Rational Antimicrobial Selection & Antimicrobial Prophylaxis

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Rational Antimicrobial Selection

- **The initial selection of antimicrobial therapy may be empirical, prior to documentation and identification of the offending organism.**
- **A delay in antimicrobial therapy for some infections may result in serious morbidity and mortality.**

serious or life threatning

* if Trx without taking samples to identify the pathogen it's not empirical it's Random → not scientific

Rational Antimicrobial Selection

Empirical antimicrobial therapy selection should be based on:

1. **The patient's history and physical examination.**
2. **Results of Gram stains or other rapidly performed tests on specimens from the infected site.**
3. **Knowledge of the most likely offending organism for the infection in question.**
4. **Institution's local microbial susceptibility patterns.**

Rational Antimicrobial Selection

- **Identification of the pathogen and its antimicrobial susceptibility are the most important factors in determining the choice of antimicrobial therapy.**

Rational Antimicrobial Selection

Infected materials must be sampled with starting antimicrobial therapy for two reasons:

a) **A Gram stain might reveal bacteria, and an acid-fast stain might detect mycobacteria.**

b) **The premature use of antimicrobials can suppress the growth of pathogens which might result in false-negative cultures results.**

Rational Antimicrobial Selection

- **Blood cultures should be performed in the acutely ill and febrile patient.**
- **Infected materials (blood, sputum, urine, stool, abscesses, wound or sinus drainage, spinal fluid, and joint fluid, …), from the suspected infection site must be obtained and tested.**
- **When a pathogenic microorganism is identified, antimicrobial susceptibility testing should be performed.**

Rational Antimicrobial Selection

- **When the pathogen has been identified, specific definitive antimicrobial therapy should be promptly administered.**

Selection of presumptive therapy:

A variety of factors must be considered:

1) **The severity and acuity of the disease.**
2) **Local epidemiology and antibiogram.** → susceptibility results.
3) **Patient's history and host factors.**
4) **Factors related to the drug(s) to be used.**
5) **The necessity for using multiple agents.**

Rational Antimicrobial Selection

- **In addition, there are generally accepted drugs of first choice for the treatment of most pathogens.**
- **Drugs of choice are compiled from a variety of sources and are intended as guidelines rather than as specific rules for antimicrobial use.**

Antibiograms (antibiotic susceptibilities):

- **Local antimicrobial susceptibility data, NOT that from other institutions or national compilations.**
- **Susceptibility of bacteria can differ substantially among hospitals within a community.**

Rational Antimicrobial Selection

Patient History:

- As part of the medical history, the place where the infection was acquired should be determined: home (community acquired), nursing home environment, or hospital (nosocomial).
- Nursing home patients can be exposed to potentially more resistant organisms because they are often surrounded by ill patients who are receiving antibiotics.

*cephalosporin and Penicillin are Both B-lactam → there's 10% cross sensitivity

Rational Antimicrobial Selection

@ cause when apts is sensitive to Penicillin there's 10% they are sensitive to cephalosporin and vice versa

Host Factors:

Allergy:

- **Allergy to an antimicrobial agent generally precludes its use.**
- **Cephalosporins should be avoided in patients allergic to penicillin for immediate or accelerated reactions (anaphylaxis, laryngospasm), but can be given under close supervision in patients with skin rash.**

life threatening

← for mild rxn (you may use it)

*the chance of 10% we don't take it cause it's considerd high

Rational Antimicrobial Selection

Age: the extreme of age → elderly (Kidney and liver function ↓) ↓ elemination; → children (immaturity of elemination system)

- **Age is an important factor for identification of the likely etiologic agent and in the ability to eliminate the drug.**
- **In bacterial meningitis, the pathogens differ as the patient grows from the neonatal period through infancy and childhood into adulthood.**
- **For neonates, hepatic and liver functions are NOT well developed.**

* Co-trimexazole (contain sulfamexazole) for UTI shouldn't be given to neonate and children

Rational Antimicrobial Selection

- **Neonates (especially when premature) can develop kernicterus when given sulfonamides, because of displacement of bilirubin from serum albumin.**
  - cross the BBB
- **The major change in the elderly is decreased renal function, leading to increased adverse effects of antimicrobials eliminated by the kidney (aminoglycosides).**
  - → Accumulation
  - → needs smaller dose

Rational Antimicrobial Selection

Pregnancy:

- During pregnancy, the fetus is at risk of drug teratogenicity.
- The disposition of certain drugs by the mother may be altered.
- Penicillins, cephalosporins, and aminoglycosides are cleared more rapidly during pregnancy, because of increases in intravascular volume, glomerular filtration rate, and hepatic metabolic activities.

