Selected New Antibiotics

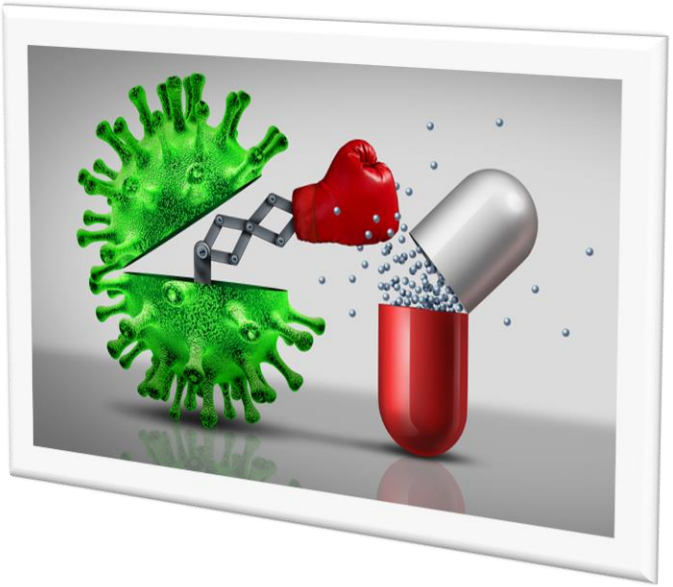
NEW ANTIBIOTICS IN CLINICAL PRACTICE; APPLICATION AND DOSING

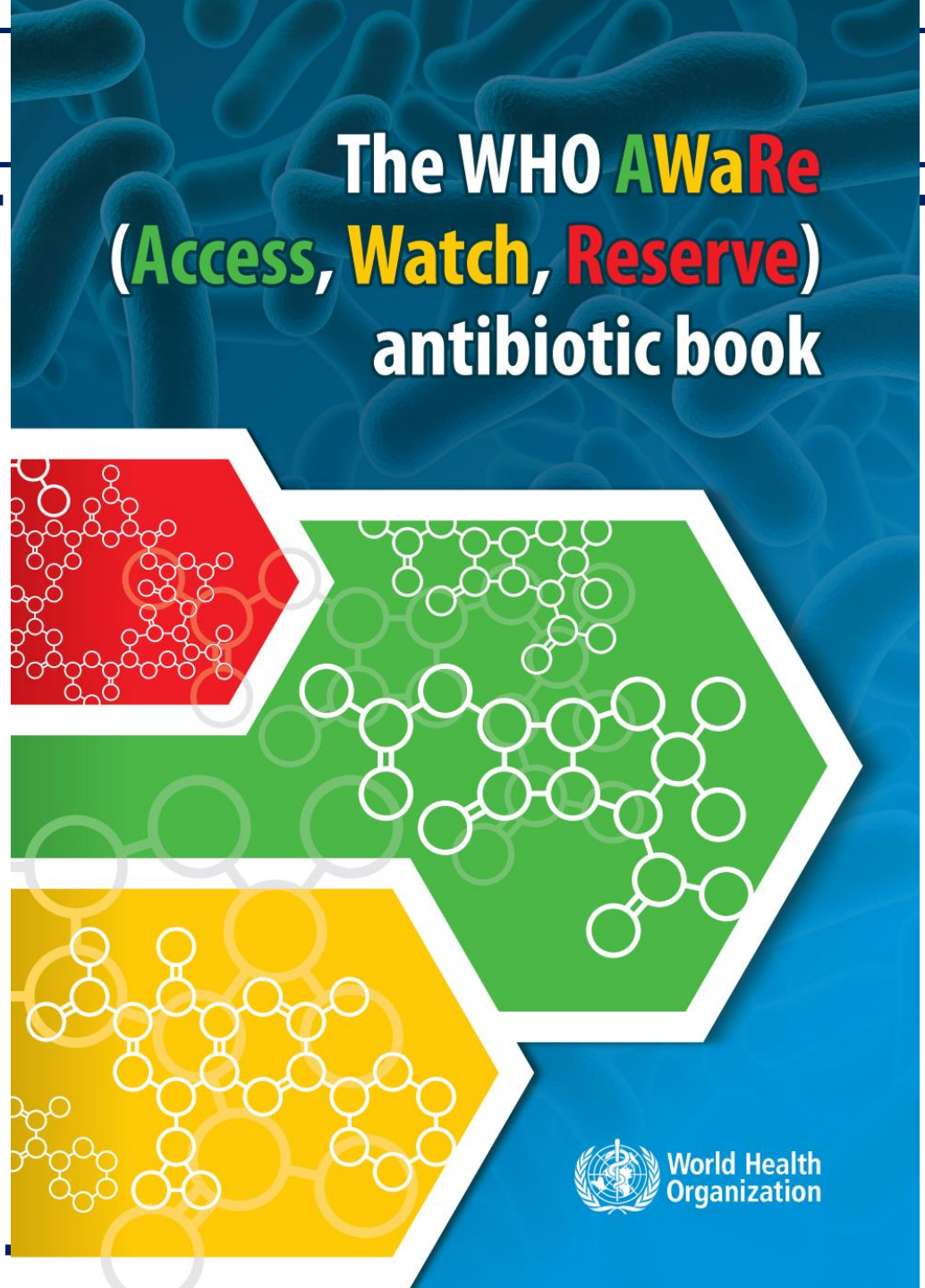
Dr. Keyhan Mohammadi

Assistant Professor of Clinical Pharmacy

Tehran University of Medical Sciences

2023-11-24




The WHO AWaRe
(Access, Watch, Reserve)
antibiotic book
World Health
Organization

AWaRe

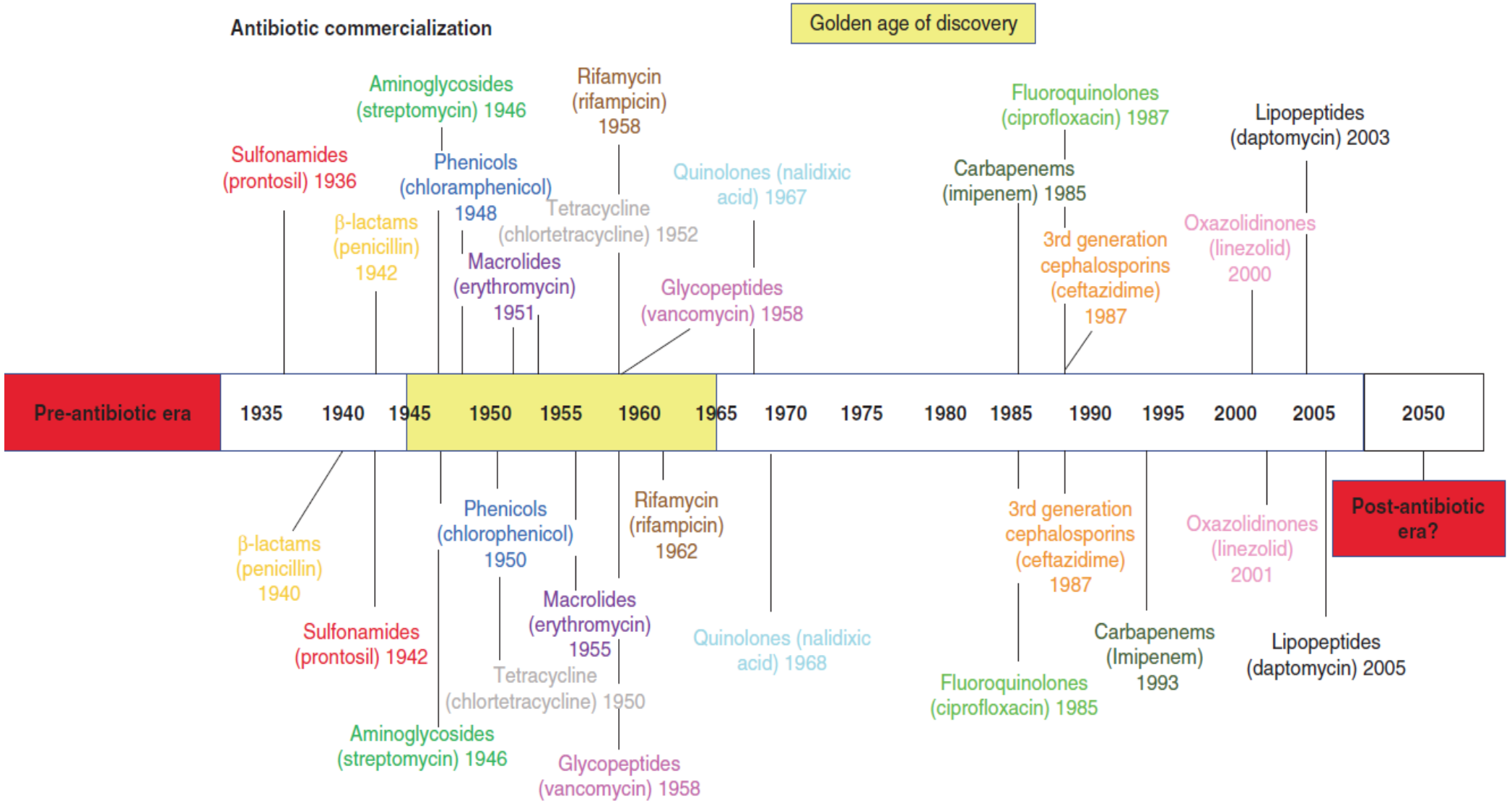
The AWaRe book gives guidance on first- and second-choice antibiotics for common infections in line with the recommendations in the EML and EMLc *(8,9)*. WHO has classified antibiotics into four groups, Access, Watch, Reserve (AWaRe) and a fourth – Not Recommended – group. As well as the antibiotics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

