Introduction to Antibiotics and MRSA

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Objectives

- Antibiotic classes and what they cover
- MRSA coverage
- Cases

Penicillins

- General Class properties
  - Beta-lactam antibiotics that inhibit penicillin binding proteins (PCBs)
  - Bactericidal
  - In general, gram positive coverage is good in earlier generations with gram negative coverage increasing in later generations
- 1st generation: Good gram + coverage, some anaerobes and few gram negative cocci (neisseria)
  - Penicillin G (procaine): IV form, used primarily for neurosyphilis but also specific infections including enterococcal endocarditis and actinomyces
  - Penicillin benzathine: IM form, used for non-neuro syphilis
  - Penicillin V: PO form (Rarely used)

Penicillins

- 2nd generation: Improved gram negative coverage, especially when paired with beta-lactamase inhibitor
  - Ampicillin: IV form, can be paired w/ sulbactam
  - Amoxicillin: PO form, can be paired w/ clavulanate
- Anti-staphylococcal: Effective against penicillinase producing staph, but lose enterococcus, listeria, and neisseria coverage
  - Nafcillin: IV form
  - Oxacillin, dicloxacillin, cloxacillin: PO forms

Penicillins

- 3rd/4th generation: Dramatically increased gram – coverage, including pseudomonal coverage.
  - Ticarcillin: IV form; paired w/ clavulanate
  - Piperacillin: IV form; paired w/ tazobactam; often used for hospital empiric gram negative coverage

Cephalosporins

- General properties:
  - 2-5% cross-reactivity with PCN allergy.
  - As with PCNs, gram + and gram – coverage are inversely proportional with gram negative coverage increasing by generation (except 5th)
  - Cidal
- 1st generation: Good gram + coverage including MSSA, but no enterococcal coverage or listeria. Some gram – coverage including E. coli, K. pneumoniae
  - Cefazolin: IV form
  - Cephalexin, cefadroxil: PO forms

Cephalosporins

- 2nd generation: Increased gram - coverage, decreasing gram + coverage from 1st generation.
  - Cefuroxime: IV form; has activity vs. H. flu but not Bacteriodes; induces chromosomal beta-lactamases in Enterobacter & Proteus
  - Cefoxitin, cefotetan: IV forms; have activity vs. Bacteriodes but not H. flu; same inducing of chromosomal beta-lactamases in Enterobacter & Proteus
  - Cefaclor, cefprozil: PO forms

Cephalosporins

- 3rd generation: highly active vs. enteric gram negative bacilli, lose some activity vs. gram positives and are inactive vs. enterococci, Listeria, and Acinetobacter
  - Ceftriaxone, cefotaxime: IV forms, no P. aeruginosa
  - Ceftazidime: IV form; has activity vs. Pseudomonas aeruginosa
  - Cefixime, cefdinir: PO forms
- 4th generation: added coverage vs. inducible chromosomal AmpC beta-lactamase producers and P. aeruginosa
  - Cefepime: IV form; beware seizures (especially in ESRD)

Cephalosporins

- 5th generation: Lose P. aeruginosa coverage, but gain MRSA coverage
  - Ceftaroline: IV form

Monobactams

- General properties: No cross-reactivity with PCN allergy. Good gram negative, including Pseudomonas, coverage. No gram + or anaerobic coverage.
  - Aztreonam: IV form

Fluoroquinolones

- General Properties:
  - Directly inhibit bacterial DNA synthesis by inhibiting DNA gyrase & topoisomerase IV.
  - Cidal
  - Bioavailability 100% for orals (so don't use IV unless the patient can't swallow!)
  - Good gram - coverage, gram + coverage increases with generation. Also generally covers atypical PNA microbes.
- 1st generation:
  - No longer used (cinoxacin, nalidixic acid)

Fluoroquinolones

- 2nd generation: No strep pneumo coverage, so not used for pneumonia
  - Ciprofloxacin: PO & IV; no activity vs. pneumococcus so not useful for pneumonia (can be used as an adjunct for anti-Pseudomonal coverage in HCAP).
  - Norfloxacin: PO; similar to cipro, SBP prophylaxis
  - Ofloxacin: PO; similar to cipro
- 3rd generation: Better strep pneumo coverage
  - Moxifloxacin: PO & IV; only FLQ w/ clinical activity vs. anaerobes; less gram negative coverage than cipro; Unable to achieve therapeutic levels for Pseudomonas coverage
  - Levofloxacin: PO & IV; similar coverage as cipro for gram negatives except slightly less active vs. Pseudomonas.
  - Gemifloxacin: PO

