What every MD should know about antibiotics

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It all seems pretty confusing, there are literally hundreds of antibiotics—including new ones being released daily—and it is difficult to keep them all straight. Try to think of them as families with each member having their own peculiar quirks. What follows is a brief overview of each family highlighting important points about their use and abuse.

1. Penicillins

Despite the passage of time, the penicillin agents remain some of the most common antimicrobials prescribed by physicians. When using these drugs, keep the following in mind:

The "Historical" development of Penicillin agents	
"Natural" penicillins (1940s) Penicillin G Phenoxymethyl PCN (PenVK)-oral	The "first" penicillin is still good for treatment of strep infection (group A strep cellulitis; viridans streptococci) and less common diseases such as syphilis and actinomycosis. When appropriate, use amoxicillin (500 mg PO Q 6hr) or phenoxymethyl penicillin (PenVK) for oral Rx.
Anti-staphylococcal PCNs (1950s) Oxacillin Nafcillin Methicillin Dicloxacillin (oral)	Poor activity of PCN G against *Staph* aureus led to development of the "anti-staphylococcal penicillins" such methicliin and oxacillin/ nafcillin. Although methicillin is no longer used (+ kidney toxicity), it survives as a laboratory "marker" to this class of agents. When "stepping down" to an oral agent, use dicloxacillin (250-500 Q6hr) for oral therapy.
"Gram-negative" PCNs (1950s) Ampicillin Amoxicillin (oral)	Ampicillin was the first PCN with reliable activity against *E. coli,* but also good activity against streptococci (including most enterococci), and listeria (meningitis). Amoxicillin is the oral version with the best absorption and the drug of choice when "stepping down" to oral therapy.
Extended-spectrum PCNs (1970s) Piperacillin Ticarcillin	These agents have an even better gram-negative spectrum, including activity against organisms with an "extended-spectrum" B-lactamase such as resistant *E coli, Enterobacter*—and in some cases--*Pseudomonas aeruginosa.* They are effective against streptococci, and have considerable activity against anaerobes.
B-lactam/B-lactamase inhibitors (BL/BLI) Amoxicillin/clavulanate (Augmentin) Ampicillin/sulbactam (Unasyn) Piperacillin/tazobactam (Zosyn)	In an effort to "broaden" activity of "extended spectrum penicillins", chemists added a B-lactamase "inhibitor" which gives these agents not only improved gram-negative coverage, but activity against *Staph aureus* (MSSA) and most intraabdominal anaerobe. Think of these drugs as broad-spectrum agents useful for "mixed" infections where there may be a combination of aerobes and anaerobes (e.g. aspiration pneumonia; head/neck infection; intraabdominal infection; diabetic foot infection).

Here are a few key points about using these drugs...

- **Ampicillin:** The "original" *E.coli* drug (commonly used for urinary tract infections), about 60% of community isolates are now resistant to ampicillin—don't rely on this drug in critically ill patients unless you have susceptibility in hand..
- **Oxacillin/nafcillin:** The anti-staphylococcal penicillins are the "drugs of choice" for MSSA (methicillin susceptible *Staph aureus*) but *do not* have activity against methicillin-resistant *Staph aureus* (about 50% of community isolates).
- **BL/BLI agents:** These agents have "broad" activity against streptococci, *Staph aureus,* gram negative bacilli and anaerobes, an appropriate spectrum for "mixed" infection such as intra-abdominal and diabetic foot infection.
  - **Ampicillin/sulbactam** (Unasyn) is a good broad spectrum but *lacks* activity against *Pseudomonas aeruginosa* and MRSA. **Amoxicillin/clavulanic acid** (Augmentin) has similar activity and is a good drug for a "step down" oral agent.
  - **Piperacillin/tazobactam (**Zosyn) has even broader activity (~ 50% of *Pseudomonas aeruginosa* isolates) but is expensive (~50-$100 per day) and is usually "overkill"—once you get a positive culture, cut back to a more selective (and cheaper) agent if possible (most patients with "community-acquired" infection really don't need *Pseudomonas* coverage!)

