Antibiotic Update for the Surgeon

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All too often, it seems that the utilization of antibiotics by surgeons for either prophylaxis or the treatment of established infections is shrouded in a combination of mysticism and marketing. What should be straight forward, frequently becomes confused by factors such as superstition, habit, recent interaction with an industry representative, and faulty information. The rational use of antibiotics is surprising simply, and is based on the fact that these agents are, quite simply, systemic chemotherapy against bacteria.[1] Once delivered to the patient these agents act not only locally, but, more importantly, sistemically against susceptible microorganisms. This demands that the practitioner make an educated guess as to which bacteria are likely to be present, as well as use an agent that both safe and effective in that specific patient. The types and variety of bacteria present in a surgical infection, or likely to be present, can usually be deduced by the location and/or organ system involved. The safest and most effective agent to be used against those organisms is primarily a function of the specific hospital that the patient in, and whether the infection is hospital-acquired (nosocomial) or community-acquired. The susceptibility patterns for bacteria vary from community to community (as noted by local hospitals), as well as from hospital to hospital dependent on whether it is a community hospital or a tertiary referral center. It is illogical to assume that the same drug or drugs will be just as effective in one setting as in another, regardless of whether they are used for prophylaxis or an established infection.

In this chapter, we will explore the rationale for the use of antibiotics in both surgical prophylaxis and established infections, as well as discuss new developments in antimicrobial therapy such as the mechanisms of resistance to β-lactam antibiotics and the rationale for β-lactmase inhibitor combinations, changes in dosing regimens for aminoglycosides that may increase both efficacy and safety, new uses of quinolone antibiotics for severe infections, and use of vancomycin in the face of increasing resistance from enterococci.

SURGICAL ANTIBIOTIC PROPHYLAXIS

Although the scientific basis for the use of prophylactic antibiotics in surgery was elucidated over thirty years ago,[2,3] it wasn't until the mid-seventies that good clinical trials began to prove the benefit of these agents as prophylaxis in surgical procedures.[4,5] The objective of antibiotic prophylaxis is simply to prevent the establishment and growth of a microbial inoculum in a surgical site, and thus prevent postoperative infectious complications. There are, however, certain basic rules and principles which must be followed when administering prophylactic antibiotics for a surgical procedure both to maximize the efficiency of the agents and minimize any possible problems. First, is the recognition that all the antibiotics in the world are not going to make up for poor surgical judgment and technique. Second, the antibiotic chosen must be administered prior to the bacteriologic inoculation. As recently demonstrated by Classen and his coworkers, administration of an antibiotic either more than two hours before the surgery or any time after the surgery begins results in significantly higher wound infection rates.[6] In fact, administration of the antibiotic post-operatively resulted in infection rates not dissimilar from administration of no antibiotic at all. The best time for administration of the agent is probably within an hour prior to the actual incision of the skin.

Another principle of antibiotic prophylaxis in surgery is that there must be maintenance of adequate tissue levels of the antibiotic throughout the period of contamination risk. This means that if the antibiotic has a short half-life or if the surgery is especially prolonged, redosing of the agent will be necessary. This redosing can be eliminated by using an agent with a prolonged half-life (dosing interval of every eight or twelve hours). Also, it is important that the prophylactic therapy be of brief duration. It has never been shown that a single dose of a single long-acting antibiotic is any less effective than either the use of multiple agents for prophylaxis or multiple postoperative doses for prophylaxis.[7] Finally, if an established infection is encountered, then it is no longer a prophylactic situation but rather a therapeutic one. In that case, the agent which was chosen for prophylaxis should simply be continued post-operatively in a therapeutic fashion. One should always employ full therapeutic dosing of an antibiotic appropriate to the type of bacteria anticipated when choosing a prophylactic antibiotic. This facilitates transition from a prophylactic to a therapeutic situation if the need arises.

All surgeons are familiar with the traditional wound classification system which was developed in 1964 by the Academy of Sciences National Research Council.[8] By this classification, surgical procedures are divided into clean, clean contaminated, contaminated, dirty/infected based only on the type of procedure and organ system involved. The expected wound infection rates derived from this classification is noted in Table 1. Using this data, specific antibiotic prophylaxis was recommended only for clean-contaminated operations, because the available data from the late sixties and early seventies suggested that antibiotics reduced the wound infection rates of these operations down to that of a clean operation which was the desired goal and endpoint.