Rational Antimicrobial Selection

- **This results in a maternal serum antimicrobial concentrations ~ 50% lower than in the nonpregnant state.**
- **Thus, increased dosages of certain compounds might be necessary to achieve therapeutic levels during late pregnancy.**

Rational Antimicrobial Selection

Metabolic or Genetic Variation:

- **Patients with impaired blood flow may NOT absorb drugs given by intramuscular injection well.**
- **Inherited or acquired metabolic abnormalities will influence therapy of infectious diseases in a variety of ways.** G6PD → sulfa, nitro, Phenytoin, anti-malaria — you can't use them
- **Patients who are slow acetylators of isoniazid are at greater risk for peripheral neuropathy.** Cause

Rational Antimicrobial Selection

- **Patients with severe deficiency of glucose-6-phosphate dehydrogenase can develop significant hemolysis when exposed to dapsone, sulfonamides, nitrofurantoin, nalidixic acid, and antimalarials.**
- **The antiretroviral drug abacavir is associated with severe hypersensitivity reaction (fever, rash, abdominal pain, and respiratory distress) in the presence of human leukocyte antigen allele HLA-B*5701.**

• should be adjusted in Renal Disease → Penicillin, cephalosporin, Aminoglycoside, vancomycin

Rational Antimicrobial Selection

Organ Dysfunction:

- **Patients with diminished renal or hepatic function or both will need dosage adjustment to prevent drug accumulation and toxicity.**
- **Antibiotics that should be adjusted in severe liver disease: clindamycin, erythromycin, metronidazole, rifampin.**
- **Significant accumulation can occur when both liver and renal dysfunction are present for: nafcillin, sulfamethoxazole, cefotaxime, piperacillin.**

Rational Antimicrobial Selection

Concomitant Drugs: within Abx s; with other drugs

- **May influence the drug selection, dose, and monitoring.**
- **Administration of isoniazid with phenytoin can result in phenytoin toxicity due to inhibition of phenytoin metabolism by isoniazid.** (isoniazid: metabolised by acetylation; phenytoin: metabolised by hydroxylation; Zero order Kinetic; so any change will cause out of Proportion ↑ in conce ↓ Toxicity; X competetive or substrate.)
- **Drugs that possess similar adverse effect profiles can produce enhanced adverse effects (e. g: two drugs that cause nephrotoxicity or neutropenia).**

Rational Antimicrobial Selection

Major Drug Interactions with Antimicrobials:

1. **Aminoglycosides with:**

A. **Neuromuscular blocking agents: additive NMJ block.**

B. **Nephro- and Oto-toxins (Amphotericin, cisplatin, cyclosporine [N], furosemide [O], NSAIDs [N], radiocontrast media [N], vancomycin [N]) have additive toxicity.**

Rational Antimicrobial Selection

2. Amphotericin B with nephrotoxins (aminoglycosides, cidofovir, cyclosporine, foscarnet, pentamidine): additive adverse effects.
3. Chloramphenicol decreases metabolism of phenytoin, tolbutamide, ethanol. (?!)
4. Foscarnet with pentamidine IV: increased risk of severe nephrotoxicity/hypocalcemia.
5. Isoniazid decreases metabolism of carbamazepine, phenytoin → nausea, vomiting, nystagmus, ataxia.

B-Glycoprotein → in intestinal mucosa
it prevent Zenobiotics (foreign substances) like Digoxin
→ in Kidney (Digoxin is eleminated by the kidney) ↑ concentration of Digoxin

Rational Antimicrobial Selection

→ aren't Broad spectrum Abx → So this isn't the Mechanism ⇒ Digoxin → 10% of Pt → metabolized in the microbial flora.
inhibitors of B-Glycoproteins + CYP3A4
If the Pt + Digoxin Broad Abx → flora is eradicated ⇓ ↑ Bioavalibility

6. Macrolides/azalides with

→ it's a substrate for B-Glycoprotein

A. Digoxin: increased digoxin bioavailability.

B. Theophylline: decreased metabolism of theophylline.

→ 3rd or 4th Bronchial asthma
1st choice Apnea, Premature infants → Toxicity.

7. Metronidazole with ethanol (drugs containing ethanol): disulfiram-like reaction.

actively excreted By the Kidney
little → Glomerular filtration

8. Penicillins and cephalosporins with probenecid, aspirin: blocked excretion of β-lactams.

↓ excretion

Rational Antimicrobial Selection

9. **Ciprofloxacin/norfloxacin with theophylline: decreased metabolism of theophylline.**

10. **Quinolones with:** affect Bone and Cartilage development in Premature

A. **Classes Ia and III antiarrhythmics: increased Q-T interval.** Predispose Polymorphic Ventricular Tachycardia → Fibrillation

B. **Multivalent cations (antacids, iron, sucralfate, zinc, vitamins, dairy products), citric acid, didanosine: decreased absorption of quinolones.**

Rational Antimicrobial Selection

11. Rifampin increases metabolism of azoles, cyclosporine, methadone, propranolol, protease inhibitors, oral contraceptives, tacrolimus, warfarin..

