




BEN AND MAYTEE FISCH
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New Antimicrobial Agents On The Horizon

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Objectives

- Identify new and investigational antibiotics in late phase clinical trials.
- Compare advantages and disadvantages of new antibiotics versus existing agents.
- Describe the potential place in antimicrobial formulary.
- Discuss the financial costs and potential benefits of new antibiotics.

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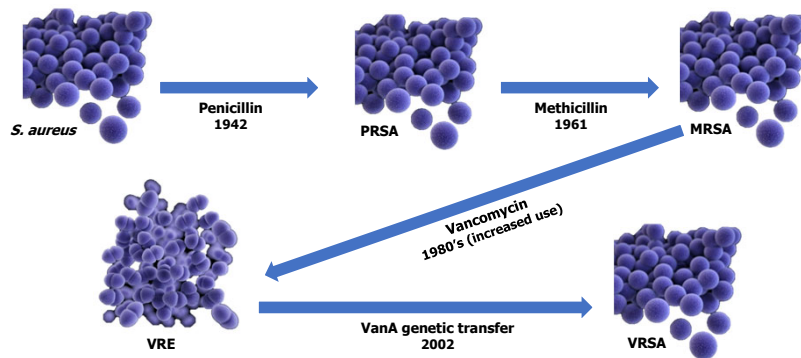
Background

- 20-50% of antimicrobial use is inappropriate
 - 30% is considered unnecessary
 - 1 out of 5 emergency department visits are for adverse drug reactions (ADRs) due to antibiotic use
 - >\$10 billion spent on antibiotics
 - >\$3.5 billion among hospitalized patients
- ❖ Direct antimicrobial drug cost
- ❖ Antimicrobials account for approximately 30% to 50% of the pharmacy drug budget

Centers for Diseases Control and Prevention. 2018 Facts about Antibiotic Resistance.
American Hospital Association. Hospital Statistics, 2018 Edition.

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Antibiotic Use Drives Resistance



Adapted from Gallagher, J. (2014). Prodigal pathogens. [PowerPoint slides].

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Risk Factors for Antibiotic Resistance

- Received antimicrobial therapy within previous 3 months
- Currently hospitalization of ≥ 5 days
- Area with high level resistance in community/institution
- Hospitalization within previous 3 months
- Residence in nursing home or extended-care facility
- Hemodialysis patients
- Home wound care/home infusion therapy
- Immunosuppressive diseases and/or therapy
- Family members with multi-drug resistance organisms

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Empiric vs. Directed Therapy

- In most medical centers **only 15-20%** of therapy is directed; 80-85% is empiric.

Empiric

- Infection not well defined ("best guess")
- Broad spectrum
- Multiple drugs
- Evidence usually only 2 randomized controlled trials
- More adverse reactions
- More expensive

Directed

- Infection well defined
- Narrow spectrum
- One, seldom two drugs
- Evidence usually stronger
- Less adverse reactions
- Less expensive

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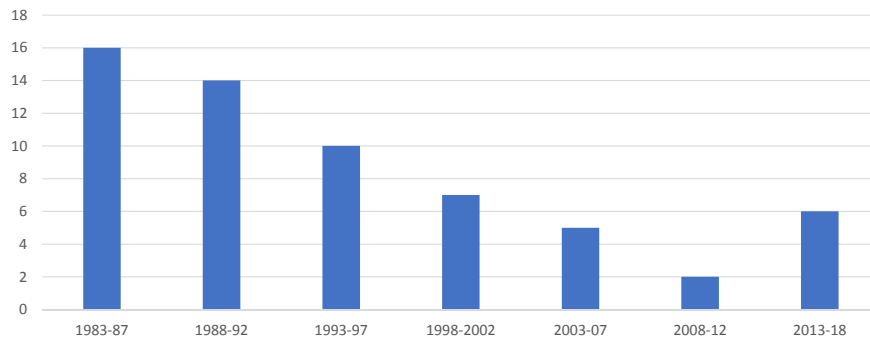
Truth vs. Myth – Polling Slide

Numerous antimicrobials have been developed making antimicrobial resistance a problem of the past.

