IDentifying Updates in Infectious Disease

GMCCP Fall Event
November 2019

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IDentifying Updates in Infectious Disease

IDentifying the Therapeutic Role of New Antimicrobials and Vaccines

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Learning Objectives

1. Discuss therapeutic uses of new antimicrobials and vaccines
2. Apply knowledge of new antimicrobials and vaccines to patient cases

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ANTIBIOTICS

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New Antibiotics

Antibiotic	FDA-Approved Indications	Year Approved
Ceftolozane/tazobactam (Zerbaxa)	cIAI cUTI Bacterial Pneumonia	2014
Ceftazidime/avibactam (Avycaz)	cIAI cUTI	2015
Meropenem/vaborbactam (Vabomere)	cUTI	2017
Plazomicin (Zemdri)	cUTI	2018
Eravacycline (Xerava)	cIAI	2018
Imipenem/cilastatin/relebactam (Recarbrio)	cIAI cUTI	2019

cIAI: complicated intra-abdominal infection
cUTI: complicated urinary tract infection

https://www.centerwatch.com/drug-information/fda-approved-drugs/therapeutic-area/25/infections-and-infectious-diseases

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Abx	Staph	Strep	Entero-coccus	Atypical	Entero-bacteria-ceae	*Pseudo-monas* spp.	Anaerobe
C/T	Limited	X			X	X	Variable
Caz/Avi	Limited	X			X	X	Variable
M/V	X Not MRSA	X	Variable		X	X	X
I/C/R	X Not MRSA	X			X	X	X
Plaz	X (MRSA)				X	X	
Erava	X (MRSA)	X	X (VRE)	*Legionella*	X		X

C/T: ceftolozane/tazobactam; Caz/Avi: ceftazidime/avibactam; M/V: meropenem/ vaborbactam; I/C/R: imipenem/cilastatin/relebactam; Plaz: plazomicin; Erava: Eravacycline; Abx: antibiotics; Staph: *Staphylococcus* spp.; Strep: *Streptococcus* spp. MRSA: methicillin-resistant *S. aureus*; VRE: vancomycin-resistant *Enterococcus* spp.

Jorgensen SCJ. Pharmacother. 2018;38:444-461.
Karaiskos I. Front Public Health. 2019;7:151.
doi:10.3389/fpubh.2019.00151.
Shaeer KM. Pharmacotherapy. 2019;39:77.
Sharma R. Clin Therapeutics. 2016;38:43—444.
Zhanel GG. Drugs. 2014;74:31-51.
Zhanel GG. Drugs. 2016;76:567-588.
Zhanel GG. Drugs. 2018;78:65-98.

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CEFTOLOZANE/TAZOBACTAM (ZERBAXA)

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Ceftolozane/tazobactam

- Therapeutic class: beta-lactam/beta-lactamase inhibitor
- Mechanism of action
  - Ceftolozane
    - Inhibits penicillin-binding proteins and ultimately cell-wall synthesis
    - Similar to ceftazidime with modification allowing for increased potency against *Pseudomonas aeruginosa*
  - Tazobactam: irreversibly inhibits beta-lactamases via secondary ring opening at the beta-lactamase active site

Zhanel GG. Drugs. 2014;74:31-51.

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Abx	Staph	Strep	Entero-coccus	Atypical	Entero-bacteria-ceae	*Pseudo-monas* spp.	Anaerobe
C/T	Limited	X			X	X	Variable
Caz/Avi	Limited	X			X	X	Variable
M/V	X Not MRSA	X	Variable		X	X	X
I/C/R	X Not MRSA	X			X	X	X
Plaz	X (MRSA)				X	X	
Erava	X (MRSA)	X	X (VRE)	*Legionella*	X		X

C/T: ceftolozane/tazobactam; Caz/Avi: ceftazidime/avibactam; M/V: meropenem/ vaborbactam; I/C/R: imipenem/cilastatin/relebactam; Plaz: plazomicin; Erava: Eravacycline; Abx: antibiotics; Staph: *Staphylococcus* spp.; Strep: *Streptococcus* spp. MRSA: methicillin-resistant *S. aureus*; VRE: vancomycin-resistant *Enterococcus* spp.

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Zhanel GG. Drugs. 2014;74:31-51.
Zhanel GG. Drugs. 2016;76:567-588.
Zhanel GG. Drugs. 2018;78:65-98.

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Spectrum of Activity

- *Pseudomonas aeruginosa*
  - Stable against many efflux pumps, porin loss and modified penicillin-binding proteins
- Not reliable against:
  - Extended-spectrum beta-lactamase (ESBL)-producing organisms
  - AmpC beta-lactamase-producing organisms
  - Carbapenemase-producing organisms
  - *Acinetobacter baumannii*
  - Gram-negative anaerobes (use in combination with metronidazole)

Zhanel GG. Drugs. 2014;74:31-51.

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Therapeutic Use

- Food and Drug Administration (FDA)-approved for:
  - Complicated UTI (cUTI)
  - Complicated intra-abdominal infection (cIAI)
  - Hospital-acquired (HAP) or ventilator-associated pneumonia (VAP)
- Multidrug-resistant *Pseudomonas aeruginosa* (confirmed or empiric in appropriate patient)

Ceftolozane/tazobactam. In: Lexidrugs. Lexicomp (Accessed 2019 Nov 9).
Zhanel GG. Drugs. 2014;74:31-51.

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Dosing and Administration

- Dose dependent on indication and organ function

	cIAI/cUTI	HAP/VAP
Normal Dose	1.5 g IV every 8 hours	3 g IV every 8 hours
CrCl 30-50 mL/min	750 mg IV every 8 hours	1.5 g IV every 8 hours
CrCl 15-29 mL/min	375 mg IV every 8 hours	750 mg IV every 8 hours
CrCl <15 mL/min	Not studied	Not studied
Hemodialysis	750 mg IV once, then 150 mg IV every 8 hours	2.25 g IV once, then 450 mg IV every 8 hours

CrCl: creatinine clearance; mL: milliliters; min: minute; g: gram; IV: intravenous; mg: milligram

- Administer each dose over 1 hour

Ceftolozane/tazobactam. In: Lexidrugs. Lexicomp (Accessed 2019 Nov 9).
Zhanel GG. Drugs. 2014;74:31-51.

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Considerations

- Adverse effects
  - Positive direct Coombs test (higher doses)
  - Increased LFTs (higher doses)
- Drug interactions
  - Warfarin (increased risk of bleeding)

Ceftolozane/tazobactam. In: Lexidrugs. Lexicomp (Accessed 2019 Nov 9).

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Clinical Trial Highlights

- Ceftolozane/tazobactam vs polymyxin or aminoglycoside-based regimens for *Pseudomonas aeruginosa*
- Results
  - Hospital mortality – no difference between groups
  - Clinical cure – ceftolozane/tazobactam independently associated with cure (adjusted Odds Ratio [OR]: 2.63, 95% confidence interval [CI]: 1.31-5.30)
  - Adverse effects - ceftolozane/tazobactam was protective against acute kidney injury (adjusted OR 0.08, 95% CI: 0.03-0.22)

Pogue JM. Clin Infect Dis. 2019; doi:10.1093/cid/ciz816.

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CEFTAZIDIME/AVIBACTAM (AVYCAZ)

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Ceftazidime/avibactam

- Therapeutic class: beta-lactam/beta-lactamase inhibitor
- Mechanism of Action
  - Ceftazidime: Binds to penicillin-binding proteins to ultimately inhibit cell-wall synthesis
  - Avibactam
    - Non-beta-lactam beta-lactamase inhibitor
    - Reversibly binds to the beta-lactamase enzyme

Sharma R. Clin Therapeutics. 2016;38:43—444.

