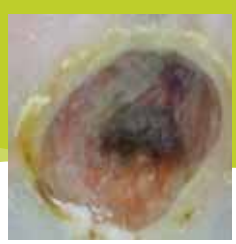
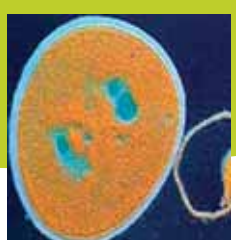
Supplement to the October 2006
OWM
OstomyWoundManagement

Infection Control
Made Easy


Providing powerful protection against wound infection and minimizing the risk and impact of infection with no change to protocol.

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Table of Contents

Continuing Education Information

Target Audience: Physicians, Nurses, and Podiatrists

Learning Objectives: Upon completion of this educational activity, participants should be able to:

- Distinguish mechanistic differences between simple cationic antimicrobials and polymeric biguanides
- Relate usage of cationic antimicrobials in the clinic to the potential for resistance development.

Accreditation:

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Avoiding the Resistance Pitfall in Infection Control

Does the use of antiseptic products contribute to the spread of antibiotic resistance?

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Antibiotics and antiseptics are the treatments of choice for controlling infection. Appropriate use of antibacterial products can help reduce the level of infection, but should be limited to situations in which they have demonstrable benefit. With the continually expanding uses of antibacterials, environmental overload from these agents and the threat of resistance are very real scenarios. Therefore, when antibacterial use is warranted, products that minimize the use of antibiotics and the potential for resistance development should be employed. The two articles in this supplement distinguish antibiotics from antiseptics and address their applications to wound care.

Antibiotics and antiseptics are the products of choice when it comes to treating and managing infections. This article addresses the issue of whether the use (and/or misuse) of these products is linked to resistance.

Antibiotic versus Antiseptic

Although often used interchangeably, the terms *antibiotic* and *antiseptic* refer to different categories of therapeutic products (see Table 1).

Antibiotics are agents generally administered systemically. In order to be safe, they have a single pharmacological target, which makes them vulnerable to resistance. Biocidal action is relatively weak. Antibiotics have been available for about 40 years. Almost as quickly as new products are introduced into practice, resistance against antibiotics develops.[1]

Antiseptics have been in use longer than antibiotics. They also are considered antibacterials and have multiple actions. Antiseptics are not elegant pharmacologic molecules; they are shotguns that attack cells (eg, bacterial cells) and are suitable for topical administration. They have multiple targets of action, which renders them less likely to trigger resistance. Since the pioneering work on antiseptic surgery and hygiene driven forward by the likes of Ignác Semmelweiss and Joseph Lister, antiseptics have been the mainstay of our defense against infection.

Antiseptics provide positive healthcare benefits in terms of home hygiene.[2,3] Appropriate use of antibacterial products can help reduce the level of infection, consequently reducing the need to use antibiotics and removing some of their negative attributes. However, antibacterial product use should be limited to situations in which it has demonstrable benefit.

Over the past 10 years, antibacterial use has expanded. Various manufacturers have increased the marketability of consumer products by including antiseptics within the formulations. Antiseptics are creeping into plastics, ceramics, dish cloths, socks, clothing, and condoms — the word *antibacterial* alone seems to sell products. The industry is now drenched in antiseptics from a variety of consumer products, which suggests environmental

Table 1. The Differences between Antibiotics and Antiseptics

Antibiotics	Antiseptics/Antibacterials
• Therapeutic agents	• Topical administration
• Administered systemically	• Multiple targets
• Single pharmaceutical target	• Strong biocidal agents
• Weak biocidal agents	

