Feature by **ROBERT S. RODA, DDS**

Did I Do That?

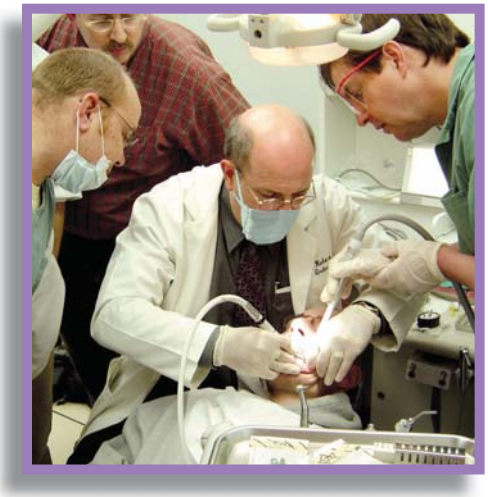
The Race Between Man and Bug

Antibiotics are miracle drugs

that since the Second World War have saved untold millions of lives that otherwise would have been lost to bacterial infections. Since Alexander Fleming accidentally discovered that a mold of the genus *penicillium* could inhibit bacterial growth on an agar plate, antibiotic synthesis and production have created some of the safest and most effective medications the world has ever seen. Their use extends beyond medical therapeutics and for many years, they have also been used to enhance the health and thus the growth of livestock including cattle and chickens.

As the use of antibiotics has become more widespread, there has been a rising concern regarding the potential side effects of these drugs. One such problem is the emergence of resistant strains of bacteria. The US Centers for Disease Control (CDC) defines antimicrobial resistance as "the result of microbes changing in ways that reduce or eliminate the effectiveness of drugs, chemical, or other agents to cure or prevent infections." [(1)]

The emergence of antimicrobial-resistant strains of bacteria has resulted in an escalating arms race between man and bug. We have been winning some battles, but so far evolution and microbes are winning the war. It's just hard to fight biology. An eminent microbiologist once told an audience at a meeting I attended that we should not feel too depressed about this since microbes have survived environments way more hostile than anything we can create. The first bacteria evolved on a planet that had a harsh nitrogen methane atmosphere with wild electrical discharges, rampant volcanism, and acidic seas that were under constant bombardment from meteors. Guess what, that was the earth 3.5 billion years ago. Bacteria evolved the ability to create biofilms and metabolic enzyme systems, which protected them from their environment, and they thrived. These same mechanisms confound us today.



Dr. Rob Roda, center

How can we hope to win a war against a foe that has won every war since before time was time? The answer seems to be that we can't. New strains of bacteria evolve before our very eyes, either through random mutation or the sharing of genetic material between and within microbial species. [(2)] Got a new antiseptic? I'll wager that a resistant bug will appear shortly that will transmit its resistance to many other bugs it contacts and -- *voila!* -- the antiseptic becomes less useful. Bacteria create enzymes to deactivate the antibiotic, such as beta-lactamase that destroys penicillin. They can alter the site that the antibiotic targets on the bug and we get methicillin resistant *Staph. aureus* (the dreaded MRSA). Through these and other mechanisms, we have used un-natural selection to create an army of antimicrobial resistant bugs that continue to cause disease.

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I suspect that most of our readers are well aware of this process and so most clinicians refrain from overprescribing antibiotics so that the next dental abscess they treat will remain easily treatable. On the other hand, based upon cases referred to one endodontist's practice (that would be me) and many others that I communicate with nationwide, there is still a lot of inappropriate prescribing of antibiotics occurring.

Why would this be? I suppose part of the reason could be lack of knowledge of current therapeutic guidelines and I know a lot of it is due to misdiagnosis of non-infectious endodontic conditions that are somehow perceived as needing antibiotics to resolve. Unfortunately, some feel that prescribing antibiotics is like chicken soup. "It couldn't hurt!"

