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Use and Abuse of Antibiotics



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For the past 80 years, antibiotic therapy has played a major role in the treatment of bacterial infectious diseases. Since the discovery of penicillin in 1928 by Fleming and sulfanilamide in 1934 by Domagk, the entire world has benefited from one of the greatest medical advancements in history. The discovery of safe, systemic antibiotics has been a major factor in the control of infectious diseases and, as such, has increased life expectancy and the quality of life for millions of people. According to the Centers for Disease Control and Prevention, life expectancy of individuals in the United States born in 1900 was 47 years, while those born in 2005 is projected to be 78 years.¹ At the beginning of the 20th century, the infant (< 1 year) mortality rate in the United States was 100/1,000 live births compared to 6.7/1,000 in 2006.² The major reason for these phenomenal achievements has been the ability to control infectious diseases.³

Development of Antibacterial Drug Resistance

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

Many worldwide strains of *Staphylococcus aureus* exhibit resistance to all medically important antibacterial drugs, including vancomycin, and methicillin-resistant *S. aureus* has become one of the most frequent nosocomial, or hospital-acquired, pathogens. The rate at which bacteria develop resistance to antibacterial drugs is alarming, demonstrating resistance soon after new drugs have been introduced. This rapid development of resistance has contributed significantly to the morbidity and mortality of infectious diseases, especially nosocomial infections.⁴

A nosocomial infection is a hospital-acquired infection that develops in a patient after admission. It is usually defined as an infection that is identified at least 48 to 72 hours following admission, so infections incubating, but not clinically apparent at admission are excluded. Nosocomial infections are costly, resulting in increased morbidity, requiring longer periods of hospitalization and limiting access of other patients to hospital resources. The direct costs of hospital-acquired infections in the United States are estimated to be \$4.5 billion per year. Nosocomial infections also contribute to the emergence and dissemination of antimicrobial-resistant organisms. Antimicrobial use for treatment or prevention of infections facilitates the emergence of more resistant organisms. Patients with infections caused by antimicrobial-resistant organisms are then a source of infection for hospital staff and other hospitalized patients. These drug-resistant infections may subsequently spread to the community.⁵

The British Society for Antimicrobial Chemotherapy published a review in the *Journal of Antimicrobial Chemotherapy*. This review examined the contributions antibiotic prescribing by general dentists in the United Kingdom has made to the selection of antibiotic resistance in bacteria of the oral flora.⁶ The review concluded that inappropriate antibacterial drug prescribing by dental practitioners is a significant contributing factor in the selection of drug-resistant bacterial strains.

The American Dental Association reported the results of a survey of antibiotic use in dentistry in the November 2000 *Journal of the American Dental Association*.⁷ The authors surveyed all licensed dentists practicing in Canada and found that confusion about prescribing antibiotics and inappropriate prescribing practices was evident, and that inappropriate antibiotic use, such as improper dosing, duration of therapy and prophylaxis are all factors that may affect development of antibiotic resistant microorganisms.

There is a Glimmer of Hope

A report from Aker University in Oslo, Norway, strongly suggests that bacterial resistance to antibacterial agents can be reversed.⁸ While dangerous and contagious staph infections kill thousands of patients in the most sophisticated hospitals in Europe, North America and Asia, there is virtually no sign of this "killer superbug" in Norway. The reason? Norway stopped taking so many antibiotics.

"We don't throw antibiotics at every person with a fever. We tell them to hang on, wait and see, and we give them a Tylenol to feel better," said Dr. John Haug, infectious disease specialist at Aker University Hospital.⁸

In Norway's simple solution, there is a glimmer of hope.