- a) Truth
- b) Myth

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Antimicrobial Drug Approval



Spellberg B, et al. *Clin Infect Dis.* 2011;52:5397-5428

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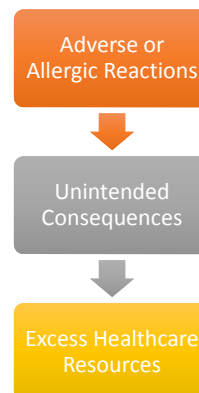
Regulatory Initiatives



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Antimicrobial Stewardship Programs

“Antimicrobial stewardship includes not only limiting inappropriate use but also **optimizing antimicrobial selection, dosing, route, and duration of therapy** to maximize clinical cure or prevention of infection while limiting the unintended consequences, such as the emergence of resistance, adverse drug events, and cost.”



Meslin — United States, January 4–April 2, 2015. MMWR. April 17, 2015.
Clin Infect Dis 2007;44:159-177.

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ASP Inpatient Uptake

7 Core Elements

Increase of hospital ASP practices from 40.9% to 48.1% in 2014-2015.

Small vs. Large

Hospitals with >200 beds were more likely to have an established ASP.

Conclusion

Comprehensive ASPs can be established in all facilities/sizes with leadership support.

Pollack LA. Clin Infect Dis. 2016;63:443-9.
O'Leary DN. Clin Infect Dis. 2017;65:1746-50.

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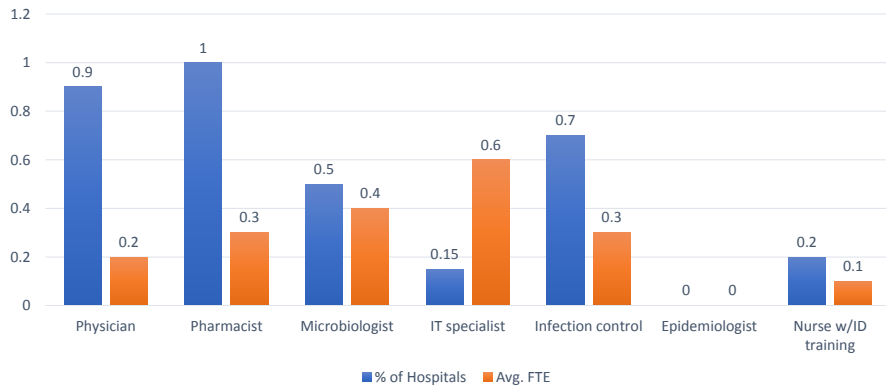
East Texas Data

Demographics	N=20 (%)
Institution setting	
Academic medical center	0
Community teaching hospital	5 (25)
Community non-teaching hospital	15 (75)
Average daily census	
0-199	19 (95)
≥200	1 (5)
Length of ASP program	
<6 months	8 (40)
6-11 months	4 (20)
≥1 years	8 (40)

Cho JC. J Hosp Infect. 2018;518:30260-3.

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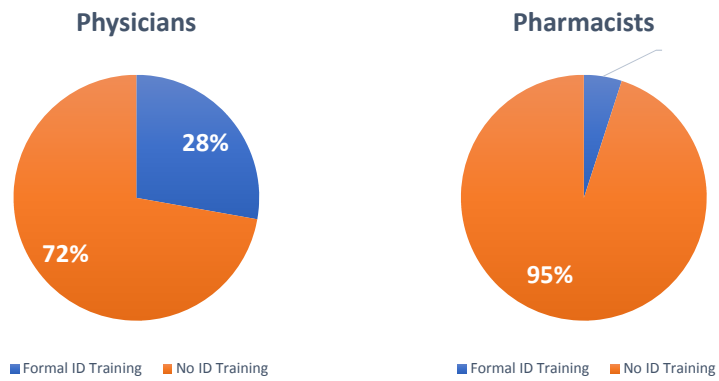
ASP Team Members and Resource Allocation



Cho J.C. J Hosp Infect. 2018;518:30260-3.

