Use and abuse of antibiotics

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By Steven G. Morrow, USA

For the past 90 years, antibacterial therapy has played a major role in the treatment of bacterial infectious diseases. Since the discovery of penicillin in 1928 by Fleming and sulfa antibiotics in 1934 by Domagk, the entire world has been able to benefit from the greatest medical advancements in history. The discovery of safe, synthetically produced antibiotics has been a major factor in the control of infectious diseases and, as such, has increased life expectancy and the quality of life for millions of people.

According to the Centers for Disease Control and Prevention, life expectancy of individuals in the United States born in 1900 was 47 years, while those born in 2005 is projected to live 78 years. At the beginning of the 20th century, the infant (< 1 year) mortality rate in the United States was 160/1,000 live births compared to 6.7/1,000 in 2000. The major reason for these decreases in mortality has been the ability to control infectious diseases.

Development of antibacterial drug resistance

Along with the dramatic benefits of systemic antibiotics, there has also been an explosion in the number of bacteria that have become resistant to a variety of these drugs. The problem is not the antibiotics themselves. They remain one of medicine’s most potent weapons against diseases. Instead, the problem is in the way the drugs are used. The inappropriate use of antibiotics has resulted in a crisis situation due to bacterial mutations developing resistant strains.

Many worldwide strains of Staphylococcus aureus exhibit resistance to all medically important antibacterial drugs, including penicillin, methicillin, and methicillin-resistant S. aureus has become one of the most frequent nosocomial, or hospital-acquired, pathogens. The rate at which bacteria develop resistance to antibacterial drugs is alarming, demonstrating resistance soon after new drugs have been introduced. This rapid development of resistance contributed significantly to the morbidity and mortality of infectious diseases.

A nosocomial infection is a hospital-acquired infection that develops in a patient after admission. It is usually defined as an infection that is identified at least 48 to 72 hours following admission, so infections inciting, but not clinically apparent at admission, are excluded. Nosocomial infections are costly, resulting in increased morbidity, requiring longer periods of hospitalization and limiting access of other patients to hospital resources. The direct costs of hospital-acquired infections in the United States are estimated to be $4.5 billion per year.

Nosocomial infections also contribute to the emergence and dissemination of antimicrobial-resistant organisms. Antimicrobial therapy has played a significant role in increasing the emergence of more resistant organisms. Patients with infections caused by antimicrobial-resistant organisms are then a source of infection for hospital staff and other hospitalized patients. These drug-resistant infections may subsequently spread to the community.

The British Society for Antimicrobial Chemotherapy published a review in the Journal of Antimicrobial Chemotherapy. This review examined the contributions of antibacterial prescribing by general dentists in the United Kingdom and has made the following recommendations to the profession: “Antibiotic resistance in bacteria of the oral flora. The review concluded that inappropriate antibacterial drug prescribing by dental practitioners contributes significantly to the selection and spread of drug-resistant bacterial strains. The American Dental Association reported the results of a survey of antibacterial use in dentistry in the November 2000 Journal of the American Dental Association. The authors surveyed all licensed dentists practicing in Canada and found that confusion about prescribing antibiotics and inappropriate prescribing practices were evident, and that inappropriate antibacterial use, such as improper dosing, duration of therapy and prophylaxis are all factors that may affect development of antibiotic-resistant microorganisms.

There is a glimmer of hope. A report from Aker University in Oslo, Norway, strongly suggests that bacterial resistance to antibacterial agents can be reversed. While dangerous and contagious staph infections kill thousands of patients in the most sophisticated hospitals in Europe, North America and Asia, there is virtually no sign of this "killer superbug" in Norway. The reason? Norway stopped using so many antibiotics.

"We don't throw antibiotics at every person with a fever. We tell them to hang on, wait and see, and we give them a Tyle-nol to feel better," said Dr. John Haug, infectious disease specialist at Aker University Hospital. In Norway's simple solution, there is a glimmer of hope.

The proper clinical use of antibiotic drugs

In 1997, the ADA Council on Scientific Affairs issued a position statement on Antibiotic Use in Dentistry. The council's position statement further identified that "Antibiotics are properly employed only for the management of active infectious disease or the prevention of metastatic infection, such as infective endocarditis, in medically high-risk patients." One method of education is to teach from errors rather than principles. Psychologists from the University of Exeter have identified an "early warning signal" in the brain that helps us avoid repeating previous mistakes. Published in the Journal of Cognitive Neuroscience, their research identifies for the first time, a mechanism in the brain that reacts, in just one-tenth of a second, to things that have failed in us making errors in the past. Evaluating the following eight misconceptions or "myths" may help to establish general guidelines to aid us in making clinical decisions regarding the use of antibiotic therapy, thereby leading to optimal use and therapeutic success.

