Host Defense and Prophylaxis Against Surgical Infection: The Adjunctive Role of Antibiotics

Part I: Prophylaxis

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Introduction

Host defense factors in the surgical patient determine resistance to infection and successful management of surgical sepsis. In this Part I, the components of opsonin, complement, and phagocytosis are discussed and the adjunctive role of antibiotic prophylaxis in potentiating innate host defense against the invading inoculum. Antibiotics are not necessary or beneficial in all or even most surgical patients, and have the potential for suppressing innate host defense rather than keeping the balance in favor of the patients' own control of the contamination. Prophylaxis must be as rational in its prescription as treatment which is discussed in Part II for both surgical and antibiotic management of established infection.

The Importance of Host Defense

Surgical infection is not a drug deficiency disease. Although we all may think we recognize that, we often say antibiotics cure infections. If you think infections are cured by antibiotics, note that these drugs can be given in wholesale quantities to the patient without white blood cells, and they are proven to be frustratingly ineffective. If nothing else, the emergence of AIDS has focused attention on the primacy of cellular and humoral immunity to prevent and control opportunist invaders. No antibiotic makes up for a complete deficiency in host defense. When we talk about what we plan to do to prevent surgical infection, first must be to avoid giving any further problems to the host than the disease has already done. A second therapeutic objective is to support those natural defense mechanisms which already exist. Nutrition is one of these support factors and hyperalimentation may have contributed more to infection control than most of the newest generations of antimicrobials.

Antibiotics: Wonderful, but Not Wonder Drugs

Antibiotics are useful agents within the context of host control of microbial invasion, and there are a number of surgical circumstances in which patients can be provably benefitted by their use. Some patients have "impaired host defense", for example, from cancer or from treatment for cancer which can cause immunosuppression. The immunosuppression deliberately induced in transplantation recipients and in some patients with inflammatory diseases, can be accomplished through the use of certain drugs. Rather recently appreciated is that the administration of some antibiotic drugs may be immunosuppressive. In many cases, while focused on the antibiotic effect on the micro-organisms, we may be actually disproportionately effecting the defense of the macro-organism, the patient. What do the drugs do in the interplay between the patient and the microbial environment? A healthy scepticism to have about the efficacy of any drug, any treatment, an operation includes the "zero option". How did we get along before they existed, and what are we now interfering with, now that we have them?

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Table 1. Antibiotic Use in Surgery Indications

A.	Prophylaxis — Prevention	
B.	Treatment	
	1.	Presumptive
	2.	Precise

Distinctions of Infections in Patients on Medical and Surgical Services

There are two different ways we use antibiotics. One is their use in the treatment of an already established infection, and the other is in the prevention of it (Table 1). If we use an antibiotic for prevention, and an infection ensues, that is to say prophylaxis fails, isn't it reasonable to assume that this antibiotic is probably not going to be very effective in treatment? After all, the organisms grew up under the selective pressure of that antibiotic. As a consequence, probably the same drugs ought not to be used in the same dose in the same way for both prevention and treatment. An unreasonable approach is the pitch: "Now, here is the drug and it is the last thing you will ever have to know about surgical infection: you use it for treatment, you use it for prevention and you give it to people who don't even have any risk of infection because, after all, it is harmless, and might do the patient some good". Anyone who pretends to have the last answer to infection risk will always be wrong because the microbes turn over a lot faster than the FDA! The microbial environment has the survival advantage of astronomic numbers and genetic variation to make possible selective adaptation more quickly than patients. The more numerous microbes are always going to outsmart the best antibiotics that we have. There is no simple permanent solution to the complex problem of surgical infection.

