Managing Antimicrobial Resistance in the Emergency Department

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KEYWORDS

• Infectious diseases • Emergency department • Multi-drug resistant organisms
• Antimicrobial resistance • Antibiotics

KEY POINTS

- A basic awareness and understanding of antimicrobial resistance and prevailing mechanisms can aid emergency physicians in providing appropriate care to patients with infection due to a multidrug-resistant organism (MDRO).
- Empiric antibiotic coverage of MDROs should be considered for patients recently treated for MDRO infection in the past 3 to 6 months and presenting with similar or recurrent infectious symptoms.
- Newer broad-spectrum antibiotics should be reserved for critically ill patients whereby there is a high likelihood of infection with an MDRO.

INTRODUCTION TO ANTIMICROBIAL RESISTANCE

Antimicrobial resistance remains an ongoing global crisis, contributing more than 2.8 million infections and more than 35,000 deaths annually in the U.S.[1] As frontline health care settings, emergency departments (ED) play an important role in recognizing and managing patients at high risk for infection due to multi-drug resistant organisms (MDRO). Timely and appropriate antimicrobial therapy can impact morbidity and mortality associated with these infections. Conversely, inappropriate selection and administration of antibiotics can lead to adverse events, patient harm, and greater antimicrobial resistance.[2]

In addition to broadening the spectrum of empirical coverage for individuals at high risk of MDROs, emergency clinicians are often responsible for the initial

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management of patients who present to the ED due to positive cultures. The most challenging among these cases are those whose culture and susceptibility results indicate a resistant organism. As such, it is critical for emergency clinicians to understand the current landscape of bacterial resistance and appropriate treatment options. Toward that aim, this article presents a deep dive review on the epidemiology of MDRO infections, describes current mechanisms of antimicrobial resistance in gram-negative and gram-positive bacteria, outlines optimal antibiotic therapy covering MDROs in emergency care, and provides an overview of several newer antibiotics now available in the U.S.

THE SCOPE OF THE PROBLEM

Infections due to MDROs have steadily increased in the U.S. over the last 3 decades. Consequently, emergency clinicians are likely to encounter and provide care to patients with MDRO infection in practice (Table 1).[3] Given the uncommon nature of these infections, empirical treatment using newer antibiotics should ideally be reserved for patients recently (within 3–6 months) treated for MDRO infection and presenting with similar or recurrent infectious symptoms. As the rise in MDRO infections is entwined with inappropriate antimicrobial prescribing, it is imperative to reserve the use of newer antibiotics to treat confirmed culture-positive MDRO infections wherever possible.

Table 1
Incidence of MDROs in the United States reported from 2017[4]

	Incidence Rates per 10,000 Hospitalizations		
MDRO	**Overall**	**Community Acquired**	**Hospital Acquired**
ESBL	57.12	49.66	7.46
CRE	3.79	2.78	1.01
CRAB	2.47	1.67	0.80
DTR Pseudomonas	9.43	6.66	2.76
VRE	15.76	10.47	5.29
MRSA	93.68	80.25	13.44

ANTIMICROBIAL RESISTANCE MECHANISMS AND ANTIBIOTIC SELECTION

Beta-lactamases

Beta-lactamases are enzymes that inactivate beta-lactam antibiotics by opening the beta-lactam ring. They are commonly classified by their amino acid structure (Ambler system).[4–8] Table 2 describes the types and features of several beta-lactamases commonly encountered in clinical practice.

Extended-spectrum beta-lactamase enterobacterales

Extended-spectrum beta-lactamase (ESBL) includes all enzymes that hydrolyze oxyimino-cephalosporins (cefotaxime and ceftazidime). All ESBL are plasmid-mediated, meaning these enzymes are encoded by plasmids and are not inducible in the presence of antimicrobials.[25] Acquisition of these plasmids by gram-negative organisms, most commonly Enterobacterales (eg, *Escherichia coli, Klebsiella pneumoniae*, *Klebsiella oxytoxa*), confers resistance against penicillins, most cephalosporins, and aztreonam. Although routine ESBL testing is not performed widely, nonsusceptibility to ceftriaxone is often used as a proxy for ESBL production (Table 3).[26]

