Diseases Caused by Gram-Negative Enteric Bacilli

Chapter 166 | Part 5: Infectious Diseases

KEY CLINICAL POINTS

1. CDC/WHO classify carbapenem-resistant Enterobacterales (CRE) as 'urgent' and 'priority one, critical' threats.
2. CRE caused >100,000 global deaths in 2019, with highest burden in low- and middle-income countries.
3. GNB isolated from sterile sites implies infection; nonsterile sites require clinical correlation to distinguish colonization vs. infection.
4. Carbapenems (except imipenem for Proteeae) are most active against Enterobacterales in vitro.
5. ESBLs are most prevalent in E. coli (ST131), K. pneumoniae, and K. oxytoca with regional gradient: China > Eastern Europe > Asia > Latin America/Africa > Western US/Canada.
6. Source control (abscess drainage, tissue resection) is often required alongside antimicrobial therapy for cure.
7. 7-day treatment may suffice for non-critically ill patients with source control and clinical response.
8. Polymyxins B/E (colistin) are last-line agents against MBL-producing strains but have nephrotoxicity/neurotoxicity risks.
9. Universal decolonization (chlorhexidine bathing) is supported to prevent ICU/nursing home infections.
10. Fever/back pain suggests pyelonephritis progression; persistent fever/flank pain/neutrophilia warrants abscess/obstruction evaluation.

DEFINITION & CLASSIFICATION

- **Enteric Gram-Negative Bacilli (GNB):** species within the order Enterobacterales causing extraintestinal infections.
  - Key genera: Escherichia coli, Klebsiella, Proteus, Enterobacter, Serratia, Citrobacter, Morganella, Providencia, Cronobacter, and Edwardsiella.
  - Note: Salmonella, Shigella, and Yersinia are in this order but primarily cause gastrointestinal infections.
- **Pathogenic Features:**
  - Extracytoplasmic outer membrane components (capsule, lipopolysaccharide) critical for pathogenesis and antimicrobial resistance.
  - Mechanisms: Permeability barrier, efflux pumps, and secreted products like iron acquisition molecules and type VI secretion systems.
- **ExPEC (Extraintestinal Pathogenic E. coli):**
  - Most common GNB causing community-acquired and healthcare-associated infections.

– Distinction: Commensal E. coli lacks virulence genes; ExPEC has acquired accessory genes (adhesins, toxins) for extraintestinal infection.

– Risk Factor: Entry from colonization sites (colon, vagina) to sterile sites (urinary tract, lungs) is the rate-limiting step.

Table 1 — Interactions of ExPEC with the Human Host

- **Table 166-1** highlights how ExPEC overcomes host barriers:
  – Attachment: Multiple adhesins (type 1, S, F1C fimbriae; P pili) overcome flow of urine/mucociliary escalator.
  – Nutrient Acquisition: Cell lysis (via hemolysin) allows access to sequestered iron.
  – Initial Defense: Capsular polysaccharide and lipopolysaccharide evade complement and phagocytes.
  – Late Defense: Cell entry and acquisition of antimicrobial resistance allow evasion of antibodies and drugs.

EPIDEMIOLOGY

- **Prevalence:** E. coli is the predominant GNB in human colonic microbiota, followed by Klebsiella and Enterobacter.
- **CRE Threat:**
  – Classified as 'urgent' and 'priority one, critical' by CDC/WHO.
  – >100,000 global deaths in 2019; highest burden in low- and middle-income countries (e.g., Indian Subcontinent).
- **ESBL Distribution:**
  – Regional gradient: China > Eastern Europe > Asia > Latin America/Africa > Western US/Canada.
  – Risk Factor: Travel to high-prevalence regions increases colonization risk.

ETIOLOGY & PATHOPHYSIOLOGY

- **Virulence Factors:** Specialized genes required for host infection; many remain unidentified.
  – Adhesins: Required for binding.
  – Siderophores: Required for iron acquisition (though not sufficient alone).
  – Hemolysin: Facilitates tissue damage and nutrient access.
- **Host Response:**
  – Innate immunity (barriers, complement, phagocytes) is the primary defense.
  – PAMPs (e.g., lipid A) → pro-inflammatory response; excessive activation causes shock.
  – DAMPs (e.g., HMGB1) → propagate inflammation.
- **Antigenic Variability:** >150 O antigens in E. coli impede vaccine development.

