How Can We As Dentists Minimize Our Contribution to the Problem of Antibiotic Resistance?

Drew B. Havard, DMD, J. Michael Ray, DDS*

The discovery of antibiotics in the early 20th century was not only a turning point in medicine, but in human history as well. A serious consequence of the use of these lifesaving and wondrous medicines, appropriate or otherwise, has been the development of resistance. Bacterial resistance to antibiotics is multifactorial. In medicine, antibiotic resistance has been attributed to long-term and repetitive use of broad-spectrum antibiotics. Some resistance occurs intrinsically, but much of the blame is attributable to decades of use by medical practitioners, nontherapeutic use in agriculture, and careless disposal of waste by the pharmaceutical industry as a whole.

The first discovered antimicrobial family, the sulfonamides, were reported and became available for commercial use in 1937. Penicillin became mass-produced in the 1940s and available to the American public in the 1950s without a prescription and was widely used to treat a wide array of infections and other maladies. But only a few years after the discovery of antibiotics, resistance to these drugs and their mechanism of resistance were reported. Mutant strains of Mycobacterium tuberculosis were identified shortly after streptomycin was introduced in 1944 that were resistant to the therapeutic levels used to treat tuberculosis. Over the next several decades, the discovery of new antimicrobial agents was soon followed by the discovery of resistant organisms. This problem has proved to be unrelenting and a constant source of frustration for researchers, health care providers, and patients alike.

Ingestion of food animals treated with prophylactic or therapeutic dosings of antibiotics may add to the problem of antibiotic exposure and eventual resistance in humans. Although the agriculture and animal husbandry industry uses massive amounts of antibiotics, the actual quantity is difficult to assess and compare. The most recent data reported by the Food and Drug Administration (FDA) on the quantity of antibiotics sold and distributed in the United States for food production are listed in Table 1. The FDA estimates that more than 13 million kilograms of antibiotics (nearly 29 million pounds) were sold and distributed for animal use in food production. In comparison of these data with a recent estimate of antibiotic use in humans of approximately 3 million pounds annually in the United States, one can loosely extrapolate that the agricultural industry may use upwards of 90% of all antibiotics distributed in the United States. The relative proportion of antibiotic use in humans and animals is illustrated in Fig. 1. The use of antibiotics in such massive quantities has undoubtedly contributed to resistant bacteria in chickens, swine, and cattle, but the impact of this on humans has been difficult to assess and compare.
Food poisoning caused by fluoroquinolone-resistant Campylobacter jejuni has been reported and extensively analyzed. The FDA has reported that about 8000 to 10,000 persons per year are infected by fluoroquinolone-resistant C. jejuni from chicken. Even more disturbing is that the same resistant strains responsible for infections in humans were found in the raw meat of chicken. Even when food animals are not therapeutically treated with antibiotics for infections, antibiotics enter the food environment through the animals’ food and water sources, thus providing another means of passing antibiotics and potentially resistant bacteria to humans. The extensive use of nontherapeutic (prophylactic) antibiotics in animal agriculture in food animals, to compensate for infections related to unsanitary conditions and to synthetic feeds designed to accelerate muscle growth, causes contamination of environmental water supplies and the entire food chain. This “cycle” of contamination of the environment with trace antibiotics and resistant bacteria is illustrated in Fig. 2.

It is difficult to estimate the amount of antibiotic compounds released into the environment in the form of manufacturing waste products, but the quantity is likely in the many millions of metric tons. Many of these noxious compounds are resistant to biodegradation and therefore accumulate in soil, rivers, and reservoirs. One of the most shocking examples of this are the results from water samples taken near a major pharmaceutical manufacturing plant in Hyderabad, India, in 2009. Lakes nearby not known to be contaminated by the plant’s effluent demonstrated concentrations...
of ciprofloxacin of up to 6.5 mg/L. This alarmingly high concentration suggests the plant’s effluent alone is not responsible for such contamination and that other sources are contributing. Although this may seem an extreme example, similar stories are probably untold throughout the world.

Antibiotic resistance occurs by both intrinsic defenses and by genetic mutation in bacteria. The mutations happen both spontaneously and as a result of horizontal gene transfer. Planktonic bacteria typically acquire resistance in 1 of 4 ways: (1) alteration of a drug’s target site, (2) inability of a drug to reach target site, (3) inactivation of an antimicrobial agent, or (4) active elimination of an antibiotic from the cell. Gene transfer via plasmids results in a change of the microbe’s DNA, and the resistant genes are passed to subsequent generations.

It is important to understand that infections of the oral cavity are not caused by planktonic, or “free-floating,” bacteria. Rather, all infections encountered in the practice of dentistry are caused by bacteria that live and flourish in a biofilm. A biofilm is a highly organized community of a multitude of bacterial species that are surrounded and protected by an exopolysaccharide produced by the resident bacteria. Bacteria that began as free-floating bacteria come in contact with a surface and become adherent. Immediately, these newly attached bacteria begin laying down an exopolymeric matrix that provides additional surface area for the attachment of other bacteria and provide a means of trapping nutrients. Within the biofilm lie water channels that allow for the flow of nutrients and for the elimination of waste products.

Bacteria in a biofilm are uniquely resistant to conventional antibiotics even beyond the mechanisms of antibiotic resistance discussed previously. Bacteria communicate with each other via numerous complex mechanisms, including quorum sensing, a complex method of alteration of gene expression and gene transfer even among different species of bacteria and nanowiring involving electrically conductive pili used for long-range electrical and energy transfer. The exopolysaccharide may also provide a resistant barrier to some antibiotics.