Myth No. 1: Antibiotics cure patients. Except in patients with a compromised immune system, antibiotics are not curative, but instead function to assist in the re-establishment of the proper balance between the host's defenses (immune and inflammatory) and the invasive agent(s). Antibiotics do not cure patients; patients cure themselves.

Myth No. 2: Antibiotics are substitutes for surgical intervention. Very seldom are antibiotics an appropriate substitute for removal of the source of the infection (extraction, endodontic treatment, infection and drainage, periodontal scaling and root planing). Occasionally, when the infection is too diffuse or disseminated to identify a nidus for incision, or the clinical situation does not allow for immediate curative treatment, the prudent dentist will choose to place the patient on appropriate antibacterial therapy until such time as curative treatment can be implemented. It is imperative to remove the cause of the infection prior to, or concomitantly with, antibacterial therapy, when the cause is readily identifiable. Whenver antibiotic therapy is used, the risk of bacterial selection for antibiotic resistance is present.

Myth No. 3: The most important decision is which antibiotic to use. To avoid the deleterious effects of needless antibiotics on the patient and the environment, the most important initial decision is not which antibiotic to prescribe but whether to use one at all. It has been estimated that up to 60 percent of human infections resolve by host defenses alone following removal of the source of the infection without antibiotic intervention. Endodontic disease is infectious. Microorganisms cause virtually all pathoses of the pulp and periapical tissues. There is ample evidence to support that opportunistic normal oral microflora colonize in a symbiotic relationship with the host, resulting in endodontic infections. The majority of endodontic infections are systemic antibiotic therapy when the cause of the infection

Table 1. (Table Provided by American Association of Endodontists)

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<th>Primary Reasons for Revision of Infective Endocarditis Guidelines</th>
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<td>1. IE is much more likely to result from frequent exposure to random bacteremias associated with daily activities than from bacteremias caused by a dental, GI tract or GU tract procedure.</td>
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<td>2. Prophylaxis may prevent an exceedingly small number of cases of IE, if any, in individuals who undergo a dental, GI tract or GU tract procedure.</td>
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<td>3. The risk of antibiotic-associated adverse events exceeds the benefit, if any, from prophylactic antibiotic therapy.</td>
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<td>4. Maintenance of optimal oral health and hygiene may reduce the incidence of bacteremia from daily activities and is more important than prophylactic antibiotics for a dental procedure to reduce the risk of IE.</td>
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Fig. 1. Asymptomatic aortic valve endocarditis. Source: Provided by American Association of Endodontists.

Fig. 2. Chronic apical abscess. Source: Provided by American Association of Endodontists.

Fig. 3. Acute apical abscess with intracanal localization. Source: Provided by American Association of Endodontists.
Medical Conditions for Which Endocarditis Prophylaxis is Recommended:

Premedication is recommended ONLY for patients with the following conditions associated with the highest risk of adverse outcomes from endocarditis:

1. Prosthetic cardiac/heart valve.
2. History of IE.
3. Cardiac transplant recipients.
4. Asymptomatic apical periodontitis. This usually presents with a chronic abscess or with diffuse facial cellulitis. However, when the patient presents with a diffuse facial swelling (cellulitis) resulting from an acute apical abscess or an infection with systemic involvement (fever or malaise) (Fig. 4), debridement of the pulp space with placement of calcium hydroxide, surgical incision for drainage, and systemic antibiotics is recommended.
5. Special situations and circumstances:
   - Patients already receiving antibiotics—Occasionally, a patient may be receiving an antibiotic when a dental appointment is scheduled. The antibiotic should be continued at least 30 minutes after the dental procedure.
   - Failure to administer pretreatment antibiotic dose—If the patient is not taking an antibiotic normally used for endocarditis prophylaxis, the antibiotic should be administered 30 minutes before the dental procedure.
   - Individuals with kidney dialysis shunts—Individuals with permanent kidney dialysis shunts should be placed on prophylactic antibiotics using the same protocol as for IE.