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

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

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

Antibiotic Discovery



WHO's **Critical** Priority

Carbapenem- and 3rd generation cephalosporin-resistant Enterobacteriaceae

Carbapenem-resistant *Pseudomonas aeruginosa*

Carbapenem-resistant *Acinetobacter baumannii*

CDC's **Urgent** Threats

Carbapenem-resistant Enterobacteriaceae

Clostridium difficile

Neisseria gonorrhoeae

WHO's **High** Priority

Clarithromycin-resistant *Helicobacter pylori*

Fluoroquinolone-resistant *Campylobacter* and *Salmonella* spp.

MDR *Neisseria gonorrhoeae*

Others: vancomycin-resistant *Enterococcus faecium*, methicillin- and vancomycin-resistant *Staphylococcus aureus*

CDC's **Serious** Threats

MDR *Acinetobacter* spp.

ESBL-producing Enterobacteriaceae

MDR *Pseudomonas aeruginosa*

MDR *Salmonella*, *Shigella*, and *Campylobacter* spp.

Others: MRSA, *Streptococcus pneumoniae*, *Mycobacterium tuberculosis*, VRE, fluconazole-resistant *Candida* spp.

WHO's **Medium** Priority

Penicillin-non-susceptible *Streptococcus pneumoniae*

Ampicillin-resistant *Haemophilus influenzae*

Fluoroquinolone-resistant *Shigella* spp.

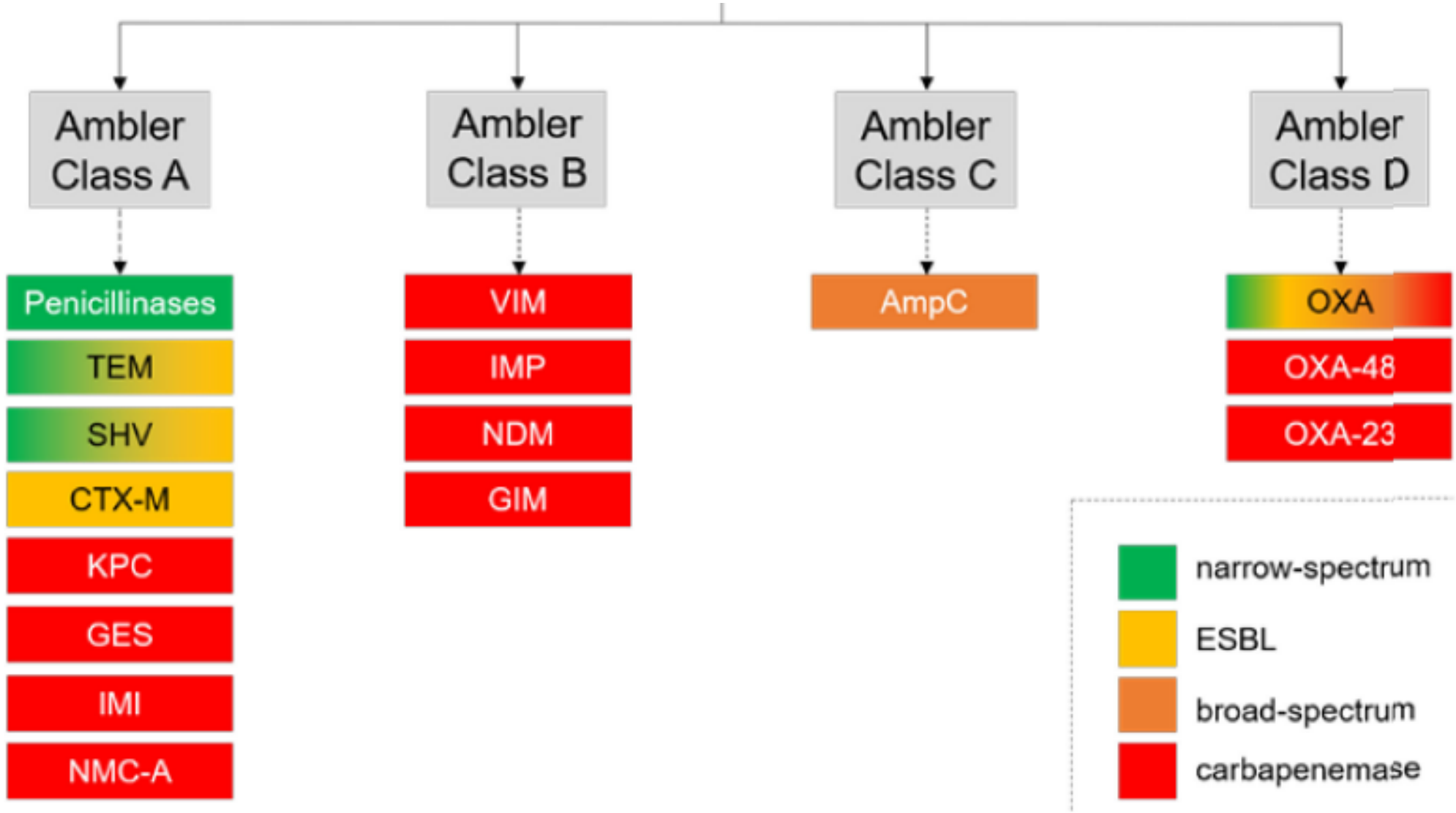
CDC's **Concerning** Threats

Vancomycin-resistant *Staphylococcus aureus*

Erythromycin-resistant Group A *Streptococcus*

Clindamycin-resistant Group B *Streptococcus*

Type of Beta-lactamase



New Drugs for MDR Gram-negatives

β-lactam Combination Agents

- Ceftazidime-avibactam
- Ceftolozane-tazobactam
- Cefepime-tazobactam
- Aztreonam-avibactam
- Ceftaroline-avibactam
- Imipenem-relebactam
- Meropenem-vaborbactam
- Cefepime-zidebactam
- Meropenem-nacubactam

Non-β-lactam Agents

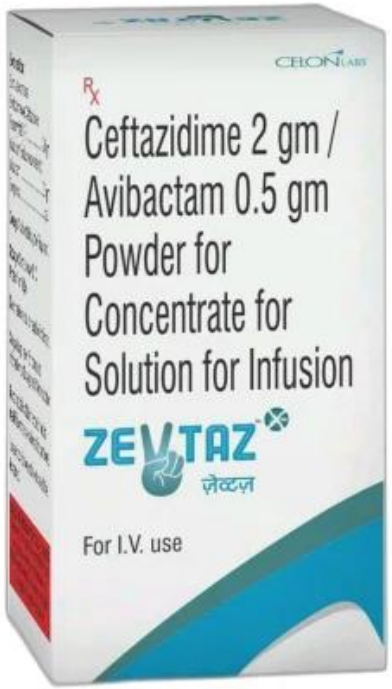
- Cefiderocol
- Murepavadin
- Finafloxacin
- Eravacycline
- Omadacycline
- Plazomicin
- Delafloxacin

Avery LM & Nicolau DP. *Expert Opinion on Investigational Drugs* 2018;27:4:325-38.

