# From Pseudomonas to Stenotrophomonas: Navigating the Treatment of Non-Fermenting Gram-Negative Bacteria

A presentation for HealthTrust Members

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# Objectives

1. Recall non-fermenting gram-negative bacteria and their resistance mechanisms.
2. Identify alternative therapies for *Pseudomonas aeruginosa* (P. aeruginosa), Carbapenem-resistant *Acinetobacter baumannii* (CRAB), and *Stenotrophomonas maltophilia* (S. maltophilia) according to current evidence-based guidelines.
3. Recognize patient-centered guideline recommendations regarding nebulized antibiotics in the treatment of ventilator-associated pneumonias.

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# Abbreviations

AMR: Antimicrobial-resistant

AST: antimicrobial susceptibility testing

BAT: best available therapy

BL: beta-lactam

BLI: beta-lactam inhibitor

CRAB: carbapenem

CR-GNB: carbapenem resistant gram-negative bacteria

CDC: Centers for Disease Control and Prevention

cIAIs: complicated intra-abdominal infections

cUTIs: complicated urinary tract infections

DTR: difficult-to-treat resistance

HABP: hospital acquired bacterial pneumonia

MBLs: metallo-beta-lactamases

MDR: multi-drug resistance

MICs: minimum inhibitory concentration

NFGNB: non-fermenting gram-negative bacteria

PBPs: penicillin-binding proteins

PK/PD: pharmacokinetic/pharmacodynamic

PsAg: Pseudomonas aeruginosa

UTI: urinary tract infection

TMP-SMX: sulfamethoxazole-trimethoprim

VABP: ventilator-associated bacterial pneumonia

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# Why this is important?

- Antimicrobial-resistant (AMR) infections are a global crisis, accounting for 2.8 million infections and over 35,00 deaths annually from 2012 to 2017 in the U.S. alone - Centers for Disease Control and Prevention (CDC) Antibiotic Resistance Threats in the United States Report

- AMR is one of the top global public health and development threats; it is estimated by the World Health Organization that AMR was directly responsible for 1.27 million global deaths in 2019 and contributed to 4.95 million deaths

Source: *Antimicrobial Resistance Facts and Stats. (2025)*

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# CDC Antimicrobial Resistance Threats

| | Threat | Change in Rates or Number of Infections*** | | | |
|---|---|---|---|---|---|
| | | 2020 vs. 2019 | 2021 vs. 2020 | 2022 vs. 2021 | 2022 vs. 2019 |
| URGENT* | Hospital-onset CRE | ▲ Increase | ▲ Increase | — Stable | ▲ Increase |
| URGENT* | Hospital-onset Carbapenem-resistant *Acinetobacter* | — Stable | — Stable | — Stable | ▲ Increase** |
| URGENT* | Clinical Cases of *C. auris* | ▲ Increase | ▲ Increase | ▲ Increase | ▲ Increase |
| SERIOUS* | Hospital-onset MRSA | ▲ Increase | — Stable | ▼ Decrease | — Stable |
| SERIOUS* | Hospital-onset VRE | ▲ Increase | ▲ Increase | — Stable | ▲ Increase |
| SERIOUS* | Hospital-onset ESBL-producing Enterobacterales | ▲ Increase | — Stable | — Stable | ▲ Increase |
| SERIOUS* | Hospital-onset MDR *Pseudomonas aeruginosa* | ▲ Increase | ▲ Increase | — Stable | ▲ Increase |

Source: *Antimicrobial Resistance Threats in the United States, 2021–2022. (2024)*

# Antimicrobial Pipeline

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- 22 antimicrobials approved between 2012-2022

| Antibacterial | Approval Year | Structural Classification | Primary Use |
|---|---|---|---|
| Ceftolazone-tazobactam | 2014 | Cephalosporin and beta-lactamase inhibitor (BLI) | complicated intra-abdominal infections (cIAIs); complicated urinary tract infections (cUTIs); hospital-acquired bacterial pneumonia (HABP) |
| Ceftazidime-avibactam | 2015 | Cephalosporin and beta-lactamase inhibitor (BLI) | cIAIs, cUTIs, HABP |
| Imipenem-cilastatin-relebactam | 2019 | Penem antibacterial, renal dehydropeptidase inhibitor, and BLI | cUTI; cIAI; HABP/ventilator-associated bacterial pneumonia (VABP) |
| Cefiderocol | 2019 | Cephalosporin | cUTI, including pyelonephritis and HABP/VABP |

Source: García-Castro M, et.al. (2023)

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# Why this is important?

- The misuse and overuse of antimicrobials in humans, animals and plants is primary cause of the development of drug-resistant pathogens
- AMR resistance affects countries in all regions and at all income levels
- There is an inadequate research and development pipeline despite rising levels of resistance
- AMR has significant economic costs; the World Bank estimates that AMR could result 1 trillion additional healthcare costs by 2050

Source: *Antimicrobial Resistance Facts and Stats. (2025)*

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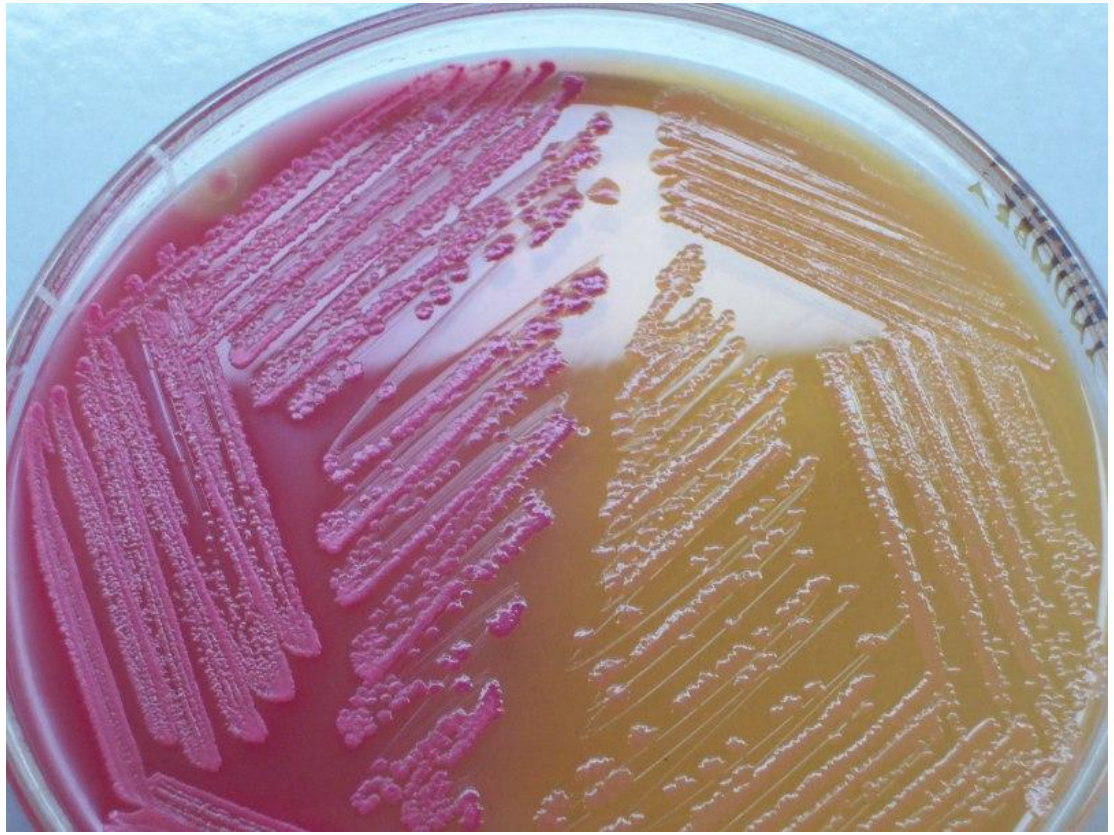
# Non-fermenting Gram-negative Bacteria

