Antibiotic Update!
A rapid update and pearls for the Hospitalist

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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:
  - Site-specific antibiogram and empiric antibiotic recommendations
  - 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:

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/inflammation 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 TO 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 ~ 4gm
- Vancomycin AUC monitoring is coming...

<table>
<thead>
<tr>
<th>CrCl</th>
<th>Each Dose</th>
<th>Interval</th>
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<tbody>
<tr>
<td>&gt; 45</td>
<td>15-20mg/kg Q8-12h</td>
<td></td>
</tr>
<tr>
<td>30-45</td>
<td>15-20mg/kg Q24h</td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>15-20mg/kg Q48h</td>
<td></td>
</tr>
<tr>
<td>HD</td>
<td>15-20mg/kg Post-HD</td>
<td></td>
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Treating CDiff

Oral vancomycin 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

Optimal antibiotics for severe Staph aureus infections

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

MRSA:
- Vancomycin
- Daptomycin
- Linezolid (tedizolid)
- (Tigecycline, Cefaroline, 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%)
Newer Agents

• 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, cephalaxin
  • For MSSA (if PCN-resistant):
    • Amoxicillin-clavulanate, cephalaxin, 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, asptic meningitis, bone marrow suppression, hepatitis, methemoglobinemia (with severe G6PD deficiency)
• Renal: pseudo elevation in serum Cr, reversible hyperkalemia, real nephrotoxicity (interstitial nephritis)

FDA updates warnings for fluoroquinolone antibiotics

• 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 β-lactam
• However, should not be used for sinusitis, uncomplicated UTI, chronic bronchitis, when alternatives exist, due to toxicities:
  • Tendons, muscles, joints, nerves and CNS toxicities
  • Deterent, 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)

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
• Ceftazidine – effective, low toxicity
• Cefepine – effective, low toxicity except rare encephalopathy
• Pipercillin/piperacillin-tazobactam – effective, moderate toxicity
• Aztreonam – rising resistance, other agents for β-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 β-lactam for empiric use
• Colistin, Polymyxin B
• Cefazidime/avibactam, cefotolozane/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!

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

Case 3 – Alternate ending!

Blood cultures grow: PSEUDOMONAS AERUGINOSA

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC (mcg/mL)</th>
<th>Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>&lt;8</td>
<td>Susceptible</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>&gt;16</td>
<td>Resistant</td>
</tr>
<tr>
<td>Cefepime</td>
<td>32</td>
<td>Resistant</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>&gt;16</td>
<td>Resistant</td>
</tr>
<tr>
<td>Colistin</td>
<td>1</td>
<td>Susceptible</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>&gt;2</td>
<td>Resistant</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>4</td>
<td>Susceptible</td>
</tr>
<tr>
<td>Imipenem</td>
<td>8</td>
<td>Resistant</td>
</tr>
<tr>
<td>Levoflaxacin</td>
<td>&gt;8</td>
<td>Resistant</td>
</tr>
<tr>
<td>Meropenem</td>
<td>&gt;8</td>
<td>Resistant</td>
</tr>
<tr>
<td>Piperacillin/Tazobactam</td>
<td>&gt;128</td>
<td>Resistant</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>&lt;=2</td>
<td>Susceptible</td>
</tr>
</tbody>
</table>

* Nonstandardized susceptibility

Now what do you do?

What is this???

New β lactam + β lactamase inhibitor combos:

- Ceftolozane-tazobactam
  - Activity against MDR Pseudomonas aeruginosa
  - Activity against some carbapenem-resistant Enterobacteriaceae (CRE)
  - Not active against NDM-1 CRE

- Ceftazidime-avibactam
  - Activity against MDR Pseudomonas aeruginosa
  - Activity against some carbapenem-resistant Enterobacteriaceae (CRE)
  - Does NOT improve activity vs Pseudomonas, Acinetobacter, Stenotrophomonas

- 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**

<table>
<thead>
<tr>
<th>Type</th>
<th>Class</th>
<th>Characteristics</th>
<th>Example Enzyme/Pathogen</th>
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<tbody>
<tr>
<td>Narrow-spectrum A</td>
<td>A</td>
<td>Hydrolyze penicillin</td>
<td>TEM, SHV</td>
</tr>
<tr>
<td>ESBL (extended spectrum β-lactamase)</td>
<td>A</td>
<td>Hydrolyze narrow and extended spectrum Beta-lactams</td>
<td>TEM, SHV, CTX-M15</td>
</tr>
<tr>
<td>Some carbapenemases</td>
<td>A</td>
<td>Hydrolyze carbapenem</td>
<td>KPC, IM</td>
</tr>
<tr>
<td>Metallo-β-lactamases B</td>
<td>B</td>
<td>Hydrolyze carbapenem</td>
<td>VIM, IMP, NDM</td>
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<tr>
<td>Cephalosporinases C</td>
<td>C</td>
<td>Hydrolyze cephalosporins &amp; oxyiminobeta-lactams</td>
<td>AmpC</td>
</tr>
<tr>
<td>OXA-type enzymes D</td>
<td>D</td>
<td>Hydrolyze oxacillin, oxyiminobeta-lactams, carbapenems</td>
<td>OXA</td>
</tr>
</tbody>
</table>

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), Strept, VRE, some 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 ABSSSI and CABP
    - Emerging data for Mycobacterium abscessus infections
    - Lower GI side effects than tigecycline
    - Decreased parasympathetic tone -> Increasing HR by 8-10 bpm
  - **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?

  **Get some grass, and call me in the morning**

  **Empiric antibiotics to treat bowel flora in immunocompetent patient without significant past antibiotic exposure:**
  - Ampicillin/subbactam
  - 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 → anaerobes 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. (e.g., 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?

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

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 with fevers, severe headache, malaise, low platelets, elevated AST/ALT...

Tetracyclines

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

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, MA/mycobacteria, H. pylori
  - More GI intol, metallic taste, QT prolongation, CYP3A4 inhibitor
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


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...