CLINICAL MANAGEMENT

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Silver-Containing Dressings and the Need for Evidence

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PURPOSE

To present the practitioner with detailed information on silver-based dressings, including evidence of their efficacy and current practice related to these dressings.

TARGET AUDIENCE

This continuing education activity is intended for physicians and nurses with an interest in better understanding the evidence for and current use of silver-based dressings.

OBJECTIVES

After reading this article and taking the test, the reader should be able to:

1. Describe the indications, actions, and adverse effects related to silver compounds used in wound care.
2. Review the chemical properties and actions that affect the action of silver compounds.
3. Discuss the limitations of current evidence related to silver-containing dressings, along with some of the rating systems used for evaluating scientific evidence.

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Silver is a broad-spectrum agent effective against a large number of Gram-positive and Gram-negative microorganisms, many aerobes and anaerobes, and several antibiotic-resistant strains such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci.[1] Within the last decade, the field of wound care has been inundated with active dressings—those that deliver biologically active substances to the wound site—and much attention has been given to those containing silver.

Historically, silver has been used for numerous health care applications. The Greeks and Romans stored water in silver vessels to keep it fresh, and Americans traveling west during the 1800s put silver coins in water barrels to retard the growth of bacteria and algae.[2–4] The compound silver nitrate ($AgNO_3$)

was used to treat ophthalmia in neonates beginning in the mid-1800s.[2] In the 1960s, 0.5% silver nitrate solution[5,6] and 1% silver sulfadiazine cream[6] (Silvadene and others) became widely used as topical agents in burn care; silver sulfadiazine remains the standard of care in burn management.[7,8] In these compounds, the silver provides the primary microbicidal effect (although sulfadiazine, a sulfonamide, also has bacteriostatic properties). However, other substances in these compounds usually produce some adverse effects; for example, nitrate may cause hyponatremia and hypochloremia. To eliminate those adverse effects, pure silver is used.

More than 10 different silver-containing dressings, including silver-containing hydrogels, hydrofibers, and alginates, are currently available worldwide. Although all are assumed to be safe and effective, evidence of their efficacy is scant; few clinical trials have been performed with them. Moreover, claims about how the dressings work, how effective the silver in a specific dressing is, and why one dressing is better than another are based on sometimes scientifically complex methods of testing and results that yield contradictory or inconclusive statements.

It is important for clinicians to be aware of the ways in which silver acts physically and chemically, especially when trying to understand the statements made by companies that market silver-containing dressings.

PHYSICAL AND CHEMICAL PROPERTIES

• ***Isotopes.*** All elements—of which atoms are the smallest units—exist in slightly different versions called *isotopes*. Different isotopes of a given element share the same number of protons, or positively charged particles, in their nuclei (the atomic number), but have different numbers of neutrons, or electrically neutral particles. (The number of protons and neutrons combined is known as the atomic mass, so an element and its isotopes have different atomic masses.)

Different isotopes of the same element behave the same chemically but have different physical properties. Certain physical properties affect the clinical behavior of a compound. For example, the total amount of silver in a dressing, as well as its crystalline structure, contributes to how much and how quickly silver is dispersed from the dressing onto the wound surface. If a given amount of silver is divided among a large number of smaller crystals, its chemically active surface area will be greater than when the same amount is divided among fewer, larger crystals. There is ongoing debate regarding whether a higher concentration or a larger total amount (or both) of silver in a dressing would result in greater quantities of biologically active silver in the dressing and on the wound surface.[9,10]

• ***Ions.*** Atoms with overall positive or negative electrical charges are called *ions*. An atom with fewer protons than electrons has a negative charge and is called a negative ion or *anion;* an atom with more protons than electrons has a positive charge and is called a positive ion or *cation*. The state of ionization determines the chemical behavior of an element. One form of silver, atomic silver, Ag^0, is electrically neutral. One of the most common ions is Ag^+, also called ionic silver.

Ag^+ ions react with a number of elements and compounds. For example, Ag^+ ions readily bond with negative chlorine ions (Cl^-) to form silver chloride (AgCl), which has a very low level of solubility. In a solution (such as an exudate) that contains a high percentage of Cl^- ions, a high percentage of Ag^+ ions will become bound and will precipitate as AgCl, which has not been shown to be biologically active. Thus, only a small fraction of Ag^+ will remain available as an antimicrobial agent.

