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Host Defense and Surgical Infection: The Adjunctive Role of Therapeutic Antibiotics

Part II: Surgical and Pharmacologic Treatment of Sepsis

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Introduction

Treatment of a surgical infection usually requires a surgical operation. Antibiotics alone are not the treatment of an established surgical infection, and operation is often the critical component tipping the balance in favor of the host defenses to infecting microbes. Both operation and antibiotics must be ancillary to the host defense, and ideally, each would benefit that resistance, and at a minimum not interfere with it or further impair the patient in combating the infection.

In Part I of this series on "Host Defense and Surgical Infection" the principles of antisepsis and antimicrobial prophylaxis were described with the primacy of host defense factors as the essential determinant that prevented infection. In this Part II, an examination of the principles of treatment is described focusing on the adjunctive role of antibiotics to operation, both of which are only techniques in support of the fundamental process of host defense. This last feature is not only necessary for control of surgical infection, but in some cases may also be sufficient, which neither operation nor antibiotic can be without innate defense factors.

Surgical Treatment of Sepsis

Treatment of a surgical infection is most often an operation. There are three "big D's" in surgical infections, drainage, debridement, diversion, and drug is another one of the D's important only at the margin, assisting the first principles of defense and drainage.

If we rely upon a drug as the treatment for a patient with a localized abscess, we have treated the patient inappropriately. Drainage of that abscess is not only necessary, but may also be sufficient, and drug may be, in many simpler instances, unnecessary. If the patient has a heavy bacterial inoculum, the surgical task is to reduce it as swiftly and as completely as possible. If the patient has a perforated colon, for example, diversion is appropriate. If the problem is an eschar that is infected, debridement is appropriate. If the problem is an abscess, drain it. These procedures should be obvious, but they are made explicit in order to point out that no antibiotic makes up for a lack of these primary surgical procedures nor can substitute for them.

Recent advances have brought about modern abscess localization techniques: the scanners of nuclear medicine, sonography, computed tomography, and even magnetic resonance imaging. Each of these techniques may be helpful in some cases finding abscesses, and even ancillary in treating some of them, by percutaneous directed drainage. However, it is the treatment of the *last* abscess that determines the patient's course. Surgical treatment is inadequate if one drains a pelvic abscess and leaves a subphrenic abscess, since the patient will respond as the last pus is drained. If another "big D" were listed ahead of "drug" it would be "diet", since nutrition is fundamental in support of primary host defense, the biggest "D" and the only *sine qua non*.

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Choosing and Using Antibiotics

Following the acknowledgement of these fundamentals, we must often use antibiotic drugs in patients for whom they are indicated. If we are going to use them, how do we pick them and how do we use them rationally ?

Let us look first at the global rationale for giving an antibiotic, remembering the difference in indications between prophylaxis and treatment. We want to select one that has optimal efficacy. A second objective in antibiotic selection is to minimize patient toxicity, and that may limit our use of some effective agents. And, a later concern, although important, it does come *after* our concerns of efficacy and toxicity for our patients, we wish to achieve beneficial effect efficiently, while containing or reducing costs. The last concern is the one area in which the most precise numbers have been compiled, and in the economic environment of "DRG-consciousness" many policy makers remind us that cost is easily measured and antibiotics draw considerable attention as being among the highest volume cash flow in our pharmacies. What the DRG (Diagnosis-Related Group) policy means is that the physician can try to fix patient problems with any surgical or medical means, including third generation expensive new agents, but the prospective reimbursement is fixed by the patient's admission diagnosis, not the cost of the treatment selected. Cost control must now enter physician's judgement, and treating physicians must take on the additional role of comptroller.

As reviewed in Part I, choice of a prophylactic agent for those patients for whom it is indicated is safety first, with concern also that resistance does not rapidly emerge to the agent used. These are the first concerns, since the majority of patients who get a prophylactic antibiotic would never be infected, whether or not the drug is given. Cost is also a major concern of prophylaxis, since there will be less complaint about alternative treatment drugs' relative cost than in prophylaxis, since it is easier to demonstrate a life-threatening need for the former. How do the different criteria by which treatment antibiotics are judged affect their selection ?

