CORE PRINCIPLES OF ANTIMICROBIAL THERAPY

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APPROACHING THE PROBLEM

1. Before initiating therapy, it is important first to confirm an infectious versus noninfectious process.

2. Once infection has been documented, the most likely site must be identified, and signs and symptoms (e.g., erythema associated with cellulitis) generally direct the clinician to the likely source.

3. Because certain pathogens are known to be associated with a specific site of infection, empirical therapy often can be directed against these organisms.

4. Additional laboratory tests, including the Gram stain, serologic analysis, and antimicrobial susceptibility testing, generally identify the primary pathogen and active agents.

5. Spectrum of activity, established clinical efficacy, adverse effect profile, pharmacokinetic disposition, and cost considerations ultimately guide the choice of therapy.

6. Once an agent has been selected, the dosage and duration should be based on the size of the patient, site of infection, route of elimination, and other factors.

PROBLEMS IN THE DIAGNOSIS OF AN INFECTION

Confabulating Variables

Various factors, including major surgery, acute myocardial infarction, and initiation of corticosteroid therapy, are associated with an increased WBC count.

Unlike infection, however, a shift to the left does not occur with these disease states or drugs.

The presence of bands, strongly suggests a bone marrow response to an infectious process.

Drug Effects

The ability of corticosteroids to mimic or mask infection is noteworthy. Corticosteroids are associated with an increased WBC count and glucose intolerance with the initiation of therapy or when doses are increased.

Although corticosteroids mimic infection, they also have the ability to mask infection. Bowel perforation in a patient with ulcerative colitis would result in significant peritoneal contamination. Considering their potent anti-inflammatory effects, concomitant receipt of glucocorticoids may,

however, reduce the classic findings of peritonitis. Furthermore, corticosteroids can reduce and sometimes ablate the febrile response. Thus, these corticosteroid-treated patients may be asymptomatic but at great risk for gram-negative septic shock.

Another example of the influence of corticosteroids on the diagnosis of infection relates to neurosurgical procedures. Dexamethasone is a corticosteroid commonly used to reduce the inflammation and swelling associated with neurosurgical procedures. Certain neurosurgical procedures are associated with significant trauma to the meninges; however, the patient often is asymptomatic while receiving high-dose dexamethasone. When the dexamethasone dose is decreased, the patient subsequently may experience classic meningismus, including stiff neck, photophobia, and headache. The lumbar puncture may demonstrate cloudy cerebrospinal fluid (CSF), an elevated WBC count, high CSF protein, and low CSF glucose. Although the signs and symptoms are consistent with infectious meningitis, if no bacteria grow from the CSF sample, this disease state represents an aseptic meningitis (i.e., inflammation of the meninges without an infectious origin). Certain drugs may cause aseptic meningitis, including nonsteroidal anti-inflammatory agents, sulfonamides, and certain antiepileptics.

Fever

Fever also is a common finding with autoimmune diseases, such as systemic lupus erythematosus and temporal arteritis.

One evaluation of fever of unknown origin (FUO) in community hospitals demonstrated a 25% incidence of FUO caused by cancer.

After infection, autoimmune disease, and malignancy have been ruled out, drug fever should be considered. Drugs, including certain antimicrobials, have been associated with drug fever. Drug fever generally occurs after 7 to 10 days of therapy and resolves within 48 hours of the drug's discontinuation. Some clinicians claim that patients with drug fever generally feel "well" and are unaware of their fever. A re-challenge with the offending agent usually results in recurrence of fever within hours of administration.

Neoplasms may be radiographically indistinguishable from an abscess. An example of this dilemma is the differential diagnosis of toxoplasmosis versus lymphoma in patients with human immunodeficiency virus (HIV) with brain lesions documented by a computed axial tomography scan. One method for diagnosis is to use empirical therapy against Toxoplasma gondii. If the lesions are unresponsive to therapy, a presumptive diagnosis of malignancy can be made.

ESTABLISHING SITE OF THE INFECTION

A thorough physical examination often documents the source of infection.

Urosepsis, the most common cause of nosocomial infection, may be associated with dysuria, flank pain, and abnormal urinalysis (>50 WBC/HPF).

Tachypnea, increased sputum production, altered chest radiograph, and hypoxemia may direct the clinician toward pneumonia

Evidence for an infected IV line might include pain, erythema, and purulent discharge around the IV catheter.

The abdominal pain, absent bowel sounds, and recent surgical procedure suggest an intra-abdominal infection.

Other potential sites of infection include pelvis, bone, and CNS.