The Proper Clinical Use of Antibacterial Drugs

In 1997, the ADA Council on Scientific Affairs issued a position statement on *Antibiotic Use in Dentistry*.⁹ The Council stated: "Microbial resistance to antibiotics is increasing at an alarming rate. The major cause of this public health problem

is the use of antibiotics in an inappropriate manner, leading to the selection of dominance of resistant microorganisms and/or the increased transfer of resistance genes from antibiotic-resistant to antibiotic-susceptible microorganisms.”⁹

The Council’s position statement further identified that “Antibiotics are properly employed only for the management of active infectious disease or the prevention of metastatic infection, such as infective endocarditis, in medically high-risk patients.”⁹

One method of education is to teach from errors rather than principles. Psychologists from the University of Exeter have identified an “early warning signal” in the brain that helps us avoid repeating previous mistakes. Published in the *Journal of Cognitive Neuroscience*,¹⁰ their research identifies for the first time, a mechanism in the brain that reacts, in just 0.1 of a second, to things that have resulted in us making errors in the past. Evaluating the following eight misconceptions or “myths” may help to establish general guidelines to aid us in making clinical decisions regarding the use of antibiotic therapy, thereby leading to optimum use and therapeutic success.¹¹

Myth #1: Antibiotics cure patients. Except in patients with a compromised immune system, antibiotics are not curative, but instead function to assist in the re-establishment of the proper balance between the host’s defenses (immune and inflammatory) and the invasive agent(s). Antibiotics do not cure patients; patients cure themselves.

Myth #2: Antibiotics are substitutes for surgical intervention. Very seldom are antibiotics an appropriate substitute for removal of the source of the infection (extraction, endodontic treatment, incision and drainage, periodontal scaling and root planing). Occasionally, when the infection is too diffuse or disseminated to identify a nidus for incision, or the clinical situation does not allow for immediate curative treatment, the prudent dentist will choose to place the patient on appropriate antibacterial therapy until such time as curative treatment can be implemented. It is imperative to remove the cause of the infection prior to, or concomitant with, antibiotic therapy, when the cause is readily identifiable. Whenever antibiotic therapy is used the risk of bacterial selection for antibiotic resistance is present.

Myth #3: The most important decision is which antibiotic to use. To avoid the deleterious effects of needless antibiotics on patients and the environment, **the most important initial decision is not which antibiotic to prescribe but whether to use one at all.** It has been estimated that up to 60% of human infections resolve by host defenses alone following removal of the cause of the infection without antibiotic intervention.

Endodontic disease is infectious. Microorganisms cause virtually all pathoses of the pulp and periapical tissues. There is ample evidence to support that opportunistic normal oral microbiota colonize in a symbiotic relationship with the host, resulting in endodontic infections.¹² The majority of endodontic infections do not require systemic antibiotic therapy when the cause of the infection has been properly managed (complete debridement of the pulp space and proper obturation and sealing of the pulp space from the oral environment).

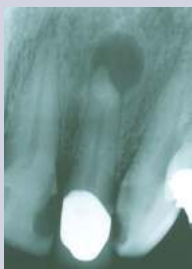


Fig. 1. Asymptomatic apical periodontitis.

Apical periodontitis lesions of pulpal origin are generated by the immune system and are the result of intraradicular infections (Figure 1). In most situations, this inflammatory process successfully eliminates the bacteria emerging from the apical foramen and prevents their spread to the periapical tissues. This process is primarily facilitated by the polymorphonuclear leukocytes that eventually phagocytize and kill the bacteria.¹³ Asymptomatic apical periodontitis of pulpal origin does not routinely require systemic antibiotic therapy for satisfactory resolution and healing. Endodontic therapy alone is usually sufficient.

When the intraradicular infection is able to overwhelm the host’s immune response, viable bacteria are able to gain access to the periapical tissues and colonize forming an active infection. This results in the formation of an apical abscess. A chronic apical abscess usually presents with gradual onset, no to mild symptoms and the presence of a sinus tract or parulis (Figure 2). The



Fig. 2. Chronic apical abscess.

majority of chronic apical abscesses of endodontic origin do not require systemic antibiotic therapy for satisfactory resolution and healing.

An acute apical abscess usually presents with rapid onset, spontaneous pain and swelling, both localized and intraoral, sometimes with exudate present, or with diffuse facial cellulitis. When the abscess is intraoral and localized (Figure 3), debridement of the pulp space and placement of calcium hydroxide and surgical incision for drainage is usually sufficient to resolve the problem. Systemic



Fig. 3. Acute apical abscess with intraoral localized swelling.



