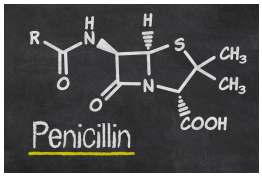
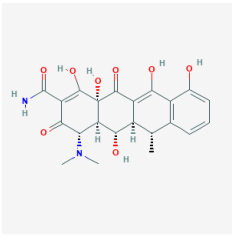


Antibiotic Update!
A rapid update and pearls for the Hospitalist: Part I



Jennifer A. Johnson, MD
Assistant Professor of Medicine, Harvard Medical School
Co-Director, BWH Antimicrobial Stewardship Program

GET SMART About Antibiotics Week
WWW.CDC.GOV/GETSMART

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

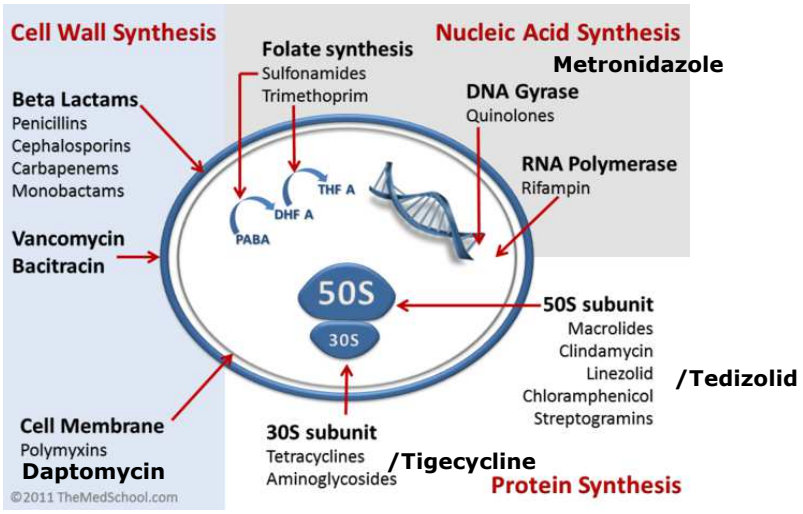
BWH BRIGHAM AND WOMEN'S HOSPITAL

No disclosures

Some basic tenets:

- Think about the **site of infection, the possible bugs and the host** when choosing a regimen
- More is not always better – many complications of antibiotic therapy
- Consider the toxicities, check for drug-drug interactions,
- Ok to go broad overnight when patients are sick
- Ok to pare down once stabilized and diagnosed
- Use your resources:
  - www.uptodate.com
  - https://www.hopkinsguides.com/hopkins/index/Johns_Hopkins_ABX_Guide/All_Topics/A
  - www.sanfordguide.com

Obligatory slide on site/mechanism of action…

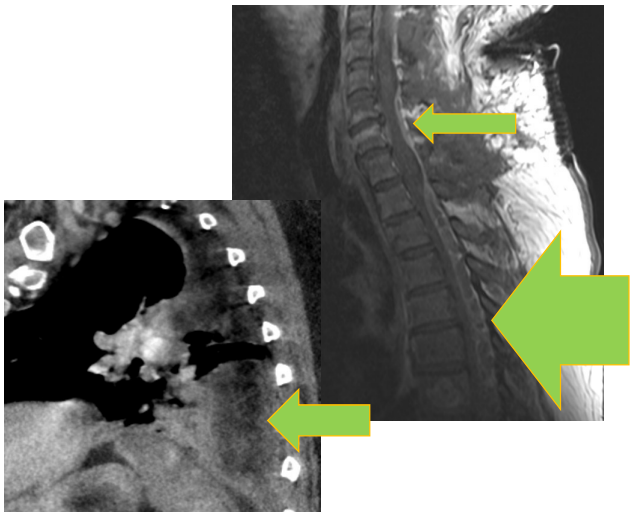


Case 1: 44yo man with type 2 DM, BMI 42, presented to local hospital with severe neck pain, developed acute quadriparesis