EXPECTED POST-OPERATIVE WOUND INFECTION RATES BASED ON 1964 SURVEY

TYPE OF OPERATION	EXPECTED WOUND INFECTION RATE (%)
CLEAN	2 - 5
CLEAN-CONTAMINATED	8 - 10
CONTAMINATED	15 - 20
DIRTY / INFECTED	30 - 45

Table 1. *(Adapted from Academy of Sciences National Research Council[8])*

PERCENTAGE RISK OF WOUND INFECTION FOR SOME COMMON OPERATIONS BASED UPON RISK INDEX

OPERATION	TIME "X" (HOURS)	RISK FACTORS PRESENT 0	1	2	3
ABD. HYSTERECTOMY	2	1.4%	4.1%	5.1%	*
AMPUTATION, MAJOR	1	3.9%	4.6%	5.5%	7%
APPENDECTOMY	1	2.4%	2.3%	9.4%	9.7%
CABG	5	1.1%	3.5%	6.7%	33.3%
CHOLECYSTECTOMY	2	1.4%	2%	7.1%	11.5%
COLONIC	3	3.2%	8.5%	16.1%	22.2%
C-SECTION	1	4.2%	5.9%	11.4%	*
CRANIOTOMY	4	0.6%	2.5%	2.6%	*
EXP. LAPAROTOMY	2	1.5%	4.1%	14%	14%
GASTRIC	3	4.9%	6.9%	15%	*
HERNIORRAPHY	2	1%	1.9%	5.2%	*
HEAD AND HECK	4	1.3%	3.5%	9%	*
JOINT PROSTHESIS	3	1.2%	2.6%	4.8%	*
MASTECTOMY	2	0.8%	2.4%	5.2%	*
ORIF	2	1%	1.8%	3.5%	3.7%
SKIN	2	1 .3%	1 .8%	6. 1%	1 1.1%
SPINAL	3	0.7%	1.9%	4%	*
VASCULAR	3	1.6%	2.1%	6.1%	14.8%

* Numbers too small to analyze

Table 2. *(Adapted and modified from Culver et al [11])*

However, about 15 years ago reports began to emerge suggesting that these accepted wound infection rates were probably too high. A report on wound surveillance in a single institution for the years 1977 and 1981 demonstrated that the post-operative wound infection rates for clean-contaminated cases were consistently less that five percent (and therefore not significantly different from the clean wound rate), and that the infection rates for contaminated wounds were only ten percent.[9] Findings such as these resulted in investigators looking at factors other than just the type of operation performed as being important determinants of post-operative infection rates.

Haley, in 1985, reported that more patient specific factors such as abdominal operation, an operation lasting greater than two hours, the patient having three or more diagnoses on the discharge summary, or a contaminated/dirty operation, were significant determinants of post-operative wound infection rate,[10] and were probably more realistic indicators of actual risk. Based upon the presence or absence of these four factors, he proposed a simple wound infection risk index. This showed wound infection rates of 1.0% if none of the factors occurred, 3.6% if one factor was present, 8.9% if two factors were present, 17.2% if three factors were present, and 27% if all four factors were present. It was suggested that antibiotic prophylaxis only be used in those cases with two or more risk factors present.

More recently, this same group has modified this post-operative wound infection risk index.[11] With information on nearly 85,000 operations, they altered the risk factors to be: 1) a patient having an American Society of Anesthesiologist (ASA) pre-operative assessment score of three, four, or five; 2) an operation classified as either contaminated or dirty/infected; and 3) an operation where the duration on the surgery exceeds X hours (where X is dependent upon the operative procedure being performed). For all operations, this index reveals that if no risk factors were present, the infection rate was 1.5%, for one risk factor present 2.9%, for two risk factors present 6.8%, and if all three risk factors present, the infection rate was 13%. Table 2 shows the infection risk for some common operations, based upon this system, and Table 3 gives some specific antibiotic recommendations for surgical prophylaxis based upon type of operation performed or area being operated upon.