# Fermenting vs. Non-fermenting

- Fermenting gram-negative metabolize carbohydrates via fermentation pathways, producing acid and/or gas
  - These characteristics are used in laboratory identification
  - MacConkey medium

- Non-fermenting gram-negative bacilli (NFGNB) are aerobic organisms that do not use carbohydrates as a source of energy





Source: *Non-Fermenting Gram-Negative Bacterium*

# NFGNBs

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NFGNBs are most often niche pathogens that cause infections in critically ill or immunocompromised patients

These bacteria are intrinsically resistant to common antibiotics such as ampicillin, first-third generation cephalosporins

They are also known for rapidly acquiring resistance to other classes of drugs and multi-drug resistance is common

Source: *Non-Fermenting Gram-Negative Bacterium*

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# Most Common NFGNB

*Pseudomonas aeruginosa*

*Acinetobacter baumannii*

*Stenotrophomonas maltophila*

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# *Pseudomonas aeruginosa*

# Intrinsic resistance mechanism

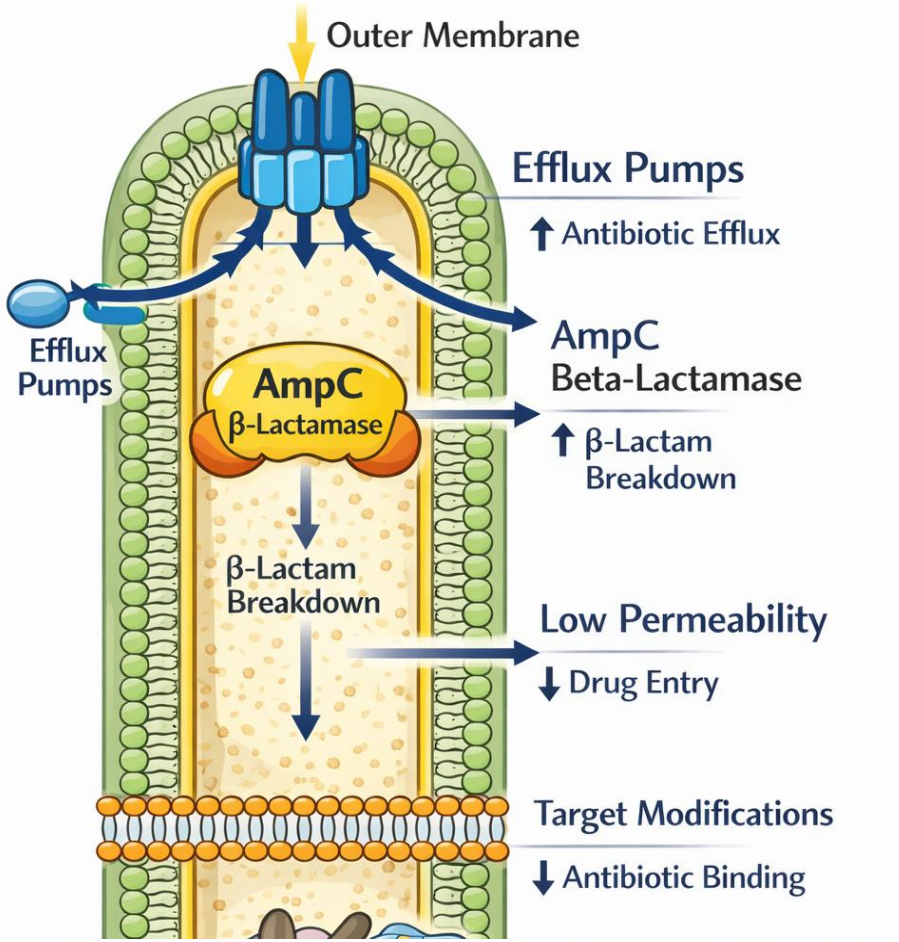
- *Pseudomonas aeruginosa* (PsAg) is an incredibly versatile pathogen with three key characteristics:

  - High adaptive capacity enables the pathogen to generate mutations at a high rate
  - Large arsenal of virulence factors (exotoxins, proteases, biofilm formation, etc.)
  - High potential to generate and transmit antibiotic resistance

Source: Pina-Sánchez M, et.al. (2023)

# Acquired resistance mechanisms - mutations

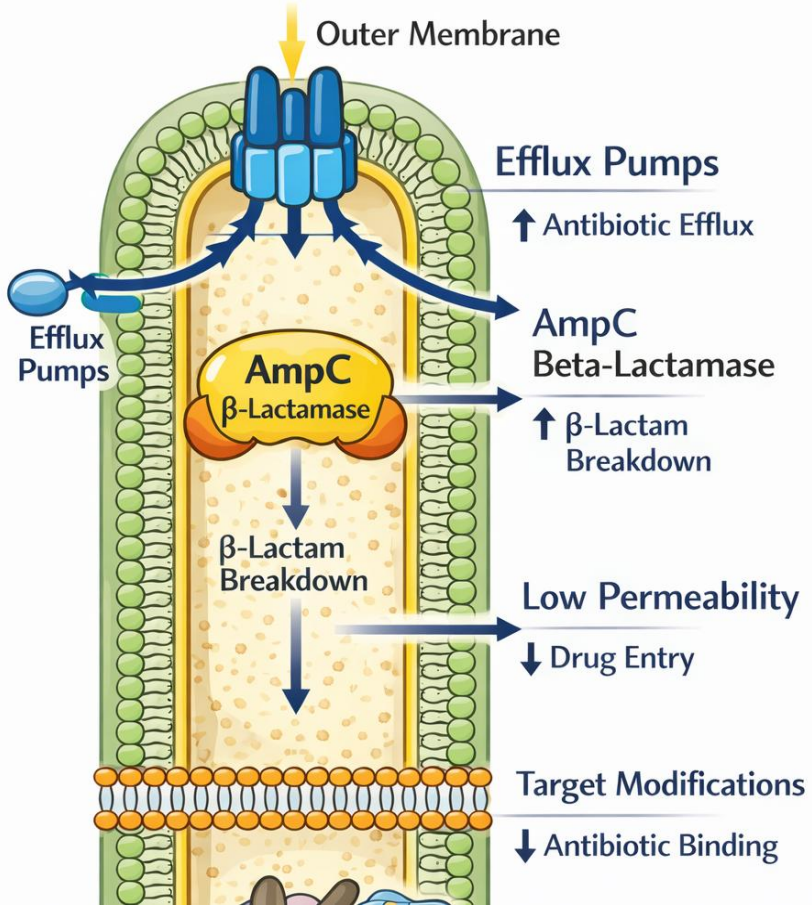
- Decreased expression of outer membrane porins
    - Loss or decrease of the OprD is a frequent cause of carbapenem resistance, as this is the primary channel for carbapenem entry into the cell