Blood — BLOOD CULTURE — STAPHYLOCOCCUS AUREUS
Critical Result. Results callec

Susceptibility

	MIC METHOD		Staphylococcus aureus DISK DIFFUSION METHOD PRELIM	
.Comment			SEE NOTES	No Interpretation [1]
.Comment			SEE NOTES	No Interpretation [2]
Ceftaroline	0.25	Susceptible		
Chloramphenicol			25	Susceptible
Ciprofloxacin	<=0.5	Susceptible		
Clindamycin	0.25	Susceptible	30	Susceptible
Daptomycin	0.5	Susceptible		
Erythromycin	0.5	Susceptible	30	Susceptible
Gentamicin	<=0.5	Susceptible	30	Susceptible
inducible clindamycin		Negative		
Levofloxacin	0.25	Susceptible	30	Susceptible
Linezolid	2	Susceptible	33	Susceptible
Minocycline	<=0.5	Susceptible		
Moxifloxacin	<=0.25	Susceptible		
Oxacillin/cephalosporins	0.5	Susceptible	23	Susceptible
Penicillin	>=0.5	Resistant	27	Resistant
Rifampin	<=0.5	Susceptible	33	Susceptible
Tetracycline	<=1	Susceptible	30	Susceptible
Tigecycline	<=0.12	Susceptible		
Trimethoprim/sulfamethoxazole	<=10	Susceptible	35	Susceptible
Vancomycin	1	Susceptible		



B-lactams for severe/complicated gram-positive infections

Penicillin

- If PCN-susceptible (with laboratory testing to confirm absence of beta-lactamase), still drug of choice for Staph aureus infection!
- Outstanding efficacy for all beta-hemolytic Strep infections and for penicillin-susceptible alpha-hemolytic Strep infection, though may be logistically difficult due to q4hr infusions
- Benzathine penicillin given IM is treatment of choice for primary and secondary syphilis, IV penicillin for neurosyphilis

Cefazolin

- Dosed Q8h for normal renal function
- Equivalent to nafcillin/oxacillin for most MSSA infections, with fewer toxicities

Nafcillin

- Q4h dosing, **high salt/water load**, risk of AIN

Oxacillin

- Q4h dosing, **high salt/water load**, risk of hepatitis

Antibiotic strategies for difficult MSSA infections

- Cefazolin (and cephalosporin, in general) inoculum effect: a prominent rise in antibiotic MIC when the susceptibility test is performed with a high bacterial inoculum
  - Some clinical data associating first-line cefazolin use for MSSA bacteremia with increased mortality in setting of inoculum effect. **One strategy is to start with induction antibiotic therapy with oxacillin or nafcillin and then transition to cefazolin**.
- Combination antibiotic strategies for persistent MSSA bacteremia
  - 8 patient series with persistent MSSA bacteremia despite cefazolin → rapid bacteremia clearance with ertapenem + cefazolin, with some additional case reports of successful combination tx
  - 7 patient series with persistent MSSA bacteremia despite Blactam therapy → median 48 hours to bacteremia clearance with daptomycin/oxacillin combination therapy
- Use of cefazolin for CNS infections
  - Longstanding recommendation ("**antibiotic myth**") to avoid cefazolin for CNS infections, but some in vitro and clinical data support drug distribution and efficacy appropriate for treatment of CNS infections

Ulloa ER et al. CID 2020.
Miller WR et al. OFID 2018.
Kufel WD et al. Ann Pharmaco 2023.
McCreary EK et al. CID 2023.

Case 2

- 32yo man with opioid use disorder admitted with fever and low back pain. MRI spine shows L3-4 discitis/osteomyelitis with adjacent epidural phlegmon with cord compression. Blood cultures are pending.

- Initial antibiotics?

vancomycin + ceftriaxone

Case 2

- 32yo man with opioid use disorder admitted with fever and low back pain. MRI spine shows L3-4 discitis/osteomyelitis with adjacent epidural phlegmon with cord compression. Blood cultures w MRSA.

- Treated with IV vancomycin, further blood cultures negative, undergoes operative debridement of epidural area, does well on IV vancomycin.

