for 5 days Clindamycin (Wt < 70 kg) 7 mg/kg/dose po tid for 10 days Pen VK 25-50 mg/kg/day div q6h x 10 days

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- Clindamycin (Wt < 70 kg) 7 mg/kg/dose po tid for 10 days

- Pen VK 25-50 mg/kg/day div q6h x 10 days

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- Other later generation cephalosporins also efficacious and perhaps offer less risk of cross hypersensitivity. Of interest, Cefdinir and Cefpodoxime are FDA approved for 5 days of therapy

- NOTE: Sulfonamides (to include trimethoprim/sulfamethoxazole), doxycycline and other tetracyclines, and fluoroquinolones are NOT indicated due to either high rates of resistance and/or clinical failure to eradicate in vitro susceptible organisms from the pharynx

- Pockets of resistance. Check local antibiograms

- If compliance is an issue, can use IM repository Penicillin G:

- If history of penicillin allergy manifest as a skin rash (non-IgE-mediated allergy), could use a cephalosporin

- If history of IgE-mediated allergic reaction to penicillins, cephalosporins, or carbapenems:

Alternative Regimens

- Alternatives listed above by clinical syndrome and presence of absence of allergy to beta-lactam antibiotics

Antimicrobial Stewardship

- Bacteremia, TSS: Do not use a fluoroquinolone, sulfonamide (to include TMP/SMX) or doxycycline (or other tetracyclines) due to high rates of resistance or documented clinical failures.

Comments

- TMP/SMX 1-2 DS bid may be effective for uncomplicated cellulitis in out-patients without medical co-morbidities (e.g., diabetes) (N Engl J Med 372:1093, 2015).

- Fluoroquinolones may be effective for treatment of uncomplicated skin and soft-tissue infections, but should not be used for treatment of pharyngitis or invasive infection.

- Susceptibilities of non-Group A streptococci (Groups B, C, F, G) are similar to Group A and treatment of infection due to these species is also similar.

- Clindamycin felt superior to Penicillin because antibacterial effect is not affected by the number of bacteria present (inoculum) or the stage of bacterial growth.

- Resistance to Clindamycin: <1% of clinical isolates with standard in vitro test procedures.

- Increasing resistance to macrolide antibiotics (J Clin Micro 49:439, 2011).

- Omadacycline ref: Clin Infect Dis. 2019;69:S23-S32.

- References: N Engl J Med. 2017;377:2253; Med Clin North Am 2013; 97:721

- IDSA Practice Guideline (soft tissue infections): Clin Infect Dis. 2014;59:e10

Streptococci, viridans group

Clinical Setting

- Oral flora

- Common clinical manifestations are infective endocarditis, brain abscess, empyema, and neutropenic sepsis (associated with mucositis).

- Streptococcus anginosus group is frequently associated with abscesses (e.g., brain and liver).

- In neutropenic patients these streptococcal species may cause bacteremia or neutropenic enterocolitis (often referred to as Typhlitis when the cecum is involved).

Etiologies

- Gram positive cocci in chains Streptococcus mitis Streptococcus sanguis Streptococcus mutans Streptococcus anginosus group Streptococcus anginosus Streptococcus constellatus Streptococcus intermedius Streptococcus gordonii Streptococcus parasanguinis Streptococcus sanguinis Streptococcus thermophilus

- Streptococcus mitis

- Streptococcus sanguis

- Streptococcus mutans

- Streptococcus anginosus group Streptococcus anginosus Streptococcus constellatus Streptococcus intermedius

- Streptococcus anginosus

- Streptococcus constellatus

- Streptococcus intermedius

- Streptococcus gordonii

- Streptococcus parasanguinis

- Streptococcus sanguinis

- Streptococcus thermophilus

Primary Regimens

- Preferred agents are Penicillin, Ceftriaxone, or Vancomycin

- Empiric therapy: Neutropenic host with viridans group streptococcal bacteremia: Vancomycin 15 mg/kg IV q12h (penicillin resistance is common) Can deescalate to a beta-lactam (e.g., Penicillin or