As mentioned, there is disagreement regarding whether the *total* amount of silver present or the *chemically available* amount has more import in antimicrobial activity. For example, some experts suggest that when excess Cl^- is present, it may be possible to overcome the precipitation with a relatively massive amount of silver in the wound.[9,10] Others have stated that it is the amount of available soluble silver in a dressing that determines the dressing's efficacy.[11] However, it has not been shown that a larger amount of silver in a dressing necessarily results in better clinical outcomes.

Laboratory experiments have shown that in a protein-rich environment, silver-containing dressings kill a variety of microorganisms, although kill rates vary according to microorganism.[12] Even low silver concentrations were found to be effective; for most microorganisms, only a minute amount of Ag^+—concentrations of one part per million or even lower, depending on the target microorganism[3]—was necessary to achieve a microbicidal effect.[13] Figure 1 illustrates silver ion dressings.

ANTIMICROBIAL EFFECTS AND TOXICITY

To date, no common wound pathogens have demonstrated resistance to pure silver. Resistance to silver sulfadiazine by some microorganisms, including some strains of *Pseudomonas aeruginosa*, has been demonstrated.[5,14] In addition, a *Salmonella* strain (not a wound pathogen) has shown resistance to pure silver.[15]

The literature on the antimicrobial efficacy of silver is often inconclusive or contradictory regarding findings about the degree of biologic activity of Ag^+ and Ag^0, the minimal and optimal amounts of active agent needed, and the effectiveness