DETERMINING LIKELY PATHOGENS

Bacterial pneumonia is caused by various pathogens, including Streptococcus pneumoniae, Enterobacteriacae, and atypical pathogens (e.g., Legionella pneumophila). However, empirical antimicrobial therapy directed against all the above organisms is NOT necessary in all patients.

-Community-acquired pneumonia in normal hosts is generally associated with S. pneumoniae, Haemophilus influenza, and “atypical” bacterial pathogens.

-Nosocomial pneumonia is associated with gram-negative bacilli (e.g., Escherichia coli, Klebsiella species, Enterobacter species, and Pseudomonas aeruginosa) and Staphylococcus aureus.

-If the pneumonia is a result of a gastric aspiration, empirical antibacterial treatment of mouth anaerobes generally takes place; however, their true pathogenicity in aspiration pneumonia is not clear.

-For the empirical treatment of hospital-associated pneumonia or ventilator-associated pneumonia, knowledge of a hospital epidemiology is useful. If P. aeruginosa or Enterobacter cloacae

predominate in an institution, then broad-spectrum agents should be used directed against these pathogens.

-Similarly, prior or concurrent receipt of antimicrobial therapy significantly impacts on the choice of empirical therapy.

Age is an important determinant in the epidemiology of infection. For example, meningitis in a neonate is commonly caused by group B streptococci, E. coli, and Listeria monocytogenes, whereas these bacteria are uncommon meningitis pathogens in normal adults.

The presence of concomitant diseases, such as chronic obstructive pulmonary disease (COPD) or alcohol and IV drug use, also influences the specific pathogen. As an example, patients with COPD-associated pneumonia are more likely to be infected by S. pneumoniae and H. influenzae, whereas chronic alchoholics are more likely to have Klebsiella species as a source of pneumonia.

Immune status is an important predictor of likely pathogens. HIV/AIDS patients or those receiving Atgam, cyclosporine (or tacrolimus), and corticosteroids have lymphocyte deficiency or dysfunction-associated infections, including those caused by cytomegalovirus, Pneumocystis jiroveci, atypical mycobacteria, and Cryptococcus neoformans.

Patients with leukemia and neutropenia are at risk for infection caused by aerobic gram-negative bacilli, including P. aeruginosa, Candida species, and Aspergillus species, as well as the above-mentioned pathogens.

Intra-abdominal infection is likely caused by aerobic gram-negative enteric bacteria, Bacteroides fragilis, and possibly enterococcus

Nosocomial urinary tract infection is usually caused by aerobic gram-negative bacteria.

IV catheter infection suggests infection caused by staphylococci, including Staphylococcus epidermidis and S. aureus.

MICROBIOLOGIC TESTS AND SUSCEPTIBILITY OF ORGANISMS

Once the site of infection has been determined and host defense and other epidemiologic factors have been evaluated, additional tests can be performed to identify the pathogen.

If the Gram stain of the tracheal aspirate demonstrates gram-positive cocci in clusters, empirical antistaphylococcal therapy is indicated.

The acid-fast bacilli (AFB) stain is critical in the diagnosis of infection caused by Mycobacterium tuberculosis or atypical mycobacteria.

Culture and Susceptibility Testing

Culture and susceptibility testing provides final identification of the pathogen, as well as information regarding the likely effectiveness of various antimicrobials.

Although these tests provide more information than the Gram stain, they generally require 18 to 24 hours to complete. After the pathogen has been identified, references can be used in conjunction with institution-specific susceptibility studies to select the most appropriate antimicrobial.

Disk diffusion

Based on guidelines provided by the Clinical and Laboratory Standards Institute (CLSI), the diameter of inhibition is reported as susceptible, intermediate, or resistant.

Although these tests provide an accurate assessment of in vitro susceptibility, the time delay (18–24 hours) can hinder streamlining of therapy.

An alternative efficient, but more expensive, MIC test is the E test, which uses an antibiotic-laden plastic strip with increasing concentrations of a specific antimicrobial from one end to the other. The strip is placed on an agar plate with the actively growing pathogen. Inhibition of growth observed at specific marks on the strip coincides with the MIC of the organism. Numerous studies have confirmed that the E test is as effective as traditional susceptibility testing.

Several automated antimicrobial susceptibility systems are available in the United States. Two major advantages of automated susceptibility methodologies include a reduction in labor and faster reporting of susceptibility results, potentially leading to the earlier initiation of appropriate antibiotic therapy.

Although susceptibility testing is relatively well standardized for aerobic gram-negative and gram-positive organisms, its utility is not as established for anaerobes and fungi.

In general, despite improvements in the standardization of testing in anaerobes, institutions do not routinely perform susceptibility testing for these bacteria. In contrast, susceptibility testing is now available for Candida species, and these in vitro data have been demonstrated to predict clinical success by azoles in the patient care setting.

