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Critical Care Medicine Simplified for Exams

A Case-based Review



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JAYPEE

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37 CHAPTER Multidrug-resistant Organisms

Shankar Vallapu

CASE VIGNETTE 1: INITIAL MANAGEMENT

A 67-year-old male with type 2 diabetes and hypertension presents to the ER with h/o fever and burning micturition for 5 days associated with altered mental status for 2 days. On arrival, she is febrile with 39.2°C, tachycardia, and hypotension and requires norepinephrine infusion. Her GCS is 12/15. Initial investigations reveal neutrophilic leukocytosis, acute kidney injury, and pyuria. A presumptive diagnosis of septic shock secondary to Urinary tract infections is made. This case will evolve across multiple vignettes, illustrating key challenges in managing MDRO infections.

Q1. What is the most essential principle in the initial management of sepsis with suspected infection?

Ans. The most essential principle in the initial management of sepsis with suspected infection is the **rapid initiation of appropriate empiric antibiotic therapy**.

Elaboration

Early antimicrobial therapy is a cornerstone of sepsis management; however, **appropriateness of the antibiotic is as essential as its timing**.

- Large observational studies have demonstrated a **linear increase in hospital mortality with each hour delay** in the administration of effective antibiotics in patients with sepsis and septic shock.
- Importantly, patients who receive **inappropriate empiric antibiotic therapy**—defined as agents lacking in vitro activity against the causative pathogen—have **significantly higher mortality** compared with those who receive appropriate initial treatment.
- Thus, administering an antibiotic early but with an inadequate antimicrobial spectrum does not confer survival benefit and may worsen outcomes by delaying effective therapy.

Empiric antibiotic selection should therefore be guided by:

- Likely site of infection
- Severity of illness
- Risk factors for multidrug-resistant (MDR) organisms
- Local antimicrobial resistance patterns

Q2. How to choose an empiric antibiotic of choice after procuring blood culture and urine cultures?

Ans.

Empirical Antibiotic Selection

Identify the Infection Syndrome

Empirical therapy should cover likely pathogens based on clinical syndromes, infection site, local prevalence, and previous culture report, if available.

Clinical syndromes include:

- Uncomplicated/complicated urinary tract infections like pyelonephritis/acute bacterial prostatitis
- Community-acquired pneumonia in immunocompromised hosts or hosts with underlying structural lung disease or severe community acquired pneumonia requiring ICU care

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- Skin-soft tissue infections with the presence of sepsis or with features of necrotizing fasciitis
- Acute meningitis in patients with neurosurgical procedures
- Community-acquired sepsis of unknown origin
- Intra-abdominal infections with recent antibiotic use or hospital admission within the last 90 days
- Hospital-acquired infections, e.g., CLABSI/CAUTI/VAP/HAP **(central line-associated bloodstream infection/catheter-associated urinary tract infection/ventilator-associated pneumonia/hospital-acquired pneumonia)**
- Febrile neutropenia

Assess Patient Risk Factors for Multidrug-resistant Gram-negative Bacteria

Antibiotic resistance: WHO defines it as microorganisms that are not inhibited by the usually achievable systemic concentration of an antimicrobial agent with a regular dosage schedule and/or fall in the MIC range.

- **MDR:** Nonsusceptible to ≥1 agent in >3 antimicrobial categories.
- **XDR**: Nonsusceptible to ≥1 agent in all but ≤2 categories.
- **PDR:** Nonsusceptible to all antimicrobial agents.
- Empirical coverage for MDR is needed in high-risk patients:
  - Previous colonization/infection with MDR-GNB, recent hospitalization or ICU stay, prior broad-spectrum antibiotic use, mechanical ventilation, dialysis, and travel to high-prevalence regions.
  - If ≥2 factors are present, initial therapy should cover MDR-GNB.

Consider Local Epidemiology and Resistance Rates

Extended-spectrum β-lactamase (ESBL) rates in Asia are 30–80%; carbapenem resistance in *Klebsiella* is >50% in parts of Asia/Southern Europe; and CRAB is >80% in Asia. Hence, empirical coverage for ESBL or CRE is justified in ICU patients in these regions.

Match Empirical Therapy to Likely Mechanism of Resistance

Likely organism	***Resistance mechanism***	***Empirical treatment options***
Extended-spectrum β-lactamase-producing Enterobacterales	CTX-M type β-lactamase, TEM type β-lactamase, SHV type β-lactamase	**Carbapenem** (meropenem or imipenem)
Carbapenemase-producing Enterobacterales	*Klebsiella pneumoniae* carbapenemase, New Delhi metallo-β-lactamase, oxacillinase-48-like carbapenemase	**Ceftazidime–avibactam ± aztreonam**
Difficult-to-treat resistant *Pseudomonas aeruginosa*	Increased efflux pump activity, loss of outer membrane porins, and inducible AmpC β-lactamase production	**Ceftolozane–tazobactam** or **imipenem–relebactam**
Carbapenem-Resistant *Acinetobacter baumannii*	Oxacillinase-23 carbapenemase production	**Sulbactam–durlobactam** plus a **carbapenem**

Empirical Regimen Selection

Carbapenems would be the appropriate empirical drug of choice for severe ESBL GNB infections. A patient with septic shock with prior carbapenem use suggests high MDR risk (ESBL/CRE, *Pseudomonas*, and *Acinetobacter*). Empirical regimen should include:

Target pathogen	***Empirical drug***	***Notes***
Extended-spectrum β-lactamase (ESBL)-producing and carbapenem-resistant Enterobacterales (CRE)	**Ceftazidime–avibactam ± aztreonam**	Provides coverage against ***Klebsiella pneumoniae* carbapenemase** and **oxacillinase-48-like carbapenemase** producers; **New Delhi metallo-β-lactamase** producers are covered when aztreonam is added.