Table 2 — Common Antimicrobial Resistance Mechanisms

- **Table 166-2** details mechanisms of resistance in Enterobacterales:
  – Efflux: Affects Tetracyclines, fluoroquinolones (FQ), and Fosfomycin.
  – Target Site Alteration/Overproduction: Affects FQ, TMP-SMX (DNA gyrase/topoisomerase IV or folic acid enzymes), and Polymyxins (Lipid A).
  – Enzymatic Modification: Affects Aminoglycosides (via AAC, ANT, APH).

CLINICAL FEATURES

- **General Presentation:** GNB can infect nearly any organ; mortality is high in severe cases (pneumonia, sepsis: 20–60%).
- **Pathogen-Specific Syndromes:**
  - E. coli & Klebsiella: Most common extraintestinal causes.
  - Edwardsiella tarda: Causes both intestinal and extraintestinal infections.
  - Providencia alcalifaciens & E. coli albertii: Associated with gastroenteritis.
- **Urinary Tract Infection (UTI):**
  - Common in ambulatory patients; E. coli is the primary pathogen.
  - Cystitis: 80–90% of cases in premenopausal women; 20% recur frequently.
  - Pyelonephritis: Suggested by fever/back pain; persistent symptoms require evaluation for abscess or obstruction.
- **Other Sites:**
  - E. coli: Found in decubitus ulcers, diabetic foot ulcers, and osteomyelitis (vertebral).

Intestinal Pathogenic E. coli Syndromes

- **Table 3** categorizes intestinal syndromes:
  - STEC/EHEC/ST-EAEC: Hemorrhagic colitis, HUS; caused by Shiga toxin (Lambda-like phage).
  - ETEC: Traveler's diarrhea; caused by heat-stable/labile enterotoxins.
  - EPEC: Watery/persistent diarrhea; characterized by LEE pathogenicity island.
  - EAEC: Traveler's/acute/persistent diarrhea; regulated by AggR.

DIFFERENTIAL DIAGNOSIS

- **Site Correlation:**
  - Sterile sites (e.g., blood, CSF) → implies infection.
  - Nonsterile sites (e.g., open wounds, respiratory tract, catheterized urine) → require clinical correlation to distinguish colonization vs. infection.
- **Treatment Strategy:** All identified GNB should be treated as potentially pathogenic; individual roles in polymicrobial infections are often uncertain.

DIAGNOSTIC APPROACH

1. **Identification:** Use MALDI-TOF-MS, NAATs, and sequencing to identify pathogens and resistance genes rapidly.
2. **Clinical Correlation:** For nonsterile sites, correlate findings with clinical signs to rule out colonization.
3. **Source Control:** Perform abscess drainage or tissue resection when required for cure.
4. **Monitoring:** Assess patient response to treatment as in vitro results may not perfectly predict clinical outcome.

MANAGEMENT & TREATMENT

1. **Initial Strategy:**

– Culture site before starting antimicrobial therapy.
– Blood cultures recommended for systemically ill patients.
– Initial dual-agent therapy may be prudent pending susceptibility results.

2. **Optimization:**
   – Transition to narrower agents once susceptibility is available.
   – Stewardship: Reduce resistance, C. difficile risk, and costs.
3. **Antimicrobial Selection (In Vitro Activity):**
   – Carbapenems (except imipenem for Proteeae), amikacin (except Proteeae), cefepime, β-lactamase inhibitor combinations (e.g., piperacillin-tazobactam, ceftolozane-tazobactam, ceftazidime-avibactam, meropenem-vaborbactam, imipenem/cilastrin-relebactam), and cefiderocol.
4. **Specific Resistance Scenarios:**
   – Polymyxins: Last-line for MBLs (e.g., NDM) despite nephrotoxicity; poor activity against carbapenemase-producing strains.
   – Ceftazidime-avibactam: First-line for KPC-producing CRE; note suboptimal efficacy in pneumonia/renal replacement.
   – Cefiderocol: Promising for CRE but limited data outside UTIs/pneumonia.
   – Aztreonam plus avibactam: Under investigation for MBL-producing CRE.
5. **Non-Targeted Therapy:**
   – Avoid treating colonization (e.g., positive sputum/urine without clinical signs).

Treatment of Carbapenem-Resistant Enterobacterales (CRE)

1. **Class A/D (KPC, OXA):** Ceftazidime-avibactam is emerging as first-line for bacteremia.
2. **Class B (MBLs/NDM):** Polymyxins remain last-line; Aztreonam plus avibactam is a promising alternative.
3. **Cefiderocol:** Active against KPC/MBL/OXA-48 but limited real-world data.
4. **Tigecycline/Eravacycline/Omadicallyne:** Limited by pharmacokinetics and poor activity against Proteeae/Serratia.
5. **Fosfomycin:** Active in vitro; clinical data for serious CPE are limited.