Figure 1.
SILVER ION DRESSING

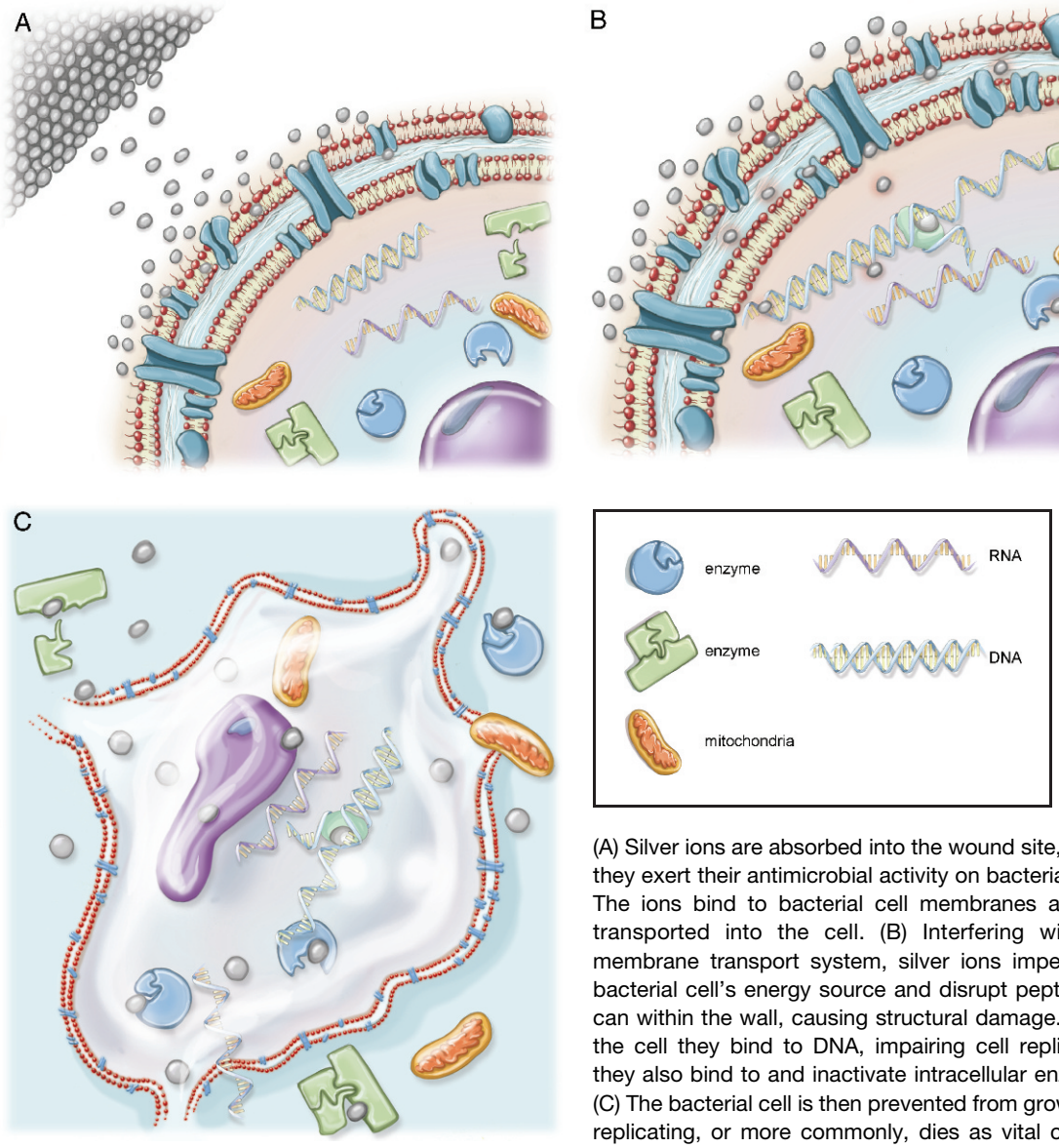

Illustration by Annelisa Ochoa

(A) Silver ions are absorbed into the wound site, where they exert their antimicrobial activity on bacterial cells. The ions bind to bacterial cell membranes and are transported into the cell. (B) Interfering with the membrane transport system, silver ions impede the bacterial cell's energy source and disrupt peptidoglycan within the wall, causing structural damage. Inside the cell they bind to DNA, impairing cell replication; they also bind to and inactivate intracellular enzymes. (C) The bacterial cell is then prevented from growing or replicating, or more commonly, dies as vital components leak through a weakened cell wall no longer able to maintain osmotic pressure.

of various dosage regimens. Moreover, the variety of testing methods adds to the confusion. Many types of in vitro tests can be used to examine different aspects of the antimicrobial properties of dressings. However, results are not always easily comparable, and extrapolating in vitro results to a clinical (in vivo) situation should be done with caution[16]; many clinical circumstances may have been excluded from a study or simply cannot be simulated in in vitro testing.

That said, the antimicrobial activity of Ag^+ is generally attributed to 4 mechanisms. Ionic silver:

• binds to the bacterial cell membrane, damaging it and interfering with various receptors

• interferes with bacterial electron transport, impeding the production of adenosine triphosphate, the cell's energy currency
• binds to bacterial DNA, impairing cell replication
• causes the intracellular formation of insoluble compounds with certain nucleotides, proteins, and the amino acid histidine, making them unavailable as intracellular building blocks.[3,17,18]

Some antimicrobial effect is claimed for Ag^0, particularly with respect to the reduction of matrix metalloproteinases (MMPs)—a subgroup of enzymes that break down proteins such as collagen and elastin-in chronic wounds.[10,19] Although the mechanisms for this phenomenon are unclear, high levels of certain MMPs have been implicated in preventing chronic pressure ulcers from healing,[20,21] and reduction or inhibition of these enzymes would be beneficial.

Many silver compounds produce toxicity or other adverse effects, but these effects are usually caused not by the silver but by anions (such as nitrate) bound to it or compounds (such as sulfadiazine) associated with it.

Silver nitrate is hypotonic and may cause serious hyponatremia and hypochloremia.[22] It also causes a gray and black discoloration. Certain types of bacteria (such as *Klebsiella*) are not very susceptible to it.[22] A disadvantage of silver nitrate is that when it is used as a solution, dressings have to be soaked regularly with it in order to maintain the patient's exposure to the silver.