Table 2
Beta-lactamase classification and features

Ambler Class	Enzyme Type	Examples	Possible Substrates	Host Organisms	Beta- Lactamase Inhibitors
A	Extended- spectrum beta-lactamase (ESBL)	TEM SHV CTX-M	Penicillin, amoxicillin, piperacillin, narrow-spectrum cephalosporins (cefazolin, cefuroxime), ceftriaxone, aztreonam	Enterobacteriaceae and nonfermenting gram-negative bacilli	Avibactam, vaborbactam, relebactam, tazobactam, durlobactam, clavulanic acid, sulbactam
	Carbapenemase	KPC	Same as ESBL plus carbapenems		Avibactam, vaborbactam, relebactam, durlobactam
B	Metallo-beta-lactamase	NDM VIM IMP	All beta-lactams except for aztreonam		EDTA, divalent cation chelators
C	Cephalosporinase	AmpC	Same as ESBL plus cephamycins	*Hafnia alvei*, *Enterobacter cloacae*, *Citrobacter freundii*, *Klebsiella aerogenes*, *Yersinia enterocolitica* and *Pseudomonas aeruginosa*	Avibactam vaborbactam, relebactam, durlobactam
D	Carbapenemase	OXA-48	Same as ESBL plus carbapenems	Enterobacteriaceae and nonfermenting gram-negative bacilli	Avibactam, relebactam, durlobactam, clavulanic acid, sulbactam

Table 3
Example of an ESBL-producing organism phenotype[9]

	Ampicillin	Amp-Sulbactam	Ceftriaxone	Meropenem	Aztreonam	Ciprofloxacin	Nitrofurantoin
E. Coli	R	S	R	S	R	S	S

This is an example phenotype of an organism that harbors ESBL. Please refer to local antibiogram or susceptibility testing to determine appropriate empiric treatment.

Optimal antibiotic therapy to treat ESBL infections include[11]:

- Uncomplicated cystitis:
  - *(Preferred)* Nitrofurantoin or trimethoprim-sulfamethoxazole (TMP-SMX)
  - *(Alternative)* Single-dose aminoglycosides, oral fosfomycin (*E coli* only), carbapenems, levofloxacin, or ciprofloxacin
  - If cefepime or piperacillin-tazobactam was initiated as empirical therapy and later identified as an ESBL-E and clinical improvement occurs, no change or extension of antibiotic therapy is necessary
- Pyelonephritis and complicated UTI:
  - *(Preferred)* TMP-SMX, ciprofloxacin, or levofloxacin
  - *(Alternative)* Ertapenem, meropenem, imipenem-cilastatin, or aminoglycosides
- Infections outside of the urinary system:
  - *(Preferred)* Carbapenem
    - *(Critically ill and/or experiencing hypoalbuminemia):* meropenem or imipenem-cilastatin
  - Can consider transitioning to oral fluoroquinolone or TMP-SMX
  - Piperacillin-tazobactam and cefepime are not suggested for treatment, even if susceptibility to agent is demonstrated

AmpC beta-lactamase-producing enterobacterales

AmpC beta-lactamases inactivate cephalosporins and are produced by a variety of gram-negative organisms, as production can arise from inducible chromosomal resistance in the presence of certain antibiotics (aminopenicillins, narrow spectrum cephalosporins, and cephamycins).[27] Antibiotic susceptibility testing of AmpC producing organisms may initially demonstrate sensitivity to cephalosporins; however, resistance on repeat testing after exposure to these inducers can occur. Similar to ESBL, AmpC can also be plasma mediated with the tip-off being demonstrated resistance to ceftriaxone on susceptibility testing.