Source: ina-Sánchez M, et.al. (2023)

# Acquired resistance mechanisms – mutations, *continued*

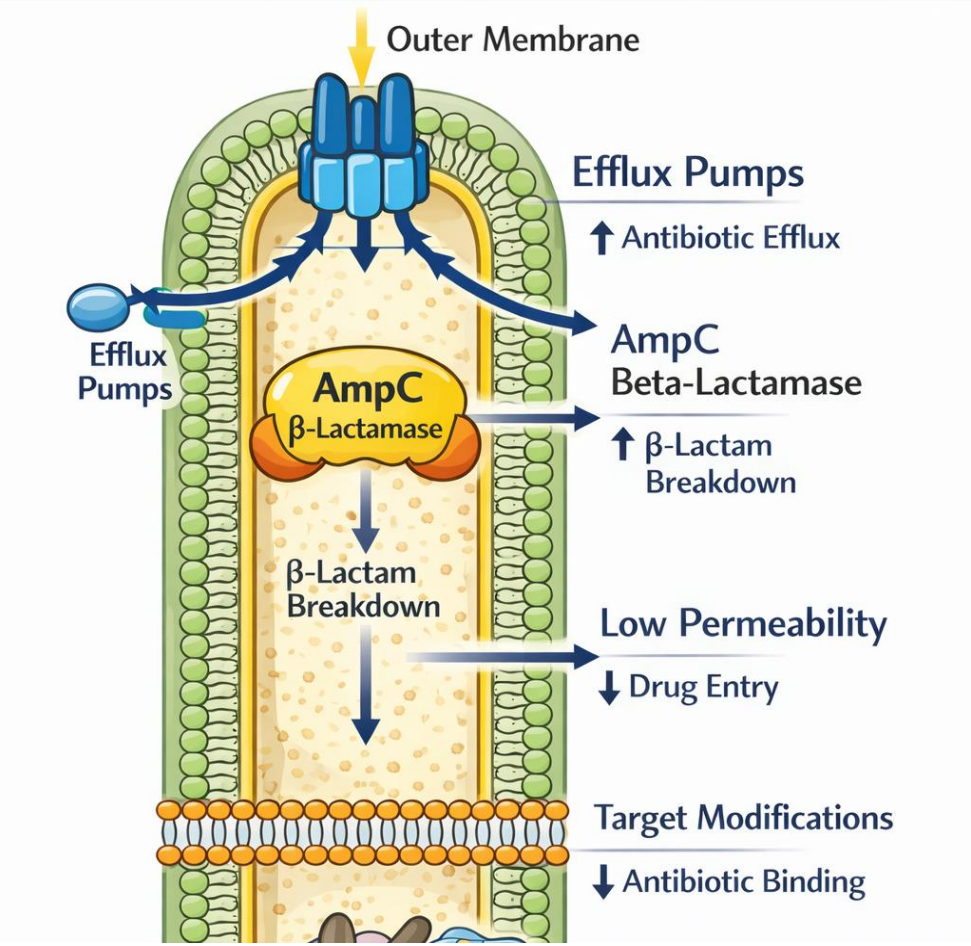
- PsAg carries an inducible AmpC cephalosporinase
  - Wild-type strains of P. aeruginosa only produce low levels of AmpC and are susceptible to antipseudomonal penicillins, penicillin-inhibitor combinations, and cephalosporins
  - When AmpC production is significantly increased, PsAg develops resistance to all beta-lactams, including cefepime




Source: Pina-Sánchez M, et.al. (2023)

# Acquired resistance mechanisms – mutations, *continued*

- Target Modifications
  - Penicillin-binding proteins (PBPs) are bacterial enzymes that build up the cell wall
  - Mutations in PBPs (PBP3 and PBP4) reduce beta-lactam binding affinity
- Efflux Pump Overexpression
  - Mutations in regulatory genes disrupt normal efflux pump expression and cause overexpression, allowing faster removal of antibiotics from the cell




Source: Pina-Sánchez M, et.al. (2023)

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# Infectious Diseases Society of America 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections

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# Classifications

## Multi-drug resistance (MDR) *P. aeruginosa*

Not susceptible to at least one antibiotic in at least three antibiotic classes for which PsAg susceptibility is generally expected: penicillins, cephalosporins, fluoroquinolones, aminoglycosides, and carbapenems

## Difficult-to-Treat Resistance (DTR) *P. aeruginosa* (defined in 2018)

Non-susceptibility to all of the following: piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem-cilastatin, ciprofloxacin, and levofloxacin

Source: *IDSA 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections*

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# Antimicrobial Susceptibility Testing (AST)

- The panel encourages all clinical microbiology laboratories to perform AST for both MDR and DTR P. aeruginosa isolates against new beta-lactams (ceftolazone-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and cefiderocol)

- Understanding local DTR P. aeruginosa ASTs can help guide empiric antibiotic decision when AST results are pending

- Carbapenemase production is uncommon in U.S. P. aeruginosa isolates and is currently not deemed critical

Source: *IDSA 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections*

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# Ceftolazone-tazobactam (Zerbaxa®)

- Cephalosporin and beta-lactamase inhibitor combination
- Dose for DTR PsAg infection: 3 grams IV every 8 hours
- ADR: hypersensitivity reactions, abdominal pain, diarrhea
- AWP per vial: $229.96

Source: Lexicomp. Accessed Jan 2026.

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# Ceftazidime-avibactam (Avycaz®)

Cephalosporin and beta-lactamase inhibitor combination

Dose for DTR PsAg infection: 2.5 grams IV every 8 hours

- Requires renal dose adjustment

ADRs: hypersensitivity reactions, neurotoxicity, pruritis, constipation, diarrhea

AWP price per vial: $523.36

Source: Lexicomp. Accessed Jan 2026.

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# Imipenem-cilastatin-relebactam (Recarbrio®)

Penem antibacterial, renal dehydropeptidase inhibitor, and BLI

Dose: 1.25 g every 6 hours

- Requires renal dose adjustment

ADR: CNS effects, hypersensitivity reactions

AWP price per vial: $390.76

Source: Lexicomp. Accessed Jan 2026.

# Cefiderocol (Fetroja®)

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Fifth-generation cephalosporin

Dose: 2 grams every 8 hours

- Requires renal dose adjustment
- Use caution in patients with renal impairment or with history of seizure disorder

ADR: hypersensitivity reactions, neurotoxicity

AWP price per vial: $296.17

Source: Lexicomp. Accessed Jan 2026.