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C/T	Limited	X			X	X	Variable
Caz/Avi	Limited	X			X	X	Variable
M/V	X Not MRSA	X	Variable		X	X	X
I/C/R	X Not MRSA	X			X	X	X
Plaz	X (MRSA)				X	X	
Erava	X (MRSA)	X	X (VRE)	*Legionella*	X		X

C/T: ceftolozane/tazobactam; Caz/Avi: ceftazidime/avibactam; M/V: meropenem/ vaborbactam; I/C/R: imipenem/cilastatin/relebactam; Plaz: plazomicin; Erava: Eravacycline; Abx: antibiotics; Staph: *Staphylococcus* spp.; Strep: *Streptococcus* spp. MRSA: methicillin-resistant *S. aureus*; VRE: vancomycin-resistant *Enterococcus* spp.

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Zhanel GG. Drugs. 2018;78:65-98.

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Spectrum of Activity

- Gram-negative resistant pathogens including:
  - ESBL-producing organisms
  - AmpC-producing organisms
  - *Klebsiella pneumoniae* carbapenemases (KPC)- and OXA-producing organisms
- Not reliable against:
  - *Acinetobacter baumannii*
  - Metallo beta-lactamases (New Dehli Metallo Beta-Lactamase [NDM])
  - Gram-negative anaerobes (use in combination with metronidazole)

Sharma R. Clin Therapeutics. 2016;38:43—444.

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Therapeutic Use

- FDA-approved for
  - cUTI
  - cIAI
  - HAP/VAP
- Consider as first line therapy option for KPC-producing organisms

Ceftazidime/avibactam. In: Lexidrugs. Lexicomp (Accessed 2019 Nov 9).

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Dosing and Administration

- Dependent on renal function

Renal Function	Dose
CrCl > 50 mL/min	2.5 g IV every 8 hours
CrCl 31-50 mL/min	1.25 g IV every 8 hours
CrCl 16-30 mL/min	0.94 g IV every 12 hours
CrCl 6-15 mL/min	0.94 g IV every 24 hours
CrCl < 6 mL/min	0.94 g IV every 48 hours
Hemodialysis	0.94 g IV every 24-48 hours

CrCl: creatinine clearance; mL: milliliters; min: minute; g: grams; IV: intravenous

- Administer each dose over 2 hours

Ceftazidime/avibactam. In: Lexidrugs. Lexicomp (Accessed 2019 Nov 9).
Sharma R. Clin Therapeutics. 2016;38:43—444.

20

Considerations

- Adverse effects
  - Positive direct Coombs test
  - Neurotoxicity (more likely with renal impairment)
- Drug interactions
  - Nephrotoxic drugs (aminoglycosides, loop diuretics) – nephrotoxicity may be potentiated by ceftazidime/avibactam
  - Warfarin (may increase INR)

Ceftazidime/avibactam. In: Lexidrugs. Lexicomp (Accessed 2019 Nov 9).
Sharma R. Clin Therapeutics. 2016;38:43—444.

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Clinical Trial Highlights

- Ceftazidime/avibactam as salvage therapy for KPC-producing *K. pneumoniae*
  - Ceftazidime/avibactam was started as salvage after a median duration of 7 days
  - Combination therapy with another active agent occurred in 78.9% of cases
  - 30-day mortality in patients with bacteremia
    - Ceftazidime/avibactam-containing regimen: 36.5% P=0.005
    - Alternative agents: 55.8%
    - Use of ceftazidime/avibactam independently predicted survival

Tumbarello M. Clin Infect Dis. 2019;68:355—364.

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MEROPENEM/VABORBACTAM (VABOMERE)

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Meropenem/vaborbactam

- Therapeutic class: beta-lactam/beta-lactamase inhibitor
- Mechanism of Action
  - Meropenem: inhibits penicillin-binding proteins and ultimately cell-wall synthesis
  - Vaborbactam
    - Non-beta-lactam boronic acid beta-lactamase inhibitor
    - Boronic acid binds to serine in certain beta-lactamases to form a reversible covalent bond

Jorgensen SCJ. Pharmacother. 2018;38:444-461.

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Abx	Staph	Strep	Entero-coccus	Atypical	Entero-bacteria-ceae	*Pseudo-monas* spp.	Anaerobe
C/T	Limited	X			X	X	Variable
Caz/Avi	Limited	X			X	X	Variable
M/V	X Not MRSA	X	Variable		X	X	X
I/C/R	X Not MRSA	X			X	X	X
Plaz	X (MRSA)				X	X	
Erava	X (MRSA)	X	X (VRE)	*Legionella*	X		X

C/T: ceftolozane/tazobactam; Caz/Avi: ceftazidime/avibactam; M/V: meropenem/ vaborbactam; I/C/R: imipenem/cilastatin/relebactam; Plaz: plazomicin; Erava: Eravacycline; Abx: antibiotics; Staph: *Staphylococcus* spp.; Strep: *Streptococcus* spp. MRSA: methicillin-resistant *S. aureus*; VRE: vancomycin-resistant *Enterococcus* spp.

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Zhanel GG. Drugs. 2014;74:31-51.
Zhanel GG. Drugs. 2016;76:567-588.
Zhanel GG. Drugs. 2018;78:65-98.

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Spectrum of Activity

- Gram-negative resistant pathogens, including ESBL-, AmpC-, and KPC-producing organisms
- Does not add additional activity over meropenem alone for certain pathogens
  - *Pseudomonas aeruginosa*
  - *Acinetobacter baumannii*
- Not reliable against
  - Metallo beta-lactamases
  - OXA beta-lactamases

Jorgensen SCJ. Pharmacother. 2018;38:444-461.

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Therapeutic Use

- FDA-approved for cUTI
- Consider as first line therapy for KPC-producing Enterobacteriaceae

Meropenem/vaborbactam. In: Lexidrugs. Lexicomp (Accessed 2019 Nov 9).
Jorgensen SCJ. Pharmacother. 2018;38:444-461.

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Dosing and Administration

- Dependent on renal function

Renal Function (mL/min/1.73 m^2)	Dose
eGFR $\geq$ 50	4 g IV every 8 hours
eGFR 30-49	2g IV every 8 hours
eGFR 15-29	2g IV every 12 hours
eGFR < 15	1 g IV every 12 hours

eGFR: estimated glomerular filtration rate; mL: milliliters; min: minute; g: grams; IV: intravenous

- Administer each dose over 3 hours

Meropenem/vaborbactam. In: Lexidrugs. Lexicomp (Accessed 2019 Nov 9).
Jorgensen SCJ. Pharmacother. 2018;38:444-461.

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Considerations

- Adverse effects and drug interactions are similar as with meropenem alone

Meropenem/vaborbactam. In: Lexidrugs. Lexicomp (Accessed 2019 Nov 9).
Jorgensen SCJ. Pharmacother. 2018;38:444-461.

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Clinical Trial Highlights – TANGO II

- 28-day all cause mortality
  - Meropenem/vaborbactam: 15.6%
  - Best-available therapy: 33.3%

  P=0.20
- Clinical cure
  - Meropenem/vaborbactam: 65.6%
  - Best-available therapy: 33.3%

  P=0.03
- Renal impairment
  - Meropenem/vaborbactam: 31.3%
  - Best-available therapy: 80.0%

  P<0.001

Wunderink RG et al. Infect Dis Ther. 2018; 7:439-55.

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IMIPENEM/CILASTATIN/RELEBACTAM (RECARBRIO)

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Imipenem/cilastatin/relebactam

- Therapeutic class: beta-lactam/beta-lactamase inhibitor
- Mechanism of Action
  - Imipenem: inhibits penicillin-binding proteins and ultimately cell-wall synthesis
  - Cilastatin: dehydropeptidase (DHP)-1 inhibitor (prevents imipenem degradation)
  - Relebactam: non-beta-lactam beta-lactamase inhibitor, related to avibactam

Zhanel GG. Drugs. 2018;78:65-98.