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Target pathogen	*Empirical drug*	*Notes*
Difficult-to-treat resistant (DTR) ***Pseudomonas aeruginosa***	**Ceftolozane–tazobactam** or **imipenem–relebactam**	Demonstrates the most potent in vitro and clinical activity against highly resistant *Pseudomonas aeruginosa* strains
Carbapenem-resistant *Acinetobacter baumannii (CRAB)*	**Sulbactam–durlobactam** plus **meropenem**	Preferred first-line therapy for severe infections caused by *A. baumannii*
Carbapenem-resistant *Acinetobacter baumannii* (when novel agents are unavailable)	**High-dose carbapenem** + **polymyxin B** + **tigecycline**	Salvage combination regimen used in resource-limited settings or when newer β-lactam/β-lactamase inhibitor combinations are unavailable

Tailor Therapy Once Diagnostics Arrive

Rapid molecular or proteomic diagnostic techniques, **including** polymerase chain reaction (PCR), matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF), and whole-genome sequencing (WGS), **facilitate** early antimicrobial de-escalation within 24–48 hours. PCR-based detection of the *blaKPC* [*Klebsiella pneumoniae* carbapenemase (KPC)] **gene has been associated** with earlier initiation of effective antimicrobial therapy and a significant reduction in mortality

Source Control and Stewardship

Ensure source control, limit therapy to 7–10 days if clinically improved, and step down to narrow or oral agents when possible (e.g., pivmecillinam and tebipenem for ESBL UTIs).

Empirical Therapy Algorithm

- Assess risk factors + local resistance data
- Start broad coverage if high-risk: ESBL → carbapenem; CRE/NDM → ceftazidime–avibactam + aztreonam; *Pseudomonas* → ceftolozane–tazobactam; CRAB → sulbactam–durlobactam.
- Send rapid diagnostics (PCR/MALDI-TOF/WGS)
- De-escalate once the mechanism is known.
- Ensure source control + antibiotic stewardship

CASE VIGNETTE 2

Blood and urine cultures are sent. Empiric therapy—piperacillin–tazobactam was started. After 24 hours, the laboratory reports gram-negative bacilli on culture.

Q1. What is the most likely mechanism of resistance when an *Escherichia coli* (*E. coli*) isolate is nonsusceptible to third-generation cephalosporins but remains susceptible to carbapenems?

Ans. The most likely mechanism of resistance is **ESBL production**.

Elaboration

- Resistance to **third-generation cephalosporins** (such as ceftriaxone and ceftazidime) with **preserved susceptibility to carbapenems** is the classical susceptibility profile of **ESBL-producing Enterobacterales**.
- **ESBL** enzymes, most commonly from the **cefotaximase-Munich (CTX-M)**, **Temoneira (TEM)**, and **sulfhydryl variable (SHV)** families, hydrolyse **oxyimino-cephalosporins** and **monobactams (aztreonam)**.
- Carbapenems remain active because they are **structurally stable to ESBL-mediated hydrolysis**.
- *ESBL* genes are typically **plasmid-encoded**, facilitating rapid dissemination within hospitals and increasingly in the community.

Clinical Pearl

Third-generation cephalosporin resistance with carbapenem susceptibility should always prompt suspicion of ESBL production.

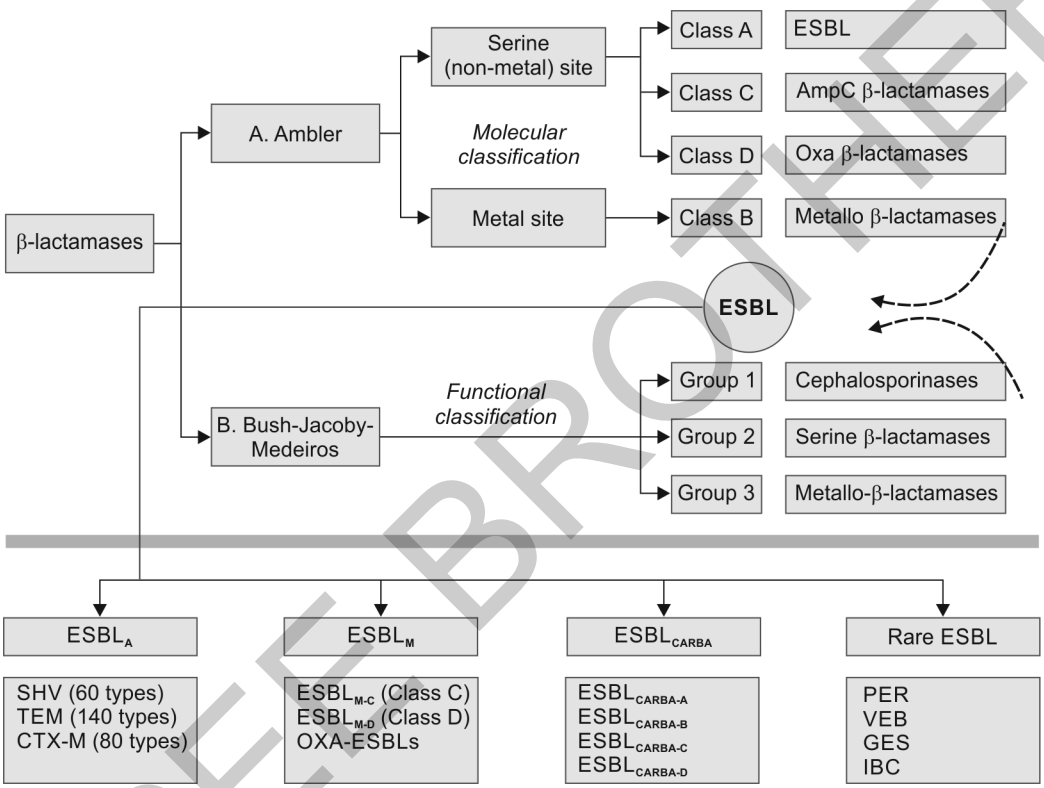
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Q2. To which Ambler molecular class do ESBL enzymes belong?