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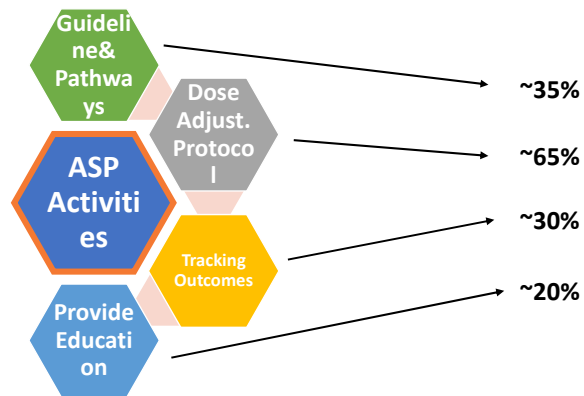
Formalized ID Training



Cho J.C. J Hosp Infect. 2018;518:30260-3.

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Stewardship Initiatives



Cho JC. J Hosp Infect. 2018;518:30260-3.

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Truth vs. Myth – Polling Slide

Antimicrobial usage rates differ between small and larger hospitals.

Antimicrobial resistance rates are lower in smaller hospitals.

- a) Truth
- b) Myth

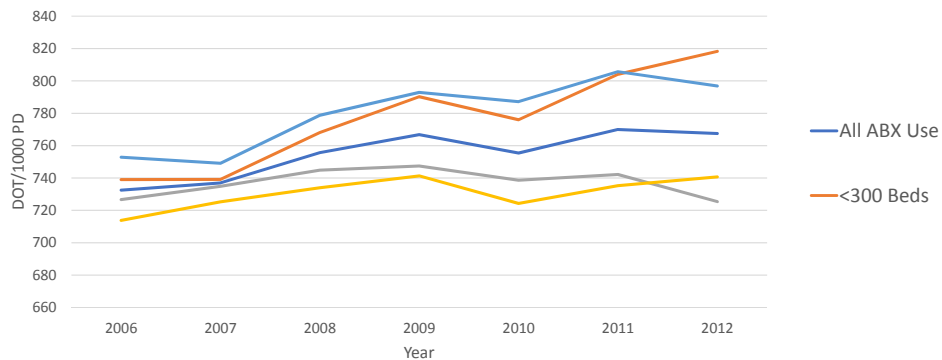
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Truth vs. Myth

- Setting**
 - Utah; National Healthcare and Safety Network Reports from 2011-2013
 - 15 small-community hospitals (SCHs) vs. 4 large-community hospitals (LCHs)
- Results**
 - SCHs (median, 436 DOT/1000PD) vs. LCHs (509 DOT/1000PD)
 - Broad-spectrum antibiotics accounted for 26% of use in SCHs and 32% in LCHs
- Key Points**
 - Antibiotic usage rates did not differ between SCHs and LCHs
 - Spectrum of antibiotics used did not differ between SCHs and LCHs

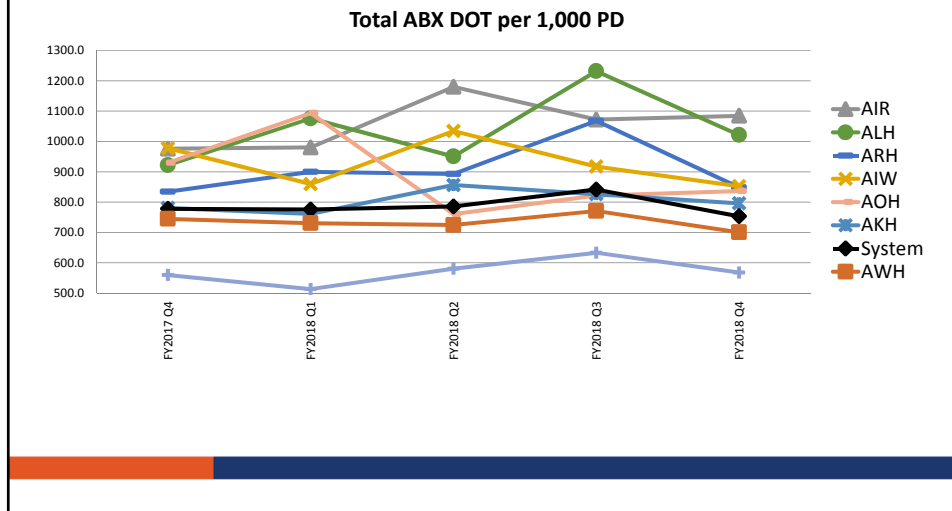
Stenehjem E. Clin Infect Dis. 2016;63:1273-80.

