Practice Guidelines

Recommendations for Appropriate use of Antimicrobials at Hospitals in Pakistan

(First of two parts)

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INTRODUCTION

The inappropriate and excessive use of antimicrobials worldwide including Pakistan has led to resistance of common pathogens. This has led to limited options for use of antibiotics in both outpatient and inpatient settings. There is now a greater stress to restrict antibiotics use in large setups as one major step. An antibiotic policy in any institution will help in ensuring that physicians follow guidelines that aid in patient overall management. In most health institutions there is no antibiotic policy. Physicians are often unaware or do not follow such policies. This paper will review some aspects of antibiotic use and provide a basis for controlled and appropriate use of antimicrobials in major hospitals across Pakistan.

OBJECTIVES of this paper are to implement an antibiotic policy that is consistent, aid physicians to choose the most appropriate antibiotic in a clinical situation and reduce antibiotic-related costs

THE FOLLOWING POLICY should be strictly followed in the hospitals.

1. All physicians are encouraged to consult an "Infectious Disease" (ID) Physician as early as possible in the following clinical situations: Sepsis, meningitis, encephalitis, fever of unknown origin, fever in immunocompromised host, including fever and neutropenia, endocarditis, bone and joint infections, severe pneumonia (RR >30, DBP <60, O2 saturation <90, or age >65), intra-abdominal abscesses, complicated pyelonephritis, nosocomial infections, unusual culture results or multiply resistant etiologic agent(s), complicated malaria (recurrent, resistant, cerebral), systemic fungal infections, tuberculosis (extra pulmonary, MDR TB, or complicated TB) and systemic parasitic infections

2. It is strongly recommended the routine use of the following antibiotics be limited: Amphotericin B, acyclovir, amikacin, ceftazidime, cefaperazone, cefperome, imipenem, meropenem, piperacillin/ tazobactam, piperacillin, teicoplanin, vancomycin (except prophylactic use for dialysis patients).

After 72 hours of initiation of these antibiotics the primary physician should review the need to continue these antibiotics. The pharmacy will call the primary physician to discontinue the above antibiotic after 72 hours. If the primary physician feels that the clinical and microbiologic data warrants continuation of these antibiotics beyond 72 hours, he is encouraged to do so in consultation with an ID Physician.

3. The pharmacy and therapeutic committee should continuously review the appropriate

use of these and other antibiotics for all patients. The pharmacist will involve the ID physician where appropriate to discuss potential over - and misuse of major antibiotics.

4. This policy should be reviewed periodically after every 6 months.

GENERAL PRINCIPALS

Antibiotics are indiscriminately used most often in emergency and ICU settings. It is important that before initiation of antibiotics appropriate cultures are done for correct identification of the infecting organism(s) i.e. **appropriate specimen(s) for culture, stains, or histopathologic** examination be obtained in a proper fashion. Often physicians fail to obtain cultures and stains initially, when the yield is maximal. Gram stain can be performed on all body fluids, particularly those that are normally sterile body sites such as CSF, pleural, pericardial and synovial fluid. Cultures and stains from draining sinuses may not represent true infection and may only represent superficial colonization. This can have major impact as these yield mostly resistant organism and inappropriate use of broad-spectrum antibiotics. This leads to increased costs, resistance and superimposed fungal infections.

Antibiotic susceptibilities should be performed on all clinically important isolates. A number of factors should be kept in mind when interpreting these results. Firstly, most laboratories do not perform susceptibility testing on all antibiotics because of cost and time. In general, class compounds are used. For example, cefazolin represents first generation cephalosporins. Secondly, failure to delineate clones of subpopulations of organisms that are resistant to an agent may be present in a susceptible population. For

example, enterobacter may appear susceptible to cefotaxime, ceftriaxone, and azactam but serious infection may fail with these agents because of selection of clones that produce large amounts of beta-lactamase that have altered outer membrane proteins. Thirdly, it is important to recognize that resistance may appear during therapy of infections. Organisms that are well known to do this include pseudomonas aeroginosa, acinetobacter, serratia marscens, proteus and providencia species.

