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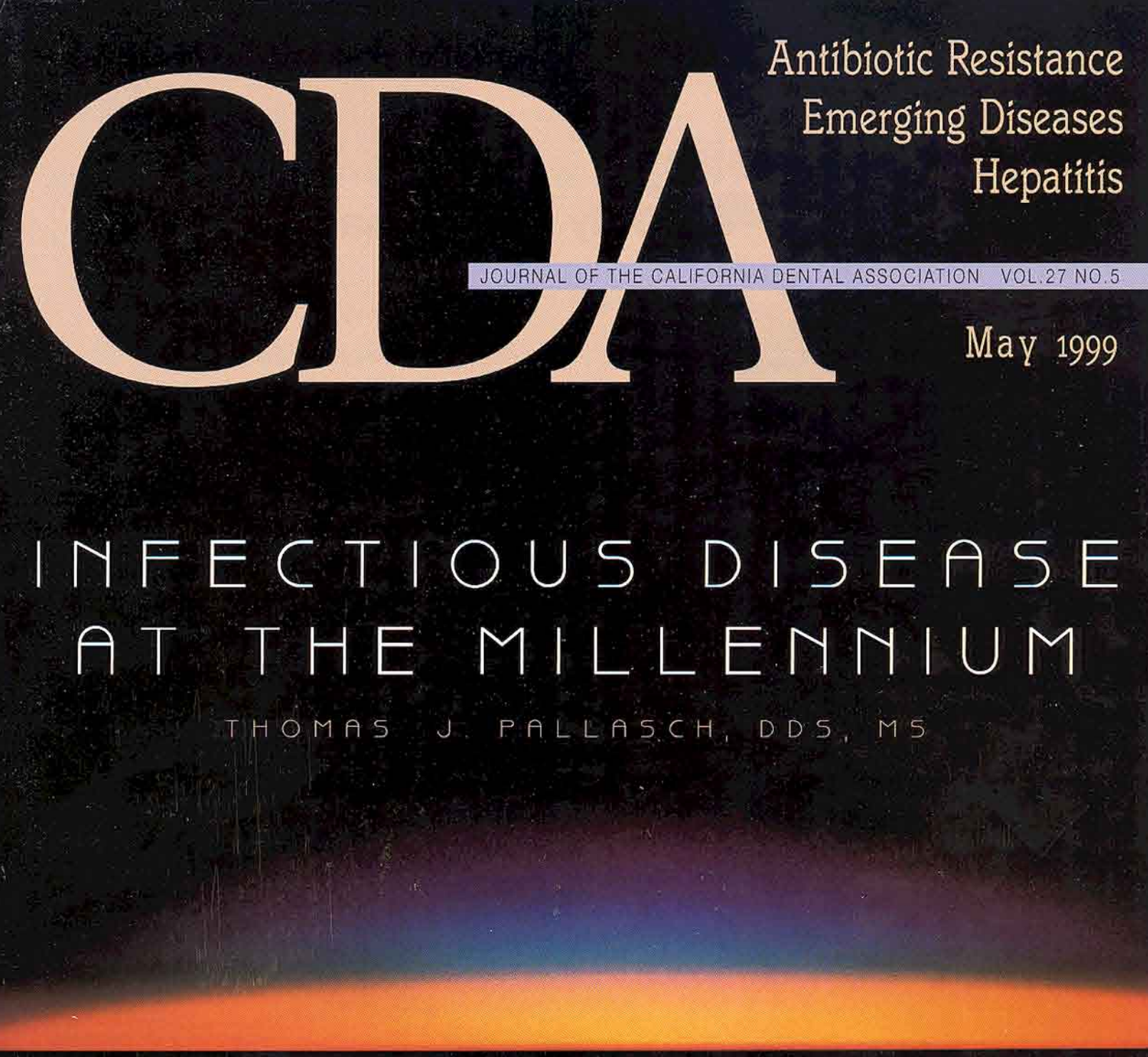
INFECTIOUS DISEASE AT THE MILLENNIUM

THOMAS J PALLASCH, DDS, MS



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DEPARTMENTS

FEATURES

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Increasing Professional Responsibility to Society

Jack F. Conley, DDS

Recent actions of the California Dental Association Board of Trustees should focus our attention on one inescapable fact. The professional responsibilities of the practicing dentist as related to the expectations of the society in which we are participants continue to increase.

There was a time when treatment skills and dental diagnostic skills dominated the dentist's scope of responsibilities. During our time in the profession, we have seen a considerable expansion in the scope of responsibility. Practice administration or management has always been a small part of the dental school experience; but, until the 1970s, there was minimal emphasis on the importance of the dentist's role as an employer and manager of a business. Each year, the increasing number of dental plans and delivery systems and the advancement in technologies available for the conduct of our business has increased our responsibility to review new systems, equipment, and technologies so that we can conduct a sound and successful business that enables us to provide treatment that meets the acceptable standards of care.

While it would seem that new technologies would simplify this process, that is often not the case. Some colleagues find themselves frustrated by change and refuse to accept the responsibility to improve their knowledge in required areas or to upgrade the business systems in their practices. They add to their frustration by believing that organized dentistry is their agent to fend off new requirements or regulations. If their association is unable to bring them relief from a new responsibility enforced from outside the profession, their dissatisfaction is often directed at their profession. They fail to recognize that these expanding societal responsibilities of a professional person have become an expectation by society.

The attitudes against acceptance of this expansion must change. We must accept these expanded societal responsibilities if we are to successfully pursue the standards expected by the public we serve -- the dental patient.

That brings us to two of the newest "responsibilities" that we see as important to our role as professionals. Many readers will recognize that they have been previously introduced to one or both. What is new is that CDA leadership, by its actions, has formalized a role for dentistry in resolving societal issues linked to these responsibilities.

The first of these actions by the CDA Board of Trustees was: "Since all licensed dental care providers in California are mandated reporters, the California Dental Association urges its members to become familiar with and report all physical signs of child abuse, child neglect, elder abuse, elder neglect, and domestic violence that are observable in the normal course of the dental visit and report the suspected cases to the proper authorities." What is new about this responsibility is that it extends beyond the current policy of the American Dental Association, which

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has previously addressed child abuse and neglect. Concern for domestic violence and elder abuse/neglect are significant additions to the existing policy.

This responsibility recognizes that the dentist is one of a select few who has a firsthand opportunity to observe the signs of neglect or violence that plague our society. Despite the liability that the reporting requirement can place on the dentist, the responsibility is also a legal requirement that cannot be taken lightly.

A second action taken by the Board of Trustees that we believe has significant importance to the responsibility of each dentist is that of initiating steps to deal with unlicensed practitioners who practice in illegal "dental facilities." The Board action initiated association legislative steps aimed at strengthening penalties for individuals guilty of illegal practice in order to serve as a stronger deterrent to this activity. Several Los Angeles television outlets have carried features on "unlicensed dentists" in southern California in the past five months. We believe that the individual licensed dentist also has a responsibility to help resolve this problem.

The rationale for action is not related to reduced economics or the competition for licensed practitioners, but is for the education of legislators, legal authorities, and the public at large (patients) regarding the dangers that this form of dentistry presents to the dental health and well-being of the public. Reports show that these establishments ignore proper health and safety guidelines and pose a considerable risk to those who undergo treatment there. Education is extremely important because that is the only mechanism by which laws can be made more stringent in order to discourage these businesses from starting up. Aside from the danger to the public, these facilities reflect poorly on the image of the profession. These unlicensed individuals are thought to be "dentists" by an uneducated public that is usually unaware that the illegal operator is unlicensed. Thus, we must make it our business to educate the public and report any suspected illegal activity to those who can help investigate and terminate such practices.

These expanding responsibilities may be unrelated to the business health of the individual dental practice. However, they make up a very important and growing scope of responsibility for the contemporary practitioner. While these Board decisions commit association resources to support efforts to manage these societal problems, solutions will not be successful without the responsible efforts of all individual practitioners.

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Periodontal Regeneration: Myth or Reality?

EDITOR'S NOTE: Occasionally, response to an issue or article featured in the Journal requires more than just the printing of a Feedback letter so that the issue or controversy can be further explored to benefit the understanding of our readers. The article "Periodontal Regeneration: Myth or Reality?" published in February 1999, presents such a circumstance. It is our belief that the reader should have the opportunity to review information pertinent to the controversy on this subject; thus, we have assembled the Feedback mini-forum that follows.

Readers are reminded that all scientific manuscripts published in the CDA Journal have received blind peer review by individuals on CDA's consultants list that is updated regularly by the Council on Dental Research and Developments, which is composed of clinicians and academicians throughout the state. An editorial decision to approve publication is not made until the author has presented a manuscript that either receives approval of the reviewers or has been modified so that it satisfactorily removes the basis for initial criticism upon further review prior to publication. Letters on other topics follow.

The article "Periodontal Regeneration: Myth or Reality" presents a view that is significantly different from the current scientific thought and evidence on periodontal regeneration. It is stated that periodontal regeneration procedures are only slightly better than flap debridement, that improvements were not significantly enhanced by guided tissue regeneration, and that these procedures (bone grafting and guided tissue regeneration) may not provide patient benefits in terms of improved periodontal health.

The opinions expressed run counter to current periodontal research findings. In the article, the author chose to reference 54 articles, only one of which has been published since 1996. Most of the studies cited -- and many more -- were reviewed, compared, and critically examined at the 1996 World Workshop on Periodontics, sponsored by the American Academy of Periodontology, which brought together 135 participants from around the world.

At the 1996 World Workshop, periodontal research was evaluated and measured using an evidence-based approach, a comprehensive and rigorous literature evaluation process applied by scientists and clinicians. This methodology

was used by participants in the World Workshop to assess the evidentiary status of periodontal and implant treatment. At the World Workshop, the Section on Periodontal Regeneration Around Natural Teeth evaluated 352 papers in the area of regeneration. The consensus findings of the section and all the other sections were sent to all members of the American Dental Association as a supplement to the September 1998 issue of JADA.

The following highlights of the consensus findings of the Section on Periodontal Regeneration Around Natural Teeth differ greatly from the opinions in the article.

- **Bone grafting:** "Several bone replacement grafts have demonstrated significant clinical improvement. Well-documented human investigations have demonstrated periodontal regeneration with demineralized freeze-dried bone allograft."
- Barrier membranes: "Multiple studies using occlusive (barrier) membranes have demonstrated significant clinical improvement."
- **Long-term stability:** "Long-term studies of five years indicate that regenerative procedures result in periodontal stability in patients who are compliant with plaque control and receive effective supportive periodontal therapy at approximate intervals."
- **Open flap debridement:** "There is no evidence that open flap debridement techniques promote periodontal regeneration."

Further, a review of the current periodontal research from 1997 and 1998 published in the Journal of Periodontology (Vol. 68, Nos. 1-12; Vol. 69, Nos. 1-12) and the Journal of Clinical Periodontology (Vol. 24, Nos. 1-12; Vol. 25, Nos. 1-12) shows findings that are remarkably consistent with those of the World Workshop.

Barrier membranes — 22 human studies:

- Fourteen studies showed clinical attachment gain greater than 3 mm.
- Four studies showed clinical attachment gain of 2-3 mm.
- Two studies showed clinical attachment gain of 1-2 mm.

In those studies that compared a barrier membrane technique to flap debridement, the barrier technique was 1-2 mm superior to open flap debridement in all the papers, except two pilot studies by the same research group in Sweden, which found the two procedures equal, with each procedure gaining only 1-2 mm of clinical attachment. It is interesting that the only recent study included in the review was one of these studies.

Bone allografts — 11 human studies:

- Eight studies found an increase in attachment greater than 2 mm.
- One study reported an increase in attachment greater than 4 mm.
- Two studies reported the allograft equal to open flap debridement.

Molar furcations:

- Five studies found an increase in attachment of 2 mm or greater in buccal furcations.

The current scientific findings speak for themselves: Periodontal regeneration is a clinically significant therapeutic technique. It is one of many modalities of periodontal treatment and, logically, is not applicable to all clinical situations. Periodontal therapy is both science and art. The art being the appropriate and skillful application of the science. Periodontal diseases are complex and multifaceted clinical entities that require the clinician to bring to bear the entire range of therapeutic options. Today, periodontal regeneration procedures are important and predictable clinical therapies that enhance and improve treatment outcomes and provide for repair and reversal of the damage to the periodontium by periodontal disease in appropriately selected areas.

In evaluating periodontal therapy, we must not let our biases cloud our judgment. We must be willing to evaluate and accept emerging research even if the findings are not to our personal liking. Unfortunately, omitted and misrepresented in this paper has been the large body of evidence supporting periodontal regeneration as a significant clinical therapy.

Gordon L. Douglass, DDS
Sacramento, Calif.

As contributing editor to the February issue of the *Journal of the California Dental Association*, I asked Dr. William Becker to write the article on periodontal regeneration. Dr. Becker is a full-time practicing periodontist. He is not on the payroll of any company and is not a full-time academician. Dr. Becker is able to run clinical studies out of his office as well as contribute significantly to the periodontal literature. As a private-practice periodontist first and researcher second, Dr. Becker has worked extensively with bone grafts and barrier membranes and has a comprehensive knowledge of periodontal regeneration. He was one of the first to publish results on periodontal regeneration and, therefore, has some of the longest follow-up on these patients. Dr. Becker is frequently on the forefront of current thinking in the treatment of periodontal disease as is evidenced by his numerous clinical studies that have been reported in the periodontal literature.

In his review of regenerative procedures, Dr. Becker was not only honest about his personal results with the long-term use of periodontal regeneration, but also presented references from reviewed journals to further illustrate the possible

shortcomings of regenerative therapy. He did not suggest that demineralized freeze-dried bone or barrier membranes not be used. He merely questioned whether gains reported from most comparative studies are so clinically and statistically significant as to compel all practitioners to use regenerative materials.

There is little doubt that in limited defects, some amount of regeneration is possible. Material from the 1996 World Workshop in Periodontology showed that there was significant gain in clinical attachment from regenerative procedures. However, as most of these studies were not comparative studies, little information is available on how these defects would have responded without regenerative materials. The Annals of Periodontology, which presented findings from the 1996 World Workshop,1 states that significant decreases in probing depth and gains in clinical attachment level and bone can be predictably anticipated when deep intrabony defects are treated with or without barrier membranes.

A review of the current literature shows that in those studies that compared a barrier membrane technique to flap debridement, the barrier membrane was 1-2 mm superior to open flap debridement in all the papers except two, which reported the two procedures to be equal. The question remains, are these gains so clinically and statistically significant to compel all practitioners to use these materials. Are these additional gains in clinical attachment stable over the long term? Do the additional 1-2 mm of attachment gain justify delaying necessary restorative treatment for an additional six to 12 months? After regenerative therapy, can I predictably expect defects to fill?

Finally, I would like to quote a guest editorial by Drs. Pamela McClain and Robert Schallhorn from the January 1999 Journal of Periodontology, Page 103. Drs. McClain and Schallhorn have reported in the periodontal literature on long-term results utilizing regeneration with bone grafts and bone grafts with barrier membranes and have been proponents of the use of regeneration in periodontal therapy. In this editorial, they state: "The variability in the degree of response to regenerative therapy helps maintain a cautious attitude regarding the state of the science and influence of other factors not yet clarified such as the impact of root trunk length and morphology, content of BMP, or other factors important to periodontal regeneration in the DFDBA, intraradicular morphology, and other factors not adequately delineated for their effect on the regenerative outcome." They go on the state: "Surrogate evidence of periodontal regeneration has been shown to be predictable in narrow two- and three-walled intrabony defects (IBD) using a variety of techniques and materials, while wide two- and three-walled IBD, one-wall hemiseptal, class II and III furcations, and horizontal/crestal osseous defects remain less predictable as evidenced by the variability of results in the literature."

With the knowledge that only a minimal amount of additional attachment gain may be achieved using regenerative materials as opposed to not using regenerative materials, with many defects responding less predictably and possible not holding up long term, I believe that as Dr. Becker suggested, in a clinical situation, we must question the current advantage of regenerative materials.

David F. Levine, DDS
Burbank, Calif.

The article, "Periodontal Regeneration: Myth or Reality?" does not imply that demineralized freeze-dried bone allograft (DFDBA) or barrier membranes not be used. The question we ask is, are gains reported from most comparative furcation studies so clinically and statistically significant as to compel all practitioners to use these materials. I think not. Significant decreases in probing depth and gain in clinical attachment level and bone can be predictably anticipated when deep intrabony defects are treated with or without barrier membranes.1

Is commercially available demineralized freeze-dried bone a bone-inductive regenerative material? There is a preponderance of scientific literature that questions the bone inductivity of this material. "Commercially available" is the underlying concept. There is no question that special preparations of DFDBA induce bone in ectopic sites (muscle) in mice and rats. Commercially available DFDBA is considered to be osteoconductive. Articles have appeared in peer-reviewed journals that demonstrate the shortcomings of DFDBA as an inductive material.2-10

Periodontics has made major strides during the past 20 years. We have improved surgical techniques for teeth and dental implants, are at the forefront of improving dental esthetics for our patients, and are investigating methods to regenerate tissues adjacent to teeth and dental implants. We are identifying systemic diseases related to periodontal disease, take a leadership position in preventive dentistry, and are capable of improving periodontal health for all forms of the disease. We have and will continue to share knowledge with all of our colleagues. We will continue to make significant progress for the benefit of our patients. In America, there is room for differences. General dentists as well as all specialists have the educational background to make informed decisions based on the current state of knowledge.

William Becker, DDS, MSD
Tucson, Ariz.

Kudos to Dr. Bob

Congratulations to Dr. Horseman on his article "Animal Welfare Acts" in the January 1999 issue. He says what needs to be said in a clear, firm, but amusing manner.

Francis V. Howell, DDS, MS
La Jolla, Calif.

No Case for Competency Assessment

In the editorial in the February 1999 issue of *Journal of the California Dental Association*, Dr. Jack Conley asserts that it is a "right thing" for the dental profession to acquiesce to some form of continuing competency assessment. By the use of the word "right," one is led to believe he is speaking of a moral issue, yet the preponderance of his concerns appear to focus on the alleged nebulous repercussions to the economic status and reputations of the profession if this is not accepted. The only evidence supporting a moral concern is found in the quote from former U.S. Sen. George Mitchell: "We became convinced there is today, a public system which isn't protecting the public."

For me, as I hope all in the dental profession would agree, the moral and ethical issues are paramount. This is not to say the economic consequences and public perception are unimportant. The case has not been made for dentists supporting an increase in government meddling in our profession. The government is already too expensive, too intrusive, and usually incompetent.

J. Dennis Lewis, DDS
Brea, Calif.

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Making the Case

By David G. Jones

"Evidence-based care," experiencing growing use in medicine but still in its infancy relative to dental care, is gaining notice.

Dental education, organized dentistry and the insurance industry are taking closer looks at a system that challenges long-accepted thinking about the way dental care is provided.

With evidence-based care, not all patients are equal. Some, at higher risk for dental disease, are treated more aggressively than patients at low risk, who receive more conservative and preventative treatment. In theory, evidence-based care would help most patients to have fewer cavities and less periodontal disease, and costs to both dentists and insurers would decrease.