Common inducible AmpC producers, often referred to as the "HECK-Yes" organisms include: *Hafnia alvei, Enterobacter cloacae, Citrobacter freundii, Klebsiella aerogenes,* and *Yersinia enterocolitica*. IDSA guidelines suggest that only *E*nterobacter *cloacae, K aerogenes* and *C*itrobacter *freundii* are organisms at moderate to high risk for becoming clinically significant AmpC producers (**Table 4**).[11]

Optimal antibiotic therapy to treat AmpC infections include:[11]

- Uncomplicated cystitis with any AmpC producer:
  - *(Preferred)* Nitrofurantoin OR TMP-SMX
  - Ceftriaxone (if susceptible)
  - *(Alternative)* Single-dose aminoglycoside, ciprofloxacin OR levofloxacin
- Invasive infection
  - Cefepime MIC less than 4 mcg/mL*: cefepime.
  - Cefepime MIC $\geq$4 mcg/mL*: carbapenem
    - **Refer to local antibiogram if MIC is not available*
  - TMP-SMX or fluoroquinolone after:
    - Susceptibility demonstrated
    - Patient is hemodynamically stable
    - Reasonable source control has occurred
    - Concerns about insufficient intestinal absorption are not present
  - Avoid oral step-down to nitrofurantoin, fosfomycin, doxycycline, or amoxicillin-clavulanate for bloodstream infections

Table 4
Example of an AmpC-producing organism phenotype[10]

	Ampicillin	Amp-Sulbactam	Ceftriaxone	Meropenem	Aztreonam	Ciprofloxacin	Nitrofurantoin
E. Cloacae	R	R	R	S	R	S	S

*This is an example phenotype of an organism that harbors an AmpC beta-lactamase. Please refer to local antibiogram or susceptibility testing to determine appropriate empiric treatment.

Carbapenem-resistant enterobacteriaceae

Any Enterobacteriaceae resistant to at least one carbapenem antibiotic or identified as producing a carbapenemase is termed a carbapenem-resistant Enterobacteriaceae (CRE). The most common carbapenemases in the U.S. are *K. pneumoniae* carbapenemases (KPCs) with *E. coli* also ranked high. Carbapenemase enzymes exhibit different levels of resistance to beta-lactamase inhibitors including KPC can be inhibited by avibactam, relebactam, and vaborbactam, OXA-48 can be inhibited by avibactam, while NDM cannot be inhibited by the newer beta-lactamase inhibitor agents (**Table 5**).[28,29]

Optimal antibiotic therapy targeting infection with a CRE include:[11]

- If susceptibility to meropenem and imipenem (MIC $\leq$1 μg/mL): the use of extended infusion meropenem is suggested (unless carbapenemases identified)
- Uncomplicated cystitis
  - *(Preferred)* Nitrofurantoin, TMP-SMX, ciprofloxacin, or levofloxacin
  - *(Alternative)* single dose aminoglycoside, fosfomycin (*E. Coli* only), colistin, ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, or cefiderocol
- Complicated UTI and pyelonephritis
  - *(Preferred if susceptibility demonstrated)* TMP-SMX, ciprofloxacin, or levofloxacin
  - *(Preferred)* Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol
  - (*Alternative*) aminoglycoside
- Infections outside of the urinary tract
  - Carbapenemase testing results are not available or negative
    - *(Preferred)* Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam
  - Empiric treatment
    - For patients with CRE infections with recent (previous 12 months) medical care received in countries with a relatively high prevalence of metallo-β-lactamase-producing organisms or who have previously had a clinical or surveillance culture whereby a metallo-β-lactamase-producing isolate was identified, preferred treatment options include:
      - Ceftazidime-avibactam plus aztreonam, or cefiderocol as monotherapy while awaiting susceptibility
  - Confirmed KPC
    - *(Preferred)* Ceftazidime-avibactam, meropenem-vaborbactam, OR imipenem-cilastatin-relebactam
    - *(Alternative)* cefiderocol
  - Confirmed NDM
    - *(Preferred)* Cefiderocol or Ceftazidime/avibactam plus azetronam
    - *(Alternative)* tigecycline or eravacyline
      Not recommended as monotherapy for the treatment of UTIs or blood stream infections
  - OXA-48 like carbapenemase identified
    - *(Preferred)* Ceftazidime-avibactam
    - *(Alternative)* Cefiderocol

Difficult-To-Treat Resistant Pseudomonas aeruginosa

P aeruginosa with difficult to treat resistance is defined as exhibiting nonsusceptibility to all of the following antibiotics: piperacillin-tazobactam, ceftazidime, cefepime,