Antisepsis vs. Antibiosis

To prevent infection, we might try two methods, one better developed than the other: either improve the host or suppress the microbes. One technique typically attempted is that we try to reduce the inoculum. Reducing the inoculum takes several forms. Since Semmelweiss we wash our hands; since Lister we prep the skin in some fashion; and no one would think of operating electively on the colon, for example, without at least a mechanical bowel prep. Each of these three do nothing but reduce the inoculum. Have they done anything at all to improve or impair the host? A "bowel prep" washes nutrients through the gut and the patient is in as bad a situation as had he been in starvation for a period of time because that is exactly what the bowel prep is: a nasogastric tube and catharsis is nutrient starvation. Prepping the skin should probably not impair the host, unless it is done with a razor, having the patient nicked and scraped in violating the "first line of

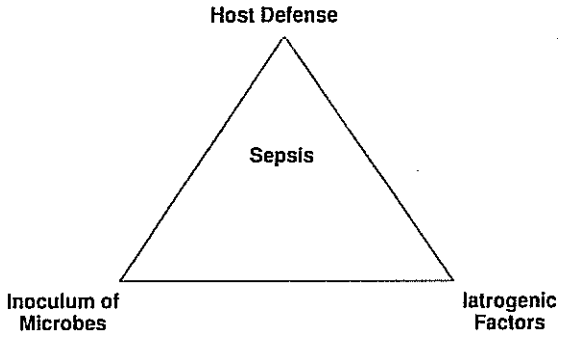

Figure 1. There are three factors determining whether sepsis occurs and whether it overwhelms the patient; the focus has usually been on the lower two, ignoring the supremacy of the third factor.

defense" and then have that patient lying around in the hospital flora in the worst possible selected microbial environment. Our antiseptic techniques decrease ambient flora, through hand washing, skin prepping and decontaminating our operating rooms, which means that only the most resistant organisms survive. So when the patient is going to be recolonized, he will be colonized by selected hospital microflora. The patient would be better exposed in the wilderness flora than surrounded by an antibiotic-selected environment.

There are three factors that sum to determine whether a patient will be infected (Figure 1). Our focus has been altogether too much on two of the three factors, ignoring the third. Sepsis results when there is either a very high inoculum of organisms such as coliforms or flora that would ordinarily be commensals, or a low inoculum of virulent organisms like meningococci. The invading flora interact against a host defense that is in some way impaired, through some breach such as trauma, a primary disease like cancer, or a failure of inflammatory containment. For example, peritoneal contamination as would happen in a colon perforation might give rise to a synergistic flora combination that leads to sepsis. The two things upon which we have focused a good deal of attention include the inoculum and what we physicians do to combat it, but we have overlooked the factor that ultimately is the solution to sepsis. We presume that iatrogenic factors, and by that we would include operation and drug therapy of any kind, do something to impair the inoculum and improve the host. Can you think of a single thing that we do, in surgery for example, that accomplishes that? To date, no specific agents have been used to selectively improve host defense against invading micro-organisms, such as the administration of levamisole has been used in adjunctive therapy of cancer. Such biologic response modifiers that we have would be rather global in their effect, and might stimulate autoimmune disorders such as collagen vascular disease or generalized inflammatory response.

Further for the surgical patient, an operation is carried out with the first step of that procedure being incision through skin. Obviously, in so doing, the host is exposed to environmental contamination. An operation takes the patient off feeding, and the only thing that we do to replace normal nutrition is add salt water and a little bit of sugar to prevent ketosis. We really are not doing anything to enhance the patient whose first defenses are violated and who is not getting nutrients.

But further treatments include radiation and drugs that impact white cells and bone marrow reserves. Some drugs are given to suppress inflammation and cellular growth and function such as steroids, antimetabolites, chemotherapy, immunosuppressive agents. What role do "antibiotics" play not only against the microbes, but also in the host? These drugs have a descriptive name: "anti-bios", not precisely targetted like "smart weapons" against microbes. The antibiotics are selective in that they are more active in interfering in the metabolism of rapidly proliferating cells. Some of these cells are microbes. But these drugs aren't antimicrobials alone because some of them interfere with mammalian cells or against substances other than plant cell wall systems as well. The largest of the targets the drug will inevitably hit is the patient.

