The ethics of prophylactic antibiotics for neurosurgical procedures

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Preventive medicine is an ancient and honourable practice. For example, the ancient Chinese paid their doctors while they remained healthy, but stopped paying when they became ill.1

In the clinical setting, some medical procedures cause complications which can be averted with proper preventive techniques. For instance, patients on steroid therapy are given antihistamines (H2 blockers) to prevent peptic ulcers. Patients with valvular disorders are advised to take antibiotics before undergoing oral surgery and other dental procedures because scraping of the gums can create an entry for bacteria into the blood, leading to an inflammatory condition of the heart.

Surgery in general allows bacteria to invade the skin barrier of the body, and in high risk operations such as urologic, orthopaedic, vascular, and neurological surgery, antibiotics are given as prophylaxis to stem a potential infection. For example, compared to other surgical subspecialties, neurosurgery carries a low risk of infection, around 2–3%.2 3 The consequences of a neurosurgical infection can, however, be devastating. Wound infection following neurosurgical procedures may rapidly result in meningitis, cerebritis, abscess formation, and death. At the very least, the effects are subjective discomfort and prolonged hospitalisation. To minimise or even eliminate postoperative infection, many neurosurgeons have incorporated prophylactic antibiotics into their antiseptic regimens. A number of placebo-controlled clinical trials have proven the efficacy of antibiotics in preventing wound infection following brain and spine surgery.2 4

Yet, despite these results, both the prophylactic use and testing of antibiotics for surgical procedures has been a controversial issue since the beginning of the antibiotic era and remains problematic.5 6 Some neurosurgeons depend upon meticulous aseptic techniques rather than considering antibiotics. Arguments against the use of antimicrobials include promotion of antibiotic-resistant strains of bacteria, superinfection, and adverse drug reactions.

In this paper, we pose ethical questions about the testing, commission, and omission of antibiotic prophylaxis for neurosurgical procedures. In our new era of managed care that recognises the need for both cost-effectiveness and the rationing of health care resources we hope to promote a greater awareness of the ethical considerations of chemoprophylaxis in other surgical disciplines and the broader medical community.

WHAT HAS TRADITIONALLY BEEN CONSIDERED RESPONSIBLE PROPHYLACTIC ANTIBIOTIC USAGE?
The effectiveness of antibiotics to treat bacterial infections led to their use as prophylactics to protect healthy individuals exposed to pathogenic bacteria, to prevent chronically ill patients from developing an infection, and to prevent infection in patients undergoing surgery.7 The prophylactic indication of antibiotics rests on the concept that they should eliminate infections in a subclinical stage and prevent one that has not yet started. Antibiotic prophylaxis in neurosurgery began with the use of the antiseptic, hexamine, in 1925 and has continued up to the present time as newer drugs have become available, from penicillin to vancomycin. Several surgeons have reported substantial reductions in their postoperative infection rate after resorting to antibiotics.8 9 and a few have even reported no infections over a 20 year period.10 11

Despite these successes, prophylaxis presents certain dangers to the individual patient and the population at large, including the development of antibiotic resistance, superinfections, and drug side effects. As a result, doctors have wide ranging opinions on the responsible use of antibiotics as a preventive measure.

IS IT RESPONSIBLE TO USE ANTIBIOTICS IF THEIR ADMINISTRATION LEADS TO BACTERIAL RESISTANCE?
Although antibiotics are given to treat infections, their improper use results in bacterial resistance. When an antibiotic attacks a group of bacteria, those cells highly vulnerable to the drug will die, but other cells resistant to the medicine will persist and continue to grow. The consequences of producing drug-resistant bacteria are potentially devastating because these strains can spread readily to the environment and to other patients. Hospitalised patients with compromised immune systems are most susceptible to these strains.
Antibiotics that inhibit the growth of a variety of different types of bacteria (broad-spectrum antibiotics) carry additional dangers. These drugs also eliminate benign bacteria that help protect us from disease by competing with and limiting the spread of pathogenic bacteria. Broad-spectrum antibiotic production can produce profound changes in the composition of a given bacterial population and provoke the outgrowth and invasion of antibiotic resistant strains called superinfections.