Watch Out!

Penicillin allergy: The main potential "downside" of penicillin therapy is allergy—especially the possibility of IgE mediated "hives" or "anaphylaxis. Before you use these agents, always ask the patient (or a close family member) about a previous history of rash or penicillin allergy. This is not a minor problem—in the United States, an estimated 250-400 patients die each year following penicillin anaphylaxis. Although many cases can be avoided by a proper history, an acute allergic reaction can occur in anyone, even in those who have previously tolerated the agent.

2. Cephalosporins

The cephalosporins are safe, reliable and are some of the most common antibiotics used in the hospital. Here is a quick way to keep the many agents in mind, thinking of them as different "generations" with successive variations in coverage:

The "Quick" Cephalosporin spectrum

Good staph/strep → Good anaerobe → ↑ GNR:+ Pneumo;+CSF → + Pseudo activity → + MRSA

1st Generation	2nd Generation	3rd Generation	4th Generation	5th Generation
Cefazolin Cephalexin (PO) Cephradine (PO) Use for cellulitis and MSSA infections	Cefotetan Cefoxitan Good for mixed infections (Intraabd; diabetic foot) c anaerobes	Cefotaxime Ceftriaxone Cefdinir(PO) Cefixime (PO) Cefpodoxime (PO) Ceftibuten (PO)	Cefepime + *P. aeruginosa* but no MRSA or anaerobe; useful for nosocomial infections	Ceftaroline + MRSA; pneumo E. coli (No Pseudo)

Here are a few key points about using these drugs...

- **Cefazolin:** This drug is quite inexpensive and has excellent strep and staph (MSSA) coverage—it remains quite useful for management of skin/soft tissue infection (except MRSA) and surgical antibiotic prophylaxis.

- **Anti-anaerobic cephalosporins:** Cefotetan and cefoxitan have the best anti-anaerobic activity of any cephaloporins—they remain good agents for "mixed" infection including intraabdominal (appendicitis; diverticulitis; cholecystitis), aspiration pneumonia (lung abscess) and "mixed" skin/soft tissue infection.
- **CNS penetration:** Third generation cephalosporins (cefotaxime; ceftriaxone) have good (20%) CSF penetration—since they have excellent activity against *Streptococcus pneumonia,* they are drugs of choice for bacterial meningitis (but they don't cover Listeria—for this but you need ampicillin).
- **GNR bacteria**: "Higher" generation cephalosporins (3rd and 4th generation) have improved GNR coverage. Cefepime has generally good *Pseudomonas* coverage and is excellent for nosocomial infection (e.g aspiration pneumonia).
- **? MRSA:** The new drug ceftaroline is the first B-lactam with activity against MRSA—this is a good choice when patients have complicated skin/soft tissue infection (50% of community staph isolates are MRSA). The drug is active against penicillin resistant *Streptococcus pneumonia* and is now licensed for community acquired pneumonia.

Tough question

Can you use cephalosporins in PCN "allergic" patient? It depends. In general, avoid cephalosporins in patients with a strong hx of anaphylaxis (e.g. hives, SOB, angioedema, hypotension)—cepalosporins are generally safe in patients with a hx of PCN rash (maculopapular) alone. Nevertheless, always use caution when giving cephalosporins to a patient with suspected PCN allergy (10% x reactivity)—if possible, give first cephalosporin dose in monitored setting.

3. Carbapenems

These B-lactam agents have extremely broad spectrum and are generally reserved for septic patients—especially in those with hx of recent hospitalization or possible nosocomial infection. Note…they ***do not*** have MRSA activity and pending culture results, you may need to add vancomycin in a critically ill patient.

Imipenem; Doripenem, Meropenem	Broad activity including nosocomial GNR (Pseudomonas; Acinetobacter; ESBL GNR), staph/strep (but not MRSA) and excellent anerobic activity. Watch out for seizures, especially with imipenem All these agents are pretty much the same—use what hospital has on formulary.
Ertapenem	Similar to other carbapenems except for no *Pseudomonas* activity. Once daily dosing is good for home administration when treating diabetic foot infection or ESBL bugs.