Estimates of Antibiotic Usage Trends



Baggs J. JAMA Intern Med. 2016;176:1639-48.

Estimates of Antibiotic Usage Trends



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What About the Outpatient Setting?

- >60% of ABX use occurs in outpatient settings
- At least 30% of antibiotic courses prescribed in the outpatient setting are unnecessary
 - No antibiotic is needed at all
- Total inappropriate antibiotic use may approach 50% of all outpatient antibiotic use
 - Unnecessary antibiotic use, inappropriate antibiotic selection, dosing, and duration
- Antibiotics are the most common cause of adverse drug events in children

CDC. <https://www.cdc.gov/od/oc/ohrt/antibiotic-use-in-outpatient-settings.html>

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ABX Prescriptions by Specialty

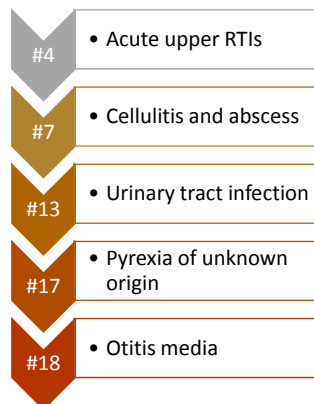
Provider specialty	No. antibiotic prescriptions	Percent of total ABX prescriptions
Family practice	61,000,000	23%
Physician Assistants & Nurse Practitioners		
Internal medicine	48,000,000	18%
Pediatrics	32,000,000	12%
Dentistry	27,000,000	10%
Emergency Medicine	25,000,000	9%
All providers (total)	268,600,000	100%

Hicks CD 2015: 60(9):1308-16; CDC. Outpatient antibiotic prescriptions — United States, 2013. Available via the internet: http://www.cdc.gov/getsmart/community/pdf/annual-reportsummary_2013.pdf

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20 Leading Primary Diagnosis

1. Abdominal pain
2. Chest pain
3. Confusion with intact skin surface
4. Acute upper respiratory infections, excluding pharyngitis
5. Spinal disorders
6. Open wound, excluding head
7. Cellulitis and abscess
8. Sprains and strains, excluding ankle and back
9. Fractures, excluding lower limb
10. Rheumatism, excluding back
11. Headache
12. Urinary tract infection
13. Open wound of head
14. Arthropathies and related disorders
15. Sprains and strains of neck and back
16. Diseases of the teeth and supporting structures
17. Pyrexia of unknown origin
18. Otitis media and eustachian tube disorders
19. Complications of pregnancy, childbirth
20. Asthma

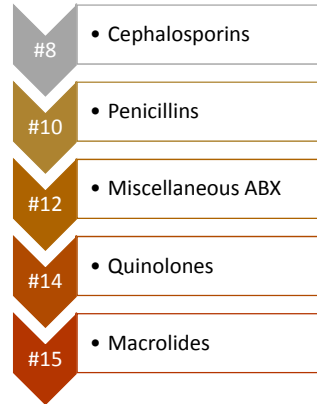


<http://www.cdc.gov/nchs/health/emergency-department.htm>
National Hospital Ambulatory Medical Care Survey, 2011 Emergency Department

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20 Frequently Used Medications

1. Analgesics
2. Antiemetic or antivertigo
3. Minerals and electrolytes
4. Anxiolytics, sedatives, hypnotics
5. Miscellaneous respiratory agents
6. Antihistamines
7. Bronchodilators
8. Cephalosporins
9. Adrenal cortical steroids
10. Penicillins
11. Anticonvulsants
12. Miscellaneous antibiotics
13. Antiparkinson agents
14. Quinolones
15. Macrolides
16. Antiarrhythmics
17. Dermatological agents
18. Local injectable anesthetics
19. Muscle relaxants
20. Antiplatelet agents