Reports of the improper administration of broad-spectrum antibiotics in neurosurgery date back to the 1970s.12 Resistant bacteria, resulting from the introduction of antibiotics, had already begun to rise in the 1950s and 1960s. Nevertheless, some surgeons, intent on sterilising the operative field and eliminating both benign and pathogenic bacteria, gave broad-spectrum drugs without any consideration as to whether they were appropriate to their particular hospitals. As a result, they produced superinfections in their patients. Faced with increasing rates of pneumonias, urinary tract infections, and seven deaths due to Klebsiella meningitis, the neurosurgical staff at one hospital discontinued the use of both prophylactic and therapeutic ampicillin and cloxacillin. Afterwards, there was an immediate reduction in postoperative infection.13 These surgeons practised procedures which, although well-intentioned, worsened the outcome of many of their patients.

The problem of resistance creates a potential moral conflict between the doctor’s responsibility to his or her patient and a possible responsibility to keep resistance in the general population at a minimum. The doctor’s role in treating the individual patient is to facilitate the patient’s control over his own body. The doctor’s responsibility to society derives from at least two different possible sources. First, the ideal of medicine as a profession is to serve the public health. Second, arguably, the doctor should give as much consideration to the welfare of future patients as to current patients. A patient who doesn’t know whether he will be treated now and benefit from antibiotic protection or treated later and be exposed to resistant bacteria would prefer that the doctor treat all patients in a way that minimises resistance in the community. Therefore, the fairest way to respect the wishes of all patients is to treat both present and future patients the same.

These conflicts are apparent in the use of prophylactic antibiotics and difficult to resolve. If a doctor produces superinfections with the use of antibiotics, he has failed in his ethical responsibility to his patient. If the doctor uses antibiotics irresponsibly and causes resistant bacteria in the hospital or the community at large, he has failed in his ethical responsibilities to society. Unfortunately, our present limited medical knowledge does not indicate which competing moral interests are being served or failed. Currently, we are not sure how likely it is that future patients are going to be harmed, we do not know the extent of bacterial resistance, and lastly we do not know which antibiotic regimes strike the most appropriate balance between efficacy and breeding resistance.

To minimise the promotion of resistance and superinfections, responsible doctors should first identify the causative agents of their postoperative infections and sample the pathogenic bacteria flourishing in the operating room. These drugs are to be managed in the operating room. They should then choose antibiotics active against those specific microbes rather than blindly administering unnecessary or inappropriate antibiotics. Unfortunately, surgeons do not always engage in ethical deliberations about using antibiotics and sometimes arbitrarily give these medications with no consideration as to whether they are suitable to the microbes of their hospitals. One study has shown that French surgeons inexplicably administer antibiotics that are ineffective against the pathogens growing in their operating rooms, while others misuse broad-spectrum drugs which are too powerful and unnecessary.14

Even the appropriate use of antibiotics over a prolonged period of time could potentially lead to bacterial resistance in the community in the future. Due to an increase in antibiotic resistant strains, microbiologists predict that an increasing number of antibiotics will lose their effectiveness over time. The rise of antibiotic resistant bacteria poses serious therapeutic difficulties. Certain variants of bacteria are already untreatable by every known antibiotic.10 Protecting the health of the individual patient, therefore, is not necessarily in the interests of a future society.

This conflict could potentially lead to a possible paradox—that is, using an antibiotic over many years may eventually lead to bacterial resistance at which point the antibiotic will no longer protect future patients. The decision to use antibiotics should partly rest upon the different level of certainties. (a) We know that antibiotics are effective against bacteria and can reduce the probability of developing a postoperative infection, the evidence for which is discussed later in this paper. (b) We are less certain about the definite development of bacterial resistance. Prior observations have demonstrated, however, that prolonged antibiotic use over years leads to resistance—for example, penicillin. If we are comparing (a) and (b), doctors might be more in favour of treating the patient because the magnitude of (b) is not well defined. However, this uncertainty emphasises the need for further studies. Surgeons who believe that preventing infection in individual patients is more important than the potential cost to the overall population11,15 should at the very least monitor their patients for any incipient resistance. If resistance develops, the doctor would have to switch to another antibiotic active against the bacteria in the operating room.