Table 5
Example of a CRE phenotype

	Piperacillin- Tazobactam	Cefepime	Meropenem	Meropenem-Vaborbactam	Ceftazidime-Avibactam	Ciprofloxacin	Nitrofurantoin
K. Pneumoniae	R	R	R	S	S	S	S

*This is an example phenotype of an organism that harbors a carbapenemase. Please refer to local antibiogram or susceptibility testing to determine appropriate empiric treatment.

aztreonam, meropenem, imipenem-cilastatin, ciprofloxacin, and levofloxacin.[26] The main 3 mechanisms of resistance in *Pseudomonas* include AmpC beta lactamase production, loss of porins, and induction of efflux pumps (**Tables 6 and 7**).[7,30]

Carbapenem-resistant Acinetobacter baumannii

Carbapenem-resistant *A baumannii* (CRAB) is most commonly isolated from the respiratory tract or wounds, and can be challenging to differentiate as a true pathogen or colonizer. *A baumannii* exhibits resistance to most antibiotics through mechanisms including metallo- and serine beta lactamases the modification of 16S rRNA methyltransferases or upregulation of efflux pumps.[31] Sulbactam has proven success in overcoming resistance in *A baumannii*, however it remains unclear the full extent of the mechanisms of resistance in this species (**Table 8**).[32]

Optimal antibiotic therapy to treat CRAB infection include:[11]

- Combination with high-dose ampicillin-sulbactam (9gm IV q8h more than 4 hours OR 27 g IV q24 h continuous infusion) plus at least one other agent
  - High dose ampicillin-sulbactam (even if CRAB isolate is not susceptible to ampicillin-sulbactam, it is still reasonable to consider in combination therapy)
  - Minocycline
  - Tigecycline
  - Polymyxin B
  - Cefiderocol should be limited to CRAB infections refractory to other antibiotics or intolerance to other agents precludes their use and be used in combination
  - *Sulbactam-durlobactam* (newer agent, see later in discussion regarding the additional details)

Stenotrophomonas maltophilia

Stenotrophomonas maltphilia is a gram-negative bacillus that is ubiquitous in water environments. It is generally less pathogenic than other nosocomial organism, however it has virulence factors leading to difficulty to treat in certain hosts when it is a true pathogen.[33] *S. maltophilia* can harbor resistance genes such as metallo- and serine beta lactamases, intrinsic resistance to aminoglycosides, and efflux pumps that reduce the activity of tetracyclines and fluoroquinolones.[34] Similar to CRAB, combination therapy is recommended with limited options for treatment (**Table 9**).[31]

Treatment of choice:[11]

- Combination therapy with at least 2 active agents until clinical improvement: TMP-SMX, minocycline, tigecycline, cefiderocol, or levofloxacin

Table 6
New beta lactam-beta-lactamase inhibitor activity against MDR *Pseudomonas* resistance mechanisms

Agents	Stable Against AmpC Overproduction	Stable Against Loss of Porins	Stable Against Efflux Pumps
Ceftolozane-tazobactam	+ (ceftolozane)	+ (ceftolozane)	+ (ceftolozane)
Ceftazidime- avibactam	+ (avibactam)	-	-
Meropenem- vaborbactam	+ (vaborbactam)	- (OprM)[a]	- (MexAB)[a]
Imipenem/cilastatin/relebactam	+ (relebactam)	- (OprD)[a]	+
Cefiderocol	+	+	+

[a] MexAB-OprM is a common efflux pump in *P. aeruginosa* and oprD protein is a common porin channel for imipenem efflux.

Table 7
Example of a DTR *Pseudomonas* phenotype

	Piperacillin- Tazobactam	Cefepime	Ceftazidime	Meropenem	Aztreonam	Ciprofloxacin	Tobramycin
P. aeruginosa	R	R	R	R	R	R	S

Infectious Source	*Preferred*	*Alternative*
Uncomplicated Cystitis	Ceftolozane-tazobactam Ceftazidime-avibactam	Cefiderocol Single dose Tobramycin or Amikacin
Pyelonephritis and cUTIs	Imipenem-cilastatin-relebactam	
Infectious outside of the urinary tract		Cefiderocol

This is an example phenotype of an organism that harbors *P. aeruginosa* resistance mechanisms. Please refer to local antibiogram or susceptibility testing to determine appropriate empiric treatment.