Ceftazidime-Avibactam

Formulations

- Powder for intravenous infusion: 2 g + 500 mg in vial



Ceftazidime-Avibactam

- Ceftazidime-avibactam is a combination of a third-generation cephalosporin (ceftazidime) and a new non-beta-lactam beta-lactamase inhibitor (avibactam).
- Avibactam is a novel broad-spectrum beta-lactamase inhibitor that has minimal antibacterial activity on its own
- The addition of avibactam to ceftazidime extends the spectrum of activity to include most Enterobacterales (including those that produce AmpC beta-lactamase, ESBL, and some K. pneumoniae and OXA-type carbapenemases) as well as P. aeruginosa species with high MICs to ceftazidime alone but not strains producing metallo-beta-lactamases
- Ceftazidime-avibactam does not have activity against Acinetobacter species or organisms that produce metallo-beta-lactamases and is less active against anaerobes than other beta lactam-beta-lactamase combinations (Give with Metronidazole)

Ceftazidime-Avibactam

Rx Pharmacology

- Combination of a third-generation cephalosporin (ceftazidime) and a novel non-β-lactam β-lactamase inhibitor (avibactam)
- **Mechanism of action**:
  - Ceftazidime inhibits bacterial enzymes responsible for cell wall synthesis
  - Avibactam inactivates certain serine β-lactamases, protecting ceftazidime from degradation

Ceftazidime-Avibactam

Targeted Treatment

- Severe infections caused by laboratory-confirmed carbapenem-resistant Enterobacterales or *P. aeruginosa* (not *A. baumannii*) susceptible to ceftazidime+avibactam (CAZ-AVI)

Ceftazidime-Avibactam

Empiric Use

- Only in very select cases of seriously ill patients (e.g. patients with sepsis/septic shock):
  - who have not responded to carbapenems if other causes of treatment failure have been excluded first and there is strong suspicion that the infection is caused by a carbapenem-resistant pathogen
  - who have previously been treated for infections caused by carbapenem-resistant pathogens susceptible to CAZ-AVI
  - who are known to be colonized with carbapenem-resistant pathogens susceptible to CAZ-AVI

Ceftazidime-Avibactam

Important Considerations

- When used to treat complicated intra-abdominal infections CAZ-AVI should be given with metronidazole due to its unpredictable activity against anaerobes
- Since it is not active against MBLs, it is important to know the local epidemiology of the most prevalent genotypes for aerobic Gram-negative bacteria

Spectrum of Activity

- **Active against**:
  - Aerobic Gram-negative bacteria including ceftazidime-resistant and many carbapenem-resistant Enterobacterales and *Pseudomonas aeruginosa*
    - Carbapenemases: KPC and OXA-48
    - ESBL and AmpC β-lactamases
- **Variable activity against**:
  - *Streptococcus* spp.
  - *Staphylococcus* spp.
  - Anaerobes
- **Not active against**:
  - MBL-producing Gram-negative bacteria (inactive against NDM, VIM, IMP carbapenemases unless co-prescribed with aztreonam)
  - *Enterococcus* spp.
  - *Acinetobacter* spp.
- **Emerging resistance to CAZ-AVI in Enterobacterales and *Pseudomonas aeruginosa***:
  - The proportion of isolates resistant to CAZ-AVI is low (higher for *P. aeruginosa*) with geographical variability

Dose

Antibiotic Treatment Duration

- Treatment duration varies according to indication and should be as short as possible
- Usually between **7-14 days**

Adults

Dosage is for normal renal function; dose adjustment required in case of renal impairment

RESERVE

Ceftazidime+avibactam 2.5 g (2 g ceftazidime + 500 mg avibactam) q8h **IV**

Children

Dosage is for normal renal function; dose adjustment required in case of renal impairment

RESERVE

Ceftazidime+avibactam 62.5 mg/kg/dose q8h **IV** (50 mg/kg/dose ceftazidime + 12.5 mg/kg/dose avibactam)
Max: 2 g ceftazidime + 500 mg avibactam per dose

Ceftazidime-Avibactam

Altered kidney function (Ref):

Note: Estimation of renal function for the purpose of drug dosing should be done using the Cockcroft-Gault formula.

IV:

CrCl >50 to <130 mL/minute: No dosage adjustment necessary.

CrCl >30 to 50 mL/minute: 1.25 g every 8 hours.

CrCl >15 to 30 mL/minute: 0.94 g every 12 hours.

CrCl >5 to 15 mL/minute: 0.94 g every 24 hours.

CrCl ≤5 mL/minute: 0.94 g every 48 hours.

Augmented renal clearance (measured urinary CrCl ≥130 mL/minute/1.73 m^2):

Note: Augmented renal clearance (ARC) is a condition that occurs in certain critically ill patients without organ dysfunction and with normal serum creatinine concentrations. Young patients (<55 years of age) admitted post trauma or major surgery are at highest risk for ARC, as well as those with sepsis, burns, or hematologic malignancies. An 8- to 24-hour measured urinary CrCl is necessary to identify these patients (Ref).

IV: 2.5 g every 8 hours (Ref).

Hemodialysis, intermittent (thrice weekly): Dialyzable (~57% ceftazidime; 55% avibactam (Ref)): 0.94 g every 24 hours; in patients with minimal residual kidney function and less severe infections, may consider administering 0.94 g every 48 hours. When scheduled dose falls on a dialysis day, administer after hemodialysis

Ceftazidime+avibactam

Pharmacology

- Combination of a third-generation cephalosporin (ceftazidime) and a novel non-β-lactam β-lactamase inhibitor (avibactam)
- **Mechanism of action**:
  - Ceftazidime inhibits bacterial enzymes responsible for cell wall synthesis
  - Avibactam inactivates certain serine β-lactamases, protecting ceftazidime from degradation

Indications for Use

Targeted Treatment

- Severe infections caused by laboratory-confirmed carbapenem-resistant Enterobacterales or *P. aeruginosa* (not *A. baumannii*) susceptible to ceftazidime+avibactam (CAZ-AVI)

Empiric Use

- Only in very select cases of seriously ill patients (e.g. patients with sepsis/septic shock):
  - who have not responded to carbapenems if other causes of treatment failure have been excluded first and there is strong suspicion that the infection is caused by a carbapenem-resistant pathogen
  - who have previously been treated for infections caused by carbapenem-resistant pathogens susceptible to CAZ-AVI
  - who are known to be colonized with carbapenem-resistant pathogens susceptible to CAZ-AVI

Important Considerations

- When used to treat complicated intra-abdominal infections CAZ-AVI should be given with metronidazole due to its unpredictable activity against anaerobes
- Since it is not active against MBLs, it is important to know the local epidemiology of the most prevalent genotypes for aerobic Gram-negative bacteria

Formulations

- Powder for intravenous infusion: 2 g + 500 mg in vial

Toxicity

- Side effects are similar to those previously reported for ceftazidime alone
- The most frequent are diarrhoea, nausea and vomiting

Spectrum of Activity

- **Active against**:
  - Aerobic Gram-negative bacteria including ceftazidime-resistant and many carbapenem-resistant Enterobacterales and *Pseudomonas aeruginosa*
    - Carbapenemases: KPC and OXA-48
    - ESBL and AmpC β-lactamases
- **Variable activity against**:
  - *Streptococcus* spp.
  - *Staphylococcus* spp.
  - Anaerobes
- **Not active against**:
  - MBL-producing Gram-negative bacteria (inactive against NDM, VIM, IMP carbapenemases unless co-prescribed with aztreonam)
  - *Enterococcus* spp.
  - *Acinetobacter* spp.
- **Emerging resistance to CAZ-AVI in Enterobacterales and *Pseudomonas aeruginosa***:
  - The proportion of isolates resistant to CAZ-AVI is low (higher for *P. aeruginosa*) with geographical variability

Dose

Antibiotic Treatment Duration

- Treatment duration varies according to indication and should be as short as possible
- Usually between **7-14 days**

Adults

Dosage is for normal renal function; dose adjustment required in case of renal impairment

RESERVE — Ceftazidime+avibactam 2.5 g (2 g ceftazidime + 500 mg avibactam) q8h **IV**

Children

Dosage is for normal renal function; dose adjustment required in case of renal impairment

RESERVE — Ceftazidime+avibactam 62.5 mg/kg/dose q8h **IV** (50 mg/kg/dose ceftazidime + 12.5 mg/kg/dose avibactam)
Max: 2 g ceftazidime + 500 mg avibactam per dose

Plazomicin

Formulations

- Intravenous injection: 500 mg/10 mL

Rx Pharmacology

- New semisynthetic aminoglycoside
- **Mechanism of action**: Inhibition of bacterial protein synthesis