Some major problems with antimicrobial agents that are strongly discouraged in any hospital settings include the following:

MAJOR PROBLEMS with antimicrobial use that should be discouraged in any hospital setting:

1. Initiation of antibiotics before appropriate cultures are sent to microbiology lab
2. Use of broad spectrum agents when more restricted agents would suffice
3. Use of combination antibiotics when one agent is equally effective
4. Institution of antibiotics with worst scenario, i.e. *Pseudomonas* or MRSA when these organisms are highly unlikely
5. Failure to consult ID Physician to aid in the selection of drugs
6. Failure to alter therapy when susceptibility data is available
7. Treatment by oral route or failure to switch to oral therapy when indicated clinically and microbiologically
8. Treatment for too long a time
9. Failure to use a dosage program that is appropriate to the renal and hepatic function or failure to recognize toxic side effects of antibiotics because of polypharmacy

ANTIBIOTIC REVIEW

The following is a brief review of major classes of antibiotics. This is not an exhaustive list since newer antibiotics are being introduced.

Aminoglycosides

Aminoglycosides are bactericidal antibiotics active against many aerobic gram-negative and some aerobic gram-positive bacteria. Anaerobic bacteria are resistant because transport of aminoglycosides into cells is oxygen dependent. Aminoglycosides are inactive against fungi and viruses. In combination with penicillin or vancomycin, aminoglycosides often act synergistically to inhibit gram-positive bacteria. Aminoglycosides have a post-antibiotic effect against gram-negative bacteria, which allows less frequent dosing. Aminoglycosides include amikacin, gentamicin, kanamycin, and tobramycin. Gentamicin is recommended as initial therapy unless resistance to or infection with pseudomonas is suspected, in which case, initial therapy may begin with amikacin.

Amikacin may also be given as empiric therapy if patient has sepsis, an outbreak of multi-drug resistant gram-negative infection susceptible to amikacin is identified or when infection due to gentamicin or tobramycin resistant organisms is suspected. Gentamicin therapy should be used when culture indicates the organism is susceptible. Furthermore, empiric therapy begun with amikacin or tobramycin should be discontinued when culture indicates an organism susceptible to gentamicin. Remember that amikacin is 10-fold expensive as compared to gentamicin. Gentamicin may be continued to provide synergy for treatment of endocarditic or osteomyelitis caused by gram-positive organisms. Amikacin is active against some strains of bacteria, such as Proteus,

Pseudomonas, and Serratia, which may not susceptible to other aminglycosides. For this reason, amikacin should **only** be used when resistance to or failure of gentamicin and tobramycin is documented.

Extended Spectrum Penicillins

Extended spectrum penicillins are bactericidal. They are more active against enteric gram-negative bacilli than natural penicillins, penicillinase-resistant penicillins, and aminopenicillins because they are more resistant to inactivation by B-lactam producing gram-negative bacteria. These drugs may also penetrate the outer membrane of gram-negative organisms more readily than their penicillin precursors. Extended spectrum penicillins are active in vitro against more gram-positive and gram-negative aerobic cocci (except penicillicase- producing strains), some gram-positive aerobic bacilli, and many gram-negative aerobic or anaerobic bacilli. They are inactive against mycobacteria, Mycoplasma, Rickettsia, fungi, and viruses.

The intravenous extended spectrum pencillins include ticarcillin, piperacillin, mezlocillin ticarcillin-clavulanate and piperacillin-tazobactam. These agents may be used in combination with an aminoglycoside for empiric therapy of infection with Pseudomonas infection.

Empiric therapy with piperacillin is indicated for suspected pseudomonas cepacia infection or ticarcillin resistant anaerobic infection. Piperacillin therapy should be continued for documented susceptible pseudomonas infection.

Piperacillin-tazobactam or piperacillin may be used for initial therapy and treatment in the following situations: Suspected polymicrobic pneumonia, suspected anaerobic infection, patient with fever and neutropenia, hospital-acquired aspiration pneumonia,

and intra-abdominal infection.

Cephalosporins

Cephalosporins are bactericidal in action. They are classified as first, second, third or fourth generation based on their spectrum of activity. The first generation cephalosporins are active in vitro against gram-positive cocci. They have limited activity against gram-negative bacteria. The second-generation cephalospirins are active in vitro against organisms susceptible to first generation cephalosporins. In addition, second generation organisms are more active against gram-negative organisms. Third generation cephalosporins have an extended spectrum against gram-negative organisms. The newer fourth generation cephalosporins are active against organisms susceptible to third generation cephalosporins and have activity against gram-positive organisms, including staphylococcus aureus. The intravenous cephalosporins include the first generation such as - cefazolin, second-generation - cefoxitin and cefuroxime, third generation - cefotaxime, ceftriaxone, and ceftazidime and fourth generation - cefperome.