Ans. Ambler class A

Elaboration

- ESBLs are **class A serine β-lactamases**, characterized by the presence of a serine residue at their active site.
- They are **inhibited by β-lactamase inhibitors** such as clavulanic acid, tazobactam, and avibactam.
- This molecular classification explains both their **susceptibility pattern** and the rationale for using β-lactam/β-lactamase inhibitor combinations in selected clinical settings.



Classification of extended-spectrum β-lactamases (ESBLs).

Q3. Which gene family is most frequently associated with ESBL production in *E. coli*?

Ans. The ***CTX-M* gene family** is the **most frequently identified genetic determinant** responsible for **ESBL** production in ***E. coli***.

Elaboration

- **CTX-M-type ESBLs** have **globally replaced** the earlier **TEM and SHV** β-lactamase families as the **predominant ESBL enzymes** in *E. coli* and other Enterobacterales.
- This epidemiological shift is attributed to the **high transmissibility of CTX-M genes**, which are frequently located on **conjugative plasmids**, facilitating rapid **horizontal gene transfer** across bacterial species.
- Among the CTX-M variants, **CTX-M-15** has emerged as the **most prevalent subtype**, particularly in **Asia and the Indian subcontinent**, where it is strongly associated with **community-acquired urinary tract infections, bloodstream infections, and sepsis**.
- CTX-M-15 exhibits **potent hydrolytic activity against third-generation oxyimino-cephalosporins**, especially **cefotaxime and ceftriaxone**, leading to **high-level resistance** to these commonly used agents.

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- The **global dominance of CTX-M enzymes** explains the **rising incidence of ESBL-producing infections** not only in **hospital (nosocomial) settings** but also increasingly in the **community**, blurring the traditional distinction between community-acquired and healthcare-associated infections.
- Clinically, this epidemiological trend has resulted in **greater reliance on carbapenems** for severe infections and underscores the importance of **antimicrobial stewardship** and **rapid diagnostic testing** to prevent inappropriate empirical therapy.

Clinical Pearl

Cefotaximase-Munich ESBLs should be assumed in any third-generation cephalosporin-resistant E. coli isolate.

Below is a **slightly elaborated, examination-oriented refinement** of each answer, preserving your structure, tone, and clinical pearls while adding depth without overexpansion.

Q4. What is the confirmatory laboratory test for the detection of ESBL production?

Ans. The **double-disk synergy test (DDST)** using a **cephalosporin and clavulanate**.

Elaboration

- The **DDST** is a **phenotypic confirmatory method** recommended for identifying **ESBL** production in Enterobacterales.
- In this test, **ceftazidime or cefotaxime disks** are placed at a defined distance from a **clavulanate-containing disk** (such as amoxicillin–clavulanate).
- An **increase in the inhibition zone of ≥5 mm** toward the clavulanate disk indicates **synergy**, confirming ESBL production.
- The test exploits the principle that **ESBL enzymes are inhibited by β-lactamase inhibitors**, thereby restoring the activity of the cephalosporin in the presence of clavulanate.
- DDST remains widely used in **resource-limited laboratories** due to its simplicity and cost-effectiveness.

Q5. What is the empirical drug of choice for a serious infection caused by ESBL-producing *E. coli*?

Ans. Meropenem (or imipenem).

Elaboration

- **Carbapenems**, including **meropenem and imipenem**, are **structurally resistant to ESBL-mediated hydrolysis**, ensuring consistent and reliable bactericidal activity.
- They achieve **predictable pharmacokinetic–pharmacodynamic exposure** in severe infections such as sepsis, pneumonia, and bloodstream infections.
- The **MERINO trial** demonstrated **significantly lower 30-day mortality** with **meropenem** compared with **piperacillin–tazobactam** in ESBL bloodstream infections.
- Consequently, **IDSA 2024 guidelines** recommend carbapenems as **first-line therapy for severe ESBL-producing Enterobacterales infections**.

Clinical Pearl

*In severe ESBL infections, **carbapenems remain the benchmark therapy** against which other agents are compared.*

Q6. Which newer β-lactam/β-lactamase inhibitor combination may be used for ESBL infections when carbapenems cannot be administered?

Ans. Ceftazidime–avibactam

Elaboration

- **Avibactam** is a **non-β-lactam β-lactamase inhibitor** that effectively inhibits **class A ESBL enzymes** and **KPC**.
- The combination serves as a **carbapenem-sparing option** in selected clinical scenarios such as carbapenem intolerance, allergy, or stewardship-driven de-escalation.