Dentistry has made slow, careful steps toward evidence-based care over the course of the last several years. In California, Delta Dental began investigating the concept in 1996 when it undertook a study at the University of California, San Francisco, School of Dentistry to demonstrate whether its use could lower costs and improve the oral health of patients. One of the principal researchers was Steven J. Silverstein, DMD, a UCSF professor of dental public health and hygiene for 28 years.

"We wanted to look at the evidence, and determine whether we could characterize people by their risk," Silverstein says. "We wanted to know if those with low to moderate risk could have a dental benefit that was cheaper and that emphasized maintenance and prevention, while those at higher risk might have a benefit at a different level."

He says that people at lower risk may not need all the restoration and replacement, once a hallmark of dentistry.

"There's still no scientific evidence that low-risk people need to visit a dentist once a year, or have their teeth cleaned twice a year," Silverstein says.

With the study results in hand, R. Steven Bull, DDS, senior vice president for Delta Dental of California, Public and Professional Services, sees data that indicates evidence-based care could work.

"But we found there's no consensus in the industry, among insurers, organized dentistry and academics, as to what is the new standard of care," he says. "We're talking about a lot of dramatic changes in dentistry, but we haven't seen this addressed by any of these parties."

Charles J. Goodacre, DDS, dean of the Loma Linda University School of Dentistry, agrees with Bull, and says he believes dental education has fallen behind in embracing evidence-based care.

"But we're beginning to catch up rapidly in the area of doing things and training people on the basis of evidence," he says. "Today's graduates are getting more information, so we're starting to turn out graduates who increasingly will use evidence in making diagnosis and treatment plans in the future. I encourage the profession to go in this direction. It's absolutely the future of training."

Roger K. Rempfer, DMD, chairman of CDA's Council on Dental Care, says that he has a particular interest in the issue.

"I'm interested in any entity that may prove it can offer enhanced quality of care and increased availability and affordability of care," he says.

One West Coast dental insurer is beginning to make inroads on implementing evidence-based care. Max Anderson, DDS, dental director at Washington Dental Service, a Delta Dental Plan Association member, says dentistry must change the way it has operated for many decades in order to embrace the new way of thinking.

"When insurance companies wrote their first programs in the '50s, caries was pandemic," Anderson says. "We had a payment system and dental industry designed to repair disease. Now we have through available science the ability to prevent the vast majority of disease."

Anderson says that since we can prevent most dental disease in many people who are not at risk, he won't have as much repair work to do.

"So I will have to become a better diagnostician, and a good risk prevention specialist," he says.

Anderson says his organization addressed a possible decline in income under this scenario by determining how to change the payment system to reward dentists for doing the right thing.

"We redirected resources into those areas where we can apply appropriate science, and to (make than an economic advantage) for the dentist and the patient," he says.

Twice-yearly fluoridated varnishes are included as a benefit for patients who are at risk for caries, for example, Anderson says.

As dental schools begin to implement an evidence-based care approach into their curriculums, ans as the dental insurance industry gets on board to help propel the new standard of care, organized dentistry is cautiosly optimistic.

Change has its risks, yet so does standing still, Rempfer said. Will the new be better than the old? Will it be a better standard, or one that looks good on paper but is yet more disjointed? Only time with tell.

Take Three Steps -- That's the Plan

By Marios P. Gregoriou

Many people work to accumulate assets with a goal of leaving a solid financial legacy to their heirs. But building an estate is just one part of the equation. Plan-

ning its distribution, even if the estate is moderate, is as important.

A carefully crafted estate plan ensures that assets reach the people chosen to receive them, in a chosen manner. A well-prepared estate plan ensures that property is distributed to a person's spouse, children and chosen others.

Equally important, such a plan may reduce or eliminate estate taxes.

The first step is assessing the value of one's estate. Current federal law allows an unlimited amount to be left to a spouse free of federal estate tax. Applying the unified federal tax credit of $211,300 (for 1999) against estate taxes allows one to leave as much as $650,000 tax-free to beneficiaries other than a spouse.

Any amount over $650,000 is subject to a federal estate tax starting at 37 percent and rising as high as 55 percent, depending on the estate size. An estate can reach the $650,000 threshold quickly with the combination of a home's market value, investments, personal property, owned businesses, retirement benefits, and face value of life insurance policies.

A second step is review of one's family situation and objectives, and consideration of: whether the spouse is a capable money manager, or if funds should be left in a trust (with determination of a trustee); where property should go after the spouse's death; whether all children are to be treated equally, or if any have special medical or educational needs; whether there will be other beneficiaries, such as a university or charity; if one's business includes a "buy-sell" agreement to ease transfer of the company stock, and if sufficient cash is available to fund the agreement.

The primary concern of a person with a family probably is to ensure that the estate is passed on to spouse and children in the amounts intended. An unmarried person might want to designate beneficiaries and provide for management of financial affairs in the event of becoming disabled.

The third step is to consult a financial adviser and tax professional, as well as an attorney who can draft an appropriate will and appropriate trust agreements.

Depending on the value of the estate, an approximately drafted will can help reduce, defer or even eliminate estate tax on one's property. For example, a will that leaves all assets to a spouse guarantees estate taxes won't be levied because of the "unlimited marital deduction." However, if a spouse does not remarry and dies with a combined estate of more than $650,000, the heirs may face estate taxes.

One way to lower heirs' future tax bite is to set up a "bypass" trust. Trusts are legal devices that hold property for the benefit of named beneficiaries. Via a trust agreement (established either outside or within a will), a manager is named for the assets placed in the trust with instructions about how distributions are to be made.

Since money in a bypass trust does not go directly to the spouse, it is not considered part of his or her estate, but he or she can benefit from having the income and a limited amount of principal from the trust. Heirs receive the balance of the principal upon the spouse's death.

Marios Gregoriou is associate vice president and financial adviser with Morgan Stanley Dean Witter in Sacramento. He can be reached at (800) 755-8041. Information in this article was obtained from sources considered to be reliable. This article does not constitute investment or tax advice. Consult an investment adviser or tax attorney before making investment decisions.

Crunching Practice Numbers

The ADA Survey Center has released two new reports on dental profession statistics.

"Income from the Private practice of Dentistry" is the first in a series of five reports from the 1997 Survey of Dental Practice. The report provides national and regional income figures for general practitioners and specialists as a group. Income is further broken down by dentist age, years in practice and hours worked. Gross billings are included.

The "1997 Survey of Dental Graduates" provides information on 1996 dental school graduates one year after graduation and includes comparison with previous graduating classes. The survey, mandated by the ADA House of Delegates, is part of Distribution of Dentists, a census-type survey of all known dentists. Information collected from the survey includes primary and secondary occupation; state(s) and types(s) of licensure; self-reported area of practice; research or administration; gender; race; ethnicity; and date of birth.

"Income from the Private Practice of Dentistry" (catalog No. 5197) is available to members for $35 shipping and handling. The price to members for the "1997 Survey of Dental Graduates" report (catalog No. 5SD7) is $15 plus shipping and handling. Order directly from the ADA Survey Center by calling the members' toll-free number, extension 2568.

Flossed in Space

What if a patient suddenly had a toothache -- in space?

As common wisdom holds, prevention is the key, especially for astronauts. Regular preventive care has virtually eradicated dental problems for astronauts during space missions.

Dr. Jerold W. Miller, president of the Philadelphia County Dental Society, shared with the opening session of the

68th annual Liberty Dental Conference information from NASA's first report on dental problems in space. The report, from Dr. Michael Hadatt, head of NASA Dental Clinic in Houston, indicates that astronauts are carefully examined prior to space missions.

"Astronauts are also instructed to brush and floss every day -- even when in a weightless condition -- during their space flights," according to Hadatt.

NASA's objective is to avoid dental emergencies during missions. However, should an emergency occur, a flight crew member -- generally a physician -- is prepared with medication and equipment to treat most dental situations.

NASA's Dental Department and Flight Medicine Department conduct studies in bone mass changes during and after space missions.

"Only slight changes in bone mass have been noted," Hadatt reports, "but nothing intense. In addition, follow-up examinations are regularly scheduled after the missions to determine if further treatment is necessary."

The last major dental emergency occurred two years ago on MIR, the Russian space station, when an astronaut had to return to Earth because his condition proved too serious for in-flight treatment.

Doing the Work Where It's Needed Most

English researchers have determined that water fluoridation is actually better at reducing tooth decay in areas of socioeconomic deprivation.

Researchers at the North West Dental Public Health Resource Centre in Wesham, England, conducted a study of 6,638 children age 12 in the north of England who had a dental examination. Half were in Newcastle, where the water has been fluoridated for more than 20 years, and the other half were in nonfluoridated Liverpool.

The two areas were further divided into 30 areas defined by social deprivation. As expected, in both Newcastle and Liverpool, the amount and severity of tooth decay increased with socioeconomic deprivation. However, the study also found that the improvement in levels of tooth decay in deprived areas with water fluoridation at one part per million was over and above that which would be expected simply because there was more decay.

In England as a whole, there was a 37 percent reduction in the amount of tooth decay in 12-year-olds in fluoridated areas. However, researchers found that in very deprived areas the reduction was more than 50 percent. More than half of all potential tooth decay was prevented.

Dr. Colwyn Jones, the research director of the Northwest Dental Public Health Resource Centre, says, "I estimate that there are 50,000 rotten teeth in 12-year-old children in the northwest of England. With water fluoridation, the number of rotten teeth would be almost halved."

Forget the VCR, Will My ATM Work?

With everyone scrambling to get ready for the Y2K computer glitch, it's easy to get caught up in the excitement -- especially when it comes to money. But what's real and what's just hype?

The latest information about being protected against possible financial hitches can be found in "The Year 2000, Your Bank and You" from the Federal Deposit Insurance Corp.

A question-and-answer section provides information about who is monitoring banks' Y2K efforts and how people can tell if their bank has taken steps to prepare. An eight-point checklist offers specific tips on how a person can be protected. To order a free copy, call (888) 878-3256 and ask for item 613F; or send name and address to Consumer Information Center, Dept. 613F, Pueblo, CO 81009.

Normal banking routines should not be disrupted, but all bank records from the last six months of 1999 and the first few months of 2000 should be kept. Comparison of personal bank records and bank statements also is encouraged.

Flu Vaccines Helps Keep Health Professionals on the Job

Annual flu shots are effective in preventing infection and onset of respiratory illness and may reduce work absences, according to an article in the March 10 issue of the Journal of the American Medical Association.

James A. Wilde, MD, formerly of Case Western Reserve University School of Medicine in Cleveland, and colleagues studied 264 young health care professionals without chronic medical problems at two teaching hospitals in Baltimore to determine the effectiveness of an influenza vaccine.

The researchers reported that the flu vaccine was 88 percent effective in preventing influenza type A infection and 89 percent effective in preventing influenza type B infection, compared to the placebo group. The researchers also report that the flu vaccine reduced the number of days absent from work by 53 percent and reduced the number of days of respiratory illness accompanied by fever by 29 percent.

Gum Disease Linked to Respiratory Problems

Scientists have found that when a person inhales some of the bacteria that grow in the mouth and throat, they enter the lungs and can cause respiratory diseases, including pneumonia, reports the American Academy of Periodontology.

This is especially true in people who have gum disease. In particular, those

with chronic obstructive pulmonary disease appear to be more vulnerable to this route of infection. These patients often have poor protective systems, so it's difficult to throw off the bacteria.

Studies are now in progress to learn to what extent oral hygiene, such as careful flossing, may prevent this problem, according to Respiratory Health Monitor, newsletter of Data Centrum Communications, Winter 1999.

Smokers Don't See Increased Risk

Most smokers do not perceive themselves at increased risk of experiencing heart disease or developing cancer, according to an article in the March 17 issue of the Journal of the American Medical Association.

John Z. Ayanian, MD, MPP, of Brigham and Women's Hospital, and Paul D. Cleary, PhD, of Harvard Medical School, both in Boston, conducted a survey to assess smokers' perceptions of their risks of heart disease and cancer. The survey included 3,031 adults aged 25 to 74 years, including 737 current smokers (24.3 percent).

The authors found that only 29 percent of current smokers in the study believed they have a higher-than-average risk of myocardial infarction, while only 40 percent believed they have a higher-than-average risk of cancer.

The researchers also found that only 39 percent of heavy smokers (greater than 40 cigarettes per day) acknowledged the increased risk of myocardial infarction and 49 percent acknowledged the increased risk of cancer. Among smokers who had hypertension or a family history of MI, fewer than half perceived their risk of myocardial infarction as higher than average (48 percent and 39 percent, respectively).

Honors

Albert O.J. Landucci, DDS, of San Mateo, Calif., has been elected president of the California Association of Orthodontists.

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Infectious Disease at the Millennium

Thomas J. Pallasch, DDS

Contributing Editor

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As we approach the year 2000, one would have to be totally impervious to the lay media not to realize that serious problems confront us emanating from the microbial world. Some may view these developments with great alarm and fear that the final days are upon us. Indeed this issue might be construed by some as alarmist. Yet, the underlying theme of this issue is that forewarned is forearmed and that dentistry -- as a prominent member of the health care professions -- must face these issues; place them in perspective; attend to these problems where appropriate; and, above all, end any semblance of denial that such problems are real.

As an educator, I have come to realize that reality is not easily accepted and that many will deny as long as possible. Also, I find that many individuals do not have a firm grasp of the history of infectious disease. Prior to the advent of immunization, personal and civic hygiene, and antimicrobial agents, life was commonly brutish and short. Typhus, typhoid, diphtheria, whooping cough, smallpox, cholera, bubonic plague and yellow fever routinely devastated entire populations. Staphylococci and streptococci were the scourge of hospitals (as they are again today). The constant fear of our parents was the "dreaded disease of summer": poliomyelitis. Yet, today most of these infections have been eliminated from first world populations. How truly fortunate we are.

Yet as Murphy aptly cautions: "Optimism indicates that the situation is not clearly understood." So to place our current infectious disease situation in perspective in the limited space allotted, I prevailed upon three acknowledged experts in infectious disease to present their ideas on emerging diseases, hepatitis in its multiple forms, and microbial resistance to antibiotics particularly with reference to the oral cavity. Their efforts are followed by discussions on questions arising from the 1997 American Heart Association Prevention of Bacterial Endocarditis Guidelines, an update on patients who have taken fenfluramine/dexfenfluramine, and finally a review of the current status of antibiotic-associated Clostridium difficile colitis.

Having spent many hours talking with Dr. Jack Beierle on the topic of emerging and re-emerging infectious disease, I asked him to put this in writing as a general overview of the topic with special emphasis on what is and what can be done to manage these problems. This he has done admirably and, to those who might say this is not pertinent to dentistry, I must caution that infectious disease does not begin nor end at the dental office door.

I have known Dr. Michael Glick for many years and am most impressed

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with his knowledge of infectious disease and his expertise in treating medically complicated dental patients. He has provided us with a most expert and comprehensive discussion of hepatitis and its many etiologic agents, including the new TT virus. Surely hepatitis must be a major concern for us all.

After listening to a program by Dr. John Molinari on dental office infection control and being totally enthralled for hours, I asked him to present a general review of microbial resistance to antibiotics and was delighted with his suggestion that this be tailored to the oral cavity. He has done well on a topic (resistance of oral microbes to antimicrobial agents) that has received very little study due to limited finances and few investigators. We face an age of abundant use of chemicals to treat relatively innocuous diseases, and Dr. Molinari warns us of our past and present misguided use of antimicrobial agents.

Since the 1997 publication of the American Heart Association guidelines for the prevention of bacterial endocarditis, several members of the committee have answered questions regarding these recommendations put to us by dental practitioners and hygienists. Drs. Kathryn Taubert and Tommy Gage have assisted in putting our best advice answers to the questions on the printed page. These answers are not "official" from the AHA and are not intended to supplant the dentist's best clinical judgment in a given situation but seem reasonable and prudent to three who were present at the conception, gestation, and delivery of the AHA guidelines.

The discussion of the current status of the cardiac valvulopathy associated with fenfluramine and/or dexfenfluramine includes a review of all the published studies up to December 1998 (the deadline for submission to the Journal for these papers) and a discussion of the now operant three recommendations for the management of these patients. Also included is a discussion of the primary pulmonary hypertension caused by these agents, which is a greater short-term risk than the potential lifetime risk for endocarditis due to the valvulopathy. The table included in this paper should be very useful in a discussion with physicians who may not be aware of these recommendations.

Finally, the effort on antibiotic-induced Clostridium difficile colitis is the only update on this topic for dentistry since 1981, and it brings us a bit of good news. It appears that colitis in general and the dreaded pseudomembranous colitis associated with the community use of antibiotics is quite rare. This will be important if the widespread resistance of viridans streptococci to the penicillins seen today in hospitals spreads to the community as is likely. Clindamycin may return as the drug of choice in orofacial infections, particularly if such resistant streptococci become a community hazard. The downside is that Clostridium difficile is now a major pathogen in hospitals.

This issue of the Journal is intended as a strong dose of reality. It is not intended to frighten but to educate and motivate. It should put us beyond the learning curve of medicine on these topics. Hopefully, that is where we want to be.

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A Viewpoint on the Coming Impact of Emerging Diseases

JOHN W. BEIERLE, PHD

ABSTRACT Infectious disease is now the third leading cause of death in the United States, and the first leading cause in the Third World. These diseases are the most important public health crisis facing the health care community. As part of that community, dentists must be armed with the knowledge necessary to take their part in the war against these infectious agents.

AUTHOR

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During the past two decades, the world of public health has undergone radical changes in the thought processes regarding infectious diseases. It was once assumed that antibiotics and chemotherapeutic agents, along with vaccines, would reduce the spread of infectious diseases and bring them under control with a massive reduction in incidence.[1] The emergence of AIDS and the re-emergence of tuberculosis in the 1980s brought the assumptions of worldwide control of disease to a disappointing halt. The appearance and rapid spread of human immunodeficiency virus throughout the Western world forewarned of the AIDS pandemic, which unfortunately has come to fruition. Tuberculosis, which was virtually unheard of in the United States in 1985, crawled out of ancient history and back into the forefront of public health concern.[2] The appearance of multiple-drug-resistant strains of TB and a rapid spread of the disease in cities that had not seen the disease in 40 years have cast a pall on predictions of secure health. Infectious disease has become the third leading cause of death in the United States – following heart disease and cancer – and the No. 1 cause of death in the Third World.3

Under the leadership of the World Health Organization in Geneva and the Centers for Disease Control and Prevention in Atlanta, major steps are being taken to combat the emergence of new disease and re-emergence of older diseases. The entire world is taking up the challenge to combat the new plagues.

Never before have communication and networking been brought into play for prevention and treatment at the level this globe is now seeing.[4] The new enemy threatening us all is no longer worldwide destruction by nuclear weapons or even global starvation. It is infectious disease. We can no longer ignore these threats or fail to act to develop new controls that will slow the worldwide advance of pathogenic microbes.

