Escherichia coli

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E. coli: susceptible, ESBLs, KPCs, metallo-beta-lactamases

Clinical Setting

- *Escherichia coli* causes a variety of infections ranging from uncomplicated urinary tract infections to life-threatening infections of the abdomen, skin and soft tissue, lung, CNS and other sites in both normal and immunocompromised hosts.
- Suggested treatment regimens are for parenteral therapy of more serious infections and based on status of pathogen detection and results of in vitro susceptibility. The clinical settings:
  - **Empiric therapy**: Pathogen detected but in vitro susceptibility pending/unavailable
  - **Specific therapy:** Pathogen detected and in vitro susceptibility reported
  - For detailed discussion of beta-lactam drug resistance classes and mechanisms Gram Negative Bacilli, Resistance to Beta-lactams, Overview.
- For treatment of uncomplicated urinary tract infections, see Cystitis (adult female) or Cystitis (adult male)
- See Comments for selected drug details, emerging data, literature citations and more

Classification

- *E. coli*, susceptible and antibiotic-resistant strains

Primary Regimens

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

Lab reports:	Modifying Circumstances	Recommended Regimens	Comments
Isolation of E. coli, Empiric Therapy, susceptibility results pending	Local rate of resistance <10%	Ceftriaxone 2 gm IV q24h (age < 60 years) 1 gm IV q24h (age ≥ 65 years) Ciprofloxacin 400 mg IV q12h or Levofloxacin 750 mg IV q24h Piperacillin-tazobactam 4.5 gm IV over 30 min then 4 hrs later start 3.375 gm IV over 4 hr and repeat q8h	
	Local rates of ESBL (extended spectrum beta-lactamase) resistance >10%	Meropenem 1-2 gm IV q8h or Ertapenem 1 gm IV q24h	
Susceptibility to Aztreonam, Ceftriaxone, Cefotaxime, Ceftazidime, or Cefepime	Not an ESBL producer; choice of agent based on confirmed susceptibility	Ceftriaxone 2 gm IV q24h (age < 60 years) 1 gm IV q24h (age ≥ 65 years) Ciprofloxacin 400 mg IV q12h or Levofloxacin 750 mg IV q24h	Ampicillin 1-2 gm IV q4-6h if susceptible
Resistance to Aztreonam, Ceftriaxone, Cefotaxime, Ceftazidime, or Cefepime (ESBL), susceptible to carbapenems	Likely ESBL producer	Meropenem 1-2 gm IV q8h Imipenem-cilastatin 500 mg IV q6h Ertapenem 1 gm IV q24h	*E.coli* may be susceptible to Piperacillin-tazobactam in vitro but may fail clinically. not recommended for bacteremia, serious infections. Ref: Clin Infect Dis 72:1109, 2021. Consider use of higher dose of Meropenem infused over 3 hours q8h for more serious infections
Resistance to above agents and Meropenem or Imipenem or both but susceptible to Ceftazidime-avibactam and Meropenem-vaborbactam and Imipenem-cilastatin-relebactam	Pattern consistent with production of Klebsiella pneumoniae carbapenemase (KPC)	Ceftazidime-avibactam 2.5 gm IV over 2 hrs q8h Meropenem-vaborbactam 4 gm IV infused over 3h q8h Imipenem-cilastatin-relebactam 1.25 gm IV over 30 min q6h if CrCl > 90 mL/min	Infectious diseases consultation recommended See Clin Infect Dis 2019; 68:519; Antimicrob Agents Chemother. 2019;63:e01551-18 for discussion of emergence of resistant mutants with these agents See Comments
Resistance to above and Ceftazidime-avibactam, Meropenem-vaborbactam, fluoroquinolones, aminoglycosides, TMP-SMX	Pattern is consistent with production of a metallo-carbapenemase	Ceftazidime-avibactam 2.5 gm IV over 3h q8h + Aztreonam 2 gm IV over 3h q6h (see Comments) OR Cefiderocol 2 gm IV over 3h q8h	Infectious diseases consult recommended. Based on in vitro susceptibility, meropenem-vaborbactam plus aztreonam may be an option although efficacy unproven. See comments below