Spectrum of Activity

- **Active against**:
  - Aerobic Gram-negative bacteria including many carbapenem-resistant Enterobacterales
    - Carbapenemases: KPC and OXA-48
    - ESBL and AmpC β-lactamases
  - Bacteria producing aminoglycoside-modifying enzymes
- **Variable activity against**:
  - Strains producing metallo-β-lactamases
- **Not active against**:
  - *Acinetobacter baumannii*
  - *Pseudomonas aeruginosa*
- **Emerging resistance to plazomicin in Enterobacterales**:
  - Very limited data

Plazomicin

Targeted Treatment

- Severe infections caused by laboratory-confirmed carbapenem-resistant Enterobacterales susceptible to plazomicin (not *P. aeruginosa* or *A. baumannii*)
- Infections caused by Gram-negative bacteria resistant to other aminoglycosides if non-Reserve antibiotic options cannot be used

Plazomicin

Empiric Use

- Only in very selected cases of seriously ill patients (e.g. sepsis/septic shock caused by urinary tract infections if used as monotherapy - for other infections aminoglycosides are usually used in combination with other antibiotics):
  - who have not responded to carbapenems if other causes of treatment failure have been excluded first and there is strong suspicion that the infection is caused by a carbapenem-resistant pathogen
  - who have previously been treated for infections caused by carbapenem-resistant pathogens susceptible to plazomicin
  - who are known to be colonized with carbapenem-resistant pathogens susceptible to plazomicin

Plazomicin

Important Considerations

- Efficacy demonstrated in clinical trials only for complicated urinary tract infections in adults
- Very limited evidence for other infections and use in children

Dose

Antibiotic Treatment Duration

- Treatment duration varies according to indication and should be as short as possible
- Usually between **7-14 days**

Adults

Weight-based once-daily dosing is used; dosage is for normal renal function

RESERVE

Plazomicin 15 mg/kg q24h **IV**

Children or Neonates

No data for children or neonates

Plazomicin

Dosing: Kidney Impairment: Adult

Note: CrCl estimated by Cockcroft-Gault formula using TBW (or IBW for patients with TBW ≥25% IBW)

CrCl ≥60 mL/minute: No dosage adjustment necessary.

CrCl 30 to <60 mL/minute: 10 mg/kg every 24 hours

CrCl 15 to <30 mL/minute: 10 mg/kg every 48 hours

CrCl <15 mL/minute: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).

Plazomicin

Toxicity

- Side effects similar to other aminoglycosides
- The most frequent are:
  - Kidney damage (monitor creatinine levels regularly)
  - Hearing loss and vestibular toxicity

Plazomicin

Pharmacology

- New semisynthetic aminoglycoside
- **Mechanism of action**: Inhibition of bacterial protein synthesis

Indications for Use

Targeted Treatment

- Severe infections caused by laboratory-confirmed carbapenem-resistant Enterobacterales susceptible to plazomicin (not *P. aeruginosa* or *A. baumannii*)
- Infections caused by Gram-negative bacteria resistant to other aminoglycosides if non-Reserve antibiotic options cannot be used

Empiric Use

- Only in very selected cases of seriously ill patients (e.g. sepsis/septic shock caused by urinary tract infections if used as monotherapy - for other infections aminoglycosides are usually used in combination with other antibiotics):
  - who have not responded to carbapenems if other causes of treatment failure have been excluded first and there is strong suspicion that the infection is caused by a carbapenem-resistant pathogen
  - who have previously been treated for infections caused by carbapenem-resistant pathogens susceptible to plazomicin
  - who are known to be colonized with carbapenem-resistant pathogens susceptible to plazomicin

Important Considerations

- Efficacy demonstrated in clinical trials only for complicated urinary tract infections in adults
- Very limited evidence for other infections and use in children

Formulations

- Intravenous injection: 500 mg/10 mL

Spectrum of Activity

- **Active against**:
  - Aerobic Gram-negative bacteria including many carbapenem-resistant Enterobacterales
    - Carbapenemases: KPC and OXA-48
    - ESBL and AmpC β-lactamases
  - Bacteria producing aminoglycoside-modifying enzymes
- **Variable activity against**:
  - Strains producing metallo-β-lactamases
- **Not active against**:
  - *Acinetobacter baumannii*
  - *Pseudomonas aeruginosa*
- **Emerging resistance to plazomicin in Enterobacterales**:
  - Very limited data

Toxicity

- Side effects similar to other aminoglycosides
- The most frequent are:
  - Kidney damage (monitor creatinine levels regularly)
  - Hearing loss and vestibular toxicity

Dose

Antibiotic Treatment Duration

- Treatment duration varies according to indication and should be as short as possible
- Usually between **7-14 days**

Adults

Weight-based once-daily dosing is used; dosage is for normal renal function

RESERVE Plazomicin 15 mg/kg q24h **IV**

Children or Neonates

No data for children or neonates

Meropenem-Vaborbactam

Formulations

- Powder for intravenous infusion: 1 g + 1 g in vial

2 single-dose vials = 4 g dose

- Vaborbactam is a novel broad-spectrum beta-lactamase inhibitor that potently inhibits class A carbapenemases (including KPC).
- It is not active against class B or D carbapenemases (ie, metallo-beta-lactamases and OXA-type enzymes).
- Vaborbactam does not enhance the clinical activity of meropenem against carbapenem-resistant P. aeruginosa or Acinetobacter spp.

Spectrum of Activity

- **Active against**:
  - Aerobic Gram-negative bacteria including many carbapenem-resistant Enterobacterales
    - KPC carbapenemases
    - ESBL and AmpC β-lactamases
  - Aerobic Gram-positive bacteria
  - Anaerobes
- **Variable activity against**:
  - *Acinetobacter baumannii*
  - *Pseudomonas aeruginosa*
- **Not active against**:
  - Gram-negative bacteria producing metallo-β-lactamases (NDM, VIM, IMP) or Ambler class D carbapenemases (such as OXA-48)
- **Emerging resistance to meropenem+vaborbactam in Enterobacterales**:
  - Very rare in clinical practice

Meropenem-Vaborbactam

Important Considerations

- Since it is not active against metallo-β-lactamases (Ambler class B) or class D carbapenemases (such as OXA-48), it is important to know the local epidemiology of the most prevalent genotypic variants for aerobic Gram-negative bacteria

Table 46.1 – Expected activity of meropenem+vaborbactam against third-generation cephalosporin and carbapenem-resistant bacteria based on the type of beta-lactamase produced

Type of beta-lactamase	ESBL[a]	KPC[b]	NDM, VIM, IMP[b]	AmpC	OXA-48[b]	Non-fermenters[c]
Ambler class[d]	A[e]	A[e]	B (MBLs)	C[e]	D[e]	NA
Expected activity of meropenem+ vaborbactam	+	+	–	+	–	+/–

Meropenem-Vaborbactam

Indications for Use

Targeted Treatment

- Severe infections caused by laboratory-confirmed KPC-producing Enterobacterales, including bacteria resistant to ceftazidime+avibactam but susceptible to meropenem+vaborbactam

Empiric Use

- Only in very selected cases of seriously ill patients (e.g. sepsis/septic shock):
  - who have not responded to carbapenems if other causes of treatment failure have been excluded and there is strong suspicion that the infection is caused by a carbapenem-resistant pathogen
  - who have previously been treated for infections caused by carbapenem-resistant pathogens susceptible to meropenem+vaborbactam
  - who are known to be colonized with carbapenem-resistant pathogens susceptible to meropenem+vaborbactam

Adults

Dosage is for normal renal function; dose adjustment required in case of renal impairment

RESERVE

Meropenem+vaborbactam 4 g (2 g meropenem + 2 g vaborbactam) q8h **IV**

Children or Neonates

Currently not licensed for use in children or neonates

Meropenem-Vaborbactam

Table 46.2 – Meropenem+vaborbactam suggested doses

Dose in adults	Dose in children	Dose in neonates
IV: 4 g (2 g meropenem + 2 g vaborbactam) given every 8 hours	Currently not licensed for children	Currently not licensed for neonates

Note: Estimation of renal function for the purpose of meropenem/vaborbactam dosing may be done using the Modification of Diet in Renal Disease (MDRD) formula (manufacturer's labeling). Dosage recommendations are expressed as grams of meropenem/vaborbactam combination.