Well, that's no longer true (if it ever was). We can possibly throw out scripts for antibiotics and not worry about the future; ignoring the long term damage to our antimicrobial war efforts the way politicians don't worry about how my grandchildren will pay for the budget deficits run up today. And, like the politicians, we don't fear this on a personal level since the paying of the piper is long disconnected from the crime. The politician will be well out of office before my grandchildren have to live in poverty and the patient will never connect my having prescribed amoxicillin for non-infectious irreversible pulpitis with the death of their grandchild from MRSA or pan-resistant tuberculosis.

Unfortunately, we now have a problem that forever separates us from the immunity of time. For a long time, antibiotic related pseudomembranous colitis has been known to occur rarely when antibiotics are prescribed. Its mechanism was not well understood until 1978 when it was discovered that the disease is caused by a bacterium called *Clostridium difficile*. [3] *C. Diff*, as it is called, is a spore forming, anaerobic, gram-positive bacillus that is resistant to most antibiotics and is a commensal organism living in the colon of a minority of the population.

This bug can be cultured from hospital surfaces where it is usually acquired through the fecal-oral route due to inadequate disinfection and hand washing. The problem is that most hospital personnel substitute antibacterial, alcohol-based hand gels for simple soap and water. These antiseptics don't kill *Clostridium* [4] and without soap and water hand washing, the *bacillus* stays on their hands to be passed to the next unsuspecting patient. The longer a patient stays in hospital, the greater the chance of picking up *C. diff.* Spores and vegetative cells are ingested. Passing through the stomach kills most of the vegetative cells, but the spores pass through unharmed and germinate in the small bowel finally lodging in the large intestine. If they are allowed to grow and reproduce unobstructed, they produce two toxins (A and B) that provoke a severe inflammatory bowel disease that creates pseudomembranes and watery diarrhea [4]. This disease now has a new name. It is called *Clostridium difficile* Associated Disease or CDAD. Fortunately, *Clostridium* is not very good at competing for space and resources in the large intestine, and the presence of multitudes of our normal gut bacteria prevents this pathogen from becoming a dominant species.

For CDAD to progress, the normal microbial flora of the gut must be disrupted, generally by antibiotic therapy. Over 90% of cases of health care associated *C. difficile* infections occur after or during antimicrobial therapy and all of the antibiotics used in dentistry have been associated with CDAD. [4] Fortunately, it rarely occurs in the antibiotic dosages used in dentistry today but it can and does happen. Concurrent use of antibiotics and proton pump inhibitors, such as Prilosec®, Prevacid®, and Nexium® appear to increase the risk of acquiring CDAD [4] although the mechanism for this is unclear. Treatment of the classic form of the disease includes supportive therapy plus the antibiotics vancomycin and/or metronidazole.

"So what?" you might say. "This is something we've dealt with for decades and it's

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never happened to one of my patients." Well, nothing lasts forever, and the war, predictably, just got ramped up.

Recently, a new "epidemic strain" of *C. difficile* has emerged called NAP-1 that produces 16 to 23 times more toxins than other strains and has caused numerous outbreaks of clinically severe disease since 2001. It occurs in younger, healthier patients including peripartum females, is more resistant to therapy, has a higher recurrence rate, and has been responsible for multiple deaths in North America and Europe [5]. Yes, it is occurring here in Arizona and the incidence of NAP-1 CDAD seems to be increasing worldwide. The death rate from CDAD in the United States has quadrupled from 5.7 deaths per million in 1999 to 23.7 in 2004. [6] Estimates of hospital discharges with CDAD as a listed diagnosis rose from thirty-one per 100,000 population (82,000) in 1996 to sixty-one per 100,000 (178,000) in 2003. [7] Overall mortality rate has been quoted as high as 16.7% of people who contract NAP-1 CDAD. [8] That's pretty high for an iatrogenic illness. Treatment of the epidemic strain of CDAD is similar to the classic form of the disease including antibiotic therapy (vancomycin and metronidazole), supportive therapy, occasionally surgical resection of the colon in severe cases, and even a treatment called fecal bacteriotherapy involving taking feces from another person and placing it in the colon of the CDAD patient to restore the non-*clostridium* flora. [9]