**SHOULD DOCTORS DISCUSS THE USE OF PROPHYLACTIC ANTIBIOTICS WITH THEIR PATIENTS AS PART OF INFORMED CONSENT?**

Like all drugs, antibiotics have side effects, including disturbances in body metabolism, specific organ toxicities, and allergic episodes varying in severity from mild skin rashes to fatal attacks of anaphylaxis. The risk of relevant, adverse reactions to a drug should always be taken into account when planning a programme of prophylaxis. Informed consent requires doctors to divulge this information. Even rare side effects which are very serious should also be disclosed.

Whatever regime a doctor recommends must be consented to in advance (except occasionally in an emergency) by the patient. The ethical principle of respect for autonomy dictates that a patient cannot be given any treatment unless they have consented to it. Informed consent is valid only when the consent is voluntarily given, the patient has been properly informed, and the patient is deemed competent to give consent. It must be noted that competent patients can refuse treatment that is not in their best interests and against the advice of their physicians. How much information should be given to the patient is not clear cut. In the case of prophylactic antibiotics for neurosurgery, however, it is our opinion that surgeons should give patients their view of the risks with and without the antibiotics and the risks and benefits of the particular antibiotics they plan to use. Similarly, if the surgeon knows that antibiotics will lessen the risk of infection for the patient but decides not to offer them to the patient he must explain his decision. In both cases unless he does so, the consent he needs cannot be regarded as being “informed”.

What if the patient refuses, for whatever reason, to accept the antibiotics the surgeon recommends? First, it is the patient’s absolute moral and legal right to refuse treatment. The surgeon is, however, both morally and legally entitled to refuse to operate on the patient. No doctor can be made to treat a patient if he does not wish to do so.

As part of informed consent, does a surgeon have a responsibility to inform the patient about the risks of promoting bacterial resistance to the community? It is doubtful that any
reason able patient would deny himself antibiotic protection in order to minimise resistance in the community. Nonetheless, involving patients in this discussion as part of obtaining their informed consent furthers the doctor's commitment to society. Educating patients one by one might help to generate a public awareness of antibiotic resistance.

CAN EMPIRICAL EVIDENCE OF EFFICACY ALONE JUSTIFY THE USE OF AN ANTIBIOTIC REGIMEN THAT SOME CONSIDER DANGEROUS AND THEREFORE UNWARRANTED?

In 1974, Dr Leonard Malis, the chief of the neurosurgical service at the Mount Sinai Hospital at that time chose a prophylactic programme of antibiotics based on a review of all the bacteria responsible for his postoperative wound infections over the previous five years. He used three different antibiotics and as a result essentially eliminated all primary postoperative infections over the next 20 years. The regimen consisted of two parenteral drugs, vancomycin and gentamicin, and one topical drug, streptomycin. Vancomycin is one of the most powerful antibiotics that can kill a group of bacteria called, Staphylococci, and is the only drug effective against one bacterial species called methicillin resistant Staphylococcus aureus (MRSA), a pathogen responsible for many hospital epidemics around the world. Malis chose gentamicin and streptomycin to cover the other types of bacteria sampled from his prior wound infections. After the first five years of infection-free operations, Malis was convinced of the programme’s efficacy, and was unwilling afterwards to contemplate altering this regimen due to the statistically expected wound infections that would occur. His seminal report in 1979 set a standard for other surgeons to achieve.

Malis, however, has come under sharp criticism by others for subjecting patients to a broad spectrum regimen which could breed bacterial strains resistant to vancomycin. Indeed, infectious disease personnel at other hospitals have prevented surgeons from using prophylactic vancomycin because such resistance would be a devastating challenge to eliminate. Malis eventually expected to find resistant strains and was performing a randomised control trial that would show which components of his regimen were crucial to his success and which were superfluous. For Malis, the choice was clear: it was between his responsibility to his patients and his moral obligation to society. He applied all existing knowledge for the best possible management of individual patients. He would not place them at risk by testing his regimen. Such data would have been helpful to future patients and society at large. Other surgeons have duplicated Malis’s success in eliminating postoperative infection over the past 20 years with their own cocktail of antibiotics suitable to the bacteria of their hospital operating suites. No drug toxicities or superinfections have been reported in their work. Nor has there been any willingness to risk a single patient in a controlled study to determine what aspects of their regimen are vital to their success.

