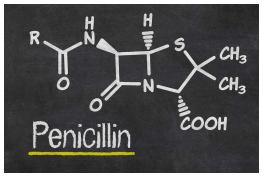
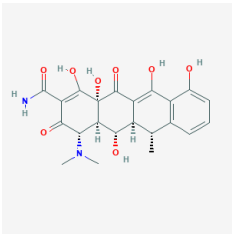


Antibiotic Update!
A rapid update and pearls for the Hospitalist: Part II



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

Case 3

- DF is a 47yo man with T4 spinal cord injury c/b paraplegia and neurogenic bladder w suprapubic catheter in place and recurrent UTIs. Admitted with fever and hypotension, responded to IV fluids. Prior history of Pseudomonas UTI and Pseudomonas bacteremia.

- Which antibiotic(s) to use for initial empiric regimen?

Treating Pseudomonas

- Ciprofloxacin/levofloxacin – rising resistance
- Ceftazidime – effective, low toxicity
- Cefepime – effective, low toxicity except rare encephalopathy
- Piperacillin/piperacillin-tazobactam – effective, moderate toxicity
- Aztreonam – rising resistance, other agents for B-lactam allergies
- Imipenem
- Meropenem
- Aminoglycosides (Amikacin, Tobramycin, Gentamicin)
  - "Synergy" = predominantly for patients w CF + pneumonia
  - "Double coverage" = critically ill, awaiting susceptibilities
  - High toxicity and narrow therapeutic window, use in combination with B-lactam for empiric use
- Colistin, Polymixin B
- Ceftazidime/avibactam, ceftolozane/tazobactam

IV cephalosporins

- **Cefazolin**
  - Ideal for severe MSSA infections – non-inferior to nafcillin/oxacillin for almost all cases, with fewer side effects
  - Also treats Strep sp., and few gram negatives
  - Dose 2gm IV Q8h if GFR high (can be dosed with HD)
- **Ceftriaxone**
  - Ideal for severe Strep infections, some gram-negative infections, probably good for MSSA
  - Dose 2gm IV QD for severe infections, not adjusted for renal function
- **Ceftazidime**
  - Treats most **Pseudomonas** and other gram negatives (no gram-positives, no anaerobes)
  - Dose 2gm IV q8h (can be dosed with HD)
- **Cefepime**
  - Treats most **Pseudomonas** and other gram negatives, also Strep, some activity vs MSSA and amp-susceptible enterococci, oral anaerobes
  - Rarely complicated by encephalopathy but can be significant (GABA pathway, more common in setting of alcohol/benzo withdrawal, older age)
  - Dose 2gm IV q12h or q8h

Case 3

- DF is a 47yo man with T4 spinal cord injury c/b paraplegia and neurogenic bladder w suprapubic catheter in place and recurrent UTIs. Culture below…
- Treated w ceftazidime, does well!

PSEUDOMONAS AERUGINOSA

Antibiotic	Sensitivity	Result	Method	Status
Amikacin	Susceptible	24	FINAL KB PANEL	Final
Aztreonam	Susceptible	25	FINAL KB PANEL	Final
Cefepime	Susceptible	21	FINAL KB PANEL	Final
Ceftazidime	Susceptible	25	FINAL KB PANEL	Final
Ciprofloxacin	Resistant	6	FINAL KB PANEL	Final
Colistin	Susceptible	15	FINAL KB PANEL	Final
Gentamicin	Susceptible	19	FINAL KB PANEL	Final
Levofloxacin	Resistant	6	FINAL KB PANEL	Final
Meropenem	Resistant	10	FINAL KB PANEL	Final
Piperacillin	Susceptible	24	FINAL KB PANEL	Final
Tobramycin	Susceptible	21	FINAL KB PANEL	Final

Comments PSEUDOMONAS AERUGINOSA
4+ PSEUDOMONAS AERUGINOSA

Case 3 – Alternate ending!