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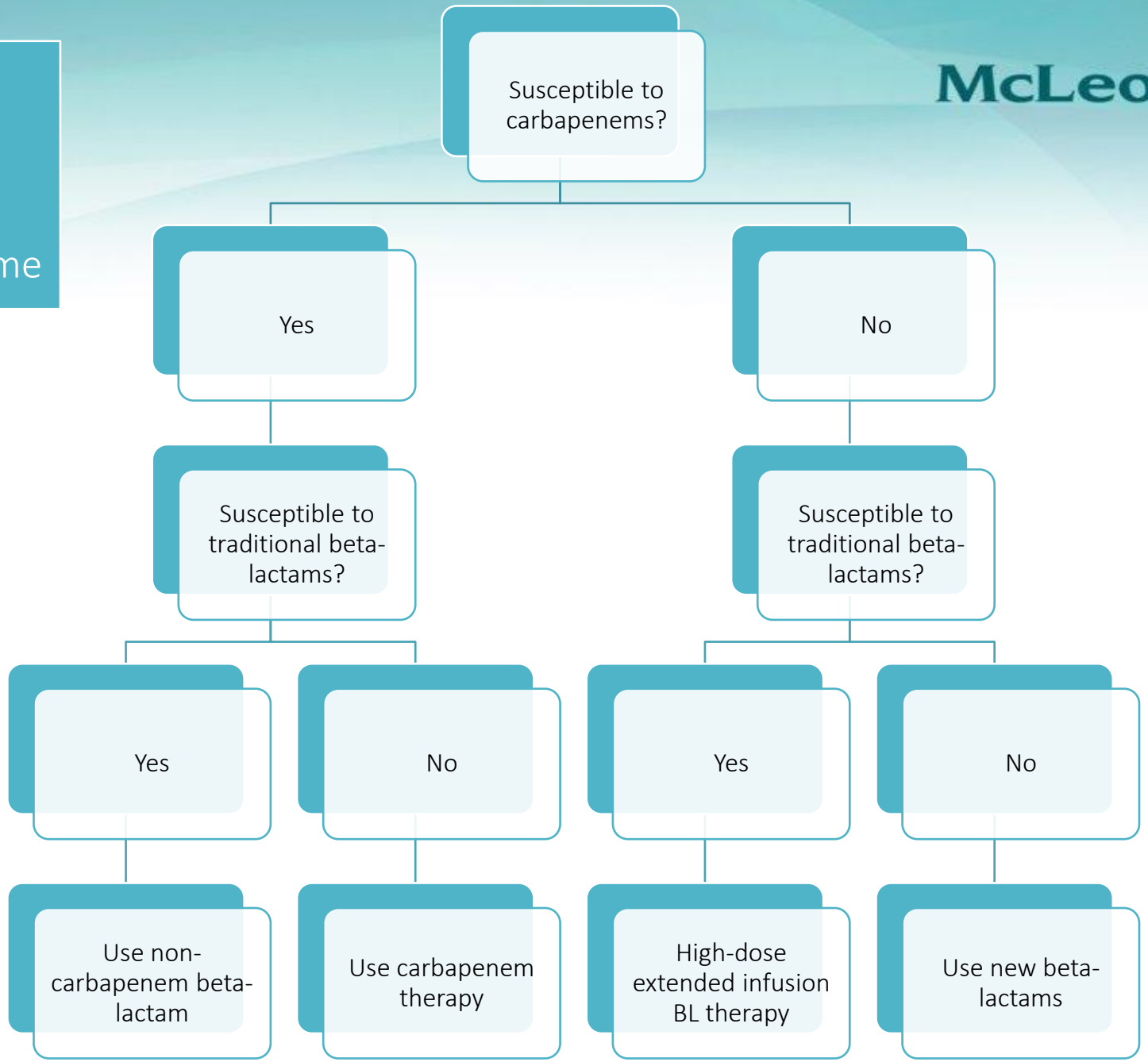
# MDR *Pseudomonas aeruginosa*

- When isolates are susceptible to both non-carbapenem beta-lactam agents and carbapenems, the non-carbapenem agents are preferred
  - In attempt to preserve the activity of carbapenems for future, increasingly drug-resistant infections
- For isolates not susceptible to carbapenems but susceptible to traditional beta-lactams, high-dose extended-infusion therapy is recommended
  - Approximately 20-60% of isolates
- For isolates resistant to carbapenems but susceptible to traditional beta-lactams, use of newer beta-lactam agents is reasonable for critically ill patients or those with poor source control

Source: *IDSA 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections*

# Traditional beta-lactams

- Piperacillin-tazobactam, cefepime




Source: *IDSA 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections*

# MDR Pseudomonas aeruginosa

- Regardless of the antibiotic administered, patients should be monitored for clinical improvement as PsAg can express additional mechanisms after exposure to antibiotic therapy
- An analysis of 767 episodes of PsAg bacteremia identified the emergence of resistance to traditional beta-lactam agents within 30 days with the following likelihood: piperacillin-tazobactam (8%), ceftazidime (12%), meropenem (14%), and imipenem (27%)
- Recommended to repeat AST of subsequent MDR PsAg isolates obtained from the same patient to monitor resistance

Source: *IDSA 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections*

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# Classifications

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Source: *IDSA 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections*

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# DTR *Pseudomonas aeruginosa*

- Newer beta-lactam agents may be active against DTR PsAg infections outside of the urinary tract
  - Activity against carbapenem-non-susceptible PsAg isolates
    - Ceftolozane-tazobactam: 90%
    - ceftazidime-avibactam: 85%
    - imipenem-cilastatin-relebactam: 86%
    - Cefiderocol: 99%