12. Sulfonamides with sulfonylureas, phenytoin, warfarin: displacement from binding to albumin.

13. Tetracyclines with:

A. Antacids, iron, calcium, sucralfate: decreased absorption of tetracycline.

B. Digoxin: **increased** digoxin bioavailability (**WHY?**).

mainly due the eradication of the flora that metabolizes Digoxic

Rational Antimicrobial Selection

2Types of Abx → Concentration dependant
→ Time dependent

Drug Factors:

PK and PD Considerations:

- Important parameters to be considered are the minimal inhibitory concentration (MIC) and the time the concentration is above MIC.
- Aminoglycosides exhibit concentration-dependent bactericidal effects, which allows a once-daily aminoglycosides administration.

↑ Peak concentration enough to supress the infxn

- These drugs are given as a single large daily dose to maximize the peak/MIC ratio.

per day → 3 doses → steady state concentration
1 large dose → ↑ peak, low TRUF
] efficacy is the same but in 1 large dose the toxicity is less

Rational Antimicrobial Selection

- They also possess a postantibiotic effect (persistent suppression of organism growth after concentrations decrease below the MIC), which appears to contribute to the success of high-dose, once-daily administration.
- Fluoroquinolones also exhibit concentration-dependent killing activity, but optimal killing appears to be characterized by the AUC/MIC ratio. Rather than Plasma Concentration/MIC Area Under the Curve

Rational Antimicrobial Selection

- **β-Lactams display time-dependent bactericidal effects.** Maintain the concentration → multiple MIC → multiple doses not single dose
  steady state
- **Therefore, the important pharmacodynamic relationship for these antimicrobials is the duration that drug concentrations exceed the MIC.**
- **Frequent small doses, continuous infusion, or prolonged infusion of β-lactams appears to be correlated with positive outcomes.**

Rational Antimicrobial Selection

Tissue Penetration:

- **One important factors in treating an infection is the presence of the antimicrobial agent in an active form and at adequate concentration at the site of infection.**
- **Drugs that have low biliary fluid concentrations are NOT useful in the treatment of cholecystitis and cholangitis.**

Between penicillins only Mezlocillin achive conce in Bile = in plasma

Rational Antimicrobial Selection

- Some drugs have poor penetration to deep infections, such as abscesses, where various factors such as acidic pH, WBC products, and various enzymes can inactivate even high concentrations of certain drugs.
- Drugs that do NOT reach significant concentrations in the CSF should NOT be used in treatment of bacterial meningitis.

Rational Antimicrobial Selection

- **Body fluids where drug concentration data are clinically relevant include CSF, urine, synovial fluid, and peritoneal fluid.**
- **Parenteral therapy is indicated in: febrile neutropenia, meningitis, endocarditis, and osteomyelitis.** → switch to oral
- **Severe pneumonia often is treated initially with IV antibiotics then switched to oral therapy with clinical improvement.**

Rational Antimicrobial Selection

- **Patients treated in the ambulatory setting for upper respiratory tract infections (pharyngitis, bronchitis, sinusitis, and otitis media), lower respiratory tract infections, skin and soft-tissue infections, uncomplicated urinary tract infections, and selected sexually transmitted diseases can usually receive oral therapy.**

Rational Antimicrobial Selection

Drug Toxicity:

- Toxic drugs should be avoided.
- Antibiotics associated with CNS toxicities, when not dose-adjusted for renal function, include penicillins, cephalosporins, quinolones, and imipenem. especially in ↑ dose
- Reversible nephrotoxicity classically is associated with aminoglycosides and vancomycin.
- Irreversible ototoxicity can occur with aminoglycosides. → first it's reversible

→ [Shouldn't Be used >5 days]

Rational Antimicrobial Selection

- **Hematologic toxicities occur with prolonged use of nafcillin (neutropenia), piperacillin (platelet dysfunction), cefotetan (hypoprothrombinemia), chloramphenicol (bone marrow suppression, both idiosyncratic and dose-related toxicity), and trimethoprim (megaloblastic anemia).**

Rational Antimicrobial Selection

- In the outpatient setting, patients must be counseled regarding photosensitivity with azithromycin, quinolones, tetracyclines, pyrazinamide, sulfamethoxazole, and trimethoprim. – Protect your skin from Direct Sunlight –
- Many antibiotics have been implicated in causing diarrhea and colitis secondary to *Clostridium difficile* superinfection. **********

Important

Rational Antimicrobial Selection

Penicillins & Cephalosporins:

- **Hypersensitivity reactions (skin rash ….. anaphylaxis), drug fever, diarrhea, emesis, abdominal pain, hepatitis, interstitial nephritis, leukopenia, thrombocytopenia, Coomb's positive-hemolytic anemia, *C. difficile* colitis, electrolyte abnormalities, seizures.**

allergic Manifestations

Rational Antimicrobial Selection

Carbapenems (imipenem):