	Staphylococcus aureus	
Ceftaroline	0.5	Susceptible
Ciprofloxacin	<=0.5	Susceptible
Clindamycin	<=0.12	Susceptible
Daptomycin	1	Susceptible
Erythromycin	>=8	Resistant
Gentamicin	<=0.5	Susceptible
inducible clindamycin		Negative
Levofloxacin	<=0.12	Susceptible
Linezolid	2	Susceptible
Minocycline	<=0.5	Susceptible
Moxifloxacin	<=0.25	Susceptible
Oxacillin/cephalosporins	>=4	Resistant
Penicillin G	>=0.5	Resistant
Rifampin	<=0.5	Susceptible
Tetracycline	<=1	Susceptible
Tigecycline	<=0.12	Susceptible
Trimethoprim/sulfamethoxazole	<=10	Susceptible
Vancomycin	1	Susceptible

Vancomycin – basics

Inhibits cell wall synthesis of gram-positive bacteria

Longest and largest breadth of data for severe B-lactam resistant gram positive infections

Large hydrophilic molecule NOT absorbed orally (PO does not achieve blood levels), and IV does not penetrate intestinal lumen

Toxicities:

- Vancomycin infusion reaction – histamine-mediated, not a contraindication to future use
- local pain/phlebitis at injection sites
- Leukopenia, thrombocytopenia, fever
- Nephrotoxicity
- Ototoxicity
- Rarely, linear IgA dermatosis
  - bullous lesions

Vancomycin Dosing, PK/PD

CrCl	Each Dose	Interval
> 45	15-20mg/kg	Q8-12h
30-45	15-20mg/kg	Q24h
< 30	15-20mg/kg	Q48h
HD	15-20mg/kg	Post-HD

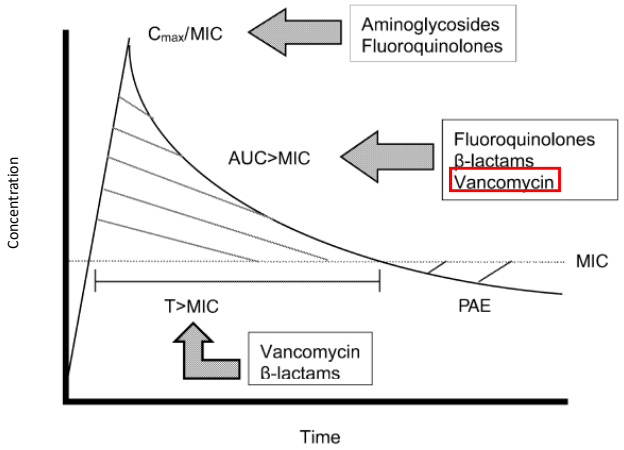
Weight-based dosing
- 15-20mg/kg IV q8-12h
- Consider loading dose (e.g. 20mg/kg x 1)

Activity based on AUC:MIC ratio

Troughs have been used as a surrogate for AUC

Phasing out dosing by trough levels
- 10-20 if giving empirically or for "routine infection in normal host"
- 15-20 for "complicated infections"

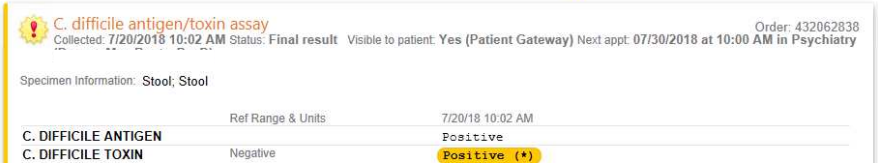
Transitioning to dosing by AUC
- Goal AUC_{24h} 400-600mg-h/L for most infections
- Dosing according to AUC is associated with similar efficacy with reduced toxicity, compared with trough-based dosing



Slide adapted from slide by Jeff Pearson, PharmD, BCIDP

McKinnon PS, Davis SL. Eur J Clin Microbiol Infect Dis. 2004;23:271-288

Oral/Enteral vancomycin: ONLY for intraluminal bowel infection, ie. Clostridium difficile associated disease

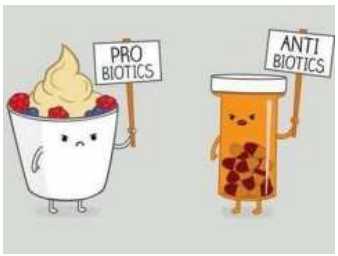


C. difficile antigen/toxin assay
Collected: 7/20/2018 10:02 AM Status: Final result Visible to patient: Yes (Patient Gateway) Next appt: 07/30/2018 at 10:00 AM in Psychiatry
Order: 432062838