In the process, we must learn new biotechniques, educate the public, and develop new clinical treatments. Preventive public health measures are critical. Public health agencies and public health infrastructure functioning at high levels are essential to the security of our citizens and stand as the first line of defense.[5] Education of health care professionals with regard to all these issues must be a key element in this endeavor. For once, we have a chance to prevent a public health crisis. The dental profession is in a primary position to be interactive with public health care agencies and other members of the health care community in recognizing and combating emerging diseases. Oral examination often reveals key findings relating to extensive disease in the whole body. Oral lesions often signal childhood diseases, AIDS, venereal disease, and other conditions. As part of the health care community, dentists must be aware of the integrated attack on emerging disease and play their role in the allied effort to recognize and control infectious diseases. The dental profession by its very nature of exposure to blood, other body fluids, and the generation of aerosols by dental instrumentation with its resultant respiratory transfer potential must be in a ready state of awareness. Whether health care professionals have the time, commitment, resources, or communication to take proper action remains to be seen.

TABLE 1

New World Infectious Agents of Recent Discovery

Virus	Year of Discovery	Country
Tacaribe	1956	Venezuela
Junin	1958	Argentina
Tamiami	1964	USA - Florida
Amapari	1964	French Guiana
Machupo	1963	Bolivia
Parana	1965	Paraguay
Latino	1965	Bolivia
Pichindo	1965	Columbia
Flexal	1975	Brazil
Sabia	1990	Brazil
Oliveros	1990	Argentina
Guarerito	1990	Venezuela
Whitewater Arroyo	1995	USA - New Mexico

Why the Spread of Emerging Diseases?

With the Cold War over, the world no longer competes militarily and instead entered into an era of global trade, modernization, and economic development. International trade and travel increased. Human entry into remote areas of the world increased in the search for raw materials and led to contact with insect vectors and animals with zoophytic diseases not previously encountered. Further complicating the problem is the fact that modern modes of transportation can move disease from one end of the earth to another in as little as 24 hours.[6] As employment opportunities increase in the industrial world, Third World citizens migrate for jobs on a legal or illegal basis. The dental profession cares for both sick and well people of every race and ethnicity. Dentists are exposed to everyone and everything because care and well-being are their credos. Dentists, therefore, must be aware of the rapid changes in public health policy and information transfer.

Insect or arthropod vectors are also being moved across the globe, further complicating disease transmission. One concern is that imported mosquitoes would be capable of feeding on native animal species harboring exotic microbes such as Hantaan virus or Lyme disease. If such a new invader is also capable of feeding on human blood, it would be a vector of transmission of rodent diseases to humans.

Global warming and emerging weather patterns are also being monitored as geobiologic mechanisms for the spread of disease.[7] If, because of climate changes, mosquitoes migrate to areas once too dry or too cold, then they may transmit new diseases to these areas, which were formerly out of their ecological range. Another concern is whether they will then transmit the new disease directly to humans. Will mutations arise that allow different modes of disease transmission? The Hantavirus, or Four Corners Disease, became a newly discovered agent only because of climatic changes with excess rain leading to a huge increase in grasses subsidizing the rodent population.8 The Hantavirus, however, was not a new agent introduced to the United States, but one found throughout the country in traceable

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migration patterns over a period of tens of thousands of years.

Emerging Diseases: Population and Geography

The world's population rate is actually subsiding, but the population increase will still represent several billion more people in the next century. Environmental and economic conditions will intensify, and the results will affect the world's health as well. The gap between the richest and poorest will expand. Urbanization is increasing, and more people are being jammed together in closer quarters. Migration of peoples from crowded lands with limited opportunities and major problems is a continuing event. Illegal migration will help to spread disease from one land to another. World travel from sheer population growth in an expanding international economy will shrink the earth and its peoples. The United States will maintain its indigenous population with a low birth rate. The United States will, however, still increase its total population by 120 million in the next 50 years because of immigration.[9]

The disruption of health care services and, most vitally, public health services usually leads to the dissemination of disease. In many instances, large cities in wealthy nations may provide better health services, sanitation, and medical facilities. These services are dictated in many ways by the availability of monetary funds. Large increases in population in Third World nations can only lead to greater stresses on their already weakened infrastructure. The issue of infectious diseases will be a major factor for humanity in the next century. Dentistry, as a member of the health care society, must maintain its place of awareness in that interactive community.

Drug Resistance and Re-emergence of Disease

Microbial drug resistance has resulted in a decline of efficacy of antimicrobial agents, be they antibiotic or chemotherapeutic in nature. Microbes have the uncanny ability to slip out of drug control by mutation, which removes one of the clinician's most powerful weapons. Previously susceptible microbes, controlled by antibiotics for 50 years, have in the past decade jumped to drug resistance at a remarkable level.[10] Vancomycin-resistant enterococci, methicillin-resistant staphylococci, penicillin-resistant pneumococci, and multiple-drug-resistant tuberculosis are just a few of the drug-resistant strains that have appeared with a wrath at the door of the embattled clinician.11 The race is between the development of new drugs and the evolution of mutations, and that is a race the microbes are winning.

How Do We Combat the Selection of Resistant Microbes?

- Reduce the overprescribing of antimicrobials to reduce the selection of resistant microbes. This is an area where dentistry must do its part.
- Reduce excessive use of antimicrobials in commercial animal food.
- Interrupt the global spread of disease, if possible.
- Closely monitor the development and appearance of drug-resistant strains throughout the world.
- Continue to develop new drugs.

Current Status for Immunization of Health Care Workers

Recommendations have been made recently for the immunization of health care workers.[12] These suggestions include vaccines for hepatitis B, influenza, measles, mumps, rubella, and varicella. Immunization of all adults is recommended for tetanus, diphtheria, and pneumonia.

Vaccines for tuberculosis, such as the BCG vaccine, are not currently recommended in the United States. The TB vaccine is not sufficiently efficacious to be used, and the vaccine would interrupt TB skin testing because antibodies raised by vaccination would yield false positives.[13] Intensive work is under way to develop a fully workable TB vaccine. Vaccines, however, take time and testing; and no set date can yet be assigned to a successful TB vaccine program.

To monitor the well-being of health professionals, immunization records should be kept for each health care worker. The record should reflect vaccination histories and documented disease. Records are expected to be updated and maintained.[14] Vaccines remain a main line of defense against the invasion of infectious disease. The question remains whether vaccines can be developed rapidly enough and with sufficient ability to neutralize invading microbes. Vaccines are not easy to produce at a feasible cost for worldwide use. The human race has also been stymied in an attempt to develop vaccines against venereal disease, AIDS, influenza, hepatitis type C, and tuberculosis, to name a few. Still, vaccines are the best means of prophylaxis available. Yet the question remains, will vaccines be successful with newly emerging diseases. Rapid mutation of viruses and bacteria from antibiotic-susceptible types to multiple-drug-resistant forms will greatly challenge scientists working in drug therapy.

The importance in updating health care workers and the public on vaccines has prompted the CDC and the public health training network to sponsor a

live satellite broadcast in September 1998. This communication outreach was designed to update and inform health care professionals on both vaccination and patient counseling. Topics included information on new vaccines, such as those for rotavirus, Lyme disease, and attenuated influenza. Recommendations on measles and the vaccination of health care workers were important topics. Participants were able to interact with instructors via toll-free telephone and fax lines, in addition to obtaining continuing education credits. It is expected that this style of communication will continue to be used and expanded. Additional information and registration will be available from county and state health agencies via their immunization programs. A list of state immunization coordinators is available on the World Wide Web at http://www.cdc.gov/phtn.[15]

The effectiveness of childhood vaccination programs continues to be impressive.[16] The current measles, rubella, mumps, and chicken pox vaccine program has led to a reduction in childhood disease approaching elimination in the United States. The critical issue is to be able to continue vaccine production against new diseases. DNA-type viruses are basically more resistant to mutational changes than are RNA viruses. RNA viruses act through the enzyme reverse transcriptase to make DNA from RNA, and they have a tendency to make errors in replication. This loss of fidelity leads to higher mutational rates, thereby adding to the difficulty of vaccine production.[17]

Governmental Concerns

The fiscal year 1999 budget reflect the U.S. government's concern regarding health care matters. The CDC is receiving $2.6 billion, an increase of $95 million over fiscal year 1998. The emerging infectious disease program is expected to receive $79 million, some $20 million more than fiscal year 1998. All other elements of research -- both basic and applied -- are receiving substantial increases, which indicates the federal government's increasing interest in infectious diseases.18 The long-range governmental approach views containment, early diagnosis, and international cooperation as areas of primary importance. Information exchanged with the World Health Organization, international health agencies, and U.S. health agencies will be further enhanced to reinforce efforts toward awareness and combating emerging diseases.

Emerging vs. Re-emerging Diseases

There are numerous diseases, such as TB, that disappear, then re-emerge years later to attack society again. In other instances, diseases re-emerge on a continuous basis, as is the case of influenza, which returns on a yearly basis in a genetically modified form. In still other instances, a disease may lie dormant or be found at low levels and suddenly and inexplicably break out in huge numbers.

An example of this phenomenon is the respiratory syncytial virus (RSV). The disease appears in a few short months and soon after explodes into widespread dissemination.[19] The epidemiology is constantly studied while also being monitored in other countries around the world. At present, no clear-cut mechanism of transmission and rapid dissemination is known.[20]

Hemorrhagic Fevers

Emerging diseases appear from unknown quarters and enter society from unknown backgrounds. The hemorrhagic fevers are a group of emerging diseases that have received public recognition through movie and media exposure. Ebola virus has been widely publicized yet is only one of a number of hemorrhagic diseases. In fact, there are Old World and New World hemorrhagic fever viruses found in the Arena Virus Group. A listing of current New World infectious agents is shown in **Table 1**.

Hemorrhagic fever viruses have mortality rates ranging from 15 percent to 30 percent with exceptions such as Ebola and Marburg viruses, which range up to 80 percent mortality.21 Ebola has received the greatest amount of publicity, yet its animal reservoir in nature has never been found, though hundreds of animal species in Africa have been examined for presence of the virus. There is no treatment for Ebola, and the virus is lethal. Outbreaks have been contained in Africa, although monkey-targeted strains have appeared in an animal colony in the United States. The virus is on the skin of patients, and it is presumed transmittable via topical skin. Needle transfer occurs readily, but other modes of transmission, vector or otherwise, are entirely feasible. Will Ebola strains targeted for humans ever appear in the United States? The more appropriate question seems to be not whether, but rather, when, where, and how severe.

Old World Emergers and Relevant Outbreaks

Old World emergers and relevant outbreaks are shown in **Table 2**. Ebola and Marburg agents make up the filovirus group. Ebola virus has four very distinct types, almost four different groups. The animal reservoir is unknown, and it is quite possible that there are more than four types. There are no therapies, and no vector is known. We are in a vulnerable position if the agent appears in the United States.[22]

The spread of European diseases such as measles and smallpox into the New

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TABLE 2

Old World Emerging Infectious Agents

Virus	Year	Area
Rift Valley Fever	1993	Egypt
Lassa Fever	1994	Nigeria, Sierra Leone
Crimean Congo Fever	1994	Middle East
Ebola	1994	Ivory Coast
	1995	Zaire
	1994-1996	Gabon

World after its discovery, exploration, and colonization gives us a historical perspective of what could lie in the future in the third millennium.[23]

Dengue Fever

Dengue and yellow fevers are members of the Flavivirus group. Yellow fever has an effective vaccine and is under general control. The Dengue virus can be partly controlled by vector control and has some supportive therapy. Yet Dengue has spread throughout South America, Central America, the Caribbean, and even into the U.S. Gulf Coast in the past two decades. Generally not life threatening, it has a severe morbidity and lasts from three to seven days. A sudden onset of fever, frontal headache, nausea, vomiting, and liver enzyme elevation are followed by several other signs and symptoms. Convalescence may be prolonged for weeks. Dengue and the mosquito Aedes aegyptai are linked. The spread of the mosquito makes a trail for the Dengue virus. Urbanization and economic expansion in Third World countries mark the increase of Dengue transmission. Epidemics become larger as geographic expansion of the virus continues. Unprecedented population growth is also a major factor in Dengue spread. There are no vaccines. Mosquito control is a must along with improvement in the public health system infrastructure. Research for a workable vaccine and into epidemiology and pathogenesis is an absolute necessity.

Tuberculosis

With TB, one never knows where or how severe an outbreak may be. Source or index people are capable of widespread disease transmission be they in small rural communities or large cities. Increased virulence within strains capable of rapid dissemination and transmission has been reported with only minimal exposure.[24]

Tuberculosis has been on the list for disease elimination, but the disease has resisted all efforts to be subdued. Vaccines are under test, but these are long-term ventures. Environmental control methods such as ventilation, HEPA air filtration, and ultraviolet light radiation have reduced TB transmission in some health care settings.[25]

The CDC has actually recommended chemotherapy as a preventive measure for the control of TB in people who are at high risk for the disease but do not actually have it. Without a quality vaccine, however, TB control is an illusion. Easily spread by aerosol transmission, Mycobacterium tuberculosis will remain a problem in the health care industry. The slow-growing nature of the microbe, coupled with the emergence of multiple-drug-resistant strains, has added to the current problem.26 The recognition of a continuous, productive cough is perhaps the best sign for the presence of disease. Skin testing for exposure to TB will continue to be expanded in the attempt to monitor the disease spread in health care workers.

The Global Picture of HIV

In 1996, a decline in the deaths from AIDS finally occurred in the United States. This downward trend was apparently due to the introduction of multidrug therapy or "cocktails" containing protease inhibitors and other chemotherapies. Unfortunately, HIV mutations soon appeared, bypassing the efficacy of these therapy regimens.[27] Furthermore, ceasing therapy will allow the re-appearance of the AIDS virus in serum and some virus is found in semen even when serum levels are undetectable. While the drugs are at least temporarily effective at costs of $10,000 to $30,000 per year in First World nations, that expense option is not easily accommodated in the Third World, so the worldwide pandemic is increasing in intensity.[28] Developing nations with large populations, low income levels, and inadequate public health infrastructures truly have severe problems with AIDS. It is estimated that the number of people with HIV is currently 900,000 in North America and 600,000 in Western Europe. Yet, since the advent of AIDS in the early 1980s, more than 40 million people throughout the world have contracted the virus, with almost 12 million dead. Some 16,000 people in the world contract HIV on a daily basis. Sub-Saharan countries and nations in Southeast Asia have extremely high rates of HIV Infection. The sub-Saharan area contains two-thirds of the world's AIDS population and 90 percent of all the childhood AIDS.[29] Unprotected sex and untested blood supplies are the main causes behind Southeast Asia's recent explosion of AIDS, and India soon will lead the world in HIV-positive people, with up to 5 million infected. Burma, Vietnam, and parts of China are also entering levels in the danger zone.

What are the causes behind disease expansion? Social levels are extremely important. The disease may first appear

among the wealthier, well-traveled classes, but rapidly spread to the poor and the disenfranchised. Sexual exploitation and lack of access to social and public health services are factors in the dissemination of AIDS. Education is always a major control mechanism in the spread of disease, at any level of society. Areas where AIDS has not previously been detected, or has been at low levels, are now starting to explode with large numbers of infected people. Southern Africa and Cambodia are starting to experience this new onslaught. The spread of this disease into populations not yet touched is virtually certain to happen.[30] Chemotherapy is very expensive and limited in long-term use based on the mutational abilities of the virus. The same problem exists for vaccines. Can we develop a vaccine that works for multiple strains? It must be noted that the serological test for AIDS is not for the presence of the virus, but for the presence of the antibody. If we already mount an antibody immune attack on the AIDS virus by being infected, how much better can a vaccine induced by artificial immune response be? Protected sex and monogamous relationships are of paramount importance. There are no easy solutions to HIV, but society must take the difficult ones. We really have no choice.

Centers for Disease Control and Prevention Strategies for the 21st Century

To prevent emerging diseases in the next century, the CDC has recently updated its strategy.[31] The CDC has been compelled to assume new standards of strategy because of increased global poverty, rapid growth of the world's population, migration, international travel, food distribution, and increased travel. The CDC's strategy is to deal with today's diseases with treatment and tomorrow's with prevention. The four main goals of the CDC's strategic approach are:

- Surveillance and response;
- Applied research;
- Infrastructure and training; and
- Prevention and control.

Ultimately, a stronger and more flexible public health system will be expected to evolve, one that is capable of rapid response to existing disease and simultaneously capable of controlling anything from an emerging disease outbreak to a bioterrorist attack. To implement such a strategy will require an enormous effort of all parties: the health care industry, health departments, universities, and virtually every segment of society. Dentistry, as part of the health care community, must be aware of the international problems and remain prepared in infection control measures and the recognition of disease in patients.

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Know Thy Hepatitis: A Through TT

Michael Glick, DMD

ABSTRACT Several viruses have been identified as causative agents of hepatitis in humans. Other hepatotropic viruses have been implicated as potentially disease-causing. This article reviews the present knowledge of hepatitis A virus through the newly discovered hepatitis TT virus and their implication for dentistry.

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Recent epidemiological data suggest that more than one in every 50 dental patients in the United States can be expect to be a chronic carrier of hepatitis B virus (HBV) or hepatitis C virus (HCV). Both of these viruses are associated with a high degree of morbidity and mortality. Other bloodborne and enterically transmitted hepatotropic viruses may also cause disease in humans, and it is important for oral health care providers to recognize the impact these viral infections have on dental practice standards. This article will provide an overview of hepatitis A through TT viruses and their implications in a dental setting.

The term "hepatitis" describes an inflammation of the liver but does not necessarily denote a cause or outcome of this specific condition. Although hepatitis as a disease has been recognized for more than 2,500 years, it was not until 1979 that the first "hepatitis virus" was isolated in cell culture.[1] Numerous toxic substances and pathogens, including several viruses, have been implicated in inducing hepatitis. From the 1940s through the 1960s, only an enterically transmitted infectious hepatitis virus and a parenterally transmitted serum hepatitis virus were recognized. These two viruses were designated hepatitis A virus (HAV) and hepatitis B virus, respectively. However, in 1965, Blumberg and colleagues identified the "Australian antigen," which was later shown to be part of the envelope protein of HBV.[2] With the ability to test for HBV in serum, it became clear that at least one more

Table 1

Characteristics of Hepatitis Viruses Causing Disease in Humans

Virus	Family	Nucleic acid type	Envelope	Chornicity	Size	Main known routes of transmission
HAV	Picornavirus	RNA	No	No	27 m m	Fecal-oral
HBV	Hepadnavirus	DNA	Yes	Yes 3-5%	42 m m	Sexual contact, parenteral
HCV	Flavivirus	RNA	Yes	Yes >85%	30-50 m m	Parenteral, sexual contact
HDV	Satellite	RNA	Yes	Yes 20-70%	40 m m	Sexual contact, parenteral
HEV	Calicivirus	RNA	No	No	32 m m	Fecal-oral

hepatitis-causing virus was present in blood. The existence of a third agent became even more evident in 1973 when specific tests could distinguish between HAV and HBV. This new transfusion-associated virus was coined non-A, non-B (NANB) as a new specific virus had not yet been identified, and a diagnosis was made by exclusion of HAV and HBV.[3,4] Today, five distinct viruses causing disease in humans have been designated as hepatitis viruses. They are HAV, HBV, HCV, hepatitis D virus (HDV), and hepatitis E virus (HEV) (**Table 1**). HAV and HEV are mainly enterically transmitted while HBV, HCV, and HDV are most commonly transmitted parenterally. Although all these viruses share a common target organ, the liver, and may cause similar clinical signs and symptoms, they have very little else in common.