"Prophylaxis" Trials

I have done a couple of studies and I have read a number of others in which a "prophylactic" trial drug is compared in a group of patients who are going to have an operation or going to undergo some invasive risk for infection. We are going to give the antibiotic drug to half this group of patients and we are going to give a placebo to the other half of the group of patients who are going to be the control group. Now, if that "prophylactic antibiotic", whatever drug it might be, doesn't work, shouldn't the infection rates then be equal in each group? There are several studies that I have done or read about in which equivalence has not proven to be the case. In many reported trials of antibiotic prophylaxis, the antibiotic treatment group has a higher infection rate than the group given the placebo. Now how is it possible that giving the antibiotic results in a higher infection rate?

An answer to this question may come from another branch of medical practice, and that is transplantation. Some of the most potent immunosuppressive drugs that I had used in transplantation started out life as antibiotics: cyclosporin, daunorubimycin as examples. The reason these drugs are still useful is no longer the effect they might have against microbes; they are given deliberately now to impair host defense. Is it any wonder that some of the antibiotics that we are giving with all good intent to suppress an inoculum are actually impacting heavily on the patient? We have to look at that at every point when we are using a drug which we think is effective: are we getting some differential in that effect against the microbes in favor of the host? What processes occur in the host naturally to prevent or combat that infection?

Components of Host Defense

Throughout pre-history, and until only very recently in modern history, there were no antibiotic drugs. But people were fighting wars, were injured in the daily struggle for existence, and fell victim to disease at least as regularly as they do today. People were exposed to a microbial contaminated environment even before germ theory was recognized, and these people did not all die or routinely suffer sepsis. Why not? Because each carried at least three components that were present a long time before antibiotics which combated infection: opsonin, complement (humoral components) and phagocytosis (a cellular one). These three endogenous factors of host defense acted without (and later had to act with or despite) antibiotics within a system of defense against microbial invasion. If a microbial inoculum gets past the "first line of defense" barriers, mobile defenses are mounted by the host: opsonin, complement and phagocytosis (Figure 2). Opsonin is a protein. It is a globulin, and to be more specific, a gamma globulin. Some of our antibiotics impair protein synthesis: opsonin is a protein. Giving a patient a 10 g dose of chloramphenicol, whatever its antimicrobial effect might be, would impair the production of host protein in rapidly proliferating bone marrow. An appropriate dose of antibiotic agents is designed to suppress the more rapidly proliferating cells; many times that is the microbe, thereby impairing bacterial synthesis more than mammalian metabolism. If higher doses of the same drugs that interfere in protein synthesis is given, they will interfere with the mammalian cells as well.