While these doctors have been content with empirical results, a placebo-controlled, blinded, prospective study of the Malis regimen was conducted in 1984 at a different university hospital in the US. This study found an infection rate of 3.5% in the control group compared to 0.5% in the antibiotic group. Four out of 203 patients who received the Malis regimen had a transient, generalised rash and one developed subjective exacerbation of prior hearing loss and was diagnosed with a chronic ear infection unrelated to the surgery. Other hospitals in Mexico and Canada saw no need to perform their own controlled studies and have adopted the Malis regimen; they have apparently remained essentially infection free and have had no significant adverse reactions to the antibiotics. Other institutions have sought to compare the Malis regimen with less toxic antibiotic programmes. One study found no statistical difference in infection rates between patient groups receiving either a combination of vancomycin and gentamicin or cefotaxime. Unimpressed, Malis did not perform his own comparison trial.

ARE DOUBLE BLIND, PLACEBO CONTROLLED ANTIBIOTIC TRIALS ETHICALLY SUPPORTABLE?

The foregoing discussion demonstrates the importance of clinical trials to test the efficacy of antibiotics, given their potential to harm patients or produce resistant strains of bacteria. In neurosurgery, five prospective, double-blind studies were performed in the mid-1970s and the rest in the 1980s and early 1990s. According to a meta-analysis published in 1994, a sufficient number of placebo trials had
been conducted by 1988 at the end of four studies to support the efficacy of antibiotics. The subsequent four more blinded studies merely furnished additional evidence. The authors of the last reported 1991 study stated that previous controlled investigations had not included enough patients (fewer than 400), although it appears that these prior studies had sufficient power to detect significant differences between the antibiotic and control groups. This last trial included 711 patients and documented with a p <0.001 a 5.1% infection rate in the control group versus 0.3% in the antibiotic group. Out of the 32 patients in the control group who developed infection, two developed organ failure, went into coma, and died. Four more were severely disabled and the 26 others completely recovered or were slightly impaired. Among the 12 patients who received antibiotics and subsequently developed infection, one required reoperation to treat his infection but had no clinical sequela. No patients experienced adverse reactions from the antibiotic.

Based on the results of meta-analysis, we find it difficult to justify any further placebo studies. Withholding a procedure of proven efficacy clearly violates the doctor’s commitment to patient welfare unless there is good reason to do otherwise. If future investigations do include a placebo arm, the physician must discuss with his patients, as part of the informed consent process, why he feels such a study is necessary and how the results would help him determine the best way to handle the prevention of postoperative infections.

As new antibiotics become available, there will be a temptation to determine whether they will provide greater protection against infection compared to standard drugs. Indeed, a randomised controlled trial is the only acceptable method of establishing the efficacy of new drugs and minimising the use of ineffective ones. The allocation of patients to a control group consisting of standard antibiotic prophylaxis does not violate the principle of non-maleficence because they are receiving a procedure known to be protective. In any new investigation, however, it is important to assess the investigator’s intention. The aim of the research is to benefit future patients. Like all randomised studies, a full explanation of such a trial to all participating patients is mandatory. No activity should be undertaken within biomedical research which aims to increase knowledge without also serving to prevent, treat, or mitigate disease.

**SHOULD ANTIBIOTIC TRIALS COMPLETE THEIR STUDIES WHEN THEY ENCOUNTER EPIDEMICS AND PATIENTS BEGIN TO DIE?**

Two of the five placebo controlled studies, the first one in 1976, and the other in 1986, were terminated before completion due to an epidemic, that is, an increased rise in the infection rate that was traced to the control group. The first study made an ad hoc decision, the other was terminated by a formal stopping rule. In the three other completed studies, antibiotic prophylaxis was shown to be effective at the cost of several deaths. Bullock and colleagues recorded 12 infections in the control group leading to two deaths and one case of severe disability. Out of 197 patients receiving antibiotic, four developed consequential infections and none experienced an adverse reaction. In the 1990 study by Djindjian, nine infections in the control group resulted in two deaths and at least three other cases of severe morbidity while only one patient in the antibiotic group developed a self resolving infection and none of the antibiotic-treated patients developed drug side effects.