- **Hypersensitivity reactions and rash, headache, nausea, diarrhea, seizures, drug fever, eosinophilia, thrombocytopenia, hepatitis, *C. difficile* colitis.**

narraw spectrum But

Monobactams (aztreonam): Gram -ve spectrum

- **Rash, diarrhea, nausea, hepatitis, thrombocytopenia, *C. difficile* colitis.**

Rational Antimicrobial Selection

Aminoglycosides:

- **Tubular necrosis and renal failure, vestibular and cochlear toxicity, neuromuscular blockade, vertigo, anemia, hypersensitivity.**

Glycopeptides (vancomycin):

- **Red man syndrome (due to release of histamine independent on IgE), phlebitis, renal dysfunction, neutropenia, leukopenia, eosinophilia, thrombocytopenia, drug fever.**

Mainly

Rational Antimicrobial Selection

when organism → Resistance to vancomycin

Lipopeptides (daptomycin):

- **Hepatotoxicity, CPK elevation with or without myopathy, diarrhea, eosinophilic pneumonia, *C. difficile* colitis.**

Oxazolidinones (linezolid):

- **Myelosuppression (thrombocytopenia, leukopenia, and anemia), peripheral neuropathy, optic neuropathy, blindness, lactic acidosis, diarrhea, nausea, serotonin syndrome, interstitial nephritis.**

Rational Antimicrobial Selection

Tetracyclines:

- **GI upset, nausea, vomiting, diarrhea, hepatotoxicity, esophageal ulcerations, photosensitivity, azotemia, visual disturbances, vertigo, hyperpigmentation, deposition on teeth, hemolytic anemia, pseudotumor cerebri, pancreatitis, *C. difficile* colitis.**

due to accumulation of water in inappropriate ADH secretion

Chloramphenicol:

- **Myelosuppression, aplastic anemia, "gray baby syndrome," optic neuritis, peripheral neuropathy, digital paresthesias, GI upset, *C. difficile* colitis, hypersensitivity.**

Rational Antimicrobial Selection

Rifamycines:

- **Discoloration of urine, tears, contact lenses, saliva, sweat; hepatotoxicity, GI upset, flu-like syndrome, hypersensitivity, thrombocytopenia, leukopenia, drug fever, interstitial nephritis, thrombocytopenia.**

Macrolides/azalide:

- **GI intolerance, diarrhea, prolonged QTc, *torsade de pointes*, cholestatic hepatitis, reversible ototoxicity, rash, hypothermia, exacerbation of myasthenia gravis.**

Rational Antimicrobial Selection

Clindamycin:

- **Diarrhea, *C. difficile* colitis, nausea, vomiting, generalized rash, hypersensitivity.**

Fluoroquinolones:

- **GI intolerance, headache, malaise, insomnia, dizziness, photosensitivity, QTc prolongation, tendon rupture, peripheral neuropathy, crystalluria, seizure, interstitial nephritis, Stevens-Johnson syndrome, allergic pneumonitis, *C. difficile* colitis.**

cartilage abnormalities

Rational Antimicrobial Selection

Sulfonamides and trimethoprim: → Hemolysis Mainly

- **GI intolerance, rash, hyperkalemia (by blocking amiloride-sensitive sodium channels in the cortical collecting duct), bone marrow suppression (anemia with folate deficiency, thrombocytopenia, and leukopenia), serum sickness, hepatitis, photosensitivity, crystalluria with azotemia, urolithiasis, methemoglobinemia, Stevens-Johnson syndrome, toxic epidermal necrolysis, aseptic meningitis, pancreatitis, interstitial nephritis, neurologic toxicity.**

Rational Antimicrobial Selection

Metronidazole:

- **GI intolerance, headache, metallic taste, dark urine, peripheral neuropathy, disulfiram-like reactions with alcohol, insomnia, stomatitis, aseptic meningitis, dysarthria.**

Polymyxins (polymyxin B & colistin):

- **Nephrotoxicity, neurotoxicity (paresthesia, vertigo, ataxia, blurred vision, slurred speech), neuromuscular blockade, bronchospasm (administered via inhalation).**

Rational Antimicrobial Selection

Failure of antimicrobial therapy:

- **Patients who fail to respond over 2 - 3 days require a thorough reevaluation.**

Causes:

a) **The disease is NOT infectious or is nonbacterial in origin.**

b) **There is an undetected pathogen in a polymicrobial infection.**

c) **Factors directly related to drug selection, the host, or the pathogen.**

d) **Laboratory error in identification, susceptibility testing, or both.**

Rational Antimicrobial Selection

Failures Caused by Drug Selection:

1) **Inappropriate selection of drug, dosage, or route of administration.**
2) **Reduced absorption of a drug, resulting in subtherapeutic concentrations, because of:**

a. **GI disease (short-bowel syndrome).** Diarrhea ...

b. **Drug interaction (complexation of fluoroquinolones with multivalent cations).**

Rational Antimicrobial Selection

3) Accelerated drug elimination (cystic fibrosis or during pregnancy), resulting in low concentrations.