Antibiotic Treatment Duration

- Treatment duration varies according to indication and should be as short as possible
- Usually between **7-14 days**

Toxicity

Meropenem+vaborbactam is well tolerated and has side-effects similar to those previously reported for meropenem alone. However, meropenem+vaborbactam is less damaging to the kidneys than other antibiotics used to treat infections caused by carbapenem-resistant Enterobacterales.

Meropenem+vaborbactam

Pharmacology

- Combination of a carbapenem (meropenem) and a novel non-β-lactam β-lactamase inhibitor (vaborbactam)
- **Mechanism of action**:
  - Meropenem inhibits bacterial enzymes responsible for cell wall synthesis
  - Vaborbactam inactivates certain serine β-lactamases, thus protecting meropenem from degradation

Indications for Use

Targeted Treatment

- Severe infections caused by laboratory-confirmed KPC-producing Enterobacterales, including bacteria resistant to ceftazidime+avibactam but susceptible to meropenem+vaborbactam

Empiric Use

- Only in very selected cases of seriously ill patients (e.g. sepsis/septic shock):
  - who have not responded to carbapenems if other causes of treatment failure have been excluded and there is strong suspicion that the infection is caused by a carbapenem-resistant pathogen
  - who have previously been treated for infections caused by carbapenem-resistant pathogens susceptible to meropenem+vaborbactam
  - who are known to be colonized with carbapenem-resistant pathogens susceptible to meropenem+vaborbactam

Important Considerations

- Since it is not active against metallo-β-lactamases (Ambler class B) or class D carbapenemases (such as OXA-48), it is important to know the local epidemiology of the most prevalent genotypic variants for aerobic Gram-negative bacteria

Formulations

- Powder for intravenous infusion: 1 g + 1 g in vial

Spectrum of Activity

- **Active against**:
  - Aerobic Gram-negative bacteria including many carbapenem-resistant Enterobacterales
    - KPC carbapenemases
    - ESBL and AmpC β-lactamases
  - Aerobic Gram-positive bacteria
  - Anaerobes
- **Variable activity against**:
  - *Acinetobacter baumannii*
  - *Pseudomonas aeruginosa*
- **Not active against**:
  - Gram-negative bacteria producing metallo-β-lactamases (NDM, VIM, IMP) or Ambler class D carbapenemases (such as OXA-48)
- **Emerging resistance to meropenem+vaborbactam in Enterobacterales**:
  - Very rare in clinical practice

Toxicity

- Generally well tolerated
- Side effects similar to meropenem alone

Dose

Antibiotic Treatment Duration

- Treatment duration varies according to indication and should be as short as possible
- Usually between **7-14 days**

Adults

Dosage is for normal renal function; dose adjustment required in case of renal impairment

RESERVE

Meropenem+vaborbactam 4 g (2 g meropenem + 2 g vaborbactam) q8h **IV**

Children or Neonates

Currently not licensed for use in children or neonates

Cefiderocol

Formulations

- Powder for intravenous infusion: 1 g/vial

IV: Administer by intermittent IV infusion over 3 hours.

Cefiderocol

- Cefiderocol is only active against aerobic Gram-negative bacteria
- Active against many carbapenem-resistant Enterobacterales, Pseudomonas aeruginosa and Acinetobacter baumannii clinical isolates
- Cefiderocol has no, or only limited, activity against Gram-positive bacteria or anaerobes.
  - Ceftaroline is a fifth-generation cephalosporin with anti- MRSA activity.
- Not degraded by ESBL KPC, oxacillinase-48 (OXA-48) and MBL such as ND-MBL.
- Active agaist MBL. The other such antibiotics are colistin/ polymyxin B, fosfomycin and aztreonam combined with avibactam, in the form of ceftazidime+avibactam

Spectrum of Activity

- **Active against**:
  - Aerobic Gram-negative bacteria including many carbapenem resistant Enterobacterales, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*
    - Carbapenemases: KPC, OXA-48 and MBLs
    - ESBL and AmpC β-lactamases
- **Not active against**:
  - Gram-positive bacteria and anaerobes
- **Emerging resistance to cefiderocol in Enterobacterales, *A. baumanii* and *P. aeruginosa***:
  - The proportion of isolates resistant to cefiderocol is low but data is very limited

Cefiderocol

Indications for Use

Targeted Treatment

- Severe infections caused by laboratory-confirmed carbapenem-resistant Enterobacterales and/or *P. aeruginosa* (particularly infections caused by MBL-producing pathogens)
  - Caution needed with *A. baumannii* infections because of higher mortality than best available alternative therapy described in a clinical trial (https://pubmed.ncbi.nlm.nih.gov/33058795/)

Empiric Use

- Only in very selected cases of seriously ill patients (e.g. sepsis/septic shock):
  - who have not responded to carbapenems if other causes of treatment failure have been excluded first and there is strong suspicion that the infection is caused by a carbapenem-resistant pathogen (especially in settings with a high prevalence of MBL-producing pathogens)
  - who have previously been treated for infections caused by carbapenem-resistant pathogens susceptible to cefiderocol
  - who are known to be colonized with carbapenem-resistant pathogens susceptible to cefiderocol

Cefiderocol

Important Considerations

- Efficacy demonstrated in clinical trials for empiric use for complicated UTI, VAP/HAP, BSI and sepsis in adults
- Very limited evidence for other infections and use in children

Antibiotic Treatment Duration

- Treatment duration varies according to indication and should be as short as possible
- Usually between **7-14 days**

Adults

Dosage is for normal renal function; dose adjustment required in case of renal impairment

RESERVE

Cefiderocol 2 g q8h **IV**

For patients with CrCl ≥120 mL/minute, increase dose to 2 g every 6 hours

Children or Neonates

No data for children or neonates

Cefiderocol

Toxicity

Well tolerated with side effects similar to other beta-lactams (mostly gastrointestinal)

Cefiderocol

Pharmacology

- Siderophore cephalosporin
- **Mechanism of action**: Inhibition of bacterial enzymes responsible for cell-wall synthesis

Indications for Use

Targeted Treatment

- Severe infections caused by laboratory-confirmed carbapenem-resistant Enterobacterales and/or *P. aeruginosa* (particularly infections caused by MBL-producing pathogens)
  - Caution needed with *A. baumannii* infections because of higher mortality than best available alternative therapy described in a clinical trial (https://pubmed.ncbi.nlm.nih.gov/33058795/)

Empiric Use

- Only in very selected cases of seriously ill patients (e.g. sepsis/septic shock):
  - who have not responded to carbapenems if other causes of treatment failure have been excluded first and there is strong suspicion that the infection is caused by a carbapenem-resistant pathogen (especially in settings with a high prevalence of MBL-producing pathogens)
  - who have previously been treated for infections caused by carbapenem-resistant pathogens susceptible to cefiderocol
  - who are known to be colonized with carbapenem-resistant pathogens susceptible to cefiderocol

Important Considerations

- Efficacy demonstrated in clinical trials for empiric use for complicated UTI, VAP/HAP, BSI and sepsis in adults
- Very limited evidence for other infections and use in children

Spectrum of Activity

- **Active against**:
  - Aerobic Gram-negative bacteria including many carbapenem resistant Enterobacterales, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*
    - Carbapenemases: KPC, OXA-48 and MBLs
    - ESBL and AmpC β-lactamases
- **Not active against**:
  - Gram-positive bacteria and anaerobes
- **Emerging resistance to cefiderocol in Enterobacterales, *A. baumanii* and *P. aeruginosa***:
  - The proportion of isolates resistant to cefiderocol is low but data is very limited

Toxicity

Well tolerated with side effects similar to other beta-lactams (mostly gastrointestinal)

Dose

Antibiotic Treatment Duration

- Treatment duration varies according to indication and should be as short as possible
- Usually between **7-14 days**

Adults

Dosage is for normal renal function; dose adjustment required in case of renal impairment

RESERVE

Cefiderocol 2 g q8h **IV**

Children or Neonates

Table 41.1 – Expected activity of Reserve antibiotics against third-generation cephalosporin- and carbapenem-resistant bacteria based on the type of beta-lactamase produced

Type of beta-lactamase	ESBL[a]	KPC[b]	NDM, VIM, IMP[b]	AmpC	OXA-48[b]	Non-fermenters[c]
Ambler class[d]	A[e]	A[e]	B (MBLs)	C[e]	D[e]	NA
Cefiderocol	+	+	+	+	+	+[f]
Ceftazidime+ avibactam	+	+	–	+	+	– *Acinetobacter baumannii*
						+ *Pseudomonas aeruginosa*
Fosfomycin (IV) (consider using only in combination therapy)	+	+/–	+/–	+	+/–	– *Acinetobacter baumannii*
						+/– *Pseudomonas aeruginosa*
Meropenem+ vaborbactam	+	+	–	+	–	+/–

continues

Table 41.1 *continued*

Type of beta-lactamase	ESBL[a]	KPC[b]	NDM, VIM, IMP[b]	AmpC	OXA-48[b]	Non-fermenters[c]
Plazomicin	+	+	+/−	+	+	−
Polymyxin B and colistin	+	+	+	+	+	+