ANTIBIOTIC USAGE IN ESTABLISHED INFECTIONS

The use of antibiotics as adjunctive therapy for the established infections encountered by surgeons is an important aspect of the global care of the patient's disease process. As with the use of antibiotics in surgical prophylaxis, the usage of antibiotics in the treatment of established infections is also governed by certain principles. As with prophylaxis, the first principle that must thoroughly understood is that antibiotics by themselves will not substitute for adherence

SUGGESTED AGENTS FOR SURGICAL PROPHYLAXIS FOR ELECTIVE OPERATIONS

OPERATION	PATHOGEN(S)	ANTIBIOTIC
SKIN Long operation (>2 hrs), use of prosthetic material	*Staph.epi., Staph. aureus*	1st generation cephalosporin or vancomycin*
VASCULAR Abd. aorta, prosthesis, groin incision	*Staph. epi., Staph. aureus,* enteric gram - bacilli	1st generation cephalosporin or vancomycin*
VASCULAR ACCESS FOR HEMODIALYSIS	*Staph. epi., Staph. aureus*	vancomycin
CARDIAC	Staph. epi., Staph, aureus, *Corynbacterium,* enterie gram-bacilli	1st generation cephalosporin or vancomycin*
HEAD AND NECK Enter oral eavity or pharynx, ORIF	*Staph. aureus,* streptococci, oral anaerobes	1st generation cephalosporin or β-lactamase inhibitor comb.
NEUROSURGERY	*Staph. epi., Staph. aureus*	1st generation cephalosporin or vancomycin*
ORTHOPEDICS Total oint ORIF	*Staph. epi., Staph. aureus*	1st generation cephalosporin or vancomycin*
OPHTHALMOLOGIC	Staph. epi., Staph. aureus, streptococci, enteric gram-bacilli	Topical aminoglycoside or Topical triple antibiotics
GASTRODUODENAL	Enteric gram - bacilli, gram + coeci	2nd generation cephalosporin or β-lactamase inhibitor comb.
BILIARY TRACT	Enteric gram - bacilli, enterococci, anaerobes	2nd generation cephalosporin or β-lactamase inhibitor comb.
COLORECTAL	Enteric gram- bacilli, anaerobes	Oral:neomycin + erythromycin plus IV: 3rd generation cephalosporin or β-lactamase inhibitor comb.
GYNECOLOGIC	Enteric gram - bacilli, anaerobes, streptococci, enterococci	1st generation cephalosporin or β-lactamase inhibitor comb.

*where MRSA or MRSE is a problem.

Table 3.

to good surgical technique and judgment. Second, one should match the antibiotic used to the type of bacteria found either on a previous culture specimen or on the flora which might be expected to be present. Also, the use of a single antibiotic agent for all infections in all locations and circumstances is both dangerous and foolish. Since each antibiotic has more or less a specific antimicrobial spectrum of action, it is illogical to assume that one specific agent can be effective in every infection a surgeon might encounter. Such inappropriate use of antibiotics is one of the leading causes of the emergent of resistant organisms. As a corollary, the choice of the drug should be made based upon known bacterial sensitivity data. If possible, this data should be institutionally specific. Each hospital should publish at least quarterly an antibiogram listing the specific antibiotic susceptibilities based upon the bacteria seen in that institution. This is probably the best guide to both the pool of community microflora and the expected nosocomial pathogens in that institution.

Another principle of antibiotic usage in established infection, is that where possible a single agent should be employed. Although the treatment of nosocomial infections may require multiple agents because of drug resistance, there has never been a good randomized, prospective trial which has demonstrated the superior efficacy of multi-antibiotic therapy over a single-agent therapy for a mixed community-acquired infection. It goes without saying that when there are multiple choices of equivalent therapeutic agents, the safest should be employed. Also, once treatment has been started with a specific antibiotic, that agent should only be changed if there is a true therapeutic failure. Mid-course changing of antibiotics based solely upon culture and sensitivity data in a patient otherwise doing well should be discouraged since this increases the likelihood of the emergence of resistant organisms. Finally, the antibiotics should be discontinued when there is patient-specific evidence that the infection has been controlled, such as return of the white blood cell count to normal limits, lack of a fever, etc. The use of an arbitrary number of days of treatment (whether strictly parenteral or combined parenteral/oral) is an example of the physician treating him or herself rather than treatment of the individual patient.

Although there have not been many new antibiotics approved by the FDA over the last five years, there are several new agents which may soon become available over the couple of years. These include new parenteral quinalones, cephalosporins, and carbapenems. In the following section, some of these new agents will be discussed as well as newer dosing regimens of currently accepted antibiotics such as aminoglyeosides will be explored.