An additional two viruses, hepatitis G virus (HGV) and a virtually identical virus, hepatitis GB virus type C (GBV-C), have been discovered. But, unlike hepatitis A through E, no causal relationship has been established between HGV and GBV-C and acute hepatitis.[5,6] Most recently, novel virus, designated as TTV, or TT virus, was discovered in 1997 and may be associated with post-transfusion hepatitis.[7] A few cases of a hepatitis F virus (HFV) have been described in France, but it has not been linked to either acute or chronic disease in humans.[8]

Acute hepatitis in the United States is most commonly associated with HAV (47 percent), HBV (34 percent), or HCV (17 percent).9 Although acute hepatitis is associated with low morbidity, chronic hepatitis is linked to 16,000 deaths per year. Seventy percent of these cases are associated with HCV, 20 percent with HBV, and 10 percent with concomitant HCV and HBV infection.[10] The rate of progression to permanent liver damage differs among types of viruses, yet cirrhosis and hepatocellular carcinoma (HCC) invariably follow long-term chronic infection. In cases of both HBV and HCV infections, it may take 25 to 30 years for HCC to develop. With co-infection of more than one virus, underlying chronic liver disease from other causes, or concomitant alcohol consumption, a much more rapid progression can occur.

Hepatitis A Virus

Hepatitis A virus is a single-stranded RNA virus belonging to the picornavirus family. Only one serotype of HAV has been recognized, and immunity to any of the seven known genotypes confers immunity and protection against all others.11 Transmission of HAV occurs almost exclusively by the oral-fecal route. Primarily from person to person, but also by contaminated food or water. Transmission by blood can occur during the incubation period and the early acute phase, when titers as high as 105 infectious doses per milliliter of blood have been documented.[12] Although rare, transmission of HAV by blood transfusion has been reported.[13] Even though HAV can be detected in saliva during the incubation period, transmission by saliva has not been reported.[14] Most exposures to HAV, as with most exposures to all hepatitis viruses, are from unknown sources.

The incubation period of HAV infection ranges from 15 to 50 days with an average of 28 days. However, the two weeks preceding clinical signs of the disease are considered the most infectious period. Immunoglobulin M (IgM) anti-HAV can be detected in the serum five days following exposure to HAV while IgG anti-HAV is produced during the convalescent phase. This latter immunoglobulin will confer lifelong protection against reinfection.

Hepatitis A is an acute, self-limiting disease with symptoms typically lasting for approximately two weeks, but they may persist for as long as two to six months.[15] Prognosis for patients contracting HAV infection is good, and a chronic state does not develop. The severity of HAV infection increases with age and in individuals with underlying chronic liver disease from other causes. It is estimated that the mortality rate of hepatitis A infection in the United States is less than 0.2 percent, which results in approximately 100 deaths per year. In

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TABLE 2

Serologic Markers for HBV and Their Significance

Serologic marker	Significance
Hepatitis B surface antigen (HbsAg)	Indicates chronic or active HBV carrier status.
Antibody to hepatitis B surface antigen (anti-HbsAg)	Indicates immunity to HBV.
Antibody to hepatitis B core antigen (anti-HbcAg)	Indicates exposure to HBV.
Immunoglobulin M antibody to hepatitis B core antigen (IgM-HbcAg)	Indicates acute infection with HBV or active disease during flare-up in a chronic HBV carrier.
Immunoglobulin G antibody to hepatitis B core antigen (IgG-HbcAg)	Indicates exposure to HBV and possible carrier state.
Hepatitis B e antigen (HbcAg)	Indicates active HBV replication and infectivity.
Antibody to hepatitis B e antigen (anti-HbeAg)	Indicates resolved HbeAg viremia.
HBV DNA	Indicates active HBV replication and infectivity.

children younger than 6, 70 percent of infections are asymptomatic, while more than 70 percent of infections in older children and adults are symptomatic.

There are two hepatitis A vaccines licensed in the United States, Havrix (SmithKline Beecham Pharmaceuticals) and Vaqta (Merck & Co., Inc.). Both vaccines contain formalin-inactivated viral particles and are equally effective in conferring up to 100 percent protection against symptomatic hepatitis A.[16,17]

There is also a combination hepatitis A and B vaccine, Twinrix (SmithKline Beecham Pharmaceuticals), that may be used for travelers to endemic areas.[18]

Hepatitis A is not considered an occupational hazard to dentists, and routine vaccination for dental personnel is not recommended.

Hepatitis E Virus

Hepatitis E virus, a single-stranded RNA virus closely resembling the calicivirus family, was first described in 1983.[19] As with HAV, HEV is an enterically transmitted virus, mainly through fecally contaminated water. Interestingly, even though anti-HEV may be found in 1 percent to 5 percent of blood donors in the United States,[20] this virus rarely causes disease in this country. However, HEV poses a risk to people traveling to endemic regions.[21] Signs and symptoms of HEV disease are similar to those of HAV, and it has an incubation period averaging 40 days. During the incubation period, viremia is present; but an infectious titer has not been determined. An increased mortality rate, of up to 30 percent, has been reported among pregnant women outside the United States.[22] Protective immunity after exposure has not been documented, and no human vaccine is available.[23]

Similarly to HAV, HEV is not associated with a chronic disease state and poses no occupational risk to dental providers.

Hepatitis B Virus

Evidence of the hepatitis B virus was first reported in 1965,[2] and it was soon evident that this virus was a leading cause of chronic hepatitis, cirrhosis, and primary HCC. It is estimated that more than 350 million people are infected worldwide, with 1.25 million chronic HBV carriers in the United States.[24] The most common modes of transmission in the United States are sexual contact and injection drug use. However, occupational exposure in health care settings also occurs. Other, much less common, modes of transmission include that of infected health care workers to patients.[25] Nine clusters of infected patients have been documented where dentists have been identified as the source of HBV.[26] However, no HBV transmission from a dentist has been documented since 1987. Large quantities of HBV can be found in serum of infected individuals, 108 to 1010 virions/ml, but also to a lesser extent in other body fluids, including saliva, making this virus highly infectious. It is estimated that the risk of acquiring HBV infection after a percutaneous needlestick from an HBeAg carrier is approximately 30 percent, while the risk decreases to approximately 6 percent if the carrier is only a hepatitis B surface antigen-positive carrier.[27] Dentists are at an increased risk of acquiring HBV compared to the general population, but this risk is drastically reduced by employing standard precautions, including immunizations.[28]

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Hepatitis B is a double-stranded DNA virus belonging to the hepadnavirus family. Five genotypes of HBV have been reported, all of the same serotype. The incubation period for HBV infection ranges from 45 to 160 days, and the ensuing disease is associated with a mortality rate of 0.2 percent to 2.0 percent. The immune response to HBV is complex but determines the outcome of the infection, both the hepatic damage and protective immunity. Among healthy adults, the infection is self-limiting in 95 percent of cases resulting in the production of protective antibodies indicating resolution, while 3 percent to 5 percent remain chronically infected.[29] The opposite is found among infected infants; 95 percent become chronic carriers.

There are several serological markers associated with HBV infection that will indicate the status of the disease (**Table 2**). The whole virion, also called the Dane particle, is a sphere containing a core that encloses the viral DNA. The outside envelope is associated with the hepatitis B surface antigen, or HBsAg. Development of cellular and specifically humoral immunity to HBsAg, anti-HBsAg, will confer protection from reinfection. The production of these antibodies is also the basis for the two HBV vaccines available in the United States. The antigen associated with the viral core, the hepatitis B core antigen, or HBcAg, induces the cellular immune response that is ultimately responsible for destroying cells infected with HBV. Routine serologic assessment of HBcAg is not available, but anti-HBcAg is used to determine exposure to HBV because it is present in all people exposed to HBV. This antibody, unlike anti-HBsAg, is not protective but instead is used to distinguish acute from chronic infections. The early antibody to HBcAg, IgM-HBcAg, usually disappears within a couple of months of an acute infection but can sometimes resurface during flare-ups in chronic HBV carriers.

Another antigen derived from the core gene, hepatitis B e antigen, or HBeAg, is a marker for active viral replication. Although HBeAg-positive individuals are regarded as highly infectious, there is a group of infected individuals with a precore mutant strain of HBV that prevents expression of HBeAg, yet allows for expression of infectious virus.[30] A more accurate expression of viral replication and infectivity is the presence of HBV DNA in serum. There are no standardized tests to determine the degree of infectivity of an individual based on quantitative HBV DNA analysis or level of HBeAg. Furthermore, detection of HBV DNA in both in serum and peripheral blood mononuclear cells after a serological cure suggests that reactivation of infection may occur due to immune suppression.[31]

The vigor of the infected person's immune response will determine the outcome of the infection. If the immune response is successful, there is complete destruction of all infected cells, halted viral replication, and production of protective antibodies. If the immune response is inadequate, or if the infected person's immune system does not have the means to eradicate the infection, a chronic state will ensue.[32] Hepatitis B is not cytopathic in itself; instead, it is the persistent immune assault in chronically infected individuals that is ultimately responsible for liver complications. The constant inflammatory state and repeated cellular generation increases the risk for the development of cirrhosis and HCC. It is estimated that chronic carriers of HBsAg have a 12- to 79-fold increased risk of dying from cirrhosis as compared to healthy individuals.[33]

A plasma-derived vaccine, Heptavax-B (Merck & Co., Inc.) was introduced in the United States in 1981; and later two recombinant vaccines, Recombivax HB (Merck & Co., Inc.) in 1987 and Engerix-B (SmithKline Beecham Pharmaceuticals) in 1989, were licensed and are now available. These vaccines have proven to be highly effective, protecting more than 96 percent of vaccinated young, healthy adults. The acceptance of these vaccines has resulted in a decline from 17,000 annual HBV infections among health care workers in 1983 to only 400 in 1995.34 In 1983, the incidence of HBV infections among health care workers was 386 per 100,000 but has since declined dramatically to 9.1 per 100,000 in 1995, which is less than one-fifth the incidence of HBV among the general population (50 per 100,000). Investigations of the long-term (five-to-11-year), effect of HBV vaccination have revealed no acute or chronic cases of HBV among vaccine responders, although 2.6 percent developed anti-HBeAg, suggesting subclinical infections.[34] These longitudinal investigations indicate that vaccine-induced protection from HBV persists for at least 11 years. Although guidelines have suggested that individuals with antibody levels below 10 mIU should receive booster doses, this has not been substantiated in clinical studies. Subsequently, recommendations have been proposed to limit booster doses only to individuals who have demonstrated failure of the vaccine to protect against clinically significant HBV infection, viremia, or development of chronic infection.[34]

Hepatitis D Virus

Hepatitis D virus was initially reported by Rizzetto and colleagues in 1977 as a co-infection with HBV.[35] This defective negative-stranded RNA virus is unique

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among animal viruses because it depends on HBV for propagation. Although transmissibility is dependent on the HBsAg, HDV virions can replicate without the helper HBV.[36] The HBV virion consists of the HDV RNA genome, a hepatitis delta antigen (HDAg), and an envelope of HBsAg. Thus, the infectivity and survival of HDV depends on the integrity of HBV since HDV needs only the HBsAg to form the envelope of the virus. Once the HDV virion or genome is within a permissive cell, it can replicate without the helper HBV.

There are three different HDV genotypes with different geographic and demographic distributions and, possibly, severity of disease.[37] Genotype 1 is the predominant type in North America and Europe. In the United States, HDV infections are most commonly found among injecting drug users and hemophiliacs.[38] The incubation period for HDV averages 35 days and carries a mortality rate of from 2 percent up to 20 percent.[39]

Co-infection of HBV and HDV implies a simultaneous exposure to the two viruses, while superinfection consists of HDV exposure of an already chronic carrier of HBV. Acute co-infections are mostly self-limiting with approximately 2 percent to 5 percent of exposed individuals becoming chronic carriers of both viruses. Superinfections are commonly not resolved spontaneously, with 70 percent to 80 percent of infected individuals becoming chronic carriers. Chronic HDV infections often progress to cirrhosis, accounting for approximately 50 percent of this condition among chronic HBsAg carriers.[40]

Immunization with HBV vaccine also confers immunity to HDV.

Hepatitis C Virus

It is estimated that 3.9 million Americans, or 1.8 percent, are chronically infected with the hepatitis C virus, making HCV infection the most common bloodborne infection in the United States.[41] However, this may be a conservative estimate because many individuals at high risk for HCV are not included in the national surveys conducted to establish prevalence of infections such as HCV.

HCV is an RNA virus with at least six different genotypes and more than 90 subtypes.[42] The most common genotype in the United States is type 1, which accounts for approximately 70 percent of infections.[43] The virus mutates often, and an infected individual may carry a heterogeneous population of HCV and even different types. It is possible that this genetic diversity enables the virus to escape the body's immune surveillance, causing its high chronicity rate.

The rate of new infections has declined dramatically since the cloning of the virus in 1988, from an average of 230,000 to 36,000 infections per year by 1996.44 However, due to the high rate of chronicity (85 percent to 90 percent of all individuals infected with HCV) and poor long-term response to therapy, deaths related to chronic HCV are expected to increase dramatically. It is estimated that 20 percent of all individuals assessed in inner-city emergency rooms and more than 30 percent of prison inmates are carriers of HCV.

Infected individuals develop antibodies to HCV that can be detected serologically. These antibodies are markers of infection but do not confer immunity, and only 10 percent to 15 percent of acutely infected individuals have a self-limited disease.

Only 25 percent to 35 percent of individuals with acute HCV infections will exhibit clinical symptoms, such as malaise, anorexia and jaundice, which may appear on an average of six to seven weeks after exposure. This low rate of clinical disease contributes to the high incidence of infected individuals not being aware of their infectious status. The major causes of death secondary to chronic HCV infection are cirrhosis, liver failure, and HCC. Over a period of 20 to 30 years, 10 percent to 20 percent of chronically infected individuals will develop cirrhosis, while 1 percent to 5 percent develop HCC. A combination of cirrhosis and HCC may result in a rate of HCC as high as 1 percent to 4 percent per year. It appears that geographic variations, age greater than 40 at the time of acquiring the infection, male gender, co-infection with other viruses such as HIV and HSV, and alcohol consumption are all associated with increased severity of disease. Mode of transmission may be a risk factor to develop complications secondary to HCV infection. Patients with post-transfusion HCV appear to be at a greater risk to develop progressive liver complications, particularly hepatic cirrhosis, compared to people contracting HCV through other modes of transmission.[45] Serum albumin, prothrombin time, and platelet count are independent laboratory predictors of progressive hepatic destruction.[45] The effect of alcohol consumption on HCV infection has been debated. It appears that total lifetime alcohol consumption as well as even very low levels of continuous alcohol consumption by HCV carriers will have a detrimental effect on disease outcome, increasing viremia and hepatic cirrhosis.[46,47]

Presently, the annual mortality rate of HCV in the United States is more than 10,000, but this number is expected to triple in the next 20 to 30 years.

Extrahepatic manifestations of HCV have been reported. Two of these

TABLE 3

Estimated Prevalence of HCV Infection in the United States41

	HCV Infection prevalence (%)
Hemophiliacs treated prior to 1987	87
Current injection-drug users	79
People with abnormal alanine aminotransferase levels	15
Chronic hemodialysis patients	10
People with multiple sex partners (lifetime)	
50	9
10-49	3
2-9	2
People reporting a history of sexually transmitted diseases	6
People receiving blood transfusions before 1990	6
Infants born to HCV-infected mothers	5
Men who have sex with men	4
General population	1.8
Health care workers	1

conditions are of interest to dentists -- lichen planus and a Sjögren-like syndrome. Several studies have suggested that individuals with lichen planus have a high prevalence, 34 percent to 62 percent, of HCV.[48,49] Furthermore, patients with chronic HCV infections have been found to have a higher prevalence of lichen planus compared with the general population.[50,51] Most of these studies have been performed in Italy and Japan, whereas epidemiological studies from the United States have yet to show a significant association between lichen planus and HCV. It has been suggested that such a relationship may have a geographic predilection.

A Sjögren-like syndrome has also been associated with HCV-infection.[36] It has been documented that HCV-infected individuals have both salivary and lacrimal abnormalities, and it has also been reported that up to 40 percent of individuals with Sjögren's syndrome may have HCV infections.[52] A relationship between virus infections and salivary gland dysfunction has been reported with other viruses and although the exact pathogenesis of this association has not been elucidated, it is possible that HCV may exert a similar effect.

Another confounding relationship has been suggested between HCV and oral cancer. Studies from Japan have indicated a high prevalence of HCV infection among patients with oral cancer.[53] It is not clear if HCV has a causative relationship with the development of oral neoplasms or if the presence of the infection is only an indicator.

Treatment of HCV infection with interferon has not shown long-term efficacy and seems to be a function of its genotype. HCV type 1 is associated with more progressive liver disease and poor response to interferon treatment.[43] Combination therapy with interferon and ribavirin may have a beneficial effect on disease progression. Recent studies have indicated that initial treatment, as well as treatment of patients after relapse of chronic HCV infection, with interferon and ribavirin may produce a sustained undetectable viral load.[54] In the initial treatment group, 38 percent of patients showed undetectable serum HCV RNA after 48 weeks, while 49 percent of patients in the relapse group had undetectable serum HCV RNA after 24 weeks.

HCV is mainly transmitted by direct percutaneous exposure to contaminated blood, primarily through blood transfusions and by injection drug use.[44] However, since the institution of effective screening processes for HCV in donated blood in May 1990 and again in July of 1992, no transfusion-associated HCV infection has been reported to the Centers for Disease Control and Prevention. Still, it is estimated that the risk of acquiring HCV through blood transfusions in the United States is 0.001 percent per unit transfused. The highest prevalence of HCV is found among injection drug users, which accounts for approximately 60 percent of all new infections44 (**Table 3**). The risk of sexual transmission of HCV is slight, yet contributes to a high number of HCV infections. It is estimated that 1 percent of sexual partners of HCV-infected individuals will be infected per year.[55] This risk can be reduced to one-sixth of that figure by giving uninfected partners bimonthly injections with immune serum globulin.[55] As with many other bloodborne viral infections, the risk of transmission is higher from male to female than from female to male.

Only tests measuring anti-HCV are approved by the U.S. Food and Drug Administration for diagnosis of HCV infection. The sensitivity of these tests is more than 97 percent, but they cannot discriminate between acute, chronic, or resolved stages of infection.[56] The average time between exposure and seroconversion is estimated to be from eight to nine weeks. Within 15 weeks after exposure, 80 percent of

TABLE 4

Managemnet of People Exposeda to Blood[74]

Once an exposure has occurred, the blood of the individual from whom exposure occurred should be tested for hepatitis B surface antigen (HBsAg), antibody to HCV (anti-HCV), and antibody to human immunodeficiency virus (HIV antibody). Local laws regarding consent for testing source individuals should be followed. Testing of the source individual should be done at a location where appropriate counseling is available; posttest counseling and referral for treatment should be provided.