Macrolides

- General Properties:
  - Bind to the 50S subunit of bacterial ribosomes to ultimately inhibit protein synthesis.
  - Static
  - Active vs. gram positives and atypicals (Mycoplasma, Ureaplasma, Chlamydophilia, and Chlamydia).
  - Anti-inflammatory

- Agents:
  - Erythromycin: PO & IV; significant GI side effects, now used mainly as gastric emptying agent in gastroparesis.
  - Clarithromycin: PO; used for MAC prophylaxis when CD4<50
  - Azithromycin: PO & IV; used for MAC prophylaxis when CD4<50; somewhat better vs. H. flu than clarithro & erythro
  - Telithromycin: PO; technically a Ketolide, so resistance to the macrolides does not always confer resistance to telithromycin; beware hepatotoxicity, myasthenia gravis, and visual disturbances (therefore not recommended as first line agent)

Tetracyclines

- General properties:
  - Bind to the 30S subunit of bacterial ribosomes to ultimately inhibit protein synthesis.
  - Active vs. rickettsial infections, spirochetes, atypicals, chloroquine-resistant malaria (doxy, and only somewhat), gram positives (including CA-MRSA), many enteric gram negs, actinomycosis, nocardiosis, tularemia.
  - Don't give with penicillins, or to children < 8
- Agents:
  - Doxycycline: PO & IV; best vs. tick borne disease/spirochetes, and malaria. Good PNA and skin/soft tissue coverage.
  - Minocycline: PO & IV; used often for acne
  - Tigecycline: IV; technically a glycylcycline; has better MRSA and VRE coverage but has black box warning for increased mortality). 4P's of tigecycline (holes in activity spectrum): Providencia, Proteus, Pseudomonas, and Pee.

Metronidazole

- Works via production of toxic free radicals
- Good anaerobe coverage
- Some coverage against parasites (trichomonas, amebiasis)
- Used for C diff treatment

Carbapenems

- General Properties:
  - < 5% cross-reactivity with PCN allergy
  - Very broad spectrum, including gram negatives (including extended spectrum beta-lactamases [ESBL]), anaerobes, and gram positives (including Enterococcus faecalis & Listeria).
  - Generally not active vs. Stenotrophomonas maltophilia, Burkholderia cepacia, Enterococcus faecium, MRSA
- Agents:
  - Doripenem, imipenem, meropenem: IV forms; active vs. Pseudomonas aeruginosa. Beware CNS toxicity w/ imipenem. Imipenem is given w/ cilastin to prevent proximal tubule necrosis.
  - Ertapenem: IV form; once daily, but less coverage vs. Pseudomonas aeruginosa, Acinetobacter, and gram positives (specifically enterococci & PCN resistant pneumococci)

Aminoglycosides

- General Properties:
  - Bind the 16S portion of the 30S ribosomal subunit, leading to inhibition of protein synthesis.
  - Cidal
  - Active vs. many gram negs (enterics, Pseudomonas, Acinetobacter, H. flu), but usually not vs. Burkholderia cepacia, Stenotrophomonas maltophilia, and anaerobes.
  - Generally active in vitro vs. gram positives, but NEVER as monotherapy (as previously stated, can be used for synergy).
  - Somewhat vs. mycobacteria (streptomycin vs. MTB, amikacin vs. M. fortuitum/abscessus/chelonae).
  - Beware of nephro/ototoxicity (dose dependent).

Aminoglycosides

- Agents:
  - Streptomycin: IM only; first of the class, derived from the actinobacterium Streptomyces griseus, active vs. Mycobacterium tuberculosis
  - Tobramycin: IV & nebulized; dose based off ideal body weight (IBW), Often used for pseudomonas and in CF patients
  - Gentamicin: IV; used often in combination for invasive enterococcal infections
  - Amikacin: IV & IM; active vs. Mycobacterium fortuitum, abscessus, & chelonae

Colistin

- Polymixin antibiotic
- Cidal
- Disrupts the outer cell membrane by competitively displacing divalent cations from the phosphate groups of membrane lipids (i.e. acts as a detergent).
- Can overcome cell wall resistance mechanisms (i.e. to meropenem, so can give meropenem to resistant organism if also giving colistin)
- Active vs. some gram negs (primarily vs. P. aeruginosa & A. baumannii).
- Antibiotic of last resort, nephrotoxocity and peripheral neuropathy are major side effects

MRSA antibiotics

- Mechanism of resistance: : *mecA* conveys resistance by encoding PBP 2a, an inducible protein that establishes resistance to the semisynthetic penicillinase resistant beta-lactams as well as all cephalosporins (except ceftaroline).