Fig. 4. Acute apical abscess with extraoral diffuse facial cellulitis.

antibiotic therapy is not routinely indicated, depending on the patient's general medical status. However, when the patient presents with diffuse facial swelling (cellulitis) resulting from an acute apical abscess or an infection with systemic involvement (fever or malaise) (Figure 4), debridement of the pulp space with placement of calcium hydroxide, surgical incision for drainage, when possible, and an appropriate regimen of systemic antibiotics (oral or IV) are the treatments of choice.

Understanding the enemy is an important factor in winning any battle. The rational choice and use of antimicrobial agents begins with the knowledge of the microorganisms most likely responsible for common dental infections of pulpal origin. The bacterial flora found in endodontic infections is indigenous, mixed (Gram-positive and Gram-negative) and predominately anaerobic. Several species have been implicated with acute apical abscesses. These species include dark-pigmented bacteria (*Prevotella* and *Porphyromonas*), eubacteria, fusobacteria and *Actinomyces*.¹²

Baumgartner and Xia published a report of the susceptibility of bacteria recovered from acute apical abscesses to five commonly used antibiotics in dentistry. Antibiotic susceptibility data from 98 species of bacteria recovered from 12 acute apical abscesses led to the following conclusions:

1. Pen-V-K is the antibiotic of choice for endodontic infections due to its effectiveness in polymicrobial infections, its relative narrow spectrum of activity against bacteria most commonly found in endodontic infections, its low toxicity and low cost.
2. Clindamycin is the antibiotic of choice for patients allergic to penicillins.
3. While amoxicillin and augmentin (amoxicillin plus clavulanate) demonstrated a higher antibacterial effectiveness than Pen-V-K, due to the broader antibacterial spectrum of amoxicillin and the increased cost of augmentin, the authors recommended that amoxicillin/augmentin be reserved for unresolved infections and patients who are immunocompromised.
4. Metronidazol demonstrated the greatest amount of bacterial resistance and is only effective against anaerobes. Therefore, it should not be used alone for the treatment of endodontic infections.¹⁴

Myth #4: Antibiotics increase the host's defense to infection. The increased prevalence in organ and tissue transplants, resulting in patients with compromised immune systems, has heightened the interest in the potential effects of antimicrobial drugs on the host's resistance to infection.¹⁵ *In vivo* and *in vitro* studies are highly variable and sometimes contradictory. However, the following considerations appear valid: 1) Antibiotics that can penetrate into the mammalian cell (erythromycin, tetracycline, clindamycin and metronidazole) are more likely to affect the host defenses than those that cannot (beta-lactams); 2) Tetracyclines may suppress white cell chemotaxis; 3) Most antibiotics (except tetracycline) do not depress phagocytosis; and 4) T- and B-lymphocyte transformation may be depressed by tetracyclines. The greatest potential harm to the host defenses may result from antibiotics that easily penetrate into the mammalian cell and the least harm is observed with bactericidal, nonpenetrating agents (penicillins and cephalosporins).

Myth #5: Multiple antibiotics are superior to a single antibiotic. It is often assumed that a combination of antibiotics is superior to a single carefully chosen antibacterial agent. When the purported benefits of antibiotic combinations are weighed against the possible consequences to the host as well as to the bacterial environment, this assumption is not always reality. The usual sequela to combined antibiotic therapy results in a greater selective pressure on the microbial population to develop drug resistance. The greater the antibacterial spectrum of the antimicrobials used, the greater the number of drug-resistant microorganisms that develop, and the more difficult it is to treat a resulting superinfection. The primary clinical indication for combined antimicrobial therapy is a severe infection in which the offending organism(s) is unknown and major consequences may ensue if antibiotic therapy is not instituted immediately before culture and sensitivity tests are available.³

Myth #6: Bactericidal agents are always superior to bacteriostatic agents. Bactericidal agents are required for patients with impaired host defenses.³ However, bacteriostatic agents are usually satisfactory when the host's defenses against infections are unimpaired. Postantibiotic effects (PAEs—persistent suppression of bacterial growth after previous exposure to antibiotics) are more persistent and reliable with bacteriostatic agents (erythromycin, clindamycin) than with bactericidal agents (beta-lactamase) because the clinical effects of bacteriostatic agents are less dose-dependent.