Rational Treatment

Treatment indications are quite different from prophylaxis, because the majority of prophylactic antibiotic usage would not have provable benefit for a given patient. All patients receiving an antimicrobial will definitely experience the cost, possibly the toxicity, and probably a benefit depending on their risk. In the patients considered for *treatment* antibiotics 100% of them are infected. The first demand of a treatment drug is that it be effective (Table 1). We may tolerate several factors which we would never tolerate from prophylactic drugs, such as toxicity. A treatment antibiotic is not going to be selected principally because it is innocuous (although that was the first criterion of consideration for a prophylactic drug) if it is less than optimally effective. Aminogl-

Table 1. Criteria for Antibiotics Selected for Treatment of Established Infection

Treatment Drugs
• Effectiveness Required • Toxicity Tolerated • Resistance Generation Accepted • Often used in combination to Cover Mixed Flora (Cost is less an issue than effectiveness)

ycosides are often selected in the context of treatment.

No physicians deny that aminoglycosides work effectively as antimicrobials. They have proven to be effective, but most physicians are so sensitized to their toxic potential that I believe that the single biggest hazard of aminoglycoside use is that they are often used in doses that are inadequate for their effect. There is an obviously high mortality associated with septic shock, and that risk generally outweighs the morbidity potential. It is not rational to say that "in this patient with a high risk of mortality, I am not going to use an effective antimicrobial therapy appropriately, because I am worried about the drug's morbidity". In the context of treatment antimicrobials, toxicity can be tolerated that would rule out the use of the same agent for prophylaxis. If there were alternative treatments with the same effectiveness, the drug with the lesser toxicity might be favored, but that would not be the first requirement of a treatment drug. The first requirement is also not going to be overturned by concern for resistance generation in the context of a patient with serious surgical sepsis. If multiple drugs have the same antimicrobial spectrum, and potential utility, perhaps one or more could be "banked" so that resistance was not generated to all the treatments available; however, the most effective drug has high utility in the sickest patients with the highest risk of mortality; it is that patient that has priority over protection of our hospital antibiogram.

Rationale for Combination Therapy

There have been highly effective agents with narrow antimicrobial spectrum that have often been used in combination. Until recently, we have had effective drugs to cover aerobic or anaerobic flora but few that would cover both. For example, the aminoglycosides are good agents for coverage of the coliform organisms but they do not cover *Bacteroides* species. This specificity is more obvious with agents that cover the *Bacteroides* but do not cover the coliforms. Because of the triple risks of the febrile morbidity, cellulitis and abscess of Gram-positive aerobic skin flora, the endotoxic mortality associated with Gram-negative aerobic bacteria, and the abscessogenic potentiation of Gram-negative anaerobic flora, surgeons had become polypharmacists in order to give drug coverage specifically for each of these three risks. As newer antimicrobial agents were developed with high effectiveness, broad spectrum, and a low toxicity profile, they have gradually replaced the use of combinations of single agents for each of these risks. "Triple therapy" had been reduced to the double therapy of aminoglycoside and a single agent that might cover both *Bacteroides* and the Gram-positive aerobes such as clindamycin, and with further evolution monotherapy with a broad spectrum, highly effective, and safe use of an agent such as imipenem in monotherapy has been replacing the "gold standard" of combination antimicrobial therapy for serious surgical sepsis.

Antibiotic Selection According to Risk Flora

Specific antibiotic selections can be made on the basis of the highest probability of the flora causing the infection risk. Table 2 demonstrates the three principle risk flora groupings and the potential agents that might be appropriate for each.

Choices for Gram-Positive Aerobes: Penicillin, one of the first highly effective antibiotics, remains an example of one of the best. This ß-lactam is bactericidal, has relatively low toxicity, and can even be injected into such highly sensitive body cavities as the intra-thecal space or synovial joint linings. Such use of an antimicrobial could never be employed with an agent such as tetracyline because of its highly irritating properties.

Penicillin can be given as the native compound, or it can be modified so as to be resistant to penicillinase, in the synthesis of such an agent as methicillin. Although this clever pharmacologic maneuver has been effective against organisms that produce penicillinase, the numerous microbes can outmaneuver the slower process of new drug development and they have countered with methicillin-resistant staphylococci. For this unsolved problem, vancomycin is an expensive agent being applied in the absence of more appropriate alternatives. Penicillin can be further modified to stretch its spectrum over some Gram-negative aerobes, such as ampicillin, and it can be stretched still further to cover some of the anaerobes, such as piperacillin and mezlocillin.