Treatment of choice[11]

Table 8
Example of a CRAB phenotype

	Ampicillin-Sulbactam	Meropenem	Ceftazidime	Levofloxacin	Gentamicin	TMP-SMX	Cefepime
A. Baumanni	R	R	R	R	R	R	R

This is an example phenotype of an organism that harbors CRAB resistance mechanisms. Please refer to local antibiogram or susceptibility testing to determine appropriate empiric treatment.

Table 9
Example of an *S. maltophilia* phenotype[12]

	Ceftazidime	Levofloxacin	TMP-SMX	Minocycline
S. maltophilia	R	R	S	S

This is an example phenotype of an organism that harbors *S. maltophilia* resistance mechanisms. Please refer to local antibiogram or susceptibility testing to determine appropriate empiric treatment.

- *(Clinical instability or intolerance or inactivity toward the above agents)* Ceftazidime-avibactam plus aztreonam

Vancomycin-resistant Enterococcus

Vancomycin-resistant enterococci (VRE) are a leading cause of health care associated infections with limited treatment options. Enterococci are commensal organisms in the gastrointestinal tract; therefore, the risk for VRE colonization commonly arises through exposure to antimicrobials. *Enterococcus faecium* has the biggest risk of developing resistance, whereas *Enterobacter faecalis* commonly retains susceptibility to ampicillin. All enterococci have intrinsic resistance to all cephalosporins, anti-staphylococcal penicillins, aminoglycosides, and TMP-SMX, leading to few options for treatment when resistance develops (**Tables 10 and 11**).[35]

Methicillin-resistant Staphylococcus aureus

S aureus is a leading cause of bacteremia, cellulitis, and endocarditis. MRSA spread through health care and community settings is declining overtime but remains very high with more than 300,000 estimated cases in hospitalized patients in 2017.[36] Choice of treatment may depend on infection severity, availability, cost, and patient factors rather than resistance.

Table 10
Antibiotic options for VRE based on site of infection[13–18]

	Cystitis[d]	Pyelonephritis	Blood	Endocarditis[a]	Intraabdominal[c]	CNS
Nitrofurantoin	X					
Amoxicillin[b]	X					
Ampicillin[b]	X	X	X	X	X	X
Fosfomycin	X					
Linezolid	X	X	X	X	X	X
Daptomycin			X[e]	X[e]	X[e]	

Disclaimer: off-label treatment with oritavancin and tigecycline can be used if susceptible but would encourage an infectious disease consult.[17,18].

[a] Please refer to the infective endocarditis guideline for synergy options based on susceptibility and valve type.

[b] Confirm susceptibility before use. Would not recommend empirically.

[c] Not recommended to cover VRE empirically in intraabdominal infections unless the patient is high risk such as a liver transplant recipient with an intra-abdominal infection originating in the hepatobiliary tree or patient known to be colonized with VRE.

[d] Frequent colonizer or cause of asymptomatic bacteriuria. Once GI colonization, eradication is not possible and hence it may frequently appear in the urinary system.

[e] 8 to 12 mg/kg/day if normal renal function dosing recommendation.

Table 11
Example of a VRE phenotype

	Ampicillin	Vancomycin	Levofloxacin	Tetracycline	Linezolid	Daptomycin	Nitrofurantoin
E. Faceium	R	R	R	R	S	S	S

This is an example an organism that harbors *E. faecium* resistance mechanisms. Please refer to local antibiogram or susceptibility testing to determine appropriate empirical treatment.