Blood cultures grow: PSEUDOMONAS AERUGINOSA

RAPID MIC METHOD

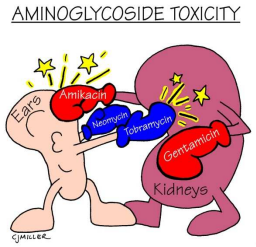
Antibiotic	MIC (mcg/ml)	
Amikacin	<=8	Susceptible
Aztreonam	>16	Resistant
Cefepime	32	Resistant
Ceftazidime	>16	Resistant
Colistin	1	Susceptible
Ciprofloxacin	>2	Resistant
Gentamicin	4	Susceptible
Imipenem	8	Resistant
Levofloxacin	>8	Resistant
Meropenem	>8	Resistant
Piperacillin/Tazobactam	>128	Resistant
Tobramycin	<=2	Susceptible

* Nonstandardized susceptibility

Now what do you do?

Aminoglycosides

- Gentamicin, Tobramycin, Amikacin
- PRO:
  - Bactericidal
  - Synergy with B-lactams for enterococci (+/- Staph)
  - Inexpensive
  - Active vs. many resistant gram-negatives, Pseudomonas
- CON:
  - Nephrotoxicity
  - Ototoxicity
  - monitoring levels
  - frequently incorrectly dosed – call Pharmacy!!!
  - poor activity in acid pH (abscesses)
  - many less-toxic alternatives



Major toxic effects of Aminoglycosides are Ototoxicity & Nephrotoxicity

Case 3 – Alternate ending!

PSEUDOMONAS AERUGINOSA
RAPID MIC METHOD

Antibiotic		MIC (mcg/ml)
Amikacin	<=8	Susceptible
Aztreonam	>16	Resistant
Cefepime	32	Resistant
Ceftazidime	>16	Resistant
Ceftazidime-avibactam		Resistant*
Ceftolozane-tazobactam	**4**	**Susceptible***
Colistin	1	Susceptible
Ciprofloxacin	>2	Resistant
Gentamicin	4	Susceptible
Imipenem	8	Resistant
Levofloxacin	>8	Resistant
Meropenem	>8	Resistant
Piperacillin/Tazobactam	>128	Resistant
Tobramycin	<=2	Susceptible

* Nonstandardized susceptibility

What is this???

New β lactam + β lactamase inhibitor combos:

- **Ceftolozane-tazobactam**
  - Activity against MDR *Pseudomonas aeruginosa*
- **Ceftazidime-avibactam**
  - Activity against MDR *Pseudomonas aeruginosa*
  - Activity against some carbapenem-resistant Enterobacteriaceae (CRE)
    - Not active against NDM-1 CRE
- **Meropenem-vaborbactam**
  - Activity against many carbapenem-resistant Enterobacteriaceae (CRE)
  - Does NOT improve activity vs Pseudomonas, Acinetobacter, Stenotrophomonas
- ALL require add on microbiology testing, use with ID guidance at most sites

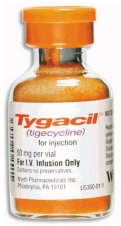
β -lactamases – Ambler Classification

Type	Class	Characteristics	Example Enzyme/Pathogen
Narrow-spectrum	A	Hydrolyze penicillin	TEM; SHV Enterobacteriaceae
ESBL (extended spectrum β-lacatmase)	A	Hydrolyze narrow and extended spectrum Beta-lactams	TEM; SHV; CTX-M-15 Enterobacteriaceae
Serine carbapenemases	A	Hydrolyze carbapenems	KPC; IMI Enterobacteriaceae
Metallo-β-lactamases	B	Hydrolyze carbapenems	VIM; IMP; NDM Enterobacteriaceae, Pseudomonas spp., Acinetobacter spp.
Cephalosporinases	C	Hydrolyze cephamycins & oxyiminobeta-lactams	AmpC Enterobacter spp., Pseudomonas spp., Citrobacter spp.,
OXA-type enzymes	D	Hydrolyze oxacillin, oxyiminobeta-lactams, carbapenems	OXA Enterobacteriaceae, Acinetobacter spp.