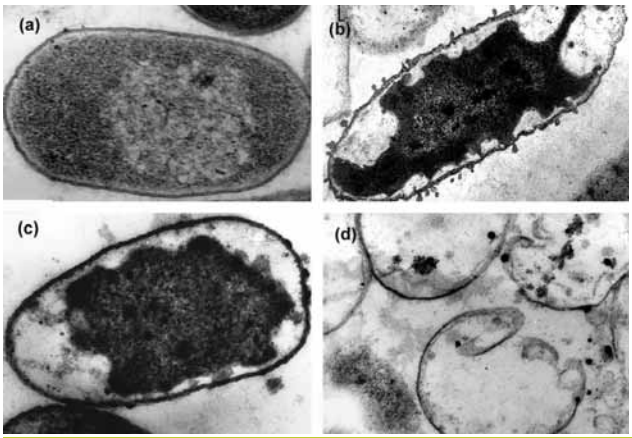

Figure 1. The above images are from a series of electron micrographs of Escherichia coli (a) exposed to concentrations of a cationic biocide that inhibit growth (b) and kill at moderate (c) or rapid rates (d).

overload from these agents. The real worry is that overuse of antiseptics may incite resistance.[1]

The Making of a Superbug: All Things Efflux

Antibiotic resistance. Many bacteria have the capability to remove antibacterial drugs from their cytoplasm and cell membranes by expressing efflux pumps. When the bacterial cells are exposed to toxic agents at low levels, often their response is to up-regulate these pumps, some of which are non-specific and able to remove a wide range of molecules including antibiotics. Bugs possessing such multidrug efflux pumps are often referred to as *superbugs* (multiantibiotic-resistant able to remove the antibiotic from the center of a cell by pumping it back out across the cell envelope).

All bacteria can respond to noxious materials by expressing this up-regulation reflex. The literature shows that this expression is induced by sublethal exposure to a range of antibiotics and solvents, as well as to some antibacterial products, the use of which could actually induce efflux.[4,5] In infection, induction of efflux pumps is sufficient to confer clinically relevant levels of antibiotic resistance. Antibiotic resistance is the evolved ability of a micro-organism to withstand the effects of an antibiotic.

Antiseptic resistance: Does it exist? One of the most widely abused antiseptics is triclosan, contained in many commercial products. A substrate for efflux, triclosan can be pumped out of a cell, but it will not itself induce expression of the pumps. Therefore, if a population of bacteria is sublethally exposed to triclosan, the pumps will not be induced, but cells that are already pumping will be selected for survival. These bacterial cells are mutants, lacking control of efflux, and will normally grow at slow rates because of the fitness cost associated with mutation (ie, in the absence of the triclosan stress, these bulimic bugs will be overgrown and out-competed by the wild types; therefore, efflux pump induction only marginally affects susceptibility to antiseptics).

Pumps will alter the susceptibility of many bacteria to a wide range of antibiotics and biocides. (Susceptibility means that the micro-organism will become ill or possibly die in the face of the stressful event.) The measurement of susceptibility relates to minimum growth inhibitory concentrations. Although they are close to the use level for antibiotics, they are less than 1% of the concentration used for topical antisepsis.

Are All Antiseptics Created Equal?

Monocationic antiseptics. Monocationic antiseptics include quaternary ammonium compounds (QACs) (eg, cetrimide, benzalkonium chloride) and dimeric agents (eg, Hibiscrub® [Regent Medical, Norcross, Georgia]). No resistance to such antiseptics has ever been reported to develop, but changes in susceptibility have been noted and where efflux pumps are switched on through QAC use antibiotic susceptibility is marginally affected.

The positive charge of monocationic antibacterials interacts with the negatively charged phospholipids that comprise the cell membrane. The fatty tail of the QAC then inserts itself into the membrane, crowding the outer more than the inner leaflet, thus distorting the bi-layer arrangement of the membrane. Efflux pumps can actively remove drugs from the membrane core in this instance. At this low exposure, the membrane is stressed, but efflux pumps can compensate and maintain bacterial stability.

As the time or the concentration of drug to which the cell is exposed increases, more of these cationic molecules are inserted into the membrane. Sufficient surface pressure will stretch or strip away the outer leaflet from the inner leaflet. However, efflux pumps can still play a role in reducing this damage. The membrane is increasingly distorted with time. No longer a lipid barrier, it cannot contain nutrients within the cell. The cell starts leaking, allowing the QAC to pierce the barrier and attack deep within the cytosol, disrupting the outer leaflet and entering the cell.

