SESSION I: THEORETICAL AND PRECLINICAL EXPERIMENTAL BASES OF PROPHYLAXIS

Perioperative Antibiotic Prophylaxis of Wound and Foreign Body Infections: Microbial Factors Affecting Efficacy

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Numerous microbial factors are responsible for perioperative infections and influence the efficacy of antibiotic prophylaxis. These factors include the staphylococcal carrier state, bacterial adherence to a number of host proteins, the production of glycocalyx by sessile bacteria, and shifts in antibiotic resistance. A full understanding of the mechanisms involved will lead to further reductions in the number of postoperative infections. Unfortunately, the microbial factors affecting prophylaxis cannot be evaluated separately under clinical conditions; they are easier to study under circumstances whose bacteriologic features are well defined and in which the presence of foreign materials (e.g., sutures) greatly potentiates pathogenic mechanisms. Such circumstances exist, for example, in infections developing after "clean" surgery and in experimental models. Since even clean wounds are found to be contaminated when sampled carefully, the control of infection is more a quantitative than a qualitative problem. The critical period for the development of infection is short: an antibiotic course not exceeding 24 hours seems effective in preventing infection.

Wounds produced by surgical intervention, their spontaneous healing, their complications (including infections), and methods to accelerate their closure have been described for thousands of years. The use of sutures, for example, is clearly depicted in the Smith papyrus, which dates back to 4000 B.C. [1]. Postoperative infection evidently has always been a feared complication of surgical procedures, and many techniques and devices have been developed throughout history to prevent such infection. With the advent of antibiotics, it was believed that the prevalence of this type of infection would decrease drastically. This was not the case. For instance, in a study on herniorrhaphy between 1937 and 1957, the incidence of postoperative infection hovered steadily around 4% [2]. Over the past 15 years, however, considerable work has shown the benefit of short courses of antimicrobial agents for the prevention of infection in a wide variety of surgical procedures [3–5].

The fact that skin incision, organ manipulation, or the consequences thereof increase the incidence of local infection points toward alteration of local *host* factors influencing microbial elimination. Demonstrations of the efficacy of antimicrobial agents are indicative of the impact of *bacterial* factors on the postsurgical evolution of wounds. The role of bacterial factors is further underscored by the clear demonstration that prophylactic antibiotics are effective in contaminated and clean-contaminated surgery, whereas their efficacy is more controversial in clean surgery—a situation in which the bacterial load is very low and therefore more difficult to evaluate.

It has become almost axiomatic to categorize surgical procedures as clean, clean-contaminated, contaminated, and purulent. Each category probably has common as well as specific risks and pathogenic factors [1]. Each also has its own typical group of pathogenic organisms, among which *Staphylococcus aureus* is found at a rate close to 50% [6] and gram-negative enteric bacteria almost as often (table 1). In a representative study extending over 5 years and encompassing 247 postoperative infections, *S. aureus* was responsible for 138 infections and gram-negative enteric organisms for the majority of the others [7]. Although recent studies have described the growing role of many other microorganisms, including anaerobes, the control of *S. aureus* and coagulase-negative staphylococci would reduce the prevalence of postsurgical infections by >50%. The present review will therefore concentrate essentially on these organisms and their pathogenic factors.

It is difficult to delineate the role of a single pathogenic factor leading to postoperative infection, since host factors and microbial factors are in a state of perpetual interaction. Nevertheless, three important observations at least help to define the boundaries of this problem. First, bacterial infection of a surgical wound necessarily starts by the contamina-

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Table 1. Most likely pathogens in postoperative wound infections.