Specimen Information: Stool; Stool

	Ref Range & Units	7/20/18 10:02 AM
C. DIFFICILE ANTIGEN		Positive
C. DIFFICILE TOXIN	Negative	Positive (*)

Oral vancomycin or fidaxomicin is the first line treatment



Case 2

- 32yo man with opioid use disorder admitted with fever and low back pain. MRI spine shows L3-4 discitis/osteomyelitis with adjacent epidural phlegmon with cord compression. Blood cultures w MRSA.

Alternate ending!

- Real life!
- Does poorly on IV vancomycin due to:
  - Intolerance, toxicity
  - Treatment failure with ongoing bacteremia
  - Unable to discharge from hospital with PICC due to safety concerns
- What are the other options????

Case 2: persistent MRSA bacteremia

What is the best antibiotic management at this point?

A. Continue IV vancomycin goal AUC 400-600
B. Switch to daptomycin 10mg/kg alone
C. Switch to daptomycin + ceftaroline
D. Switch to ceftaroline alone
E. Switch to tigecycline
F. Switch to linezolid
G. Switch to dalbavancin

Rose W et al. CID 2021.

Case 2: persistent MRSA bacteremia

What is the best antibiotic management at this point?

A. Continue IV vancomycin goal AUC 400-600
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E. Switch to tigecycline
F. Switch to linezolid
G. Switch to dalbavancin

We don't know!

Wrong options:
- Tigecycline
- Linezolid
- Dalbavancin

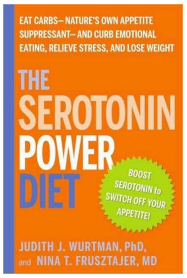
Potentially right options:
- Continue vancomycin
- High-dose daptomycin
- Combination daptomycin (or vancomycin) with ceftaroline (or other B-lactam)
- Ceftaroline alone

Optimal antibiotics for severe Staph aureus infections

MSSA:
- Nafcillin/oxacillin
- Cefazolin
- (Ceftriaxone)

MRSA:
- Vancomycin
- Daptomycin
- Linezolid (tedizolid)
- (Tigecycline, Ceftaroline, Oritavancin, Dalbavancin)

Linezolid – basics



- Inhibits protein synthesis
- Adverse effects: GI, headaches, BM suppression, mitochondrial toxicities
- Drug interactions: weak reversible non-selective MAO inhibition
- 100% oral bioavailability (PO = IV)
- No dose adjustments in renal or hepatic failure
- Tedizolid - similar spectrum of activity, once daily, fewer side effects, more $$$

Daptomycin – basics

- Bursts cell membranes
- Low penetration into CSF
- Inactivated by surfactant – no lung activity (NOT USED FOR PNEUMONIA)
- IV formulation only
- Adverse effect: myopathy, monitor CPK

Ceftaroline

- A B-lactam that treats MRSA?!?!?!?
  - FDA approved for community acquired pneumonia, including MRSA (no good data on Pseudomonas)
  - In practice – more and more often used for tough MRSA cases from many infection site (if not responding to vancomycin/daptomycin, or if difficulty tolerating these)
  - Dose is 600mg IV q12h routine or q8h for MRSA
- Safety
  - Weekly CBC w diff (cytopenias very common), BUN/Cr, LFTs
  - Similar toxicity profile as most IV cephalosporins, apart from increased risk of cytopenias