Eventually, the ingress of the quaternary into the outer leaflet is sufficient to strip it away. The cell will cease growing, die, and lyse.

Polycationic antiseptics. A third group of cationic antiseptics have multiple cationic charges (polycationics) and include polymeric biguanides such as polyhexamethylene biguanide (PHMB), an active ingredient in various products ranging from contact lens solutions to swimming pool sanitizers. All of these compounds have been in use for at least 60 years in various applications and so far their effectiveness has not changed.

Figure 1 shows a series of electron micrographs of *Escherichia coli.* When exposed to cationic antimicrobials, plasmolysis is immediately seen. Inability to control the movement of ions across the cell membrane causes the cytoplasm to shrink. At the same time, lipopolysaccharide and phospholipids are dissolved away from the cell envelope. An increase in either antimicrobial concentration or time results in further plasmolysis, which strips all of the fatty components off the wall. Further treatment or higher concentrations cause the cells to rupture, leaving ghost-like remnants of the bacteria. Many different antiseptic agents act in a similar fashion to PHMB, notably the bisbiguanides (chlorhexidine and alexidine) and phenolics, which are often included within coal tar soaps and liquid soaps.

Polycationics are long polymer chains. With polymeric molecules, integration into the outer membrane structure is not feasible. Biguanide groups are separated by six carbons (a hexamethylene chain), a length that allows them to join together two head groups but does not allow them to bend and integrate into the membrane. When PHMB lands on a membrane, it settles on the surface, preferring to bind with acidic phospholipids as one particular category of lipid.

As the PHMB binds to the membrane, it drags acidic phospholipids to that location to reorganize the membrane, creating an acidic lipid domain. Efflux is completely ineffective at removing that agent because it has not entered the lipid domain that efflux pumps require. As the damage increases, the domain formation also increases. The cell is now in need of repair, not because of increased surface pressure in this membrane, but because puddles of acidic phospholipid impede the membrane's function. Again, efflux will not affect this action. As the concentration increases even further, the membrane will be stripped of acidic phospholipids and the cell will die.

Although these agents are classified as cationic antiseptics, distinct differences in action between the monocationic and polycationic antibacterial agents are noted. Monocationic agents are vulnerable to efflux defense, whereas polycationic agents tend to reorganize the membrane and are invulnerable to this efflux defense. Therefore, PHMB is not just another cationic antimicrobial — it is a polycationic compound with increased ability to impact bacterial cell death. For example, in a 2004 study, PHMB killed common ulcer-derived bacteria in the presence of human wound fluid. The infection and consequent protein degradation was reversed by PHMB.[6]

A Future Without Resistance

Specifically targeted hygiene has a place in the clinic. Situations where antiseptic products should be used and can produce a demonstrable benefit should be identified. In wound care and sutures, antisepsis and disinfection of critical areas is absolutely essential. When antibacterial use is warranted, products that minimize the use of antibiotics and the potential for resistance development should be used. Possible consequences of long-term, chronic use of antiseptics must be acknowledged and efforts to select products that pose the least chance of resistance should be employed.

Some antiseptics are better than others — even if they fall under the same generic umbrella term, they are distinct and different from one another.[7]

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Reducing the Risk of Wound Infections

Examining the role of antimicrobial resistance in the management of lower extremity infections.

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Antimicrobial resistance is encountered in every healthcare setting; however, dealing with resistance issues detracts from the ultimate goal of wound healing. This article reviews the diagnosis of foot infections, including causes and treatment options and ways to prevent infection and minimize resistance.

Bacteria and Antimicrobials

Antibiotics are often overused in the treatment of open wounds, dramatically increasing the chance of encountering antibiotic resistance[1] (see Figure 1). Only infected wounds should receive antibiotic therapy. Where the confusion lies is in the difference between infection and colonization. All open wounds will be *colonized*. This simply means that bacteria are present; however, these wounds do not exhibit the clinical signs of infection. *Infection* implies the actual invasion and multiplication of bacteria within the tissue.