When a microbe invades a normal intact host, it is attacked by

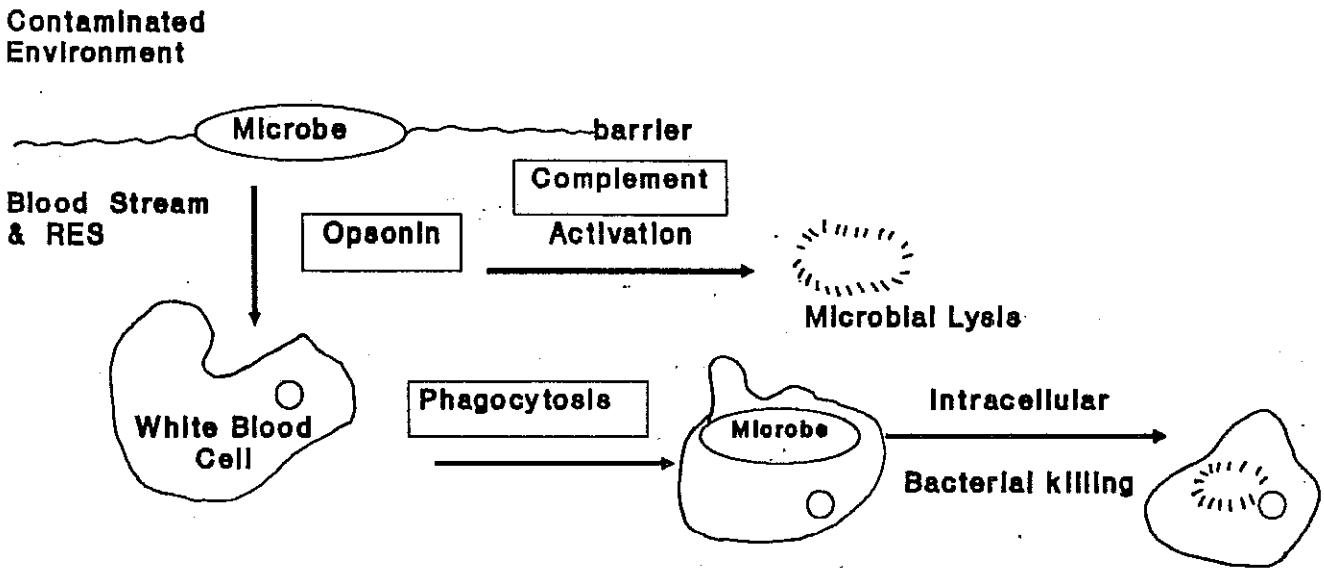

Figure 2. The principle three components of natural host defense are opsonin, complement (humoral factors) and phagocytosis (a cellular factor) which must operate with or without addition of antimicrobial drugs.

a phagocyte. A white blood cell comes to that organism and engulfs it. When it is engulfed, typically that microbe is killed inside that white cell. What would happen if that didn't occur in that final step? If a white blood cell engulfs a microbe but doesn't kill it, it then circulates around with the blood stream and releases that microbe again to potentially multiply. All that this white cell has done is facilitate the spread of the infection, if it does not destroy the organism. There are such diseases; chronic granulomatous disease is one such problem. In this disease, white cells pick up microbes but because of peroxidase or other intracellular enzyme deficiencies, the microbes are not destroyed intracellularly. I had treated a patient who had all the right drugs for a demonstrably sensitive microbe in septicemia, yet he died of uncontrolled sepsis. He was a patient with chronic granulomatous disease, which we had known for some time. But this case is a demonstration that you cannot make up for fundamental host deficiency with an antibiotic. Possibly white blood cell transfusions might put one of the cellular host factors back to restore such a septic patient. But an antibiotic typically does *not* do that.

Cell-Bound Antibiotics as "Smart Weapons"

Skillful use of some antibiotics might concentrate them at the site of natural host defense so that they might act as adjuncts to cellular host defense. For example, if the phagocyte that engulfs the microbial organism contains an abundance of effective antimicrobials, the natural host defense is enhanced. Some antibiotics are white cell bound, particularly the macrolides. One of them, for example, clindamycin is concentrated 40 fold in the white cell over serum levels. Some of the cephalosporins are white cell tagged. They seem to be almost like "smart weapons". Antibiotics, if they are tagged to a white cell, are going to go wherever the microbes might be since chemotactic factors draw the white cells to the inoculum site. In this instance, the antibiotic would be enhanced in its activity by the host defense mechanisms.

The same humoral factor, opsonin, can act as an antibody, and when antigen and antibody complex the complement cascade is initiated. This draws in further inflammatory response and the complement activation can directly lead to the destruction of a bacterium. We point out that these events occur naturally in the absence of an antibiotic. If we add an antibiotic into this system, in what way may it interfere with what is going on naturally? Interference is possible if humoral or cellular response were impaired as might be the case with higher doses of protein synthesis chemotherapy. As already suggested, enhancement of antimicrobial activity might occur in the phagocytic and antimicrobial action in concert against the microbe. At the very least, we do not want to interfere with this fundamental process in the patient at risk for infection.

Mixed Flora and Pathogenesis of Surgical Sepsis

The differences between infectious risk for patients on the medical or surgical services (Table 2) will determine different objectives and treatment using antibiotics. These defenses include differing organisms, number of organisms, virulence, pathogenesis, principle of therapy and the culture of organisms and sensitivity guidance of this therapy.