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Abx	Staph	Strep	Entero-coccus	Atypical	Entero-bacteria-ceae	*Pseudo-monas* spp.	Anaerobe
C/T	Limited	X			X	X	Variable
Caz/Avi	Limited	X			X	X	Variable
M/V	X Not MRSA	X	Variable		X	X	X
I/C/R	X Not MRSA	X			X	X	X
Plaz	X (MRSA)				X	X	
Erava	X (MRSA)	X	X (VRE)	*Legionella*	X		X

C/T: ceftolozane/tazobactam; Caz/Avi: ceftazidime/avibactam; M/V: meropenem/ vaborbactam; I/C/R: imipenem/cilastatin/relebactam; Plaz: plazomicin; Erava: Eravacycline; Abx: antibiotics; Staph: *Staphylococcus* spp.; Strep: *Streptococcus* spp. MRSA: methicillin-resistant *S. aureus*; VRE: vancomycin-resistant *Enterococcus* spp.

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Zhanel GG. Drugs. 2014;74:31-51.
Zhanel GG. Drugs. 2016;76:567-588.
Zhanel GG. Drugs. 2018;78:65-98.

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Spectrum of Activity

- Gram-negative resistant pathogens, including ESBL-, AmpC-, and KPC-producing organisms
- Demonstrates increased activity over imipenem/cilastatin for *P. aeruginosa*
- Not reliable against
  - Metallo beta-lactamases
  - OXA beta-lactamases
  - Does not add additional activity over imipenem/cilastatin alone for *A. baumannii*

Zhanel GG. Drugs. 2018;78:65-98.

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Therapeutic Use

- FDA-approved for
  - cIAI
  - cUTI
- May be considered as first line therapy for KPC-producing organisms – too soon to tell

Imipenem/cilastatin/relebactam. In: Lexidrugs. Lexicomp (Accessed 2019 Nov 9).
Zhanel GG. Drugs. 2018;78:65-98.

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Dosing and Administration

- Dependent on renal function

Renal Function	Dose
CrCl > 90 mL/min	1.25g IV every 6 hours
CrCl 60-89 mL/min	1g IV every 6 hours
CrCl 30-59 mL/min	750 mg IV every 6 hours
CrCl 15-29 mL/min and hemodialysis	500 mg IV every 6 hours
CrCl < 15 mL/min	Do not administer, unless on hemodialysis

CrCl: creatinine clearance; mL: milliliters; min: minute; g: grams; IV: intravenous

- Administered as 30-minute intermittent infusion due to poor stability

Imipenem/cilastatin/relebactam. In: Lexidrugs. Lexicomp (Accessed 2019 Nov 9).
Zhanel GG. Drugs. 2018;78:65-98.

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Considerations

- Adverse effects and drug interactions are similar as with imipenem/cilastatin alone

Imipenem/cilastatin/relebactam. In: Lexidrugs. Lexicomp (Accessed 2019 Nov 9).
Zhanel GG. Drugs. 2018;78:65-98.

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Clinical Trial Highlights – RESTORE-IMI 1

- 28-day mortality
  - Imipenem/relebactam: 10% 95% CI: -46.4 to 6.7
  - Imipenem plus colistin: 30%
- 19% of patients had a KPC-producing infection

Motsch J. *Clin Infect Dis.* 2019; pii: ciz530. doi: 10.1093/cid/ciz530.

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PLAZOMICIN (ZEMDRI)

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Plazomicin

- Therapeutic Class: aminoglycoside
- Mechanism of Action
  - Bactericidal
  - Protein synthesis inhibitor: binds to 30S ribosomal subunit

Shaeer KM. Pharmacotherapy. 2019;39:77.

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Abx	Staph	Strep	Entero-coccus	Atypical	Entero-bacteria-ceae	*Pseudo-monas* spp.	Anaerobe
C/T	Limited	X			X	X	Variable
Caz/Avi	Limited	X			X	X	Variable
M/V	X Not MRSA	X	Variable		X	X	X
I/C/R	X Not MRSA	X			X	X	X
Plaz	X (MRSA)				X	X	
Erava	X (MRSA)	X	X (VRE)	*Legionella*	X		X

C/T: ceftolozane/tazobactam; Caz/Avi: ceftazidime/avibactam; M/V: meropenem/ vaborbactam; I/C/R: imipenem/cilastatin/relebactam; Plaz: plazomicin; Erava: Eravacycline; Abx: antibiotics; Staph: *Staphylococcus* spp.; Strep: *Streptococcus* spp. MRSA: methicillin-resistant *S. aureus*; VRE: vancomycin-resistant *Enterococcus* spp.

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Zhanel GG. Drugs. 2014;74:31-51.
Zhanel GG. Drugs. 2016;76:567-588.
Zhanel GG. Drugs. 2018;78:65-98.

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Spectrum of Activity

- Expanded gram-negative spectrum from other currently available aminoglycosides
  - Carbapenem-resistant Enterobacteriaceae: KPC- and NDM-producing organisms
  - ESBL-producing Enterobacteriaceae
  - Not susceptible to aminoglycoside modifying enzymes (may have activity when other aminoglycosides do not)
- Not reliable against
  - *Streptococcus* spp. and *Enterococcus* spp.
  - *Acinetobacter* spp.

Shaeer KM. Pharmacotherapy. 2019;39:77.

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Therapeutic Use

- FDA-approved for the treatment of cUTI
  - May be useful when organism is resistant to other aminoglycosides
- Option for treatment of NDM-producing Enterobacteriaceae

Plazomicin. In: Lexidrugs. Lexicomp (Accessed 2019 Nov 9).
Shaeer KM. Pharmacotherapy. 2019;39:77.

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Dosing and Administration

- Dependent on renal function

Renal Function	Dose
CrCl ≥ 60 mL/min	15 mg/kg IV daily
CrCl 30-59 mL/min	10 mg/kg IV daily
CrCl 15-29 mL/min	10 mg/kg IV every 48 hours
CrCl < 15, dialysis	Not studied

CrCl: creatinine clearance; mL: milliliters; min: minute; mg: milligram; kg: kilogram; IV: intravenous

- Use actual/total body weight unless actual/total weight is 25% or more above ideal body weight
- If actual/total body weight is 25% or more above ideal, use adjusted body weight

Plazomicin. In: Lexidrugs. Lexicomp (Accessed 2019 Nov 9).

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Dosing and Administration

- Therapeutic drug monitoring recommended
  - Goal trough (30 minutes prior to dose): < 3 mcg/mL

Renal Function	Dose Adjustment for Trough ≥ 3 mcg/mL
CrCl ≥ 60 mL/min	Change interval to every 36 hours
CrCl 30-59 mL/min	Change interval to every 36 hours
CrCl 15-29 mL/min	Change interval to every 72 hours

CrCl: creatinine clearance; mL: milliliters; min: minute; mcg: microgram

- Each dose is administered over 30 minutes

Plazomicin. In: Lexidrugs. Lexicomp (Accessed 2019 Nov 9).
Shaeer KM. Pharmacotherapy. 2019;39:77.

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Considerations

- Adverse effects
  - Nephrotoxicity
  - Neurotoxicity
  - Adverse effects were reported at lower incidences than older aminoglycosides; however short duration of therapy must be considered
- Drug interactions
  - Concomitant nephrotoxins

Plazomicin. In: Lexidrugs. Lexicomp (Accessed 2019 Nov 9).
Shaeer KM. Pharmacotherapy. 2019;39:77.

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Clinical Trial Highlights

- Plazomicin vs meropenem for cUTI
  - Optional step-down to oral therapy after 4 days of IV therapy for a total duration of 7-10 days
  - Results
    - Composite cure (clinical cure and microbiological cure)
      - Plazomicin: 88.0% at day 5 and 81.7% at days 15-19
      - Meropenem: 91.4% ad day 5 and 70.1% at days 15-19
    - Higher microbiologic eradication found with plazomicin at day 5
      - Including ESBL-producing Enterobacteriaceae and organisms demonstrating aminoglycoside resistance

Wagenlehner FME. N Engl J Med. 2019;380:729.