Cephalosporins are ß-lactam antibiotic congeners of penicillin adding further range to the organisms covered over the basic Gram-positive aerobic coverage shared with penicillin. "First generation" cephalothin or cefazolin is enhanced in the "second generation" agent such as cefoxitin, and still further modification produces the broader spectrum "third generation" agents such as ceftriaxone.

The cephalosporins share with penicillin a relatively good safety profile, although there may be allergenic reactions and cross reactivity with penicillin in this sensitization. With the first generation affording good coverage of the Gram-positive aerobe, there is often a loss of some activity against the Gram-positives in the upscaling and broadening the flora coverage of the later generations. Although cephalosporins have been well used in prophylaxis, particularly in the first generation, or in lesser indications for the second, they are unaffordable in the third generation used as prophylaxis; further, since most prophylactic concern is with Gram-positive aerobic skin flora coverage for elective operations, the first generation would not only be less expensive but also superior in its skin flora coverage.

There may be high utility in precise therapy of some specific infections such as pediatric meningitis or some hospital-acquired pneumonia instances, but I would see little or rare surgical indication for third generation cephalosporins. Since they are too expensive for prophylaxis and not first line treatment drugs, the higher generations would fit neither indications for prophylaxis or presumptive monotherapy, and might well be limited to precise therapy for which there are often more narrow spectrum specific drugs competing for such indication.

Gram-Negative Aerobes: Aminoglycosides are effective, as are some expanded ß-lactams such as ampicillin for such microbes as enterococci. There is a trend away from the use of ami-

Table 2. Choices of Antibiotics for Treatment of Major Flora

Gram-Positive Aerobes	ß-lactam Penicillin Cephalosporin Macrolides
Gram-Negative Aerobes	Aminoglycosides Ampicillin
Gram-Negative Anaerobes	Clindamycin Cefoxitin Choramphenicol Metronidazole

noglycosides despite their demonstrated efficacy to avoid their well-known toxicity and substitution of such agents as aztreonam. However, there are some broader spectrum monotherapy agents that have Gram-negative aerobic coverage of the coliforms without the aminoglycoside toxicity that might be better candidates for monotherapy of presumptive surgical antibiosis.

Gram-Negative Anaerobes: There are several antibiotics that cover the *Bacteroides* species such as chloramphenicol, clindamycin, cefoxitin, metronidazole, and broader spectrum agents such as imipenem. Several of these agents have toxicity that would limit their utility, and still others have such a narrow spectrum as necessarily combining them with other agents. In some community-acquired polymicrobial inocula, agents such as the second generation cephalosporin cefoxitin might be appropriate, but for most hospital-acquired inocula that would include the *Bacteroides* species in the entire spectrum, either an agent such as imipenem as monotherapy or combination therapy with antimicrobial agents covering each of the three flora risks should be employed.

Presumptive Treatment of Surgical Infection

Presumptive antibiotic treatment initiation is that therapy given in advance of the identification of the infecting microbial organisms. If the microbial inoculum precedes the drug administration, there is *no* prophylaxis indication (for example, no prophylaxis is initiated in the recovery room !). For all such acquired infections or contamination that has already taken place such as trauma or a primary disease process that has caused a breach in the containment of flora contained within the GI tract, presumptive therapy is initiated on the basis of the highest risks associated with the flora presumed to be present. For a breach of the skin barrier, that would most likely be Gram-positive aerobic flora, and ß-lactam antibiotic selection would be appropriate. If this occurred within a hospital setting, it is presumed that the flora resident there are selected for their resistance to the commonly used antibiotics, a modified penicillin such as nafcillin might be employed to circumvent penicillinase-producing flora. For most community-acquired inocula in trauma, a first generation cephalosporin might be appropriate for presumptive treatment initiated in trauma patients, unless they were at a high likelihood of additional anaerobic risk such as with penetration of the lower GI or GU tracts. Cefoxitin might be appropriate presumptive treatment for community-acquired mixed flora, or piperacillin might be a second choice. For the hospital-acquired polymicrobial risk, either combination therapy, often employing aminoglycoside with an antianaerobic agent (for example, clindamycin/gentamicin) or imipenem monotherapy would be appropriate. The choice is particularly critical in the polymicrobial inoculum in the hospital setting of the intensive care unit in a patient who is immunocompromised.