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- However, it has **no activity against metallo-β-lactamases (MBLs)**, including **New Delhi metallo-β-lactamase (NDM)**, limiting its spectrum.
- Its use should be guided by **microbiological susceptibility and local resistance patterns**.

Q7. In an uncomplicated ESBL urinary tract infection, which oral agent can be used if susceptibility is confirmed?

Ans. Fosfomycin (also **pivmecillinam**)

Elaboration
- **Fosfomycin** retains in vitro and clinical activity against many **ESBL-producing *E. coli*** strains.
- It achieves **high urinary concentrations**, making it particularly effective for **uncomplicated lower urinary tract infections**.
- As an **oral step-down agent**, fosfomycin facilitates **early hospital discharge**, improves patient comfort, and supports **antimicrobial stewardship**.
- Its use should be limited to **uncomplicated infections** and guided by susceptibility testing.

Q8. What genetic mechanism explains the rapid dissemination of *ESBL* genes among Enterobacterales?

Ans. Horizontal gene transfer via plasmids

Elaboration
- ***ESBL* genes** are commonly located on **mobile plasmids**, enabling efficient **horizontal gene transfer**.
- These plasmids can spread between:
  - *E. coli*
  - *Klebsiella* species
  - Other members of **Enterobacterales**
- Plasmids often carry **multiple resistance determinants**, leading to **MDR phenotypes**.
- This mechanism explains the **rapid dissemination** of ESBL organisms in both **hospital and community settings**.

Q9. What is the most effective infection-control measure to limit the spread of ESBL-producing organisms in hospitals?

Ans. Strict contact precautions and hand hygiene

Elaboration
- **Hand hygiene compliance**, along with **contact isolation precautions** and **thorough environmental cleaning**, is the cornerstone of preventing nosocomial transmission.
- ESBL-producing organisms are commonly spread via **healthcare worker hands and contaminated surfaces**.
- Strategies such as **antibiotic cycling or routine prophylactic antibiotics** do not prevent transmission and may actually **accelerate resistance**.
- Effective infection control requires **institutional adherence and regular auditing**.

Q10. After 48 hours of targeted meropenem therapy, the patient stabilizes clinically. What is the next best step?

Ans. De-escalation to an appropriate oral agent, such as fosfomycin, if feasible and susceptible.

Elaboration
- **Antimicrobial de-escalation** reduces **selective resistance pressure**, drug toxicity, and overall treatment costs.
- Step-down to oral therapy is appropriate when:
  - There is **clear clinical improvement**
  - **Source control** has been achieved
  - Microbiological **susceptibility supports oral therapy**
- This approach aligns with the principles of **antimicrobial stewardship** while maintaining clinical efficacy.

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Clinical Pearl

Effective stewardship ***begins once the patient improves—not when antibiotics are started****.*

CASE VIGNETTE 3: CLINICAL DETERIORATION

After 7 days of meropenem, patient had new onset fever with elevated procalcitonin. Blood and urine cultures repeated. Blood cultures grew *Klebsiella pneumoniae*, resistant to carbapenems. MALDI-TOF confirms species identification within 2 hours.

Q1. What are the resistant patterns and treatment options for carbapenem-resistant *Klebsiella pneumonia*?

Ans.

Resistance Patterns and Treatment Options

Resistance Mechanisms

Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) develops resistance primarily through:

- **Carbapenemase enzyme production:** Enzymes such as KPC, NDM, or OXA-type carbapenemases hydrolyze carbapenem antibiotics, making them ineffective.
- **Porin mutations or loss:** Changes or loss of outer membrane porins (OmpK35 and OmpK36) decrease drug uptake.
- **Efflux pump upregulation:** Increased export of antibiotics out of the cell.
- **Coexisting ESBL or AmpC enzymes:** ESBLs and AmpC β-lactamase contribute to broader resistance profiles.

Carbapenem-resistant *Klebsiella pneumoniae* strains often exhibit multidrug resistance, limiting the availability of effective antibiotics.

Therapeutic Options for CRKP

Treatment should be tailored according to susceptibility tests. Options include:

- **Novel β-lactam/β-lactamase inhibitor combinations:**
  - **Ceftazidime–avibactam**
  - **Meropenem–vaborbactam**
  - **Imipenem–relebactam**
  - **Aztreonam–avibactam** (especially for MBL producers)
- **Other antibiotics and combinations:**
  - **Plazomicin** (aminoglycoside)
  - **Eravacycline/tigecycline** (tetracycline derivatives)
  - **Colistin/polymyxin B** (last-resort option; nephrotoxic)
  - **Fosfomycin**
  - **Cefiderocol** (new siderophore cephalosporin)

Empiric therapy should be guided by local resistance data and modified once susceptibility results are available.

Q2. Which resistance mechanism most likely explains the observed susceptibility pattern when PCR detects the *blaNDM-1* gene?

Ans. The resistance mechanism is **production of a MBL (NDM)**.

Elaboration

- **NDM** hydrolyzes **all β-lactam antibiotics**, including carbapenems, **except aztreonam**.
- NDM enzymes are **not inhibited by currently available β-lactamase inhibitors**, such as clavulanate, tazobactam, or avibactam.
- NDM-producing organisms therefore demonstrate resistance to:
  - Carbapenems
  - Cephalosporins
  - Most β-lactam/β-lactamase inhibitor combinations

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- NDM predominates in the **Indian subcontinent** and is associated with **limited therapeutic options and high mortality**.