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ERAVACYCLINE

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Eravacycline

- Therapeutic Class: tetracycline (fluorocycline)
- Mechanism of Action
  - Bacteriostatic
    - Some cidal activity has been demonstrated against *Klebsiella pneumoniae* and *Escherichia coli*
  - Protein synthesis inhibitor: binds to 30S ribosomal subunit

Zhanel GG. Drugs. 2016;76:567-588.
Xerava (Eravacycline). Package Insert. 2018.

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C/T	Limited	X			X	X	Variable
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M/V	X Not MRSA	X	Variable		X	X	X
I/C/R	X Not MRSA	X			X	X	X
Plaz	X (MRSA)				X	X	
Erava	X (MRSA)	X	X (VRE)	*Legionella*	X		X

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Spectrum of Activity

- Expanded coverage of resistant organisms
  - Gram-positive: Methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus* spp.
  - Gram-negative:
    - ESBL-producing organisms
    - Carbapenemase-producing organisms (KPC, NDM, OXA)
    - *Acinetobacter baumannii*

Karaiskos I. Front Public Health. 2019;7:151. doi:10.3389/fpubh.2019.00151.
Zhanel GG. Drugs. 2016;76:567-588.

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Therapeutic Use

- FDA-approved for the treatment of cIAI
- Evaluated for cUTI and failed to meet non-inferiority compared to levofloxacin and ertapenem

Eravacycline. In: Lexidrugs. Lexicomp (Accessed 2019 Nov 9).
Karaiskos I. Front Public Health. 2019;7:151. doi:10.3389/fpubh.2019.00151.

52

Dosing and Administration

- Normal dose: 1 mg/kg IV every 12 hours
- Administer each dose over 60 minutes
- Dependent on hepatic function
  - Child Pugh Class C hepatic impairment
    - 1 mg/kg IV every 12 hours on day 1, then
    - 1 mg/kg IV every 24 hours
- Dependent on drug interactions
  - Strong CYP3A inducers: 1.5 mg/kg IV every 12 hours

Eravacycline. In: Lexidrugs. Lexicomp (Accessed 2019 Nov 9).
Xerava (Eravacycline). Package Insert. 2018.

53

Considerations

- Adverse effects
  - Infusion reactions (thrombophlebitis)
  - Nausea/vomiting
  - Tooth discoloration (pregnancy, age < 8)
- Drug interactions
  - Strong CYP3A inducers: rifampin, phenytoin, carbamazepine, phenobarbital
  - Warfarin (increased INR)

Eravacycline. In: Lexidrugs. Lexicomp (Accessed 2019 Nov 9).
Xerava (Eravacycline). Package Insert. 2018.
Zhanel GG. Drugs. 2016;76:567-588.

54

Clinical Trial Highlights – IGNITE 4

- Eravacycline vs meropenem for cIAI
- Results
  - Clinical cure (all organisms)
    - Eravacycline: 90.8%
    - Meropenem: 91.2%
  - Clinical cure (ESBL-producing organisms)
    - Eravacycline: 87.5%
    - Meropenem: 84.6%

Solomkin JS. Clin Infect Dis. 2019;69:921-929.

55

A 55-year-old female patient currently undergoing chemotherapy for acute leukemia was admitted to the hospital with fevers and dysuria 2 days ago. The patient was found to have a urinary tract infection growing > 100,000 cfu/mL of *Pseudomonas aeruginosa* that was found to be resistant to amikacin/tobramycin, cefepime, ceftazidime, imipenem, and piperacillin/tazobactam.

What would be the best antibiotic to treat at this time in the absence of further testing?

A. Meropenem/vaborbactam
B. Ceftazidime/avibactam
C. Ceftolozane/tazobactam
D. Plazomicin

56

Which of the following antibiotics can be used for the treatment of infections harboring a *Klebsiella pneumoniae* carbapenemase (more than 1 answer may apply)?

A. Ceftolozane/tazobactam
B. Meropenem/vaborbactam
C. Eravacycline
D. Ceftazidime/avibactam

57

Summary

- Ceftolozane/tazobactam is best used for MDR *Pseudomonas aeruginosa* infections
- Novel beta-lactamase inhibitors expand beta-lactam spectrum of activity to cover KPC-producing organisms
  - Ceftazidime/avibactam (also covers OXA producers)
  - Meropenem/vaborbactam
  - Imipenem/cilastatin/relebactam
- Plazomicin covers NDM, KPC and ESBL producers
  - TDM data best described for UTIs
- Eravacycline has broad spectrum carbapenemase coverage and MDR *Acinetobacter baumannii* coverage (but not *Pseudomonas aeruginosa* coverage)

58

VACCINES

59

Human Papilloma Virus (HPV) Vaccine

- Brand name: Gardasil
- Current version contains 9 viral subtypes
- Most effective if administered before exposure
- Administration can prevent HPV-related cancers and genital warts

https://www.cdc.gov/hpv/hcp/schedules-recommendations.html. Accessed 2019 November 11.
Gardasil. In: Lexidrugs. Lexicomp (Accessed 2019 Nov 11).

60

Human Papilloma Virus Vaccine

- Centers for Disease Control and Prevention (CDC) recommendations
  - 2-dose series
    - Patients aged 9-14 years (male and female)
    - Second dose given 6-12 months after first
  - 3-dose series
    - Patients aged 15-26 years (male and female)
    - Second dose 1-2 months after first
    - Third dose 6 months after first
  - No need to repeat doses if timeframe exceeded
  - Any product may be used to complete series

https://www.cdc.gov/hpv/hcp/schedules-recommendations.html. Accessed 2019 November 11.

61

Human Papilloma Virus Vaccine

- Patients aged 27 or older
  - FDA-approved from ages 27 through 45
  - CDC recommendations state decision to vaccinate should be determined by patient and provider based on risks and benefits

https://www.cdc.gov/hpv/hcp/schedules-recommendations.html. Accessed 2019 November 11.
Gardasil. In: Lexidrugs. Lexicomp (Accessed 2019 Nov 11).

62

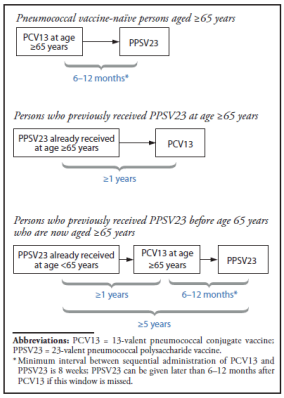
Pneumococcal Vaccines

- Brand names
  - Prevnar-13 (pneumococcal conjugate)
  - Pneumovax-23 (pneumococcal polysaccharide)
- Vaccination recommendations
  - Prevnar-13 is administered as part of routine childhood vaccination schedule
  - Both vaccines are recommended in immunosuppressed patients
  - Pneumovax-23 is recommended for certain chronic conditions and smokers
  - Adults 65 years and older??

https://www.cdc.gov/vaccines/vpd/pneumo/. Accessed 2019 November 11.

63

Adults 65 and Older



https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6337a4.htm. Accessed 2019 November 11.

64

Adults 65 and Older

- CDC's Advisory Committee on Immunization Practices (ACIP) changed their recommendation on use of Prevnar-13 earlier this year
  - Current vaccine recommendations by CDC do not reflect this
- If patients have not received Prevnar-13 after age 65, it is no longer recommended
  - Due to declining rates of disease covered by Prevnar-13
  - Prevnar-13 may still be administered based upon a decision between provider and patient
  - Pneumovax-23 is still recommended

https://www.healio.com/infectious-disease/vaccine-preventable-diseases/news/online/%7B08133dca-8136-42d7-a679-027c27a3cdfa%7D/acip-changes-recommendations-for-hpv-pneumococcal-vaccines. Accessed 2019 November 11.

65

Meningococcal B Vaccine

- Brand names
  - Bexsero: given as 2 doses, separated by at least 1 month
  - Trumenba
    - Given as 3 doses at 0 months, 1-2 months, and 6 months
    - If time between 1st and 2nd dose is 6 months or greater, a third dose is not needed
- Products are not interchangable

https://www.cdc.gov/mmwr/volumes/66/wr/mm6619a6.htm. Accessed 2019 November 11.
Meningococcal Group B vaccine. In: Lexidrugs. Lexicomp (Accessed 2019 Nov 11).