A primary concern is whether the combination antimicrobials are assisting or actually impairing host defense that ultimately must control the sepsis with the assistance of surgical diversion of the continuing inoculum. Such agents as chloramphenacol used in combination with other agents might be effective against *Bacteroides*, but might also impair the second line of host defense if the dosage is pushed to higher levels or protracted. Additionally, most commonly used surgical antibiotics are bactericidal rather than bacteriostatic, and combinations of bactericidal and bacteriostatic antibiotics may actually run interference on each other.

The Potential for Host Enhancement

Although some antibiotics in inappropriate dose or combination may impair the immunocompetence of the host, some may actually be used to enhance it. For example, submicrobicidal doses of aminoglycosides and some of the agents of the macrolide class (for example, clindamycin) have actually been proven to enhance phagocytosis. Less toxic antibiotics are effective in organ preservation, particularly if specific toxicity such as nephrotoxicity can be avoided. At present, we do not have a specific agent with which to enhance host defense that might not cause generalized autoimmune disorders such as arthritis or trigger multiple organ failure by generalized inflammatory response. But the judicious use of antibiotics and earlier search for and drainage of localized collections of purulence are "organ function sparing procedures" that may help the patient return to homeostatic balance. The general host defense enhancement that is safe and widely applicable is the support of nutrition such as with hyperalimentation.
Experimental use of biologic response modifiers will have to be carefully studied for the potential risk that might come along with the intended benefit of host enhancement.

The most effective means of managing surgical sepsis are already well known rather than experimental. In the first instance, since surgical operation is the most effective method of controlling surgical sepsis, a ready and recurrent question in the failing patient should be "where is the pus?" An aggressive and early search for and drainage of focal collections is enhanced with the liberalized use of noninvasive scanning methods, sometimes extending them through percutaneous draining techniques radiographically directed. Antibiotic usage that is appropriate might support rather than impair the host, and should never interfere with the primary surgical process such as through interference with clotting or enhancing bleeding risk. The trend toward monotherapy is not only for the sake of limiting toxicity against alternative treatment combinations it might also be proven cost-effective.

Conclusion

Today the treatment of surgical infection is well beyond the "drug versus bug". The concentration of the physician is on the patient's control of the sepsis and what can be done to enhance this resistance. A surgical procedure is often employed to tip the balance in favor of host resistance by diverting a continuing inoculum. Medical microbiology has helped in the identification of specific superinfections, but for most surgical infections the polymicrobial inoculum is assumed and treatment is initiated presumptively, covering the major flora risks to which the patient is exposed. The future may bring further improvements in host defense enhancement beyond the nutrition and general support that can be presently furnished, but until a specific antimicrobial defense enhancement is achieved, the clinician will seek to continue to support that host resistance and at minimum not interfere with it through drug toxicities added to microbial invasion.

Addendum
Microbiology Laboratory Support in Clinical Patient Care

Why should we not leave it to the laboratory to tell us whether we are treating the surgical infection appropriately? All that we need to ask is a culture and sensitivity and if the sensitivity comes back showing the drug is appropriate, we will continue to use it. If it is not appropriate we will stop. Well, what can the laboratory tell you? The laboratory can tell you that the drug is appropriate by culture and sensitivity or that the drug is inappropriate by culture and sensitivity. Who is telling me what? The laboratory takes a Petri dish and they streak on it an isolate and then they put discs that are permeated with antibiotic on the agar and look for zones of inhibition around those discs largely determined by diffusion into the agar medium. In that Petri dish there is not one white cell and there is not one globulin and there is not one cellular or humoral mechanism of defense. So the laboratory setting is not exactly like the situation in the patient.