The MIC is the minimum concentration at which an antimicrobial inhibits the growth of the organism; the test does not provide information regarding whether the organism is actually killed.

In some disease states (e.g., endocarditis), bactericidal therapy is necessary. The minimum bactericidal concentration (MBC) is the test that can be used to determine the killing activity associated with an antimicrobial. The MBC is determined by taking an aliquot from each clear MIC tube for subculture onto agar plates. The concentration at which no significant bacterial growth (i.e., 99.9% of the original inoclum) is observed on these plates is considered the MBC.

DETERMINATION OF ISOLATE PATHOGENICITY

A positive culture may represent colonization, contamination, or infection.

In summary, culture results do not solely identify true pathogens. For example, the Serratia in a patient with pneumonia may be a pathogen, contaminant, or colonizer. Nevertheless, considering the severity of illness and the associated respiratory symptoms, treatment directed against this pathogen is necessary.

ANTIMICROBIAL TOXICITIES

Adverse Effects and Toxicities

Before antimicrobial therapy is started, it is important to elicit an accurate drug and allergy history. When "allergy" has been reported by the patient, it is necessary to determine whether the reaction was intolerance, toxicity, or true allergy.

For example, gastric intolerance caused by oral erythromycin or doxycycline is common; however, this adverse effect does not represent an allergic manifestation.

A reasonable recommendation pending susceptibility results would be to discontinue imipenem and gentamicin in an old patient with epilepsy background and treat with meropenem or doripenem with or without a fluoroquinolone.

Concomitant Disease States

Older patients with hearing deficits are poor candidates for potentially ototoxic aminoglycoside therapy.

Diabetic or kidney transplant patients with candidemia may be better treated with fluconazole or an echinocandin rather than nephrotoxic amphotericin B products.

Patients with a pre-existing seizure history should not receive imipenem if less toxic therapy can be used.

ANTIMICROBIAL COSTS OF THERAPY

Although acquisition cost traditionally has been the primary factor in the overall cost of therapy, drug administration labor costs (i.e., nursing and pharmacy) and the use of IV sets, piggy-back bags, and infusion control devices must be included in the analysis.

As a result, a drug that must be administered several times daily, such as intravenous penicillin, will incur increased administration costs compared with one, such as ceftriaxone, that requires once-a-day dosing.

Some drugs, such as aminoglycosides, are associated with increased laboratory costs (e.g., aminoglycoside serum concentrations, serum creatinine, and audiometry) that are not required for other agents such as the third-generation cephalosporins and quinolones.

Costs that are difficult to quantitate include those associated with failure of antimicrobial therapy and antimicrobial toxicity. Ineffective or toxic therapy can prolong hospitalization and may require expensive interventions, such as hemodialysis, mechanical ventilation, and intensive care unit admission. The net effect of these latter costs can be significantly greater than the acquisition and administration costs of antimicrobial therapy.

ROUTE OF ADMINISTRATION

The proper route of antibiotic administration depends on many factors, including the severity of infection, antimicrobial oral bioavailability, and other patient factors.

In patients who appear “septic,” blood flow often is shunted away from the mesentery and extremities, resulting in unreliable bioavailability from the gastrointestinal (GI) tract or muscles. Consequently, hemodynamically unstable patients should always receive antimicrobials by the IV route to ensure therapeutic antimicrobial levels.

Furthermore, some drug interactions with oral agents can result in subtherapeutic serum concentrations (e.g., reduced bioavailability associated with concomitant quinolone or tetracyclines and antacid administration and the decreased absorption of itraconazole with concurrent proton-pump inhibitor [PPI] therapy).

ANTIMICROBIAL DOSING

Patient-specific factors, including weight, site of infection, and route of elimination, also must be considered in dosage selection.

Weight

The patient's weight is important, particularly for agents with a low therapeutic index (e.g., aminoglycosides, imipenem, flucytosine); these drugs should be dosed on a milligram per kilogram per day basis. Other agents with a more favorable adverse effect profile, such as cephalosporins, are less likely to require weight-specific dosing in most disease states.

Site of Infection

An uncomplicated urinary tract infection requires lower doses considering the high urinary drug concentrations that are achieved with most renally cleared agents. In contrast, a more serious upper urinary tract infection, such as pyelonephritis, requires increased doses to ensure therapeutic drug levels in tissue and in serum.

Anatomic and Physiologic Barriers

For example, penetration into cerebrospinal fluid requires high doses to ensure adequate antimicrobial concentrations. Vitreous humor and the

prostate gland are additional sites in which therapeutic antimicrobial concentrations are more difficult to achieve.