66

Meningococcal B Vaccine

- Booster doses are recommended for those at increased risk of disease
  - Complement deficiency
  - Asplenia
  - Microbiologists
  - Outbreaks
- 1 year after primary series then every 2-3 years while still at risk
- Approved by ACIP in June 2019, not yet on CDC website

https://www.immunize.org/askexperts/experts_meningococcal_b.asp. Accessed 2019 November 11.

67

Meningococcal B Vaccine

- May be recommended for patients aged 16-23 years with risk for meningococcal disease
  - College attendees
  - Local disease outbreak
- Should be recommended for patients with
  - Complement deficiencies or complement inhibitor drug therapy (eculizumab)
  - Asplenia
  - Microbiologists exposed at work

https://www.cdc.gov/vaccines/vpd/mening/index.html. Accessed 2019 November 11.

68

Influenza – Live-attenuated Virus Vaccine (FluMist)

- Returned as an option in 2018 after it was not recommended for 2 years for patients aged 2-50 years
  - Removed in 2015 due to low performance against H1N1 2009 pandemic strain
  - New strain of H1N1 incorporated into vaccine that showed improved immunogenicity

http://www.cidrap.umn.edu/news-perspective/2018/02/cdc-vaccine-panel-brings-back-flumist-2018-19-season. Accessed 2019 November 11.
Influenza Virus Vaccine (Live/Attenuated). In: Lexidrugs. Lexicomp (Accessed 2019 Nov 11)

69

Recombinant Herpes Zoster Vaccine (Shingrix)

- Indicated for healthy adults aged 50 years and older to prevent herpes zoster and post-herpetic neuralgia
  - 2 dose series at 0 and 2-6 months
  - Administer even if prior shingles infection
  - Administer even if patient had received live, attenuated herpes zoster vaccine (Zostavax)
- Immunosuppressed patients
  - Recommended in those taking low-dose immunosuppressive medications
  - Not recommended for severe immunocompromise although studies suggest benefit in hematologic malignancy

https://www.cdc.gov/vaccines/vpd/shingles/public/shingrix/#who-should-not-get-shingrix. Accessed 2019 Nov 11
Zoster Vaccine (Recombinant). In: Lexidrugs. Lexicomp (Accessed 2019 Nov 11)
Dagnew AF. Lancet Infect Dis. 2019;19:988-1000

70

A 65-year old male patient presents to his primary care provider for an annual check-up. His past medical history is significant for hypertension which is controlled on lisinopril 20 mg po daily. The patient has a significant needle phobia and wishes to receive the minimal amount of injections for vaccines as possible. What vaccination recommendation would you make (no prior vaccines have been given this year)?

A. Prevnar-13 and inactivated influenza vaccine
B. Pneumovax and inactivated influenza vaccine
C. Pneumovax and live-attenuated influenza vaccine
D. Prevnar-13 and live-attenuated influenza vaccine

71

Which of the following vaccines is recommended to have a booster dose 1 year after completion of the primary series?

A. Meningococcal B vaccine
B. HPV vaccine
C. Prevnar-13 vaccine
D. Pneumovax vaccine

72

Summary

- HPV vaccine is recommended for all males and females aged 9-14 years old
  - May be administered to patients aged 27-45 years based on risk
- Prevnar 13 (pneumococcal conjugate) vaccine may not be necessary for patients aged 65 years or older
- Meningococcal b vaccine should have booster doses administered at 1 year then every 2-3 years for patients at increased risk
- FluMist may now be recommended for patients aged 2-50 years
- Shingrix is recommended for all healthy patients aged 50 years or older and may provide benefit in some immunocompromised patients

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IDentifying Updates in Infectious Disease

IDentifying the Therapeutic Role of New Antimicrobials and Vaccines

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Antimicrobial Pharmacokinetics

PEAKING Your Practicality, Not Just TROUGHING it Out

Lynne Fehrenbacher, PharmD, BCPS-AQ ID
Associate Professor of Pharmacy Practice
Concordia University Wisconsin School of Pharmacy

75

Objectives

- Compare and contrast pharmacokinetic approaches to vancomycin dosing and monitoring
- Construct a practical approach to antimicrobial pharmacokinetic monitoring that incorporates learners

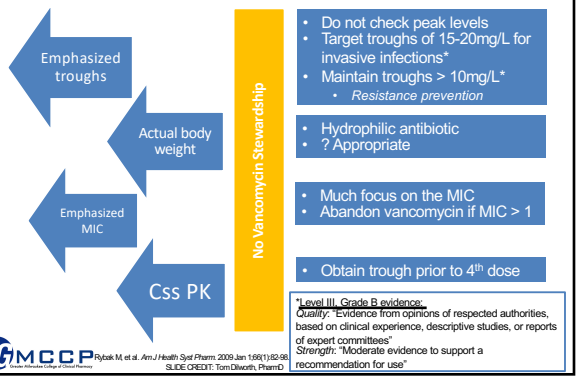
76

Our Old Friend (or Nemesis?)

- Some key vancomycin basics
  - Approximately "61" years old
  - Slowly bactericidal against MRSA
  - Bacteriostatic against Enterococci
  - Two-compartment kinetics with distribution and elimination phases
  - AUC/MIC predictor of efficacy (MRSA)

77

2009 Guideline Takeaways



Rybak M, et al. *Am J Health Syst Pharm.* 2009 Jan 1;66(1):82-98.
SLIDE CREDIT: Tom Dilworth, PharmD

78

2019 Draft Guideline Takeaways

- Target AUC/MIC$_{BMD}$ ratio of 400 - 600
  - *Achieve efficacy & minimize toxicity*
  - Preferred: Bayesian (2 level > 1 level)
  - Alternative: 2-level calculation
- No longer recommending troughs > 10mg/L to prevent resistance

- Assume vancomycin MIC of 1mg/L for most
  - *Based on contemporary surveillance data and limitations in susceptibility testing methodology (e.g. lack of precision)*

- Highlight the importance of early, appropriate antibiotic therapy

No Vancomycin Stewardship

Emphasize AUCs, de-emphasize troughs

De-emphasize MIC

First 24-48h PK

SLIDE CREDIT: Tom Dilworth, PharmD

Rybak M, et al. Am J Health Syst Pharm. 2009 Jan 1;66(1):82-98.
Rybak MJ, et al. 2019 DRAFT – https://www.ashp.org/-/media/assets/policy-guidelines/docs/draft-guidelines/draft-guidelines-ASHP-IDSA-

79

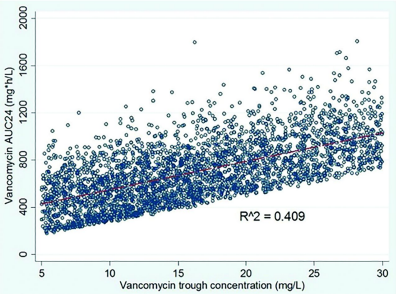
2019 Vancomycin Draft Consensus

"The vast majority of PK/PD data generated on vancomycin has focused on treatment of serious **methicillin-resistant Staphylococcus aureus (MRSA) infections**. Therefore, extrapolation of these recommendations to methicillin-susceptible strains, coagulase-negative staphylococci, and other pathogens should be viewed with extreme caution."

https://www.ashp.org/-/media/assets/policy-guidelines/docs/draft-guidelines/draft-guidelines-ASHP-IDSA-PIDS-SIDP-therapeutic-vancomycin.ashx Accessed 10/30/19.

80

How does TROUGH relate to AUC?



Up to 60% of patients with a therapeutic AUC/MIC ≥400 will have a trough concentration <15 mg/L

Pai MP, et.al. Innovative approaches to optimizing the delivery of vancomycin in individual patients. Adv Drug Deliv Rev 2014;77:50–7.