- Always recommended to obtain AST results to guide treatment decisions

Source: *IDSA 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections*

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# Urinary Infections

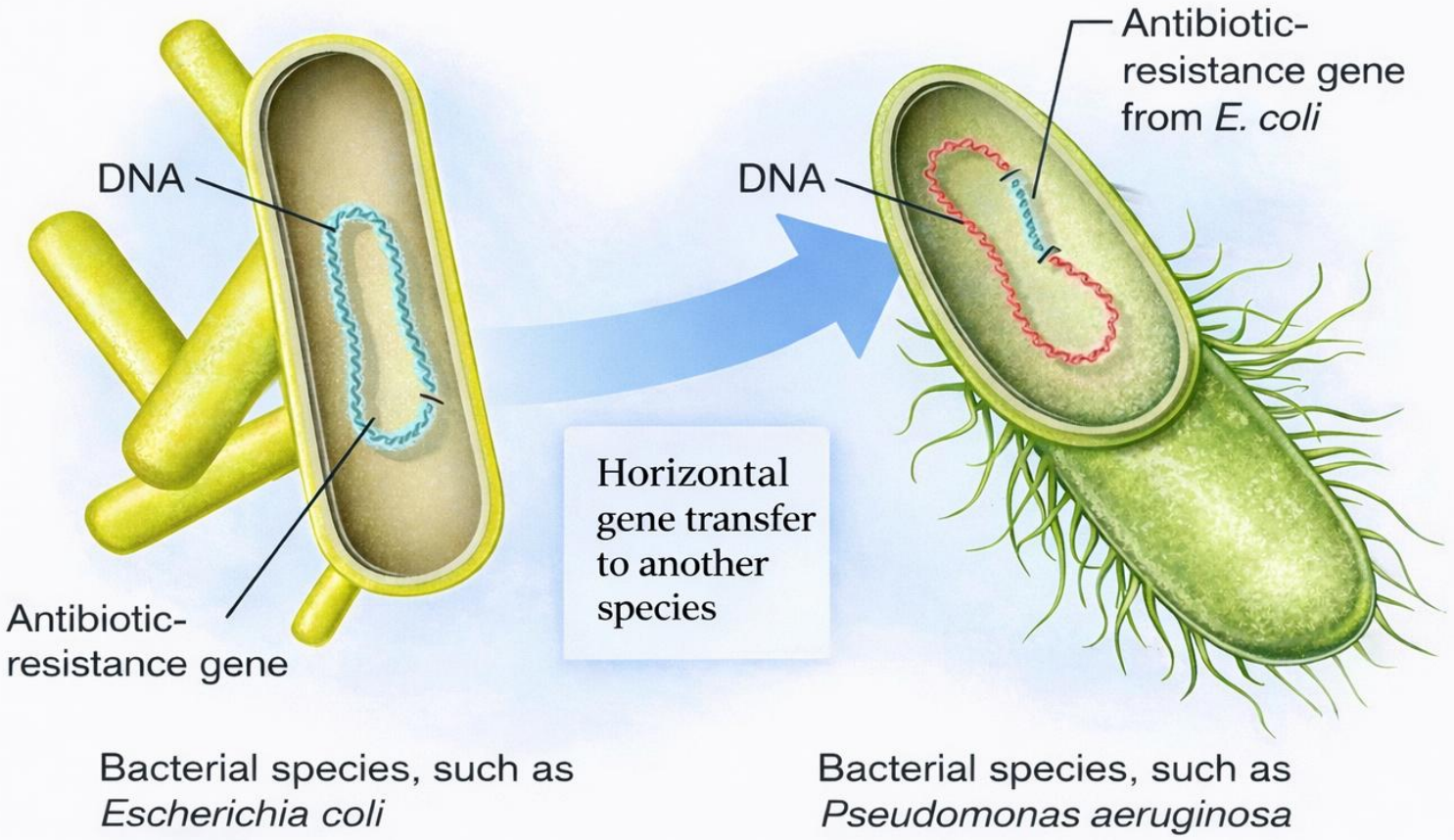
Uncomplicated cystitis, pyelonephritis or cUTI

- Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and cefiderocol are the preferred treatment options
- Tobramycin or amikacin (as a single dose) are alternative treatment options

Colistin is an alternate consideration for cystitis as it converts to its active form in the urinary tract

Source: *IDSA 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections*

# Metallo-beta-lactamases



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# Metallo-beta-lactamases (MBLs)

- PsAg isolates producing MBLs are uncommon in the United States
- Isolates that exhibit resistance to all available beta-lactam-beta-lactamase inhibitors should raise suspicion for MBL production
- Cefiderocol is the preferred treatment for MBL-producing PsA

Source: *IDSA 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections*

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# Metallo-beta-lactamases (MBLs)

| Study | Population | Comparator | Outcomes | Key Result |
|---|---|---|---|---|
| CREDIBLE-CR | Severe CR-GNB infections (incl. MBLs) | Best available therapy (often colistin-based) | Clinical cure | 52% cefiderocol vs 50% BAT |
| | | | 28-day mortality | 34% cefiderocol vs 18% BAT (driven by Acinetobacter subgroup) |
| APEKS-NP | HAP/VAP | High-dose meropenem | Day-14 mortality | 12.4% cefiderocol vs 11.6% meropenem (non-inferior) |
| | | | Clinical cure | 64% vs 67% |

Source: *IDSA 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections*

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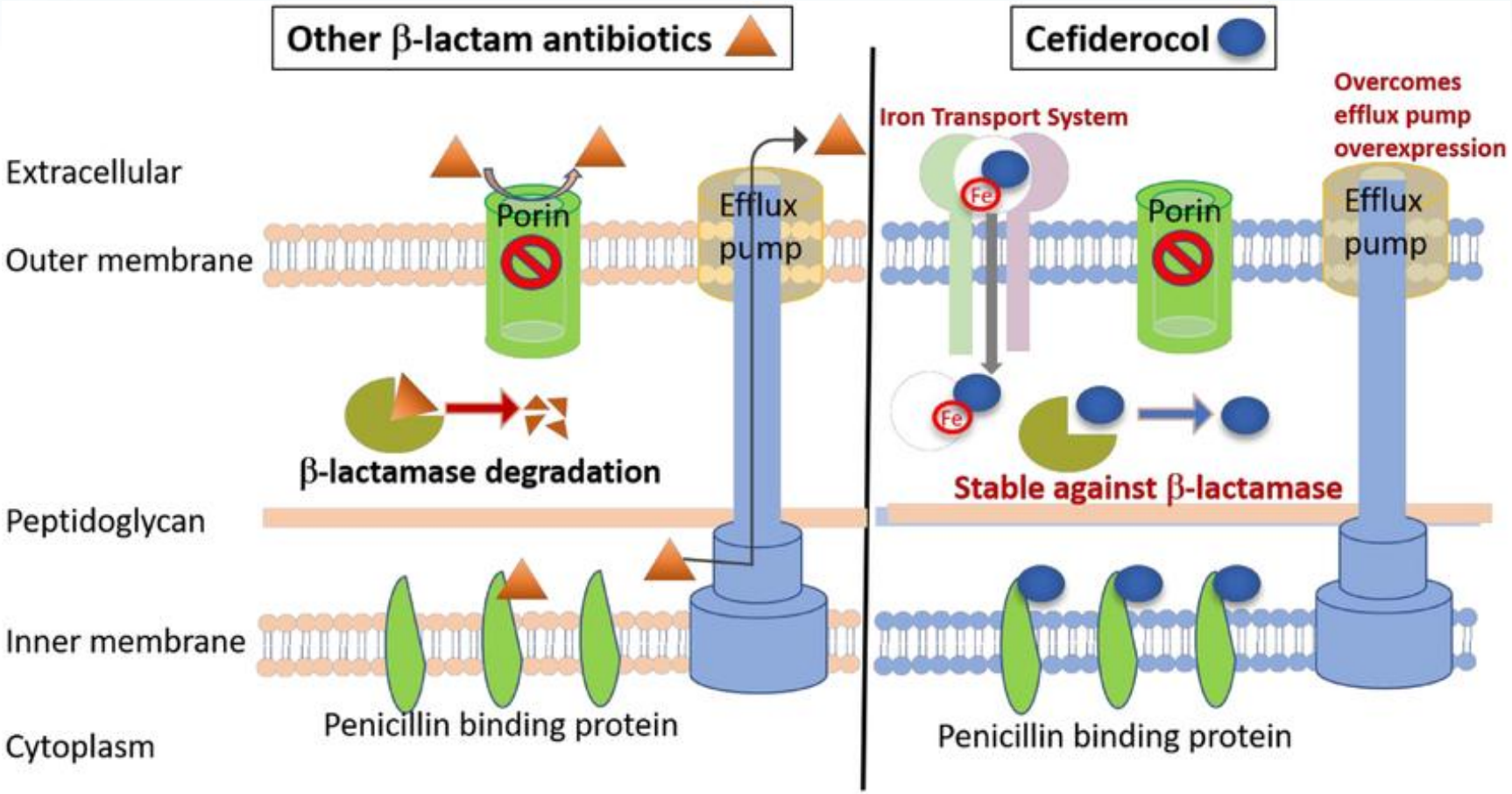
# Cefiderocol (Fetroja)