To establish whether a wound is infected or merely colonized, the literature supports the use of clinical signs and symptoms to determine the need for wound culturing.[2,3] Several signs indicate the presence of an infection — most notably erythema, pain, pus, induration of the skin, and lymphangitis.[4] Systemic signs include fever, elevated white blood cell count, and loss of glycemic control. In wounds that demonstrate these signs, it is important to identify the organism responsible for infection (versus simple colonization) to guide appropriate antimicrobial therapy (see Table 1).

Currently, the collection of a biopsy specimen is the gold standard for determining the presence and identity of an infecting organism. Needle aspiration is generally considered the next best method; whereas, the more common swab technique is far less effective by comparison.[5] It is also important to secure bacterial load counts from the laboratory in addition to the culture and sensitivity. Soft tissue requires a bacterial load of 10^5/g of tissue to cause infection. Bone requires slightly more than 10^6/g of tissue, while patients with implants require less than 10^4/g of tissue. Once the infecting organism has been identified, it is important to focus on how to best prevent antibiotic resistance.

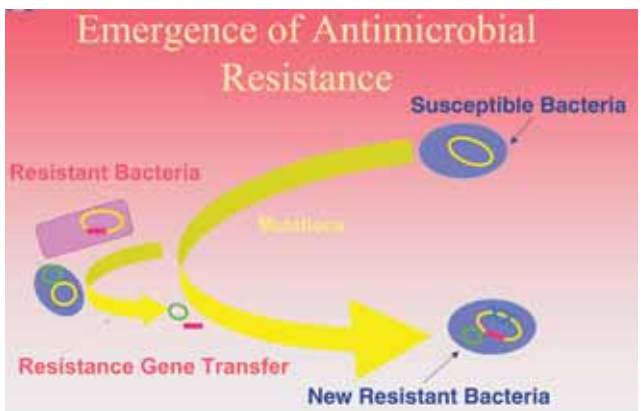

Figure 1. This graphic shows the chain of events that lead to antimicrobial resistance.

The History of Resistance

Penicillin arrived on the market in 1940 and the first case of penicillin resistance was described in 1941. In 1960, methicillin was released; methicillin resistance was first documented in 1961. Therefore, it can be argued that resistance to antibiotics is both rapid and imminent.

Repeated exposure to an antibiotic, along with genetic mutations in bacterial DNA, are keys to the emergence of antimicrobial resistance. Examples of

Figure 2. This patient presented for evaluation of her foot wound for cellulitis and possible osteomyelitis.

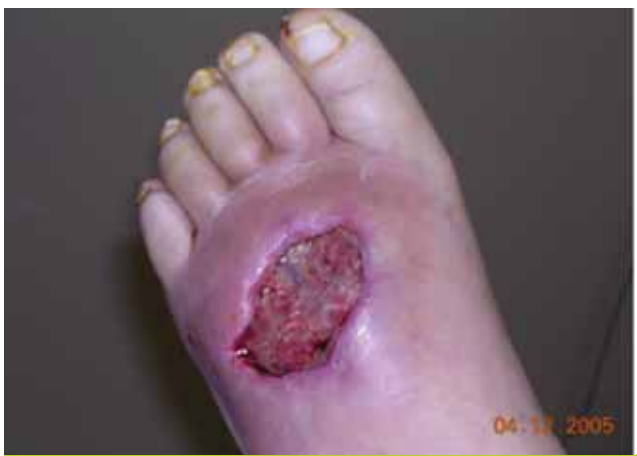

Figure 3. The wound after treatment with polyhexamethylene biguanide gauze and debridement.

common resistant organisms include methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*. Antibacterial resistance is a problem that impacts both patient mortality and rising healthcare costs. To combat this growing problem, some clinicians employ tactics such as *crop rotation* (rotation of prescribed antibiotics every 3 to 6 months). The Centers for Disease Control and Prevention (CDC) offers 12 steps for preventing antimicrobial resistance in hospitalized adults (see Table 2).