Myth #7: Antibiotic dosages, dosing intervals and duration of therapy are established for most infections. After more than 80 years of antibiotic usage, the proper dosages, dosing intervals and duration of therapy are essentially unknown for most specific

infections.³ Infectious diseases are associated with a high number of variables that affect treatment outcome (microbial characteristics and drug sensitivity, diverse resistance mechanisms, tissue barriers to antibiotic diffusion, and the integrity and activity of the host's defense mechanisms). However, basic principles are available to guide the dental health care provider in establishing proper dosages, dosing intervals and duration of therapy once the microbial pathogen(s) is suspected or identified and a rational choice of antimicrobial agent is made.

The following principles of antibiotic dosing are adapted from Dr. Thomas J. Pallasch³:

1. The current recommendation is to employ an antimicrobial on an intensive basis with vigorous dosage for as short a period of time as the clinical situation permits. The major factor in the clinical success of most antimicrobial agents is the height of the serum concentration of the drug and the resulting amount in the infected tissue(s). Also important is to expose the host to the antimicrobial agent for as short a duration of therapy as possible. The shorter the duration of therapy the lower the risk to the patient for the development of antibiotic-induced toxicity and/or allergy, and a reduced risk of developing resistant microorganisms.
2. The goal of antibiotic dosing is to achieve drug levels **in the infected tissue** equal to or exceeding the minimal inhibitory concentration of the target organism. Serum levels of antibiotics do not necessarily reflect those in tissues. Blood concentrations of the antibiotic should exceed the MIC by a factor of two to eight times in order to offset the tissue barriers that restrict access of the drug to the infected site.
3. It is advisable to initiate antibiotic therapy with a loading dose (an initial dose higher than the maintenance dose). An antibiotic loading dose should be used whenever the half-life of the drug is longer than three hours or whenever a delay of 12 hours or longer to achieve a therapeutic blood level is expected. Most antibiotics used in the treatment of orofacial infections have a half-life shorter than three hours but, due to their acute nature, most orofacial infections require therapeutic drug blood levels sooner than 12 hours. Steady-state blood levels of any drug are usually achieved in a time equal to three to five times the drug's half-life. Amoxicillin has a half-life of one to one-and-a-half hours. A steady-state blood level would then be achieved in three to seven-and-a-half hours thereby leading to a substantial delay in achieving therapeutic antibiotic blood levels. A loading dose of two times the maintenance dose is recommended for acute orofacial infections, which better achieves the goal of rapid, high blood levels rather than initiating therapy with the maintenance dose.
4. An oral antibiotic should ideally be administered at dosing intervals of three to four times its serum half-life, particularly if steady-state blood levels are desired (as may be indicated with beta-lactam agents). For example, the serum half-life of Pen-V-K is 0.75 hours. Higher continuous blood levels of this antibiotic are more likely to be obtained with four-hour rather than six-hour dosing intervals. The shorter the serum half-life of the drug, the shorter the dosing interval will need to be in order to maintain continuous therapeutic blood levels of the drug. When determining the appropriate dosing interval, it is also important to consider the following: 1) The postantibiotic effects of the drug; and 2) the relative merits of continuous or pulse dosing. PAEs are more persistent (two to seven hours) with antibiotics that act intracellularly within the microbial cytoplasm (erythromycin, clindamycin and tetracycline) or by suppression of nucleic acid synthesis (metronidazole, quinolones). As a result, these antibiotics are more effective with pulse dosing (high antibiotic dosing at widely spaced intervals). The beta-lactam antibiotics however, have a slow, time-dependent killing activity and demonstrate very little PAE. Beta-lactam microbial killing requires microbes in the process of cell division (interference with cell wall development); hence, they must be continuously present (steady-state blood levels) because bacteria divide at different rates or times.