# Nebulized Antibiotics

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Nebulized antibiotics are not recommended for the treatment of respiratory infections caused by DTR P. aeruginosa

- One trial compared the outcomes of 100 adults with pneumonia (34% caused by P. aeruginosa) treated with nebulized colistin versus placebo (537)
- A second trial compared the outcomes of 142 adults with pneumonia (22% caused by P. aeruginosa) treated with nebulized amikacin/fosfomycin versus placebo (538)
- A third trial compared the outcomes of 508 adults with pneumonia (32% caused by P. aeruginosa) treated with nebulized amikacin versus placebo (539)

None of the trials demonstrated improved outcomes or survival benefit with nebulized antibiotics compared to placebo, including the sub-group analyses of patients with drug resistant pathogens (539)

Source: *IDSA 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections*

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# Carbapenem-resistant *Acinetobacter baumannii* (CRAB)

# Pathogenic vs. Colonization

- CRAB is most often recovered from respiratory specimens or wounds and colonization is common in certain patient populations
- Positive culture without other signs of infection > colonization
  - Absolute neutrophil count, C-reactive protein levels
- Prior to treatment, paramount to determine if the isolate is a pathogen or colonization
  - Colonization: previous cultures etc.

Source: Sheng J, et.al. (2017)

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# Resistance Mechanisms

- Low outer membranepermeability (fewer andsmaller porins)
- Efflux pumps, raising theMICs of recommendedtherapies
- Native beta-lactamases

Class A (ex. CTX-M, KPC) primarily hydrolyze penicillins and cephalosporins

Class B (metallo-beta-lactamases) catalyze hydrolysis of virtually all beta-lactam antibiotics

Class C (AmpC type beta-lactamases) typically combined with a promoter resulting in high resistance to ceftazidime

Class D (OXAs) hydrolyze carbapenems

Source: Sheng J, et.al. (2017)

# Carbapenem resistance

- Combination of these mechanisms leads to carbapenem resistance however, the standout mechanism is OXA enzymes

- In a study of 92 patients in the US with CRAB isolates, the percentages of specific OXA enzymes were:
  - OXA-51-like (intrinisic): 98% (90/92 isolates)
  - OXA-23-like (acquired): 49% (45/92 isolates)
  - Overall 73% of isolates in the study harbored at least one additional OXA gene beyond the intrinsic one

Source: Kyriakidis I, et.al. (2021)

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# Initial CRAB Treatment

It is recommended to use an antibiotic regimen including a sulbactam-containing agent, preferably sulbactam-durlobactam in combination with imipenem-cilastatin or meropenem

- If unavailable, an alternative regimen is high-dose ampicillin-sulbactam (total daily dose 9 grams of the sulbactam component) with at least one other agent (polymyxin B, minocycline, tigecycline, or cefiderocol)

In settings of resistance to sulbactam-durlobactam, the panel suggests consider optimally-dosed non-sulbactam based combinations (i.e., cefiderocol, minocycline, tigecycline, polymyxin B) as sulbactam-based therapy is unlikely to be of substantial therapeutic value

Source: *IDSA 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections*

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# Sulbactam-durlobactam (Xacduro)

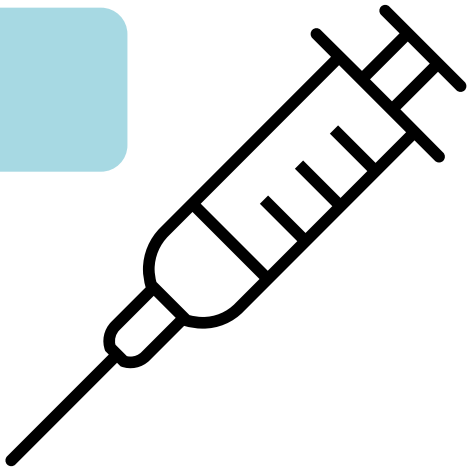
Beta-lactam, beta-lactamase inhibitor

Dose: sulbactam 1 gram and durlobactam 2 every 6 hours

- Requires renal dose adjustment

ADR: hypersensitivity reactions, hyperkalemia, abnormal hepatic function, anemia

AWP cost per vial: $210.00



Source: Lexicomp. Accessed Jan 2026.

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# Combination therapy

- Except for sulbactam-durlobactam, there is a lack of robust clinical data supporting the treatment of CRAB infections with any single agent; the use of two agents may increase the likelihood that at least one active agent is being administered
- Studies suggest that the combination of sulbactam-durlobactam and imipenem-cilastatin lowers the MIC of sulbactam-durlobactam by 1-2-fold
- The use of multiple beta-lactams targets additional PBPs and the use of durlobactam increases the likelihood of the antibiotics reaching their target
- Meropenem is likely a reasonable substitute for imipenem-cilastatin, as they have similar PBP targets

Source: *IDSA 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections*.

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# Polymyxins

- Polymyxin B and colistin have reliable in vitro activity against CRAB isolates and can be considered in combination with at least one other agent for the treatment of CRAB infections
- Colistin is favored for CRAB UTIs, as it converts to it's active form in the urinary tract
- Polymyxin monotherapy is not recommended
  - Concentrations in the serum are highly variable and may be inadequate for bactericidal activity
  - Doses required for systemic treatment approach the threshold for nephrotoxicity
  - Two trials evaluating colistin monotherapy, resulted in a 46% mortality rate

Source: *IDSA 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections*.

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# Tetracyclines

- High-dose minocycline or tigecycline can be considered in combination with at least one other agent for the treatment of CRAB infections
  - Neither agent has any primary literature to support use
  - Recommendation based on observational reports and case series
- Eravacycline was studied in an observational study with 93 patients with CRAB pneumonia and was associated with longer durations of mechanical ventilation (11 vs 7 days), and higher 30-day mortality (33% vs 15%) compared to alternative regimens)
  - Limit use to situations when other agents are not active, intolerable or unavailable

Source: *IDSA 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections*.

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# Cefiderocol

Limit use to treatment of CRAB infections refractory to other antibiotics or in cases of intolerability or resistance to other agents, in combination with other antibiotics

Surveillance studies indicate that approximately 95% of CRAB isolates are susceptible to cefiderocol using the CLSI breakpoint of <4 ug/mL

Weak efficacy data

- 54 patients with CRAB infections identified mortality at the end of the study to be 49% (19 of 39 patients) versus 18% (3 of 17 patients) in the cefiderocol versus alternative therapy arms (primarily polymyxin–based regimens)
- In an observational study, 30-day mortality was 34% versus 56% for 124 patients with CRAB infections receiving cefiderocol versus colistin-based regimens, with the rate of recurrent CRAB infections found to be more likely in the cefiderocol arm (17% versus 7%)

Recommend cautious use and only in combination with other agents to increase the likelihood that at least one effective agent is included as part of the treatment regimen

Source: *IDSA 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections*.