Dealing with Real Cases

Proactive wound management offers options for minimizing the use of systemic antibiotics. It is well documented that bacterial bioburden in the wound bed negatively impacts epithelialization and ultimately, healing.[6,7] Clinicians have many tools (products) available in their armamentariums that minimize bacterial proliferation and prepare the wound environment for healing without risking bacterial resistance. Silver dressings such as Acticoat Antimicrobial Barrier Dressing (Smith & Nephew, Largo, Fla) elute silver crystals into the wound bed, helping to minimize bacterial growth.[8] However, silver dressings are often cost-prohibitive and therefore must be utilized sparingly — usually only once signs of infection are present. Debate over potential bacterial resistance to silver products continues.

Another recent technology that provides infection prophylaxis is wound dressings impregnated with polyhexamethylene biguanide (PHMB). Tyco Healthcare/Kendall recently launched a range of standard wound dressings called AMD designed to prevent bacterial growth within and penetration through the dressings. These dressings have been proven effective against a wide range of bacteria, including methicillin-resistant *S. aureus* and vancomycin-resistant *Escherichia coli*. Additionally, these dressings are priced at only a slight premium to traditional gauze, making them cost-effective for prophylactic use on all wounds. There is no known resistance for PHMB, making it safe for everyday use. PHMB dressings are often used in helping to prevent wound infections, improving outcomes and minimizing treatment costs.

Some key considerations:

• Keeping the wound clean with daily washing and a clean dressing can greatly reduce the chance of developing an infection. After cleaning the wound, applying a clean, 50-cent roll of gauze as a dressing can prevent the need for $100 worth of antibiotics.

• Two common home remedies that patients unfortunately try are petroleum jelly and hydrogen peroxide. Petroleum jelly traps exudates within wound beds and can quickly lead to a macerated, foul-smelling, infected wound. Over-the-counter ointments should be avoided because they contain about 97% petroleum jelly. Hydrogen peroxide is cytotoxic and often leads to maceration and rapid wound dehiscence.

The following case studies are real-world examples of relevant clinical situations experienced by wound care clinicians.

Case Studies

Osteomyelitis. A 45-year old, noninsulin-dependent female patient with diabetes mellitus presented at the time of consult for evaluation for cellulites and possible osteomyelitis of the foot (see Figure 2). Magnetic resonance imaging was consistent for changes associated

Table 1. Wound Culture and Antibiotic Considerations

Wound Culture
- Determines the number of bacteria present
- Identifies the organism causing the infection
- Guides the choice of antibiotic therapy

Potential Antimicrobial Consequences
- Colitis
- Fungal infection
- Resistance

Topical Therapy
- Minimal role for antibiotic ointment in preventing or treating infection

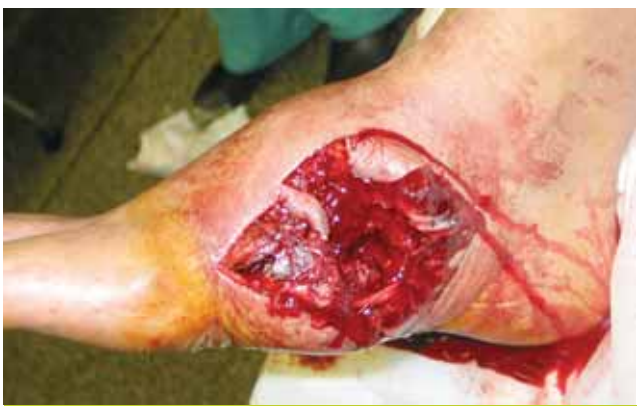

Figure 4. Gunshot wounds such as this are sometimes impossible to close. Antiseptics should be used to prevent infection.