Category of surgery	Most likely pathogen(s)
Clean	
Cardiac/vascular	*Staphylococcus epidermidis*, *Staphylococcus aureus*, GNB*
Breast	*S. aureus*
Orthopedic	*S. aureus*, *S. epidermidis*, GNB
Dialysis access	*S. epidermidis*, *S. aureus*
Neurologic	*S. epidermidis*, *S. aureus*, GNB
Clean-contaminated	
Burn	*S. aureus*, *Pseudomonas aeruginosa*
Head and neck	Streptococci, *S. aureus*, anaerobes
Gastrointestinal tract	GNB, anaerobes
Urogenital tract	GNB, group D streptococci
Dirty	
Ruptured viscera	GNB, anaerobes
Traumatic wound	*S. aureus*, group A streptococci, *Clostridium*

GNB = gram-negative bacteria.

tion of the wound with the microorganism. Second, this contamination cannot be totally prevented even under the most stringent aseptic conditions; this point is demonstrated by the observation of bacterial growth in 68% of 350 wounds after clean operations [8]. Thus a prerequisite for the prevention of the observation of bacterial postoperative staphylococcal infections is a better understanding of the colonization/anchoring mechanisms of these organisms. Moreover, the control of infection is more a quantitative than a qualitative problem, since, after all, most wounds are contaminated to a greater or lesser extent. Third, prophylactic antibiotic therapy has been shown to be effective even if given over a short period. This observation applies not only to clean orthopedic procedures but also to abdominal surgery [9, 10]. It can therefore be concluded that the pathogenic mechanisms – both host-mediated and microbial – are operational over a brief period during and after surgery. The data published most recently by Platt et al. [11] on two types of surgery (mastectomy and herniorrhaphy), with similar suppression of infection by short-term antibiotic therapy, suggest that the pathophysiologic mechanisms are the same despite major differences in the surgical procedures.

In clean surgery the risk of infection essentially depends on the contamination of the wound during the procedure [12] and on the presence of sutures, as has been repeatedly demonstrated [13]. No specific stimulation of bacterial pathogenicity can be ascribed to a particular type of suture [14]. Most infections after clean surgery are due to *S. aureus* and coagulase-negative staphylococci. The growing importance of the latter group of organisms has become clear in recent years.

Problems in the Evaluation of Microbial Factors

Clinical evaluation of microbial factors affecting perioperative antibiotic prophylaxis is hampered by many logistic and technical problems. Several factors in surgical intervention, all known to increase the prevalence of infection, may affect the microbial flora directly or indirectly, qualitatively or quantitatively; however, the individual factors are difficult to assess. Variations in surgical technique limit the feasibility of multicenter studies. Whereas the duration of an operation can be clearly determined, other important factors are not only variable but difficult to quantify, such as trauma, ischemia, tissue hypoxia, and edema. Moreover, hypotension and shock (also difficult to quantitate) have been associated with an increased risk of infection. Finally, emergency surgery – an elusive term – is associated with increased risk. It is particularly difficult to assess the importance and possible interaction of various microbial factors in mixed infection, such as that following abdominal surgery. Microbial factors due to organisms colonizing or infecting a site during surgery may be difficult to differentiate from those originating from microorganisms acquired in the intensive care unit or from those linked to invasive procedures or therapeutic devices. Finally, if these factors are assessed indirectly by perioperative prophylaxis, the dosage and the pharmacokinetic profile of the antibiotic are variables that cannot be standardized under all circumstances.

All of these difficulties can be overcome to some extent by the use of animal models [15], whose development has been rather slow. More specifically, evaluation of the efficacy of preventive antibiotics can be facilitated through an analysis of the microbial factors leading to infection and/or inhibited by perioperative antibiotics in the simplified model system of clean surgery, in which the epidemiology and bacteriology of infection are relatively well defined [16] and staphylococci are the organisms primarily implicated. Several experimental models are available for the study of host or microbial factors in this setting [17].

The presence of foreign material – including sutures, indwelling devices, and prostheses – has been clearly documented as a major pathogenic factor, overshadowing the majority of other pathophysiologic influences [18]. For example, Elek and Cohen [19] and later James and MacLeod [20] and Noble [21] showed that the presence of subcutaneous foreign material resulted in a decrease of the minimal infecting dose of staphylococci from $>10^6$ to $<10^3$. In experiments using polymethacrylate or Teflon tissue cages in guinea pigs, Zimmerli et al. [22] demonstrated a similar potentiation of bacterial infectivity and quantitatively assessed both bacterial growth and the inflammatory reaction. As we shall see, this animal model has proven to be of great help in the assessment of bacterial pathogenic factors influencing antibacterial prophylaxis.

