Antibiotic Update for the Surgeon

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Infection remains a significant source of morbidity and expense in the treatment of surgical patients therefore, antibiotics continue to be an important part of the general surgeon's armamentarium. Unfortunately, physicians, and surgeons in particular, continue to order too many antibiotics too often, and for too long. Optimal use of antibiotics, as for any therapeutic modality, requires consideration of the risks and benefits associated with available agents and regimens. Although the desired benefit is always successful eradication or avoidance of offending pathogens, the best way to acheive that goal may not be obvious. Decisions regarding choice of antimicrobial agent, duration of therapy, and route of administration are primarily based upon anticipation of clinical efficacy.

However, choices should also reflect consideration of important secondary issues, including antibiotic related toxicities, alterations in microbial environment, and cost of treatment. This article discusses aspects of antibiotic use and treatment of infectious diseases that can be useful to the general surgeon in daily practice. While basic principles of antibiotic use are reviewed, emphasis is placed on current concepts in antibiotic choice and administration. Recently developed antibiotics with antimicrobial spectra that include pathogens frequently encountered in surgical patients are also discussed. The goal is to present pertinent information concisely and provide a basis for safe, effective, and cost-conscious use of antibiotics.

PROPHYLACTIC ANTIBIOTICS

In the broadest terms, antibiotic administration can be classified as either prophylactic or therapeutic. The latter refers to those instances in which antibiotics are administered with curative intent in the treatment of an established infection, whereas the former refers to administration of antibiotics when infection is presumed not to exist, but the potential for infection does. Antibiotic prophylaxis is, therefore, preventive rather than curative. Prophylaxis against postoperative wound infection is the most common reason for antibiotic use in surgery.[1] Postoperative wound infections have the potential to tax already strained healthcare resources, prolonging hospital stay and increasing hospital costs.[2] In the current environment

of strict resource conservation and cost containment, and with the growing influence of managed care systems and capitated reimbursement, avoidance of even "minor" postoperative complications becomes important. Therefore, familiarity with the basic principles of antibiotic prophylaxis, including choice, timing, and duration of administration of an appropriate agent should be considered an integral part of the fund of knowledge for the practicing surgeon.

Antibiotic administration limited to the perioperative period, or immediately surrounding invasive procedures, is generally accepted as prophylactic treatment despite the fact that the temporal relationship between surgery (or the invasive procedure) and the establishment of a bacterial inoculum may vary. For example, whereas antibiotics administered prior to elective cholecystectomy presumably establish adequate tissue levels before potential bacterial dissemination, such may not be the case when antibiotics are administered prior to laprotomy for gangrenous appendicitis or penetrating abdominal trauma. Nonetheless, antibiotics are frequently administered in these situations with "prophylactic" intent, prompting some authors to subclassify various applications of antibiotic prophylaxis.[3]

General principles of antibiotic prophylaxis include the use of an agent with an appropriate antimicrobial spectrum and sufficient penetration to establish bactericidal levels in the involved tissues. Moreover, the agent should be relatively inexpensive, easy to administer, and with a low potential for toxicity. Consideration of these basic requirements have led to recommendations for use of specific antibiotics for prophylaxis with a variety of surgical procedures. In most instances, first and second generation cephalosporins have been shown to be as effective as any of the newer agents, including later generation cephalosporins, and are available at a low cost. Alternatives must be found for patients with a history of hypersensitivity to cephalosporins or anaphylactoid reactions to any beta lactams. Detailed lists of recommended agents have been published elsewhere and are available for review by the interested reader.[1]