β-LACTAMS

The β-lactam group of antibiotics is the single largest group of antimicrobial compounds currently available, and comprises the penicillins, eephalosporins, monobaetams, and earbapenems. During the 1980's, a large number of β-lactam antibiotics, especially cephalosporins, were released by the pharmaceutical industry. Aided by their general effectiveness against a wide range of mixed aerobic and anaerobic infections, this group of agents also benefits from an excellent safety profile when compared with the more traditional aminoglyeoside-based therapy. However, all β-lactam drugs (to a greater or lesser degree) were quickly noted to be vulnerable to resistance mediated by beta-lactamases.

β-lactamases are ubiquitous enzymes that occur in almost all bacteria. All β-lactam antibiotics share a four-membered ring with a nitrogen in one corner and a carbon with a double-bonded oxygen adjacent to it as part of their basic structure. β-lactamases are able to noncovalently bond to this ring between the nitrogen and the carbon with the double-bonded oxygen, and through hydrolysis open it up. This destroys the drug's activity. In general, gram-positive bacteria produce large amounts of β-lactamases that are excreted extra-cellularly. So much so that in some gram-positive bacteria, the β-lactamases expressed can actually constitute up to 1% of the dry weight of the bacterium. In gram negative bacteria, β-lactamases are found in lesser amounts, but are located in the periplasmic spaces between the inner and outer cell membranes. Table 4 lists the commonly accepted classes of the β-lactamases. Some bacteria, especially members of the Enterobacteriaceae, have the ability to synthesis large amounts of, β-lactamases if challenged with a β-lactam drug (induction). Some drugs, such as cefamandole, are potent inducers of these enzymes with resultant treatment failure. Some evidence is reported suggesting that Enterobacteriaceae species, especially *Enterobacter,* are able to rapidly develop resistance to some β-lactam drugs (especially cephalosporins) with an increase in mortality rate.[13] Two new third-generation cephalosporins (cefepime and cefpirome) are in the FDA approval pipeline and appear to demonstrate some enhanced activity, which may be due to increased resistance to the action of these induced, β-lactamases.[14] Whether this is intrinsic to the drugs or is simply a matter of their being new compounds to which resistance will eventually occur is unknown at this time.

β-LACTAMASE GROUPS AND THEIR CHARACTERISTICS AS DEFINED BY BLACTAMASE INHIBITOR ACTIVITY

β-Lactamase Group	Bush Class	Clavulanate	Sulbactam	Tazobactam
Staphylococcal Penicillinases (e.g. PCl)	2a	+++	+++	+++
Transferable, β-Lactamases (e.g. TEM-I, SHV-I)	2b	+++	++	+++
Chromosomal Cephalosporinases (e.g. P99, S2)	1	--	+	++
Extended-Spectrum β-Lactamases (e.g. TEM-3 TEM- 10)	2b'	+++	++	+++
Metallo-BLactamases (e.g. CcrA, L1)	3	--	--	--

Table 4. *(Adapted and modified from Bush et al[12])*

β-lactamase inhibitor combinations are a group of β-lactam antibiotics which were specifically designed to attempt to deal with β-lactamase induced resistance. The members of this group of drugs include ampicillin/sulbactam (Unisyn®), ticarcillin/clavulanate (Timentin®), and a third compound, which was just gained FDA approval this year, piperacillin/tazobactam (Zosyn®). This group of drugs works by suicide inhibition of the β-lactamases, where the sulbactam, clavulanate, and tazobactam all bind to the β-lactamases in a high-affinity, non-covalent complex which is not hydrolyzed. Table 4 shows the relative activity of these β-lactamase inhibitors against the commonly occurring β-lactamase groups. As is shown, none of the current β-lactamase inhibitors are highly effective against the chromosomally mediated β-lactamases produced by many of the more resistant varieties of Enterobacteriaceae (such as *Enterobacter, Citrobacter, Pseudomonas,* etc.), although tazobactam and sulbactam appear to be more active against this group of enzymes than clavulanate.