Bush K and Jacoby GA. Antimicrob Agents Chemother 2010 54:969. Hall BG and Barlow M. J Antimicrob Chemother

Other options for resistant gram-negatives

- **Polymixin B**
  - Same as Colistin, but less toxic
  - No dose adjustment for renal failure
- **Colistimethate** (Colistin):
  - For MDR E. Coli, Klebsiella, Pseudomonas, Acinetobacter
  - Topical (ENT) and inhaled (CF pts) forms available
  - Nephrotoxicity (~ 20%)
  - Phlebitis, Neurotoxicity
  - Bronchospasm w inhaled
- **Tigecycline**: glycylcycline
  - For Staph (+ MRSA), Strep, VRE, many Gm neg, anaerobes, some mycobacteria (? For CDiff?)
  - NOT for Pseudomonas, Proteus
  - GI side effect
  - BLACK BOX WARNING FOR SEPSIS (rapid tissue distribution)



New tetracycline derivatives

Eravacycline

- Available IV only
- Approved 2018 for cIAI (failed cUTI trial)
- Very broad activity including ESBL Enterobacteriaceae, CRE, some carbapenem resistant *Acinetobacter* spp

Omadacycline

- Available IV and PO
- Approved 2018 for ABSSI and CABP
- Emerging data for *Mycobacterium abscessus* infections
- Lower GI side effects than tigecycline
- Decreased parasympathetic tone -> Increases HR by 8-10 bpm

	Eravacycline	Omadacycline
S. aureus / CoNS	X	X
Streptococci	X	X
Enterococci	X	X
Anaerobes	X	X*
ESBL Enterobacteriaceae	X	X
CRE	X	?
CR-*Acinetobacter*	X	?

* Potent activity against *Clostridioides difficile*

Cefiderocol

- FDA approved in 2019 for complicated UTIs
- Novel cephalosporin with an attached siderophore moiety
  - High stability to serine and zinc proteases
  - High penetration through the outer membrane
- Trojan horse mechanism
- High activity
  - KPC (class A), NDM-1 (class B), OXA-type enzymes (class D)
  - MDR non-fermenters
    - *Stenotrophomonas*
    - CR-*Acinetobacter*
    - *Burkholderia*

Case 4

- GR is a 52yo man with prior history of diverticulitis, admitted with sudden onset of LLQ abdominal pain and fever within past 24 hours, hemodynamically stable.

- Initial antibiotics?

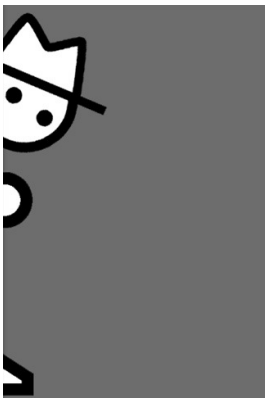
"Eat some grass, and call me in the morning."

Case 4

- GR is a 52yo man with prior history of diverticulitis, admitted with sudden onset of LLQ abdominal pain and fever within past 24 hours, hemodynamically stable.

- Empiric antibiotics to treat bowel flora in immunocompetent patient without significant past antibiotic exposure:
  - Ampicillin/sulbactam
  - Ceftriaxone + metronidazole
  - Cefotaxime
  - Ciprofloxacin or levofloxacin + metronidazole
  - (if concern for resistance then: piperacillin-tazobactam, cefepime + metronidazole, meropenem, imipenem, ertapenem)

Could anaerobes also be there?



- Oral/GI source → anerobes too?
- Require special culture collection
- Difficult to culture
- Long time to grow
- Have a high clinical suspicion for concomitant anaerobic infection when you suspect a GI source!