It may be argued by some that a clinical trial should run until completion or continue, despite morbidity and mortality, until a sufficient number of subjects have been included to detect a statistical significance between the control and treated groups, if such a difference really exists. Such practitioners would say that the disability or even loss of patients in the control arm of such trials is of course most unfortunate, but must be weighed against the greater number of lives that might be saved as a result of the new antibiotics. The greater good that such trials will generate in the long run is the ultimate goal that an investigator should strive to achieve. This philosophy justifies those studies that completed their investigations.

We are more inclined, however, to agree with surgeons who feel ethically mandated to carry out their obligations for patient welfare rather than adhere to scientific obligations to society overall. For the first study, Savitz and Malis discontinued their investigation because it was unacceptable to them not to investigate the epidemic. Once they determined that all except one of the infections were found in the control group, they were no longer in a state of equipoise as to whether or not to use prophylactic antibiotics, without performing statistical analysis. They concluded that patients unprotected by antibiotics were at an unacceptable risk of postoperative infection and decided that all patients admitted to the neurological service would from that point forward be given intraoperative antimicrobial agents. The other study in 1986 by Shapiro et al was forced to end the investigation after exceeding an institutionally imposed stopping boundary of infected placebo recipients. In the control group, six patients developed infections during the study and three more after the stopping order went into effect, compared to two patients in the antibiotic group. The stopping boundary ensured that only an excess of four placebo recipients became infected compared to the antibiotic recipients, but permitted the investigator to continue their study despite the outbreak of an epidemic, and to terminate the study upon collection of a sufficient sample of patients to detect a statistical difference between the two groups.

Similar issues have recently been discussed with respect to trials on breast cancer prevention. American investigators decided to halt a study early after they found a 45% reduction in the incidence of breast cancer among women who took Tamoxifen compared to placebo recipients. Other coinvestigators running parallel trials in Britain and Italy were appalled by the US decision to release their findings early because the studies were to be combined to address additional questions such as in which women the drug is most effective—balancing the benefits against the risks and for how long. Given the robust protection of Tamoxifen, the American investigators deemed any continuation of the study unethical because it denied placebo patients at risk for breast cancer a known preventive procedure.

**WHAT ARE THE ETHICAL ISSUES TO CONSIDER WHEN DECIDING NOT TO EMPLOY ANTIBIOTICS IF THE SCIENTIFIC LITERATURE SUPPORTS THEIR USE?**

Having addressed ethical concerns about testing antibiotics and their prophylactic applications in a responsible manner, we now raise one more problematic issue when surgeons choose not to use antimicrobial agents. Morley in 1976 posed the following unanswered question: If the wound infection rate in clean cases at a hospital is very low, is it wrong not to employ antibiotics? For example, should a neurosurgeon with a 1–2% rate of postoperative infection rest on his laurels or try to improve his performance with the use of antibiotic prophylaxis? Some neurosurgical authorities contend that antimicrobial agents can reduce an infection rate by one half and that with their routine use, an infection rate of less than one per cent can be achieved. Meta-analysis suggests that even with a very low infection rate, a regimen that does not include antibiotics may still benefit from the addition of prophylaxis. Furthermore, as previously stated, zero or nearly zero infection rates have been achieved utilising intraoperative antibiotics.
Given these facts, the question arises: why would a neurosurgeon choose not to use antibiotics? Because the baseline infection rate in neurosurgery is low compared to other surgical specialties, it is possible to attain very low infections rates without antibacterial agents. The percentage of infection in the absence of antibiotics varies in the literature from 1% to 15%. Indeed, surgeons with low infection rates often cite that Harvey Cushing, the father of American neurosurgery, achieved an infection rate of less than one per cent using only soap and water. If a surgeon who does not use antibiotics could cut in half his one per cent infection rate by resorting to antibiotics, the numbers needed to treat would be 200 patients. In other words, the surgeon would have to treat 200 patients before a single patient would derive any added benefit from the antibiotics. 