Clinical Pearl
Detection of blaNDM-1 should immediately prompt avoidance of carbapenem monotherapy.

Q3. Which component of the ceftazidime–avibactam combination functions as the β-lactamase inhibitor?

Ans. Avibactam acts as the β-lactamase inhibitor

Elaboration
- Avibactam is a **non-β-lactam β-lactamase inhibitor** designed to protect ceftazidime from enzymatic degradation.
- It inhibits **class A (ESBL and KPC)** and some **class C and D β-lactamases**.
- Avibactam **does not inhibit MBLs**, such as NDM.

Q4. Against which carbapenemase is ceftazidime–avibactam particularly ineffective?

Ans. NDM-1 metallo-β-lactamase

Elaboration
- Avibactam lacks activity against **MBLs**, which require zinc at the active site.
- Consequently, **ceftazidime–avibactam monotherapy is ineffective** against NDM-producing organisms.
- This limitation underpins the need for **combination therapy with aztreonam** in such infections.

Q5. What is the primary bactericidal mechanism of action of ceftazidime?

Ans. Ceftazidime exerts its bactericidal effect by **inhibiting penicillin-binding proteins (PBPs)** involved in bacterial cell wall synthesis.

Elaboration
- Ceftazidime binds to essential **PBPs**, disrupting the **cross-linking of peptidoglycan layers**.
- This interference weakens the bacterial cell wall, leading to **cell wall instability and osmotic lysis**.
- Like other β-lactam antibiotics, ceftazidime exhibits **time-dependent killing**, emphasizing the importance of optimized dosing strategies.

Clinical Pearl
Beta-lactams kill by collapsing the bacterial cell wall—enzyme inhibition, not membrane disruption or DNA damage.

Q6. What is the importance of ceftazidime–avibactam + aztreonam?

Ans. The combination of ceftazidime–avibactam and aztreonam is especially important in treating infections caused by MBL-producing gram-negative bacteria, including carbapenem-resistant *Klebsiella pneumoniae*. MBLs (such as NDM, VIM, and IMP) can inactivate most β-lactam antibiotics, including carbapenems and ceftazidime–avibactam. However, MBLs cannot hydrolyze aztreonam. Despite this, aztreonam is frequently rendered ineffective in these organisms because they often coproduce other β-lactamases (like ESBLs, KPCs, or AmpC), which do hydrolyze aztreonam.

Avibactam (from ceftazidime–avibactam) inhibits these coproduced non-MBL β-lactamases, protecting aztreonam from degradation and allowing it to act against the pathogen. Therefore, the combination acts synergistically: aztreonam provides coverage against MBL producers, while avibactam protects it from other β-lactamases, allowing effective treatment of difficult, MDR infections.

This combination is now used as an important therapeutic option for severe infections due to organisms harboring both MBLs and other β-lactamases.

CASE VIGNETTE 4

The laboratory employs Carba NP and a multiplex PCR panel that directly detects KPC, NDM, OXA-48, VIM, and IMP from positive blood cultures. Results available in 5 hours confirm NDM.

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Q1. What is the importance of the above tests, and what is the importance of confirming NM+M presence?

Ans. The laboratory uses both the Carba NP test and a multiplex PCR panel to rapidly detect carbapenemase enzymes directly from positive blood cultures. The Carba NP test is a rapid biochemical method that detects carbapenemase production by measuring imipenem hydrolysis, which results in a color change via a pH shift; this highlights the organism's ability to degrade carbapenem antibiotics, indicating possible resistance.

The multiplex PCR panel detects and differentiates common carbapenemase genes: *KPC, NDM, OXA-48, VIM,* and *IMP*. Together, these tests offer both phenotypic (Carba NP) and genotypic (PCR) confirmation of resistance mechanisms. In this scenario, results were available within 5 hours and confirmed the presence of NDM, an MBL that confers high-level resistance to most β-lactams, including carbapenems, except aztreonam. Rapid detection of NDM is crucial, as it guides infection control and steers therapy toward effective options, such as aztreonam combined with ceftazidime–avibactam.

Q2. Explain how MALDI-TOF mass spectrometry detects antibiotic resistance?

Ans. MALDI-TOF mass spectrometry detects antibiotic resistance through several advanced approaches that provide rapid results directly from clinical samples or bacterial cultures.

Key Mechanisms

Detection of β-lactamase Activity

- When a bacterium produces β-lactamase, it hydrolyzes the β-lactam ring of antibiotics like penicillins or carbapenems.
- In a MALDI-TOF-based β-lactamase assay, the bacterium is incubated with the antibiotic. If hydrolysis occurs (indicating β-lactamase production), hydrolyzed products with distinct mass signatures appear.
- By analyzing the spectra, a loss of the antibiotic peak and appearance of hydrolysis products confirm resistance mediated by β-lactamase activity.

Analysis of Resistance-Related "Peak Patterns" or Biomarkers

- Some resistance mechanisms cause specific protein or peptide changes in the bacterium's proteome, which are reflected as unique "peaks" in the MALDI-TOF spectrum.
- Comparing spectra of susceptible and resistant strains can reveal characteristic resistance profiles.

Growth and Biomass Analysis After Antibiotic Exposure

- In specialized protocols (such as MBT-ASTRA), bacteria are incubated with and without antibiotics.
- If the strain is susceptible, growth is inhibited in the presence of the antibiotic (low spectral signals); if resistant, similar signals are observed in both conditions, since the drug does not inhibit the organism.