What kind of inoculum is anticipated in surgical patients? To begin with barrier breaches below the diaphragm peritonitis may be used as an example. Any kind of gastrointestinal contamination of the peritoneal cavity is likely to give rise to mixed different flora with at least two very distinct pathogenicities. Using *E.coli*

Table 2. Similarities and Differences in Infectious Complications Observed on the Medical Service and the Surgical Service among Hospitalized Patients

Medical Infection	Rx	Surgical Infection
Pathogenic Organism	Pathogenesis	Commensel Flora Invade
Monobacterial	Number of Organisms	Polymicrobial
Organism Known	Culture	Organism Unknown
Sensitivity-guided	Therapy	Empirically Initiated
Principal Therapy	Purpose of Rx	Adjunctive Only
Monotherapy (the rule)	Number of Rx	Combination Therapy
Drug	Primary Treatment	Operation
Superinfection	Redox Potential	Synergistic

Table 3. Bacterial Risk for the Surgical Patient

Class	Source	Type	Pathogenesis
A. Gram-Positive Aerobes	Skin, Environment	*Staphylococcus* *Streptococcus*	Cellulitis
B. Gram-Negative Aerobes	Gut	Coliforms	Endotoxic Shock
C. Gram-Negative Anaerobes	Gut	*Bacteroides*	Peritonitis, Abscesses

as an example, the whole group of aerobic Gram-negative organisms may be called "coliforms". The coliforms' pathogenesis is based in their invasion into the bloodstream where they release endotoxins that lead to circulatory instability. A phrase commonly used, though inappropriate, is "Gram-negative shock". Endotoxic shock is consequence of bacteremia of Gram-negative aerobes. Gram-positive aerobes are largely from skin or environmental contamination (always a risk in any surgical invasion). Our principle concern will be the enteric flora in a septic patient who has not yet had an operation (Table 3).

Another set of flora are the anaerobic Gram-negative microbes, and for practical purposes they might all be grouped as "*Bacteroides* species". *Bacteroides* do not typically give rise to endotoxic shock. Anaerobic morbidity is through later abscess formation. This combination flora exhibits toxicity of the polymicrobial gut flora invading the surgical patient.

Virulence of Mixed Enteric Flora

This mixed flora combination from enteric contamination has peculiar virulence. Biochemical potentiation in synergy occurs, since aerobic and anaerobic flora are synergistic when combined in contamination. Organisms that are aerobic facilitate the growth of anaerobes as the oxygen is used up in the microenvironment of the bacterial invasion, and vice versa. This is a properly of conjoined redox potentials.

Rational Prophylaxis

Antibiotic prophylaxis is being given to huge numbers of patients who never will be infected, whether or not the drug is given. What is the most immediate consequence of that statement? If the infection rate without antibiotic prophylaxis could be anticipated to approximate 5% and you have a reasonably good drug that is so effective that it reduces the number of infections to 2.5%, you reduce the 5% infection rate to 2.5% by giving the drug to 100% of the patients at risk. But what if this effective drug also exhibits toxicity in 10% of the patients who receive it? This "prophylaxis" is no favor to anyone who received it; I would take my chances with the infection risk, which is smaller. One hundred per cent of the patients receiving the drug are exposed to the cost and risk of toxicity, but 97.5% of them would not realize benefit in any case. The marginal payout in prophylaxis is usually small. So the first and most obvious consequence of these projections is that we need a drug which is non-toxic. There are none which are absolutely non-toxic. The ß-lactams, including cephalosporins, to an amazing extent are reasonably non-toxic. To continue our look at prophylaxis we follow with further requirements for the agents chosen for prophylaxis (Table 4). Besides the first requirement that we tolerate no toxicity, we want something which, though effective against the risk flora is not our best treatment drug. If a demonstrably highly effective drug is available, do not use it in prophylaxis, but save its utility for treatment, avoiding using up its usefulness. If resistance is engendered to it, its utility for a life threatening infection may not be available later. So a potent or toxic drug is reserved for someone who needs it in treatment (i.e., has a 100% infection risk) and not in use for prophylaxis.