Table 2. (Tables/Provided by American Association of Endodontists)

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Myth No. 5: Multiple antibiotics are superior to a single antibiotic. It is often assumed that a combination of antibiotics is superior to a single antibiotic. However, the benefits of using a combination of antibiotics are not yet clear. When comparing the benefits of using a combination of antibiotics versus a single antibiotic, it is essential to consider the potential side effects and the cost of each antibiotic. In general, using a single antibiotic is recommended to reduce the risk of antibiotic resistance.

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Myth No. 4: Antibiotics increase the host's defense to infection. The increased prevalence in organ and tissue transplants, resulting in patients with compromised immune systems, has heightened the interest in the potential effects of antimicrobial drugs on the host's resistance to infection. In vitro and in vitro studies are highly variable and sometimes contradictory. However, the following considerations appear valid: 1) Antibiotics that can penetrate into the mammalian cell (erythromycin, tetracycline, clindamycin and metronidazole) are more likely to affect the host defenses than those that cannot (beta-lactams). 2) Tetracyclines may suppress white cell chemotaxis. 3) Most antibiotics (except tetracyclines) do not depress phagocytosis; and 4) T- and B-lymphocyte transformation may be depressed by tetracyclines. The greatest potential harm to the host defenses may result from antibiotics that easily penetrate into the mammalian cell and the least harm is observed with bactericidal, non-nurturing agents (penicillins and cephalosporins).

Fig. 4. Acute apical abscess with extrudal diffuse facial cellulitis.
bined antibiotic therapy results in a greater selective pressure on the microbial population to develop resistance. The greater the antibiotic spectrum of the antimicrobials used, the greater the risk of emergence of drug-resistant microorganisms that develop, and the more difficult it is to treat a resulting superinfection. The primary clinical indication for combined antimicrobial therapy is a severe microbial infection in which the offending organism(s) is unknown and more than one microorganism may ensue if antibiotic therapy is not instituted immediately before culture and sensitivity tests are available.3

Myth No. 6: Bactericidal agents are always superior to bacteriostatic agents. Bacteriostatic agents are required for patients with impaired host defenses.4 However, bacteriostatic agents are usually satisfactory when the host’s defenses against infections are unimpaired. Postoperative suture removal (in selected circumstances that may create significant bleeding) should be used whenever the host’s defense against infections is impaired.5

Myth No. 7: Antibiotic dosages, dosing intervals and duration of therapy are established for most infections. After more than 90 years of antibiotic usage, the proper dosages, dosing intervals and duration of therapy are essentially unknown for most specific infections.6,7 Infectious diseases are associated with a high number of variables that affect treatment outcome (microbial characteristics and drug sensitivity, diversity resistance mechanisms, tissue barriers to antibiotic diffusion, and the integrity and activity of the host’s defense mechanisms). However, basic principles are available to guide the dental health care provider in establishing proper dosages, dosing intervals and duration of therapy once the microbial pathogen(s) is/are suspected or identified and a rational choice of antimicrobial agent is made.

The following principles of antibiotic dosing are adapted from Dr. Thomas J. Pallaschke.8

1. The current recommendation is to employ an antimicrobial on the basis of an infection with a single drug dosage for as short a period of time as the clinical situation permits. The major factor in the clinical success of most antimicrobial agents is the height of the serum concentration of the drug and the resulting amount of the antibiotic in the infected tissue(s). Also important to expose the host to the antimicrobial agent for as short a duration of therapy as possible is the incidence of antimicrobial toxicity and/or allergy, and a reduced risk of developing resistant microorganisms.

2. The goal of antibiotic dosing is to achieve drug levels in the infected tissue equal to or exceeding the minimal inhibitory concentration of the target organism. Serum levels of antibiotics do not necessarily reflect those in tissues. Blood concentrations of the antibiotic should exceed the MIC by a factor of two to eight times in order to offset the tissue barriers that restrict access of the drug to the infected site. 3. It is advisable to initiate antibiotic therapy with a loading dose (an initial dose higher than the maintenance dose). An antibiotic loading dose should be used whenever the half-life of the drug is longer than three hours or whenever a delay of 12 hours or longer to achieve a therapeutic blood level is expected. Most antibiotic dosages used in the treatment of oral infections have a half-life shorter than three hours, but, due to their acute nature, most or oral infections require therapeutic drug blood levels sooner than 12 hours. Steady-state blood levels of any drug are usually achieved in a time equal to three to five times the drug’s half-life. Amoxicillin has a half-life of one to one-and-a-half hours. A steady-state blood level would then be achieved in three to seven-and-a-half hours, thereby leading to a substantial overlap in the peak and trough levels of achieving therapeutic antibiotic blood levels. A loading dose of two times the maintenance dose is recommended for acute oral infections, which better achieves the goal of rapid, high blood levels rather than initiating therapy with the maintenance dose. Prolonged therapy should ideally be administered at dosing intervals of three to four times the serum dosing intervals, if steady-state blood levels are desired (as may be indicated with penicillin). For example, the serum half-life of Pen-V-K is 0.75 hours. Higher continuous blood levels of this antibiotic are more likely to be obtained with four-hour rather than six-hour dosing intervals.