HEPATITIS B VIRUS POSTEXPOSURE MANAGEMENT

	Treatment when source is found to be:		
Exposed Worker	HbsAg-positive	HbsAg-negative	Unknown or not tested
Unvaccinated	1. Initiate hepatitis B vaccine - AND - 2. Worker should receive a single does of hepatitis B immune globulin (HBIG) as soon as possible and within 24 hours, if possible.	Initiate hepatitis B vaccine	Initiate hepatitis B vaccine
Previously Vaccinatedb Known[b] Responder	No treatment	No treatment	No treatment
Known Nonresponder	1. Worker should receive 2 doses HBIG (give second dose 1 month after the first dose) - OR - 2. Worker should receive 1 dose HBIG hepatitis B vaccine	No treatment	If known high-risk source, may treat worker as if source were HbsAg-positive
	No treatment		
Response Unknown	Test exposed worker for anti-HbsAg: 1. In inadequate, 1 dose HBIG plus hepatitis B vaccine booster dose 2. If adequate,c no treatment	No treatment	Test exposed worker for anti-HbsAg: 1. If inadequate, initiate revaccination. 2. If adequate,c no treatment

a. Being "exposed to blood" means having blood, blood-contaminated saliva, or a blood-contaminated object come into contact with broken skin or mucous membranes, or pierce the skin as through a needlestick injury.

b. Exposed worker has already been vaccinated against hepatitis B.

c. Adequate anti-HbsAg is 10 milli-international units.

infected individuals will demonstrate presence of anti-HCV, while more than 90 percent of infected individuals will have detectable anti-HCV within five months after exposure. A diagnosis of HCV infection can also be established by qualitative measurements of HCV RNA by polymerase chain reaction. HCV RNA can be detected one to two weeks after exposure, which is before the appearance of both abnormal liver function tests, such as alanine aminotransferase, and anti-HCV.

HCV transmission from patients to health care workers has been documented.[57] The seroconversion rate after a percutaneous injury varies from 0 percent to 7 percent but may be higher, possibly dependent on geographical variations and infectivity of the patient.[58,59] There are no standardized assays to determine infectivity. Furthermore, it is not known what concentration of HCV is necessary to establish infection.

HCV RNA has been detected on surfaces in a dental operatory after treatment of an HCV-infected patient.[60] Although HCV RNA can be detected on surfaces in room temperature for

up to five days, it is not clear if inert contaminated objects can transmit HCV. HCV RNA can also be found in saliva from HCV-positive individuals, and it has been suggested that transmission of HCV has occurred through human bites.[61,62] Although dentists are exposed to both saliva and blood, epidemiological studies have not indicated that dentists are at an increased occupational risk of contracting HCV.28 In cases of percutaneous injuries, no prophylaxis is recommended because no postexposure measures have shown to be effective.[63] It appears that for interferon to have a beneficial response, an established infection need to be present.

Hepatitis G Virus

In 1995, two independent groups of researchers identified a new agent tentatively called GB virus C (GBV-C) or hepatitis G virus (HGV).[64,65] GBV-C was discovered in a 34-year-old surgeon, with the initials GB, who presented with acute sporadic hepatitis, while HGV was isolated from a HCV carrier. Subsequently it was shown that these two agents represented the same virus with a homology of 86 percent and 95 percent of its nucleotide level and amino acid level, respectively.[66] Three, and possibly four, major groups of HGV have been identified in various regions of the world.[67] It is not clear if different variants are the reason for the difference in prevalence seen in geographically separate areas. Studies have indicated prevalence rates of up to 15 percent in West Africa to less than 1 percent to 2 percent in the United States.[68] Much higher prevalence rates have been documented in the United States in subsets of patient populations such as intravenous drug users (15.8 percent to 33.3 percent).[68] A higher prevalence can also be expected among hemodialysis patients and hemophiliacs. It is clear that the primary mode of transmission of HGV is parenteral as in multiple blood transfusions. Vertical and sexual transmissions have been documented; but other modes of transmission may also be present since HGV has been found in numerous body fluids, including saliva.[69] Nonparenteral transmission of HGV may also occur as suggested by the high proportion of HGV seen in apparently healthy blood donors and in the general population.[70]

The question that needs to be answered is if HGV actually causes disease. There is little evidence that HGV independently can cause hepatitis, since the vast majority of patients with HGV and hepatitis are also infected with either HBV and/or HCV. Also, the high prevalence of HGV viremia in the general population without any indication of hepatitis would further support the assumption that HGV is not independently responsible for causing disease. However, it has been speculated that although HGV seems to be benign in most cases, it may become virulent under certain conditions.[70]

TT Virus

The latest of hepatitis viruses has been named TT virus, or TTV.[7] "TT" are the initials of the Japanese patients from whom the virus was isolated and cloned. However, "TT" is also used to designate this virus as the "transfusion-transmitted" virus.[71] The prevalence of TTV among patients with liver disease is not known, but TTV DNA has been detected in 25 percent of 72 patients with chronic liver disease and in 10 percent of individuals without liver disease.[71] Reports from North America suggest a prevalence of TTV of 1 percent among blood donors, 15 percent among patients with cryptogenic cirrhosis, 27 percent among patients with fulminant hepatic failure, 18 percent among individuals exposed to blood products, and 4 percent among individuals without parenteral risk factors.[72]

It is not yet clear if this virus, similar to HGV, is a disease-causing agent in humans, although there are suggestions that TTV may be responsible for non-A-G post-transfusion hepatitis.[73]

Dental Considerations

The main concerns for oral health care providers treating chronic HBV and HCV carriers are contagion and liver abnormalities. Employment of standard precautions, including appropriate immunization, has shown to decrease occupational transmission of both HBV and HCV. Although total elimination of risk cannot be achieved and personal bias as to what constitutes a risk always needs to be considered, the occupational hazard to oral health care providers who are using standard precautions are at a professionally acceptable level. It is estimated that dentists sustain an average of approximately two percutaneous injuries per year. Such injuries are obviously accompanied by a risk of exposure to bloodborne pathogens. Therefore, after percutaneous exposures, it is advisable to obtain permission from the source patient to have his or her blood tested for anti-HCV; HBsAg, when the health care worker is not immune to HBV; and human immunodeficiency virus. Post-exposure prophylaxis is not advisable for exposure to HCV; but for health care workers susceptible to HBV, specific guidelines have been proposed (**Table 4**). Postexposure prophylaxis guidelines for HIV have also been published.[75] The vast majority of chronic hepatitis HBV and HCV patients are asymptomatic and

unaware of their infectious status. There is no need to modify any dental practices for these patients. Any patient identified as high risk for acquiring either HBV or HCV should be encouraged to be tested because early recognition of disease will decrease morbidity as well as subsequent transmissions.

Patients exhibiting liver disease secondary to their viral infection need to be assessed for extent of liver damage. Up to 80 percent of the liver can be destroyed before impaired hemostasis and drug metabolism become evident. Both of these conditions have an important impact on provision of dental care. Although elevated liver transaminases indicate active liver cell damage, liver function can be assessed for the purpose of dental care by a prothrombin time test.[76] Any general dental procedures, including simple extractions, can be safely performed in patients with a normal prothrombin time (10 to 12 seconds) and a platelet count above 60,000 per milliliter. Administration of lidocaine for local anesthesia for dental procedures can be utilized in patients with moderate to severe liver disease. However, certain analgesics, such as acetaminophen, need to be used with caution.[76] Patients with liver disease are not usually more susceptible to infections, and routine antibiotic prophylaxis is not indicated.

Summary

The growing population of chronic hepatitis virus carriers poses a challenge to dental professionals. Increased understanding of the pathogenesis and transmission of these viruses will impact implementation of appropriate dental practices. Furthermore, incorporation of oral health care providers into the overall health care of patients will enhance the quality of life for infected individuals.

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Antibiotic Resistance and Maxillofacial Pathogens: Emerging Treatment Issues

JOHN A. MOLINARI, PHD

ABSTRACT The practice of using antibiotics to treat and control microbial infections is a little more than 50 years old. Widespread administration of multiple classes of antibiotics over the years has had the unfortunate secondary effect of inducing the emergence of an increasing array of drug-resistant microbial strains. This article will discuss the evolution of certain forms of antibiotic resistance, as well as the mechanisms by which bacteria render numerous antimicrobials ineffective. Special emphasis is placed on emerging issues relating to organisms making up portions of the normal oral microflora.

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The introduction of antibiotic chemotherapy for the treatment and prevention of microbial infections in the 1940s represented a historical milestone for modern medicine. Documented clinical successes with penicillin, sulfonamide, and streptomycin regimens were viewed as early indicators of an ensuing "golden age" of antimicrobial chemotherapy. For the remainder of the 1940s and through a major portion of the 1950s, infections caused by many common bacterial pathogens were successfully treated in both hospitalized patients and outpatients. Prominent on the list of susceptible microorganisms were strains of Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, and Mycobacterium tuberculosis.

With widespread antibiotic use, and the sometime misuse of readily available drugs, subsequent observed patterns of infectious disease were very different from those previously studied. Unfortunately, a subtle characteristic of microbial life was asserting itself at the same time that dramatic cures were being chronicled against microbial infection – the incredible potential for microorganisms to adapt to and survive adverse environmental conditions. Early manifestations of bacterial adaptability to antibiotics were apparent soon after the introduction of penicillin G. Certain strains of E. coli and S. aureus were found to develop an adaptive mechanism aimed at surviving exposure to this bactericidal agent. A bacterial enzyme, termed penicillinase, was synthesized by bacteria that had acquired resistance to penicillin G. This adaptive product was

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capable of inactivating a core structural component (the beta-lactam ring) of the antibiotic.[1,2] At present, more than 90 percent of S. aureus strains are resistant to penicillin G, with a significant percentage also resistant to later generation beta-lactamase-resistant penicillins.

By the mid-1960s, resistance to penicillins and numerous other antibiotics was also well-documented among Pseudomonas aeruginosa, Haemophilus influenzae, Klebsiella pneumoniae, and other gram-negative bacilli. Among these important findings was the observation that gram-negative bacteria synthesize a greater variety of penicillin-inactivating beta-lactamases than do gram-positive bacteria.[3,4] With continued discoveries of emerging resistant bacteria, viruses, and mycotic organisms, certain common antimicrobials became less viable treatment choices or were eliminated altogether as treatment considerations for many hospital- and community-acquired infections (**Table 1**).[5] The developmental significance of these resistance mechanisms cannot be overstated, as therapeutic approaches during medical encounters with nosocomial infections had to be dramatically modified. As a result, people presenting with infections harboring resistant microorganisms are more likely to require hospitalization, remain hospitalized longer, and have higher mortality rates than are patients with more antibiotic-susceptible strains.6-8 Even after successful treatment of clinical infection, some patients become carriers, where antibiotic-resistant organisms remain as components of the host's resident microflora. Depending on the primary carrier site within the host's system, the potential exists for later infections demonstrating very different antibiotic sensitivity profiles.

TABLE 1

Emergence of Resistant Microorganisms

Microbial group or genus	Agent	Decade
Staphylococcus auereus	Penicillin	1940
Escherichia coli	Penicillin	1940
Pseudomonas aeruginosa	Multiple antibiotics	1950
Staphylococcus aureus	Methicillin	1960
Enterobacteriaceae	Multiple antibiotics	1960
Neisseria gonorrheoae	Penicillin	1970
Bacteroides fragilis	Penicillin	1980
Haemophilus influenzae	Ampicillin	1980
Mycobacterium tuberculosis	Multiple antimycobacterial agents	1980
Herpes simplex viruses	Acyclovir	1980
Enterococcus	Vancomycin	1980
Candida albicans	Azoles	1990
Staphylococcus aureus	Vancomycin	1990

Mechanisms of Acquired Resistance

A common misunderstanding among health profession students is that exposure of infectious microorganisms to antibiotics in affected tissues will typically destroy all of the invaders. In the world of clinical infections, however, administration of even the most appropriate microbiocidal agent can still induce a small percentage of target organisms to mutate, develop acquired resistance, and survive. The strong selective pressures exerted by antimicrobial agents will by necessity tend to eliminate weaker organisms rather quickly, while at the same time allowing the more resistant forms to remain viable for extended periods. Destruction and elimination of the latter microbes is then largely determined by the efficiency of the patient's innate and specific immune defenses. Since acquired drug resistance can be genetically transferred between members of the same strain, species, genus, or even between different genera, subsequent infections caused by surviving, cross-infected microorganisms may be more difficult to treat. In a very simplified sense, whatever does not kill pathogenic microorganisms can make them stronger and more difficult to destroy later.

Investigation of how acquired resistance develops has been a major focus of chemotherapy research since the early demonstrations of penicillinases, and several distinct mechanisms have been described (**Table 2**).[7-10] It is important to note that even as more-sophisticated techniques are used to investigate specific genetic alterations and stable passage of nucleic acid segments between microorganisms, decades of accumulated scientific information continues to reinforce a few basic trends:

- Bacteria eventually develop resistance to every new antibiotic. Acquisition and the extent of resistance is a matter of degree.[9]
- Selective pressure is exerted on microbial populations by antimicrobials. Early spontaneous mutations provide survivors with a growth advantage over susceptible targeted members of the population.
- Repeated antibiotic use to treat multiple

infections in hospitalized patients is more efficient in selecting for emergence of resistant microorganisms. In some cases, multiple-drug resistance will develop in a species.

Antibiotic Resistance and Maxillofacial Pathogens

As can be seen in **Table 2**, some bacterial groups responsible for the onset and progression of a variety of maxillofacial infections have also developed resistance against commonly used antibiotics. This situation continues to create increased concerns and challenges for attending physicians, dentists, and infectious disease specialists alike on multiple fronts, including treatment of symptomatic infections, colonization and development of asymptomatic microbial carrier conditions, and cross-infection of susceptible people via carriers.

The presence of antibiotic-resistant pathogens in intra- and/or extraoral infections can complicate antibiotic therapy subsequent to drainage and debridement of symptomatic tissues. This may be more of a potential problem in the increasing percentage of patients with a variety of chronic immunosuppressed conditions. Multiple microbial groups listed in **Table 2** have been shown to present this therapeutic dilemma; two will be briefly discussed – S. aureus and anaerobes such as members of the genus Bacteroides.

The ability of S. aureus to develop acquired resistance mechanisms against multiple generations of antibiotics has allowed this adaptive, gram-positive coccus to be among the most common causes of life-threatening hospital and community infections.[10] Documented staphylococcal resistance against many antibiotic groups has made this

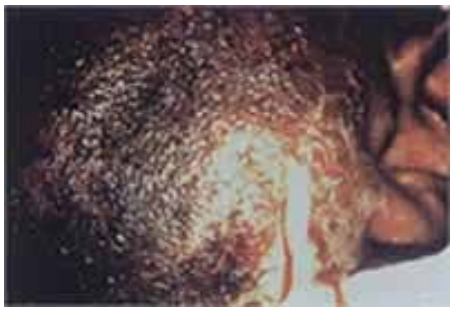

Figure 1. Drainage of mandibular abscess. Analysis of bacterial cultures revealed methicillin-sensitive S. aureus as the major microbial species.

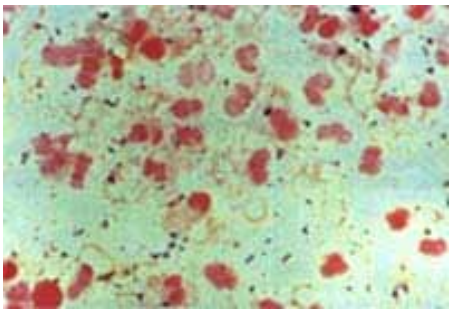

Figure 2. Gram stain of a suppurative exudate smear taken from a periodontal abscess. The predominance of polymorphonuclear leukocytes as acute inflammatory cells is evident, as well as the presence of a mixed microbiota. Aerobic and anaerobic cultures of collected fluid specimens revealed streptococcal and staphylococcal species, along with multiple strict anaerobes, including Fusobacterium, Bacteroides, Prevotella, and Porphyromonas species. Clindamycin chemotherapy was successful in resolving the infection after appropriate debridement of the infection site.

a formidable adversary in nosocomial infections. While not a common etiology of intraoral infections, S. aureus is often isolated from exudates of many maxillofacial soft tissue and osteomyelitis infections. Fortunately, drainage and debridement of localized abscesses (**Figure 1**) can mechanically remove much of the infectious microbial population, thereby making prescribed antibiotic therapy more efficient against remaining pathogens in tissues. Where S. aureus is determined to be the primary microbial type, care must be taken in administering antibiotics. The antibiotic sensitivity profile of the isolates provides very important treatment information. Antistaphylococcal penicillins (beta-lactamase-resistant penicillins), such as nafcillin, oxacillin, and methicillin, have been effectively used to eradicate many of these soft tissue and bone infections.

With regard to antibiotic resistance in anaerobic bacteria, many infections of the oral cavity and most odontogenic infections involve anaerobes. Since anaerobes are among the most sensitive bacteria to environmental conditions and the metabolic activities of other bacteria, multiple facultative microbial forms will also be routinely found in cultured specimens (**Figure 2**). Presence of the latter, such as staphylococci and alpha- and nonhemolytic streptococci, typically provide conditions necessary for subsequent colonization and growth of the more fastidious strict anaerobes. Because necrosis and abscess formation are characteristic of most anaerobic infections, surgical drainage and/or debridement is the cornerstone of treatment. Antimicrobial chemotherapy is an important adjunct treatment modality, with a narrow-spectrum penicillin being a historically useful choice. However, treatment failures with these antibiotics have been reported,[11] with an increasing prevalence of beta-lactamase-producing anaerobes suspected as major causes. Strains of Bacteroides fragilis and Prevotella melaninogenica, among others, have become relatively penicillin-resistant due their acquired ability to produce beta-lactamases.12 For example, in one study, more than 70 percent of 43 non-fragilis strains of Bacteroides were found to be penicillin-resistant.[13] In addition, a gradual increase (20 percent to 40 percent) in beta-lactamase-synthesizing strains of P. melaninogenica has been noted in orofacial infections.[14] Although decreasing effectiveness of other beta-lactams, such as cefoxitin, has been noted with members of the Bacteroides fragilis

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TABLE 2

Major Mechanisms of Antigiotic Resistance

Microorganisms	Mechanism	Antibiotic Representative
Induction of specific drug- inactivating enzymes	Beta-lactams; aminoglycosides	Numerous gram-positive & gram-negative bacteria Examples: Staphylococcus aureus Enterococcus faecium Escherichia coli Pseudomonas aeruginosa Haemophilis influenzae Klebsiella pneumoniae Bacteroides fragilis Prevotella sp. Porphyromonas sp.
Alteration of microbial membrane permeability	Beta-lactams; quinolones; tetracyclines; erythormycin; aminoglycosides	E. coli P. aeruginosa Salmonella typhimurium
Alteration of target site	Beta-lactams; macrolides; vancomycin; clindamycin; sulfonamides; aminoglycosides; rifampin	Streptococcus pneumoniae Enterococcus sp. S. aureus N. gonorrhoeae B. fragilis Campylobacter sp. Clostridium perfringens
Antibiotic efflux from cell	tetracyclines; macrolides; quinolones	E. coli Staphylococcus epidermidis
Alteration in concentration of drug receptor	Sulfonamides	E. coli Proteus sp. Klebsiella sp. Enterobacter cloacea

group,[15] clindamycin resistance continues to remain relatively low.[16] As a result, when traditional beta-lactam agents such as penicillins or cephalosporins are not options because of patient allergic reactions or bacterial resistance, clindamycin and metronidazole or new generations of beta-lactams with clavulanic acid have proven to be efficacious treatment alternatives.[17,18]

Summary

The emergence of increasingly resistant microorganisms requires constant vigilance on the part of health care professionals with regard to utilizing alternative antimicrobial treatment approaches. As the number of hospitalized patients and outpatients presenting with infections containing drug-resistant strains rises, careful identification of etiologic organisms and their sensitivity profiles will continue to take on increased importance in ensuring successful treatment. What was once thought primarily to be a medical issue in hospitals has gradually involved more oral surgeons, periodontists, endodontists, and other dentists. In addition to symptomatic infections, affected patients may become colonized as short-or long-term carriers of strains of multiple-drug-resistant S. aureus or other potentially dangerous pathogens. It should also be remembered that colonization is much more common than clinical infection and also more difficult to eliminate. Judicious use of antibiotics only when needed and strict adherence to routinely effective infection control practices have been shown to reverse some of the described trends, and these approaches need to be expanded.