81

Select AUC Calculation Methods

Rodvold	Trapezoidal	Bayesian

• No levels
• Empiric dosing
• Population kinetics
• Function of CrCl
• AUC = dose/[(CrCl × 0.79) + 15.7] · 0.06
• May underestimate AUC
• Not individualized beyond CrCl
	• Two steady state levels
	  • Peak 60 min after END of infusion
	  • Trough 30 min prior to next infusion
	• First order kinetics
	• Individualized
	• No "software" required
	• Challenge of level timing
		• Most accurate
		• Most complex
		• Population and patient based
		• Two samples, within same dosing interval – timing less critical
		• Can account for covariates
		• Requires software

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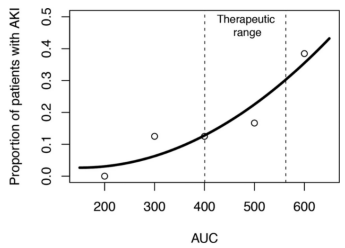
AUC Relative to Nephrotoxicity



Relationship of vancomycin dose (AUC) versus nephrotoxicity. This study found that the cutoff which best predicted nephrotoxicity was an AUC >563. This cutoff varies between studies, which most recommending avoidance of an AUC >600 or >700. (Chavada et al 2017 PMID 28242672)

General vanco nephrotoxicity
- Doses >4g/day
- Baseline CKD or h/o AKI
- RX >2 weeks
- Obesity
- Concurrent nephrotoxins
- Critical illness/sepsis
- High troughs or AUCs

83

Should We Flip the Switch?

- AJHP editorial published Nov 1, 2019
- Authors advocate that sum of evidence is not strong enough to implement universal AUC method
  - – Weak overall evidence
  - – Predominance of retrospective research looking at first 24-48 hours
  - – Bias in the literature
  - – Lack of pharmacoeconomic analyses

Dalton B, et al. *Am J Health-Syst Pharm 2019*; 21:1718-21
Heil EL, et al. *Am J Health-Syst Pharm.* 2018; 75:1986-95.

84

What are Our Colleagues Doing?

- Vizient® network survey (63% response rate)
- 23% using AUC monitoring
  - Target 400-600 mg·hr/L (58%)
  - 67% using 2-point, 28% Bayesian
- 77% using trough monitoring
  - Of these, 88% unsure or not planning to change to AUC dosing
  - Various reasons cited including cost, time, lack of familiarity

Kufel WD, et al. *Am J Health-Syst Pharm.* 2019; 76:889-894

85

Incorporating Learners into PK

- Recognize that most don't love kinetics
- To date, most of your learners will not have learned AUC-based vancomycin calculations in school
- Orienting residents/students to your SITE protocol may require background/history
- Students may be learning different approaches from site-to-site

86

Incorporating Learners into PK

- Perfect use of layered learning model
  - Work to have conceptual, not just mathematical, competency
  - Independent calculations to avoid bias
  - If discordance, encourage stepwise calculation and learner-check-learner with preceptor guidance

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Incorporating Learners into PK

- Charge your resident with being the lead communicator
  - If using trapezoidal AUC, TIMING will matter
  - Use your learners for verbal pharmacist shift handoff and direct RN communication
  - Care transition communications

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Incorporating Learners into PK

- Delegate documentation (with review) to your learner
- Emphasize PATIENT RESPONSE in the context of numbers; be the voice of reason

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Involve Learners in Vancomycin **STEWARDSHIP**

- Likely more important than number crunching, not well-discussed in guidelines
- Let your learner do the deeper dive
- **Does the patient NEED vancomycin?**
  - Learner can do a more complete allergy investigation and documentation, including previous β-lactam exposure/tolerance (leverage your EHR)
  - MRSA nares screening results to encourage vancomycin DC if used as empiric pneumonia RX
- Antibiotic Time Out

Parente DM, et al. *Clin Infect Dis.* 2018;67(1):1-7.
Smith MN, et al. *Ann Pharmacother.* 2019;53(6):627-638

90

Summary

- "2019" Vancomycin guideline is likely to recommend (universal ?) AUC dosing
- Implementation is likely to be variable
- More prospective studies are needed with focus on outcomes
- Leverage your learners beyond the math
- Incorporate STEWARDSHIP into the PK process for all patients

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Antimicrobial Pharmacokinetics

PEAKING Your Practicality, Not Just TROUGHING it Out

Lynne Fehrenbacher, PharmD, BCPS-AQ ID
Associate Professor of Pharmacy Practice
Concordia University Wisconsin School of Pharmacy

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Shorter is better? A review of shortened courses of antibiotics for bacterial infections

Tracy Zembles, PharmD, BCPS-AQ ID
Email: tzembles@chw.org
@tracyzembles

Children's Wisconsin
Kids deserve the best.

93

Objectives

1) Recognize strategies to optimize antimicrobial use
2) Summarize the evidence on shortened courses of antibiotic therapy for the treatment of bacterial infections
3) Identify covariates which may modify the effectiveness of short course treatment

94

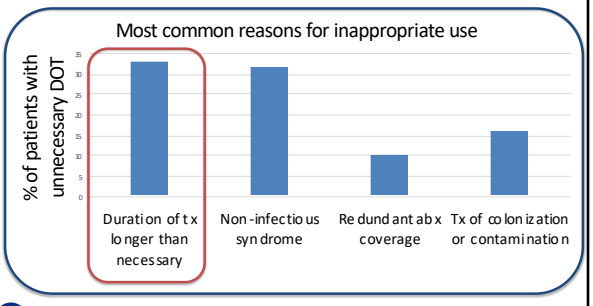
How to pick a duration of therapy

Diagnosis → Severity of illness → Time to clinical improvement

Risk, fear, anxiety

95

CDC estimates up to 50% of antibiotic use is inappropriate



Hecker et al. Arch Intern Med. 2003;163(8):972-8.

96

What's the risk in one more day?

- Retrospective cohort study
- Adults w/ severe sepsis/shock (n = 7,118)
- Treated with cefepime, meropenem, pip/tazo
- Objective: to correlate duration of exposure with development of new resistance

Teshome et al. Pharmacotherapy 2019;39(3):261-268.

97

Every day counts! 4% ↑ risk of new resistance for each additional day

	Adjusted hazard ratio (95% CI)
Any	1.04 (1.04-1.05)
Cefepime	1.08 (1.07-1.09)
Meropenem	1.02 (1.01-1.03)
Pip/tazo	1.08 (1.06-1.09)

Teshome et al. Pharmacotherapy 2019;39(3):261-268.

98

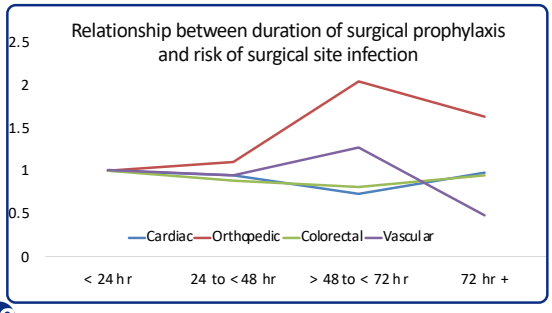
Each additional day ↑ risk of ADR

- Retrospective cohort study
- Adults hospitalized post cardiac, orthopedic, colorectal, or vascular surgery (n=79,058)
- Objective: characterize relationship b/w duration of surgical prophylaxis with surgical site infection (SSI) and drug-related effects

Branch-Elliman, et al. JAMA Surg 2019; 154(7):590-598.

99

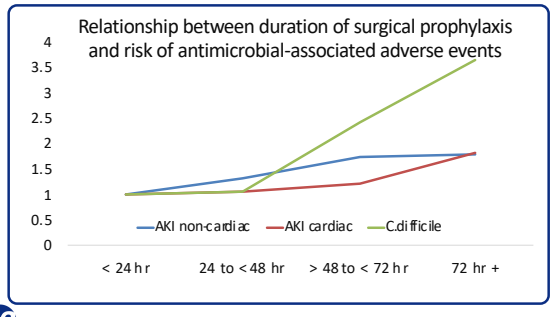
No difference in rate of SSI



Branch-Elliman, et al. JAMA Surg 2019; 154(7):590-598.