Until recently, data that could be used to define the optimal time to administer preoperative prophylactic antibiotics was lacking, and antibiotics were frequently ordered to be given "on call" to the operating room or even the night prior to surgery. However, recent in vivo studies, in which both serum and tissue levels of antibiotics given at various times preoperatively were measured, appear to have answered this question.[4] The results showed that antibiotics administered rapidly through an intravenous route immediately prior to incision achieved tissue levels well above the minimal inhibitory concentration (MIC) for anticipated organisms, and that tissue concentrations remained in the bactericidal range until wound closure. On the basis of these results, we would suggest that for each surgical procedure in which prophylactic antibiotics are used, rapid, intravenous administration immediately prior to the skin incision should be done to avoid early dosing and potentially subtherapeutic levels at the time of incision. Depending upon the half-life of the agent being used and the duration of the operative procedure, attention should still be paid to the potential need for repeated intraoperative dosing. Because recommended agents tend to demonstrate wide therapeutic windows, a valid strategy might be to administer a full dose of antibiotics after each half-life of the drug. If detailed information is unavailable, a reasonable rule of thumb is to re-dose every 2 to 3 hours.

Few surgeons today would consider continuing prophylactic antibiotics for more than 48 hours following an elective surgical procedure, and most now limit the interval to 24 hours or less. However, the results of numerous studies demonstrate no benefit from any antibiotics being given postoperatively for elective procedures (clean and clean contaminated cases), and therefore only a single preoperative dose of antibiotics (or for prolonged procedures, intraoperative doses) is recommended.[5] The issue is not as clear for "prophylaxis" of non-elective, contaminated operations. In these situations each case must be considered individually, with decisions being based upon clinical and laboratory data, operative findings and the degree of intraperitoneal soilage. Since the bacterial density of the proximal gastrointestinal tract is quite low, as compared with the distal small intestine and colon, when the proximal gastrointestinal tract is the source of contamination, 24 hours of perioperative antibiotics should suffice, following vigorous intraoperative peritoneal lavage. On the other hand, if massive spillage of lower gastrointestinal contents is found, antibiotic administration should probably no longer be considered prophylactic, but rather therapeutic, and a five to seven day course of antibiotics should be given postoperatively. The selected agent should be active against gram negative aerobes, and anerobes.

Past recommendations for the duration of postoperative antimicrobial therapy in penetrating abdominal trauma have varied from 24 hours to five days or longer. However, prospective clinical data have shown that prolongation of antibiotics beyond 24 hours offers no improvement in the incidence of postoperative wound infections or major abdominal infections, irrespective of the severity of abdominal trauma or the presence or absence of colonic injury.[6] In contrast, prolonged use of prophylactic antibiotics has been associated with complications due to alterations in bacterial flora, including an increased incidence of Clostridium dificile colitis and development of methicillin resistant staphylococcus epidermidis (MRSE), and is therefore to be avoided.[8,9] In selecting an antibiotic one should be careful to use an agent with activity against enterics and anaerobes, since colonic injuries occur in approximately 20% of cases of penetrating abdominal trauma.[10] A second generation cephalosporin, such as cefoxitin or cefotetan, is generally sufficient.

In summary, prophylaxis for most elective operations should consist of a single preoperative dose of antibiotics administered rapidly through an intravenous route, with the infusion completed immediately prior to the incision being made. For procedures lasting longer than the half-life of the agent (or approximately 2-3 hours), re-dosing is suggested. No postoperative antibiotics need be given. When antibiotics are given with prophylactic intent to patients with intra-abdominal sepsis, intraoperative findings should dictate the duration of the postoperative course of antibiotic therapy. For patients with traumatic injuries of abdominal viscera, antibiotics should be given for 24 hours postoperatively. If after cessation of antibiotics the patient shows signs of infection, the treatment algorithm should shift to antibiotic administration with therapeutic, not prophylactic, intent.

THERAPEUTIC ANTIBIOTIC USE

General surgeons routinely deal with a variety of infectious maladies involving any or all body cavities and extremities. While surgical debridement is frequently a valuable therapeutic tool, dissemination of the offending pathogens often requires use of antimicrobial agents to eradicate residual infection. Moreover, despite our best

efforts, patients can and do develop infectious complications following surgery, and while treatment may not require surgical expertise, one should be able to manage these problems comfortably, capably, and intelligently. Prudent use of antibiotics in these situations requires an algorithmic approach that includes consideration of the microbiology of the involved tissues, the microbial environment within the institution, the spectrum of antibiotics that may be used effectively, and methods for minimizing toxicity and cost while maximizing clinical outcome.