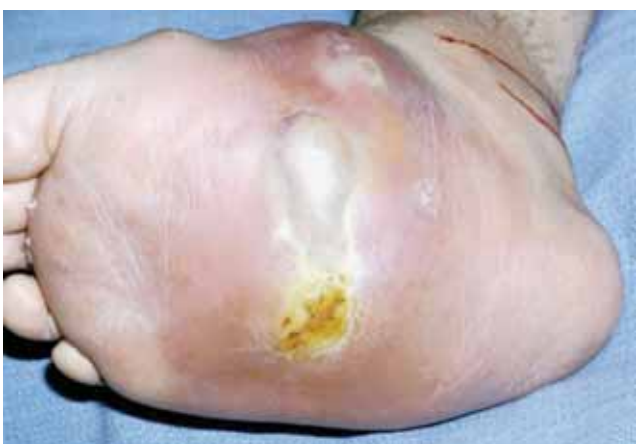

Figure 5. This foot was infected for several weeks before the patient presented for treatment. Fortunately, the physician was able to save the foot from amputation.

Table 2. The CDC's 12 Steps

Below are general guidelines suggested by The Centers for Disease Control and Prevention (CDC) to prevent antimicrobial resistance in hospitalized adults.[9]

Prevent Infection
1. Vaccinate
2. Remove catheters

Diagnose and Treat Infection Effectively
3. Target the pathogen
4. Access the experts

Use Antimicrobials Wisely
5. Practice antimicrobial control
6. Use local data
7. Treat infection, not contamination
8. Treat infection, not colonization
9. Know when to say "no" to vancomycin
10. Stop treatment when infection is cured or unlikely

Prevent Transmission
11. Isolate the pathogen
12. Break the chain of contagion

with osteomyelitis. The patient had been on intravenous (IV) antibiotics for 3 weeks; the wound site and foot continued to worsen. No debridement had been attempted and cultures had not been procured.

This patient was subsequently taken to the operating room for incision and drainage of the wound with possible amputation. This procedure revealed a hematoma with no sinus tracts, pus, or malodor. Bone biopsies were negative for osteomyelitis. The IVs were discontinued and the patient was treated with PHMB gauze and debridement. The wound healed within 5 weeks with the patient restored to complete weight-bearing status (see Figure 3).

Gunshot wounds. A 38-year-old presented with a highly contaminated gunshot wound. A strict protocol of flushing and packing was prescribed and the wound was prepared for closure by secondary intention. As is common with such traumatic wounds, necrotic tissue presented several days post injury (see Figure 4). The nonviable tissue was mechanically debrided and PHMB-impregnated gauze was utilized for packing and as a secondary layer to minimize bacterial contamination. The wound was fully closed within 6 weeks.

Patients with diabetes mellitus. According to the National Institute of Diabetes and Digestive and

Kidney Diseases, nearly 21 million Americans have diabetes, and another 41 million have pre-diabetes;[10] of these, 15% will develop foot ulcers, of which 85% will lead to amputation.[11–13] Diabetic foot infections account for 20% of all diabetes-related hospital admissions. They require proper wound care, surgical interventions, and appropriate antibiotic therapy.[15] On average, three to five different types of micro-organisms (eg, *S. aureus*, group B *Streptococcus*, *E. coli*, coag-negative *Staphylococcus*, enterococci and proteus species) are present in the typical diabetic foot infection.[14]

In this case presentation, a patient with diabetes presented to the clinic with a blood glucose level of approximately 800 mg/dL. His wound history included a toe amputation 3 months prior; he was noncompliant with wound care instructions. This patient presented with exposed first and second metatarsal heads surrounded by black, necrotic tissue. His treatment course consisted of local debridement followed by 3 months of negative pressure wound therapy (NPWT). Once the wound was too small for NPWT, it was packed with PHMB gauze for 3 weeks and the wound healed.

Infection. A patient presented with a long-term wound to his foot for which he had previously refused to seek treatment (see Figure 5). At this visit, the patient adamantly refused amputation. During surgical debridement for which the patient received a popliteal block for anesthesia, the foot was found to be filled with a large amount of purulence. A general surgeon was on call should the patient require below-knee amputation, but the periwound skin was found to be viable. Little blood was lost, no tourniquet was used, and no major nerves were impacted by either the presenting condition or the procedure. Pulse lavage was used to thoroughly irrigate the wound. The patient was placed on IV antibiotics and NPWT while in the hospital. When discharged 3 days later, the patient was prescribed Kerlix AMD™ (Tyco Healthcare/Kendall) dressings and a PICC line was placed. The wound continued to heal without incident and without signs of further infection.