Alternative Regimens

- **ESBL-negative strain and susceptibility confirmed to the specific agent**
  - Cefazolin 2 gm IV q8h
  - TMP-SMX administered as 10 mg/kg/d of TMP component in 2-3 divided doses
  - Amoxicillin-clavulanate 1.2-2.4 gm IV q8h (where available; not available in US)
  - Ampicillin-sulbactam 3 gm IV q6h
  - (Gentamicin or Tobramycin) 5-7 mg/kg q24h, dose adjusted for renal function
- **Other alternatives for ESBL-positive strains:**
  - Ceftolozane-tazobactam 1.5 gm IV q8h
  - Cefepime-enmetazobactam recently FDA approved for treatment of complicated UTIs
  - Ceftazidime-avibactam 2.5 gm IV over 2 hrs q8h
  - Temocillin 2 gm IV q12h (available in Belgium and United Kingdom but not the US)
  - (Gentamicin or Tobramycin) 5-7 mg/kg q24h, if susceptible
  - Plazomicin 15 mg/kg once daily x 4-7 days (if available)(FDA-approved for complicated UTI only)
  - For UTI, another option:
    - Cystitis: Fosfomycin 3 gm po x one dose
    - Pyelonephritis and where IV formulation is available: Fosfomycin 6 gm IV q8h
  - NOTE: Piperacillin-tazobactam is not recommended due to treatment failures perhaps due to inoculum effect
- **Carbapenemase resistant strain, suspected metallo-beta-lactamase phenotype (resistant to Ceftazidime-avibactam and Meropenem-vaborbactam)**
  - Infectious Diseases consultation recommended
  - Plazomicin 15 mg/kg once daily x 4-7 days (if available)(FDA-approved for complicated UTI only)
  - Ceftazidime-avibactam 2.5 gm IV over 3 hrs q8h + Aztreonam 2 gm IV over 3 hrs q6h.
    - A last resort recommendation based entirely on in vitro data and case reports: Antimicrob Agents Chemother 2017 Mar 24;61(4). pii: e02243-16)
    - Based on the resistance of aztreonam to hydrolysis by metallo-beta-lactamases; use the ceftazidime-avibactam to protect the aztreonam from hydrolysis by concomitant ESBLs. See J Antimicrob Chemother 2018; 73:1104.
  - Meropenem-vaborbactam 4 gm IV infused over 3h q8h + Aztreonam 2 gm IV over 3 hrs q8h.
    - Similar in vitro activity to aztreonam plus ceftazidime-avibactam against Enterobactales producing NDM and other non-OXA serine β-lactamases but no clinical data (Antimicrob Agents Chemother 2019; 63: e01426-19).
  - Cefiderocol 2 gm IV over 3 hrs q8h (see Comments)

Antimicrobial Stewardship

- Carbapenems should be reserved for polymicrobial infections for which anaerobic coverage is required or for treatment of infections due to ESBL-producing strains
- Although active against ESBLs and related beta-lactamases, use of Ceftazidime-avibactam, Imipenem-relebactam, and Meropenem-vaborbactam should be reserved for patients with documented carbapenemase mechanism of resistance.

Comments

- Aztreonam is not hydrolyzed by metallocarbapenemases (ceftazidime is) but is inactivated by ESBLS which are often produced concomitantly with the carbapenemase. Avibactam inactivates ESBLs. See Antimicrob Agents Chemother 2017 Mar 24; 61(4). pii:e02243-16
- **Cefiderocol:** FDA-approved for patients with complicated UTI due to cefiderocol susceptible bacteria and with limited or no alternative treatment options.
  - In an open label randomized trial of cefiderocol vs Best Available Therapy (BAT) in patients with sepsis, pneumoinia, bacteremia or cUTI, mortality at 28 days was 24.8% for cefiderocol pts. vs 18.4% for BAT pts (not statistically significant).
  - Reference: Clin Infect Dis 2019; 69 (suppl.7): S519-S575
- If Ertapenem resistance, check for susceptibility to Meropenem or Imipenem; if the isolate is susceptible to both of the latter either may be used.
- Combination of Meropenem + Polymyxin (either Polymyxin B or Colistin) for therapy of MDR gram-negative bacillii is **not** recommended based on treatment failures in controlled clinical trial :
  - Failures occurred in a randomized controlled trial (Lancet Infect Dis 2018 ; 18:391):
    - 77% of enrolled patients had infections due to *Acinetobacter baumannii*
    - Study was underpowered to assess comparative efficacy vs other carbapenemase producing gram-negative bacteria.
- Suspected metall0-beta-lactamase producer: Meropenem-vaborbactam 4 gm IV infused over 3h q8h + Aztreonam 2 gm IV over 3 hrs q8h.
  - Similar in vitro activity to aztreonam plus ceftazidime-avibactam against Enterobacterales producing NDM and other non-OXA serine β-lactamases but no clinical data (Antimicrob Agents Chemother 2019; 63: e01426-19).
- **Plazomicin**
  - FDA approved for the treatment of complicated UTI and pyelonephritis (N Engl J Med 2019;380:729);
  - Limited observational experience with Plazomicin in combination with Tigecycline or Meropenem for treatment of MDR bloodstream infections or hospital-acquired or ventilator-associated pneumonia (N Engl J Med 2019; 380:791).
- **Investigative agents** in late clinical development with activity vs MDR gram-negative bacilli
  - Aztreonam-avibactam
- IDSA Guideline on treatment of ESBL, AmpC, and carbapenemase producers: Clin Infect Dis. 2023 Jul 18:ciad428.