Silver sulfadiazine 1% cream is water soluble and must be applied twice daily for optimal effect, according to its manufacturers. The cream causes discoloration of the wound bed (pseudo eschar[23]), which, after several applications, interferes with judging wound status. Allergic reactions to the sulfonamide compound have been described. It has limited efficacy against Gram-positive microorganisms,[24] and resistant strains of *P aeruginosa* have also been reported.[25]

With the exception of wound bed discoloration, pure atomic or ionic silver does not cause most of these adverse effects. Pure silver is generally considered nontoxic when used at clinical dosages.[26] Although urinary excretion of silver may increase by more than 1000 times when silver compounds are used to treat large areas for prolonged periods (for example, in the care of extensive burns),[27] that appears to have no clinical implications. Bone marrow toxicity,[28] leukopenia, and renal or hepatic damage through silver deposition have been described as well, but only with silver compounds; such reports, therefore, probably have limited significance regarding the use of atomic or ionic pure silver.[29] Still, with silver widely used not only in medical devices such as indwelling catheters but also in products such as cosmetics and vegetable washes, exposure is not uncommon; some caution may be needed to prevent the occurrence of systemic toxicity.[30]

EVIDENCE OF EFFICACY OF SILVER-CONTAINING DRESSINGS

According to the manufacturers of dressings currently available, each enhances wound healing through the antimicrobial activity of silver. However, with many of these dressings, such claims are not based on clinical trials, but rather on case histories and in vitro studies.

Traditionally, testing the efficacy of a device or dressing is done in 2 stages, a preclinical stage (laboratory and animal models) and a clinical stage (clinical trials in humans). For silver as a compound, and for many silver-containing dressings, preclinical proof of antimicrobial efficacy has been established in many in vitro and animal models. However, some of these test models bear no relevance to clinical situations. For example, if the test medium in which Ag^+ concentrations are measured contains only distilled water, the concentration of Ag^+ reached can be much higher than in solutions that, like exudate, contain Cl^- ions. As mentioned, in solutions that contain Cl^-, large amounts of Ag^+ will precipitate as AgCl, which is not biologically active.

The type of dressing used influences the efficacy of the biologically active agent.[16] For example, hydrogel dressings allow diffusion of an agent to the wound surface in ways that differ from those of gauze or hydrocolloid dressings. This is one reason why data generated for one type of dressing cannot be extrapolated to another type, even if they both contain the same active agent (such as silver).

Evidence-based wound care should rely on well-designed, well-executed, and well-analyzed clinical trials. Unfortunately, in wound care, it is virtually impossible to conduct double-blind clinical trials and, therefore, impossible to perform grade A studies.[31] However, prospective, randomized, controlled studies can be conducted and should serve as the basis of clinical evidence of the efficacy of silver-containing dressings. To analyze what types of studies are presented at symposia and what information is available in the public domain, the author analyzed the posters presented at a national wound care conference in 2005. A literature search for articles about silver-containing dressings used for a specific indication was also conducted.

The conference chosen for the analysis was one of the largest general wound care conferences held in the United States. The author expected that sound evidence regarding the use of silver in wound care would be presented. However, of a total of 243 poster presentations, only 5 (2%) concerned clinical trials of silver (contained in 3 different dressings) that were conducted with appropriate protocols, inclusion and exclusion criteria, statistics, and so on, thus representing grade B studies. Five additional posters covered clinical trials of silver-containing dressings that were not properly conducted

AN EVIDENCE GRADING SYSTEM

The grading system used by the United Kingdom-based Centre for Evidence-Based Medicine aims to analyze to what extent various statements—assumptions about clinical diagnosis and treatment—have proven to be scientifically valid. Such statements can be categorized as pertaining to 5 areas of study: therapy—prevention and etiology—harm; prognosis; diagnosis; differential diagnosis and symptom prevalence; and economic and decision analyses. For a given statement, the available data and literature are collected and analyzed with respect to both the type of source (eg, randomized controlled clinical trials, expert opinions, or case histories) and the level of scientific evidence presented (such as the types of statistical calculations and results).

Each data set is given a rating, ranging from 1a to 5 (see Table 1 for an example of one area of study). A specific modality (such as a diagnostic procedure with regard to false negatives and false positives, or a treatment with respect to outcomes) is then given a grade of recommendation from A to D:[31]

- A-consistent level 1 studies
- B-consistent level 2 or 3 studies or extrapolations from level 1 studies
- D-level 5 evidence or troublingly inconsistent or inconclusive studies of any level.

This rating system allows a clinician to see whether a given intervention has been validated without having to do extensive research himself or herself. For example, if evidence for a certain procedure is graded A, one can be certain that the scientific process to prove claims made about that procedure was well executed and the claims themselves are trustworthy.