The spread of biofilm bacteria occurs by 3 means: expansion of bacteria within the biofilm, detachment of bacterial “clumps,” or shear from environmental flow forces. Even as the bacteria may once again become planktonic before they reattach, they retain the biofilm-specific resistance genes and gene expression acquired as a part of the biofilm. Therefore, the now planktonic bacteria still possess the same enhanced antibiotic resistance as the parent biofilm and are not susceptible to conventional antibiotics.

An example of a biofilm in the oral cavity is dental plaque. More than 700 bacterial species comprise what we know as “normal oral flora.” As most of these bacteria exist as biofilms, they are resistant to antibiotics, as described previously.

Fig. 2. Interaction of antibiotics, bacteria, food animals, humans, and the environment. (From Witte W. Medical consequences of antibiotic use in agriculture. Science 1998;279:996–7; with permission.)
In early odontogenic infections, facultative streptococci and anaerobes are most frequently involved, and the specific species have been well-documented. Penicillins are used most often in these infections, as they offer excellent coverage over the susceptible streptococci and other aerobic species involved. As the infection progresses, anaerobes predominate and the effectiveness of penicillin alone is reduced. Adding metronidazole or changing to clindamycin is recommended for better anaerobic coverage. Clindamycin is especially useful for treating odontogenic infections for its excellent bone and abscess penetration and is the preferred antibiotic if the patient is penicillin allergic. If the patient is not responding to complete removal of the infective source, appropriate incision and drainage and empiric antibiotic therapy, then culture and sensitivity testing may provide additional insight into the infective organisms and necessitate an alteration in antibiotic therapy.

Recent international studies have shown that, on average, dentists write at least 2 to 3 prescriptions for antibiotics per week. These studies have examined multiple aspects of antibiotic use, including specific drug prescribed, reason for prescribing, and duration of antibiotic therapy. In each of these studies, reasons such as patient demands and lack of updated knowledge of the prescriber have influenced the practitioners’ decisions to prescribe antibiotics at least as much as the patients’ clinical diagnosis. The results also demonstrated a wide array of prescribing practices with regard to clinical indications, choice of antibiotic, and length of therapy. With regard to duration of therapy, one survey found that the average prescribed course of antibiotics is just fewer than 7 days. An American study showed that endodontists average 8 days for an antibiotic regimen.

Prophylactic administration of oral antibiotics may be indicated in some cases, but the data and literature to support their use are inconsistent. Many recent studies have demonstrated that neither preoperative nor postoperative prophylactic administration of antibiotics has shown any statistically significant benefit with regard to surgical site infection or alveolar osteitis over patients who did not receive antibiotic prophylaxis. However, some recent studies have demonstrated a decrease in surgical site infections and pain with prophylactic preoperative administration of antibiotics. This argument has continued for decades and likely will persist, given the numerous conflicting reports available. Prophylaxis for patients with certain cardiac conditions and with total-joint prostheses may require antibiotic prophylaxis before some dental procedures. The American Dental Association, American Heart Association, and American Academy of Orthopedic Surgeons have updated their recommendations on the need for prophylaxis based on recent research. Even still, the data that support these practices are also controversial, and clinicians are advised to use their best judgment in the given clinical situation.

Prophylactic antibiotics may be indicated in treatment of the immunocompromised patient as well. Patients with poorly controlled diabetes, chronic steroid users, and patients with immune-deficiency diseases (eg, HIV+) may benefit from preoperative antibiotic prophylaxis before surgical procedures. But as mentioned before, preoperative antibiotic prophylaxis in other patients is not supported by current literature.

Pain experienced from pulpitis, periodontitis, alveolar osteitis, or peri-implantitis is not an indication for antibiotics. The antibiotics may serve to decrease local inflammation caused by surface biofilm bacteria and, therefore, reduce the patient’s symptoms. These patients require mechanical or surgical intervention in the form of caries control, extractions, root canal therapy, scaling, and root planing, for example, and not systemic antibiotics. Patients presenting with cellulitis or abscess involving fascial planes may benefit from systemic antibiotics, however. In these circumstances, antibiotics serve as an adjunctive measure to surgical or mechanical removal of the infective source that may prevent the hematogenous or local spread of the infective bacteria. These recommendations are summarized in Table 2.

Although circumstances exist when systemic antibiotics are indicated, proactive local measures are usually sufficient in treating bacterial infections.

Table 2
Recommended treatment of common oral conditions

<table>
<thead>
<tr>
<th>Operative Intervention</th>
<th>Antibiotics with Operative Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reversible pulpitis</td>
<td>Lateral periodontal abscess</td>
</tr>
<tr>
<td>Irreversible pulpitis</td>
<td>Pericoronitis</td>
</tr>
<tr>
<td>Periodontal periodontitis</td>
<td>Fascial space infection (cellulitis/abscess)</td>
</tr>
<tr>
<td>Alveolar osteitis</td>
<td>Osteomyelitis</td>
</tr>
<tr>
<td>Gingivitis</td>
<td>Bisphosphonate-related osteonecrosis of the jaws</td>
</tr>
<tr>
<td>Chronic periodontitis</td>
<td>Peri-implantitis</td>
</tr>
</tbody>
</table>
of the oral cavity before antibiotics are truly indicated. Strict adherence to universal precautions and sterile technique when applicable may help prevent disease transmission as well. As dentists, we can do little to limit the use of antibiotics in agriculture or regulate dumping of antibiotic manufacturing by-products into the environment. But we can strive to practice responsible, evidence-based medicine and dentistry.

REFERENCES

3. Summary report on antimicrobials sold or distributed for use in food producing animals. Silver Spring (MD): Food and Drug Administration, Department of Health and Human Services; 2009.