Glyco/Lipo-peptide + β-lactam for MRSA

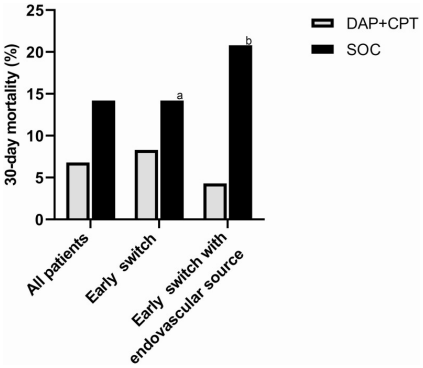
- CAMERA-1 trial (2016):
  - RCT Australia, 60 patients w MRSA bacteremia
  - Vancomycin vs. vancomycin + flucloxacillin
  - Decreased duration of bacteremia, no change in mortality or other complications
- CAMERA-2 trial (pub 2/2020):
  - RCT Australia, 352 patients w MRSA bacteremia
  - Vancomycin/daptomycin + flucloxacillin/cloxacillin/cefazolin vs. monotherapy
  - No difference in endpoints
- Daptomycin + various Blactams (pub):
  - Retrospective, 229 patients w MRSA bacteremia
  - Daptomycin alone vs + Blactam (pip-tazo, cefepime, ertapenem, cefazolin, ceftriaxone, etc…
  - OR clinical failure 0.39 in combination group vs daptomycin alone

CAMERA trial: Davis JS et al. CID 2016. CAMERA 2 trial: Tong SYC et al. JAMA 2020.
Jorgensen SCJ et al. CID 2020.
Holubar M et al. Infect Dis Clin North Amer 2016.

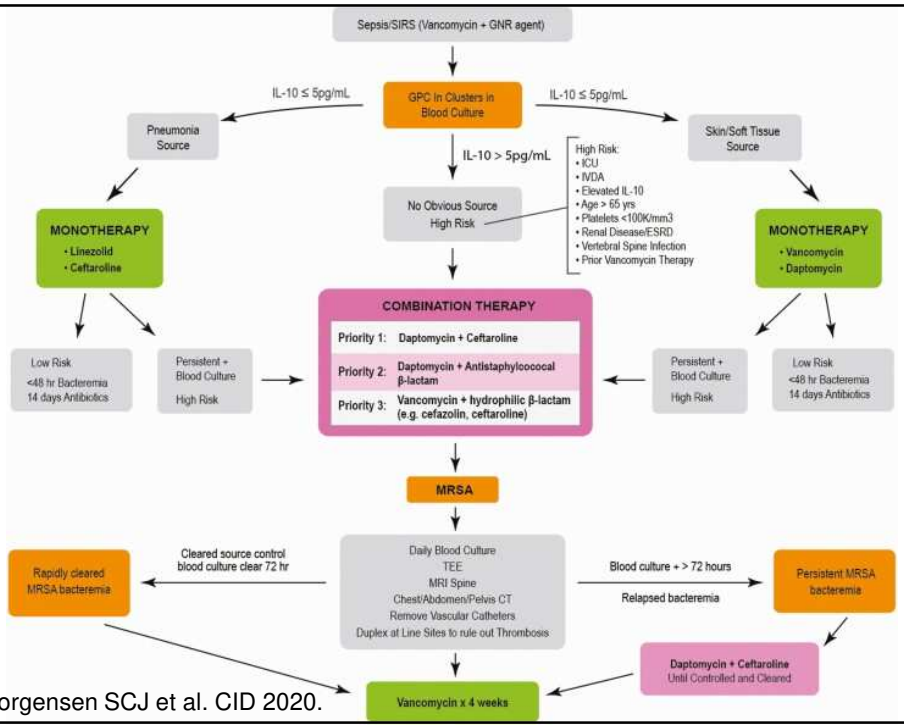
Daptomycin + ceftaroline

- Multiple case reports and some retrospective data suggest decreased duration of bacteremia
- 40 patient RCT 2019 halted d/t increased mortality in monotherapy (vancomycin) group (26%) vs. DAP + CPT (0%)

- Large retrospective matched cohort study across 3 institutions comparing early switch to DPT+ceftaroline vs SOC: earlier clearance of bacteremia + trend to improved mortality w combination



Geriak M et al. Antimicrob Agents Chemother 2019.
McCreary EK et al. OFID 2020.



Jorgensen SCJ et al. CID 2020.