Table 1.
RATING THE EVIDENCE

Level	Therapy—Prevention and Etiology—Harm
1a	Systematic review (with homogeneity*) of randomized controlled trials
1b	Individual randomized controlled trial (with narrow confidence interval†)
1c	All or none (all patients died before the treatment became available, but some now survive when using it; or some patients died before the treatment became available, but none now die when using it)
2a	Systematic review (with homogeneity) of cohort studies
2b	Individual cohort study (including low-quality randomized controlled trial; for example, one with <80% follow up)
2c	Outcomes research; ecologic studies
3a	Systematic review (with homogeneity of case-control studies)
3b	Individual case-control study
4	Case series (and poor-quality cohort and case-control studies‡)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research, or ''first principles''§

*Homogeneity is defined as ''systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies.''
†Confidence interval (CI) ''quantifies the uncertainty in measurement; usually reported as 95% CI, which is the range of values within which we can be 95% sure that the true value for the whole population lies.''
‡A poor-quality cohort study is one that ''failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known as confounders and/or failed to carry out a sufficiently long and complete follow-up of patients.'' A poor-quality case-control study is similarly defined.
§''First principles'' are ''the pathophysiologic principles used to define clinical practice,'' many of which have never been proven in clinical trials.
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(eg, statistical analysis was absent or not properly executed). Moreover, many trials involved noncomparable types of wounds, without proper stratification of patients and their lesions. Other posters on silver-containing dressings were either about preclinical models or case histories; their conclusions were often not supported by the research described or, with regard to the case histories, were substantiated only for the individuals described.

In September 2005, a literature search was performed using the search engines Google and Yahoo; the PubMed database of the National Library of Medicine and the archives of several wound care journals were searched as well. The goal of the literature search was to find clinical evidence of silver-containing dressings used for a specific indication: partial-thickness burns. Different criteria (including all brand names) were used as keywords. Articles that were nonclinical or not about silver-containing dressings were excluded. The search returned 355 results, of which 4 (1%) were for prospective, randomized clinical trials using appropriate and relevant protocols and statistics. These trials were conducted with just 2 brands of silver-containing dressings. Only these trials provided reliable, grade B data that may prove to be useful in creating guidelines for product choice and usage in a specific indication. As was the case with the conference poster presentations, all other results involved poorly conducted trials, research with preclinical models, or case histories.

SO MANY DRESSINGS, SO LITTLE INFORMATION: CHOOSING A TREATMENT WHEN EVIDENCE IS LIMITED OR CONFLICTING

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What should clinicians do when asked about using a wound dressing for which, as Michel Hermans observes, ''evidence of efficacy is scant? Insufficient evidence isn't unusual in the area of wound care.'' Indeed, evidence-based practice remains a challenge in various settings,[34,35] and treatments have been marketed with little or no evidence of efficacy for decades.[36] But an infected wound can be life threatening, and the use (and overuse) of antimicrobial agents has caused problems of its own.[37]

When to use a silver-containing dressing. In deciding whether a topical antimicrobial is necessary, clinicians are guided by the appearance and history of the wound. Although a consensus has not been reached on whether and how specific microorganisms affect healing, many wounds will exhibit at least one of the classic symptoms of infection: redness, warmth, increased tenderness or skin anesthesia, skin sloughing, or pus.

These symptoms indicate that bacteria have at least invaded the tissues.[37,38] Some chronic wounds, such as leg ulcers, pressure ulcers, and foot ulcers in patients with diabetes, will also exhibit symptoms of infection, but most will simply stop healing or deteriorate.

Recognizing serious wound infection can be difficult because the signs and symptoms of heavy contamination with pathogens or infection in chronic wounds can be ambiguous. But a wound should be assessed regularly (how often can depend on the history of the wound and the patient's status). Indeed, several studies have shown that a reduction in wound size after a few weeks of care is a predictor of healing, suggesting that if a wound does not get smaller after several weeks of care, the patients should be reexamined and all care procedures reviewed.[39,40]

Preventive measures and monitoring strategies include thorough wound cleansing, removal of necrotic tissue (which can also support infection), and obtaining a quantitative wound culture. To avoid culturing superficial contaminants, a deep swab culture, needle aspiration, or punch biopsy is recommended; some wounds may require further assessment for osteomyelitis.[38,41,42] Laboratory findings will also help clinicians to decide whether systemic or topical antimicrobial therapy is necessary.[38]

Why silver? Silver is known to be, as Hermans writes, ''a broad-spectrum agent effective against a large number of Gram-positive and Gram-negative microorganisms, many aerobes and anaerobes, and several antibiotic-resistant strains such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci.'' Silver-containing dressings may be an appropriate choice for heavily contaminated or infected wounds.