Here are a few key points about using these drugs…

- **Broad-spectrum drugs for nosocomial infection:** The top three drugs on the list (imipenem; doripenem; meropenem) are essentially equivalent (with minor variations) and have broad activity against most nosocomial GNR (including Pseudomonas: Acinetobacter), staph (MSSA), strep and anaerobes. Reserve these agents for seriously ill patients with suspect nosocomial pathogens.
- **"Once a day" Ertapenem:** This agents lacks *Pseudomonas* coverage but has the advantage of once-daily dosage—patients can be sent home on the convenient dosing of one gram daily (c NL renal function).
- **What they don't cover:** Emerging carbapenem-resistant *Enterobacteriaceae* (CRE)—usually strains of *E. coli* and *K. pneumonia*—are resistant to carbapenems and require alternative agents (e.g. colistin or tigecycline). Carbapenems are also inactive against MRSA (cover these with vancomycin).
- **Toxicities:** These drugs are similar to cepahalosporins—in addition to warnings regarding penicillin toxicity, they may cause seizures, especially when used in high doses in patients with underlying renal disease (this is most common with imipenem and less common with other agents in the class).

4. Quinolones

Because of their excellent absorption (PO levels are close to IV levels), and broad spectrum (including GNRs such as *Pseudomonas aeruginosa*), these have become commonly prescribed agents, especially for urinary tract and respiratory infections. Here is a quick review of the pertinent agents…

1st Generation	2nd Generation	3rd Generation
Ciprofloxacin	Levofloxacin	Moxifloxacin/Gatifloxacin
Mainly GNR (includes Pseudomonas) 50% *Staph aureus* Poor pneumococcal coverage	Respiratory quinolone Good S. pneumonia + Atypicals (mycoplasma; legionella) + *Pseudomonas aeruginosa*	Respiratory quinolones Excellent S. pneumoniae Good GNR (No *Pseudomonas*) Fair anaerobe (Moxifloxacin)

Some key points about using the quinolones…

- **"Once" or "Twice " daily pharmacokinetics:** These drugs are often given once daily (levofloxacin; moxifloxacin) or BID (ciprofloxacin). They have excellent PO absorption—levels similar to that with IV dosing.
- **Toxicity:** Be cautious with the use of these agents in older patients or those with risk factors for prolonged QT interval (electrolyte disorders; selected drugs)—these patients are at risk for ventricular tachycardia.
- **Clinical use:** Respiratory quinolones (levo; moxi; gati) have activity against *both* pneumococcus (including PCN resistant pneumococcus) and "atypical" pathogens such as *Mycoplasma, Chlamydophila* and *Legionella*. Ciprofloxacin has less "gram positive" activity and is usually reserved for gram negative infection.
- **Increased resistance:** Widespread use of these drugs in the community has led to increased resistance, both among staphylococci (over 50% of strains are now resistant) and *E. coli* (~ 20-30% of strains are resistant).

5. Aminoglycosides

Because of the potential for nephro- and ototoxicity, these drugs (gentamicin; tobramycin; amikacin) have lost some of their previous favor; however, with the rise of more resistant GNRs, they are making a comeback. Here are a few key points about using these agents…

- **Pharmacokinetics:** Aminoglycosides have "concentration-dependent" killing—they are as effective (and less toxic) when given as "once-daily" dosing when compared to Q8hr dosing.
- **Activity:** These drugs are active against "facultative" gram negative bacilli such as *Enterobacteriaceae* (*E.coli; Klebsiella; Enterobacter*) and *Pseudomonas aeruginosa.* In general, amikacin seems to have the "best" activity and lowest rate of resistance when compared to other members of the class (gentamicin; tobramycin).
- **Toxicity:** Be careful using these drugs in older patients and those with underlying renal insufficiency—these individuals have a greater risk for ototoxicity and nephrotoxicity. Use aminoglycosides require serum monitoring (work with your pharmacist) and auditory monitoring (for patients receiving more prolonged therapy).
- **An antibiotic "combo"?** These agents have some gram positive activity and are useful as part of a "synergistic" regimen against endocarditis with enterococci, (AG + ampicillin), streptococci (AG + PCN G) and staphylococci (AG + oxacillin).