Therapeutic use of antibiotics implies the presence of an identified, established infection. If the infection is suspected but not identified, or the source of infection or pathogen are unidentified, antibiotics may be administered on an "empiric" basis. Philosophically, empiric use of antibiotics is carried out with therapeutic intent, yet the distinction is made to illuminate the fact that empiric antibiotic therapy entails some degree of uncertainty, and is therefore based upon "best guess" information. Empiric antibiotic therapy should commence after appropriate and complete diagnostic workup has been performed, directed at identifying a source of infection, and potentially obtaining a specimen for identification of pathogens and antibiotic susceptibility patterns. Antibiotics should be selected based upon anticipated pathogens and the likelihood of obtaining therapeutic levels in tissues that are suspected of being involved. In general, knowledge of institutional flora and antibiotic susceptibilities is invaluable in these considerations.

Suspected intra-abdominal infections should be treated with agents that demonstrate activity against gram negative aerobic bacilli, including E. coli, Proteus mirabilis, Klebsiella pneumoniae, Enterobacter cloacae, and Pseudomonas aeruginosa; and anaerobes, primarily Bacteroides spp. Empiric use of cephalosporins for treatment of severe intra-abdominal infections is not recommended, as Enterobacter and Pseudomonas frequently demonstrate beta lactamase activity.[11] On the other hand, the beta lactam/beta lactam inhibitor combination of tazobactam/piperacillin would be an excellent choice for empiric treatment of most intra-abdominal infections.[12,13] In addition, despite past uncertainty as to the role of the enterocci in intra-abdominal infections, they are now being recognized as potentially important pathogens, particularly in the critically ill, immunocompromised patient.[14,15] Moreover, enterococcal sepsis arising from abdominal sources, though uncommon, has been associated with a high mortality rate.[14] Therefore, since enterococci frequently demonstrate limited susceptibility patterns and have the capacity to develop resistance to a variety of antimicrobial agents,[16] we believe an effort should be made to treat enterococci swiftly and aggressively when isolated. Ampicillin, piperacillin, and vancomycin are generally effective anti-enterococcal agents, as is the combination of tazobactam/piperacillin.

Infection of the urinary tract may be due to ascending enteric organisms, particularly in females, or hematogenous dissemination of bacteria from distant sites. The most commonly isolated pathogen is E. coli, although other gram negative rods are frequently found, particularly in hospitalized patients.[17] The fluoroquinolones are excellent agents for treating gram negative urinary tract infections due to their broad spectrum of activity (including Pseudomonas) and high concentration in urine.[18] Enterococcal urinary tract infections, however, require treatment with an appropriate anti-enterococcal agent, such as ampicillin. Enterococci represent 10-15% of all urinary isolates, and are frequently associated with previous antibiotic therapy and urinary tract manipulation.[17]

Pulmonary infections are most readily classified as community acquired or hospital acquired, each being associated with a different set of likely pathogens. Community acquired pneumonias are usually due to a single pathogen, most commonly pneumococcus or H. influenza; Klebsiella pneumoniae may be seen in alcoholics or institutionalized patients.[19] Colonization and invasion of the respiratory tract by hospital flora generally takes approximately 4 to 5 days, therefore isolates from hospitalized patients who develop pneumonias soon after admission will frequently be community acquired organisms. The third generation cephalosporins, ceftriaxone, ceftizoxime and cefotaxime, demonstrate good to excellent activity against all of these pathogens, and would be reasonable choices for initial therapy, pending speciation. Less expensive beta lactams, such as ampicillin, may be substituted once the pathogen is identified and susceptibilities ascertained. If aspiration is being entertained as a likely cause of the infection, oropharyngeal, gram positive anaerobes may be involved.[19] The third generation cephalosporins will cover these pathogens as well. Hospital acquired pneumonias generally are caused by gram negative enterics, most commonly Pseudomonas.[19] Because of this, double antibiotic coverage is recommended as initial, empiric treatment until pathogens are isolated and identified. Traditionally, this consists of a beta lactam, such as ceftazidime, piperacillin, or ticarcillin, and an aminoglycoside. One of the fluoroquinolones may be used with a beta lactam if concern exists for renal toxicity. Pneumonias arising from aspiration occurring in the hospital need no added antibiotic coverage, since the aspirated pathogens are generally gram negatives that have colonized the oropharynx.[19]