Ceftriaxone) once in vitro susceptibility is confirmed Treat for at least 14 days

- Vancomycin 15 mg/kg IV q12h (penicillin resistance is common)

- Can deescalate to a beta-lactam (e.g., Penicillin or Ceftriaxone) once in vitro susceptibility is confirmed

- Treat for at least 14 days

- See Endocarditis, Streptococcal

- See Brain Abscess, Bacterial

Alternative Regimens

- Clindamycin (if in vitro susceptibility confirmed)

Antimicrobial Stewardship

- Duration of therapy for neutropenic bacteremia should be at least 14 days and continued through recovery of neutropenia.

- Considerations in antimicrobial selection: Viridans group streptococci are susceptible to most penicillins, cephalosporins, carbapenems, beta-lactam/beta-lactamase inhibitor combinations, and Linezolid, which may be appropriate for empirical therapy, but a penicillin, first-generation cephalosporin, or Ceftriaxone is a preferred agent for definitive therapy unless the isolate is resistant. Daptomycin not recommended because resistance emerges rapidly (Antimicrob Agents Chemother 2015; 59:2102-12)

- Viridans group streptococci are susceptible to most penicillins, cephalosporins, carbapenems, beta-lactam/beta-lactamase inhibitor combinations, and Linezolid, which may be appropriate for empirical therapy, but a penicillin, first-generation cephalosporin, or Ceftriaxone is a preferred agent for definitive therapy unless the isolate is resistant.

- Daptomycin not recommended because resistance emerges rapidly (Antimicrob Agents Chemother 2015; 59:2102-12)

- High rates of beta-lactam resistance in neutropenic patients with viridans streptococcal bacteremia so beta-lactams not recommended for empiric therapy (BMC Infect Dis 13: 273, 2013).

Comments

- None

Syphilis, Overview

Ureaplasma urealyticum

Clinical Setting

- Colonizers or possibly pathogenic organisms of lower genital tract.

- May be associated with Mycoplasma hominis or Mycoplasma genitalium

- Transmitted between individuals by sexual contact or vertically.

- Controversial amongst experts when pathogenic vs colonizing, but most would treat if symptomatic.

- Associated with non-gonococcal urethritis in men and genital tract infections in women.

- Seen neonatal sepsis, meningitis and pneumonia syndromes.

Diagnosis

- Fastidious organisms that require special conditions for culture in vitro that are not widely available.

- NAAT tests not widely available but increasingly offered in reference labs.

- If clinical suspicion, empiric treatment may be indicated, especially in hyperammonemia patients.

- Urethral swabs better than urine, cell associated nasopharyngeal, throat, and endotracheal secretions from neonates

Classification

- Small free-living bacteria (like Mycoplasma) with no cell wall (don't stain with gram stain) so all beta-lactam drugs are ineffective.

Primary Regimens

- Doxycycline 100 mg po/IV q12h x 7-14 days (duration depending on clinical syndrome)

Alternative Regimens

- Azithromycin 500 mg po/IV x 10-14 days

- (Levofloxacin 500 mg po/IV daily or Moxifloxacin 400 mg po/IV daily) x 10-14 days

- In hyperammonemia syndromes, many would double cover to target both Ureaplasma and Mycoplasma and because of variable susceptibilities. Little definitive data, but M. hominis resistant to macrolides, so doxycycline + fluoroquinolone probably best option if double coverage planned.

Antimicrobial Stewardship

- Acquired resistance is now well documented and varies according to drug, organism, and patient population.

- In vitro susceptibility testing and molecular resistance testing may be useful to guide therapy, especially for disseminated infections but is not widely available.

Comments

- Nonhepatic hyperammonemia with CNS symptoms (encephalopathy, seizures, brain edema) has been reported in immunocompromised individuals, particularly in lung transplant recipients, and is ascribed to either Ureaplasma or Mycoplasma hominis (Curr Opin Infect Dis 35:262 2022; Clin Transplant 35:e14334 2021)

- Because diagnosis may be delayed, empiric treatment should be initiated for symptomatic individuals.