Route of Elimination

Most β-lactams are eliminated by the kidney. In contrast, ceftriaxone and most antistaphylococcal penicillins (e.g., nafcillin, oxacillin, dicloxacillin) are eliminated both renally and nonrenally.

Aminoglycosides, vancomycin, acyclovir, and ganciclovir are cleared primarily by the kidney. Thus, dosage adjustment is recommended for these drugs in patients with renal failure. Because azithromycin, clindamycin, and metronidazole are primarily eliminated by the liver, no dose reduction is required in renal failure for these agents.

Although renal function can be approximated with the use of the Cockcroft and Gault equation (or a similar equation), hepatic function is more difficult to evaluate. No standard liver function test (AST, ALT, alkaline phosphatase) has been demonstrated to correlate well with hepatic drug clearance. Some tests, such as PT, INR, and albumin, are markers of hepatic function, but even these tests do not clearly predict drug clearance.

Patient Age

It is clear that the very young and the elderly have a decreased ability to clear drugs; thus, dosage requirements for many agents are likely to be decreased in neonatal and geriatric patients.

Inoculum Effect

Inoculum effect has taken place when higher concentrations of a bacterial inoculum result in an increase in the MIC. As an example, piperacillin may demonstrate an MIC of 8.0 mcg/mL against P. aeruginosa at a concentration of 10^5 CFU/mL; however, at 10^9 CFU/mL, the MIC may increase to 32 to 64 mcg/mL. This phenomenon is well recognized, particularly with β-lactamase–producing bacteria treated with β-lactam antimicrobials. The more stable the antimicrobial is to β-lactamase, the less the influence of the inoculum effect. Aminoglycosides, quinolones, and imipenem appear to be less affected by the inoculum effect than β-lactams.

PHARMACOKINETICS AND PHARMACODYNAMICS

β-Lactams, such as cefotaxime, are not associated with increased bacterial killing with increasing drug concentrations. Pharmacodynamic activity with β-lactams best correlates with the duration of time that antimicrobial levels are maintained above the MIC.

The efficacy of quinolone and aminoglycosides antimicrobials appears to correlate with the peak plasma concentration to MIC ratio or area under the curve (AUC) to MIC ratio.

Aminoglycosides traditionally have been administered every 8 to 12 hours to achieve peak serum gentamicin levels of 5 to 8 mcg/mL to ensure efficacy in the treatment of serious gram-negative infection. Gentamicin troughs of greater than 2 mcg/mL have been associated with an increased risk for nephrotoxicity.

Once-Daily Dosing of Aminoglycosides

The greatest clinical experience has been with the aminoglycosides in the treatment of gram-negative infection. However, if the infection is severe and serum creatinine level elevated, the patient is not a

candidate for single daily dosing of aminoglycosides (i.e., 5 to 6 mg/kg every 24 hours).

Post-antibiotic effect (PAE)

Several antimicrobials (e.g., aminoglycosides and quinolones and imipenem) have been associated with a pharmacodynamic phenomenon known as a post-antibiotic effect (PAE). PAE is delayed regrowth of bacteria after exposure to an antibiotic (i.e., continued suppression of normal growth in the absence of antibiotic levels above the MIC of the organism).

In contrast to that observed with β-lactam antibiotics, if the gentamicin is removed from the system, a lag period of 2 to 6 hours takes place before characteristic bacterial growth occurs. This lag period is defined as the PAE.

ANTIMICROBIAL FAILURE

Antimicrobials may fail for various reasons, including patient-specific host factors, drug or dosage selection, and concomitant disease states.

Drug resistance

One of the most common reasons for antimicrobial failure is drug resistance.

Several clinically important pathogens have been associated with emergence of resistance during the past decade, including M. tuberculosis, enterococci, gram-negative rods, S. aureus, S. pneumoniae, and others.

Of particular concern is the isolation of glycopeptide-resistant S. aureus and multiresistant Acinetobacter and Pseudomonas.

Development of resistance during therapy, although less common than initial intrinsic resistance, may also account for failure to respond to therapy.

Organisms that produce extended-spectrum (ESBL) or amp C β-lactamases may be unresponsive to β-lactam therapy despite associated in vitro susceptibility.

Superinfection also may play a role in the unsuccessful treatment of infection. Superinfection has taken place when a new pathogen resistant to the current antimicrobial regimen is isolated.

For example, if ceftriaxone-treated Serratia pneumonia subsequently worsens and a tracheal aspirate returns positive for P. aeruginosa, then supercolonization and, perhaps, superinfection have occurred.

Combination Therapy

Most infections can be treated with monotherapy (e.g., an E. coli wound infection is treatable with a cephalosporin).