For most patients and in most circumstances, prudent use of antibiotics for treating established infections should be straightforward. In essence, the algorithm includes identifying the infection, drainage of any localized collections, obtaining a specimen, if possible, and commencement of empiric antibiotics. Selection of antibiotic agent(s) should be based upon consideration of tissues to which the agent must be delivered, likely pathogens, and anticipated antibiotic susceptibilities based upon institutional flora. Once pathogens are isolated and sensitivity patterns established, the selected regimen is reassessed. Alterations should then be considered if similar antimicrobial efficacy can be expected using agents with a more narrow spectrum of antimicrobial activity, at a reduced risk of toxicity, or at a lower cost.

ATYPICAL USES OF ANTIBIOTICS

General surgeons frequently attend to patients who suffer from non-infectious, inflammatory diseases. When the inflammatory process involves the gastrointestinal tract, or viscera contiguous to the gastrointestinal tract, the high local bacterial density increases the potential for superinfection. Because of this, surgeons have historically been eager to employ antimicrobial therapy early in the course of treatment. Unfortunately, these practice patterns can not always be justified. In some instances, the choice of antimicrobials or duration of treatment are irrational, based upon microbiologic or pharmacodynamic considerations; in other cases, the use of antibiotics holds little promise for improvement in outcome. In any case, imprudent administration of antibiotics risks altering the microbial environment, leading to expansion of bacterial populations with broad resistance patterns.

In addition, inefficacious use of antibiotics needlessly increases the overall cost of treatment at no benefit to the patient.

ACUTE PANCREATITIS

The spectrum of severity associated with acute pancreatitis is extremely broad, ranging from an abbreviated episode of abdominal discomfort associated with enzyme abnormalities, to overwhelming organ dysfunction with hemodynamic collapse, often progressing to death. While milder forms of pancreatitis are frequently treated by non-surgeons, patients suffering from the more virulent, necrotizing process generally fall under the care of general surgeons, despite the fact that most patients can be managed without operative intervention. Currently, less than 10% of patients with necrotizing pancreatitis will demonstrate evidence of retroperitoneal infection involving either the necrotic pancreas or peripancreatic tissues.[20] However, retroperitoneal sepsis is a highly morbid development, and has been assocated with mortality rates as high as 80%.[21] As a result, there may be a strong desire on the part of surgeons treating these patients to avoid retroperitoneal infection and start antibiotic therapy early in the course of the disease.

One of the major impediments to effective antimicrobial therapy has been the erratic and frequently poor penetration of most antibiotics into the inflammed, necrotic pancreatic bed. Recent studies have shown, however, that imipenem, a broad spectrum carbapenem with activity directed against common pancreatic pathogens, penetrates necrotic and inflamed pancreatic and peripancreatic tissue sufficiently to be of therapeutic benefit.[22] In response to these findings, a prospective, randomized study examining the benefits of a 14 day course of imipenem administered with prophylactic intent to patients with necrotizing pancreatitis was recently completed, demonstrating a significant reduction in the development of both retroperitoneal and distant infection for patients who received imipenem.[23] Patients in the treatment group demonstrated microbiologically-proven evidence of pancreatic sepsis in 12.2% of cases, compared with 30.3% of patients not receiving imipenem. There was a similar proportionate reduction in the incidence of microbiologically proven non-pancreatic sepsis. These findings led the authors to recommend routine prophylaxis with imipenem for all patients with necrotizing pancreatitis. However, the reduction in infectious episodes did not translate into parallel improvements in other outcome variables. The need for operation, development of multiple organ dysfunction syndrome, and overall mortality were all unchanged as the result of treatment. Therefore, we would not agree with the recommendations for routine use of imipenem, and would instead suggest that treating the infectious complications of necrotizing pancreatitis as they arise would be an equally effective approach, relative to overall outcome, and one that may be more economically sound.