Table 12
Antibiotic options for MRSA based on site of infection[14,15,19–24]

	SSTI	Bacteremia	Endocarditis[a]	Intraabdominal	Pneumonia	Meningitis
TMP-SMX	X[b]					X
Doxycycline	X[b]					
Clindamycin[c]	X				X	
Linezolid	X	X	X	X	X	X
Vancomycin	X	X	X	X	X	X
Daptomycin	X	X	X	X		
Telavancin	X	X				
Oritavancin	X					
Dalbavancin	X					
Ceftaroline	X[d]					

[a] Please refer to the infective endocarditis guideline for synergy options based on susceptibility and valve type.
[b] For moderate to severe purulent SSTI only.
[c] Can be used empirically if clindamycin resistance is < 10-15% at the institution. Confirm susceptibility before use.
[d] Ceftaroline is only FDA approved for SSTI, but may be used in conjunction with daptomycin or vancomycin as salvage therapy for persistently positive MRSA bacteremia[25].

Beta-lactam resistance in *S aureus* is mediated by penicillin binding protein 2a (PBP2a) production.[37] Vancomycin resistance is rare, and it is generally not recommended to empirically cover for vancomycin-resistant *S aureus* (VISA) (**Tables 12 and 13**).[19]

Oritavancin

Oritavancin is structurally similar to vancomycin but differs by having properties against vancomycin-resistant strains (hydrophobic tail and inhibition of transpeptidation).[38–40] It has activity against MRSA, Streptococcus species, and vancomycin-susceptible *E.faecalis*. The half-life of oritavancin is long (200–300 hours), which provides a complete course of SSTI with one dose. Oritavancin was found to be noninferior to vancomycin in SSTI for early clinical response (82.3% vs 28.9% SOLO I; 80.1% vs 82.9% SOLO II). Adverse events included nausea and headache, with no difference in serious adverse events reported (4.4%–7.4%). Other infectious sources have been retrospectively reviewed for off-label indications including osteomyelitis, endocarditis, bacteremia, and prosthetic joint infection. Implications of oritavancin include drug-drug interactions (warfarin) and affect coagulation tests including prolonged prothrombin time and activated partial thromboplastin time (aPTT) due to interaction with phospholipid reagent.

Table 13
Example of an MRSA phenotype

	Oxacillin	Vancomycin	Nitrofurantoin	Rifampin	SMP-TMX	Linezolid	Daptomycin
S. Aureus	R	S	S	S	S	S	S

This is an example phenotype of MRSA. Please refer to local antibiogram or susceptibility testing to determine appropriate empiric treatment.

Table 14
A quick guide to newer broad-spectrum antibiotics with activity against MDROs

Drug	Indications	Spectrum	Notes	Trial Data	
Ceftolozane/Tazobactam [Zerbaxa][44–49]	1.5 g-3g q8h* • cUTI • cIAI (+Metro) • Pneumonia *requires renal adjustment	Gram [-] ENT PSA (resistance increasing) *Ineffective against ESBL, Enterococcus, & anaerobes* *Limited efficacy against Staph or Strep*	Increased affinity for PSA PBPs, greater stability vs AmpC hydrolysis Ceftolozane has similar activity to ceftazidime but with heavier side change preventing hydrolysis	*ASPECT-cIAI* (n = 993) + Metro -non-inferior vs mero for clinical cure (83% vs 87.3%)	*ASPECT-cUTI* (n = 1083) • higher micro eradication (80.4%) vs levo (72.1%) *ASPECT-NP* (n = 726) • Noninferior vs mero 28-d mortality (24% vs 25.3%)
Ceftazidime/Avibactam [Avicaz][50–52]	2.5 g q8h * • cUTI • cIAI (+Metro) • HAP *requires renal adjustment	Gram [-] ENT +/– PSA ESBL Steno *No coverage of Staphylococcus, Streptococcus or Enterococcus*	Potent inhibition of ESBL, AmpC beta-lactamase by avibactam *No increased coverage of PSA or Acineto*	*RECLAIM* (n = 1066) + Metro -non-inferior to mero for clinical cure at 28 d in cIAI (81.6% vs 85.1%)	*REPRISE* (n = 302) • Ceftaz-R ENT and PSA cUTIs and cIAIs • cUTI: 79% micro response • similar clinical cure rates vs BAT (91% vs 91%) *REPROVE* (n = 726) • noninferior to mero (68.8% vs 73% for clinical cure) for HAP
Meropenem/ Vaborbactam [Vabomere][53–55]	4gm q8h * -cUTI *requires renal adjustment	KPC-producing CRE PSA (mero susceptible)	Vaborbactam protects from degradation by certain serine beta-lactamases (KPC) If PSA culture resistant to meropenem – Vabomere has limited efficacy	*TANGO-I* (n = 545) • Phase III vs zosyn cUTI • noninferior (overall success) *TANGO-II* (n = 77) • cUTI, HAP, VAP, BSI, cIAI • superior vs BAT in CRE (n = 47) • clinical cure rates (59.4% vs 26.7%) *BAT: carbapenem, aminoglycoside, polymixin B, colistin, tigecycline or ceftazidime-avibactam*	