Table 4. Criteria for Antibiotics Selected for Use as Prophylactic Agents.

- Low or no toxicity
- First line treatment drug efficacy *not* needed
- Broad spectrum
- Easy administration, high blood levels, short course
- Does not generate resistance or cross-reactions
- Cheap

The next requirement would be an agent with a broad spectrum for the risk flora. It does not necessarily have to be effective against all species (not a practical goal), but must work against the risks of Gram-positive, Gram-negative aerobes and Gram-negative anaerobes if all three flora are anticipated in the high volume inoculum. There is no drug that is effective against all species in each of these classes, but we want one that is reasonably broad in spectrum, covering the principle classes of risk flora. One example is that the urinary tract is not usually subjected to anaerobic flora, and no agent would be needed with high anaerobic activity against such species as *Bacteroides*. In sparing this most numerous component of lower gut flora, an agent such as a quinolone, e.g, norfloxacin, would spare lower gastrointestinal upset of the flora while treating the predominant coliform risk of the urinary tract. We want an agent which is easy to administer, giving good blood levels and one which does not generate resistance to its effectiveness.

Drugs of Choice for Prophylaxis

For prophylaxis of risks associated with skin flora, the agent chosen could be a ß-lactam, such as a first generation cephalosporin, given as three doses within 24 hours, and no more. The most important dose is the one present before the inoculum. For special indications of added risks from GI or GU flora with a high probability of significant *Bacteroides* contamination, the agent chosen might be cefoxitin.

If the inoculum precedes the drug, there is no prophylaxis indication. (There is no *prophylaxis* started in the recovery room!) When contamination is already present, antibiotics must be given according to the indication for *treatment* (discussed in Part II). *Treatment* programs should not be moved back as use for *prophylaxis* because of toxicity, cost and generation of resistance.

A Clinical Example of Inappropriate Surgical Prophylaxis

On one occasion in discussion with my surgical residents, I discovered a patient who had been begun on antibiotics following herniorrhaphy. Since the prophylaxis indication could not be justified by the postoperative administration and there was no evident treatment indication, (no clinical findings, no fever curve, no chest X-ray finding, no elevated white blood cell count, no urinalysis, no Gram stain, no culture pending, no redness, purulence or discharge) the antibiotic course failed criteria in the treatment indication as well (See discussion, Part II).

However a broader question was asked of these same residents with respect to an elective hernia repair without prosthetic implantation. "Give me an indication for prophylaxis in a patient undergoing a clean elective hernia repair without prosthetic implant" I had asked. They being very ingenious residents, responded "The patient undergoing this hernia repair has a severe host defense impairment, and therefore would require antibiotic prophylaxis". I responded, "Give me the details as to the nature of his host impairment" "This patient has acute myelogenous leukemia in blast crisis!" I certainly agreed with them that this represents a severe host defense impairment.

"For what on earth reason are you fixing the hernia?" This is a clean error in surgical judgement, since the patient with this degree of immune defense compromise should not undergo an elective operation. This is a clear error in surgical judgement that has nothing to do with antibiotics. "If you can give me the indication for a prophylactic antibiotic in a patient undergoing a clean, elective operation without prosthetic implantation, you have most likely just given me the contraindication to the operation!"

Conclusion

Owen Wangenstein said: "an antibiotic can make a third class surgeon into a second class surgeon but never into a first class surgeon".

In the prevention of infection in surgical patients, antibiotics can only be adjunct to host defense. Host defense is best supported by good nutrition, and reduction of the inoculum is accomplished for elective procedures by antiseptic decontamination. Prophylaxis is indicated in patients who will experience an unavoidable inoculum, have impaired defense mechanisms, or have increased risk by prosthetic implantation. However prophylactic antibiotics are only adjuncts to host defense in the surgical patient, and both antibiotic and operation are each effective only to the extent that they support the patient's resistance against the invading inoculum.