Novel β-lactam Combination Agents for MDR Gram-negatives

Agent	Company	Activity against indicated enzyme or MDR strains						
		AmpC	ESBL	KPC	OXA	MBL	MDR-PA	MDR-AB
Aztreonam/avibactam	Pfizer	ν	ν	ν	ν	ν		
Ceftaroline/avibactam	Pfizer	ν	ν	ν	ν			
Meropenem/vaborbactam	Melinta	ν	ν	ν				
Meropenem/nacubactam	Roche	ν	ν	ν	ν[w]		ν[a]	
Imipenem/relebactam	Merck	ν	ν	ν			ν	
Cefepime/zidebactam	Wockhardt	ν	ν	ν	ν	ν	ν	ν
WCK-5153	Wockhardt				ν (-23)	ν	ν	ν
VNRX-5133	VenatoRx	ν	ν	ν	ν	ν	NA	NA
Cefepime/AAI101	Allecra	ν	ν	ν	ν			

[a]Hyper-AmpC-producing *P. aeruginosa* only.

Novel Non-β-lactam Combination Agents for MDR Gram-negatives

Agent	Company	Activity against indicated enzyme or MDR strains								
		AmpC	ESBL	KPC	OXA	MBL	CRE	MDR-PA	MDR-AB	SM
Cefiderocol	Shionogi	ν	ν	ν	ν	ν	ν	ν	ν	ν
Plazomicin	Achaogen	ν	ν	ν		X (NDM) ν (VIM, IMP)	ν	ν	ν	
Murepavadin	Polyphor							ν		
Eravacycline	Tetraphase	NDF	ν	ν	?	ν	ν	X	ν	ν
Omadacycline	Paratek						ν[b]		ν	
Finafloxacin	MerLion	NDF	NDF	NDF	NDF	NDF	ν?	NDF	ν[a] NDF	ν
Delafloxacin	Melinta	ν	ν						ν[c]	

[a]Enhanced activity demonstrated against ciprofloxacin-resistant strains
[b]Company pursuing indication for *E. coli* only
[c]Moderate activity against carbapenem-nonsusceptible isolates (ER-*E. coli*)

Spectrum of Activity of New Antibiotics for VAP against MDR GNB

Agent	ESBL	KPC	OXA-48	MBL	MDR-PA	MDR-AB
Ceftolozane-tazobactam	ν				ν	
Ceftazidime-avibactam	ν	ν	ν			
Ceftaroline-avibactam	ν	ν	ν			
Aztreonam-avibactam	ν	ν	ν	ν		
Imipenem-relebactam	ν	ν				
Meropenem-vaborbactam	ν	ν				
Cefiderocol	ν	ν	ν	ν	ν	ν
Plazomicin	ν	ν	ν	ν[a]	ν	
Eravacyclin	ν	ν	ν	ν		ν
Murepavadin					ν	

[a]Not active against many NDMs

Agent	KPC-producer	NDM-producer	OXA-48-like-producer	Carbapenem-resistant *Pseudomonas aeruginosa*	Carbapenem-resistant *Acinetobacter baumannii*	*Stenotrophomonas maltophilia*
Aztreonam-avibactam						
Cefiderocol						
Ceftazidime-avibactam						
Ceftolozane-tazobactam						
Eravacycline						
Fosfomycin (intravenous)						
Imipenem-relebactam						
Meropenem-vaborbactam						
Plazomicin						
Polymyxin						
Tigecycline						

Table 3: Relevant Pharmacodynamic and Pharmacokinetic Considerations for Selected Agents

Anti-infective	Class	Human Pharmacokinetic (PK) Considerations[1]	Pharmacodynamic Considerations[2]
Cefepime/ zidebactam	β-lactam/ β-lactam enhancer	Data not yet available	Cefepime ***f*T>MIC** lowered by zidebactam and associated with efficacy [17]
Aztreonam/ avibactam	β-lactam/ β-lactam inhibitor	Data not yet available	***f*T>MIC** predictive of efficacy against CPE and PSA [96]
Ceftaroline/ avibactam	β-lactam/ β-lactam inhibitor	≤1,800 mg TDD of ceftaroline and avibactam well-tolerated; no relevant accumulation following 10 days of a multiple-dose study [33]	Avibactam **AUC** or $\mathbf{C_{max}}$ best related to efficacy in an *in vitro* model of β-lactamase-producing Enterobacteriaceae infection [97]
Murepavadin	Antipseudomonal peptidomimetic	Linear PK, dose proportionality observed (n=10 males); 1 mg/kg q12h, 2 mg/kg q8h, 5 mg/kg q12h studied (3-h infusions); dose-limiting toxicity not observed [98]	***f*AUC** related to efficacy in the lung; PD target (1-$\log_{10}$ reduction) achieved for 14/15 PSA isolates [99]
Finafloxacin	Fluoroquinolone	Plasma $t_{1/2}$ ~10 h permits q24h oral dosing; ~30% excreted unchanged in urine; no relevant accumulation after 7 days of dosing (≤800 mg q24h) [100]	**AUC/MIC** best related to efficacy against methicillin-susceptible *S. aureus* and *E. coli* [101]
Cefiderocol	Siderophore β-lactam	Plasma $t_{1/2}$ ~2-3 h; 60-70% excreted unchanged in urine; no accumulation after 10 days of dosing (2 gram q8h); significantly removed by iHD [102]	***f*T>MIC** targets for stasis and 2-$\log_{10}$ reduction ranged 44-95% and 62-100%, respectively, against PSA [103]
Eravacycline	Fluorocycline (Tetracycline)	Advantages over tigecycline: Oral bioavailability, higher serum concentrations [48]; ≥80% protein bound; intrapulmonary concentrations higher than free plasma concentrations [104]	***f*$\mathbf{C_{max}}$/MIC** identified as a PD driver of efficacy against Enterobacteriaceae [105]
Imipenem-cilastatin/ relebactam	β-lactam/ β-lactam inhibitor	Short plasma $t_{1/2}$ warranting q6h dosing; similar plasma and lung ELF profiles; ELF:plasma concentration ratio ~1:2 for both imipenem and relebactam [106]	***f*AUC** best related to relebactam efficacy against PSA and *K. pneumoniae*; efficacy not driven by C_{max} [107]
Omadacycline	Aminomethylcycline (Tetracycline-like)	Advantages over tigecycline: Oral bioavailability, higher plasma and epithelial lining fluid levels [108]; reduced bioavailability if administered within 2-4 of food intake [109]	**AUC/MIC** best related to efficacy for both Gram-positive and Gram-negative pathogens [110]
Plazomicin	Aminoglycoside	Linear PK, dose proportionality observed; no accumulation of 15 mg/kg dose over 5 days; plasma $t_{1/2}$ ~3 h; primarily excreted unchanged in the urine (~87%) [69,111]	**AUC/MIC** best related to efficacy [112]; Evidence of synergy (*in vitro*, time-kill analyses) with cefepime, doripenem, imipenem, piperacillin/tazobactam [69]
Delafloxacin	Fluoroquinolone	Steady-state achieved in ~3 days; food does not affect oral bioavailability; 84% protein bound; primarily metabolized via glucuronidation; eliminated in urine and feces [80]	***f*AUC/MIC** best related to efficacy [80]
Meropenem/ vaborbactam	β-lactam/ β-lactam inhibitor	Vaborbactam protein binding ~33%; vaborbactam does not undergo metabolism; both components primarily excreted in urine (>75% vaborbactam excreted unchanged) [82]	***f*T>MIC** best related to efficacy [82]

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

Important

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

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

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

Clinical Question 1

- *What are preferred antibiotics for the treatment of uncomplicated cystitis caused by ESBL-E?*
  - Nitrofurantoin and TMP-SMX are preferred treatment options for uncomplicated cystitis caused by ESBL-E.
  - Ciprofloxacin, levofloxacin, and carbapenems are alternative agents for uncomplicated cystitis caused by ESBL-E: Although effective, their use is discouraged when nitrofurantoin or TMP-SMX are active.
  - Single dose aminoglycosides and oral fosfomycin (for E. coli only) are also alternative treatments for uncomplicated cystitis caused by ESBL-E.).
  - The IDSA panel does not suggest prescribing amoxicillin-clavulanic acid or doxycycline for the treatment of ESBL-E cystitis