4) Poor penetration into the site of infection (for sites such as the CNS, eye, and prostate gland).

5) Chemical inactivation of the drug at the site of infection.

Rational Antimicrobial Selection

Failures Caused by Host Factors:

a) **Patients who are immunosuppressed (granulocytopenia from immunosuppressants, chemotherapy or AIDS) may respond poorly because their defenses are inadequate to eradicate the infection despite seemingly adequate drug regimens.**

b) **The need for surgical drainage of abscesses or removal of foreign bodies, necrotic tissue, or both. These infections will NOT be effectively treated without surgical procedures.**

* Macrolide will not act on Bacteria with no cell wall

Rational Antimicrobial Selection

* Bacteria with no cell wall → will not respond to cephalosporin

Failures Related to Pathogens (Resistance):

- **Intrinsic resistance: when the antimicrobial agent never had activity against the bacterial species. (Gram-negative bacteria are naturally resistant to vancomycin because the drug cannot penetrate the outer membrane of gram negative bacteria).**
- **Acquired resistance: occurs when the antimicrobial agent was originally active against the bacterial species but the genetic makeup of the bacteria has changed so the drug can NO longer be effective.**

Rational Antimicrobial Selection

- Penicillin and cephalosporin act on the cell wall

Bacteria develop acquired resistance by any of the following mechanisms:

a. **Alteration in the target site.**
b. **Change in membrane permeability.**
c. **Expression of an efflux pump.**
d. **Drug inactivation through either β-lactamases or aminoglycoside-modifying enzymes is the predominant mechanism of resistance.**

- **The expression of β-lactamases can be induced or constitutive.**

Rational Antimicrobial Selection

The increased resistance results from:

1. **Continued overuse of antimicrobials in the community and in hospitals.**
2. **Long-term suppressive antimicrobials for the prevention of infections in immunosuppressed patients.**

The Treatment :- ① Penicillin – Resistance Enterococci & Vancomycin + Gentamycin or Streptomycin
② Vancomycin – Resistance Enterococci (VRE) : Linezolid, Daptomycin, tigecyclin. (Nitrofurantoin for UTI)

Rational Antimicrobial Selection

- **Enterococci with multiple resistance patterns have been isolated.**
- **They may be resistant to:**

1. **β-lactams (β-lactamase production, altered penicillin-binding proteins [PBPs], or both)**
2. **Vancomycin (alterations in peptidoglycan synthesis).**
3. **Aminoglycosides (high levels of AGs-degrading enzymes.**

Rational Antimicrobial Selection

- **Pneumococci resistant to penicillins, certain cephalosporins, and macrolides are increasingly common.**
- **These organisms generally are susceptible to vancomycin, the new fluoroquinolones (moxifloxacin and trovafloxacin), and cefotaxime or ceftriaxone.**

Rational Antimicrobial Selection

- **Antimicrobial agents such as linezolid, daptomycin, telavancin (semi-synthetic derivative of vancomycin), and tigecycline (new tetracycline) have been used for resistant gram-positive bacteria.**

Rational Antimicrobial Selection

- **Treatment of infections caused by *Enterobacter*, *Citrobacter*, *Serratia*, or *P. aeruginosa* with a third-generation cephalosporin or aztreonam may produce an initial clinical response by eradicating the susceptible bacteria.**
- **Within a few days, the highly resistant subpopulations can overgrow at the infection site to produce a relapse.**
- **These bacteria usually retain susceptibility to fluoroquinolones, aminoglycosides, carbapenems, but are resistant to all other β-lactams.**

Rational Antimicrobial Selection

- Host defenses are extremely important in this scenario.
- Debilitated patients with pulmonary infections, abscesses, or osteomyelitis are at high risk for drug failure.
- In these situations, a combination regimen to prevent the emergence of resistance or the use of carbapenem or a fluoroquinolone may be used for empiric therapy.

Rationale For Combination Antimicrobial Therapy

- **Most infections should be treated with a single antimicrobial agent.**
- **Although indications for combination therapy do exist, antimicrobial combinations are often overused in clinical practice.**
- **The unnecessary use of antimicrobial combinations increases toxicity and costs and may occasionally result in reduced efficacy due to antagonism of one drug by another.**

Rationale For Combination Antimicrobial Therapy

- **Antimicrobial combinations should be selected for one or more of the following reasons:**

1. **To provide broad-spectrum empiric therapy in seriously ill patients.**
2. **To treat polymicrobial infections (intra-abdominal abscesses, which are due to a combination of anaerobic and aerobic gram-negative organisms, and enterococci).**

Rationale For Combination Antimicrobial Therapy

- The antimicrobial combination chosen should cover the most common known or suspected pathogens but not cover all possible pathogens.