Cefazolin may be used empirically for surgical prophylaxis for clean and clean-contaminated surgeries, excluding appendectomies and traumatic wounds. It should be dosed every 8 hours for all indications.

Cefoxitin may be used for surgical prophylaxis for patient with appendectomies or ruptured viscous. It may also be used for empiric therapy or treatment of atypical mycobacterial disease.

Cefuroxime should be considered for suspected community-acquired pneumonia or suspected bacterial arthritis. Treatment may be continued for documented susceptible gram-negative infection outside the central nervous system (CNS).

Cefotaxime therapy may be initiated for suspected CNS infection, gram-negative sepsis, or penicillin-resistant pneumococcal infection. Treatment should be continued for documented infections susceptible to cefotaxime.

Ceftazidime is an anti-pseudomonas cephalosporin and its use should be limited to such infections. Empiric therapy must be initiated for patients either suspected pseudomonas infection or in those patients with fever and neutropenia. Treatment should continue for documented pseudomonas infection.

Ceftriaxone is the most widely used antibiotic in both in-patient and outpatient settings since it can be given once a day. It is primarily used for suspected enteric fever, sepsis in a normal host, meningitis and pneumonia. Empiric therapy or treatment may be initiated for suspected gonococcal infection or multidrug-resistant otitis media in a noncompliant patient.

Teicoplanin/Vancomycin

Teicoplanin and vancomycin is bactericidal with activity against most gram-positive organisms. It is not active against gram-negative organisms, fungi, yeast or mycobacteria. Vancomycin or teicoplanin should be used empirically when a gram-positive infection is suspected in patients who are seriously ill or allergic to B-lactam antibiotics. It may also be used when endocarditis is suspected or bacterial meningitis due to *Streptococcus pneumoniae* is suspected. Treatment should continue in patients with serious infection caused by B-lactam resistant gram-positive organisms or for gram-positive infection in patients who have a documented allergy to B-lactam antibiotics. Oral vancomycin is indicated only for antibiotic-associated colitis resistant to metronidazole or that is life threatening.

To limit potential development of resistance to and overuse of vancomycin or teicoplanin, a 72-hour stop order, is strongly advocated worldwide. The ordering physician will receive call from the pharmacy to review continuation beyond 72 hours of initiation of vancomycin therapy. At this time culture results should be available. If cultures are negative or if the susceptibility suggests an alternative antibiotic, vancomycin should be discontinued. If the drug is not discontinued, the pharmacist will call the physician to determine why the drug was continued and encouraged to consult ID Physician.

Amphotericin B

Amphotericin B is a systemic antifungal agent active against most mycoses. It is indicated in patients with proven fungal infection or suspected fungal infections in immunocompromised patients such as those with prolonged fever and neutropenia. Its use should be limited to such patients and ID consultation should be sought in all such patients. The newer liposomal Amphotericin B formulations that are more expensive but with less toxicity are available.

Antivirals

Antiviral agents such as acyclovir, amantadine or ribavarin have been overused mostly in the outpatient settings. Their use is discouraged because of high cost, toxicity and inappropriate use. Consultation with an ID physician is encouraged in such clinical settings. Similarly the use of parenteral antivirals for suspected or confirmed systemic viral infections especially in immunocompromised patients is **encouraged** with aid from the ID physicians. Newer antiviral agents are now approved for common viral infections such as common cold but are not available in Pakistan.

Oral Antibiotics

Guidelines for several oral antibiotics have also been developed. Cephalexin may be used for treatment of pharyngitis, bone and joint infection, and skin and soft tissue infection. Augmentin, trimethoprim-sulpamethaxazole, clindamycin, loracarbef and cefprozil may be used after amoxicillin or ampicillin failure for treatment of otitis media or sinusitis. Cefpodoxime may be used as a single-dose treatment of gonorrhea, for suspected multi-drug resistant infection (otitis media, sinusitis, or urinary tract infection), or documented failure to other oral antibiotics. Clarithromycin should be reserved for documented Mycobacterium avium-intracellulare infection or multi-drug resistant tuberculosis. Azithromycin may be used for empiric use in community-acquired pneumonia in patients with documented erythromycin intolerance and for the treatment of sexually transmitted diseases. Ciprofloxacin and levofloxacin may be used to treat lower-respiratory infections in patients with community-acquired pneumonia or those with cystic fibrosis. (The second part will appear in the next issue of RMJ).

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