Myth #8: Bacterial infections require a "complete course" of antibiotic therapy. There is no such thing as a "complete course" of antibiotic therapy.³ The only guide for determining the effectiveness of antibiotic therapy, and hence, the duration of treatment, is the clinical improvement of the patient.¹⁶ A common misconception asserts that prolonged (after clinical remission of the disease) antibiotic therapy is necessary to prevent "rebound" infections from occurring. Orofacial infections do not "rebound" if the source of the infection is properly eradicated. Most orofacial infections persist for two to seven days, and often less. Patients placed on antibiotic therapy for an orofacial infection should be clinically evaluated on a daily basis. When there is sufficient clinical evidence that the patient's host defenses have regained control of the infection and that the infection is resolving or resolved, the antibiotic therapy should be terminated.

Antibiotic Prophylaxis for Medically At-Risk Patients

Antibiotic prophylaxis is the administration of antibiotics to patients without evidence of infection to prevent bacterial colonization and reduce subsequent postoperative or post-treatment complications. The only established use of antibiotic prophylaxis in dentistry is in the attempt to reduce the potential consequences of bacteremias induced by dental treatment in certain medically at-risk patients. The principle indication for antibiotic prophylaxis for dental patients is the prevention of infective endocarditis in patients with specific medical conditions that are receiving specified dental treatments. Controversial indications include dental patients with orthopedic prosthetic devices, indwelling catheters and impaired (immunosuppressed) host defenses.

Dental patients presenting for treatment with impaired host defenses (chemotherapy, organ transplant or tissue graft recipient, insulin-dependent diabetes, alcoholics) or patients with indwelling catheters (hemodialysis) may benefit from antibiotic prophylaxis if their white cell count is below 2,500 (normal = 4,000-11,000). It is not currently recommended that patients with AIDS receive routine antibiotic prophylaxis prior to dental treatment. The opportunistic pathogens common to this disorder are not susceptible to routine prophylactic antibiotics and such a practice may result in the development of antibiotic-resistant microorganisms, thereby resulting in a serious superinfection.³

Antibiotic Prophylaxis for Prevention of Infective Endocarditis

The American Heart Association has published guidelines for the prevention of IE in medically at-risk patients for more than 50 years. **The most recent guidelines, published in April 2007, represent a significant change from the previous guidelines.**¹⁷ One of the stated reasons for the development of the current revised guidelines was that the risk of antibiotic-associated adverse events exceeds the benefit, if any, from prophylactic therapy (Table 1). It is well accepted that the risk for developing bacterial resistant strains to the antibiotic drug used is considered an antibiotic-associated adverse event.

The majority of published studies regarding IE being caused by oral bacteria have focused on dental procedures. Although the infective dose required to cause IE in humans is unknown, the number of microorganisms present in the blood following a dental procedure is low. It has long been assumed that dental procedures may cause IE in patients with underlying cardiac risk factors and that antibiotic prophylaxis is effective. However, scientific proof is lacking to support this assumption. Cases of IE caused by oral bacteria probably result more from exposures to low inocula of bacteria in the bloodstream that result from routine daily activities (brushing and flossing) and not from a dental procedure.¹⁷

The 2007 AHA report regarding prevention of IE concludes: "If prophylaxis is effective, such therapy should be restricted to those patients with the highest risk of adverse outcomes from IE and who would derive the greatest benefit from prevention. In patients with underlying cardiac conditions associated with the highest risk of adverse outcomes from IE, prophylaxis for some dental procedures is reasonable, even though we acknowledge that its effectiveness is unknown."¹⁷ Therefore, the 2007 AHA guidelines suggest that antibiotic prophylaxis should be considered for patients presenting for treatment with the cardiac conditions identified in Table 2, and who are undergoing any dental procedure that involves the gingival tissues or periapical region of a tooth and for those procedures that perforate the oral mucosa. This would include procedures such as biopsies, suture removal, placement of orthodontic bands, and intraligamentary and intraosseous local anesthetic injections, but it does not include routine local anesthetic injections through noninfected tissue (Table 3).