Bacterial Factors Influencing the Efficacy of Prophylaxis

Important microbiologic determinants of the efficacy of antibiotic prophylaxis in clean surgery will now be discussed

in light of some general principles of postoperative wound infection. First, the wound must be contaminated by the offending organism; anchoring and adherence are initial mandatory steps in the development of infection. Second, on careful microbiologic assessment, most apparently clean wounds are found to be contaminated; this observation implies a quantitative rather than a qualitative microbe-host interaction in the development of wound infection. Third, antibiotic prophylaxis (i.e., activity against pathogenic bacterial mechanisms) is effective even if the regimen is given briefly, but only if the timing is right; thus these microbial factors appear to act over a brief period.

Presence of bacteria. Wound contamination with *S. aureus* starts often with a nasal carrier state and more rarely with a vaginal or rectal carrier state [23]. Treatment with systemic rifampin [24], local mupirocin [25], or other agents has been shown to reduce the rate of infection of dialysis access sites and of wound contamination, most probably via a reduction in the degree and duration of bacterial contamination, since the prophylactic effect seems to be short-lived. The problem is more complicated in the case of coagulase-negative staphylococci, since these organisms are ubiquitous skin contaminants and since culture techniques sample only part of the complex skin flora, potentially missing small, possibly infectious subpopulations [26]. Although the data from clinical studies on clean operations are still subject to controversy, prophylactic antibiotics eradicating coagulase-negative staphylococci (among other organisms) have been shown to be effective in well-defined operations such as aortocoronary bypass [27, 28]. The microbiologic price paid for such successful treatment is high, however. Coagulase-negative staphylococci carrying the gene for methicillin resistance increased dramatically in number when cultured quantitatively from the nares and the subclavian and inguinal areas of patients given high-dose prophylactic antibiotics during cardiac surgery [29]. In addition, the use of broad-spectrum antibiotics (e.g., nafcillin and rifampin) among a similar group of cardiovascular patients led to an important increase in rifampin-resistant organisms [30].

In conclusion, whereas colonization with *S. aureus* can be suppressed for short periods by antibiotics without a major risk of resistance, simultaneous multiplication of *Staphylococcus epidermidis* occurs readily and resistance develops frequently when broad-spectrum antibiotic prophylaxis is used. There is therefore a definite need to define the shortest effective prophylactic treatment period under these circumstances in order to minimize both proliferation and resistance of coagulase-negative staphylococci.

In situ multiplication of bacteria. It would be of great interest to assess the rate of bacterial multiplication after colonization as well as the effects that endogenous or exogenous substances or factors may have upon that rate. In this regard, it is worth mentioning the remarkable studies performed by Miles in 1956 [31]. Evaluating bacterial multiplication indirectly by measuring the diameter of skin lesions after subcutaneous inoculation of *Pseudomonas aeruginosa*, he showed that a full-blown lesion could be obtained in <24 hours. In addition, he demonstrated the effect of hypovolemic shock on the diameter of the lesions and brilliantly showed that adrenalin increased their size. Liquoid (polyanethol sulfonate) also increased the size of the bacterial lesions by 240-fold but exerted its effect for only 5 hours. Most important, an antibiotic (in this case, streptomycin for *P. aeruginosa* lesions) decreased the size of the lesions by a factor of 45 but exerted a protective effect for only 3 hours. Miles defined the period during which the experimental lesions could be modulated by several factors as the *decisive period*. Although considerable progress has been made in this field, the early concept of a decisive period is most useful, possibly defining the time necessary for bacteria to adhere, to multiply, and to become sheltered from host defenses and antibiotics.

Microbial multiplication in a surgical wound associated with a foreign device has been evaluated in two recent studies. Zimmerli et al. have shown that, even with small inocula of *S. aureus*, a latency period precedes active microbial multiplication [22]. The importance of this latency (decisive) period is illustrated by a study evaluating the timing of prophylactic antibiotic therapy [32]: with a delay of >6 hours between bacterial inoculation and the beginning of antibiotic therapy, bacterial growth occurred unabated despite treatment. Thus, at least in staphylococcal infections, it can be generally accepted that the decisive period during which microbial pathogenic effects are potentially reversible is ≤6 hours.