Newer Agents

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 5, 2014 VOL. 370 NO. 23

ORIGINAL ARTICLE

Single-Dose Oritavancin in the Treatment of Acute Bacterial Skin Infections

G. Ralph Corey, M.D., Heidi Kabler, M.D., Purvi Mehra, M.D., Sandeep Gupta, M.D., J. Scott Overcash, M.D., Ashwin Porwal, M.D., Philip Giordano, M.D., Christopher Lucasti, M.D., Antonio Perez, M.D., Samantha Good, Ph.D., Hai Jiang, Ph.D., Greg Moeck, Ph.D., and William O'Riordan, M.D., for the SOLO I Investigators*

Once-Weekly Dalbavancin versus Daily Conventional Therapy for Skin Infection

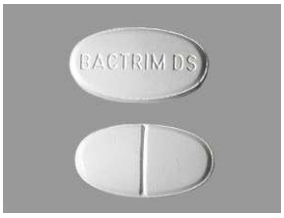
Helen W. Boucher, M.D., Mark Wilcox, M.D., George H. Talbot, M.D., Sailaja Puttagunta, M.D., Anita F. Das, Ph.D., and Michael W. Dunne, M.D.

- **Oritavancin/Dalbavancin**
  - Newer once weekly infusion therapies approved and marketed for MRSA skin and soft tissue infection, also active vs VRE
  - Many sites using predominantly for earlier transition to outpatient, or entirely outpatient, therapy for complicated infections when PICC not an option
  - ID guidance recommended, use still rare, some risks (treatment failure)

Oral drugs for Strep + Staph aureus

- For Strep:
  - Penicillin, Amoxicillin, Amoxicillin-clavulanate, cephalexin, cefadroxil
- For MSSA (if PCN-resistant):
  - Amoxicillin-clavulanate, cephalexin, cefadroxil, dicloxacillin
- For MRSA (if susceptible):
  - Bactrim, Levofloxacin, Moxifloxacin, Doxycycline, Clindamycin
  - **DO NOT USE RIFAMPIN WITHOUT ID GUIDANCE**

Trimethoprim-Sulfamethoxazole (T/S)



Many uses!
- Most common = UTI, Staph aureus skin/soft tissue infections

Dose by the trimethoprim component
PO formulations:
- SS tablet = SMX/TMP 400mg/80mg
- DS tablet = SMX/TMP 800mg/160mg

Toxicities: GI, rash (mild → Stevens Johnson), serum sickness, aseptic meningitis, bone marrow suppression, hepatitis, methemoglobinemia (with severe G6PD deficiency)

Renal effects: pseudo elevation in serum Cr, reversible hyperkalemia, real nephrotoxicity (interstitial nephritis)

Clinical controversy re activity of T/S vs Strep pyogenes, but lack of in vitro activity is likely an "**antibiotic myth**", and some clinical data on treatment of nonpurulent SSTIs supports efficacy of T/S

FDA News Release

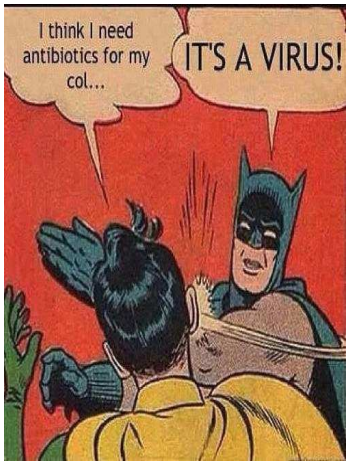
FDA updates warnings for fluoroquinolone antibiotics

Limits use for acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis and uncomplicated urinary tract infections

- Fluoroquinolones are very useful for certain indications: outpatient treatment of pyelonephritis (R-Bactrim), outpatient treatment of pneumonia (or amoxicillin, or amox/clav), infections resistant to B-lactams
- However, should not be used for sinusitis, uncomplicated UTI, chronic bronchitis, when alternatives exist, due to toxicities:
  - Tendons, muscles, joints, nerves and CNS toxicities
  - Delerium, especially in older patients or those with underlying CNS dz
  - Risk of Clostridium difficile associated diarrhea
  - QT prolongation
  - Drug-drug interactions (especially warfarin, neuropsych meds)

Antimicrobial Drug Resistance

- A tremendous global issue
- Part of conscientious prescribing includes patient education
  - Do not take antibiotics for viral infections.
  - Do not take antibiotics prescribed for someone else.
  - Do not take antibiotics for longer than needed



https://www.cdc.gov/antibiotic-use/stewardship-report/index.html

Thanks, and good luck…