Detection of Modified Proteins or Resistance Enzymes

MALDI-TOF can sometimes directly detect enzymes (like methyltransferases) or other modified proteins associated with resistance.

Clinical Role

- These methods provide results much faster than conventional susceptibility tests—some in as little as 30 minutes to a few hours.
- Detection is mainly most accurate for enzyme-mediated resistance (like β-lactamases), while other resistance types may require additional confirmation.

Matrix-Assisted laser desorption/ionization time-of-flight mass spectrometry, therefore, accelerates clinical management of infections by delivering both rapid bacterial identification and evidence-based clues about key resistance mechanisms.

Q3. Which emerging diagnostic technology can define the complete antimicrobial resistance gene profile within 24 hours and assist in outbreak tracking?

Ans. Whole-genome sequencing

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Elaboration

- WGS provides **comprehensive identification of resistance determinants**, including both **plasmid-borne and chromosomal genes**.
- It allows simultaneous detection of:
  - Carbapenemases (KPC, NDM, OXA-48, VIM, and IMP)
  - ESBLs and AmpC enzymes
  - Virulence factors and clonal relatedness
- WGS is increasingly used for **hospital surveillance, outbreak investigation, and antimicrobial stewardship**, enabling linkage between clinical isolates.

Clinical Pearl

Whole-genome sequencing moves diagnostics from "what drug works" to "why resistance occurred and how it spreads."

Q4. An isolate is a coproducer of NDM and CTX-M, resistant to carbapenems, cephalosporins, and fluoroquinolones, but susceptible to ceftazidime–avibactam plus aztreonam and cefiderocol. What is the preferred evidence-based treatment?

Ans. Ceftazidime–avibactam combined with aztreonam.

Elaboration

- **NDM (MBL)** hydrolyzes all β-lactams **except aztreonam**
- However, aztreonam is often inactivated by **coproduced ESBLs (e.g., CTX-M)**.
- **Avibactam** inhibits these serine β-lactamases, thereby **protecting aztreonam**
- This dual-drug strategy provides **functional synergy** and is supported by guideline-based evidence.

Clinical Pearl

New Delhi metallo-β-lactamase infections require aztreonam-based strategies—never ceftazidime–avibactam alone.

CASE VIGNETTE 5: CRAB HOSPITAL-ACQUIRED PNEUMONIA

The patient deteriorates with **new bilateral infiltrates, fever, and hypoxemia**, requiring **invasive mechanical ventilation**. Endotracheal aspirate culture grows ***Acinetobacter baumannii***, susceptible only to colistin (CRAB).

Q1. According to IDSA 2024 guidance, what are the preferred and alternative treatment options for infections caused by CRAB?

Ans. Preferred regimen

- **Sulbactam–durlobactam combined with a carbapenem** (imipenem-cilastatin or meropenem)

Alternative regimen: High-dose ampicillin–sulbactam (sulbactam ≥9 g/day) **plus at least one additional active agent**, such as polymyxin B, minocycline, or cefiderocol.

Elaboration

- Sulbactam has **intrinsic activity against *Acinetobacter***.
- Durlobactam inhibits **class C and class D β-lactamases**, restoring sulbactam activity.
- Historical reliance on polymyxins is discouraged due to **high toxicity and poor outcomes**.

Q2. In a ventilated patient with CRAB hospital-acquired pneumonia, should combination therapy be used?

Ans. Yes. **Combination therapy should be considered until clinical improvement is achieved**.

Elaboration

- IDSA guidance acknowledges **limited efficacy data for any single agent** in CRAB infections.
- Therefore, regimens should generally include **at least two active agents** initially.
- Once clinical response is evident, therapy may be rationalized.

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Clinical Pearl

In CRAB pneumonia, combination therapy is a strategy for survival—not excess.

Q3. What is the role of nebulized antibiotics in the treatment of CRAB respiratory infections?

Ans. Nebulized antibiotics are **not recommended** as adjunctive therapy for CRAB pneumonia.

Elaboration

- Clinical trials have failed to demonstrate mortality or outcome benefit.
- Concerns include:
  - Uneven distribution in diseased lungs
  - Bronchospasm and airway irritation
  - Technical challenges with aerosol delivery
- Systemic therapy remains the cornerstone of treatment.

Q4. What is the current evidence from major clinical trials regarding the role of sulbactam–durlobactam and colistin-based regimens in the management of carbapenem-resistant *Acinetobacter baumannii* (CRAB) and MDR gram-negative infections?

Ans. The **ATTACK trial** demonstrated that **sulbactam–durlobactam** is **noninferior to colistin** with respect to **28-day all-cause mortality** in patients with serious **CRAB** infections. Importantly, sulbactam–durlobactam was associated with **significantly lower rates of nephrotoxicity**, establishing it as a **safer and equally effective alternative** to colistin.

The clinical efficacy of this combination is attributed to the role of **durlobactam**, a novel β-lactamase inhibitor that **inhibits *Acinetobacter* β-lactamases**, particularly **class D (OXA-type)** and **class C** enzymes. By preventing enzymatic degradation, durlobactam **restores and enhances the intrinsic bactericidal activity of sulbactam** against *Acinetobacter baumannii*.

Collectively, these findings support **sulbactam–durlobactam as a preferred modern first-line therapy** for severe CRAB infections and represent a **paradigm shift away from polymyxins**, which have traditionally been limited by toxicity.