Zosyn® (the new piperacillin/tazobactam combination) appears to be a particularly potent broad spectrum antibiotic, although this may be a reflection of its newness. In mixed flora intra-abdominal infections, it was significantly more effective at eradicating pathogens than the combination therapy of gentamicin and clindamycin (90% vs. 80%, $p<0.01$), and demonstrated an equivalent clinical cure rate (88% vs. 77%, $p=0.08$).[15] Similarly, equivalent clinical cure rates have been reported for Zosyn® versus Timentin® in severe skin and soft tissue infections.[16]

There is another mechanism for acquired bacterial resistance to β-lactam antibiotics that has become increasingly important. The ultimate targets of β-lactam antibiotics are cell wall-synthesizing enzymes (penicillin-sensitive enzymes or penicillin-binding proteins). These enzymes are present in essentially all bacteria, but vary from species to species in numbers, size, amount, and affinity for β-lactam antibiotics.[17] They control such fundamental processes as cell growth and division, and therefore when inhibited by β-lactam antibiotics result in cell lysis, death, or growth arrest. The mechanism of resistance is an alteration of the β-lactam antibiotic binding site which decreases the ability of the drug to bind to the enzyme. Alteration of the enzymes are more commonly found in gram-positive than in gram-negative bacteria.[17] This is the method by which *Staphylococcus aureus* and *Staphylococcus epidermidis* have developed the resistance to methacillin that now plagues us. It is also the mechanism by which *Streptococcus pneumoniae,* veridans group streptococci, and *Enterococcus* species have increased significantly their resistance to essentially the entire group of β-lactam antibiotics during the last 10-15 years (especially *Enterococcus*).

AMINOGLYCOSIDES

For the last two decades, aminoglycosides have remained major work horses in the treatment of severe infections. However, because of the availability of new broad spectrum antibiotics with wider safety margins (β-lactams and quinolones), aminoglycosides are being reserved with increasing frequency for use in severe/life-threatening or nosocomial infections. The great fear, of course, has always been the toxicity problems (nephrotoxicity and ototoxicity) for which aminoglycosides have been known. Unlike the β-lactams, the efficacy of aminoglycosides depends primarily on the maximal concentration which is achieved in serum. There is a direct relationship between how much higher the serum concentration of the aminoglycoside is than the minimum inhibitory concentration and the rate and extent of bacterial killing.[18]

Unfortunately, fear of the toxic side effects of the aminoglyeosides has frequently resulted in the underdosing of these agents. More attention is typically placed on the antibiotic trough level than on the peak serum concentration of the antibiotic. A recent example of the effect of this fear on clinical outcome demonstrated a significant difference in the occurrence of post-operative infectious complications in abdominal trauma patients treated with a beta-lactam antibiotic combination (aztreonam + clindamycin) versus patients treated with the combination of gentamiein and clindamycin.[19] In this study, patients in the aztreonam group had a significantly lower incidence of post-operative infectious complications than those in the gentamicin group (3% versus 19%, $p<0.03$). In reviewing their data the authors felt that the reason for this difference was due to chronic underdosing of the aminoglycoside.

Most all antibiotics, aminoglycosides in particular, possess another mechanism to kill bacteria, called the post-antibiotic effect (PAE). This mechanism is the ability to continue suppression of bacterial growth after exposure to the drug at concentrations well below the drug's minimum inhibitory concentration for the infecting organism. Some of the manifestations of PAE include delayed recovery of enzyme and non-enzyme protein activities; prolonged changes in cell morphology, metabolism, growth, and generation times; changes in cell receptors and susceptibility to phagocytosis; and altered susceptibility to an antibiotic following re-exposure.[20] Although not well understood, it is PAE which helps explain many of the inconsistencies found in antibiotic dosing, such as giving gentamicin every eight hours and amikacin every twelve hours despite their serum half-lives being essentially the same. What this means for aminoglycosides is that the ability to continue bacterial growth suppression by PAE can allow for a prolonged drug washout period. This allows for lower serum trough levels of the drug, which should lead to decreased toxicity.