(*continued on next page*)

Table 14
(*continued*)

Drug	Indications	Spectrum	Notes	Trial Data
Imipenem/Cilastatin-Relebactam [Recarbrio][56–58]	1.25 gm q6h* • cUTI • cIAI • HAP/VAP *requires renal adjustment	PSA ESBL	Potent inhibition of AmpC beta-lactamase by relebactam (similar to avibactam) *Limited benefit with CRE unless produce KPC*	*RESTORE-IMI 1* (n = 47) • vs imipenem/colistin combo • HAP, cIAI, or cUTI • 71% vs 70% favorable overall response *RESTORE-IMI 2* (n-537) • HAP & VAP vs zosyn • noninferior 28 all-cause mortality (15.9% vs 21.3%)
Cefepime/Enmetazobactam[59]	0.5-2gm q8h* - cUTI *requires renal adjustment	PSA ESBL *Limited CRE data*	Enmetazobactam restores activity against ESBL producers (more potent than tazobactam)	*ALLIUM* (n = 678) • vs Zosyn for cUTI and pyelo; similar clinical cure rates (92.5% vs 88.9%) [met noninferiority] • higher rate of micro eradication (82.9% vs 64.9%) • ESBL: 73.7% vs 51.5% clinical cure and micro eradication
Cefiderocol [Fetroja][60–64]	2gm q8h* -cUTI -HAP/VAP *requires renal adjustment	ENT PSA Acineto *No Gram positive or Anaerobe coverage*	Enhanced penetration by siderophore transport (iron complex), greater stability vs AmpC hydrolysis (KPCs, OXA-48, and metallo-beta lactamases)	*APEKS-cUTI* (n = 448) • Phase II; noninferior to Imi (clin and micro response 73% vs 55%) *CREDIBLE-CR* (n = 152) • vs BAT in CRE (HAP, VAP, HCAP, bacteremia); similar clinical and microbiological efficacy; higher mortality in the Acineto group treated with cefiderocol *Falcone, et al* (n = 124) • vs colistin • Acinetobacter infections • Higher 30-d mortality in the colistin group (55.8% vs 34%, *P* = .018) *APEKS-NP* (n = 300) • vs mero GNB nosocomial PNA (HAP or VAP); found noninferiority of mortality at day 14 (12.4% vs 11.6%)

Plazomicin [Zemdri][65,66] (aminoglycoside)	15 mg/kg once daily* -cUTI *requires renal adjustment	CRE ESBL Gentamicin-resistant E.coli	Blocks interactions and inactivation by most of the AG-modifying enzymes among CREs *More potent than other AGs against KPC-producing ENT *Limited data against PSA and Acineto*	*EPIC* (n = 600) • superior vs mero in cUTI & acute pyelo • 78.5% (vs 68.9%) composite cure in cUTI and 85.7% (vs 71.8%) in pyelo *CARE* (n = 39) • invasive CRE (BSI, VAP, HAP, cUTI) vs colistin PLUS mero or tigecycline • mITT pop n = 37 • lower 28-d mortality (11.8% vs 40%)
Eravacycline [Xerava][67–70] ("4th Generation" tetracycline)	1 mg/kg q12 h -cIAI	Acineto ESBL CRE No PSA coverage **In-vitro MRSA and Enterococcus*	10x higher affinity for ribosomal binding	*IGNITE 1* (n = 541) • vs erta cIAI • Noninferior in clinical response (86.8% vs 87.6%) • Similar clinical failure rates (19 vs 11) *IGNITE 4* (n = 500) • vs Mero cIAI • Noninferior in clinical response (90.8% vs 91.2%) *IGNITE 2 & 3* (n = 908) • vs Levo or Erta cUTI • did not meet noninferiority for clinical cure/micro eradication • (60.4% vs 66.9% vs levo & 84.8% vs 94.8% vs erta)
Sulbactam-Durlobactam[71–73]	1gm/1gm q6h* • cUTI • HABP/VAP • BSI *requires renal adjustment	Acineto Limited data against ENT	Double beta-lactamase coverage Durlobactam active against A, C, and D beta-lactamases	*Sagan, et al (n = 80)* • cUTI • With imipenem vs imipenem alone • similar overall success (76.6% vs 81%) *ATTACK (n = 207)* • HABP/VAP • +IMI vs colistin • non-inferior to colistin for 28-d all-cause mortality (12% vs 32.3%)