- Source of organism in lung transplant recipients is probably the donor (Open Forum Inf Dis 9:ofac607 2022; Clin Infect Dis 73:e2531 2021). Prophylaxis of positive recipients has been proposed with variable success (Open Forum Inf Dis 9:ofac607 2022; Clin Infect Dis 73:e2531 2021)

Vibrio cholerae

Clinical Setting

- Gastroenteritis, severe acute watery diarrhea with rapid dehydration and a mortality rate that can reach 50-75%.

- Antimicrobial therapy of cholera in patients with severe dehydration or moderate dehydration with on-going net fluid loss. Treatment decreases the duration of disease, volume losses, and duration of excretion.

- Treatment decreases the duration of disease, volume losses, and duration of excretion.

- Endemic in 50 countries in Africa, Southeast Asia, Indian subcontinent, Haiti.

Classification

- Gram negative bacilli (comma shaped)

Primary Regimens

- Primary treatment is hydration. Ringer's lactate for patients who require intravenous hydration; start Oral Rehydration Salts solution as soon as the patient is able to take oral fluids. Oral Rehydration Salts are commercially available for reconstitution in potable water. If unavailable, a substitute can be made by dissolving 1/2 teaspoon of salt and 6 level teaspoons of sugar in one liter of potable water.

- Ringer's lactate for patients who require intravenous hydration; start Oral Rehydration Salts solution as soon as the patient is able to take oral fluids.

- Oral Rehydration Salts are commercially available for reconstitution in potable water. If unavailable, a substitute can be made by dissolving 1/2 teaspoon of salt and 6 level teaspoons of sugar in one liter of potable water.

- Antibiotic therapy, choice of agent guided by local susceptibility data Adults, children > 12 years of age, pregnant women Doxycycline 300 mg po single dose Azithromycin 1 gm po single dose Children < 12 years of age Doxycycline 2-4 mg/kg single dose Azithromycin 20 mg/kg (max dose 1 gm) po single dose

- Adults, children > 12 years of age, pregnant women Doxycycline 300 mg po single dose Azithromycin 1 gm po single dose

- Doxycycline 300 mg po single dose

- Azithromycin 1 gm po single dose

- Children < 12 years of age Doxycycline 2-4 mg/kg single dose Azithromycin 20 mg/kg (max dose 1 gm) po single dose

- Doxycycline 2-4 mg/kg single dose

- Azithromycin 20 mg/kg (max dose 1 gm) po single dose

Alternative Regimens

- Hydration, as above.

- Adults, children > 12 years of age, pregnant women Ciprofloxacin 1 gm single dose Erythromcyin 500 mg po qid x 3 days

- Ciprofloxacin 1 gm single dose

- Erythromcyin 500 mg po qid x 3 days

- Children < 12 years of age Ciprofloxacin 20 mg/kg (max dose 1 gm) po single dose Erythromcyin 12.5 mg/kg (max dose 500 mg) po qid x 3 day

- Ciprofloxacin 20 mg/kg (max dose 1 gm) po single dose

- Erythromcyin 12.5 mg/kg (max dose 500 mg) po qid x 3 day

Prevention

- See Cholera, Vaccine for indications, available products, dosing, and vaccine characteristics for pre-exposure prevention.

Comments

- Ciprofloxacin efficacy is poor against naladixic acid resistant strains

- Reference: Lancet. 2022; 399:1429-1440.

Vibrio parahaemolyticus

Clinical Setting

- Free-living bacterium present in marine-estuarine environments.

- Leading cause of seafood-associated gastroenteritis and shellfish in particular.

- May cause severe cellulitis, wound infections, bacteremia in patients with liver disease or diabetes.

- Manifestation of infection: diarrhea 59%, wound infection 34%, sepsis 5%, other.

- Diarrhea is usually mild and self-limited; antibacterial therapy indicated in more severe disease or in fragile patients.