Anaerobes

- "Oral" anaerobes → likely PCN-sensitive
  - Peptostreptococcus, Fusobacterium, Eubacterium, etc..
  - Treat with clindamycin, most B-lactams, **metronidazole**, carbapenems (also – vancomycin active vs. Gram-positive anaerobes)
- "Abdominal" anaerobes → likely PCN-resistant
  - Bacteroides sp. (eg. Bacteroides fragilis), Prevotella, etc..
  - Treat with **metronidazole**, pip-tazo, amp-sulbactam, carbapenems, (clindamycin)

Clindamycin vs. Metronidazole

- Excellent oral bio-availability
- Treats many/oral anaerobes
- Some Bacteroides fragilis resistance
- High risk of C. Diff
- Ribosomal inhibitor → inhibits toxin formation (useful for toxic shock, nec fasc)
- Anti-parasitic: Malaria, Babesia, Toxoplasma
- Some people tolerate poorly with GI symptoms, some tolerate well

- Excellent oral bio-availability
- Treats most/all anaerobes
- No Bacteroides fragilis resistance
- Low risk of C. Diff
- Anti-parasitic: Giardia, Entamoeba, Trichomonas
- Poor tolerability w GI symptoms, metallic taste, anorexia, nausea, and eventually peripheral neuropathy

Case 4

- GR is a 52yo man with prior history of diverticulitis, admitted with sudden onset of LLQ abdominal pain and fever within past 24 hours, hemodynamically stable.
  - Blood cultures + E coli, S to ceftriaxone on HD#1
  - Treated w IV ceftriaxone and metronidazole, no further positive blood cultures
  - Abdominal/pelvic CT shows small fluid collection adjacent to sigmoid bowel with minimal adjacent inflammation and no obvious ongoing bowel leak
  - Percutaneous aspiration of collection by IR is uncomplicated, culture also grows pan-S E coli
  - Clinically improved, ready for discharge – **how long to treat with antibiotics?**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection

R.G. Sawyer, J.A. Claridge, A.B. Nathens, O.D. Rotstein, T.M. Duane, H.L. Evans, C.H. Cook, P.J. O'Neill, J.E. Mazuski, R. Askari, M.A. Wilson, L.M. Napolitano, N. Namias, P.R. Miller, E.P. Dellinger, C.M. Watson, R. Coimbra, D.L. Dent, S.F. Lowry,* C.S. Cocanour, M.A. West, K.L. Banton, W.G. Cheadle, P.A. Lipsett, C.A. Guidry, and K. Popovsky, for the STOP-IT Trial Investigators†

STOP-IT Trial:
Study to Optimize Peritoneal Infection Therapy

- 518 patient, 23 hospitals (US + Canada) – **RCT of standard course abx (2-10 days) vs. 4 days abx after source control of intra-abdominal infections**:
  - 34% infections from colon or rectum, 14% small bowel, 14% appendix
  - 11% had cancer, 10% had IBD, 15 % had DM
  - Source control by: 33% percutaneous drainage (IR), 26% surgical resection, 21% surgical drainage alone
- Composite endpoint: surgical-site infection, recurrent intraabdominal infection, or death within 30 days after the index source-control procedure
- **Outcome – NO DIFFERENCE between 2 groups** (22% reached endpoint in each group)
- Limits: 18% nonadherence to the protocol and a lack of statistical power to ensure equivalence, lack of data on antibiotic-related adverse events, differences in postoperative hospital stays in the two study groups

Sawyer RG et al. NEJM 2015

Treating bacteremia with shorter antibiotic course

Multiple studies suggest duration of < 14 days appropriate for many patients, and/or early transition to oral antibiotics

- Cholangitis/bacteremia retrospective 263 pts: All had biliary duct drainage
  - Short course therapy (SCT, ≤ 7 days) was noninferior to long course (LCT, ≥ 8 days)
- Uncomplicated gram-neg CA-bacteremia
  - 604 pts, Enterobacteriaceae, source control
  - 7 days equivalent to 14 days