<http://www.cdc.gov/nchs/fastats/emergency-department.htm>
National Hospital Ambulatory Medical Care Survey, 2011 Emergency Department

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Newly Approved Antibiotics (2014-19)

- Gram (+) antibiotics
 - Dalbavancin (Dalvance)
 - Oritavancin (Orbactiv)
 - Tedizolid (Sivextro)
- Gram (-) antibiotics
 - Ceftolozane/tazobactam (Zerbaxa)
 - Ceftazidime/avibactam (Avycaz)
 - Meropenem/vaborbactam (Vabomere)
 - Plazomicin (Zemdri)
- “Combination” antibiotics
 - Delafloxacin (Baxdela)
 - Omadacycline (Nuzyra)
 - Eravacycline (Xerava)
- Future antibiotics
 - Cefiderocol
 - Fosfomycin IV
 - Iclaprim
 - Lefamulin
 - Imipenem-cilastatin/relebactam

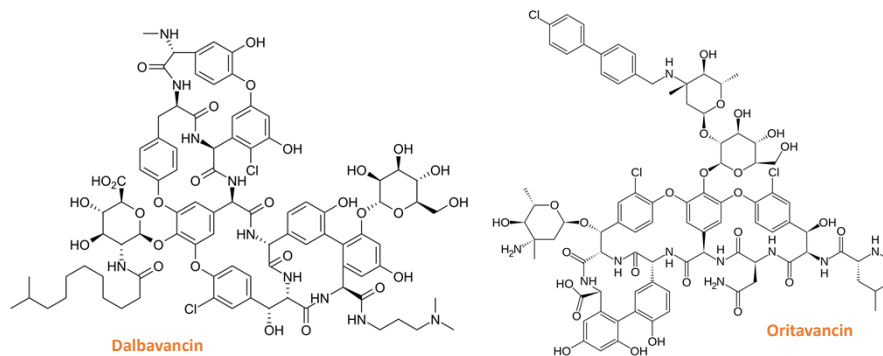
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To Add or Not To Add?

- Is this an innovative medication?
 - New indications
 - New spectrum of activity
- How does this medication compare to similar/existing medications?
- What are the adverse effect profiles?
 - Laboratory/monitoring costs need to be considered
 - Adverse effect management?!
- Is there a need for this medication?
- Direct medication cost (\$\$\$)

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Dalbavancin + Oritavancin



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Dalbavancin + Oritavancin

	Vancomycin	Daptomycin	Dalbavancin	Oritavancin
Therapeutic class	Glycopeptide	Lipopeptide	Lipoglycopeptide	Lipoglycopeptide
Spectrum of activity	MRSA	MRSA VRE	MRSA, VISA VanB	MRSA, VISA, VRSA VanA, VanB
Clinical pearls	Nephrotoxicity; "red man" syndrome	CPK elevation; sequestered by lung surfactant	Renal dosage adjustment; 30 min infusion	aPTT interaction; 3 hr infusion
Dosing	15mg/kg IV q12h	4mg/kg IV daily	1500mg IV x1	1200mg IV x1
Price (per vial)	\$3.02 (1000mg)	\$445.49 (500mg)	\$1316.25 (500mg)	\$915.40 (400mg)
Price (daily)	\$6.04	\$445.49	\$3948.75	\$2746.20
Formulary consideration	---	Yes, restricted	No, outpatient	No, outpatient

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Tedizolid

	Linezolid	Tedizolid
Therapeutic class	Oxazolidinone	Oxazolidinone
Spectrum of activity	MRSA, VISA, VRSA VRE	MRSA, VISA, VRSA VRE
Clinical pearls	Serotonin syndrome (DDI); thrombocytopenia; peripheral neuropathy; optic neuritis	Less MAO inhibition; less cumulative toxicity = less hematologic reactions
Dosing	600mg IV/PO q12h	200mg IV/PO daily
Price (per vial)	\$22.33	\$345.06
Price (per tablet)	\$4.73	\$433.19
Price (daily IV)	\$44.66	\$345.06
Price (daily PO)	\$9.46	\$433.19
Formulary consideration	Yes	No