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# Other Therapies

- Rifampin or other rifamycins are not suggested for treating CRAB infections
  - Three clinical trials compared clinical outcomes of colistin vs colistin plus rifampin and did not demonstrate any survival benefits with rifampin
- Nebulized antibiotics are not suggested for treating respiratory infections caused by CRAB
  - Three clinical trials evaluated outcomes of patients with gram-negative ventilator-associated pneumonia comparing nebulized antibiotics versus placebo
  - None of the trials demonstrated improved clinical outcomes or survival benefit with the use of nebulized antibiotics

Source: *IDSA 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections*.

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# *Stenotrophomonas maltophilia*

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# Pathogenic vs. Colonization

S. maltophilia is a common respiratory colonizer and can cause severe infections in certain patient populations

- High risk patients: immunocompromised status, chronic respiratory disease, hemodialysis, and use of broad-spectrum antibiotics

One retrospective study of patients with S. maltophilia from respiratory cultures,1604/1773 (90%) did NOT meet a clinical definition of pneumonia, suggesting ahigh rate of colonization

- Of the patients meeting clinical criteria for pneumonia, 92% had a secondary pathogen isolated alongside S. maltophilia and improved without active therapy against S. maltophilia

Source: Tamma PD, et .al. (2024)

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# Resistance Mechanisms

- Stenotrophomonas isolates intrinsically have two different metallo-beta-lactamases (MBLs)
  - L1 MBL hydrolyzes carbapenems, and most penicillins and cephalosporins
  - L2 serine MBL hydrolyzes cephalosporins and penicillins

- Chromosomal aminoglycoside transferase enzymes create resistance to aminoglycosides

- *S. maltophila* has multidrug efflux pumps that accumulate with antibiotic exposure, leading to increased resistance to TMP-SMX, tetracyclines, and fluoroquinolones

Source: *IDSA 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections*.

# Antimicrobial Susceptibility Testing

- There are six agents with established breakpoints in CLSI against *S. maltophilia*
  - Ceftazidime is no longer considered an effective treatment option therefore breakpoints are no longer available
  - Ticarcillin-clavulanate manufacturing was discontinued
  - Chloramphenicol is rarely used due to significant toxicities

- Cefiderocol, levofloxacin, minocycline, and sulfamethoxazole-trimethoprim (TMP-SMX)

Source: *IDSA 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections*.

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# First-line therapy

The preferred treatment options for S. maltophila infections are:

- Use of two of the following agents: cefiderocol, minocycline, TMP-SMX, or levofloxacin
- Combination of ceftazidime-avibactam and aztreonam

Source: *IDSA 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections*.

# Cefiderocol

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- Surveillance studies indicate susceptibility of S. maltophilia isolates to cefiderocol approaches 100%

- Limited efficacy data
  - Animal study of S. maltophilia pneumonia using human simulated dosages of cefiderocol demonstrated that cefiderocol was able to eradicate S. maltophilia in lung tissue, in contrast to TMP-SMX where residual bacteria were present; 87% of cefiderocol treated rabbits survived compared to 25% of TMP-SMX treated rabbits

Source: *IDSA 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections*.

# Tetracyclines

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- High-dose minocycline in combination with other agents is an option for the treatment of S. maltophilia
- Primarily PK/PD studies to support use
- Effective against approximately 70-90% of *S.maltophilia* isolates
- Tetracycline derivatives achieve rapid tissue distribution, resulting in limited concentrations in the urine and serum
  - Not recommended in UTIs or as monotherapy for bloodstream infections

Source: *IDSA 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections*.

# Sulfamethoxazole-trimethoprim (TMP-SMX, Bactrim)

- Surveillance studies have shown that TMP-SMX has more than a 90% likelihood of in vitro activity against S. Maltophilia, although there is an increasing recognition of S. maltophilia isolates resistant to TMP-SMX
- TMP-SMX is a treatment option when used in combination with a second agent
- A dosing range of 10-15 mg/kg (trimethoprim component) of TMP/SMX is suggested for patients with S. maltophilia infections
  - Lack of evidence to support a particular dose
  - Dosing >15 mg/kg/day leads to an increased risk of adverse events without any clinical benefits

Source: *IDSA 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections*.

# Fluoroquinolones (FQ)

- Levofloxacin used in combination with other agents is a treatment options for S. maltophilia

- Baseline susceptibilities of S. maltophilia to levofloxacin vary from 30-80%
  - Isolates often present resistance determinants that interfere with FQ binding to gyrase and topoisomerase, causing increased MICs
  - These MICs can further increase with overexpression of MDR efflux pumps

- Due to in vitro studies demonstrating suboptimal results, intrinsic mechanisms of resistance and lack of observational data, levofloxacin is only recommended as combination therapy

Source: *IDSA 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections*.

# Ceftazidime-avibactam plus aztreonam

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- The combination of ceftazidime-avibactam and aztreonam overcomes the activity of the intrinsic L1 and L2 metallo-beta-lactamases
  - L1 MBL hydrolyzes ceftazidime but not aztreonam
  - L2 MBL hydrolyzes ceftazidime and aztreonam but not avibactam
  - Aztreonam is able to bypass inactivation and reach its target PBPs

- Surveillance studies indicate that this regimen is active against approximately 92% of isolates

Source: *IDSA 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections*.

# First-line therapy

- The preferred treatment options for *S. maltophila* infections are
  1. Use of two of the following agents: cefiderocol, minocycline, TMP-SMX, or levofloxacin
  2. Combination of ceftazidime-avibactam and aztreonam

Why is combination therapy recommended first line when all of the agents have acceptable in-vitro susceptibility?

Source: *IDSA 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections*.