This disease has even hit the popular press. Along with news reports of outbreaks in the US, Canada, and England, the disease was the focus of the "Vital Signs" column of *Discover* magazine in January of 2007. [10] In that column, the author, Tony Dajer, a medical doctor in New York City, relates the story of a woman who died from CDAD after being given a prescription for clindamycin by her dentist. He states: "Had she come in sooner, her death might have been averted. Maybe a more adamant warning from her dentist about clindamycin's potential dangers would have saved her life." A damming indictment, indeed! And it is not just clindamycin. The antibiotics most closely associated with the more severe form of CDAD are the fluoroquinolones (eg: ciprofloxacin), followed by cephalosporins. [8]

So, what's a dentist to do about this increasingly scary epidemic? The CDC has a simple prescription in their MMWR of 2005. "The findings underscore the fact that antimicrobial exposure is not benign and that judicious antimicrobial use in all health-care settings should continue to be emphasized." [5]

The first step in prevention of CDAD is to restrict antibiotic prescriptions to patients who actually have an infection (and cold sensitive teeth with vital pulps are not generally infected). Use caution with the use of pre-surgical antibiotic prophylaxis, which is currently under review by medical authorities. Do not prescribe antibiotics in the presence of low grade, localized endodontic or periodontal infections (localized pain and swelling in the absence of fever, malaise, and lymphadenopathy) where local measures are indicated. Do not prescribe antibiotics simply because a sinus tract is present unless there is systemic involvement. Provide local infection control measures such as complete pulpectomy, incision and drainage, surgical debridement, or extraction as indicated. Prescribe narrower spectrum antibiotics that will attack the types of bacteria that typically cause the type of infection suspected.

In endodontic infections, use penicillin or amoxicillin and avoid the use of cephalosporins (such as cephalexin) or fluoroquinolones (like ciprofloxacin). In penicillin allergic patients, the first drug of choice for endodontic infections remains clindamycin (150mg QID). With this and any other antibiotic prescribed, however, patient counseling about the potential for CDAD must accompany every prescription, especially in patients taking proton pump inhibitors. Reassure them that the likelihood of developing CDAD is very low but they must watch for

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signs of it. If the patient develops diarrhea that lasts for more than three days or, if diarrhea is accompanied by blood in the stool or high fever, they must stop taking the antibiotic and seek out medical attention at once. [5]

Another potential preventive therapy is the use of probiotics. These procedures, which involve attempting to replenish the gut microflora that are destroyed by the antibiotics, have languished in the untested world of alternative healthcare for years. The use of probiotic therapy remains controversial with no body of evidence that it prevents CDAD in people taking antibiotics. There have been isolated scientific studies that seem to indicate a benefit [11], however there is no known regimen that seems to consistently rebalance the gut flora. People have been encouraged to take supplements of *lactobacillus acidophilus* (that can live through stomach acid to get to the colon) and yogurt with live bacterial cultures (although one has to eat a lot of it to see any possible benefit). There is even a product called Florastor® containing *Saccharomyces boulardii* that is sold for this purpose. All of these products are widely available over the counter in drug stores. As with any area of healthcare where there is no scientific consensus, the prudent practitioner should contact medical experts, weigh the risks and benefits of the therapy, and prescribe accordingly (meaning I'm not going to give you an opinion on this one).

By properly diagnosing our patients, rendering timely treatment, and using antibiotics sparingly with proper counseling, we can become part of the solution to this growing epidemic instead of part of the problem. I know it will involve some more research, more work, more time, and changing our traditions, but the alternative is to begin killing more of our patients. You never want to have to say, "Did I do that?" You must change what you do. Haven't you heard … there's a war on!

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DR. ROB RODA PRACTICES ENDODONTICS IN SCOTTSDALE. HE IS EDITOR OF INSCRIPTIONS.

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