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Ceftolozane/tazobactam

	Cefepime	Ceftolozane/tazobactam
Therapeutic class	Cephalosporin	Cephalosporin
Spectrum of activity	<i>Pseudomonas</i> sp.	<i>Pseudomonas</i> sp. (+++) ESBL
Clinical pearls		1 hour infusion
Dosing	1-2g IV q8h	1.5-3g IV q8h
Price (per vial)	\$3.14 (1g) \$5.58 (2g)	\$108.61 (1.5g)
Price (daily)	\$9.42 (1g) \$16.74 (2g)	\$325.83 (cUTI/cIAI) \$651.66 (HAP/VAP)
Formulary consideration	---	Yes, restricted

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Ceftazidime/avibactam

	Colistimethate sodium	Ceftazidime/avibactam
Therapeutic class	Polymyxin	Cephalosporin
Spectrum of activity	<i>Pseudomonas</i> sp. <i>Acinetobacter</i> sp. ESBL, CRE	<i>Pseudomonas</i> sp. ESBL CRE
Clinical pearls	Very bactericidal activity; nephrotoxicity; neurotoxicity; considered a last-line agent	2 hour infusion
Dosing	2.5-5mg/kg/day IV in divided doses	2.5g IV q8h
Price (per vial)	\$10.22 (150mg)	\$333.74
Price (daily)	\$20.44-\$30.66	\$1001.22
Formulary consideration	---	Yes, restricted

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Meropenem/vaborbactam

	Colistimethate sodium	Ceftazidime/avibactam	Meropenem/vaborbactam
Therapeutic class	Polymyxin	Cephalosporin	Carbapenem
Spectrum of activity	<i>Pseudomonas</i> sp. <i>Acinetobacter</i> sp. ESBL, CRE	<i>Pseudomonas</i> sp. ESBL CRE	<i>Pseudomonas</i> sp. ESBL CRE
Clinical pearls	Nephrotoxicity; neurotoxicity; considered a last-line agent	2 hour infusion	3 hour infusion
Dosing	2.5-5mg/kg/day IV in divided doses	2.5g IV q8h	4g IV q8h
Price (per vial)	\$10.22 (150mg)	\$333.74	\$141.88 (2g)
Price (daily)	\$20.44-\$30.66	\$1001.22	\$851.28
Formulary consideration	--	Yes, restricted	Yes, restricted

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Plazomicin

	Amikacin	Plazomicin
Therapeutic class	Aminoglycoside	Aminoglycoside
Spectrum of activity	<i>Pseudomonas</i> sp.	MRSA <i>Pseudomonas</i> sp. ESBL, CRE
Clinical pearls	Nephrotoxicity; ototoxicity; teratogenic	Nephrotoxicity; ototoxicity; teratogenic
Dosing	15mg/kg IV daily	15mg/kg IV daily
Price (per vial)	\$4.93 (500mg)	\$315 (500mg)
Price (daily)	\$9.86	\$630
Formulary consideration	---	No

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Delafloxacin

	Levofloxacin	Delafloxacin
Therapeutic class	Quinolone	Quinolone
Spectrum of activity	<i>Pseudomonas</i> sp., Atypicals	MRSA, <i>Pseudomonas</i> sp., Atypicals, Anaerobes
Clinical pearls	QTc prolongation; phototoxicity	Fewer DDIs and adverse reactions; PO option for <i>Pseudomonas</i> sp.
Dosing	750mg IV/PO daily	300mg IV q12h 450mg PO q12h
Price (per vial)	\$2.17	\$159.00
Price (per tablet)	\$0.23	\$85.05
Price (daily IV)	\$2.17	\$318
Price (daily PO)	\$0.23	\$170.10
Formulary consideration	---	No

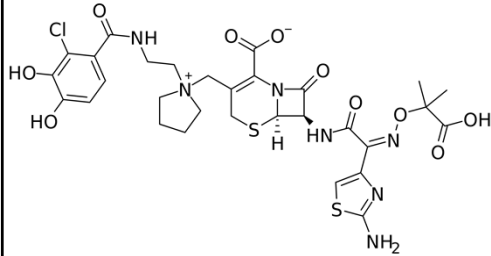
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Omadacycline + Eravacycline