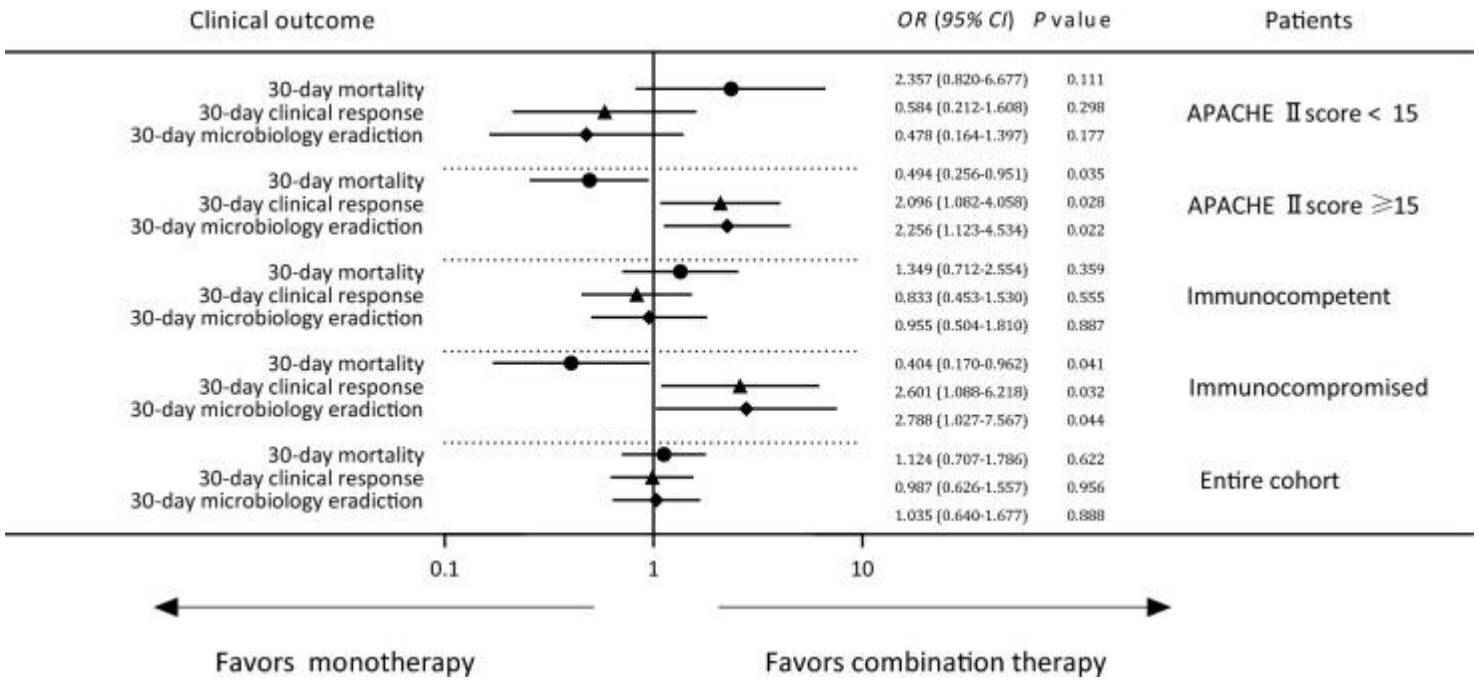
# Efficacy of combination therapy versus monotherapy in the treatment of *Stenotrophomonas maltophila* pneumonia

- Retrospective cohort study of patients who received at least 48 hours of effective therapy
- The primary outcome was clinical response after 7 days of effective therapy with combination therapy (CT) versus monotherapy (MT)
  - No difference was observed for 7-day clinical response between CT and MT (47.4% versus 39.7%, P=0.38)
  - No difference in hospital, infection-related and ICU LOS, microbiological cure, 30-day recurrence and 30-day all-cause mortality
  - Patients who received CT had higher 30-day all-cause mortality (39.5% versus 22.9%, P=0.03)

Source: Megan D Shah, et. al. (2019)

# Assessment of the relative benefits of monotherapy and combination therapy approaches to the treatment of hospital-acquired *Stenotrophomonas maltophilia* pneumonia: a multicenter, observational, real-world study

- 307 patients diagnosed with S. maltophilia hospital-acquired pneumonia
- Patients with APACHE II scores >15 or immunocompromise responded better to combination therapy




Source: Chen L., et. al. (2023)

# Why is combination therapy recommended first line when all of the agents have acceptable in-vitro susceptibility?

Available data supports the use of monotherapy for *S. maltophila* pneumonia in the absence of elevated APACHE scores and immunocompromise

Source: Chen L., et. al. (2023)

# Can one antibiotic be discontinued once susceptibility results are obtained?

- No data evaluating this question
- Based on positive monotherapy data, it is reasonable to discontinue one of the combination therapy agents after susceptibility results are finalized
- Use caution in patients with >15 APACHE II scores and immunocompromise

Source: Chen L., et. al. (2023)

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# Summary of Recommendations

| Novel Antibiotic | MDR/DTR *Pseudomonas aeruginosa* | Carbapenem-resistant *Acinetobacter baumannii* | *Stenotrophomonas maltophilia* |
|---|---|---|---|
| Cefiderocol | Active | Active | Variable |
| Ceftazidime-avibactam | Active | Not active | Not active |
| Ceftolozane-tazobactam | Active | Not active | Not active |
| Imipenem-relebactam | Active | Not active | Not active |
| Sulbactam-durlobactam | Not active | Active | Not active |

# Assessment Question #1:

Which of the following organisms is not correctly matched to its resistance mechanism?

A. Pseudomonas aeruginosa – carbapenem resistance via OprD porin loss and efflux pump upregulation
B. Acinetobacter baumannii – intrinsic AmpC hyperproduction leading to carbapenem resistance
C. Stenotrophomonas maltophilia – L1 metallo-B-lactamase and L2 serine B-lactamase production
D. All of the above

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# Assessment Question #1: Correct Response

Which of the following organisms is not correctly matched to its resistance mechanism?

A. Pseudomonas aeruginosa – carbapenem resistance via OprD porin loss and efflux pump upregulation

B. Acinetobacter baumannii – intrinsic AmpC hyperproduction leading to carbapenem resistance

C. Stenotrophomonas maltophilia – L1 metallo-B-lactamase and L2 serine B-lactamase production

D. All of the above

# Assessment Question #2

A 68-year-old ventilated patient in the MICU develops pneumonia growing carbapenem-resistant Acinetobacter baumannii (CRAB). Local testing confirms susceptibility to sulbactam. According to the most recent IDSA AMR Gram-Negative guidance, which regimen is preferred?

A. Sulbactam-durlobactam + imipenem-cilastatin
B. High-dose ampicillin-sulbactam monotherapy
C. Colistin + tigecycline
D. Cefiderocol monotherapy

# Assessment Question #2: Correct Response

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D. Cefiderocol monotherapy

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# Assessment Question #3

Which of the following best supports patient-centered guideline recommendations involving nebulized antibiotics in the treatment of ventilator-associated pneumonias?

A. Nebulized antibiotics are recommended routinely as part of initial therapy for MDR Pseudomonas and Acinetobacter ventilator-associated pneumonia.

B. Nebulized aminoglycosides are preferred over nebulized polymyxins due to superior clinical outcome data in ventilator-associated pneumonia.

C. Nebulized antibiotics are recommended as an adjunctive treatment in ventilator-associated pneumonia when patients are not improving with IV therapy.

D. Nebulized antibiotics are not recommended for adjunctive use in treatment of DTR Pseudomonas due to lack of observed benefits in clinical trials.

# Assessment Question #3: Correct Response

Which of the following best supports patient-centered guideline recommendations involving nebulized antibiotics in the treatment of ventilator-associated pneumonias?

A. Nebulized antibiotics are recommended routinely as part of initial therapy for MDR Pseudomonas and Acinetobacter ventilator-associated pneumonia.

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C. Nebulized antibiotics are recommended as an adjunctive treatment in ventilator-associated pneumonia when patients are not improving with IV therapy.

D. Nebulized antibiotics are not recommended for adjunctive use in treatment of DTR Pseudomonas due to lack of observed benefits in clinical trials.

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# Thank you!

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