Opponents of prophylactic antibiotics argue that using these drugs instills a false sense of security among the operating team, promotes a deterioration in aseptic technique, and can lead to an abandonment of basic surgical principles. They feel that greater emphasis should be placed on wound care because antibiotics will not compensate for a lack of attention to surgical detail. Aware of the potentially harmful effects of antimicrobial drugs, including drug toxicities and the promotion of antibiotic resistance, these same surgeons are not persuaded by the empirical success or more solid scientific evidence of antibiotic prophylaxis. There are surgeons who question the conclusive nature of the existing prospective studies. One could argue that the antibiotic trials have several limitations. First, postoperative infection is not a continuous variable; it can vary with respect to causative organisms and location. Second, many different antibiotics with varying dosages have been tested. Third, most antibiotic studies do not distinguish among the different types of neurosurgery. Thus, it could be argued that the results of these trials cannot be generalised to overall neurosurgical practice.

Another important issue is cost effectiveness. Although the costs of antibiotics are relatively low per patient, the application of such a procedure to all neurosurgical operations could generate costs of a million dollars or more. Prevention has always been advocated as the best way to contain the costs of health care, but treatment may be more cost-effective. For example, if a surgeon has a 4% infection rate without antibiotics, he derives no enhanced protection for 96 out of 100 of his patients when money is spent on the use of these drugs. Since the four patients who acquire an infection can still be treated, the outcome may be that only one out of four develops morbidity or dies per year. Is the loss of one life worth the investment? Should society spend large amounts of money to save four per cent of the patient population? On the other hand, the report by Shapiro et al showed a net saving of tens of dollars per patient receiving prophylaxis. One study cannot, however, be extrapolated to the generalised practice of neurosurgery.

Given an extensive literature on the efficacy of prophylactic antibiotics, a doctor has an obligation to consider using them. This decision should be based on whether the doctor will have fewer cases of morbidity and mortality as a result of a postoperative infection. At hospitals where the infection rate is very low and the majority of infections are treatable, there may not be justification if such a decision increases the likelihood of generating resistant strains. It is, however, unacceptable for some doctors to risk even a few infections in one year given the consequences, which include severe disability or death. We feel that neurosurgeons whose infection rate exceeds the overall national average of two to three per cent are morally obligated to reassess their routine of sterile technique and consider prophylactic antibiotics.

Whatever opinions doctors may hold about the correct prophylactic programme, informed consent should include a discussion and understanding of the potential risk of infection with or without antibiotics. It is accepted procedure for surgeons to inform patients that the major complications of surgery are infection, haemorrhage, paralysis, and death. In addition, the surgeon who uses antibiotics should disclose the risks of toxicities and adverse reactions. As Dr Weinstein wrote back in 1955, the risk of the development of reactions and the difficulties which they involve must always be taken into consideration in planning a programme of chemoprophylaxis. In cases where the effectiveness of prophylaxis is questionable, the situation must be carefully scrutinised before treatment is started and the benefits to be derived must be weighed against the possible dangers. This requires doctors to take it upon themselves to read the scientific literature. How can they make ethically correct decisions without having done so? Patients are capable of grasping the terms of postoperative infection, but may not understand some technical details or the differential relevance of certain data, including statistical evaluations of levels of risk.

CONCLUSION

Surgeons intent on administering antibiotic prophylaxis must carefully weigh the benefits—for example, protection against postoperative wound infection—against the costs, including drug side effects, and against superinfections. Given the rise in antibiotic resistance, physicians have a societal responsibility to use antibiotics in an appropriate manner, always using drugs active against specific microbial organisms known to have caused infections in previous operations. The predominance of studies in neurosurgery demonstrating efficacy of prophylactic antibiotics indicates that further testing of this procedure against placebo controls is unethical. It may, however, be necessary and ethical to conduct trials comparing different antibiotic regimens. While neurosurgeons have no moral obligation to use antibiotics, they are required to evaluate their aseptic techniques to provide the best protection that is suitable and appropriate for each of their patients. The cost-effectiveness of prevention versus treatment of infection should be further explored both in neurosurgery and in other surgical subspecialties.

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