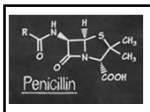
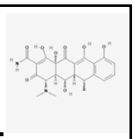


Antibiotic Update!
A rapid update and pearls for the Hospitalist: Part I



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

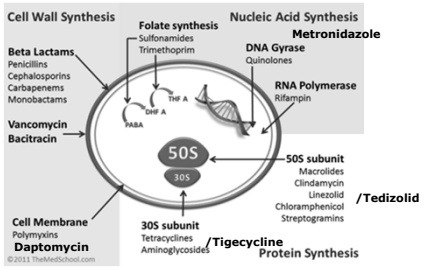
BRIGHAM AND WOMEN'S HOSPITAL

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:
  - Partners Handbook → Clinical Topics → Infectious Disease (includes BWH Empiric Antibiotic Guidelines by Condition)
  - www.uptodate.com
  - https://www.hopkinsguides.com/hopkins/index/Johns_Hopkins_ABX_Guide/All_Topics/A
  - www.sanfordguide.com
- If you have questions - page ID

Obligatory slide on site/mechanism of action…



Case 1

- JP is a 48yo woman with h/o L hip replacement, admitted with fevers and L hip pain. Blood cultures drawn at admission:

STAPHYLOCOCCUS, COAGULASE NEGATIVE FROM AEROBIC 'FAN' (BACT/ALERT) MEDIUM

Susceptibility	Staphylococcus epidermidis (ZZ00) PRELIMINARY KB PANEL		Staphylococcus epidermidis (ZZ01) VITEK MIC	
Comment	SEE NOTES	No Interpretation [1]		
Comment	SEE NOTES	No Interpretation [2]		
Chloramphenicol	25	Susceptible		
Ciprofloxacin			<=0.5	Susceptible
Clindamycin	25	Susceptible	<=0.12	Susceptible
Daptomycin			0.25	Susceptible
Erythromycin	30	Susceptible	<=0.25	Susceptible
Gentamicin	23	Susceptible	<=0.5	Susceptible
Inducible Clindamycin Resistance			Negative	
Levofloxacin	25	Susceptible	<=0.12	Susceptible
Linezolid	30	Susceptible	1	Susceptible
Minocycline			<=0.5	Susceptible
Moxifloxacin			<=0.25	Susceptible
Oxacillin/cephalosporins	20	Resistant	>=0.5	Resistant
Penicillin G	20	Resistant	>=0.5	Resistant
Rifampin	31	Susceptible	<=0.5	Susceptible
Tetracycline	25	Susceptible	2	Susceptible
Tigecycline			0.25	Susceptible
Trimethoprim/sulfamethoxazole	25	Susceptible	<=10	Susceptible
Vancomycin	19	No Interpretation	1	Susceptible

A good indication for vancomycin…

Vancomycin – basics

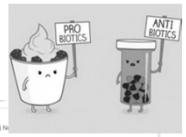
- Inhibits cell wall synthesis of gram-positive bacteria
- Large hydrophilic molecule NOT absorbed orally (PO does not achieve blood levels), and IV does not penetrate intestinal lumen
- Toxicities:
  - Red man syndrome
  - local pain/phlebitis at injection sites
  - Leukopenia, thrombocytopenia, fever
  - Nephrotoxicity
  - Ototoxicity
  - Rarely, linear IgA dermatosis – bullous lesions

Vancomycin –dosing

- Weight-based dosing
  - (15-20mg/kg IV q8-12h)
- Depends on weight, age, CrCl, and indication (can use a loading dose)
- **TITRATING UP TO HIGHER TROUGH LEVELS ONLY DATA-SUPPORTED IF TREATING KNOWN STAPH AUREUS INFECTION, BUT ALSO USEFUL FOR MONITORING FOR TOXICITY**
- Goal trough level:
  - 10-20 if giving empirically or for "routine infection in normal host"
  - 15-20 for "complicated infections"
- Careful not to overdose, especially with elderly patients and/or borderline renal function
  - Ceiling dose of 2gm per dose
  - Ceiling total daily dose ~ 6gm
- Vancomycin AUC monitoring is coming/here…