ACUTE CHOLECYSTITIS

The proper role of antibiotics in the treatment of acute cholecystitis remains unclear. Many surgeons maintain the practice of allowing patients with acute cholecystitis to "cool down" before performing cholecystectomy, using the opportunity to rehydrate a patient who may not have tolerated food or liquids recently, and prepare them for an operation. Antibiotics are often administered throughout this period as well, although the efficacy of this practice is unknown. Cultures of bile and gallbladder walls are sterile in 30-60% of patients with acute cholecystitis, indicating that bacterial invasion can not be established as the pathogenesis of gallbladder inflammation.[24] On the other hand, the remaining percentage of patients will not have sterile bile, raising the concern for bacterial superinfection. For surgeons who opt for a discriminating approach to the administration of antibiotics, the presence of fever, hyperbilirubinemia, or a leukocytosis may be useful as indicators of bacterial colonization and may help to identify patients who might potentially benefit from antibiotics preoperatively.[25] The most definitive means of treating the infection, of course, is to remove the source. Early cholecystectomy has been demonstrated to be an effective, low morbidity, cost-efficient treatment for acute cholecystitis.[24] However, in the rare instance when nonoperative treatment is employed, if a pathogen is not isolated, the choice of antibiotic should not differ substantially from those suggested for preoperative prophylaxis. If positive blood cultures are obtained, the results should guide therapy. It should be appreciated, however, that since the primary pathogenesis for acute cholecystitis is non-infectious, antibiotic therapy can only be expected to treat the bacterial superinfection, and will have no effect on the primary inflammatory process.

ANTIBIOTIC SELECTION

Rather then provide an exhaustive and extensive review of all currently available antibiotics, in keeping with previously stated goals, the following discussion highlights two relatively new classes of antibiotics that have been found to be useful in treating a variety of infectious problems encountered in surgical practice.

FLUOROQUINOLONES

The fluroquinolones were first introduced in the 1980's, and are currently represented by five agents approved for clinical use in the United States.[18] Of these, the two most common quinolones used in surgical practice are ofloxacin and ciprofloxacin. The basic bactericidal mechanism of quinolones is inhibition of DNA gyrase, leaving these agents unaffected by beta lactamases. These agents can be initiated with an anticipated wide spectrum of activity, particularly excellent against gram negative rods, including Enterobacter and Pseudomonas.[18] In our institution, ciprofloxacin and ofloxacin have been shown to have identical spectra of antimicrobial activity. Ciprofloxacin and ofloxacin exhibit a large volume of distribution, penetrate well into most tissues, and demonstrate a low toxicity profile. As a result they are useful agents for treating a variety of infections, including intra-abdominal, pulmonary, urinary tract, skin and bone. Moreover, the bioavailability of oral ciprofloxacin and ofloxacin form are excellent, allowing conversion to oral therapy to be easily accomplished.[18] The economic impact of this is readily apparent.

The main problem encountered in using the fluoroquinolones is the rapidity with which some bacteria seem to develop resistance during therapy, including Staphylococcus aureus and Pseudomonas aeruginosa.[26,27] In addition, the quinolones, primarily ciprofloxacin, interact with a number of other drugs commonly used in surgical practice. Ciprofloxacin interferes with methylxanthine clearance, so that co-administration of ciprofloxacin and theophylline formulations must be accompanied by careful tracking of theophylline levels.[28] Interestingly, ofloxacin interferes with methylxanthine clearance to a much lesser degree than ciprofloxacin, such that

changes in drug levels are probably of little or no clinical significance.[29] There have also been isolated reports of prolongation of the prothrombin time when quinolones have been administered with coumadin, and so patients receiving these drugs should have prothrombin times monitored closely.[18] Finally, administration of the oral forms of either ciprofloxacin or ofloxacin along with agents containing bivalent cations (such as are found in antacids and sucralfate) leads to chelation of the quinolone, thereby interfering with absorption and, consequently, effectiveness of these antimicrobials.[18]