4. The shorter the half-life of the drug, the shorter the dosing interval will need to be in order to maintain continuous therapeutic blood levels of the drug. When determining the appropriate dosing interval, it is also important to consider the following: 1) the postantibiotic effects of the drug; and 2) the relative merits of continuous or pulse dosing. PAEs are more persistent (two to seven hours) with antibiotics that act intracellularly within the microbial cytoplasm (erythromycin, clindamycin and tetracycline) or by suppression of nucleic acid synthesis (metronidazole, quinolones). As a result, these antibiotics are more effective with pulse dosing (high antibiotic dosing at widely spaced intervals). The beta-lactam antibiotics, however, have a slow, time-dependent killing activity and demonstrate very little PAE. Beta-lactam microbial killing requires microbiostatic agents (in whom the process of cell division (interference with cell wall development); hence, they must be continuously present (steady-state blood levels) because bacteria divide at different rates.

Myth No. 8: Bacterial infections require a “complete course” of antibiotic therapy. There is no such thing as a “complete course” of antibiotic therapy. The only guide for determining the effectiveness of antibiotic therapy and whether the duration of treatment is the clinical improvement of the patient.9 A common misconception asserts that prolonged (after clinical remission of the disease) antibiotic therapy is necessary to prevent “rebound” infections from occurring. Orofacial infections do not persist for the duration of antibiotic therapy and should ideally be administered at dosing intervals of three to four times its serum dosing intervals, if steady-state blood levels are desired (as may be indicated with penicillin). For example, the serum half-life of Pen-V-K is 0.75 hours. Higher continuous blood levels of this antibiotic are more likely to be obtained with four-hour rather than six-hour dosing intervals. The shorter the half-life of the drug, the shorter the dosing interval will need to be in order to maintain continuous therapeutic blood levels of the drug. When determining the appropriate dosing interval, it is also important to consider the following: 1) the postantibiotic effects of the drug; and 2) the relative merits of continuous or pulse dosing. PAEs are more persistent (two to seven hours) with antibiotics that act intracellularly within the microbial cytoplasm (erythromycin, clindamycin and tetracycline) or by suppression of nucleic acid synthesis (metronidazole, quinolones). As a result, these antibiotics are more effective with pulse dosing (high antibiotic dosing at widely spaced intervals). The beta-lactam antibiotics, however, have a slow, time-dependent killing activity and demonstrate very little PAE. Beta-lactam microbial killing requires microbiostatic agents (in whom the process of cell division (interference with cell wall development); hence, they must be continuously present (steady-state blood levels) because bacteria divide at different rates.

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risk of adverse outcomes from IE, and who would derive the greatest benefit from prevention. Some of the most frequently reported cardiac conditions associated with the highest risk of adverse outcomes in patients undergoing dental procedures for some dental practices is reasonable, even though we acknowledge that this effectiveness is unknown.**18**

Therefore, the 2007 AHA guidelines for dental prophylaxis should be considered for patients presenting for dental treatment identified in Table 2, and who are undergoing any dental procedures involving the gingival tissues or periapical region of a tooth and for that group of patients that are in the oral mucosa. This would include procedures such as biopsies, suture removal, placement of orthodontic bands, and intra- and extraneous local anesthetic injections, but it does not include routine local anesthetic injections through noninfected tissue (Table 5).

### Antibiotic prophylaxis for patients with prosthetic joint infection

In 1997, the ADA and the American Association of Orthopedic Surgeons convened an expert panel of dentists, orthopedic surgeons, dentists, oral medicine specialists and published an Advisory Statement on Antibiotic Prophylaxis in the Treatment of Patients with Prosthetic Joints. In a 2003 advisory statement included several updates and modifications of patients at potential risk and the stratification of harmed tissues [Table 4]. While bacteremias can cause hematogenous total joint infection (Table 5).