With increasing gram negative resistance, aminoglycosides are making a comeback—their use may well be necessary for patients with nosocomial GNR infection, provided organisms are demonstrated susceptible.

6. Macrolides

These agents have a long history of safety and tolerability making them excellent drugs for outpatient therapy. Their absorption is not always ideal (approximately 30% following oral administration) but the ability of the drug to concentrate within macrophages extends their potency. The following drugs are currently available:

Erythromycin	Still good for mild to moderate respiratory infection but tough to stomach
Clarithromycin	Similar to erythromycin (but better *H. influenza* coverage) Dosed twice daily—watch out for QT prolongation and drug interactions
Azithromycin	Once daily (Qday) dosing with high concentrations in macrophages *No* significant drug interactions or QT prolongation

Keep in mind the following key points...

- **Antibacterial spectrum:** These agents have primary activity against respiratory pathogens, including pneumococcus and "atypical" pneumonia organisms (*Mycoplasma, Chlamydophila, Legionella*). Both clarithromycin and azithromycin can be used for treatment of MAI (*Mycobacterium avium intracellulare*) infection.
- **QT prolongation:** Whenever using clarithromycin, be especially careful about QT interactions since these may lead to ventricular arrhythmias (this is much less a problem with azithromycin; however, always use caution in patients with a prolonged QT interval or meds/conditions that could lead to one).
- **Resistance:** There is increasing resistance to macrolides among pneumococcus and Group A streptococci (about 20%); be cautious about relying on these agents as sole agents in patients with life-threatening infections.

7. Anti-anaerobe agents

There are several agents that are especially active against anaerobes—these drugs are often valuable in patients with "mixed" (anaerobes + other bugs) infections such as aspiration pneumonia (lung abscess), intraabdominal and diabetic foot infection. Here are some key points about selected drugs:

Clindamycin	This drug is active against intestinal anaerobes , including *Bacteroides fragilis* and anaerobic strep For convenience, the drug can be dosed at 900 mg IV Q 8hr; oral dosing is 450 to 600 mg PO Q 6 hr. The main side effects of the drug are rash and *C. difficile* colitis (warn patients about diarrhea).
Metronidazole	Remains highly active against "strict" anaerobes such as *Bacteroides* and clostridial species; the drug has *poor* activity against microaerophilic anaerobes such as *Actinomyces, Propionobacteria* and streptococci—patients with "mixed" anaerobic infections require an additional agent (PCN or cephalosporin) to cover the "metronidazole-resistant" bacteria.
Cefoxitan	Along with cefotetan, these 2nd generation cephalosporins have the best anti-anaerobic activity
Amp/sulbactam	This drug (and piperacillin/tazobactam) also have excellent anti-anaerobic activity and are useful in mixed anaerobic infection.

Note: When using a BL/BLI drug (piperacillin/tazobactam; ampicillin/sulbactam), there is generally *no need* to add metronidazole for anaerobic coverage unless you need to treat *C. difficile* colitis.

8. Some "Old" standbys

As times change, sometimes "old" drugs make a comeback. Most of these agents are relatively inexpensive and non-toxic. Here are some agents that remain quite useful in selected situations…