BETA LACTAM/BETA-LACTAMASE INHIBITOR COMBINATIONS

In response to the growing problem of beta-lactamase production, new antimicrobial agents have been developed that couple beta lactam antibiotics with compounds that inhibit beta-lactamase activity. Three beta-lactamase inhibitors have been approved for clinical use—sulbactam, clavulanic acid, and tazobactam. Each is considered a "suicide inhibitor", in that they irreversibly bind to beta-lactamases via an acylation reaction. They are currently available in combination with penicillins as sulbactam/ampicillin, clavulanate/ticarcillin, and tazobactam/piperacillin, all of which are delivered intravenously, and sulbactam/amoxicillin, the only oral beta-lactamase inhibitor/ beta lactam combination.[30] Ampicillin/sulbactam has excellent activity against methicillin sensitive Staphylococcus aureus (MSSA), Hemophilus influenzae, Klebsiella, Proteus, and Bacteroides fragilis, while Pseudomonas, E. coli and other Enterobacteriaceae continue to demonstrate resistance. Piperacillin/tazobactam and ticarcillin/clavulanate also show increased in vitro activity against these pathogens, as well as E. coli, Enterobacter, and Acinetobacter. For all of these combinations, addition of the beta-lactamase inhibitor has no effect on the activity of the beta lactam against enterococci or Pseudomonas. Piperacillin/tazobactam is more effective against these organisms than ticarcillin/clavulanate, both of which have better activity than ampicillin/sulbactam. Ticarcillin/ clavulanate is effective against many strains of Xanthamonas maltophilia, an infrequent hospital acquired pulmonary pathogen, but one which is resistant to most other antibiotics except trimethoprim/sulfamthoxazole. Amoxicillin/clavulanate is active against organisms normally sensitive to amoxicillin, and demonstrates improved in vitro activity against beta-lactamase producing strains of H. influenzae and MSSA. All of the beta lactam/ beta lactamase inhibitor combinations have favorable toxicity profiles, with diarrhea being the commonly reported adverse reaction.[30]

The beta lactam/beta-lactamase inhibitor combinations have been tested in a number of clinical trials involving patients with intra-abdominal infections. In two studies, clinical efficacy for ampicillin/sulbactam was 86% compared with 78% of patients receiving cefoxitin,[31] and 78% compared with 89% for patients receiving gentamicin and clindamicin.[32] The differences were not statistically significant. A significantly reduced positive response rate was found for patients with gangrenous or perforated appendicitis receiving ampicillin/sulbactam (88%) in comparison with those receiving gentamicin/clindamicin (98%), presumably due to resistant pseudomonas species.[33] Ticarcillin/clavulanate has been compared with gentamicin/clindamicin for treatment of complicated appendicitis, with cure rates of 86% and 84%, respectively.[34] When tazobactam/piperacillin was compared with gentamicin/clindamicin for treatment of a variety of intra-abdominal infections the response rates were 88% and 77%,[35] although the differences did not reach statistical significance. Two trials have compared piperacillin/tazobactam with imipenem/cilastin for treatment of intra-abdominal infections, one of which showed tazobactam/piperacillin to be significantly better than imipenem/cilastin for treatment of intraabdominal infections, the other showing statistically equivalent outcomes.[36,37] When the results of these studies are pooled, it becomes apparent that the combinations of tazobactam/piperacillin and clavulanate/ticarcillin can be used with confidence to treat the majority of intra-abdominal infections, whereas sulbactam/ampicillin might best be reserved for use only in select circumstances.