While bacteremias can cause hematogenous seeding of total joint implants, it is likely that more oral bacteraemias are spontaneously induced by routine daily times that are dental treatments. Patients who have undergone total joint arthroplasty should be encouraged to perform effective daily oral hygiene procedures in order to maintain good oral health and to preserve function. Patients are at much higher in a mouth with chronic inflammation than one that is healthy and well maintained.

Occasionally, a patient with a total joint prostheses may present for dental treatment with a record of antibiotic prophylaxis from his or her physician that is inconsistent with the current guidelines. In these situations, the dentist is encouraged to consult with the patient’s physician to discuss the need for dental treatment, to review the current guidelines regarding antibiotic prophylaxis and to determine if there are any special considerations that might affect the physician’s decision regarding antibiotic prophylaxis for the patient. After this consultation, the dentist should follow the physician’s recommendation or, if in his or her professional judgment rely on mutual communication between patient, physician, dentist and other healthcare practitioners.**19** In 2014, a panel of experts convened by the American Dental Association Council on Scientific Affairs developed an evidence-based clinical practice guideline on the use of prophylactic antibiotics in patients with prosthetic joints undergoing dental procedures. This clinical practice guideline included the recommendations of the American Dental Association in January 2015 and continued the following recommendation:

> “In general, for patients with prosthetic joint implants, prophylactic antibiotics are not recommended prior to dental procedures except in special circumstances. They should be obtained from his or her patient based on the dentist’s professional judgment.”

In February 2000, the AAO published an information statement in which they recommended “that clinicians consider antibiotic prophylaxis for patients with prosthetic joints prior to any invasive procedure that may cause bacteremias.” In response to this statement, the American Academy of Oral Medicine published a position statement in June 2010 edition of the Journal of the American Dental Association.**20**

The authors of the AAMOS position statement reviewed the available literature on the subject as it relates to the AAO 2000 statement and concluded: “The risk of patients experiencing drug reactions and the cost of antibiotic medications alone do not justify the practice of antibiotic prophylaxis in all patients with prosthetic joints.” The authors called for a multifaceted, multidisciplinary, systematic review of the literature relating to antibiotic prophylaxis in patients with prosthetic joints. In the meantime, they concluded that the new AAO 2000 information statement should not replace the 2005 joint consensus statement.**21**

In December 2012, a panel of experts representing the American Academy of Orthopedic Surgeons and the American Association of Oral Medicine conducted a systematic review and clinical practice guideline, titled “Prevention of Orthopaedic Implant Infection in Patients Undergoing Dental Procedures: Evidence-based Guideline and Evidence Report.”**22** In this report the following contained the three recommendations:

> “The practitioner might consider discontinuing the practice of routinely prescribing prophylactic antibiotics for patients with hip and knee prosthetic joint implants undergoing dental procedures.”

> “We are unable to recommend for or against the use of topical oral antimicrobials in patients with prosthetic joint implants or other orthopedic implants undergoing dental procedures.”

> “In the absence of reliable evidence linking poor oral health to prosthetic joint infection, it is the opinion of the work group that patients with prosthetic joint implants undergoing dental procedures maintain appropriate oral hygiene.”

The report also stated that the above recommendations are “not intended to stand alone. Treatment decisions should be made in light of all circumstances presented for the patient. Treatments and procedures applicable to the individual patient rely on mutual communication between patient, physician, dentist and other healthcare practitioners.”


Having taught future oral healthcare professionals at Loma Linda University School of Dentistry since 1965, Steven Moses, DDS, MS, currently serves as a professor in the department of endodontics that he chaired from 1987 to 1990.

He maintains responsibilities he accepted in 2008 as director of patient care services and clinical quality assurance. He was director, District VI, of the American Association of Endodontists from 1994 to 2001, and he has also served as president of the Southern California Academy of Endodontists and as president of the California State Board of Dentistry. In 1987, he earned diplomate status from the American Board of Endodontics. Since 1988, he has been a fellow of the American College of Dentists; and since 2003, he has served on the editorial review board of the Journal of Endodontics. He is a fellow of the American Dental Association, the College of Endodontists and the California State Association of Endodontists. In 2002, he completed his second term as a member of the Dental Board of California.