3. To decrease the emergence of resistant strains – tuberculosis. we start with 3-4 Drugs 2month → 2drugs.
4. To obtain enhanced inhibition or killing.

Rationale For Combination Antimicrobial Therapy

5. **To decrease dose-related toxicity by using reduced doses of one or more components of the drug regimen.**

- **The use of flucytosine in combination with amphotericin B for the treatment of cryptococcal meningitis in non–HIV-infected patients allows for a reduction in amphotericin B dosage with decreased amphotericin B-induced nephrotoxicity.**

Rationale For Combination Antimicrobial Therapy

Broadening the Spectrum of Coverage:

- Increasing the coverage of antimicrobial therapy generally is necessary in the following cases:

1. In mixed infections where multiple organisms are likely to be present (in intra-abdominal and female pelvic infections), in which a variety of aerobic and anaerobic bacteria can produce disease.

- A combination of a drug active against aerobic Gram-negative bacilli (aminoglycoside) and a drug active against anaerobic bacteria (metronidazole or clindamycin) is selected.

Rationale For Combination Antimicrobial Therapy

2. **For critically ill patients with health care-associated infections.**

- **These infections are frequently caused by multi-drug resistant pathogens.**
- **Combination therapy is used in this setting to ensure that at least one of the antimicrobials will be active against the pathogen(s).**

Rationale For Combination Antimicrobial Therapy

Synergism:

- This is necessary for infections caused by enteric Gram-negative bacilli in immunosuppressed patients.
- Traditionally, combinations of aminoglycosides and β-lactams have been used because these drugs together generally act synergistically against a wide variety of bacteria.

Rationale For Combination Antimicrobial Therapy

- Synergistic combinations may produce better results in infections caused by *Pseudomonas aeruginosa* and *Enterococcus* species.
- The most obvious example of the use of synergy is the treatment of enterococcal endocarditis. The causative organism is usually only inhibited by penicillins, but it is killed rapidly by the addition of streptomycin or gentamicin to a penicillin.

Rationale For Combination Antimicrobial Therapy

Preventing Resistance:

- The use of antimicrobial combinations to prevent the emergence of resistance has been demonstrated in the treatment of tuberculosis.
- Combinations of drugs with different mechanisms should be used in this case.

Disadvantages of Combination Therapy

1. Increased cost.
2. Greater risk of drug toxicity (nephrotoxicity) with aminoglycosides, amphotericin, and vancomycin.
3. Superinfection with more resistant bacteria.
4. Antagonistic effects: when one drug induces β-lactamase production and the other is susceptible to β-lactamase.

- Cefoxitin and imipenem are capable of inducing β-lactamases and may result in more rapid inactivation of penicillins.

3rd Gen Ceph + Carbapenem

Antimicrobial Prophylaxis

→ against a definite known micro-organism that is likely the cause of infxn in this Patient.

- **Antimicrobial agents are effective in preventing infections in many settings.**
- **Antimicrobial prophylaxis should be used in circumstances in which efficacy has been demonstrated and benefits outweigh the risks of prophylaxis. (Evidence-Based Medicine).**

Antimicrobial Prophylaxis

Surgical Prophylaxis:

- Surgical wound infections are a major category of nosocomial infections.
- Risk factors for postoperative wound infections:

a) operations on the abdomen.

b) operations lasting more than 2 hours.

c) contaminated or dirty wound.

d) at least three medical diagnoses.

Antimicrobial Prophylaxis

what are

- **Surgical procedures that carry a significant risk of postoperative site infection and necessitate the use of antimicrobial prophylaxis include: ?**

a) **contaminated and clean-contaminated operations.**

b) **selected operations in which postoperative infection may be catastrophic such as open heart surgery.** , THR

c) **clean procedures that involve placement of prosthetic materials.**

d) **any procedure in an immunocompromised host.**

National Research Council (NRC) Wound Classification Criteria

Clean: Elective, primarily closed procedure; respiratory, gastrointestinal, biliary, genitourinary, or oropharyngeal tract not entered; no acute inflammation and no break in technique; expected infection rate ≤ 2%.

Clean contaminated: Urgent or emergency case that is otherwise clean; elective, controlled opening of respiratory, gastrointestinal, biliary, or oropharyngeal tract; minimal spillage or minor break in technique; expected infection rate ≤ 10%.

Contaminated: Acute nonpurulent inflammation; major technique break or major spill from hollow organ; penetrating trauma less than 4 hours old; chronic open wounds to be grafted or covered; expected infection rate about 20%.