Let me give you an example and ask if it has ever happened to you. I admit to the hospital a patient who is very sick. The patient

looks septic with low blood pressure and fever. I draw a culture, send it to the laboratory and start antibiotic treatment. The next day on rounds, I note that the patient's temperature is down, he is definitely looking better and there is remarkable improvement. He is not very catabolic any more, and I am really impressed with this implied therapeutic response. And then the lab calls up and says: "The drug you have given to this patient is in no way appropriate for the organism cultured". Has that ever happened to you? How do you explain that ? How can you get a therapeutic effect out of a demonstrably inappropriate drug? Remember all it tells you is what is going on in that Petri dish. It doesn't say a thing about whether there might be enhanced defense of the host. Even in that antibiotic is doing nothing whatsoever against the microorganism, it may have facilitated host phagocytic defenses or some other factors may have improved the cellular or humoral host defense.

Monitoring Hospital Prescription Practices in the Indications for Antibiotics

A more practical method of monitoring use of antibiotics in hospitals has been devised and I give you the experience of one hospital particularly because I was involved in resisting it several years ago. The hospital is the George Washington University Medical Center. In that institution, I had an opportunity to observe the policing of antibiotic use and I will show the order sheet with its little red note and what it has meant to our prescription practices. But just before I point with pride, I'll tell you that I fought this little red note all the way. I was the Chairman of the Infection Control Committee when these restrictions were first proposed, and I resisted.

We have all read articles that say something like "90% of antibiotics are inappropriately used; 50% of antibiotic treatments in hospital settings are without culture proof".

If someone said to me that 90% of what I do is inappropriate, I would ask: "Who says, by what criteria, and for what cause are they trying to make an improvement? " Here is a little red note that is trying to address that problem. What this note says is we don't know why these drugs are being used, so why don't we find out? To find out, let's make a recording of the indication, a necessary condition for getting the drug. So this little red note says: "All initial orders for antibiotics must include the reason or indication for administration". What does that mean? It means that antibiotics are now a special class of drugs. I don't have to write down "Morphine 15 mg s.q." for pain. I write "Morphine". I'm not going to tell my nurse that this is a suggestion sheet. This is an order sheet.

If I write down "Digoxin 0.1 mg", the pharmacy will fill it. I don't have to say "For congestive heart failure". I'll give digoxin whenever I think it's indicated. If I write down "Keflin 1 g" the pharmacist won't fill it. He needs a cause, an indication. You know as well as I do that you don't like the hassle of a phone call in the middle of the night, asking why you wrote this. So you must write down something, anything. I am going to write down "Keflin 1 g for hernia", and the pharmacist will fill it.

But then the next day, the utilization reviewer will come to me and say "Tell me Doctor, what literature can you cite, what personal experience do you have, or for what reason do you think this drug is useful for this indication?". So you don't want to look foolish. For example, if you are going to be dealing with a Gram-positive skin flora, you are probably going to use something that is Gram-positive in its activity. Now, that was good enough for some of the committee and that is the reason why other people are pushing this for the utilization review of our antibiotic practices. I disagreed. I said: "Look, these are licensed drugs and we are licensed physicians. We are not going to have to write down indications so you can tell us later what works or not".

Now, let me tell you what has happened after the ruling was passed over my objection; I can tell you the result of this very proudly because I had nothing positive to do with it. What it immediately did is to change our prescription practices in a very important way which I didn't foresee. Before this little red note, the single leading indication for discontinuing any antibiotic in the hospital was the discharge of the patient. You can picture the nurse running out in the parking lot, trying to get that last dose of prophylaxis in 15 days after it was started! You know that practice represents pure cost and pure toxicity and no benefit. So if I write down: "Give cefazolin 1g for prevention of contamination from blunt colon injury", the pharmacist will fill it, but at 24 hours, he won't fill it anymore, because there is no prophylactic indication at 24 hours. Now I will have to write down: "For treatment of".

When I say "treatment", I must show a cause: a white count, fever, chest X-ray, urinalysis, culture, sensitivity, Gram stain, in order to give a drug for treatment indications, and we have already established earlier that we are not going to give the same drug in the same dose for the same purpose for both prophylaxis and treatment. So this did change our prescription practices in terms of antibiotics.

This is one small administrative way in which monitoring antibiotics can be done, and again I repeat that I was against it originally. Something emerging to extend this control is a separate antibiotic sheet.

This sheet would require the cultures or other requisite information for treatment be entered into the order sheet itself. I may still have reservations on the extension of these controls on physicians' practice, rather than using educational objectives, but the success in modifying prescription writing behavior is encouraging their wider use.