Antibiotic susceptibility and resistance. Although an effective program of perioperative antibiotic prophylaxis obviously should be chosen in light of the sensitivities of the potential pathogens, this task is far from easy. For example, the development of resistance in staphylococci during prophylactic treatment with rifampin is impossible to circumvent [33]. A quantitative increase of resistant coagulase-negative staphylococci during broad-spectrum antibiotic treatment [29] and the emergence of resistant strains under similar conditions [31] have been documented [34].

Of even greater concern is the transfer of resistance between *S. epidermidis* and *S. aureus*; this problem has been well explored in gram-negative bacteria but has only recently received attention in staphylococci. Thus, gentamicin-resistant strains of *S. aureus* and *S. epidermidis* isolated during a nosocomial outbreak in a nursery showed single plasmid identity by all test methods, including restriction endonuclease analysis [35]. The emergence of antibiotic resistance in *S. aureus* during another epidemic was shown to result from genetic transfer of a plasmid from *S. epidermidis* [36]. That skin-inhabiting coagulase-negative staphylococci can be the source of intergenetic plasmid transfer of resistance has been clearly established by Naidoo and Noble [37].

Other mechanisms of bacterial resistance must be considered. Although disputed for years, the role of "foreign," solu-

ble, bacterial β-lactamase in the hydrolysis of ampicillin, which favors the multiplication of a non-β-lactamase-producing strain of *Streptococcus pneumoniae* in an animal model [38], has recently been established. This mode of interaction is probably of little clinical significance, since most antimicrobial agents used as prophylactic agents are stable to β-lactamases.

Finally, an important type of phenotypic bacterial resistance deserves discussion. In 1985 Sheth et al. presented convincing data pointing to an increase in antibiotic MBCs for coagulase-negative staphylococci when the organisms were cultured in vitro in the presence of a catheter [39]. Moreover, organisms adherent to catheters could survive bactericidal concentrations of antibiotics for prolonged periods. Similar results reported by Nickel et al. [40] were ascribed to the protective effect of an extracellular matrix secreted by many organisms. These phenomena are reversible and are probably due to genetic regulatory events or phenotypic changes [41]. They may involve a variety of mechanisms, possibly specific for each drug, but are of sufficient general importance to explain the persistence of organisms in many chronic infections associated with tissue destruction or the presence of mechanical devices. Whether this modulation of antibiotic susceptibility is associated with (or the consequence of) surface adhesion, surface growth, production of slime or other extracellular products, changes in cell wall permeability, or effects on the target structures for antibiotics warrants further investigation.

Bacterial adherence. Adherence is a prerequisite for bacterial multiplication and invasion, according to our present concepts of infection. The adherence of *S. aureus* and coagulase-negative staphylococci to wounds, various sutures, and prosthetic materials has been widely investigated, and only some aspects pertinent to perioperative antibiotic prophylaxis will be discussed here. The adherence of coagulase-negative staphylococci varies greatly with the influence of encapsulation and other surface events [42]. Pretreatment with a variety of antimicrobial agents has a pronounced impact on staphylococcal adherence to plastic, as has recently been demonstrated by Schadow and associates [43] and as has previously been established for other microorganisms [44–46]. These results indicate that antibiotics modify the interaction of microorganisms with natural or foreign surfaces, but the respective mechanisms responsible for these modifications remain unknown.

Some general comments can be made regarding the interaction of *S. aureus* and coagulase-negative staphylococci with foreign surfaces in light of work performed in our laboratory and elsewhere. First of all, foreign surfaces rapidly become coated with a variety of host proteins, which play an important role in bacterial adhesion [47]. Many of these proteins carry domains of attachment for *S. aureus* and coagulase-negative staphylococci as well as for other microorganisms. A comprehensive report on these adherence domains for staphylococci has been published by Christensen et al. [48]. The question at this stage is not so much how these host proteins express their affinity for microorganisms, but rather how the organisms interact with these domains. Kinetic studies have shown this interaction to be rapid and irreversible. Thus clinical isolates of *S. aureus* bound avidly to fibronectin and fibrinogen, and binding to laminin occurred at a lower level [49]. These results were less striking with coagulase-negative staphylococci. When strains were categorized according to their origin (intravenous device infection, septicemia, healthy carriers), no differences were found except for the adherence of a subpopulation of coagulase-negative staphylococci to fibrinogen.