- Oral Agents:
  - TMP/SMX: CA-MRSA only.
    - act synergistically to inhibit synthesis of tetrahydrofolic acid (THF);
    - Active vs. aerobic gram positives & gram negatives, Pneumocystis, and some protozoa & misc. organisms (Nocardia, Cyclospora, Isospora, Yersinia, Vibrio cholerae, and Mycobacterium marinum).
  - Doxycycline: CA-MRSA only, see tetracycline section
  - Clindamycin: CA-MRSA only; if erythromycin resistance, check the D-test (to rule out inducible resistance to clindamycin)
    - a lincosamide; binds 50S subunit of ribosome to inhibit protein synthesis; static
    - Active vs. gram positives & anaerobes.
  - Linezolid: watch out for pancytopenia & serotonin syndrome
    - Only oral option for hospital acquired MRSA

MRSA Antibiotics

- IV options
  - Vancomycin:
    - bacteriostatic;
    - good vs. invasive MRSA; beware MIC creep; want MIC < 2 (debatable if MIC=2, but would probably use something else if MIC=2 and it is a serious infection)
  - Daptomycin:
    - bactericidal; good vs. invasive MRSA; inactivated by type II pneumocytes, so not effective in MRSA pneumonia; beware MIC creep; want MIC < 1; watch CPK
  - Ceftaroline: See Cephalosporins
  - Tigecycline: See tetracyclines
  - Televancin/dalbavancin:
    - bactericidal
    - Weekly dosing, but very expensive
  - Synercid (Quinupristin-dalfopristin):
    - bactericidal (each alone is static, together is cidal)
    - well established for skin & soft tissue infections, less so for invasive MRSA
    - dosing requires central venous access

MRSA Antibiotics

- Rifampin (Cannot be used alone):
  - bactericidal
  - rapid resistance develops so NEVER used alone
  - used in combination w/ other agents for prosthetic device or bone infections

Empiric Coverage

- General principles
  - Where is the infection likely to be coming from?
  - What type of organisms live there?
  - What kind of infections has the patient before, and are they exposed to hospital-acquired organisms?
  - IV vs. PO?
  - What's in your hospital antibiogram?
    - https://uhcommunity.uhhospitals.org/AntimicrobialStewardshipProgram/Documents/2016_Antibiograms_final_2017-05-22.pdf
- Source: Urine
  - Usually E. coli, some other scattered organisms including proteus, S. saphrophyticus in the community
  - For community acquired, consider cephalexin, TMP-SFX, Nitrofurantoin (young, healthy, uncomplicated), or cipro (can induce resistance).

Empiric Coverage

- UTI continued
  - In catheter associated UTIs or recurrent or complicated UTIs, use prior culture data to guide therapy
- Pneumonia
  - CAP: Azithro or levofloxacin in outpatient, Ceftriaxone + azithro or levofloxacin inpatient
  - HCAP, HAP, VAP: Anti-pseudomonal gram negative coverage + vanc if clinical suspicion for MRSA or nares + for MRSA, + or – azithro if atypicals are a possibility

Empiric Coverage

- Skin and soft tissue Infections:
  - Purulent or not?
  - Host factors, like diabetes present?
  - Everyone needs good gram + coverage.
  - Outpatient consider doxycycline, dicloxacillin, Bactrim.
  - If purulent, high concern for staph, consider MRSA coverage if requiring hospitalization
  - Only need resistant gram negative coverage if diabetic or immunosuppressed or heavy contact with healthcare system

Empiric Coverage

- Intra-abdominal source:
  - Want good gram – and anaerobe coverage
  - Augmentin/Unasyn with good coverage
  - Can use combination (fluoroquinolone + flagyl) as well
  - For pseudomonas coverage, use Pip-Tazo or meropenem
- Neutropenic fever:
  - Resistant gram – coverage REQUIRED with pseudomonas coverage (Pip-tazo, cefepime, meropenem)
  - MRSA not mandatory, but add if pt has a line or port, or if pneumonia is suspected clinically
  - Fungal coverage only if not improvement

MKSAP 1

A 48-year-old man undergoes emergency department evaluation for a painful, swollen right thigh following a recent fall at home. The patient has multiple sclerosis and is taking a tapering course of corticosteroids. He also has long-standing type 2 diabetes mellitus complicated by peripheral sensory neuropathy and recurrent gastroparesis. Current medications are prednisone and insulin glargine and insulin lispro.

On physical examination, temperature is 38.4° C (101.2° F). BMI is 17.5. The right thigh has a fluctuant, erythematous, tender mass surrounded by an area of skin thickening and erythema extending 7 cm beyond the bulging area. Neurologic examination findings are consistent with multiple sclerosis as well as areflexia and lack of sensation and proprioception in the feet.

