

## Resistance

The true clinical and economic scope of the problem of antibiotic resistance is vast. Increasingly understood but still too often under-appreciated, antibiotic resistance is a critically important health care issue. After completion of the continuing education program, the reader will be able to:

1. Discuss emerging issues surrounding antibiotic resistance
2. Identify risk factors and treatment considerations for resistant bacteria strains
3. Describe Standard and Contact precautions
4. Discuss hand hygiene

Nearly 2 million nosocomial infections occur each year. Unfortunately, resistance is becoming a factor in virtually all of them and there is real concern that some bacterial infections, both community and health care-acquired, may soon be untreatable. Over half of nosocomial infections are caused by antibiotic-resistant pathogens, the impact of which is significant clinically, in terms of morbidity and mortality, and economically because of the

Table 1

### Contributors to the Costs of Resistance Infections

- Laboratory services
- Multiple drug switches, combination antibiotics, and/or more expensive antibiotic
- Isolation
- Increased hospital days

increased associated costs. The Institute of Medicine (IOM) estimates a \$30B price tag for the treatment of resistant infections—even more sobering with the recognition that the problem is preventable.

The literature varies in terms of specific reports, but we can stipulate to at least a two-fold increase in both hospital days and attributable costs. It has been estimated that an episode of resistant infection can add up to \$40,000 to the hospital costs per episode.<sup>1,2,3,4</sup>

### How Resistance Happens

Antibiotics work in a variety of ways; therefore resistance develops in a variety of ways.

Penicillin, cephalosporins, bacitracin, vancomycin and beta-lactam antibiotics, for example, kill bacteria by inhibiting their ability to develop a protective wall around themselves. When the cell attempts to divide, its weakened cell wall ruptures. Resistance develops as the pathogens' walls become stronger and remain intact when exposed to those antibiotics.

Drugs such as chloramphenicol, tetracycline, erythromycin, streptomycin and aminoglycosides inhibit the formation of proteins within the bacteria; protein synthesis is essential for cell life. Resistance occurs when, despite the presence of the antibiotics, protein synthesis is sustained.

Sulfonamides block the formation of folic acid, also essential for bacteria cell life. Resistance arises when a pathogen develops such that folic acid is still formed, even when exposed to the antibiotics that used to be able to block it.

### Risk Factors for Resistance

A primary reason for resistance is overuse of antibiotics, both to treat an infection and for prophylaxis—historically considered prudent. While the intent was to aggressively attack a pathogen, the result was exposure to antibiotics that were not needed and the bacteria not killed has the opportunity to develop resistance. The more exposure the more a pathogen will evolve to resist the way that antibiotic works.

Broad-spectrum antibiotics are active against a wide variety of bacteria. Administering a broad spectrum antibiotic is often clinically prudent. When the causative organism or its antibiotic sensitivities are not known, antibiotic administration to cover different kinds of bacteria can save valuable time in initiating treatment. However, broad coverage also allows non-infective pathogens to be exposed to antibiotics. Those bacteria will naturally build up a resistance and, if they do become infective in the future, may not respond to the antibiotic previously given. It is critical to switch to a narrow spectrum antibiotic as soon as the specific pathogen and sensitivity is known.

The hospital environment provides ample opportunity for the spread of infectious pathogens.

**Increased severity of illness** is seen within the hospital as more hospitals are primarily tertiary care facilities. General units are more like historic Intensive Care Units (ICUs) with increased workload, frequent patient contact, and patients with numerous invasive devices and procedures.

**Compromised infection control procedures** are significantly responsible for the dissemination of resistant organisms. In recent studies of infection control practices, 72% of healthcare workers observed omitted at least one aspect of infection control. Caregivers, for example, may not wash their hands or wear and discard gloves appropriately. Unfortunately, efforts to modify caregiver behavior have proven largely unsuccessful over the long term.

**Patient demand and compliance** impact as well. Patients often expect an antibiotic prescription even when there are no clinical indications, e.g., antibiotics for a viral cold. The CDC estimates that 50% of all prescriptions written for antibiotics are unnecessary.<sup>5</sup> People often fail to finish the full course of treatment, allowing for organism survival and the opportunity to develop resistance to that antibiotic or antibiotic class. Patients may

stockpile the leftover doses and medicate themselves, or their family and friends, with a drug that might not be the right choice or dose for whatever infection they, their family or friends actually have, or in less than therapeutic amounts.