The Importance of Prevention

Preventative treatment such as keeping a wound clean and covered is the first line of defense against both infection and antimicrobial resistance. The use of antimicrobial coverings such as PHMB-impregnated wound dressings is effective and inexpensive enough to be utilized as insurance against infection on nearly every wound. By preventing infections, we reduce the overuse of antibiotics is reduced, which further reduces the risk of developing antimicrobial resistance. Furthermore, in the face of infection, identifying the infecting organism(s), using an appropriate antibiotic, and performing acceptable wound care techniques (eg, offloading the wound, debriding nonviable tissue, selecting appropriate dressing, managing the infection, providing vascular reconstruction, and amputating along with monitoring systemic conditions and status), will significantly diminish antimicrobial resistance.

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Continuing Education Quiz

Infection Control Made Easy:

Minimizing the Risk of Wound Infections with No Change to Protocol

Choose the single best answer to the following questions:

1. ***Antibiotics:***
   a) are always biocidal
   b) have multiple targets
   c) are invulnerable to resistance
   d) are administered systemically or topically

2. ***Antibacterials are found in all of the following except:***
   a) ceramics
   b) clothing
   c) pre-packaged foods
   d) condoms

3. ***Antibiotic resistance is the evolved ability of a microorganism to withstand the effects of a(n):***
   a) antibiotic
   b) steroid
   c) bacteria
   d) solvent

4. ***As polyhexamethylene biguanide binds to the cell membrane, it will drag ____ to that location to reorganize the membrane.***
   a) cationic biocides
   b) acidic phospholipids
   c) lipopolysaccharides
   d) efflux pumps

5. ***_____ agents are vulnerable to efflux defense.***
   a) monocationic
   b) polycationic
   c) cationic

6. ***Physicians should generally avoid the use of antibiotics unless infection has been:***
   a) ruled out
   b) created
   c) confirmed

7. ***Antimicrobial resistance impacts:***
   a) cost
   b) mortality
   c) both a and b
   d) none of the above

8. ***Hydrogen peroxide is an ideal treatment option for wounds.***
   a) true
   b) false

9. ***Use of antibiotic cream is unnecessary in gunshot wounds.***
   a) true
   b) false

10. ***The first line of defense against infection is:***
    a) a strong course of antibiotics
    b) preventative treatment
    c) educating the patient

Answer and Evaluation Form

Infection Control Made Easy:

Minimizing the Risk of Wound Infections with No Change to Protocol

To successfully complete the activity, you must read this supplement, complete and submit the post-test evaluation by March 31, 2008. A passing score of 70% is required in order to receive a certificate of credit.

Please complete this evaluation form:

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Please fill in your responses below to the questions on page 8S:

1. ❑ a. ❑ b. ❑ c. ❑ d.
2. ❑ a. ❑ b. ❑ c. ❑ d.
3. ❑ a. ❑ b. ❑ c. ❑ d.
4. ❑ a. ❑ b. ❑ c. ❑ d.
5. ❑ a. ❑ b. ❑ c.
6. ❑ a. ❑ b. ❑ c.
7. ❑ a. ❑ b. ❑ c. ❑ d.
8. ❑ a. ❑ b.
9. ❑ a. ❑ b.
10. ❑ a. ❑ b. ❑ c.

Entries will be accepted for up to 18 months following publication.

Please answer the following questions by circling the appropriate rating:

The stated learning objectives were met	5	4	3	2	1
Faculty was knowledgeable on the subject matter	5	4	3	2	1
Content was objective	5	4	3	2	1
Content was balanced	5	4	3	2	1
Content was scientifically rigorous	5	4	3	2	1
Content avoided commercial bias or influence	5	4	3	2	1
Content was timely and related to my practice	5	4	3	2	1
Content will assist me in enhancing patient care	5	4	3	2	1
Information presented will improve my practice/patient outcomes	5	4	3	2	1

What other topics would be of interest to you?_____

5 = Strongly Agree
4 = Agree
3 = Neutral
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1 = Strongly Disagree

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