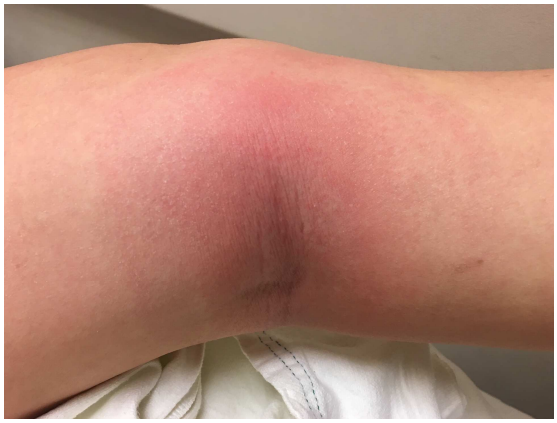
Chotiprasitsakul D et al. CID 2018.
Yahav D et al. CID 2018.

Antibiotics with excellent oral bioavailability:

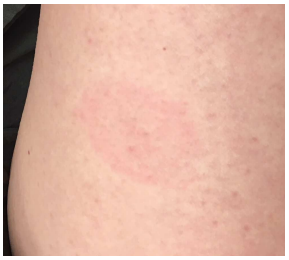
- Linezolid
- Levofloxacin, ciprofloxacin, moxifloxacin
- Doxycycline, minocycline
- Clindamycin, metronidazole
- Sulfamethoxazole-trimethoprim
- Azithromycin
- Fluconazole
- (Amoxicillin, amox-clav: variable, average around 75%)

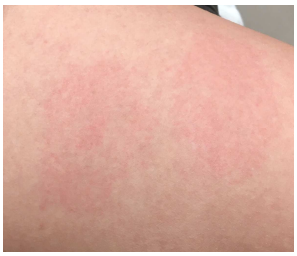
Case 5

- JC is a 50yo woman currently 36wks pregnant presenting w fevers, severe headache, malaise, low platelets, elevated AST/ALT...

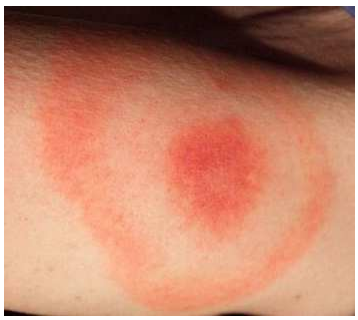


YIKES!





Tetracyclines



- Tetracycline
  - Rarely used, difficult dosing
- Doxycycline
  - Atypical resp pathogens, Staph aureus skin infections, STDs, (Enterococcus UTI), many others (Lyme, Rickettsia – RMSF, anthrax…)
  - When in doubt, add Doxy
- Minocycline
  - Same as Doxy (w more side effects) + additional activity for Stenotrophomonas

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Drug-PREGNANCY Interactions (1)

Drugs:	Severity:	Documentation:	Summary:
PREGNANCY -- DOXYCYCLINE [Systemic]	S Major	Unknown	Doxycycline is rated as US FDA Category D. Studies, adequate well-controlled or observational, in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk.

Drug-LACTATION Interactions (1)

Drugs:	Severity:	Documentation:	Summary:
LACTATION -- DOXYCYCLINE [Systemic]	S Major	Unknown	Infant risk cannot be ruled out: Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when Doxycycline is used during breast-feeding. Weigh the potential benefits of treatment against potential risks before prescribing Doxycycline during breast-feeding.

Macrolides

- Erythromycin
  - Bowel prep, gut motility agent
- Azithromycin
  - Walking pneumonia, pharyngitis, atypical respiratory pathogens, STDs, mycobacteria
  - GI intol, QT prolongation
- Clarithromycin
  - Walking pneumonia, pharyngitis, atypical resp pathogens, MAI/mycobacteria, H. pylori
  - More GI intol, metallic taste, QT prolongation, CYP3A4 inhibitor

Thanks, and good luck…