Gilbert[21] has suggested that because aminoglycosides demonstrate both significant PAE and have such a direct correlation between serum concentration and bacterial killing, once daily dosing is not only possible, but advantageous as well. Instead of the usual dosing of the patient every 8 or 12 hours (3-5 mg/kg/day for gentamicin and tobramycin, 15 mg/kg/day for amikacin), the drug is administered as a larger single dose once a day (5-9 mg/kg/day for gentamicin and tobramycin, 15-20 mg/kg/day for amikacin). Because of the higher initial peak drug concentrations, both more rapid killing of bacteria as well as a decrease in the emergent of resistant populations can be achieved.[22] Clinical trials in both intra-abdominal and other serious mixed infections have demonstrated the efficacy of this approach.[23,24] Patients who are severely neutropenic, however, may not benefit from once daily dosing of aminoglycoside because of the potential for rapid regrowth of bacteria during the last twelve hours of the dosing interval is frequently seen in these patients.[25]

In addition to providing higher peak serum levels, the other benefit of once daily aminoglycoside dosing appears to be a decreased risk of nephrotoxicity. In individuals with normal renal func-

tion, once daily dosing results in serum trough levels of less than 0.5 mg/dl. Clinical trials evaluating the efficacy of once daily aminoglycoside dosing as compared to multiple dosing do not show any significant therapeutic differences,[23,26,27] and other studies indicate a definite safety advantage for less frequent or once daily dosing of these agents.[28,29]

Another potential benefit to once daily aminoglycoside dosing is that it lessens the possibility of adaptive resistance. Closely related to PAE, adaptive resistance is a short lived (less than two to five hour) effect which causes reduced bactericidal activity following a second antibiotic exposure. Seen primarily with aminoglycosides and some quinolones, it is probably due to reduced transport of the antibiotic into the cell and is of finite duration.[30] Increasing the dosing intervals negates the effect.

QUINOLONES

The quinolones constitute an unusual group of antibiotics in that they are completely man-made. This is in contradistinction to essentially all other groups of antibiotics which are variants of chemical compounds isolated from bacteria. Because of this, it is possible that as a group, quinolones may grow to have the largest number of distinct compounds of all antibiotics (more than even the β-lactams). Acting directly on the bacteria's DNA, quinolones are potent bacterial killing agents that are very effective against a wide variety of gram negative and gram positive bacteria. Although currently licensed quinolones (e.g., ciprofloxacin and ofloxacin) are primarily effective only against aerobic organisms, there are newer experimental quinolones (e.g. clinafloxacin) which appear to be effective against not only gram positive and gram negative bacteria but both aerobes and anaerobes as well.[31] Such a quinolone would offer true single-agent therapeutics similar to many of the β-lactam antibiotics, which current quinolones lack.

Although not yet approved for the treatment of intra-abdominal infections (the indication application has been submitted to the FDA), parenteral quinolones have been approved for, and are very effective in, the treatment of other severe mixed infections in the lower respiratory tract, urinary tract, and skin and soft tissues. These agents have the distinct advantage that they not subject to the actions of inducible β-lactamases, especially those of the chromosomal group found in the gram negative bacilli, which is becoming a problem with the β-lactam antibiotics. Another advantage is the possibility of switching a patient with a serious gram negative infection from parenteral to oral therapy using the same agent. Considered by some the Holy Grail of treatment options for its potential cost and hospitalization savings, it has never been properly studied in a randomized, prospective clinical trial (though that may change very soon). However, there are groups who have been employing this form of treatment in patients with normal gut function and who have responded to initial parenteral treatment if cultures showed quinolone-sensitive organisms with success.[32]

GLYCOPEPTIDES

Effective only against gram positive organisms, the glycopeptide group of antibiotics is made up of vancomycin and teicoplanin (which is not yet commercially available in the US). Because of the emergence of significant resistance by *Enterococcus sp.,* and to a lesser extent *Staphylococcus sp.,* to β-lactarns, arninoglycosides, and even quinolones, glycopeptides have emerged over the years as the primary agents for the treatment of sepsis from gram positive bacteria, especially in the immunocompromised.[33] However, over the last couple of years enterococci resistant to vancomycin have been reported with disturbing frequency in both Europe and North American.[34,35] Caused by inducible enzymes which alter peptidoglycan precursors so as to decrease the binding ability of glycopeptide antibiotics, this resistance has forced a re-evaluation of the empiric use of these agents. Vancomycin, specifically, should not be used in a frivolous manner for either prophylaxis or treatment, but rather should be employed only when there is either a significant risk for an infectious complication due to methicillin-resistant staphylococci or for treatment of an established infection resistant to other agents but susceptible to vancomycin. Too frequent use of vancomycin, particularly in the ICU environment, may well be the major determinant of development of resistant organisms (especially entcrococci) that has plagued many large teaching centers recently. STI

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