Some infections, however, require two-drug therapy, including most cases of enterococcal endocarditis and perhaps certain P. aeruginosa infections.

-In a study on 200 consecutive patients with P. aeruginosa bacteremia, the researchers demonstrated a 47% mortality in those receiving monotherapy (antipseudomonal β-lactam or aminoglycoside) versus 27% in those in whom two-drug therapy was used. Thus, monotherapy appeared to contribute to antimicrobial failure in this specific study.

In contrast to the findings of the previous trial, more current investigations do not support the use of two drugs over monotherapy in the treatment of serious gram-negative infection, including P.

aeruginosa. An exception to this rule is bacteremia caused by P. aeruginosa in neutropenic patients.

Two concurrent drugs may present antagonism. An example of antagonism is the combination of imipenem with a less β-lactamase–stable β-lactam, such as piperacillin. If P. aeruginosa is exposed to imipenem and piperacillin, the imipenem induces the organism to produce increased β-lactamase. Imipenem is remarkably β-lactamase stable, and is not degraded by this β-lactamase. In direct contrast, piperacillin is easily degraded by the β-lactamase. Thus, imipenem antagonized the effectiveness of piperacillin. Antagonism is not unique to antibacterials; itraconazole may antagonize amphotericin B in the treatment of certain fungal infections.

Pharmacologic Factors

Subtherapeutic dosing regimens are commonplace, particularly for agents with a low therapeutic index, such as the aminoglycosides.

For example, a serious gram-negative pneumonia may not respond to aminoglycoside therapy if the achievable peak gentamicin serum levels are only 3 to 4 mcg/mL. Considering that only 20% to 30% of the aminoglycoside penetrates from serum into bronchial secretions, only

0.5 to 1.0 mcg/mL may exist at the site of infection, a level that may be inadequate to treat pneumonia.

Another example of dosing contributing to antimicrobial failure centers on the use of loading doses. Aminoglycosides or vancomycin should be intiated with a loading dose, particulary in patients with renal failure. If the clinician neglects to use a loading dose, it may take several days before a therapeutic level is achieved.

As described previously, yet another reason for subtherapeutic antimicrobial levels and potential drug failure is reduced oral absorption secondary to drug interactions (e.g., concomitant oral ciprofloxacin with antacids or iron).

An emerging problem relates to the use of vancomycin in the treatment of serious methicillin-resistant S. aureus infection (MRSA). By CLSI standards, an isolate of MRSA with an MIC of 2 mcg/mL is considered susceptible. Retrospective analyses have, however, demonstrated a high failure rate associated with vancomycin in the treatment of MRSA isolates with an MIC of 2 mcg/mL. The pharmacodynamic parameter that serves as the best predictor of vancomycin activity against S. aureus is the AUC to MIC ratio, with a value greater than 350 independently associated with success. The probability of attaining this

value with isolates with an MIC of 2 mcg/mL is 0%, even when achieving vancomycin trough concentrations of 15 mcg/mL.

The infection site also potentially contributes to antimicrobial failure. Most antimicrobials concentrate in the urine, resulting in therapeutic levels even with low doses. In some infections, such as meningitis, prostatitis, and endophthalmitis, antimicrobial penetration to the site of infection may be inadequate. Agents that penetrate well into these sites are associated with a more favorable outcome.

Another potential reason for antimicrobial failure is inadequate therapy duration. A woman with a first-time uncomplicated cystitis may respond adequately to a 3-day course of an antibiotic. In contrast, patients with recurrent urinary tract infections are not candidates for this short course of therapy, however, and failure would be expected with only 3 days of therapy.

Host Factors

Infection of prosthetic material (e.g., IV catheters, orthopaedic prostheses, mechanical cardiac valves, and vascular grafts) is difficult to eradicate without removal of the hardware. In most cases, surgical intervention is necessary. Similar to removal of prostheses, large undrained abscesses are difficult, if not impossible, to treat with

antimicrobial therapy. These infections generally require surgical drainage for successful outcome.

Diabetic foot ulcer cellulitis may not respond adequately to antimicrobial therapy. Reasons for antimicrobial failure in patients with diabetes include poor wound healing and reduced delivery of antibiotics to the infection site.

Immune status, particularly neutropenia or lymphocytopenia, also affects the outcome in the treatment of infection. Profoundly neutropenic patients with disseminated Aspergillus infections are unlikely to respond to even the most appropriate antifungal therapy.

Similarly, patients with AIDS who have low CD4 lymphocyte counts cannot eradicate various infections, including those caused by cytomegalovirus, atypical mycobacteria, and cryptococci.