Thus there does not seem to be one bacterial strain—or several strains—with surface properties particularly suited to the colonization of foreign material. This point was well illustrated in a study by Vaudaux et al. [50], in which three staphylococcal strains (*S. aureus* strain Wood 46, *S. aureus* strain Cowan I, and *S. epidermidis* strain Rp 12) showed different degrees of binding to fibrinogen- or fibronectin-coated polymethacrylate or to catheters inserted in patients (figure 1). No quantitative prediction can therefore be made for a clinical situation since bacterial binding will depend on the number of receptors on the bacterial surface (one fibronectin receptor has now been identified in *S. aureus* [51, 52]) and on the amount of fibronectin, fibrinogen, and other host proteins deposited on the foreign surface. In addition, recent work in our laboratory suggests that fibronectin molecules unfold differently depending on the nature of the surfaces, thereby liberating various binding sites for *S. aureus* [53].

In conclusion, interaction between foreign material and bacteria (at least in the case of staphylococci) presupposes the deposition of a host protein layer, which plays the role of a ligand with a binding domain on the bacteria. Some of the characteristics of the bacterial sites are now well known, but little information is available on whether antibiotic treatment or other measures can modulate these sites. Recent work has suggested that, even in the absence of foreign material, staphylococcal binding in surgical wounds may be mediated via binding to fibronectin and collagen [54] or to other extracellular matrix proteins.

Slime production and its effects on postoperative infection. Most microorganisms, when grown under sessile conditions, produce extracellular polysaccharides that are deposited as an intercellular matrix. The available information on this material, called *glycocalyx* or *slime*, has been reviewed extensively by Costerton and colleagues [55] and by Gristina et al. [56]. The production of capsular polysaccharide material, in correlation with bacterial growth, has also been demonstrated by chemical [57] and morphologic [58] criteria in an experimental model. Recent data obtained by Nickel et al. [40] suggest that glycocalyx decreases bacterial susceptibility to antibiotics. It is difficult, however, to dissociate glycocalyx production from other events such as slow growth and adhesion to a surface; critical experiments—e.g., the addi-