Dirty: Purulence or abscess; preoperative perforation of respiratory, gastrointestinal, biliary, or oropharyngeal tract; penetrating trauma more than 4 hours old; expected infection rate about 40%.

Antimicrobial Prophylaxis

- General principles of antimicrobial surgical prophylaxis include the following:

1. The antibiotic should be active against common surgical wound pathogens; unnecessary broad coverage should be avoided.
2. The antibiotic should have proved efficacy in clinical trials.
3. The antibiotic must achieve concentrations greater than the MIC of the suspected pathogens, and these concentrations must be present at the time of incision.

Give Before.

Antimicrobial Prophylaxis

4. The shortest possible course — ideally a single dose — of the most effective and least toxic antibiotic should be used.
5. The newer broad-spectrum antibiotics should be reserved for therapy of resistant infections.
6. If all other factors are equal, the least expensive agent should be used.

TABLE 51–7 Recommendations for surgical antimicrobial prophylaxis.

Type of Operation	Common Pathogens	Drug of Choice
Cardiac (with median sternotomy)	Staphylococci, enteric gram-negative rods	Cefazolin
Noncardiac, thoracic	Staphylococci, streptococci, enteric gram-negative rods	Cefazolin
Vascular (abdominal and lower extremity)	Staphylococci, enteric gram-negative rods	Cefazolin
Neurosurgical (craniotomy)	Staphylococci	Cefazolin
Orthopedic (with hardware insertion)	Staphylococci	Cefazolin
Head and neck (with entry into the oropharynx)	*Staphylococcus aureus*, oral flora	Cefazolin + metronidazole
Gastroduodenal	*S aureus*, oral flora, enteric gram-negative rods	Cefazolin
Biliary tract	*S aureus*, enterococci, enteric gram-negative rods	Cefazolin
Colorectal (elective surgery)	Enteric gram-negative rods, anaerobes	Oral erythromycin + neomycin[1]
Colorectal (emergency surgery or obstruction)	Enteric gram-negative rods, anaerobes	Cefoxitin, cefotetan, ertapenem, or cefazolin + metronidazole
Appendectomy, nonperforated	Enteric gram-negative rods, anaerobes	Cefoxitin, cefotetan, or cefazolin + metronidazole
Hysterectomy	Enteric gram-negative rods, anaerobes, enterococci, group B streptococci	Cefazolin, cefotetan, or cefoxitin
Cesarean section	Enteric gram-negative rods, anaerobes, enterococci, group B streptococci	Cefazolin

[1]In conjunction with mechanical bowel preparation.

Antimicrobial Prophylaxis

- **The selection of vancomycin over cefazolin may be necessary in hospitals with high rates of methicillin-resistant *S. aureus or S. epidermidis infections*.**
- **The antibiotic should be present in adequate concentrations at the operative site before incision and throughout the procedure.**

Antimicrobial Prophylaxis

- Parenteral agents should be administered during the interval beginning 60 minutes before incision up to the time of incision.
- In cesarean section, the antibiotic is administered after umbilical cord clamping.
- If short-acting agents such as cefoxitin are used, doses should be repeated if the procedure exceeds 3–4 hours in duration.
- Single-dose prophylaxis is effective for most procedures and results in decreased toxicity and decreased antimicrobial resistance.

Antimicrobial Prophylaxis

Common errors in antibiotic prophylaxis include:

a) **Selection of the wrong antibiotic.**

b) **Administering the first dose too early or too late.**

c) **Failure to repeat doses during prolonged procedures.**

d) **Excessive duration of prophylaxis.**

e) **Inappropriate use of broad-spectrum antibiotics.**

Antimicrobial Prophylaxis

Nonsurgical Prophylaxis:

- **Nonsurgical prophylaxis includes:**

a) **The administration of antimicrobials to prevent colonization and asymptomatic infection.**

b) **The administration of drugs following colonization by or inoculation of pathogens but before the development of disease.**

- **Nonsurgical prophylaxis is indicated in:**

a) **Individuals who are at high risk for selected virulent pathogens**

b) **Immunocompromised hosts.**

TABLE 51–8 Recommendations for nonsurgical antimicrobial prophylaxis.