Patients with **co-morbid conditions** are at risk as are patients who are *immunocompromised*.

Every additional day in the **hospital** increases the risk of exposure to and contamination by resistant organisms.

### Colonization vs. Infection

Persons who carry bacteria without evidence of infection (e.g. have no fever, elevated WBCs, etc) are **colonized**. If an infection develops it is typically caused by bacteria that colonize patients. For example, the biggest risk for a methicillin-resistant *staphylococcus aureus* (MRSA) infection is being colonized in the nose with it. Approximately 29% of persons who are MRSA colonized will develop a MRSA infection within 18 months of detection of colonization.<sup>6</sup>

### Pathogens of Highest Concern

The Infectious Diseases Society of America (IDSA) has labeled the most

serious, life threatening infections caused by drug-resistant bacteria with the acronym “ESKAPE”, because the causative organisms effectively escape the effects of antibacterial drugs.<sup>7</sup>

### Methicillin-resistant Staphylococcus aureus (MRSA)

MRSA is so important because *Staph. aureus* is so prevalent. Approximately 95 million people in the United States carry *Staph. aureus*. 2.5 million of those people (2.6%) are carriers of methicillin-resistant *Staph. aureus*.<sup>8</sup> *Staph. aureus* is the most common pathogen cultured from nosocomial infections and the most common isolated organism from hospital-acquired pneumonias, surgical site infection, and nosocomial site infections overall. *Staph. aureus* can lead to sepsis, skin and soft-tissue infections, catheter-related infectious and endocarditis, for example. In fact, MRSA is the cause of 55% of hospital-acquired infections. While most MRSA infections are mild and treatable there is significant risk of rapid spread and significant morbidity and mortality.

While the incidence of MRSA is more recently trending downward, it remains a significant problem. The proportion of healthcare-associated

Table 2

The ESKAPE Pathogens		
<b>E</b>	<i>Enterococcus faecium</i>	Third most common cause of HCA BSI. Increasing resistance to vancomycin.
<b>S</b>	<i>Staphylococcus aureus</i> (MRSA)	Emerging resistance to current drugs and significant drug toxicities. Lack of oral agents for step-down therapy.
<b>K</b>	<i>Klebsiella pneumoniae</i> , <i>Escherichia coli</i>	ESBL-producing organisms increasing in frequency and severity; associated with increasing mortality. K pneumoniae carbapenemases causing severe infections in LTCF. Few active agents; nothing in development.
<b>A</b>	<i>Acinetobacter baumannii</i>	Increasing worldwide, recent surge reported in hospitals. <sup>5</sup> Very high mortality. Carbapenem-resistant.
<b>P</b>	<i>Pseudomonas aeruginosa</i>	Increasing P. aeruginosa infections in US and worldwide. Resistant to carbapenems, quinolones, aminoglycosides.
<b>E</b>	<i>Enterobacter species</i>	MDR HCA infections increasing; resistance via ESBLs, carbapenemases, and cephalosporinases.

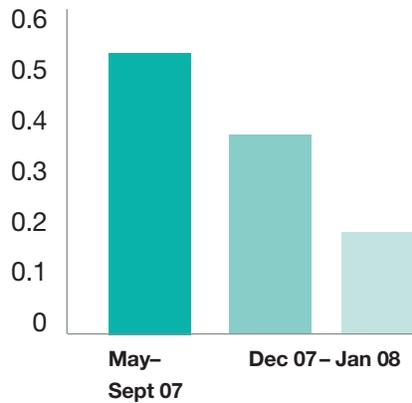
HCA = healthcare associated; BSI = bloodstream infection; MRSA = methicillin resistant S aureus; ESBL = extended-spectrum beta-lactamase; LTCF = long-term care facility; MDR = multiple drug-resistant

staphylococcal infections due to MRSA rose from 2% in 1974 to 64% in 2004. 2% of *S. aureus* infections in U.S. intensive-care units were MRSA in 1974, 22% in 1995, and 64% in 2004.<sup>9</sup>

In the years 2006-2007, 56% of *S. aureus* device-associated infections were due to MRSA.<sup>10</sup>

The CDC reported an estimated 94,360 annual cases of invasive MRSA. Nearly 19,000 of those patients did not survive.<sup>5</sup> The greatest percent of those MRSA cases (85%) were healthcare-associated, 14% community-acquired (CA-MRSA). CA-MRSA is on the rise with strains of MRSA that tend to be more virulent and more likely to cause death if inappropriately treated, but also tend to respond better to antibiotic treatment.