	Tigecycline	Omadacycline	Eravacycline
Therapeutic class	Glycylcycline	Tetracycline	Tetracycline
Spectrum of activity	MRSA, VRE, ESBL, CRE, Anaerobes	MRSA, VRE, ESBL, CRE, Anaerobes	MRSA, VRE, ESBL, CRE, Anaerobes
Clinical pearls	BBW: increased mortality Severe N/V		
Dosing	100mg x1, 50mg IV q12h	200mg x1, 100mg IV daily 450mg day 1&2, 300mg PO daily	1mg/kg IV q12h
Price (per vial)	\$72.59 (50mg)	\$414 (100mg)	\$58.80 (50mg)
Price (per tablet)	---	\$237 (150mg)	---
Price (daily IV)	\$145.18	\$414	\$235.20
Price (daily PO)	---	\$474	---
Formulary consideration	---	???	???

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Cefiderocol



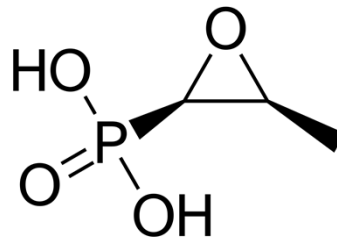
Cefiderocol	
Therapeutic class	Siderophore cephalosporin
Spectrum of activity	<i>Pseudomonas</i> sp. <i>Acinetobacter</i> sp. <i>Stenotrophomonas</i> sp. ESBL, CRE
Clinical pearls	Well-tolerated
Formulary consideration	Yes, restricted

- Current dosing studied: 2g IV q8h via 3-hr infusion
- Current indications studied: cUTI, CR-pathogens, HABP/VABP

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Fosfomicin IV

Fosfomicin	
Therapeutic class	Miscellaneous ABX
Spectrum of activity	MRSA, VRE <i>Pseudomonas</i> sp. ESBL, CRE
Clinical pearls	Phlebitis; hypokalemia; liver toxicity; skin reactions
Formulary consideration	Yes, restricted

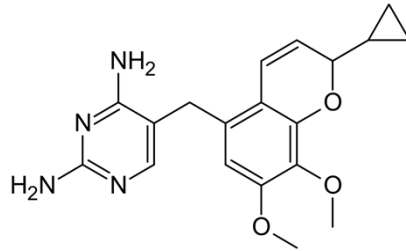


- Already available in countries outside of the United States
- Demonstrates synergy with other classes of antibiotics

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Iclaprim

Iclaprim	
Therapeutic class	Diaminopyrimidine
Spectrum of activity	<i>Streptococcus</i> sp. MRSA
Clinical pearls	Significant increases in LFTs and possible risk of thrombocytopenia
Formulary consideration	??? Possible cost savings/neutral?

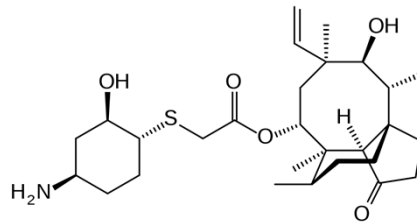


- Currently being studied for ABSSSI, HABP and VABP
- FDA required additional liver toxicity data before approval

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Lefamulin

Lefamulin	
Therapeutic class	Pleuromutilin
Spectrum of activity	<i>Streptococcus</i> sp. MRSA, VISA, VRE Atypicals MDR <i>N. gonorrhoeae</i>
Clinical pearls	Being studied for CABP Well-tolerated Both IV and PO
Formulary consideration	Probably



- Non-inferior to moxifloxacin ± linezolid for treatment of CABP

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Summary

- Many new antimicrobials recently approved/in the pipeline!
- Appropriate antimicrobial use is extremely important.
- Formulary considerations: spectrum of activity (need), cost, similarities vs. differences compared to existing agents.
- Direct antimicrobial costs is just one part of the equation.

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