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The 1997 Prevention of Bacterial Endocarditis Recommendations by the American Heart Association: Questions and Answers

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ABSTRACT Since the publication of the American Heart Association 1997 recommendations for the prevention of bacterial endocarditis, questions have arisen regarding the application of these guidelines. It is impossible for any such recommendations to include all conceivable clinical situations that might arise, and therefore questions are appropriate. Frequently asked questions are included in this article. Answers provided for the questions are the opinions of the authors, who participated in the formulation of these guidelines, and are not intended to supplant the judgment of the dental health professional who is privy to all the facts when the individual clinical decision is made.

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Note: The authors are members of the American Heart Association Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease and were co-authors of the 1997 Endocarditis Prevention Recommendations.

The 1997 American Heart Association statement on the prevention of bacterial endocarditis has appeared in several professional journals[1,2] and has generally been well-received. The new guidelines have better defined clinical circumstances that require antibiotic prophylaxis, have simplified dosing, and have provided more alternative drug choices. As with any recommendation, it was impossible to include advice on all the potential clinical situations and nuances that might occur with the implementation of these guidelines. Accordingly, a number of questions have been raised that merit appropriate clarification.

This article addresses, in question-and-answer format, actual questions that have been frequently asked during the first 15 months after the publication of the original guidelines, and this article will best be read in conjunction with them. If the reader is unfamiliar with the AHA guidelines, the Circulation paper can be obtained from the American Heart Association, 7272 Greenville Ave., Dallas, TX 75231-4596 (reprint No. 71-0117). Selected references have been employed as deemed appropriate, but the guidelines should serve as the general reference source.[1]

The answers provided are the opinions of the authors, all of whom answered these questions after inquiries to the American Heart Association (AHA). All of the authors also were members of the committee that formulated these guidelines. These opinions do not represent official statements of the AHA. These responses are the authors' best clinical judg-

ment and are not intended to replace the health professional's own best judgment in a given clinical situation. At times, only the individual present and responsible for a given clinical decision will have all the facts necessary to perform the due diligence required.

The health professional is ultimately responsible for the final decision and might well be served to incorporate into the clinical written record a notation that: "In my best clinical judgment," the action taken was the most appropriate. This will alert any subsequent reviewer that particular attention was paid to this clinical situation. Key contributing circumstances to the decision process may also need to be appropriately placed in the patient's dental record.

Questions and Answers

Antibiotic prophylaxis is to be employed when dental procedures are associated with any significant bleeding. What precisely is meant by "significant bleeding?"

One of the major goals of the 1997 guidelines was to reduce any potential contribution of unwarranted antibiotic prophylaxis to the concern of microbial resistance to antibiotics. In the case of dentistry, this was done by limiting antibiotic prophylaxis to only those dental procedures associated with a significant risk for bacteremia and not to all procedures associated with any bleeding whatsoever. As a guide to the dentist, a table was prepared to differentiate between dental procedures most likely to be associated with significant bleeding (endocarditis prophylaxis recommended) and procedures not ordinarily associated with significant bleeding (endocarditis prophylaxis not recommended) (Table 1). This arrangement more closely agrees with recommendations of other current advisory statements in this regard. It is conceivable that procedures not recommended for prophylaxis might be associated with significant bleeding, particularly in patients with poor oral hygiene; and in such a situation antibiotic prophylaxis may be appropriate.

The table on Dental Procedures and Endocarditis Prophylaxis (Table 1) does not mention the placement of dental matrix bands. Where does this fit in the listing of dental procedures?

The dental matrix band would be analogous to the placement of a gingival retraction cord where significant bleeding is not likely to be encountered, particularly in a patient with good oral hygiene. As stated in Table 1, clinical judgment may indicate antibiotic use in selected circumstances associated with significant bleeding. The case circumstances and patient risk category should be weighed together in this decision.

Antibiotic prophylaxis is not recommended for suture removal. What about oral or periodontal surgery that may require considerably more sutures than simple extractions?

The relationship between bacteremia produced in this manner and development of infective endocarditis is not documented. If extensive suturing is employed and significant bleeding is anticipated at suture removal, then antibiotic prophylaxis may be employed.

If the patient forgets to take the recommended antibiotic, can I just give the antibiotic dose in the office and start my treatment immediately?

The guidelines allow for the addition of antibiotic prophylaxis if none was employed before the dental procedure and significant bleeding occurs during treatment with immediate resumption of treatment. This is intended to allow for clinical judgment and reduce unnecessary antibiotic use since antibiotic prophylaxis may be effective if given up to two hours after the bacteremia begins. However, antibiotic prophylaxis is optimally effective when high tissue and blood levels are present before the bacteremia begins. Therefore, if the patient has not taken the antibiotic before the dental procedure, it is best to give the antibiotic in the office and wait one hour before proceeding or to reappoint the patient. The provision for administration of the antibiotic in the case of significant unanticipated bleeding should not be employed to permit immediate dosing and treatment if the patient forgets to take the recommended antibiotic.

Is there ever a situation in which a second dose of the antibiotic might be appropriate?

There are two situations in which a second dose of the prophylactic antibiotic might be appropriate. If the dental patient is seen for two appointments on the same day (one in the morning and a second in the afternoon), then antibiotic prophylaxis should be employed prior to each appointment with the same antibiotic. The other situation would be when the patient undergoes a very long procedure exceeding four to six hours after the initial dose (as is possible in the dental school setting); then a second dose might be employed. In both of these cases, the full or one-half initial prophylactic dose should be employed. Additional antibiotic would not be necessary for azithromycin or clarithromycin due to their long half-lives.

Are there any periodontal procedures that do not require antibiotic prophylaxis?

It is possible to perform a clean mouth prophylaxis in a patient with good oral hygiene and not create any significant bleeding if tissue laceration is avoided; however, as a general rule, all periodon-

tal treatment procedures should receive antibiotic prophylaxis.

Should the 1997 AHA recommendations be used when emergency treatment must be performed on patients who have taken either fenfluramine (Pondimin) – part of the fen-phen regimen – and/or dexfenfluramine (Redux)?

The current recommendations for the management of such patients is discussed in this journal issue. Such patients may have cardiac valve pathology that predisposes to a risk of endocarditis and should be managed according to the 1997 AHA guidelines (using the algorithm for mitral valve prolapse) for emergency procedures and referred for a cardiovascular examination before elective treatment. These patients may electively undergo treatment with dental procedures not associated with significant bleeding and for which no antibiotic prophylaxis is recommended as listed in Table 1 under Endocarditis Prophylaxis Not Recommended.

My patient is taking penicillin or a cephalosporin for an upper respiratory infection and required endocarditis prophylaxis. What should I do?

In a patient presently taking an antibiotic (for example, amoxicillin), merely increasing the dose of that antibiotic for prophylaxis is not advised since it is likely that significant resistant strains of microorganisms are present in the oral cavity and unlikely to be sensitive to higher antibiotic dosages.[3-5] A different class of antibiotic must be used for prophylaxis, and in this case clindamycin or one of the macrolides (azithromycin or clarithromycin) would be appropriate. Alternately, the dental treatment could be delayed for nine to 14 days after the patient has completed the current course of the antibiotic and then prophylaxis can be initiated as required.

Should patients with a history of scarlet fever or rheumatic fever receive endocarditis prophylaxis?

Scarlet fever does not cause cardiac valve pathology, and patients without evidence of such pathology from other causes do not require prophylaxis. Not all cases of rheumatic fever involve the heart; therefore, patients with a history of rheumatic fever without rheumatic heart disease do not require prophylaxis. If there is doubt about the presence of rheumatic heart disease, a reasonable attempt should be made to ascertain the cardiac valve status of the patient.

The patient has a history of allergy to penicillin, but I cannot determine the severity of the signs and symptoms that occurred. What should I do?

In such a patient, it is probably best to assume the allergy consisted of more than simple skin itching and erythema and avoid the use of a cephalosporin. Either clindamycin or one of the macrolides would be appropriate. In a patient who cannot take penicillin or a macrolide due to allergy or toxicity, clindamycin is the

TABLE 1

Dental Procedures and Endocarditis Prophylaxis[1,2]

Endocarditis prophylaxis recommended*
Dental extractions
Periodontal procedures including surgery, scaling and root planing, probing, and recall maintenance
Dental implant placement and reimplantation of avulsed teeth
Endodontic (root canal) instrumentation or surgery only beyond the apex
Subgingival placement of antibiotic fibers or strips
Initial placement of orthodontic bands but not brackets
Intraligamentary local anesthetic injections
Prophylactic cleaning of teeth or implants where bleeding is anticipated
Endocarditis prophylaxis not recommended
Restorative dentistry= (operative and prosthodontic) with or without retraction cord**
Local anesthetic injections (non-intraligamentary)
Intracanal endodontic treatment; post placement and buildup
Placement of rubber dams
Postoperative suture removal
Placement of removable prosthodontic or orthodontic appliances
Taking of oral impressions
Fluoride treatments
Taking of oral radiographs
Orthodontic appliance adjustment
Shedding of primary teeth

*Prophylaxis is recommended for patients with high- and moderate-risk cardiac conditions.
= This includes restoration of decayed teeth (filling cavities) and replacement of missing teeth.
** Clinical judgment may indicate antibiotic use in selected circumstances that may create significant bleeding.
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alternative drug of choice.

Periodontists sometimes place a patient on a two- or three-week course of antibiotics such as tetracycline for the management of periodontitis. How should I handle such a patient?

Older tetracyclines have a short half-life, but drugs such as doxycycline may have up to a 24-hour half-life in some patients. Bacteriostatic antibiotics such as the tetracyclines inhibit microbial replication while inhibitors of cell wall synthesis such as the bactericidal penicillins act only on dividing microorganisms, therefore the two drugs may be antagonistic. To ensure that doxycycline is no longer present in the patient before initiating amoxicillin prophylaxis, the doxycycline should be discontinued for at least three to four days (three to four times the half-life) prior to amoxicillin use. Also, it is imperative that the doxycycline not be resumed after the dental procedure during the most likely incubation period of endocarditis (usually two weeks) as its use may mask the signs and symptoms of endocarditis, should they occur, and delay the diagnosis. Masking of the initial symptoms of endocarditis by antibiotics generally doubles the time to hospitalization for the patient and significantly increases morbidity and mortality because early diagnosis and treatment of endocarditis are very important in its ultimate resolution.[6] However, this scenario would not hold true for a patient at risk for endocarditis who presents with an active/acute orofacial infection (such as an abscess). In this case, therapeutic antibiotics should be aggressively employed for as long as it takes to resolve the infection.[7]

I am going to do a periodontal bone grafting procedure in a patient at risk for endocarditis. What should I do?

This patient should be managed the same way as any other patient with the appropriate AHA prophylaxis regimen without posttreatment antibiotics in order to prevent the masking of any signs and symptoms of endocarditis. The risk of delaying the diagnosis of endocarditis would appear to greatly outweigh any conceivable potential benefit of posttreatment antibiotics in otherwise healthy patients at risk for endocarditis without active infection.

Should a dental patient at risk for endocarditis be advised of its early signs and symptoms (fever, malaise, anorexia, night chills, arthralgia, myalgia) so that, if these should occur, the patient will seek medical attention as soon as possible?

Bacterial endocarditis is a rare disease, and the vast majority of cases are not associated with dental treatment procedures. Therefore, such advice is probably unnecessary under the concept of informed consent and might be unduly alarming. However, early diagnosis is a very important aspect of the successful treatment of endocarditis, and the dentist can simply advise the patient to report any unusual health changes to the dentist who in turn should be fully aware of the above early signs and symptoms.

I am seeing an increasing number of patients having had various stents placed for cardiovascular disease. How do I handle such patients?

Individuals who have had coronary or noncoronary artery stents placed do not require prophylaxis six months or longer after the surgery. Those who have undergone repair of intracardiac defects (atrial septal defect, patent ductus arteriosus, ventricular septal defect) also do not require prophylaxis six months or longer after the surgery if no residual hemodynamic abnormalities are present.

What is the rationale for advising that a nine- to 14-day interval occur between dental appointments in a patient requiring endocarditis prophylaxis?

It is well-documented that antibiotic use, including AHA prophylaxis, may select resistant microorganisms in the oral cavity but that such resistance is likely not to persist nine to 14 days after the antibiotic is terminated.[3-5,8] Therefore, this interval between treatments is recommended to lower the possibility of reduced antibiotic prophylaxis efficacy due to the presence of antibiotic-resistant microorganisms. If a shorter interval is necessary, then an antibiotic selected from the alternates listed in the AHA recommendations should be employed.

The patient had periodontal scaling and root planing yesterday with amoxicillin endocarditis prophylaxis and today has a periodontal abscess. How do I manage this?

In such a situation where two prophylactic regimens are required within a short interval (12 to 24 hours), it is unlikely that significant selection of resistant organisms has occurred and reuse of amoxicillin prophylaxis prior to management of the periodontal abscess would be appropriate. The use of an alternate regimen would also be acceptable.

I understand that for a patient with a cardiac transplant I should consult with the attending physician to determine if cardiac valve pathology is present and then employ antibiotic prophylaxis if appropriate, but what about other organ transplants such as kidneys and livers?

The AHA guidelines are directed toward the prevention of bacterial endocarditis and do not address the subject of solid organ transplants other than the heart.

It is my understanding that clindamycin is more commonly associated with antibiotic-induced pseudomembranous colitis. Should I be concerned about its use for endocarditis prophylaxis?

Antibiotic-induced pseudomembranous colitis is primarily but not exclusively a nosocomial (hospital-acquired) disorder as discussed in a companion article in this issue. Pseudomembranous colitis has been associated with all antibiotics but primarily with ampicillin/amoxicillin, cephalosporins, and clindamycin. It is very unlikely that a single dose of clindamycin in a dental outpatient setting will induce pseudomembranous colitis. The incidence of community-acquired Clostridium difficile-associated diarrhea is about 1 in 10,000 antibiotic prescriptions; however, patients who have had Clostridium difficile-associated diarrhea are at greater risk for recurrence or relapse if antibiotics are administered within two months of their recovery from the diarrhea. It is not known whether a single prophylactic antibiotic dose of any agent would predispose to diarrhea/colitis recurrence or relapse, but it would appear appropriate to delay any elective dental treatment until after this two-month period.[9]

What should I do if the physician recommends a prophylaxis regimen that is different from that of the AHA?

Although the 1997 AHA guidelines are not the exclusive standard of care, they are the most generally accepted standard and undergo intense scrutiny before publication. If the dental procedure is elective, then possibly the best approach would be to share a copy of the recommendations with the physician (via fax machine, for example) with later reconsultation to further discuss the matter. If a satisfactory resolution does not occur, the dentist must follow his or her best professional and clinical judgment as the responsibility ultimately rests with the dentist when the patient is in the dental office. In making the initial consult with the physician of record, the dentist should take the initiative to indicate in the consult letter or verbal consult that the 1997 AHA guidelines are going to be used. This approach may minimize physician-initiated recommendations that differ from the AHA guidelines.

It is well-known that oral hygiene procedures such as flossing, brushing, and using water-pressure devices cause bacteremias. Can't these procedures place the patient at a greater risk for endocarditis?

It is generally accepted that the healthier the mouth the less the incidence and magnitude of bacteremias due to a reduced likelihood of bleeding, and the AHA guidelines strongly encourage good oral hygiene as a primary preventive measure for endocarditis. Therefore, procedures that promote dental bacterial plaque reduction are to be encouraged. Home-use devices pose far less risk of bacteremias in a healthy mouth than does ongoing oral inflammation. Any brief, temporary increase in bacteremias while the patient is undergoing inflammation reduction is more than offset by the future benefit of permanent elimination of inflammation.

Why was erythromycin not included in the list of alternative drugs for antibiotic prophylaxis for endocarditis?

Erythromycin was included in the 1990 AHA guidelines but generated extensive comments and complaints because of the two forms of erythromycin (succinate or stearate) and two doses (800 mg or 1 gm). The incidence of gastrointestinal complaints was significant with the larger doses of erythromycin; and, because dosing equivalence was troublesome for many, erythromycin was not included in the 1997 guidelines. Alternative macrolides, clarithromycin and azithromycin, were shown to be effective and were then substituted for erythromycin. These are more expensive drugs, but the single dose required should help reduce the impact of cost. If a patient was successfully managed in the past with erythromycin and neither the dentist nor the patient want to switch to one of the other recommended antibiotics, the 1990 AHA regimen for erythromycin can continue to be used to include the follow-up second dose.

Is clindamycin the preferred drug of choice for the patient who cannot take amoxicillin?

The alternative choices to amoxicillin were selected because of their usefulness and are not listed in specific order. Dentists should always consider the patient's prior antibiotic drug history before selecting an alternative to amoxicillin. Several choices are recommended to accommodate the patient's needs.

Does a patient with a total prosthetic joint replacement need prophylaxis for prevention of bacterial endocarditis?

Individuals with total joint prostheses are not at increased risk for endocarditis unless they have an underlying cardiac defect identified in the table of patients at risk for endocarditis. The recommendations regarding antibiotic prophylaxis for dental patients with total joint prostheses was addressed by a joint statement of the American Dental Association and the American Academy of Orthopaedic Surgeons and published in the Journal of the American Dental Association (128:1004-7, 1997).

A 30-year-old patient says that as a child she was told she had a heart murmur, and the patient has not been examined by a physician since age 18. Should I give antibiotic prophylaxis?

The patient should be questioned as to whether her murmur was referred to as "innocent" (also termed functional or physiological). Innocent heart murmurs are quite common in childhood, and most disappear when the child reaches adulthood. Innocent murmurs do not require antibiotic prophylaxis. If the patient does

not know whether it was an innocent murmur, a medical consultation will be appropriate; and the physician examining the patient will have to determine if the murmur was (is) innocent or whether it is due to an actual cardiac valvular abnormality requiring AHA endocarditis prophylaxis.

Doses for children are based on body weight, and sometimes the dose calculated cannot be easily accommodated by available dose sizes for the recommended drug. Should the dose be rounded up or down?