Given that between 1 and 8% of persons in the United States are colonized with MRSA, there is much current discussion about surveillance screening, the goal being to identify patients at the time of admission and take specific precautions to minimize the chance of spread. Some hospitals choose to screen patients at risk, some opt for ICU admission screening, and some for universal surveillance, i.e. all admissions. In one study, a large university medical center evaluated the impact of surveillance on the rate of MRSA infections in their patient population. The rate of MRSA infection per 1,000 patient days averaged .05294 prior to the initiation of a surveillance program (May thru September 2007). When MRSA screening for all patients admitted to the ICU was implemented (October thru November 2007), the incidence dropped to 0.3924. When all patient admits were screened (December 2007 thru January 2008), i.e. universal surveillance, the rate dropped to 0.1986 infections per 1,000 patient days — a 68% reduction.<sup>11</sup> Patients MRSA-positive at the time of admission are treated



with a cleansing protocol that significantly reduces the chance of spread.

Depending on the location of the infection and the site of acquisition (i.e. hospital or community), MRSA treatment may be with oral, nebulized, topical or IV antibiotics. For example, given that the nares are a common site of colonization or infection, nebulized or topical antibiotics are the treatment of choice, e.g. bacitracin or Mupirocin ointment. Currently, vancomycin remains the drug of choice for treatment of serious MRSA infections from health-care associated cases. Combination therapy may be needed. Linezolid and daptomycin also show results against MRSA. In September 2009 the FDA approved telavancin, the first drug approved specifically to target MRSA. Telavancin is a once a day injectable drug. It does have potential renal side effects and is black-boxed for pregnant women.

Community-acquired MRSA recommendations include clindamycin or vancomycin in combination with a 3rd generation cephalosporin.

### Vancomycin-resistant Enterococci (VRE)

Enterococci are bacteria normally present in our intestines, the female genital tract and in the environment. They commonly cause UTIs, blood stream infections or surgical or wound infections.

The risk of infection is slight for immunocompetent patients, but significant for patients who have weakened immune systems, e.g., the ICU, oncology and transplant patients. This pathogen was historically confined primarily to the ICU. Now it may be seen on all units.

Enterococcus is the 3rd most common organism associated with hospital acquired infections. Approximately 1 in 8 infections are due to enterococcus, about a third of which are resistant.

Vancomycin-resistant enterococcus (VRE) is most often isolated from the urinary tract, abdominal and pelvic wounds, indwelling endovascular catheters, and in endocarditis. In the health care setting, cultures have identified VRE from patient gowns, side rails of beds, floors, door handles, blood pressure cuffs, wash basins, glucose meters, hemodynamic monitoring devices, etc. In fact, VRE organisms can survive for 5-7 days on many surfaces! VRE has been recovered from the hands of healthcare workers and isolated in care partners of infected patients while at home.

Treatment is most commonly with quinupristin/dalfopristin (Synercid®) and linezolid (Zyvox®). Sometimes combination therapy is necessary, for example adding penicillin.

### Extended-spectrum Beta Lactamases (ESBLs)

Extended spectrum beta lactamases are enzymes produced by bacteria that mediate resistance to specific extended-spectrum (third-generation) cephalosporins and other beta-lactam antibiotics (aminoglycosides, quinolones, etc.). ESBLs are commonly produced by *Klebsiella pneumoniae* and *Escherichia coli*. Resistance against these two organisms is significant because they are common causes

of nosocomial infections in general, including UTI and pneumonias. It has been reported that about 14% of *Klebsiella pneumoniae* and 6.3% of *E. coli* bacteria are resistant to ceftazidime, for example.

Unfortunately, organisms that are resistant to ceftazidime will show resistance to multiple other classes of antibiotics as well such as aminoglycosides and quinolones. Carbapenams have shown some efficacy, as has formulary control, i.e. limiting or discontinuing the use of those 3rd generation cephalosporins and even closing units until an outbreak is cleared.