In contrast, evidence from the **OVERCOME trial** indicates that, for **MDR gram-negative infections**, the **addition of meropenem to colistin** does **not confer a mortality benefit** compared with **colistin monotherapy**. This suggests that routine combination therapy with carbapenems **does not improve outcomes** and should not be employed indiscriminately.

KEY TAKEAWAYS

- **Early appropriate antibiotics save lives.** Mortality in sepsis rises with every hour of delay in *effective* therapy. Inappropriate empiric antibiotics are associated with worse outcomes than delayed but appropriate treatment.
- **Empiric therapy must be risk stratified.** Infection syndrome, severity, prior antibiotic exposure, healthcare contact, and local resistance patterns should guide empiric choice. ≥2 MDR risk factors warrant broad MDR coverage.
- **ESBL-producing Enterobacterales are highly prevalent.** Resistance to third-generation cephalosporins with carbapenem susceptibility is typical. CTX-M enzymes now predominate globally.
- **Carbapenems remain the standard for severe ESBL infections.** They are stable against ESBL hydrolysis and have superior outcomes in severe disease, including septic shock and bacteremia.
- **Rapid diagnostics improve outcomes.** PCR, MALDI-TOF, and WGS enable early identification of resistance mechanisms, allowing timely escalation or de-escalation and better antimicrobial stewardship.
- **NDM producers pose major therapeutic challenges.** NDM hydrolyzes all β-lactams except aztreonam and is not inhibited by available β-lactamase inhibitors. Carbapenem monotherapy is ineffective.
- **Ceftazidime–avibactam plus aztreonam is essential for NDM infections.** Avibactam inhibits coproduced serine β-lactamases, protecting aztreonam, and restoring activity.
- **Sulbactam–durlobactam is preferred for CRAB infections.** Sulbactam has intrinsic anti-*Acinetobacter* activity, restored by durlobactam. It is safer and as effective as colistin.

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- **Polymyxins are no longer first-line therapy.** High nephrotoxicity and inferior outcomes limit their role to salvage therapy when newer agents are unavailable.
- **Stewardship begins after stabilization.** De-escalation, shortening duration, and oral step-down reduce resistance without compromising outcomes.

MULTIPLE CHOICE QUESTIONS

Q1. The most important determinant of outcome in septic shock is:

A. Early fluids
B. Early vasopressors
C. Early appropriate antibiotics
D. Mechanical ventilation

Ans. C. Early appropriate antibiotics

Explanation: Mortality correlates more strongly with appropriateness than timing alone.

Q2. Resistance to third-generation cephalosporins with carbapenem susceptibility suggests:

A. AmpC
B. ESBL
C. KPC
D. Porin loss

Ans. B. ESBL

Explanation: This is the classical ESBL susceptibility profile.

Q3. The most common *ESBL* gene family worldwide is:

A. TEM
B. SHV
C. CTX-M
D. OXA

Ans. C. CTX-M

Q4. Confirmatory test for ESBL detection is:

A. Modified Hodge test
B. Carba NP test
C. Double-disk synergy test
D. Nitrocefin test

Ans. C. Double-disk synergy test

Q5. Drug of choice for severe ESBL bacteremia is:

A. Piperacillin–tazobactam
B. Cefepime
C. Meropenem
D. Ciprofloxacin

Ans. C. Meropenem

Q6. Ceftazidime–avibactam lacks activity against:

A. KPC
B. OXA-48
C. ESBL
D. NDM

Ans. D. NDM

Q7. Best therapy for NDM + ESBL co-producing *Klebsiella* is:

A. Meropenem–vaborbactam
B. Ceftazidime–avibactam alone
C. Ceftazidime–avibactam + aztreonam
D. Colistin monotherapy

Ans. C. Ceftazidime–avibactam + aztreonam

Q8. Preferred therapy for CRAB as per IDSA 2024 is:

A. Colistin
B. Tigecycline
C. Sulbactam–durlobactam + carbapenem
D. Meropenem

Ans. C. Sulbactam–durlobactam + carbapenem

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Q9. Nebulized antibiotics in CRAB pneumonia are:

A. Strongly recommended
B. Optional
C. Not recommended
D. First line

Ans. C. Not recommended

Q10. ATTACK trial demonstrated that sulbactam–durlobactam is:

A. Inferior to colistin
B. Superior to colistin
C. Noninferior with less nephrotoxicity
D. Ineffective

Ans. C. Noninferior with less nephrotoxicity

FREQUENTLY ASKED QUESTIONS

1. **What are multidrug-resistant organisms (MDROs)?**
2. **How are MDR, XDR, and PDR organisms defined?**
3. **What are the common MDROs encountered in the ICU?**
4. **What are the risk factors for acquisition of MDROs in critically ill patients?**
5. **What are the mechanisms of antimicrobial resistance in gram-negative bacteria?**
6. **What are the mechanisms of resistance in gram-positive organisms?**
7. **How does prior antibiotic exposure influence MDRO emergence?**
8. **What is the clinical significance of ESBL-producing organisms?**
9. **How do carbapenem-resistant Enterobacterales (CRE) develop resistance?**
10. **What are the resistance mechanisms in carbapenem-resistant Acinetobacter baumannii?**
11. **How is MRSA different from MSSA in terms of resistance and management?**
12. **What are the therapeutic options for VRE infections?**
13. **How should empiric antibiotics be chosen in suspected MDRO infection?**
14. **What factors should guide de-escalation of antibiotics in MDRO infections?**
15. **What is the role of combination therapy in managing MDR gram-negative infections?**
16. **What are the newer antibiotics available for MDRO infections?**
17. **What is the role of polymyxins in current practice?**
18. **How do you manage pan-drug resistant (PDR) infections?**
19. **What is antibiotic stewardship and how does it prevent MDRO emergence?**
20. **What infection control measures reduce MDRO transmission in ICU?**