If a child weighed 38 pounds, then the calculated dose of amoxicillin would be 38 pounds divided by 2.2 (1 kg equals 2.2 pounds), which equals 17.3 kg times 50 mg/kg, which equals 865 mg of amoxicillin. Because amoxicillin has a very low toxicity and pharmacist compounding of such a dose could be complicated, the most pragmatic solution to this problem would be to have the child take four of the 250 mg or two of the 500 mg tablets or capsules (1,000 mg), thereby adjusting the dose upward. Alternately, the correct volume of 250 mg/5 mg oral suspension could be used. In any case, the maximum calculated dose for children should not exceed the recommended adult dose.

When will the next revised guidelines appear?

The AHA recommendations for the prevention of bacterial endocarditis have been revised periodically as new pertinent data became available, and such a practice will continue at approximately five- to seven-year intervals.

Summary

The 1997 Prevention of Bacterial Endocarditis Recommendations by the American Heart Association have been favorably received. The simplification of the prophylaxis regimens and better delineation of patients at risk, dental procedures recommended for prophylaxis, and ancillary procedures to reduce bacteremic risk have likely improved compliance and reduced unwarranted antibiotic prophylaxis and subsequent adverse effects. Questions have arisen regarding aspects of implementation of these guidelines in the dental setting, and these have been addressed. Future revisions of these recommendations are to be anticipated and will incorporate all new pertinent data.

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Current Status of Fenfluramine/ Dexfenfluramine-Induced Cardiac Valvulopathy

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ABSTRACT Since publication of the U.S. Department of Human and Health Services' interim recommendations in November 1997 for the management of patients having taken certain appetite suppressants, a number of studies evaluating the prevalence of cardiac valvular pathology in such individuals have been published. These studies generally support the association of fenfluramine/dexfenfluramine with cardiac valvulopathy but with significant differences in risk assessment. The analysis of these studies has produced two new guidelines for the management of such patients, including the appropriate use of antibiotic prophylaxis in these individuals. These studies are presented along with a comparison of the three present recommendations and their impact on dental practice.

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An interim public health recommendation for individuals having taken certain appetite suppressants (fenfluramine, dexfenfluramine) was issued on Nov. 14, 1997, by the U.S. Department of Human and Health Services (DHHS)[1] and was summarized in the CDA Update on Dec. 17, 1997.[2] The preliminary data gathered by the Centers for Disease Control and Prevention and the Food and Drug Administration indicated a possible 32.89 percent overall prevalence of cardiac valvulopathy in people exposed to fenfluramine (Pondimin) or dexfenfluramine (Redux). Phentermine (Apidex, Fastin, Ionamin), often combined with fenfluramine in "fen-phen," was itself not implicated. All four valves of the heart had been affected, with a definite predilection for the left side of the heart (aortic and mitral valves). The influence of dose or duration of therapy on this valvulopathy was unknown.

The DHHS then made the following recommendations:

- All people exposed to these drugs should undergo a medical history and cardiovascular examination.
- An echocardiogram should be performed on all people who exhibited cardiopulmonary signs and symptoms of cardiac valvular disease.
- An echocardiogram was to be strongly considered on all people exposed to these drugs for any period of time regardless of whether cardiopulmonary signs and symptoms were detected if the patient was to have an invasive

procedure for which antimicrobial prophylaxis is recommended by the 1997 American Heart Association (AHA) guidelines for the prevention of bacterial endocarditis.

- For emergency procedures for which a cardiac evaluation cannot be performed,
- empiric antibiotic prophylaxis should be administered according to the 1997 AHA guidelines. Dentists were then advised to:
- Identify such patients via a dialogue medical history;
- Advise the patient that an appropriate cardiovascular examination should be performed by the patient's physician;
- Avoid all elective dental procedures associated with significant bleeding from hard and soft tissues and meriting antibiotic prophylaxis for endocarditis prevention as delineated in the 1997 AHA guidelines until the patient's cardiac status could be determined;
- Provide antibiotic prophylaxis according to the 1997 AHA guidelines if valvulopathy meeting the current AHA guidelines is detected by the physician; and
- Use the 1997 AHA prevention of bacterial endocarditis guidelines if an emergency dental procedure must be performed and the cardiac status of the patient is yet undetermined.2

Since these guidelines were issued, a number of reports have appeared regarding the incidence of cardiac valvulopathy in patients taking these two drugs that range from letters to the editor to meeting abstracts to fully published well-conducted studies. They vary substantially in patient populations; dosage and length of time the drugs were taken; and, most importantly, the methodology of assessment and the skill of the physician assessor. These studies may also suffer from referral bias (the most affected patients were referred to major teaching hospitals); lack of baseline cardiac evaluations before the drugs were taken; lack of knowledge of the natural history of valve disease due to anorectic drugs; and, importantly, the lack of agreed criteria for systematic echocardiographic evaluation and general medical practitioner insensitivity to mild-moderate valvular regurgitation.3,4

A recent study of 541 physicians in training or medical students indicated that an average of only 20 percent of them recognized 12 important and commonly encountered cardiac events by auscultation.5 It is probable, then, that cardiac valvulopathy would more likely be detected by a cardiologist than an internist/primary care physician and by sophisticated echocardiography rather than by auscultation.

In three major studies recently published in the New England Journal of Medicine, the incidence of cardiac valvulopathy in patients taking fenfluramine or dexfenfluramine ranged from 13 percent to 25 percent (12 percent to 24 percent above the expected value)6 to 6.9 percent vs. 4.5 percent of controls (a 2.4 percent difference)7 to a risk ratio of 0.14 per 1,000 patient years with up to three months of drug use to 0.7 per 1,000 patient years with greater than three months of use.8 In one of these studies, the incidence of moderate to severe valvular regurgitation was 8 percent as opposed to 0 percent in controls.6 In an evaluation of these studies, it was determined that each support the association between fenfluramine and dexfenfluramine and heart valve regurgitation but differ with regard to the strength and clinical significance of that association.3 Also, it appears that obesity itself is not responsible for the valve irregularities, that the use of these drugs for less than three months was a lower risk for valve abnormalities, and that prolonged use and/or exposure to higher doses appeared to confer greater risk for cardiac valve irregularities.3 It is important for consistency that all studies to be compared use the same diagnostic FDA criteria for valvulopathy: at least mild aortic regurgitation and at least moderate mitral insufficiency.3

In six abstracts presented at the 1998 Scientific Session of the American Heart Association, the prevalence of significant valvular regurgitation ranged from a statistically insignificant 2 percent to a highly significant 28 percent (2 percent, 3.6 percent, 6.6 percent, 10 percent, 14.4 percent, and 28 percent).9-14 In 28 cases additional to the originally reported 24 cases,15 24 had mitral valve, 19 aortic valve, 11 tricuspid valve, and 1 pulmonary valve insufficiency with no resolution upon drug withdrawal and again emphasizing the problem of multiply affected valves.16 One report has appeared of regression of the valve lesions over a period of years.17

From October 1994 to July 1997, the Belgian Center for Pharmacovigilance reported 43 cases of valvular heart disease in women using anorectic drugs.18 In other reports, 15 of 23 cases had abnormal valves on color flow Doppler echocardiography and six of 20 cases had valvular heart disease but with no baseline echocardiogram taken before medication onset.20 At valve replacement or repair, the affected valves have a characteristic glistening white appearance with a plaque-like encasement of the leaflets and chordae and focal surface proliferation or fibrosis.21 These valvular lesions may produce a characteristic echocardiogram.21

TABLE 1

Summary of recommendations[1,3,4] for the management of patients who have taken fenfluramine or dexfenfluramine.

DHHS[1]	
• All people exposed to either of these two drugs for any length of time should undergo a medical history and cardiovascular examination to determine cardiopulmonary signs and symptoms.	
• An echocardiogram should be performed on all such people who exhibit cardiopulmonary signs and symptoms of cardiac valvular disease.	
• An echocardiogram should be strongly considered on all people exposed to these drugs for any period of time regardless of whether cardiopulmonary signs and symptomsm were detected if the patient is to have an invasive procedure for which antimicrobial prophylaxis is recommended by the 1997 AHA guidelines for the prevention of bacterial endocarditis.	
• For emergency procedures for which a cardiac evaluation cannot be performed, empiric antibiotic prophylaxis should be administered according to the 1997 AHA guidelines.	
Devereux[3]	
• All patients are to be examined clinically.	
• An echocardiogram should be recommended for those with a heart murmur or other evidenc eof valvular disease as well as those who have received the drugs for three or more months or at high doses.	
• The standard AHA antibiotic prophylaxis should be recommended for patients with a heart murmur, "silent" moderate or severe regurgitation on Doppler echocardiography and those with mild regurgitation associated with defined structural valvular lesions.	
ACC/AHA[4]	**Class a**
Indication	
Discontinuation of the anorectic drug(s). [b]	I
Cardiac physical examination	I
Echocardiography in patients for whom cardiac auscultation cannot be performed adequately because of body habitus	I
Doppler echocardiography in patients for whom cardiac auscultation cannot be performed adequately because of body habitus	I
Repeated physical examination in six to eight months for those without murmurs	IIa
Echocardiography in all patients before dental procedures in the absence of symptoms, heart murmurs, or associated findings.	IIb
Echocardiography in all patients without heart murmurs	III
a. Class I: Conditions for which there is evidence and/or general agreement that a given procedures or treatment is useful and effective.	
Class II: Conditions for which there is conflictingevidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.	
IIa. Weight of evidence/opinion is in favor of usefulness/efficacy	
IIb. usefulness/efficacfy is less well-established by evidence/opinion	
Class III: Conditions for which there is evidence and/or general agreement that the procedure is not useful and in some cases may be harmful.	
b. Fenfluramine or dexfenfluramine or the combination of fenfluramine-phentermine or dexfenfluramine-phentermine (ACC/AHA portion of Table 1 reprinted with permission of the ACC/AHA and *Circulation*)	

Seemingly lost in all the concern about cardiac valvulopathy is the other major clinical problem associated with anorectic drugs: primary pulmonary hypertension, which is an ordinarily rare disorder occurring at a rate of 1 to 2 per million in the general population but which rises tenfold with the use of any anorectic drug and 20-fold with greater than three months' use.22 This disorder occurs primarily in young women (median age 36 years) with early signs and symptoms of shortness of breath on exertion, syncope, tiredness, chest pain, and peripheral edema.[23] Its diagnosis is commonly delayed one to two years after onset of symptoms, and people so afflicted have a median survival time of two to three years from onset of symptoms.[23] The first report of primary pulmonary hypertension associated with fenfluramine appeared in

West Africa in 1975.[24] Fenfluramine has been associated with damage to brain serotonergic neurons in animals[25] and endocardial fibrosis in humans.[26]

Since the publication of the DHHS guidelines in 1997,[1] two other recommendations have appeared regarding the management of patients who have taken fenfluramine or dexfenfluramine, one by Devereux[3] and the other by the joint Task Force of the American College of Cardiology (ACC) and the American Heart Association.[4] These are summarized in **Table 1**.

In an editorial response to the three studies published in the *New England Journal of Medicine*,[6-8] Devereux[3] proposed the following management strategy of these patients:

- All patients are to be examined clinically.
- An echocardiogram should be recommended for those who have a heart murmur or other evidence of valvular disease as well as those who have received the drugs for three or more months or at high doses.
- The standard AHA antibiotic prophylaxis is recommended for patients with a heart murmur, those with "silent" moderate or severe regurgitation on Doppler echocardiography, and those with mild regurgitation associated with defined structural valvular lesions. Further studies will be required to determine if these patients need follow-up evaluations, and caution is indicated with the use of other serotonergic agents.[3]

The ACC/AHA statement[4] recommends that:

- All patients with a history of fenfluramine or dexfenfluramine use undergo a careful history and thorough cardiovascular physical examination to include auscultation with the patient in the upright position at the end expiration to detect aortic regurgitation and in the left lateral decubitus position to detect mitral regurgitation.
- 2-D and Doppler echocardiography should be performed in those patients with symptoms, cardiac murmurs, or other signs of cardiac involvement (e.g., widened pulse pressure or regurgitant c or v waves in the jugular venous pulse).
- Patients whose body habitus prevents adequate cardiac auscultation should also undergo 2-D and Doppler echocardiography.
- Patients with clinical and echocardiographic evidence of valvular heart disease should then undergo treatment and/or further testing according to the recommendations developed for the specific valve lesions addressed earlier in these guidelines.
- Modification of these recommendations may be necessary as more information on the natural history of these specific valve lesions becomes available.[4]

Additionally the ACC/AHA guidelines contain the following caveats:

- Considering unknown variables, it is not possible to derive definitive diagnostic and treatment guidelines for patients who have received these anorectic drugs.
- Hence, clinical judgment is important.
- In the light of current evidence, echocardiographic screening of all patients with a history of fenfluramine or dexfenfluramine use, especially asymptomatic patients without murmurs or associated findings, is not recommended
- However, because of possible progression of subclinical valvular disease, asymptomatic patients without murmurs should undergo repeat physical examination in six to eight months.

Conclusions

The vast majority of the current clinical studies on cardiac valvulopathy associated with the use of fenfluramine or dexfenfluramine support such an association. However, these studies detect significant differences in risk with some supporting the original estimate of the DHHS and others assessing considerably less risk with the use of these anorectic agents. Methodology and expertise are likely significant factors in these discrepancies, as are dosage and the length of time the drugs were taken (valvular damage increased with both higher dose and longer duration). The dentist should continue to refer these patients to their physicians for a cardiovascular examination according to the recommendations of the DHHS, Devereux, or the ACC/AHA with the expectation that the physician will follow one of these guidelines. It would be appropriate to share this information with the physician for the purposes of consultation and proceed accordingly. If valvulopathy is detected, the 1997 AHA endocarditis prophylaxis guidelines regarding the management of dental patients with cardiac valvular disorders should be followed. For emergency dental procedures before a cardiac evaluation can be performed, empiric antibiotic prophylaxis should be administered according to the 1997 AHA guidelines.

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Clostridium-Difficile-Associated Diarrhea and Colitis

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ABSTRACT Clostridium difficile-induced diarrhea (CDAD) and colitis (CDAC) are important nosocomial (hosptial)-acquired infections resulting almost exlusively from antibiotic therapy and certain host factors. The severity of these disorders may range from simple diarrhea that can be resolved easily with antibiotic cessation to fulminant pseudomembranous colitis with fever, severe dehydration, abdominal pain and distention, and plaque formation over part or all of the colon. Community-acquired CDAD and CDAC are far less problematic but nevertheless may affect 20,000 or more people in the United States every year. Knowledge of the risk factors for CDAD and CDAC, including certain antibiotics, and recognition of the entire spectrum of signs and symptoms of this disorder are imperative for good dental practice. Likewise the prevention of recurrence of CDAD by judicious use of antibiotics in its immediate posttreatment period is an important consideration.

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Approximately 25 million people in the United States are affected by diarrhea every year, with an ensuing 11,000 deaths.[1] Possibly 10 percent of more of these diarrhea cases are associated with antibiotic use, particularly broad-spectrum agents.[2] The vast majority of these antibiotic-associated diarrheas (AADs) are not pathologically significant and respond well to discontinuance of the antibiotic and rehydration, if necessary. However, a significant portion of these AADs are a sign of either "benign" colitis or the more serious and potentially fatal pseudomembranous colitis (PMC) caused by Clostridium difficile toxins. It is estimated that[3] million cases of Clostridium difficile-associated diarrhea or colitis may occur every year in the United States, primarily in hospitalized patients, esentially making it a nosocomially acquired disorder.[3-5] However, approximately 20,000 cases are diagnosed every year in the United States in outpatients (community-acquired)[5,6] with a range of 7.7 to 20 cases per 100,000 patient-years worldwide.[6,7] These estimates of community-acquired CDAD may be low due to limited fecal testing for Clostridium difficile or its toxins.[8] This review will primarily be concerned with CDAD and PMC and their relationship to dental practice, thereby updating a previous review on this subject.[9]

History

Pseudomembranous colitis was first described in 1893 as "diptheric colitis" and from the 1930s to the 1960s was thought to be due to Staphylococcus aureus (staphylococcal enterocolitis).[10] Prior to the introduction of antibiotics, PMC was associated with cardiovascular disease, colonic obstruction, heavy metal intoxication, sepsis, shock, and uremia.[11] Antibiotic-associated PMC was first noted in the 1950s with the introduction of penicillins, tetracyclines, and chloramphenicol.[10] The association of a clostridial-type toxin with PMC was discovered in 1977,[12,13] and the relationship between Clostridium difficile and AAD and PMC was established in 1977-1978.[14-16] The spectrum of terms for this disorder include pseudomembranous enterocolitis, pseudomembranous colitis, antibiotic-induced colitis (AAC), clindamycin-associated colitis (CAC), antibiotic-associated PMC (AA-PMC), and Clostridium difficile-associated colitis or diarrhea.17 The common description of this disorder as "clindamycin-associated PMC" is incorrect because virtually any antibiotic can cause this colitis, and it occurs far more commonly with the cephalosporins and extended spectrum penicillins since these agents are used much more often clinically than clindamycin.

Epidemiology

Virtually all cases of CDAD, CDAC, and PMC are associated with antibiotic use, with only a very small percent seen in antibiotic-free patients on cancer chemotherapy. In patients with CDAD or CDAC, 92 percent had antibiotics within two weeks of the onset of the diarrhea and 100 percent within eight weeks. Also, 87 percent were nosocomially acquired.[18]

The carriage (colonization) rate for colonic Clostridium difficile or its toxins in healthy adults (asymptomatic carriers) is estimated to be 0.5 percent to 5.0 percent, with an average rate of 2 percent to 3 percent.[4,19,20] Ten to 13 percent of patients entering the hospital may be symptomatic carriers.[21,22] Fourteen percent of critically ill elderly patients and 20 percent of chronically ill elderly may also be asymptomatic carriers.[23] The carriage rate in healthy neonates is 25 percent to 85 percent, which falls to 9 percent of children from age 3 months to 24 months.[5,24,25] The carriage rate for adults on antibiotic therapy may be 21 percent,[24,25] which is similar to the 21 percent carrier rate of individuals hospitalized for at least seven days.[4] This asymptomatic carrier rate may rise to 50 percent of those hospitalized for greater than four weeks.[21] Up to 40 percent of patients treated for CDAD or PMC may become asymptomatic carriers for an unknown period.[26] Asymptomatic carriers may have a reduced risk of CDAD due to colonization with nontoxigenic strains of Clostridium difficile.[4,26,27]

Clostridium difficile-associated diarrhea may occur in about 7.8 percent of hospital admissions, and Clostridium difficile is responsible for 20 percent of all nosocomial diarrhea.[22] The rate of CDAD in people undergoing hospital surgery is 5.6 percent to 6.9 percent.[18,28] Risk factors for nosocomial CDAD include increased age and length of hospital stay, type and number of antibiotics, enteral feeding, illness severity, reduced host resistance, and increased contact with hospital personnel.[22,29,30] Floors; toilets; mops; bedding; scales; furniture; bedpans; roomates; and the hands, rings and stethescopes of hospital personnel are all sources of Clostridium difficile contamination.[2]

Of greater importance to dentistry is the potential for CDAD, CDAC, or PMC in the general outpatient population exposed to antibiotics. In a study of 376,590 antibiotic prescriptions provided to more than 280,000 outpatients over four years, four cases of acute AAC were detected.[31] The incidence rate was calculated to be 1.6 per 100,000 people exposed to ampicillin, 2.9 per 100,000 for dicloxacillin, and 2.6 per 100,000 people exposed to tetracycline.[31] Interestingly, no cases of AAD were seen in 1,509 people receiving oral or topical clindamycin. In another retrospective study, 51 cases of CDAD occurred in 662,500 person-years (7.7 cases per 100,000 person-years).[6] All cases recovered, and only six were hospitalized (82 percent were treated on an outpatient basis). The overall risk rate for community-acquired CDAD is this study was less than 1 per 10,000 antibiotic prescriptions, and the risk of hospitalization was 0.5 to 1.0 per 100,000 person-years.6 It appears then that the risk for hospitalization from community-acquired, antibiotic-induced diarrhea or colitis is very low.[6,31]

It is also of interest to determine if single-dose antibiotic prophylaxis (such as recommended by the American Heart Association[32] for the prevention of bacterial endocarditis) and multiple-dose prophylaxis often used for hospital surgery place a patient at-risk for CDAD, CDAC, AAC, or AAD. Nine studies have examined the relation of surgical antibiotic prophylaxis to CDAD or AAD in the hospital setting, with six employing multiple doses[18, 33-37] and three only a single dose.[38-40] In the studies of multiple antibiotic dosing (some only 24 hours or less, some for several days or longer), such "prophylaxis" is significantly associated with CDAD.[18, 32-37] In the three studies employing a single prophylaxis dose,[38-40] appearance or selection of Clostridium difficile may occur as well as AAD; but it appears that PMC may be a very low risk since none occurred with single-dose prophylaxis even in the hospital.