100

↑ risk of AKI and *C.difficile*



Branch-Elliman, et al. JAMA Surg 2019; 154(7):590-598.

101

#shorterisbetter

If not better, then at least equally effective

102

Audience response

What are some infections where you think a shorter duration of therapy might be "better" or at least "equally effective"?

103

Stewardship: Shorter = Better

Diagnosis	Short (d)	Long (d)	Result	#RCTs
CAP	3 or 5	7-14	Equal	9
VAP	8	15	Equal	2
Pyelo	7 or 5	14 or 10	Equal	6
Intra-abd	4	10	Equal	2
GNB Bacteremia	7	14	Equal	1*
AECB	≤5	≥7	Equal	>20
Cellulitis	5-6	10	Equal	4*
Chronic Osteomyelitis	42	84	Equal	2
Septic Arthritis	14	28	Equal	1
Ortho Implant w/removal	28	42	Equal	1
Neutropenic Fever	AFx72 h	+ANC>500	Equal	1
P. vivax Malaria	7	14	Equal	1

*GNB bacteremia in UTI/cIAI studies too; 3 cellulitis studies found no diff, 1 (low dose oral flucox) had ↑relapses; references at www.bradspellberg.com 14

Slide shared with permission by Brad Spellberg

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To be covered today….

- Community acquired pneumonia
- Ventilator associated tracheitis
- Intra-abdominal infections
- Gram negative bacteremia
- Neutropenic fever

105

To be covered today….

- Community acquired pneumonia
- Ventilator associated tracheitis
- Intra-abdominal infections
- Gram negative bacteremia
- Neutropenic fever

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Comparison of shorter vs provider directed duration of therapy

Hospitalized adult patients with CAP (n=312)

Randomized @ Day 5

Control (n=150): Duration at the discretion of the physician

Intervention (n=162): Stop antibiotics @ 5 days (min) AND Afebrile x 48h

Excluded

- × Immunocompromised
- × Received abx w/in 30 days
- × Types of bacteria
  - *Pseudomonas aeruginosa*
  - *Staphylococcus aureus*
- × Required a chest tube
- × Extra-pulmonary infection

Uranga et al. JAMA Intern Med 2016;176(9):1257-65.

107

No difference in recurrence, mortality, LOS

Outcome	Short (n = 162)	Long (n = 150)	P Value
Days of antibiotics, median (IQR)	5 (5-6.5)	10 (10-11)	< 0.001
Clinical success at day 10, n (%)	86 (59.7)	67 (50.4)	NS
Recurrence by day 30, n (%)	4 (2.8)	6 (4.4)	NS
30 day mortality, n (%)	3 (2.1)	3 (2.2)	NS
Length of stay in days, mean (SD)	5.7 (2.8)	5.5 (2.3)	NS

NS: not significant

Uranga et al. JAMA Intern Med 2016;176(9):1257-65.

108

Application

- 54 yo F (70 kg) hospitalized due to CAP
- Prescribed IV Levofloxacin 750 mg Q24h

Hospital day	Max temp	WBC	CRP	PCT
1	39.1	20.2	8.6	2.7
3	37.4	15.1	3.0	1.1
5	37.0	10.0	0.4	< 0.5

- Clinically improved by day 3 and back to baseline by day 5.
- How many total days of therapy should this patient receive?
  - A. 3 days
  - B. 5 days
  - C. 7 days
  - D. 10 days

109

To be covered today….

- Community acquired pneumonia
- Ventilator associated tracheitis
- Intra-abdominal infections
- Gram negative bacteremia
- Neutropenic fever

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Antibiotics for tracheitis improve outcomes, but….

Study (date)	Study design	Population	Comparator	Outcome
Nseir (2008)	Prospective RCT	Adult, first episode of VAT (n=58)	Antibiotic vs. no antibiotic for 8 days	↓ progression to VAP, vent days & mortality
Palmer (2008)	Prospective RCT	Adult, VAT (n=43)	Aerosolized antibiotic vs. no antibiotics	↓ progression to VAP, ↑ vent weaning

Optimal duration is unknown

Nseir et al. Crit Care 2008;12(3):R62.
Palmer et al. Crit Care Med 2008;36:2008-2013.

111

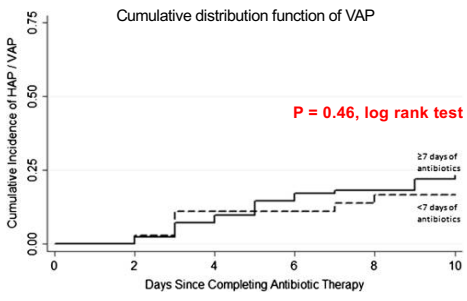
Only 1 study, in pediatrics

- Retrospective cohort study
- Children 0-18 years, intubated and diagnosed with tracheitis (n = 118)
- Objective: to determine if prolonged course
  - more protective against progression to VAP
  - more likely to result in acquisition of MDRO

Tamma et al. CID 2011 (11):1324-31.

112

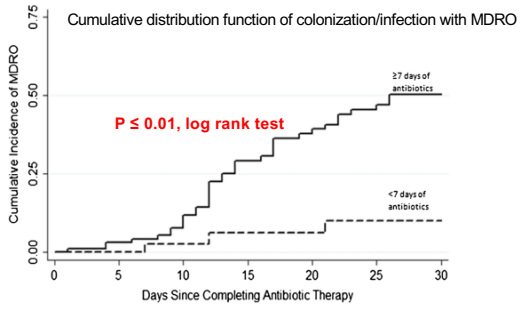
Not protective against progression to VAP (HR 1.08; 95% CI, 0.4-2.9)



Tamma et al. CID 2011 (11):1324-31.

113

Associated w/ subsequent MDRO (HR 5.15; 95% CI, 1.54-7.19)



Tamma et al. CID 2011 (11):1324-31.

114

Application

- 3 yo M (12 kg) in ICU following pedestrian vs. motor vehicle.
- Intubated, diagnosed with *Pseudomonas* tracheitis.
- Prescribed IV cefepime 50 mg/kg q12h.

Day of dx	Max temp	WBC	CRP	PCT
1	38.5	12.2	< 0.5	0.7
3	37.4	10.1	< 0.5	< 0.5
5	37.0	10.3		

- How many total days of therapy should this patient receive?
  - A. 3 days
  - B. 5 days
  - C. 7 days
  - D. 10 days

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To be covered today….

- Community acquired pneumonia
- Ventilator associated tracheitis
- Intra-abdominal infections
- Gram negative bacteremia
- Neutropenic fever

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4 vs 10 days of antibiotics for intra-abdominal infections

STOP STOP-IT trial

Age 16+ w/ complicated IAI & adequate source control (n=518)

EXPERIMENTAL: Fixed course = 4 days

CONTROL: 2 days after sx resolution; max 10 days

Sawyer RG, et al. NEJM 2015; 372:1996-2005.

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No difference in outcomes

Variable	Short (n=257)	Long (n=260)	P value
Duration of antibiotics, median (IQR)	4 (4-5)	8 (5-10)	< 0.001
Surgical site infection, n (%)	17 (6.6)	23 (8.8)	0.43
Recurrent IAI, n (%)	40 (15.6)	36 (13.8)	0.67
Death, n (%)	3 (1.2)	2 (0.8)	0.99

Sawyer RG, et al. NEJM 2015; 372:1996-2005

118

Application

- 17 yo M (62 kg), s/p appendectomy for acute appendicitis.
- Prescribed IV piperacillin/tazobactam 3 gm q8h.

Hospital day	Max temp	WBC	CRP	PCT
1	38.7	26.2		
3	37.6	19.5		
5	37.1	12.2		

- Day 3: clinically improved, tolerating general diet.
- How many total days of therapy should this patient receive?
  - A. 4 days
  - B. 7 days
  - C. 10 days
  - D. 14 days

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To be covered today….