Doxycycline	This drug has activity against *Strep pneumonia* (80% of isolates) and *Mycoplasma*—it is a cheap and effective agent for young patients with bronchitis and atypical pneumonias. Doxycycline also has activity against methicillin resistant *Staphylococcus aureus*—use it in suspected MRSA infection but remember that the drug has very little activity against group A streptococci
Minocycline	A drug with a long track record for treatment of acne, minocycline has made a comeback since it has good in vitro activity against MRSA. Minocycline has some unusual toxicities—patients may develop dizziness and rare patients develop a "lupus-like" syndrome (pneumonitis) on the drug.
Nitrofurantoin	Nitrofurantoin has excellent activity against community acquired *E. coli* (90%+ susceptible). It is considered a urinary "anti-septic"—it is useful for cystitis but shouldn't be used for serious invasive gram negative infection such as pyelonephritis. Main toxicities → Pneumonitis or peripheral neuropathy with prolonged Rx. Rare methemoglobinemia
Colistin	This drug is a membrane "detergent" , first used in the early 60s for treatment of GNR infections The drug had a relatively high rate (30%) of nephrotoxicity and fell out of favor when other agents (aminoglycosides) became available; however, it's not made a comeback as a treatment for highly resistant GNR infection (bugs resistant to all standard agents may remain susceptible to colistin).

Keep in mind the following key points…

- **Tick-borne infection:** Doxycycline is the drug of choice for many unusual "zoonotic" or spirochaetal infections such as typhus, Rocky Mountain spotted fever, tularemia, plague,leptospirosis and Lyme disease. Think of adding the agent in critically ill patients with a potential animal exposure (hiking; camping; farms) who fail to respond to standard agents.
- **MRSA:** In addition to their use for respiratory pathogens (e.g. doxycycline for *Mycoplasma pneumonia* and *Chlamydophila*), both minocycline and doxycycline often have activity against MRSA and can be used for mild-moderate MRSA infection.
- **Nitrofurantoin:** This urinary tract agent is reserved for patients with cystitis—it cannot be relied upon for patients with pyelonephritis or more serious urinary tract infections. The drug often has excellent activity against *E. coli* and has the added benefit of safety during pregnancy.
- **Colistin:** A "drug from the past", this parenteral agent may be lifesaving in patients with highly resistant, hospital acquired gram negative infections (e.g. CRE; MDR GNR).

9. Fancy New Agents:

We've seen a number of new agents introduced during the past decade. Most of these drugs tend to be relatively expensive ($50-$200 per day); however, they are a godsend for treatment of infection with selected, highly resistant pathogens.

Daptomycin	This drug has excellent activity against resistant **gram positives** (MRSA; VRE) It is also convenient since it can be dosed once-daily and doesn't require serum monitoring
Linezolid	This is another agent active against resistant **gram-positive organisms** (MRSA; VRE). It has both IV and oral preparations (600 mg PO BID), but they are expensive ($200 a day for two pills) Potential side effects: Thrombocytopenia; Optic neuropathy; Inhibits MAO c serotonin syndrome
Tigecycline	This a new tetracycline (related to minocycline) has activity against gram positives (including VRE), resistant gram negatives (but poor activity against Pseudomonas and Proteus sp) and anaerobes. Good for mixed infection including intraabdominal infection and skin/soft tissue infection Bacteriostatic c low serum levels—may have a high failure rate in septic patients Main side effect→ about 30% of patients have significant nausea/vomiting

When thinking about antibiotics, keep in mind the following...

- Aside from the real problem of allergy, penicillin agents remain excellent drugs against a wide variety of pathogens including group A streptococci and syphilis. Ampicillin, the first "gram negative" penicillin has rising rates of community resistance (E. coli ~ 50% resistant) and cannot be relied on as empiric therapy for serious infection.

- The anti-staphylococcal penicillins (oxacillin; nafcillin) are active against methicillin-susceptible *Staph aureus* (MSSA) but are ineffective against methicillin resistant *Staph aureus* (MRSA) that now accounts for approximately 50% of community acquired staphylococci.

- Extended spectrum penicillins (e.g. piperacillin) have broad gram-negative activity, including activity against nosocomial gram negatives such as *Pseudomonas aeruginosa.* Combination of these drugs with a beta-lactamase inhibitor (e.g. tazobactam; sulbactam) broadens activity to include staphylococci (MSSA) and anaerobes. Use these BL/BLI agents (Zosyn; Unasyn) for coverage of "mixed" aerobic-anaerobic infection such as intraabdominal abscess, aspiration pneumonia and diabetic foot infection.