Antibiotic Prophylaxis Recommendations (see newsletter insert)

Table 1: Primary Reasons for Revision of Infective Endocarditis Guidelines

Table 2: Medical Conditions for Which Endocarditis Prophylaxis is Recommended

Table 3: Dental Procedures for Which Antibiotic Prophylaxis is Reasonable

Table 4: Patients at Potential Risk of Experiencing Hematogenous Total Joint Infection

Table 5: Suggested Patient Type, Drug and Regimen for Antibiotic Prophylaxis for Total Prosthetic Joint Infection

Antibiotic Prophylaxis for Prevention of Delayed Prosthetic Joint Infection

In 1997, the ADA and the American Academy of Orthopaedic Surgeons convened an expert panel of dentists, orthopaedic surgeons and infectious disease specialists and published its first *Advisory Statement on Antibiotic Prophylaxis* for dental patients with prosthetic joints.¹⁸ The 2003 advisory statement included some modifications of the classification of patients at potential risk and the stratification of bacteremic dental procedures (Table 4), but no changes in terms of suggested antibiotics or antibiotic regimens.¹⁹ Antibiotic prophylaxis is not indicated for most dental patients with total joint replacements or

for patients with pins, plates or screws. However, it is advised to consider antibiotic premedication in a small number of patients who may be at potential increased risk of experiencing hematogenous total joint infection (Table 5).

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

Occasionally, a patient with a total joint prosthesis may present for dental treatment with a recommendation from his or her physician that is inconsistent with the current guidelines. In this case, the dentist is encouraged to consult with the patient's physician to discuss the nature of the needed dental treatment, to review the current guidelines regarding antibiotic prophylaxis and to determine if there are any special considerations that might affect the physician's decision regarding antibiotic prophylaxis for the patient. After this consultation, the dentist may decide to follow the physician's recommendation or, if in his or her professional judgment antibiotic prophylaxis is not indicated, decide to proceed with the needed dental treatment without antibiotic prophylaxis. The dentist is ultimately responsible for making treatment decisions for his or her patient based on the dentist's professional judgment.

In February 2009, the AAOS published an information statement in which the organization, "recommends that clinicians consider antibiotic prophylaxis for all total joint replacement patients prior to any invasive procedure that may cause bacteremia."²⁰ In response to this statement, the American Academy of Oral Medicine published a position paper in the June 2010 edition of the *Journal of the American Dental Association*.²¹

The authors of the AAOM position paper stated that they reviewed the available literature on the subject as it relates to the AAOS 2009 information statement and concluded: "The risk of patients' experiencing drug reactions or drug-resistant bacterial infections and the cost of antibiotic medications alone do not justify the practice of using antibiotic prophylaxis in (all) patients with prosthetic joints." The authors called for a future multidisciplinary, systematic review of the literature relating to antibiotic prophylaxis use in patients with prosthetic joints. In the meantime, they concluded that the new AAOS 2009 information statement²⁰ should not replace the 2003 joint consensus statement.¹⁹

Summary

Since their discovery eight decades ago, safe systemic antibiotics have revolutionized the treatment of infections, transforming once deadly diseases into manageable health problems. However, the growing phenomenon of bacterial resistance, caused by the use and abuse of antibiotics and the simultaneous decline in research and development of new antimicrobial drugs, is now threatening to take us back to the pre-antibiotic era. Without effective treatment and prevention of bacterial infections, we also risk rolling back important achievements of modern medicine such as major surgery, organ transplantation and cancer chemotherapy.²²

A fundamentally changed view of antibiotics is needed. They must be looked on as a common good, where individuals must be aware that their choice to use an antibiotic will affect the possibility of effectively treating bacterial infections in other people. All antibiotic use, appropriate or not, "uses up" some of the effectiveness of that antibiotic, diminishing our ability to use it in the future. For current and future generations to have access to effective prevention and treatment of bacterial infections as part of their right to health, all of us need to act now. The window of opportunity is rapidly closing.²²

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Exclusive Bonus Materials

This issue of the *ENDODONTICS: Colleagues for Excellence* newsletter is available online at www.aae.org/colleagues with the following *exclusive bonus materials*:

- Prevention of Infective Endocarditis: Guidelines From the American Heart Association, 2007.
- Antibiotic prophylaxis for dental patients with total joint replacements; Advisory statement from the American Dental Association and American Academy of Orthopaedic Surgeons, 2003.
- The dental treatment of patients with joint replacements: A position paper from the American Academy of Oral Medicine, 2010.

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