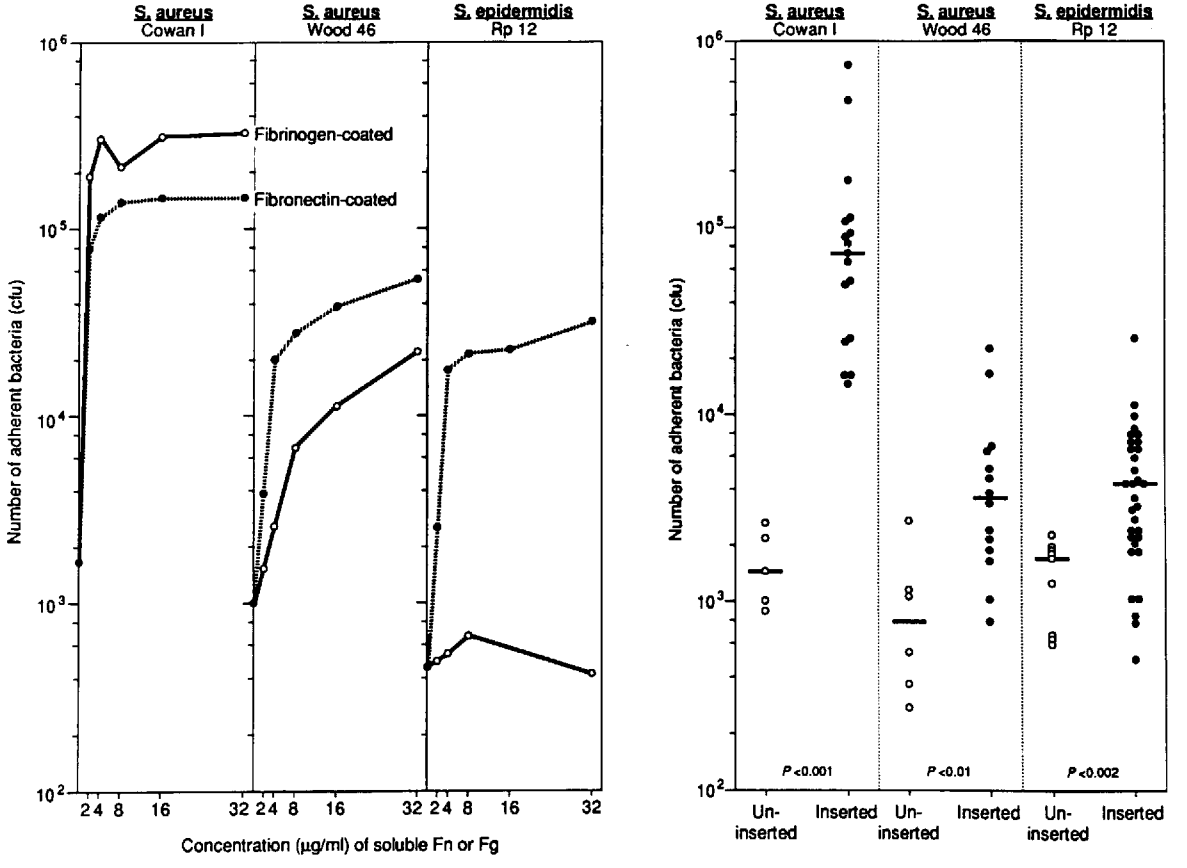

Figure 1. Promotion of adherence of three laboratory strains of staphylococci by in vitro coating of polymethacrylate coverslips with purified fibrinogen (Fg) or fibronectin (Fn) at indicated concentrations (*left*) or by blood components deposited in vivo on inserted polyvinyl chloride catheters (*right*). Bars indicate median values for each group. Reprinted with permission from [50].

tion of increasing concentrations of glycocalyx to adherent bacteria, with concomitant measurements of bacterial susceptibilities—have not, to our knowledge, been performed yet. Glycocalyx affects other mechanisms linked with perioperative infections, as summarized by Johnson et al. [59] and by Gray and associates [60]. Elucidation of the direct or indirect effects of glycocalyx on perioperative antimicrobial prophylaxis (except for the demonstrated effect on microbial permeability [40]) waits novel methods of investigation.

Timing and Pharmacokinetics of Antibiotic Prophylaxis

Clinical and experimental data suggest that there is a "decisive period," as Miles called it, during which wound infection can be modulated, i.e., during which microbial and host factors are still in a reversible stage [31]. At present, the only way to measure the reversibility of the microbial factors is to determine the optimal timing of antibiotic prophylaxis. As has been mentioned, we showed that, in the presence of foreign material, a 6-hour lapse between bacterial inoculation and the initiation of short-term antibiotic prophylaxis led to the failure of prophylaxis [32]. These first 6 hours seem, therefore (in such an experimental model, at least), to represent the decisive period described by Miles [31]. Thus the establishment of adequate antibiotic levels (exceeding bactericidal concentrations) in a wound during the first 6 hours after bacterial inoculation and the maintenance of these levels for an adequate period (here: 24 hours) should constitute efficient prophylaxis.

One example of this technique that has been shown to be effective (as studied in tissue cages in guinea pigs) consists of a single dose (30 mg/kg) of vancomycin or fleroxacin, a long-acting quinolone [61]. When, however, either of the latter prophylactic drugs was compared with equal single doses of ciprofloxacin or ofloxacin—two quinolones with a shorter half-life in tissues—the results differed quite strikingly (table 2). Protection against infection was incomplete with the short-acting quinolones, even at a bacterial inoculum as low as 10^2 cfu of *S. aureus* strain Wood 46. Moreover, levels of ofloxacin and ciprofloxacin decreased rapidly (figure 2), while those of vancomycin and fleroxacin remained predictably >0.7

Table 2. Comparison of ofloxacin, ciprofloxacin, and fleroxacin in the prophylactic treatment of tissue cage infection due to *S. aureus* strain Wood 46 in guinea pigs.