- First generation cephalosporins (cefazolin; cephalexin) generally have good activity against staphylococci, streptococci and *E. coli*—these agents are good initial therapy for skin/soft tissue infection (provided that MRSA is not present) and mild-moderate UTIs.

- Second generation cephalosporins such as cefoxitan and cefotetan add anaerobic coverage (and slightly better gram negative culture) to the spectrum of first generation cepahalosporins and are good for "mixed" aerobic-anaerobic infection such as intraabdominal abscess and diabetic foot infection.

- The "third" generation cepahalosporins such as cefotaxime and ceftriaxone have improved gram negative coverage (except for *Pseudomonas*), excellent activity against *Streptococcus pneumoniae* and good CSF penetration, making them ideal for lung and CNS infections secondary to pneumococcus.

- Cefepime is a "fourth" generation cephalosporin with good activity against hospital-acquired gram negatives (including *Pseudomonas aeruginosa*), gram positives (MSSA; strep) but has poor activity against anaerobes and MRSA. Ceftaroline is the first cephalosporin with good activity against methicillin-resistant *Staph aureus* (MRSA) and drug resistant *Strep pneumoniae*—this agent is approved for treatment skin/soft tissue infection and community-acquired pneumonia.

- Carbapenems (imipenem; doripenem; meropenem) are broad spectrum agents with activity against nosocomial pathogens such as *Pseudomonas aeruginosa, Acinetobacter* and ESBL producing gram negative bacilli (ESBL *E. coli* and *K. pneumonia*).

- Quinolones have excellent oral absorption and favorable pharmacokinetics (once or twice daily dosing). Ciprofloxacin is primarily a "gram-negative" drug—it has activity against both *Enterobacteriaceae* and *Pseudomonas aeruginosa*, although widespread use has led to increasing resistance. "Respiratory quinolones" such as levofloxacin and moxifloxacin are active against both "typical" (*Strep pneumonia*) and "atypical" (*Mycoplasma, Legionella; Chlamydophila*) pathogens.

- Aminoglycosides have primary activity against gram-negative pathogens such as *Enterobacteriaceae* and *Pseudomonas*—they must be used with caution (monitoring required) because of problems with nephro- and ototoxicity.

- Macrolides are primarily drugs for "respiratory" infections—they have activity against both pneumococci and "atypical " pathogens (e.g. *Mycoplasma; Legionella* species). Both azithromycin and clarithromycin are now more commonly used than erythromycin because of a lower incidence of gastrointestinal side effects. Be careful of adverse QT effects (e.g ventricular tachycardia) in patients with a history of prolonged QT syndrome or those with conditions (e.g. hypokalemia) or concomitant drugs that predispose to QT prolongation.

- Doxycycline remains an important agent for management of zoonotic and tick-borne infection such as plague, tularemia, psittacosis, typhus and spirochaetal disease (leptospirosis; Lyme disease). Both doxycycline and minocycline also have excellent activity against MRSA and can be sued for outpatient treatment of staphylococcal skin and soft tissue infection.

- Anti-anaerobe agents include clindamycin, metronidazole, tigecycline and the "beta-lactamase inhibitor" penicillins (e.g. piperacillin/tazobactam; ampicillin/sulbactam; amoxicillin/clavulanic acid). These agents are often useful for "mixed" aerobic-anaerobic infections such as intraabdominal abscess (diverticulitis; appendicitis; cholecystitis), diabetic foot infection and lung abscess/aspiration pneumonia.

- "Newer"antibiotic agents including daptomycin (IV) and linezolid (IV and PO) are generally reserved for infections with "resistant" gram positives such as MRSA, VRE and drug-resistant *Strep pneumonia.*

- Tigecycline—a broad spectrum tetracycline—has good activity against anaerobes, resistant gram positives (MRSA; VRE) and some resistant gram negative bacilli (e.g. *Acinetobacter;* ESBL *E.*coli); this drug is often used employed in "mixed" aerobic-anaerobic infections where resistant pathogens are present or other agents (B-lactams) are contraindicated because of resistance or allergy.