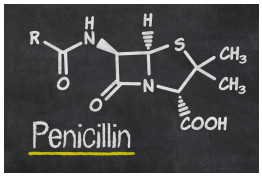
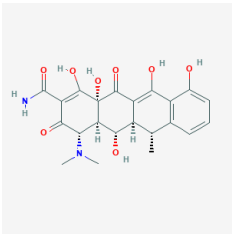



# Antibiotic Update!
## A rapid update and pearls for the Hospitalist: Part II



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

- 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
- Cefiderocol

# 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

- 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 |

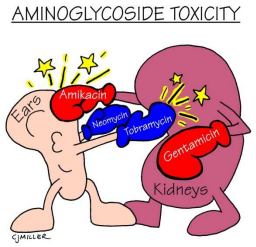
* Nonstandardized susceptibility


**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

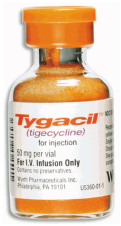
| Type | Class | Characteristics | Example Enzyme/Pathogen |
|---|---|---|---|
| Narrow-spectrum | A | Hydrolyze penicillin | TEM; SHV<br>Enterobacteriaceae |
| ESBL (extended spectrum β-lacatmase) | A | Hydrolyze narrow and extended spectrum Beta-lactams | TEM; SHV; CTX-M-15<br>Enterobacteriaceae |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

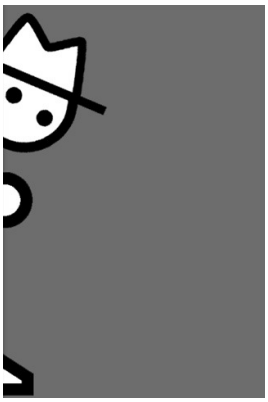

"Eat some grass, and call me in the morning."

# 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!*

* (anti-anaerobe therapy not needed for most episodes of aspiration pneumonia)

# 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 oral anaerobes and gram-positive bacteria **BUT** rising resistance among Staph aureus isolates and B-hemolytic Strep isolates (25-50%), NO LONGER reliable as an empiric agent alternative to Blactam for prevention of surgical site infection ("**antibiotic myth**")
- 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
- Lower 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

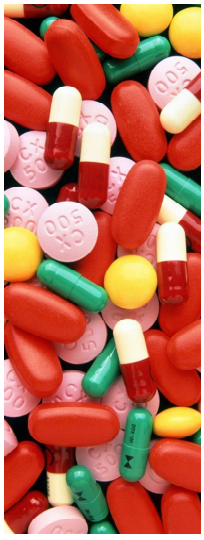
Chotiprasitsakul D et al. CID 2018.
Yahav D et al. CID 2018.



## Antibiotics with excellent oral bioavailability:

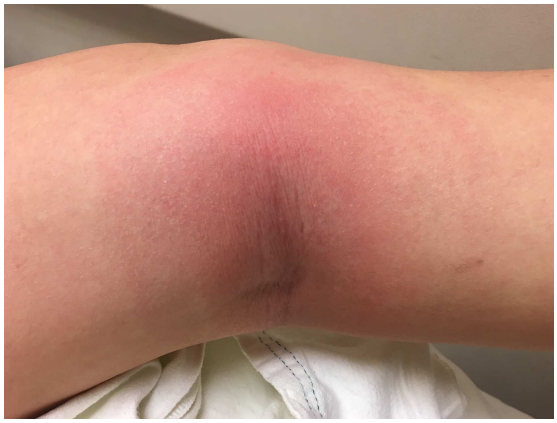
Linezolid, tedizolid
Levofloxacin, ciprofloxacin, moxifloxacin, delafloxacin
Doxycycline, minocycline, omadacycline, eravacycline
Clindamycin, metronidazole
Sulfamethoxazole-trimethoprim
Azithromycin, clarithromycin
Fluconazole, posaconazole, voriconazole
Rifampin

(Amoxicillin, amoxicillin-clavulanate: variable, average around 75%)

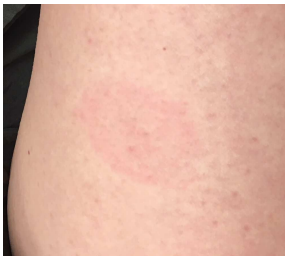


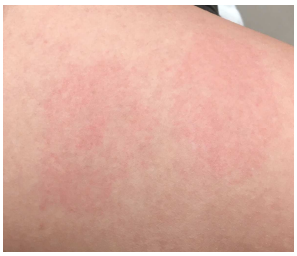
# Case 5

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

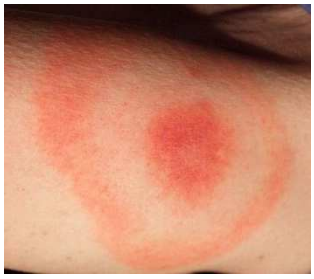


**YIKES!**





# Tetracyclines



Tetracycline
- Rarely used, difficult dosing

Doxycycline
- Atypical resp pathogens, Staph aureus skin infections, STIs (chlamydia, syphilis), (Enterococcus UTI), many others (Lyme, Rickettsia – RMSF, anthrax…)
- Guidance to avoid doxycycline in pediatric patients and pregnant women ("**antibiotic myth**") was largely based on data with tetracycline – recent evidence supports safety of doxycycline for children and pregnant women

Minocycline
- Same as Doxy (w more side effects) + additional activity for Stenotrophomonas

# Macrolides


Erythromycin
- Bowel prep, gut motility agent

Azithromycin
- Atypical respiratory pathogens, mycoplasma, mycobacteria, traveler's diarrhea
- Group A Strep antibiotic resistance to azithromycin/clarithromycin (12-15% in 2007) and clindamycin are increasingly common
- Strep pneumoniae resistance to azithromycin ~ 40% in 2021
- GI intolerance, QT prolongation

Clarithromycin
- Atypical respiratory pathogens, MAI/mycobacteria, H. pylori
- More GI intolerance, metallic taste, QT prolongation, CYP3A4 inhibitor



# Thanks, and good luck…