- Community acquired pneumonia
- Ventilator associated tracheitis
- Intra-abdominal infections
- Gram negative bacteremia
- Neutropenic fever

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7 vs 14 days for Gram-negative BSI

Hospitalized adults with Gram-negative bacteremia (n=604)

↓

Hemodynamically stable & afebrile x 48 hours

↙ ↘

7 days | 14 days

Excluded

- x Unstable patients
- x Critically ill
- x Types of bacteria
  - *Pseudomonas*
  - *Acinetobacter*
- x Infection sources
  - Lack of source control
  - Endocarditis

Yahav D. CID 2018; doi: 10.1093/cid/ciy1054.

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7 days non-inferior to 14 days

Variable	Short (n=306)	Long (n=298)	P value
90 day mortality, n (%)	36 (11.8)	32 (10.7)	NS
Readmission, n (%)	119 (38.9)	127 (42.6)	NS
Extended LOS, n (%)	15 (4.9%)	19 (6.4)	NS
Bacteremia relapse, n (%)	8 (2.6)	8 (2.7)	NS

LOS: length of stay; NS: not significant

Yahav D. CID 2018; doi: 10.1093/cid/ciy1054.

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What about *Pseudomonas*?

Hospitalized adult patients with *P. aeruginosa* bacteremia (n = 249)

↙ ↘

Short course: 7-11 days | Long course: 12-21 days

Excluded

- x Complicated BSI
  - Osteoarticular
  - Endocarditis
  - Endovascular
  - CNS
- x Received < 7 or > 21 days of therapy
- x Received aminoglycoside monotherapy
- x Failure to receive agent with in vitro activity

Fabre et al. CID 2019; 69 (11):2011-2014.

123

Similar outcomes, shorter LOS

Variable	Short (n=69)	Long (n=180)	P value
Days of therapy, median (IQR)	9 (8-10)	16 (14-17)	
Mortality, n (%)	5 (7)	6 (4)	NS
Recurrent infection, n (%)	5 (7)	20 (11)	NS
Hospital days, mean (IQR)	7 (6-8)	11 (8-13)	0.005

Fabre et al. CID 2019; 69 (11):2011-2014.

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Application

- 28 yo F (54 kg) admitted to the general ward due to *E.coli* UTI and bacteremia. Hemodynamically stable.
- Prescribed IV ceftriaxone 1 gm q24h.

Hospital day	Max temp	WBC	CRP	PCT
1	38.9	26.2	7.2	2.2
4	37.6	19.5	3.5	1.3
7	37.1	12.2	1.2	< 0.5

- How many total days of therapy should this patient receive?
  - A. 7 days
  - B. 10 days
  - C. 14 days
  - D. 21 days

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To be covered today….

- Community acquired pneumonia
- Ventilator associated tracheitis
- Intra-abdominal infections
- Gram negative bacteremia
- Neutropenic fever

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Recommendations vary among societies

Guideline	Recommendation
IDSA 2011	**Discontinue antibiotics with marrow recovery**
ECIL-4 2013	Discontinue antibiotics after 72h if patient afebrile for 48h, regardless of marrow recovery
UK NICE 2012	Discontinue antibiotics when "responded to treatment," regardless of marrow recovery
ESMO 2010	Low risk: Discontinue antibiotics after afebrile for 5-7 days High risk: Discontinue antibiotics with marrow recovery
Japan 2004	Low risk: Discontinue antibiotics after afebrile for at least 15 days High risk: Discontinue antibiotics with marrow recovery

IDSA: Infectious Diseases Society of America; ECIL: European Conference on Infections in Leukemia; NICE: National Institute for Health and Care Excellence; ESMO: European Society for Medical Oncology

Fairfield AG. *Clin Infect Dis* 2011;66:657-63; Averbuch D. *Haematologgica* 2013;98:1836-47; Phillips R. *BMJ* 2012;345:e5368; de Naurois J. *Annal Oncology* 2010;21:v252-6; Masaoka T. *Clin Infect Dis* 204;39:S49-52

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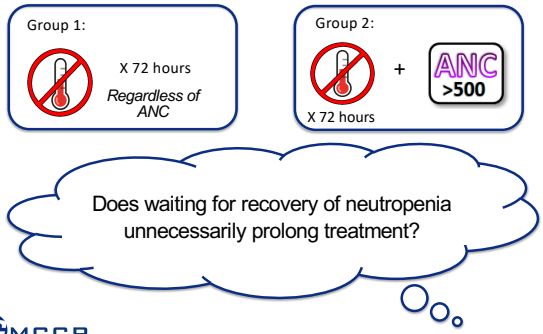
How Long Study



Aguilar-Guisado M. *Lancet Haematol* 2017;4(12):e573-83

128

No difference in outcomes

Variable	Group 1 (n=78)	Group 2 (n=79)	P value
Antibiotic free days	16.1 (±6.3)	13.6 (±7.2)	P = 0.026
All-cause mortality	1 (1.3%)	3 (3.8%)	NS
Febrile days	5.7 (±5.0)	6.3 (±5.9)	NS
New fever	11 (14%)	14 (18%)	NS

NS: not significant

Aguilar-Guisado M. *Lancet Haematol* 2017;4(12):e573-83

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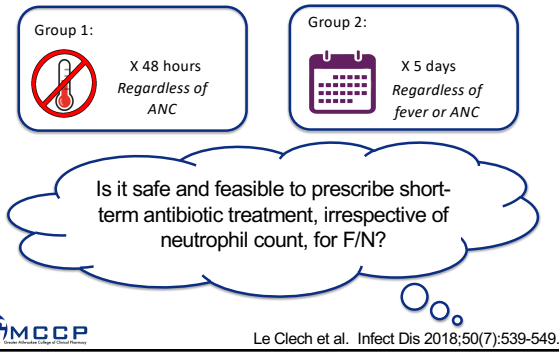
ANTIBIOSTOP



Le Clech et al. Infect Dis 2018;50(7):539-549.

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No difference in outcomes

Variable	Group 1 (n=45)	Group 2 (n=37)	P Value
In-house mortality	1 (2.2%)	2 (5.4%)	NS
ICU admit	1 (2.2%)	5 (12.5%)	NS
Relapse of fever	9 (20%)	8 (21.6%)	NS
Days of fever, median (IQR)	3 (2-4)	3 (2-4)	NS
Days of therapy, median (IQR)	7 (5-12)	5 (4-5.5)	NS

NS: not significant

Le Clech et al. Infect Dis 2018;50(7):539-549.

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Application

- 5 yo F (12 kg) with ALL in induction phase of chemotherapy, admitted to the oncology unit with febrile neutropenia.
- Prescribed IV cefepime 50 mg/kg q8h.

Hospital day	Max temp	ANC	CRP	PCT
1	38.9	0		
4	38.1	0.1		
7	37.0	0.3		

- How long should antibiotics continue?
  - A. Stop at 5 days
  - B. Until afebrile x 48 hours
  - C. Until afebrile x 72 hours
  - D. Until afebrile x 72 hours and ANC > 500

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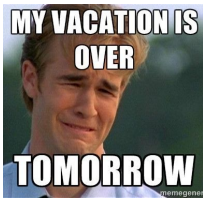
Shorter is not always better

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Think-pair-share

What are some patient populations or types of infections where a shorter duration might not be appropriate?

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Shorter is not always better

- Patients at increased risk of complications
  - Immunocompromised
  - Neonates
- Complicated infections
  - Endocarditis
  - Endovascular infection
  - Pneumonia w/ effusion/empyema
  - Necrotizing pneumonia
  - Abscesses

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Take home messages

- When appropriate, shorter courses may be as effective as longer courses
- Shorter courses may decrease:
  - Adverse events
  - Emergence of resistance
  - Hospital length of stay
  - Overall costs

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Shorter is better? A review of shortened courses of antibiotics for bacterial infections

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Children's Wisconsin
Kids deserve the best.

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