Drug (no. of doses*)	Inoculum (cfu)	No. of tissue cages yielding <10 cfu per mL/no. analyzed (%) At 48 h	At 7 d
Ofloxacin (1)	10^2	7/8 (88)	4/8 (50)†
	10^3	2/8 (25)‡	2/8 (25)‡
Ciprofloxacin (1)	10^2	4/8 (50)†	4/8 (50)†
	10^3	1/8 (13)§	0/8 (. . .)§
Fleroxacin (1)	10^2	18/18 (100)	18/18 (100)
	10^3	6/6 (100)	5/5 (100)
	10^4	10/10 (100)	4/9 (44)
Ofloxacin (2)	10^2	4/4 (100)	4/4 (100)
	10^3	3/4 (75)	3/4 (75)

NOTE. Data are from [61].
* Each dose was 30 mg/kg.
† $P < .02$ vs. fleroxacin.
‡ $P < .05$ vs. fleroxacin (Fisher's 2 × 2 exact test, two-tailed).
§ $P < .01$ vs. fleroxacin.

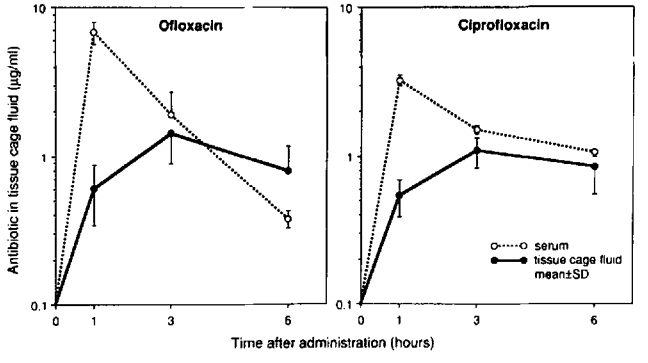

Figure 2. Pharmacokinetics of two 4-quinolones in serum and tissue cage fluid after intraperitoneal administration of 30 mg/kg.

µg/mL for 24 hours [61]. A second injection of the shorter-acting quinolone ofloxacin was necessary and sufficient at 3 hours to produce adequate tissue levels and protection (table 2). These and similar studies all indicate that microbial factors are operational—and can be brought under control—during the first 24 hours after surgery in animal models.

Conclusion

Several microbial factors are responsible for perioperative infections and influence the efficacy of antibiotic prophylaxis. Unfortunately, clinical studies do not allow the evaluation of each factor separately, and experimental studies in this field are limited. The problem can be partly solved by the exclusive study of infection after clean surgery, since in these circumstances bacteriologic features are well defined, the presence of foreign materials greatly potentiates pathogenic mechanisms, and experimental models are readily available. Analysis is based on three principles. First, the wound must be contaminated, and adherence mechanisms are therefore of paramount importance. Second, most "clean" wounds are found to be contaminated when sampled carefully, and the control of infection is therefore more a quantitative than a qualitative problem. Finally, the critical period for the development of infection is short: antibiotic prophylaxis of <24 hours' duration seems to be effective both clinically and experimentally.

With these principles as a framework, the effects of antimicrobial agents on microbial factors must be evaluated. The staphylococcal carrier state (whether involving *S. aureus* or coagulase-negative staphylococci) influences the frequency of wound infection and can be modified in a positive or negative manner by antibiotics. Bacterial adherence certainly plays a crucial role in postoperative infection and is favored by bacterial ligands interacting specifically with host proteins such as fibrinogen, fibrin, fibronectin, and laminin. Bacterial multiplication is influenced by many factors during the first few hours of wound infection—a decisive period that offers many therapeutic possibilities. The production of glycocalyx by sessile bacteria alters the susceptibility of many bacteria to antibiotics, although the mechanisms involved have not yet been elucidated. Antibiotic susceptibilities are evidently critical determinants of the efficacy of perioperative antibiotic prophylaxis: initial resistance and the emergence of resistance by selection or genetic alteration are well known phenomena, and plasmid transfer among species of staphylococci is a newly observed mechanism of potentially great danger. Variation in the susceptibility of adherent vs. fluid-phase bacteria may be a fundamental biologic phenomenon that explains many instances of treatment failure in chronic infection.

A full understanding of these mechanisms should allow us to further reduce the prevalence of postoperative infections.

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