Infection to Be Prevented	Indication(s)	Drug of Choice	Efficacy
Anthrax	Suspected exposure	Ciprofloxacin or doxycycline	Proposed effective
Cholera	Close contacts of a case	Tetracycline	Proposed effective
Diphtheria	Unimmunized contacts	Penicillin or erythromycin	Proposed effective
Endocarditis	Dental, oral, or upper respiratory tract procedures[1] in at-risk patients[2]	Amoxicillin or clindamycin	Proposed effective
Genital herpes simplex	Recurrent infection (≥ 4 episodes per year)	Acyclovir	Excellent
Perinatal herpes simplex type 2 infection	Mothers with primary HSV or frequent recurrent genital HSV	Acyclovir	Proposed effective
Group B streptococcal (GBS) infection	Mothers with cervical or vaginal GBS colonization and their newborns with one or more of the following: (a) onset of labor or membrane rupture before 37 weeks' gestation, (b) prolonged rupture of membranes (> 12 hours), (c) maternal intrapartum fever, (d) history of GBS bacteriuria during pregnancy, (e) mothers who have given birth to infants who had early GBS disease or with a history of streptococcal bacteriuria during pregnancy	Ampicillin or penicillin	Excellent
Haemophilus influenzae type B infection	Close contacts of a case in incompletely immunized children (> 48 months old)	Rifampin	Excellent
HIV infection	Health care workers exposed to blood after needle-stick injury	Tenofovir/emtricitabine and raltegravir	Good
	Pregnant HIV-infected women who are at ≥ 14 weeks of gestation; newborns of HIV-infected women for the first 6 weeks of life, beginning 8–12 hours after birth	HAART[3]	Excellent
Influenza A and B	Unvaccinated geriatric patients, immunocompromised hosts, and health care workers during outbreaks	Oseltamivir	Good

Malaria	Travelers to areas endemic for chloroquine-susceptible disease	Chloroquine	Excellent
	Travelers to areas endemic for chloroquine-resistant disease	Mefloquine, doxycycline, or atovaquone/proguanil	Excellent
Meningococcal infection	Close contacts of a case	Rifampin, ciprofloxacin, or ceftriaxone	Excellent
Mycobacterium avium complex	HIV-infected patients with CD4 count < 75/μL	Azithromycin, clarithromycin, or rifabutin	Excellent
Otitis media	Recurrent infection	Amoxicillin	Good
Pertussis	Close contacts of a case	Azithromycin	Excellent
Plague	Close contacts of a case	Tetracycline	Proposed effective
Pneumococcemia	Children with sickle cell disease or asplenia	Penicillin	Excellent
Pneumocystis jiroveci pneumonia (PCP)	High-risk patients (eg, AIDS, leukemia, transplant)	Trimethoprim-sulfamethoxazole, dapsone, or atovaquone	Excellent
Rheumatic fever	History of rheumatic fever or known rheumatic heart disease	Benzathine penicillin	Excellent
Toxoplasmosis	HIV-infected patients with IgG antibody to *Toxoplasma* and CD4 count < 100/μL	Trimethoprim-sulfamethoxazole	Good
Tuberculosis	Persons with positive tuberculin skin tests and one or more of the following: (a) HIV infection, (b) close contacts with newly diagnosed disease, (c) recent skin test conversion, (d) medical conditions that increase the risk of developing tuberculosis, (e) age < 35 y	Isoniazid or rifampin or isoniazid + rifapentine	Excellent
Urinary tract infections (UTI)	Recurrent infection	Trimethoprim-sulfamethoxazole	Excellent

[1]Prophylaxis is recommended for the following: dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa, and invasive procedure of the respiratory tract that involves incision or biopsy of the respiratory mucosa, such as tonsillectomy and adenoidectomy.

[2]Prophylaxis should be targeted to those with the following risk factors: prosthetic heart valves, previous bacterial endocarditis, congenital cardiac malformations, cardiac transplantation patients who develop cardiac valvulopathy.

[3]Highly active antiretroviral therapy. See http://aidsinfo.nih.gov/ for updated guidelines.

Tigecycline differs in spectrum:

1. ***Staphylococcus aureus*** **including coagulase-negative, methicillin-resistant and vancomycin-resistant strains.**
2. **Streptococci including penicillin- resistant strains.**
3. **Enterococci including vancomycin- resistant strains.**
4. **Gram positive rods.**
5. **Enterobacteriaceae**
6. **Acinetobacter sp**
7. **Gram positive and gram negative anaerobes.**
8. **Atypical agents, rickettsiae, chlamydia and Legionella and rapidly growing Mycobacteria.**

Adverse Effects:

1. **Hypersensitivity reactions including drug fever and skin rash, and anaphylaxis.**
2. **GIT: nausea, vomiting and diarrhea.**
3. **Superinfections: *Pseudomonas, Proteus, Staphylococcus aureus*, Coliforms, Clostridia and Candida.**
4. **Bone & teeth:**

a) **Fetal teeth: fluorescence, discoloration, and enamel dysplasia.**

b) **Fetal bone: deformity or growth inhibition.**

c) **Similar changes occur in children below 8 years of age.**

5. **Liver toxicity: hepatic necrosis and impairment of hepatic function.**
6. **Pancreatitis.**
7. **Kidney toxicity: renal tubular acidosis and other renal injury.**
8. **Local tissue toxicity: Thrombophlebitis after IV administration, Local pain after IM administration.**
9. **Photosenstivity.**
10. **Vestibular reactions: dizziness, vertigo, nausea, vomiting.**