Clinical Question 2

- *What are preferred antibiotics for the treatment of pyelonephritis and cUTI caused by ESBL-E?*
  - TMP-SMX, ciprofloxacin, or levofloxacin are preferred treatment options for pyelonephritis and cUTIs caused by ESBL-E.
  - Ertapenem, meropenem, and imipenem-cilastatin are preferred agents when resistance or toxicities preclude the use of TMP-SMX or fluoroquinolones.
  - Aminoglycosides for a full treatment course are an alternative option for the treatment of ESBL-E pyelonephritis or cUTI; Once-daily plazomicin was noninferior to meropenem
  - Fosfomycin is not suggested
  - Nitrofurantoin does not achieve adequate concentrations in the renal parenchyma and is not advised for pyelonephritis or cUTI

Clinical Question 3

- *What are preferred antibiotics for the treatment of infections outside of the urinary tract caused by ESBL-E?*
  - Meropenem, imipenem-cilastatin, or ertapenem are preferred for the treatment of infections outside of the urinary tract caused by ESBL-E.
  - For patients who are critically ill and/or experiencing hypoalbuminemia, meropenem or imipenem-cilastatin are the preferred carbapenems.
  - After appropriate clinical response is achieved, transitioning to oral trimethoprim-sulfamethoxazole, ciprofloxacin, or levofloxacin should be considered, if susceptibility is demonstrated.

Clinical Question 4

- *What is the role of β-lactam-β-lactamase inhibitor combinations and cefiderocol for the treatment of infections caused by ESBL-E?*
  - The IDSA panel suggests that ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol be preferentially reserved for treating infections caused by organisms exhibiting carbapenem resistance.
    - Avibactam is able to successfully protect ceftazidime against hydrolysis by ESBL enzymes
  - The IDSA panel suggests against the use of ceftolozane-tazobactam for the treatment of ESBL-E infections, with the possible exception of polymicrobial infections

Clinical Question 5

- *What are preferred antibiotics for the treatment of uncomplicated cystitis caused by CRE?*
  - Nitrofurantoin, TMP-SMX, ciprofloxacin, or levofloxacin are preferred treatment options for uncomplicated cystitis caused by CRE, although the likelihood of susceptibility to any of these agents is low.
  - A single dose of an aminoglycoside, oral Fosfomycin (for E. coli only), colistin, ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, cefiderocol, are alternative treatment options for uncomplicated cystitis caused by CRE

Clinical Question 6

- *What are preferred antibiotics for the treatment of pyelonephritis and cUTI caused by CRE?*
  - TMP-SMX, ciprofloxacin, or levofloxacin are preferred treatment options for pyelonephritis and cUTI caused by CRE, if susceptibility is demonstrated.
  - Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol are also preferred treatment options for pyelonephritis and cUTIs.
  - Aminoglycosides are alternative treatment options

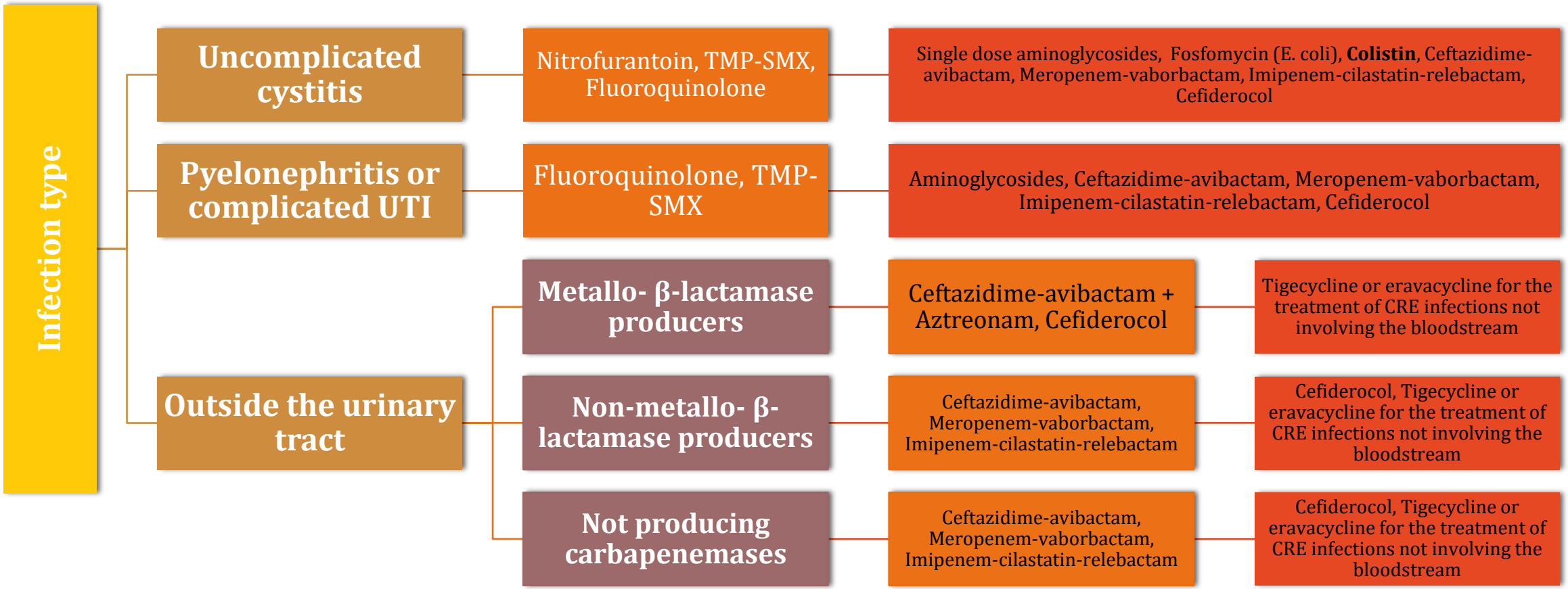
Clinical Question 7

- *What are the preferred antibiotics for the treatment of infections outside of the urinary tract caused by CRE, when carbapenemase testing results are either not available or negative?*
  - Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam are the preferred treatment options for infections outside of the urinary tract caused by CRE, when carbapenemase testing results are either not available or negative
  - For patients with CRE infections who within the previous 12 months have received medical care in countries with a relatively high prevalence of metallo-β-lactamase-producing organisms or who have previously had a clinical or surveillance culture where a metallo-β-lactamase producing isolate was identified, preferred treatment options include the combination of ceftazidime-avibactam plus aztreonam, or cefiderocol as monotherapy

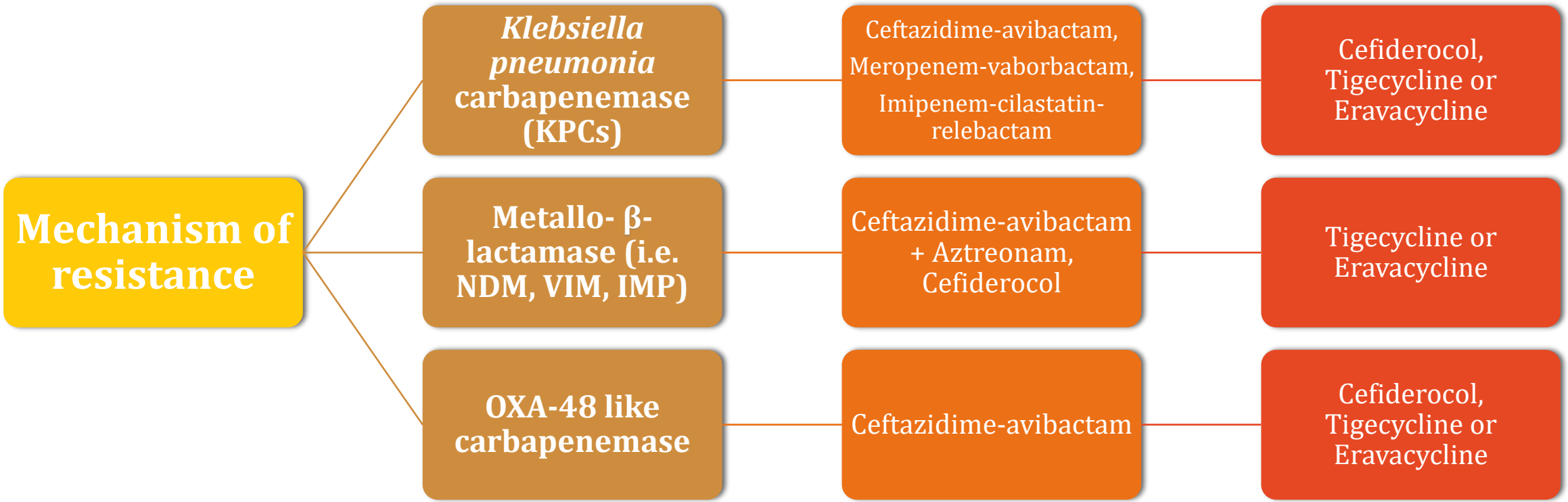
Clinical Question 8

- *What are the preferred antibiotics for the treatment of infections outside of the urinary tract caused by CRE if KPC production is present?*
  - Meropenem-vaborbactam, ceftazidime-avibactam, and imipenem-cilastatin-relebactam are preferred treatment options for KPC-producing infections.
  - Cefiderocol is an alternative option