SUGGESTED READING

1. Balaji V, Bansal N, Gopalakrishnan R, et al. Management of infections caused by Extended-spectrum beta-lactamase-producing Enterobacterales in Indian patients. Indian J Med Microbiol. 2025;58:100974.
2. Beukers AG, Jenkins F, van Hal SJ. Centralised or localised pathogen whole genome sequencing: lessons learnt from implementation in a clinical diagnostic laboratory. Front Cell Infect Microbiol. 2021;11:636290.
3. Bush K, Bradford PA. Epidemiology of β-Lactamase-Producing Pathogens. Clin Microbiol Rev. 2020;33(2):e00047-19.
4. Cotroneo N, Rubio A, Critchley IA, et al. In Vitro and In Vivo Characterization of Tebipenem, an Oral Carbapenem. Antimicrob Agents Chemother. 2020;64(8):e02240-19.
5. Evans SR, Cober E, Richter SS, et al. Colistin monotherapy versus combination therapy for the treatment of serious infections due to multidrug-resistant gram-negative bacteria: the OVERCOME randomized clinical trial. JAMA. 2023;330(6):536-48.
6. Ferrer R, Martin-Loeches I, Phillips G, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. Crit Care Med. 2014;42(8):1749-55.
7. Gato E, Anantharajah A, Arroyo MJ, et al. Multicenter performance evaluation of MALDI-TOF MS for rapid detection of carbapenemase activity in Enterobacterales: the future of networking data analysis with online software. Front Microbiol. 2022;12:789731.
8. Henderson A, Paterson DL, Chatfield MD, et al. Association between minimum inhibitory concentration, beta-lactamase genes and mortality for patients treated with piperacillin/tazobactam or meropenem from the MERINO study. Clin Infect Dis. 2021;73:e3842-50.

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9. ICMR. (2019). Treatment guidelines for antimicrobial Use in Common syndromes. [online] Available from https://www.icmr.gov.in/icmrobject/custom_data/pdf/resource-guidelines/Treatment_Guidelines_2019_Final.pdf [Last accessed February, 2026].
10. ICMR. (2025). National treatment guidelines for antimicrobial use in infectious disease syndromes. [online] Available https://ncdc.mohfw.gov.in/wp-content/uploads/2025/12/National-Treatment-Guidelines-for-AMU-in-ID-syndromes-2025.pdf [Last accessed February, 2026].
11. Jorgensen JH, Ferraro MJ. Antimicrobial susceptibility testing: a review of general principles and contemporary practices. Clin Infect Dis. 2009;49:1749-55.
12. Kaye KS, Shorr AF, Wunderink RG, et al. Efficacy and safety of sulbactam-durlobactam versus colistin for the treatment of patients with serious infections caused by Acinetobacter baumannii-calcoaceticus complex: a multicentre, randomised, active-controlled, phase 3, non-inferiority clinical trial (ATTACK). Lancet Infect Dis. 2023;23:1072-84.
13. Lizza BD, Betthauser KD, Ritchie DJ, et al. New perspectives on antimicrobial agents: ceftolozane–tazobactam. Antimicrob Agents Chemother 2021;65:e0231820.
14. Lueangarun S, Leelarasamee A. Impact of inappropriate empiric antimicrobial therapy on mortality of septic patients with bacteremia: a retrospective study. Interdiscip Perspect Infect Dis. 2012;2012:765205.
15. Macesic N, Uhlemann AC, Peleg AY. Multidrug-resistant gram-negative bacterial infections. Lancet. 2025;405(10474):257-72.
16. Maselli DJ, Keyt H, Restrepo MI. Inhaled antibiotic therapy in chronic respiratory diseases. Int J Mol Sci. 2017;18(5):1062.
17. Mendes RE, Mendoza M, Banga Singh KK, et al. Regional resistance surveillance program results for 12 Asia-Pacific nations (2011). Antimicrob Agents Chemother. 2013;57(11):5721-6.
18. Paul M, Carrara E, Retamar P, et al. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine). Clin Microbiol Infect. 2022;28:521-47.
19. Rattanaumpawan P, Lorsutthitham J, Ungprasert P, et al. Randomized controlled trial of nebulized colistimethate sodium as adjunctive therapy of ventilator-associated pneumonia caused by gram- negative bacteria. J Antimicrob Chemother. 2010;65:2645-9.
20. Tamma PD, Heil EL, Justo JA, et al. Infectious Diseases Society of America 2024 guidance on the treatment of antimicrobial-resistant gram-negative infections. Clin Infect Dis. 2024;78(6):1157-203.
21. WHO, European Centre for Disease Prevention and Control. (2022). Antimicrobial resistance surveillance in Europe 2022, 2020 data. [online] Available from Available from https://www.ecdc.europa.eu/sites/default/files/documents/Joint-WHO-ECDC-AMR-report-2022.pdf [Last accessed February, 2026].
22. Yahav D, Giske CG, Grāmatniece A, et al. New β-lactam-β-lactamase inhibitor combinations. Clin Microbiol Rev. 2020;34:e00115-20.

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