While in the emergency department, the patient vomits twice and is given intravenous fluids. In the operating room, the surgeons incise and drain the thigh lesion, and cultures are obtained. Imipenem, vancomycin, and intravenous fluids are begun, and the patient is hospitalized.

Laboratory studies immediately following surgery find a leukocyte count of 24,000/μL (24×10^9/L) with a left shift and creatinine of 0.4 mg/dL (35.4 μmol/L). Gram stain of surgical drainage fluid shows many leukocytes and occasional gram-negative rods.

On hospital day 2, his condition has stabilized and he is no longer vomiting. The culture of the drained fluid shows *Klebsiella oxytoca* that is resistant to ampicillin and cefazolin but susceptible to all carbapenems, trimethoprim-sulfamethoxazole, and colistin. The patient asks to be discharged for home care by his wife.

MKSAP 1

Which of the following is the most appropriate therapy?

A. Colistin
B. Ertapenem
C. Imipenem and vancomycin
D. Linezolid

MKSAP 1 Answer

B – Ertapenem

Good gram negative coverage, once daily dosing, less toxic than colistin

MKSAP 2

- A 24-year-old man is evaluated in the hospital for new-onset high fever, chills, and rigors. He reports no other symptoms. The patient was recently diagnosed with diffuse large B-cell lymphoma for which he received his first cycle of multiagent chemotherapy 10 days ago. He does not have an indwelling venous catheter.

- On physical examination, temperature is 39.0° C (102.2° F), blood pressure is 90/40 mm Hg, pulse rate 130/min, and respiration rate is 24/min. There is no evidence of rash or mucositis. The chest is clear to auscultation. Other than tachycardia and hypotension, cardiac examination is normal. The abdomen has normal bowel sounds and is nontender.

- There is no evidence of a perianal abscess. Laboratory studies show hemoglobin of 11.5 g/dL (115 g/L), a leukocyte count of 800/μL (0.8×10^9/L) with 10% neutrophils and 90% lymphocytes and platelet count of 100,000/μL (100×10^9/L). Chest radiograph is normal. Blood and urine cultures are pending.

MKSAP 2

Which of the following is the most appropriate immediate next step in treatment?

A. Begin empiric piperacillin-tazobactam
B. Begin targeted antimicrobial therapy once culture results are available
C. Begin vancomycin
D. Begin vancomycin, amphotericin, and acyclovir

MKSAP 2

A – Begin piperacillin-tazobactam

Neutropenic fever should be treated with broad spectrum gram negative coverage such as cefepime, piperacillin-tazobactam, or meropenem. Vanc should be added if the patient has a line or port, or if pneumonia is suspected. Fungal coverage can be added if the pt is still having fevers 4-5 days into therapy.

Case 3

A 37 yo carpenter is admitted with fever, chills, cough, headache and back pain x 1 week. He has an oral temp of 38.7° C, HR 108, BP 110/50, RR 20. Numerous puncture sites are evident in both arms. He has a 2/6 mid systolic murmur and a 1/6 early diastolic murmur, both heard best at the left upper sternal border. Small hemorrhages are noted under his fingernails.

WBC count is 22,000 with 94% neutrophils. Urinalysis reveals 1 wbc (normal < 5) and 112 rbc (normal < 3)/low powered field. 2 of 2 sets of blood cultures are positive for gram positive cocci in clusters.

Cultures are confirmed as MRSA. The cardiothoracic surgeons do not feel immediate valve replacement is indicated. 7 days later his back pain is worse. He has weakness in both lower extremities and urinary incontinence. MRI reveals vertebral osteomyelitis with a spinal epidural abscess at T8-T10. Blood cultures drawn 3 and 5 days into therapy are no growth. The neurosurgeons tell you he is failing antibiotics and you need to change therapy. The MIC (minimum inhibitory concentration) of his *S. aureus* isolate to vancomycin is 1 µg/ml. Vancomycin trough levels on days 3 and 5 are 17.2 and 18.6 µg/ml, respectively.

Case 3

What should you do?

A. Add gentamicin 1.5 mg/kg every 8 hours to the vancomycin

B. Continue vancomycin at the current dose of 1500 mg every 12 hours

C. Increase the vancomycin dose to 2500 mg every 12 hours

D. Replace vancomycin with daptomycin 10 mg/kg every 24 hours

Case 3

B – Continue current vancomycin dosing

The MRSA in vanc susceptible by MIC and the patient is in the therapeutic range. In this case, he lacks source control.