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

Treating CDiff



C. difficile antigen/toxin assay
Collected: 7/20/2018 10:02 AM Status: Final result Visible to patient: Yes (Patient Gateway)
Specimen Information: Stool; Stool

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

Oral vancomycin or fidaxomicin is the first line treatment

Case 2

- KW is a 32yo man with opiate 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

Blood cultures = Staph aureus - MRSA

Culture & Susceptibility

STAPHYLOCOCCUS AUREUS

Antibiotic	Sensitivity	Result	Method	Status
Ceftaroline	Susceptible	0.75	ETEST	Final
Vancomycin	Susceptible	1.5	ETEST	Final

Comment: *If treatment is indicated, the BWH Infectious Disease Team recommends caution when using Vancomycin to treat Staphylococcus Aureus with a Vancomycin MIC of 1.5mcg/ml to 2.0mcg/ml. Please consider a BWH Infectious Disease consultation for treatment recommendations.*

Comments STAPHYLOCOCCUS AUREUS
3+ STAPHYLOCOCCUS AUREUS

STAPHYLOCOCCUS AUREUS

Antibiotic	Sensitivity	Result	Method	Status
Ciprofloxacin	Resistant	>=8	VITEK MIC	Final
Clindamycin	Resistant	>=8	VITEK MIC	Final
Erythromycin	Resistant	>=8	VITEK MIC	Final
Gentamicin	Susceptible	<=0.5	VITEK MIC	Final
Inducible Clindamycin Resistance	Negative		VITEK MIC	Final
Levofloxacin	Resistant	>=8	VITEK MIC	Final
Linezolid	Susceptible	4	VITEK MIC	Final
Minocycline	Susceptible	1	VITEK MIC	Final
Moxifloxacin	Resistant	>=8	VITEK MIC	Final
Oxacillin/cephalosporins	Resistant	>=4	VITEK MIC	Final
Penicillin G	Resistant	>=0.5	VITEK MIC	Final
Quinupristin/Dalfopristin	Susceptible	0.5	VITEK MIC	Final
Rifampin	Susceptible	<=0.5	VITEK MIC	Final
Tetracycline	Intermediate	8	VITEK MIC	Final
Trimethoprim/sulfamethoxazole	Susceptible	<=10	VITEK MIC	Final
Vancomycin	Susceptible	2	VITEK MIC	Final

Comment: *If treatment is indicated, the BWH Infectious Disease Team recommends caution when using Vancomycin to treat Staphylococcus Aureus with a Vancomycin MIC of 1.5mcg/ml to 2.0mcg/ml. Please consider a BWH Infectious Disease consultation for treatment recommendations.*

Case 2

- KW is a 32yo man with opiate 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.

Optimal antibiotics for severe Staph aureus infections

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

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

B-lactams still better for Staph if susceptible

- Penicillin
  - If PCN-susceptible, still drug of choice for Staph!
- Cefazolin
  - Dosed Q8h for normal renal function
  - Equivalent to Naf/Oxa 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

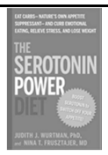
Case 2

- KW is a 32yo man with opiate 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????

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 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 + 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%)**

CAMERA trial: Davis JS et al. CID 2016. CAMERA 2 trial: Tong SYC et al. JAMA 2020.
Geriak M et al. Antimicrob Agents Chemother 2019.
Holubar M et al. Infect Dis Clin North Amer 2016.

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

C. 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*

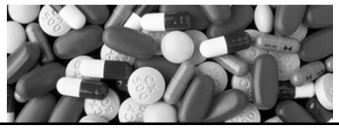
Once-Weekly Dalbavancin versus Daily Conventional Therapy for Skin Infection

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

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

FDA News Release

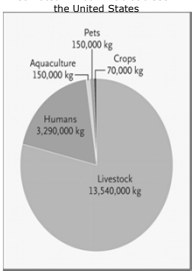
FDA updates warnings for fluoroquinolone antibiotics

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)

Preserving Antibiotics, Rationally

- 46.3 metric tons of Abx consumed daily in US
- 80% of this use is in agriculture
- FDA regulations to curtail use are ***voluntary***



Hollis A, Ahmed Z. N Engl J Med 2013;369:2474-2476

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

Thanks, and good luck…