ANTIBIOTIC ADMINISTRATION AND COST CONTAINMENT

Healthcare reform has forced physicians to focus their attention on the economics of healthcare delivery. Cost containment has become a major concern of healthcare delivery networks, and one should have little doubt that cost effectiveness is rapidly becoming an important outcome variable in judging quality of patient care. In light of the fact that the cost of antimicrobials continues to be the single largest expenditure for hospital pharmacies in the United States, cost effective management of antibiotics has become imperative. For many, this means changing old practices which are now recognized as cost-ineffective, and replacing them with updated treatment algorithms that are less expensive and promise equal or improved clinical efficacy.

One of the more needlessly expensive traditions is the practice of routinely starting multiple agent therapy for empiric treatment of severe infections. A typical regimen generally includes an antibiotic directed against gram positives, such as ampicillin, an aminoglycoside for gram negatives, and an agent with anaerobic bactericidal activity, either clindamicin, or more recently, metronidazole. Proponents of this approach point to excellent, broad spectrum coverage acheived using low cost agents. However, in reality the overall cost is extremely high, due to the complex administration schedule that is required. In fact, depending upon the antibiotics used and individual institutional charges, administration costs may be the largest contributor to the overall cost of therapy. Moreover, clinical trials comparing the efficacy of single drug therapy with multiagent antibiotic regimens have shown that routine use of multiple antibiotics holds no innate advantage over appropriately selected monotherapy.[31-35,38] Therefore, empiric use of multiple antibiotics should be limited solely to infections for which the spectrum of suspected pathogens clearly demands the use of more than one agent.

The cost of antibiotic therapy can also be reduced by improving methods of antibiotic delivery. A prime example is single daily dosing of aminoglycosides. Once a day aminoglycoside administration lowers the daily drug administration charges for antibiotic delivery and eliminates the need for routine testing of serum levels.[39] The results of animal studies and clinical experience suggest that once a day dosing of aminoglycosides also reduces the risk of ototoxicity and nephrotoxicity and, since the bactericidal activity of aminoglycosides is highly dependent upon total dose/MIC ratio and time > MIC, a single, large dose should theoretically be more effective than multiple small doses in effecting bacterial kill.[39] On the other hand, antibiotics that demonstrate primarily time-dependent bacterial killing, such as the beta-lactams, may work best when delivered in a continuous infusion, rather

than as multiple intermittent doses. Continuous infusion of beta lactams has been shown to improve outcome in both animal models and limited clinical trials.[39] Although not yet evaluated, one would also anticipate a reduction in administration costs with continuous infusions, as opposed to multiple daily doses.

Of course, administration costs approach zero when oral antibiotics are used. Administration of oral agents for treatment of moderate to severe infections has become a viable alternative due to the excellent bioavailability of the oral fluoroquinolones and their activity against common gram negative pathogens. We have also found other oral antibiotics to be effective in treating mild to moderate infections, including ampicillin, trimethoprim/sulfamethoxazole, amoxicillin/sulbacatam, and metronidazole. As a general rule, when a patient demonstrates normal gut function, every effort should be made to convert intravenous antibiotics to equivalent oral agents.

THE FUTURE

If the past holds the key to predicting the future there is no doubt that economic reform in healthcare will continue, and burgeoning healthcare costs will remain a major issue for an unknown period of time. Successful use of antimicrobials will undoubtably be defined by two parameters-clinical outcome and cost. The goals in antibiotic use will be to select the least expensive agent that will provide maximal clinical efficacy and minimal toxicity, to limit administration to the shortest time necessary, and to guarantee delivery in the most cost-effective manner. Interestingly, these goals conflict, to a large degree, with those of the pharmaceutical industry, where large amounts of time and money are spent in search of newer and better antimicrobials. These efforts are costly and are frequently reflected in the price of the product. However, recognition of growing economic concerns has led pharmaceutical manufacturers to become attentive to "pharmacoeconomics", and clinical trials are beginning to include cost efficiency as a measured outcome variable. Based upon the current political and economic climate, and attitudes towards healthcare costs, this trend can probably be expected to continue, and so one might anticipate that interest in cost effective antibiotic administration will increase within the pharmaceutical industry. Research efforts may then directed to the development of less expensive methods of antibiotic administration in addition the formulation of new antimicrobial agents. **STI**

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