PROGNOSIS & COMPLICATIONS

- **Mortality:** 20–60% in severe infections (pneumera, sepsis).
- **Complications:** Abscess formation, septic shock, and multiorgan failure.
- **Factors:** Prognosis depends on infection severity, host status, and antimicrobial resistance.

SPECIAL POPULATIONS

- **Prevention:**
  – Universal decolonization (chlorhexidine bathing) supported to prevent ICU/nursing home infections.
  – Infection control critical in LTCFs/hospitals due to high GNB colonization rates.

KEY PEARLS & HIGH-YIELD POINTS

- **CRE Status:** Urgent global threat; requires awareness of resistance trends (e.g., KPC vs MBL).
- **Source Control:** Essential for definitive cure in localized infections.

- **Treatment Duration:** 7-day treatment may suffice for non-critically ill patients with source control and clinical response.
- **Polymyxins:** Reserved as last-line due to nephrotoxicity/neurotoxicity.
- **Clinical Trap:** Do not treat colonization (e.g., asymptomatic bacteriuria) as infection.

REFERENCE TABLES

TABLE 166-1

Interactions of Extraintestinal Pathogenic Escherichia coli with the Human Host: A Paradigm for Extracellular...

BACTERIAL GOAL	HOST OBSTACLE	BACTERIAL SOLUTION
Extraintestinal attachment	Flow of urine, mucociliary escalator	Multiple adhesins (e.g., type 1, S, and F1C fimbriae; P pili)
	Nutrient sequestration (e.g., iron via intracellular storage and extracellular scavenging via lactoferrin and transferrin)	
Initial avoidance of host bactericidal activity	Complement, phagocytic cells, antimicrobial peptides	Capsular polysaccharide, lipopolysaccharide
	Intact tissue barriers	
Late avoidance of host bactericidal activity	Acquired immunity (e.g., specific antibodies), treatment with antibiotics	Cell entry, acquisition of antimicrobial resistance

TABLE 166-2

Common Antimicrobial Resistance Mechanisms Possessed by the Enterobacterales

MECHANISM	ANTIMICROBIALS MOST SIGNIFICANTLY AFFECTED	COMMON MEDIATORS OF RESISTANCE
Efflux	Tetracyclines, fluoroquinolones (FQ)	Efflux pumps
	Fosfomycin	
Target site alteration or overproduction	FQ, trimethoprim-sulfamethoxazole (TMP-SMX), and polymyxins	DNA gyrase or topoisomerase IV for FQ; enzymes for folic acid synthesis for TMP-SMX Lipid A for polymyxins
	Penicillins, cephalosporins, cephamycins, carbapenems	

MECHANISM	ANTIMICROBIALS MOST SIGNIFICANTLY AFFECTED	COMMON MEDIATORS OF RESISTANCE
Enzymatic modification of antimicrobials	Aminoglycosides	AAC, ANT, APH

TABLE 166-3

Intestinal Pathogenic Escherichia coli

PATHOTYPE	EPIDEMIOLOGY	CLINICAL SYNDROMEa	DEFINING MOLECULAR TRAIT	RESPONSIBLE GENETIC ELEMENTb
STEC/EHEC/ ST-EAEC	Food, water, person-to-person; all ages, industrialized countries	Hemorrhagic colitis, hemolytic-uremic syndrome	Shiga toxin	Lambda-like Stx1- or Stx2-encoding bacteriophage
	Food, water; young children in and travelers to developing countries	Traveler's diarrhea	Heat-stable and labile enterotoxins, colonization factors	
EPEC	Person-to-person; young children and neonates in developing countries	Watery diarrhea, persistent diarrhea	Localized adherence, attaching and effacing lesion on intestinal epithelium	EPEC adherence factor plasmid pathogenicity island (locus for enterocyte effacement [LEE])
	Food, water; children in and travelers to developing countries	Watery diarrhea, occasionally dysentery	Invasion of colonic epithelial cells, intracellular multiplication, cell-to-cell spread	
EAEC	?Food, water; children in and travelers to developing countries; all ages, industrialized countries	Traveler's diarrhea, acute diarrhea, persistent diarrhea	Aggregative/diffuse adherence, virulence factors regulated by AggR	Chromosomal or plasmid-associated adherence and toxin genes