- Diagnosis: need selective media (Thiosulfate Citrate Bile-salts Sucrose) to detect in stool; does grow in blood culture bottles.

Etiologies

- Vibrio parahaemolyticus

Primary Regimens

- Rehydration is most important

- Treatment based on drugs proven successful in the treatment of V. cholerae

- Doxycycline 100 mg IV/po bid x 5-7 days

- If suspected or proven bacteremia and in the ICU: Doxycyline 100 mg IV bid + Ceftriaxone 1 gm IV qd.

Alternative Regimens

- Azithromycin 500 mg IV/po qd x 3 days

- Ciprofloxacin 500 mg po bid x 3 days

Comments

- Atlantic coast outbreak (New Engl J Med 369:1573, 2013).

- Review comparing different Vibrio infections (Nat Rev Dis Primers 4:8 2018).

Vibrio vulnificus, V. alginolyticus, V. damsela

Clinical Setting

- Recommendations are for treatment of severe soft tissue infection and sepsis.

- Vibrio vulnificus is a gram-negative bacillus that can cause diarrhea, wound infections, and bacteremia. It is the number one cause of shellfish-associated deaths in the U.S. (Eur J Clin Microbiol Infect Dis 2019;38:1999).

- Organisms live in salt water marine environments: seawater and estuaries; wound infections result from exposure of a wound to seawater or brackish water containing the organism. Exposure can result from recreational water activities, oyster shucking, sea urchin harvesting, fish fin punctures or handling seafood.

- Wound infections are most common during the summer months when the density of organisms is greatest and can progress to necrotizing fasciitis (J Antimicrob Chemother 67:488, 2012).

- Highest risk factors for life-threatening infection:

- Cirrhosis due to alcohol or chronic viral hepatitis, alcoholism, hemochromatosis, diabetes mellitus, thalassemia major, chronic renal disease, use of TNF inhibitors, and lymphoma (Clin Infect Dis 46:970, 2008).

- General references: N Engl J Med 2018;379:375 (image of hemorrhagic bullae);N Engl J Med 2016;375:1780

Etiologies

- Vibrio vulnificus

- Vibrio alginolyticus

- Vibrio damsela (aka Photobacterium damselae)

Primary Regimens

- Adult: (Doxycycline or Minocycline 100 mg IV/po bid) + (Ceftriaxone 2 gm IV once daily or Ceftazidime 1 gm IV q8h)

- Child: Doxycycline 4.4 mg/kg/day div bid (max 200 mg/day) + Ceftazidime 150-200 mg/kg/d divided q8h NOTE: Doxycycline can be safely administered for up to 21days regardless of age (AAP Red Book 2018, Section 4; J Pediatr 166:1246, 2015).

- NOTE: Doxycycline can be safely administered for up to 21days regardless of age (AAP Red Book 2018, Section 4; J Pediatr 166:1246, 2015).

- Severe infections may require surgical debridement: Am J Surg 206: 32, 2013.

Alternative Regimens

- Levofloxacin 750 mg IV/po once daily or Ciprofloxacin 750 mg po bid or 400 mg IV bid can be substituted for Doxycycline or Minocycline (See Comments)

- Minor infections can be treated with a single agent.

Antimicrobial Stewardship

- Duration of therapy based on clinical response.

Comments

- Retrospective surveillance study found higher mortality with β-lactam alone compared to fluoroquinolone alone or combination of fluoroquinolone or a tetracycline plus β-lactam (BMC Infect Dis. 5:226, 2015).

- Due to the potential severity of disease, it is suggested that with the appropriate risk factors (ingestion of raw seafood, exposure to salt-water environment) empiric therapy for wound and septic patients include drugs active against V. vulnificus.

- Roughly 75% of patients have bullous skin lesions.

- Sepsis and septic shock in immunocompromised individuals, including hematological disease, malignancy, and liver disease (Epidemiol Infect 142:877, 2014).

- Review comparing different Vibrio infections (Nat Rev Dis Primers 4:8 2018).

- Reference: StatPearls; 2023 Jan. 2023 Jan 10.