No studies have been performed to determine if a single antibiotic dose in the outpatient setting can cause PMC. Judging from the very low incidence in outpatient use with multiple antibiotic dosages and the limited data from single-dose prophylaxis in hospitals, such a risk for CDAC or PMC with single-dose antibiotic prophyalxis is likely to be very low to none.

Pathogenesis

Clostridium difficile is a spore-forming, gram-positive obligate anaerobic bacillus often acquired as a result of cross-infection vial oral ingestion.2 It may commonly be found in river, sea, lake, and swimming-pool water; occasionally in tap water; and rarely in domestic animals and raw vegetables.[41] It may or may not be present in soil.[41] Due to its spore-forming properties, the organism may easily survive for long periods in adverse conditions.[41]

When the colonic microbial flora is disturbed by antibiotics, toxin-producing Clostridium difficile are either already present or later acquired (as in hospitals or other environments), and the host immune resistance is suppressed and/or colonization resistance (the ability of the normal gut flora to protect the mucosa from colonization by invading pathogenic microorganisms) is depressed, then CDAD may occur.[11] CDAD is then a "three hit" disease requiring antibiotic exposure; acquisition of Clostridium difficile; and a third factor relating to host susceptibility or immunity, virulence of the particular Clostridium difficile strain, and/or the type and timing of the antibiotic exposure.[26]

It appears that there may be little correlation between the genotype and toxin product of the particular strain of Clostridium difficile and the severity of the colitis. It also appears that host resistance is paramount.[42,43] The evidence is equivocal as to whether HIV/AIDS predisposes to the acquisition of CDAD.[44-46] Colonic organisms that are antagonistic to Clostridium difficile and likely to be reduced or eliminated by antibiotics include lactobacilli, Bacteroides species, group D streptococci, Clostridium bifermentans, Escherichia coli, and Peptostreptococcus productus.[47] Some but not all isolates of Clostridium difficile produce two protein exotoxins (A and B) that are generally but erroneously termed an enterotoxin (A) and a cytotoxin (B).[5,48,49] Cytotoxin A may initiate mucosal cell damage, thereby allowing cytotoxin B to gain access to the underlying mucosal cells (toxin B is much more cytotoxic than toxin A).[48] These toxins bind to specific receptors in the luminal aspect of the colonic epithelium to catalyze the alteration of Rho proteins (GTP-binding proteins), resulting in the disruption of the F-actin structures, cell rounding, and eventual cell death.[5,48,49]

Clostridium difficile-associated diarrhea or PMC may occur as a result of exposure to any antibiotic but is most commonly associated with ampicillin and amoxicillin; cephalosporins, particularly those of the third generation (ceftriaxone, ceftazidime, cefotaxime); and clindamycin.[2,8] The ability of the antibiotic to alter the anaerobic flora of the gut and eliminate colonization resistance appears important in its propensity to induce CDAD or PMC. Antibiotics infrequently associated with CDAD include tetracyclines, sulfonamides, erythromycin, trimethoprim, and the quinolones. CDAD is rarely seen with the aminoglycosides, bacitracin, vancomycin, and metronidazole.[2]

Clindamycin has been historically indicted in inducing significant PMC, possibly due to an early study that found a 10 percent incidence of colitis in patients exposed to clindamycin.[50] No other studies have reported such a high incidence of PMC with clindamycin. In 1,509 patients receiving clindamycin, none experienced AAD,[31] while in other studies, the hospital restriction of clindamycin greatly reduced the incidence of CDAD.[51-53] Extended-spectrum penicillins, third-generation cephalosporins, and clindamycin remain the primary etiologic antibiotics for PMC but much depends on the ancillary factors listed above and whether the drugs are used in hospitalized patients or outpatients.

Signs and Symptoms

The adverse colonic effects of antibiotics may range from simple diarrhea (AAD) to mucosal inflammatory diarrhea or colitis with (CDAD) or without Clostridium difficile (AAC) to the formation of yellow plaques in the colonic mucosa (PMC). Clostridium difficile is cultured in 0 percent to 19 percent of patients with AAD without colitis, 60 percent with AAC without PMC, and 95 percent with PMC.[23,25] Clostridium difficile toxins are detected in 11 percent to 27 percent of people with AAD without colitis, 32 percent of those with AAC without PMC, and 97 percent to 100 percent of people with antibiotic-associated PMC.[25]

The initial sign of diarrhea may appear as early as one to 10 days after initiation of antibiotic therapy[11,48] or as late as six to 10 weeks after the onset of antibiotic use.[11,48,54] Some propose an incubation period after exposure or acquisition of Clostridium difficile of less than a week with a median time of diarrheal onset of two days.[3,4,49] The severity of symptoms may range from a mild diarrhea to fulminant pseudomembranous colitis requiring surgical removal of part or all of the colon to maintain life. Simple "benign" AAD or AAC without fever or leukocytosis usually responds to cessation of the antibiotic.

As the disease progresses, the signs and symptoms include diarrhea with tenderness to the abdomen; profuse green, watery, foul-smelling, bloody diarrhea with abdominal distension; fever; and fecal and blood leukocytosis.[47] The onset of Clostridium difficile-associated pseudomembranous colitis is heralded by high fever, marked abdominal tenderness, dehydration, and the initiation of 2 mm to 20 mm in diameter raised adherent yellow plaques interspersed between relatively normal, mildly inflammed colonic mucosa.[2,11,26] These plaques begin as patchy epithelial necrosis with a fibrin and leukocyte exudate that may progress to more prominent exudates seen as "volcanic" or "summit' lesions and then on to diffuse epithelial necrosis and ulceration overlaid by a pseudomembrane consisting of fibrin, mucous, leukocytes,

and cellular debris.[2] The pathologic process may terminate anywhere along this continuum.

Most PMC plaques are in the rectum and sigmoid colon, but about 10 percent are found more proximally and go undetected by sigmoidoscopy.[2] In severe cases, the plaques may coalesce to cover most or all of the colon. In fulminant colitis, the colonic muscle tone may be lost, resulting in toxic colonic dilation (toxic megacolon), paralytic ileus, and/or colonic perforation with ensuing peritonitis.[2] Possibly 3 percent of patients with CDAD or CDAC develop fulminant colitis with white blood cell counts reaching 40,000 and toxic megacolon greater than 7 cm in diameter.[5] If the patient survives the CDAD or CDAC, the colon will return to its normal histology with only minor glandular irregularities.[2]

Diagnosis

Antibiotic-associated diarrhea without fever or leukocytosis is due to an imbalance of the colonic flora caused by the antibiotic; and if it does not progress to colitis, it requires no further diagnostic tests. Definitive diagnosis of CDAD, however, necessitates a certain clinical history and diagnostic information. The ideal definitive diagnostic scheme for CDAD entails a history of watery stools for more than 36 hours or at least three watery bowel movements per day for at least two consecutive days; antibiotic therapy within eight weeks of the onset of the diarrhea; a clinical cure by either metronidazole or vancomycin; no other etiology for the diarrhea; and either a colonic pseudomembrane determined by endoscopy, a stool sample positive for Clostridium difficile toxins, or a positive stool culture for Clostridium difficile.[54]

More pragmatically, CDAD or Clostridium difficile-associated PMC can be diagnosed by the presence of diarrhea and one of the following: a pseudomembrane on colonoscopy, a positive stool cytotoxin assay for toxin B, a stool enzyme assay for toxins A or B, or a positive stool culture for Clostridium difficile.[55] Testing should be done on hospitalized patients with a history of antibiotic use in the past 30 days, significant diarrhea (at least three watery, inflammed stools during a 24-hour period), or abdominal pain.[26] Preferably, the diagnosis should be made from positive tests for both the organism and its toxin,55 as the cell cytotoxic assay is the most specific for CDAD and the stool culture is the most sensitive for CDAD.

Treatment

Diarrhea will resolve without any further treatment other than antibiotic discontinuance in 15 percent to 25 percent of CDAD cases.26 The antibiotic of choice for CDAD or PMC that does not resolve is metronidazole (250 mg four times a day or 500 mg three times a day orally) for 10 days.[26] Vancomycin is generally reserved for those cases that do not respond to metronidazole or in patients who are severely ill because there are serious concerns about selection of vancomycin-resistant organisms in the hospital environment.[56] The dose of vancomycin is 125 mg four times daily orally for 10 days.[26] Other therapies that have been employed include bacitracin, fusidic acid, teicoplanin, vancomycin plus rifampin, vancomycin in tapering doses, cholestyramine after vancomycin and re-establishment of the colonic flora with lactobacillus, nontoxigenic Clostridium difficile, and Saccharomyces boulardii.[26] The use of antiperistaltic agents such as loperamide, atropine, opioids, and diphenoxylate are not indicated because they will not only reduce the diarrhea but also increase intestinal stasis and toxin retention.[47] The use of Saccharomyces boulardii, a nonpathogenic yeast, may prevent CDAD relapse57 but may be unsuccessful in preventing AAD.[58] Yogurt does not prevent CDAD in hamsters,[59] but passive immunity treatment with IgG antibodies against toxins A and B has been successful in two clinical cases.[60]

Resolution of CDAD occurs in an average of 2.4 days with metronidazole, 2.6 to 4.2 days with vancomycin, 3.4 days with teicoplanin, and 2.5 to 4.1 days with bacitracin.[55] The hospital stay for a patient acquiring AAD may be extended up to 18 to 21 days.[61,62] The mortality rates of CDAD and PMC are conspicuously absent in cases studies other than 17 deaths in a recent large-hospital outbreak of Clostridium difficile-induced diarrhea.[61]

Relapse Rate

The range for the relapse and recurrence rates of CDAD has been stated to be 4.8 percent to 66 percent,[63,64] with more common estimates of 7 percent to 28 percent,[65] 23 percent,[34] 24 percent,[64] and an average of 20 percent appearing reasonable.[64] Relapse may be due to incomplete eradication of Clostridium difficile and recurrence due to the acquisition of a new organism. The initial cure rate in one study was 93 percent to 96 percent but with a recurrence rate of 16 percent for metronidazole or vancomycin, 28 percent for fusidic acid, and 7 percent for teicoplanin.[65] The aymptomatic carriage rate for patients treated with vancomycin or metronidazole may be 13 percent to 16 percent, respectively.[65] While most individuals with recurrent or relapsing CDAD respond to the same antibiotic regimen as used initially, in a study of recurrent CDAD, the average patient had three recurrences (range 1 to 9).[64] Recurrent CDAD can become persistent and elude long-term cure for years.[64]

It is not possible to predict which patients will have a recurrence. Two subsets of patients apparently exist: those that respond well after initial treatment and those that are at risk for recurrent CDAD.[64] Risk factors for recurrence include the spring season; female gender; diarrhea that resolves but recurs within two weeks after treatment antibiotics are terminated; greater exposure to endoscopy; and, most importantly, receiving antibiotics within two months of the initial recurrent CDAD.[64] It would

then appear imperative to refrain from unnecessary antibiotics within the two-month period following cessation of CDAD. Any elective dental treatment that might require antibiotic prophylaxis or, more importantly, therapeutic antibiotics would best be postponed for two months in patients who have just recovered from CDAD or PMC to avoid possible exacerbation by the antibiotic.

Prevention

Three studies have documented the validity of restriction of antibiotic use in the reduction of nosocomial CDAD. With an 80 percent to 90 percent reduction in the use of clindamycin, a resulting 50 to 75 percent decline in CDAD cases was observed.[51-53] Reduction in clindamycin use in one study also resulted in a decline in Clostridium difficile resistant to clindamycin from 91 percent to 39 percent during a two-year period.[51] Unfortunately, this clindamycin restriction was more than offset by an increase in the use of imipenem, ticarcillin-clavulanate, and other antibiotics.[51] Other prevention measures include handwashing, gloving, patient education, reducing staff cross-infection, cleaning of surfaces (Clostridium spores are resistant to most common disinfectants), and isolation of patients with CDAD.[66,67]

Conclusions

Clostridium difficile-associated diarrhea and PMC are very significant nosocomial infections and are classic examples of antibiotic-induced disease (superinfections) or "diseases of medical progress." The initial cure rate is high with metronidazole or vancomycin, but approximately 20 percent undergo at least one relapse or recurrence. An unknown percent have chronic recurrences, and the mortality rate cannot be ascertained from the literature.

Fortunately for dentistry, the occurrence of antibiotic-induced CDAD in the community is quite rare, with an occurrence rate of 1 per 10,000 antibiotic prescriptions and a hospitalization rate of 0.5 to 1.0 per 100,000 patient-years. Besides early recognition and treatment and the known propensity of certain antibiotics to induce this condition (beta-lactams and clindamycin), an important lesson to be learned is to refrain from unnecessary antibiotics in the first two months following cessation of treatment for CDAD. Elective dental procedures that may require antibiotic prophylaxis or particularly therapeutic antibiotic therapy should be postponed until after this critical period. It is encouraging to know that the risk for CDAD and PMC with single prophylactic antibiotic doses is minimal to none and that clindamycin may once again have an important place in the dental antibiotic armamentarium, particularly against the penicillin-resistant viridans streptococci so prevalent in hospitals and likely to reach community patients in time.

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Dentistry: The Early Years

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Riffling through the Yellow Pages today, it is hard to believe that many years ago there were no dentists. There were also no lawyers, making us wonder why we didn't leave well enough alone. The reason, of course, was because the earth was a molten sphere of lava and hot gases. Dental equipment wouldn't have lasted a week. In some early accounts, this gaseous globe was thought to be the original site of Hell. Later on when things cooled off, Monday morning was accorded that designation.

When the first people appeared several million years later, if you can believe Darwin, Leakey, et al., there were still no dentists. Mainly, this was because there was no demand for dental services. Early Man complained, "Teeth, schmeeth, I'm hungry, cold and naked. I live in a bad neighborhood in this cave what don't even have an en suite bathroom, and I got no shoes." He had a point. Fortunately, he had excellent teeth and a nice complexion marred only by a Gillette-deprived beard, because two of the latter-day food groups, sugar and grease, hadn't been invented yet.

When the first man discovered sugar cane tasted better than bamboo, civilization started its long downhill slide that made the advent of dentists inevitable. The use of sugar cane became very popular. Kids would go around all day with a length of sugar cane stuck in their faces. Mothers would yell at them to not run with a stick in their mouths, but they kept bonking into things that resulted in palatal and uvular discomfort. It was a habit that persisted even among adults until the discovery of tobacco. For an alternative to sugar cane, youngsters had to wait until M & Ms came along that were just the right size to stuff up their nostrils.

Tobacco was slow in finding favor with primitive man until the discovery of fire. This was another one of those accidents that turn out to be so beneficial, like being run down by a Mercedes whose owner has a pile of liability insurance. A man sucking on a rolled leaf of tobacco was standing in an open field contemplating his navel when he was struck by lightning. Although stunned, he was quick to discover that the ignited tobacco gave him a definite lift, even though it tasted like broiled camel dung.

The prime elements that made the entrance of a professional tooth person a foregone conclusion were now in place -- sugar to rot the teeth, tobacco to stain them and enough ignorance to ensure neglect would continue. The final elements to establish dentistry as a viable business, anesthesia and VISA, would appear later.

The very first toothache treatment occurred sometime around 2000 B.C.

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when a chap who had been whining and complaining for weeks took a roundhouse right from another cave person who got tired of listening to his caviling. Luckily, the blow luxated the offending tooth and the ache promptly subsided. "Well, hey," concluded the victim, "I think we got something here."

After that, whenever a toothache manifested itself, the sufferer got a friend to knock it out for him. Certain individuals with genetic personality defects actually enjoyed knocking out peoples' teeth and became adept at it. When a toothache took its toll on a member of the group, someone would offer, "Go get Oog, he'll take care of it for you." Oog, whose last name has been forgotten, was probably the first dentist.

Eventually, Man began to see a pattern here, one that finally rendered him nearly toothless and one that prompted him to find alternative treatment modalities. Despite the fact that some early civilizations such as the Mayans, the Incas, the Egyptians, the forty-niners and the Elks had made primitive inlays and bridges, dentistry was going nowhere fast as a profession.

A breakthrough came on a Thursday in Weehawken, N.J., when a customer, asked by his barber, "Do you want a haircut?" riposted just once too often, "No, I want them ALL cut!"

When it was all over and the shop's other customers were admiring the expertise with which the barber had rendered the customer edentulous, it was decided that barbers would henceforth be the officially designated town dentist.

Besides being clever with the clippers, barbers were very good with extractions and would even do a bit of gum surgery if they had imbibed enough bay rum, but the problem of edentulous patrons was a limiting factor in their dual careers. Finally, deciding that hair grew back better than teeth and thus afforded a self-perpetuating customer base, barbers concluded that offering an eight-year course leading to a DDS or DMD degree was probably a better way to go.

If truth be known, their decision to eschew dentistry was predicated more on these considerations:

1. A little Brylcreem was the worst thing they could get on their hands.
2. Dandruff was less yucky than saliva.
3. Insurance companies didn't interfere in the sacred barber/customer relationship.
4. Iatrogenic errors grew back in two weeks, and
5. They could give away all-day suckers to little kids without feeling guilty.

In retrospect, we're inclined to consider this a wise move. I can still go the barber of my choice, unhampered by any Hair Management Organizations. Even though he spends less time with me than he did 20 years ago, that's not his fault. Although he deals with sharps on a daily basis, his hands are unsheathed, his face unmasked, and the place still looks like it did when we were kids. On the downside, I don't get offered a sucker any more, and he still doesn't think, "No, cut 'em ALL" is funny.