Choosing a dressing. In deciding on which dressing to use, the clinician should consider a dressing's physical characteristics. Silver-containing dressings, like others, are available in a variety of forms. Some are developed for deep wounds; others are for relatively shallow ulcers with little exudate.[43] Some wounds require a secondary protective dressing, whereas others do not.

After treatment has begun, healing should commence. If it does not, additional diagnostic procedures and a reevaluation of the care protocol, including the use of the silver-containing dressing, are needed. Topical antimicrobials should be discontinued when signs of infection or heavy contamination have subsided; also, although there is no evidence to guide clinicians when to stop using these dressings, the overuse of antimicrobials should always be avoided.[43]

Certainly, more research is needed, but clinicians can use what is known to optimize care and reduce the risk of complications.

CURRENT PRACTICE

Current practice in wound care is based largely on empirical and anecdotal evidence; for many products, clinical trials have not been published and no evidence of their effectiveness is available.[32] This was true for previous generations of dressings (including hydrocolloids, alginates, and foams) as well.

The Centre for Evidence-Based Medicine in Oxford, United Kingdom, defines evidence-based medicine as the conscientious,

explicit, and judicious use of current best evidence in making decisions about the care of individual patients, adding that its practice requires integrating individual clinical expertise with the best available external clinical evidence from systematic research.[33] Professional expertise is invaluable, of course, but it is impossible for any individual, or even a single wound care clinic or institution, to acquire experience with all new wound care dressings, techniques, and technologies. Providers must rely on researchers, on the wound care community at large, and on product manufacturers to provide information and insight into the merits and drawbacks of any new dressing, technique, or technology.

Unfortunately, many dressings, including the majority of silver-containing dressings, have not been tested in ways that provide clinically valuable information. In vitro tests are important, as are those using animal models, but only properly executed, prospective, comparative, randomized clinical trials can provide information that may be used as a guideline.

Proof of clinical efficacy may be obtained by taking a critical look at the literature. Questions one should ask may include the following:

- Was the study population chosen and analyzed correctly? For example, were mixed indications avoided?
- Were the inclusion and exclusion criteria sufficient to yield a patient cohort that is relevant for the indication and study objectives? For example, were all comorbidities and medications taken into account?
- Was the diagnosis confirmed according to accepted guidelines?
- Was the study setup such that the study objectives could be proven? For example, was the duration of participation sufficient? Were study outcomes measured correctly?
- Are the statistics solid and sound?

Alternatively, one may design a comparative study in which a new material is compared with the standard used in one's clinic. Dressing studies have limitations: it is very difficult to achieve blinding, and clinical conditions and comorbidities of participants typically vary significantly. Still, a simple comparison study should offer the researcher more useful information than a series of uncontrolled, noncomparative case histories.

In that context, it is also important to consider early which study outcomes one is looking for and design a protocol accordingly. For example, if the study is about bactericidal efficacy, laboratory cultures and clinical evidence of infection have to be assessed to be able to draw conclusions. ●

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- If you pass, you will receive a certificate of earned contact hours and an answer key. Nurses who fail have the option of taking the test again at no additional cost. Only the first entry sent by physicians will be accepted for credit.
- A passing score for this test is 13 correct answers.
- Nurses: Need CE STAT? Visit **http://www.nursingcenter.com** for immediate results, other CE activities, and your personalized CE planner tool. No Internet access? Call 1-800-787-8985 for other rush service options.
- Questions? Contact Lippincott Williams & Wilkins: 1-800-787-8985.

Registration Deadline: March 31, 2009 (nurses); March 31, 2008 (physicians)

PAYMENT AND DISCOUNTS:

- The registration fee for this test is $24.95 for nurses; $20 for physicians.
- Nurses: If you take two or more tests in any nursing journal published by LWW and send in your CE enrollment forms together, you may deduct $0.95 from the price of each test. We offer special discounts for as few as six tests and institutional bulk discounts for multiple tests. Call 1-800-787-8985, for more information.