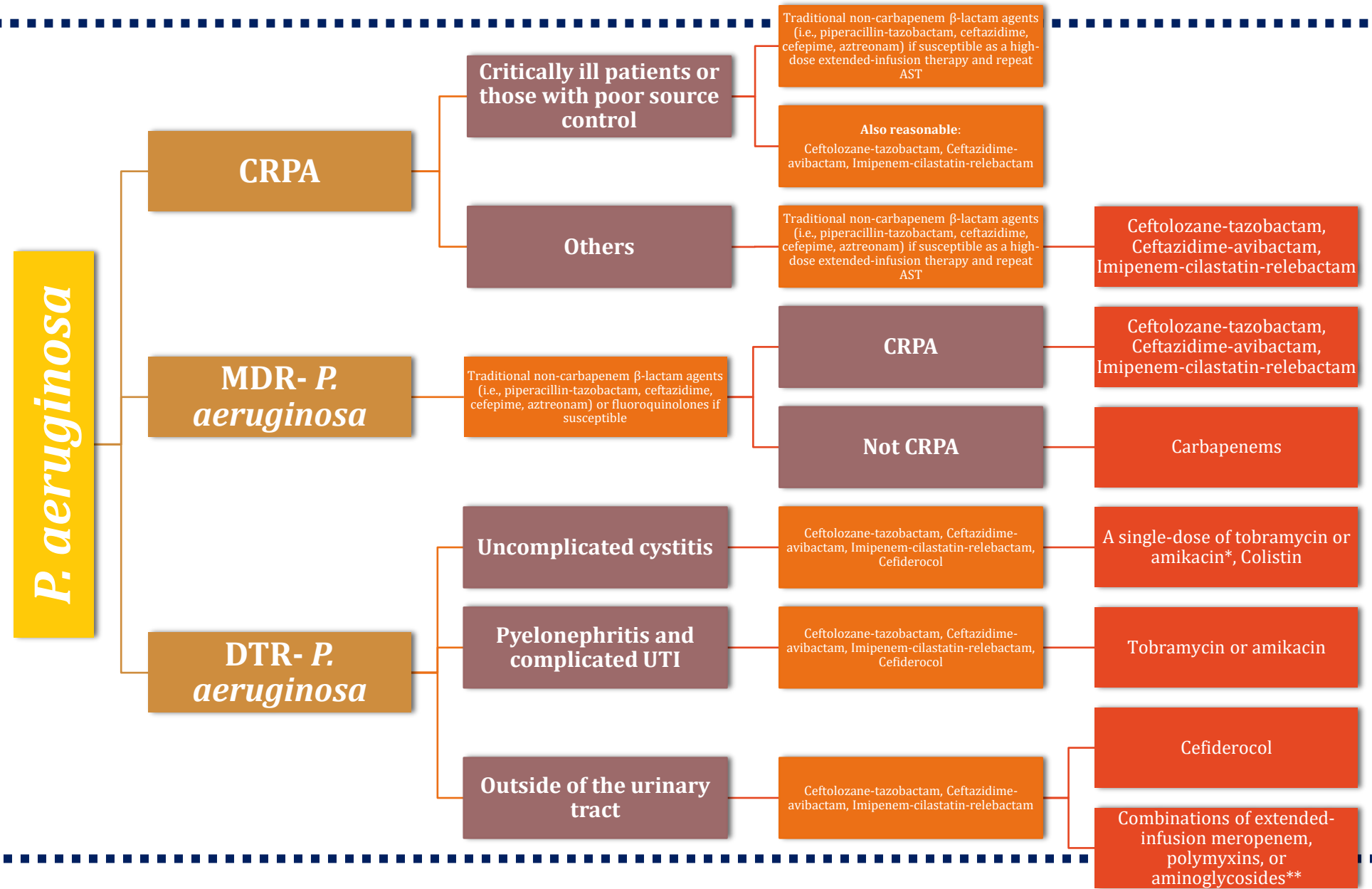
CRE infection treatment



CRE infection treatment

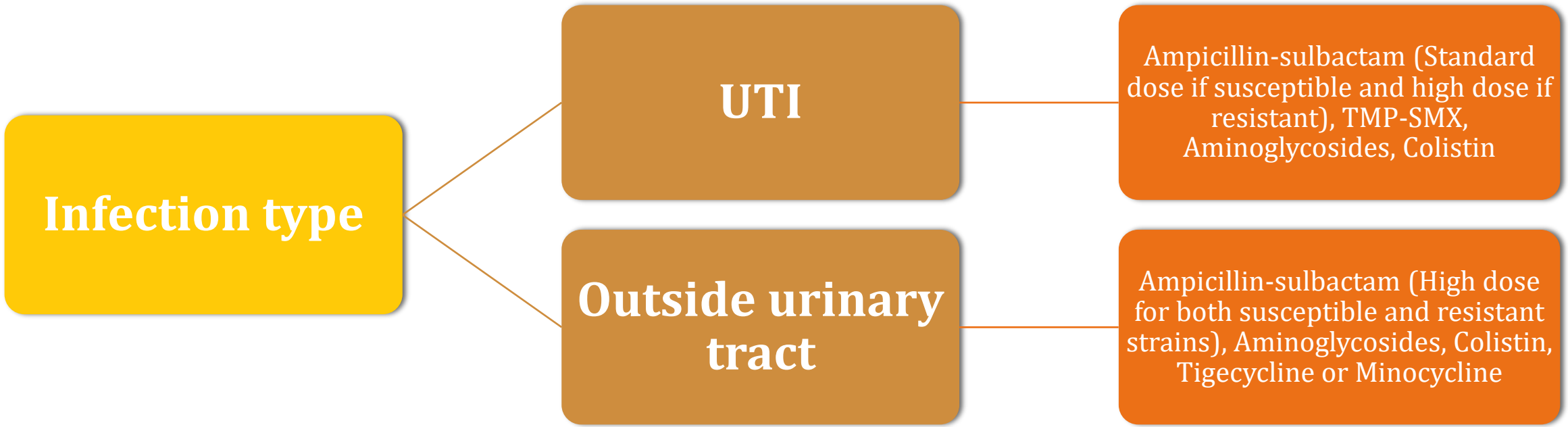


Pseudomonas aeruginosa



Acinetobacter baumannii; CRAB

Combination therapy with at least two active agents, whenever possible, is suggested for the treatment of CRAB infections.
The preferred agent in combination with **high-dose ampicillin-sulbactam** is one of minocycline, tigecycline, polymyxin B or cefiderocol.



Acinetobacter baumannii; CRAB

Polymyxins

- The panel preferentially suggests **polymyxin B**, based on its more favorable PK profile than colistin.
- Colistin is favored for CRAB UTIs.
- There is no CLSI susceptibility category for the polymyxins against A. baumannii; most evidence suggests the benefit with polymyxins would be diminished for polymyxin MICs >2 µg/mL.

Tetracycline derivatives

- **High-dose minocycline or high-dose tigecycline** can be considered in combination with at least one other agent for the treatment of CRAB infections.
- The panel prefers minocycline because of the long-standing clinical experience with this agent and the availability of CLSI susceptibility interpretive criteria; however, tigecycline is also a reasonable option.

Cefiderocol

- Cefiderocol should be limited to the treatment of CRAB infections refractory to other antibiotics or in cases where intolerance or resistance to other agents precludes their use.

با تشکر از توجه شما