Abbreviations: Acineto, Acinetobacter; AG, aminoglycosides; BAT, best available therapy; cIAI, complicated intra-abdominal infection, CRE, carbapenemase-resistant Enterobacteriaceae; cUTI, complicated Urinary Tract Infection; ENT, enterobacteriaceae, GNB, gram negative bacteria; HAP, hospital-acquired pneumonia; Imi, imipenem; Levo, levofloxacin, Mero, meropenem; Metro, metronidazole; mITT, microbiologic intention to treat group; MDR, multidrug resistant; NP, nosocomial pneumonia; PSA, Pseudomonas; Pyelo, pyelonephritis; Zosyn, piperacillin/tazobactam.

Dalbavancin

Dalbavancin is considered a semisynthetic lipoglycopeptide and has a high potency against MRSA.[41–43] It is susceptible to other gram-positive bacteremia including Streptococcus species and vancomycin-susceptible *E. faecalis*. Important properties include a long duration of action (half life of 346 hours) and no drug-drug interactions. Dalbavancin has been evaluated in two phase 3, noninferiority, randomized controlled trials in SSTI versus vancomycin (DISCOVER-1 and DISCOVER-2). Noninferiority was met in both trials of early clinical response (83.3% vs 81.8%, DISCOVER-1 & 76.8% vs 78.3%, DISCOVER-2). Adverse events included nausea and headache, with minimal serious adverse events observed (2.6% vs 4%). Dalbavancin has also been evaluated in a number of other disease states, including osteomyelitis, endocarditis, bacteremia, and prosthetic join infections with osteomyelitis. Another randomized controlled trial of dalbavancin compared with the standard of care in osteomyelitis found noninferiority of clinical response (97% vs 88%).

Oritavancin and dalbavancin are only FDA approved for SSTI but may be used off-label in special populations in the ED, such as injection drug users or patients that have poor health care access to outpatient parenteral antimicrobial therapy (OPAT) with serious infections (**Table 14**).[74]

SUMMARY

Empiric broad-spectrum antibiotic therapy to treat serious infection is common in emergency medicine as the source of an infection may not be known nor microbiological culture data may be be available. Empiric treatment of MDRO infections should be approached with caution and guided by the most likely pathogens based on the differential diagnosis, severity of the illness, suspected source of infection, patient specific factors, and local antibiotic susceptibility patterns. Newer broad-spectrum antibiotics should be reserved for critically ill patients whereby there is a high likelihood of infection with an MDRO, such as a recent infection with a carbapenem-resistant organism in the last 6 months, antibiotic exposures within the last 30 days, and local susceptibility profiles for the likely pathogen.[61]

CLINICS CARE POINTS

- A basic awareness and understanding of antimicrobial resistance and prevailing mechanisms can aid emergency clinicians in providing appropriate care to patients with infections due to a multidrug-resistant organism (MDRO).
- Empiric antibiotic coverage of MDROs should be considered for patients recently treated for MDRO infection in the past 3 to 6 months and presenting with similar or recurrent infectious symptoms.
- Newer broad-spectrum antibiotics should be reserved for critically ill patients whereby there is a high likelihood of infection with an MDRO.

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