## Acinetobacter

*Acinetobacter* is a gram negative bacteria. It is important for soil mineralization and abundant in nature. *Acinetobacter* rarely causes disease in healthy individuals. Many patients are colonized with *Acinetobacter* but will not become infected. However, in compromised patients, the risk for infection exists. Also, *Acinetobacter baumannii* can survive on dry surfaces for up to 20 days, important in a hospital setting in which many people/patients can then be exposed.

*Acinetobacter* species are difficult to treat because they are innately resistant to most antibiotics, including penicillin, chloramphenicol, and often aminoglycosides and fluoroquinolones. The carbapenems are recognized as the gold-standard and/or treatment of last resort.

## Clostridium difficile

*Clostridium difficile* is a gram-positive, spore-forming anaerobic

bacillus associated with a potentially dangerous gastrointestinal infection. *Clostridium difficile*-associated disease (CDAD) is an ever-increasing threat in both the hospital and community. CDAD appears to be increasingly difficult to treat, potentially due to a more virulent and resistant strain. *C. diff* contributes to approximately \$3.2B of healthcare costs per year.<sup>12</sup>

*C. difficile* accounts for 15-25% of all episodes of antibiotic-associated diarrhea and should be suspected in any adult with antimicrobial-associated diarrhea, even if antibiotic treatment was completed days or weeks prior to symptom development.<sup>13</sup>

*C. difficile* is shed in feces and spread via the fecal-oral route. The spores are difficult to eradicate with standard environmental cleaning solutions and any surface that becomes contaminated with feces, e.g. commodes, light switches, sinks, and hospital equipment, may serve as a reservoir for them. *C. difficile* spores are transferred to patients mainly via the hands of healthcare personnel who have touched a contaminated surface or item.

*C. difficile* spores are resistant to stomach acids so once taken in orally, they pass through the stomach intact. They change to their active form and multiply in the colon.

The *C. difficile* spore produces two toxins which cause the disease and symptoms. Toxin A attracts neutrophils and monocytes while toxin B degrades the colonic epithelial cells. Together they cause fluid and mucous secretion and

mucosal inflammation and damage, resulting in diarrhea or colitis.

Diagnosis is primarily made by symptoms. A stool sample for toxin A and B is important, but a negative result does not necessarily mean there is no infection and if a patient is symptomatic it is clinically prudent to consider empiric therapy. While accurate, a cytotoxic tissue culture assay takes at least 48 hours for results to come back and is 100 to 1,000 times more expensive. This assay, then, is often not practical.

CDAD presents as a continuum as described in Table 4.

Stopping the inciting antibiotic is the key to the treatment of CDAD. Often that is sufficient and patients recover. Oral therapy may also be needed, in the form of metronidazole (Flagyl®) or vancomycin. Historically, metronidazole has proven as effective as oral vancomycin with a 90%+ response rate and is less expensive. It also diminishes the risk of vancomycin resistance and is typically given as first-line therapy. Current recommendations are metronidazole as first-line treatment for most cases of CDAD, carefully monitoring response to therapy, and oral or intraluminal vancomycin for patients with moderate or severe disease, as seen in Table 5.

Recurrence, whether it be reinfection or relapse is one of the most frustrating and challenging complications of CDAD. 12% to 24% of patients develop a second episode of CDAD within 2 months of the initial diagnosis. If a patient has two or more episodes of CDAD, the risk of additional recurrences increases to 50% to 65%.<sup>13</sup>

Table 4

<b>Mild</b>	<ul style="list-style-type: none"> <li>• Mild to moderate nonbloody diarrhea</li> <li>• Low abdominal cramping</li> <li>• Mild abdominal tenderness</li> <li>• No systemic sx</li> </ul>
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<b>Moderate</b>	<ul style="list-style-type: none"> <li>• Fever</li> <li>• Profuse diarrhea</li> <li>• Abdominal pain</li> <li>• Leukocytosis</li> </ul>
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<b>Severe</b>	<ul style="list-style-type: none"> <li>• Profuse watery diarrhea</li> <li>• Abdominal pain</li> <li>• Distention</li> <li>• Fever, nausea, and dehydration</li> <li>• Occult blood</li> <li>• Complications of colitis</li> </ul>
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Table 5

<b>Mild to Moderate</b>	<ul style="list-style-type: none"> <li>• Stop the inciting antibiotic</li> <li>• 500 mg metronidazole po q 6° x 10–14 days</li> <li>• 90% response rate</li> <li>• Severe</li> </ul>
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<b>Severe</b>	<ul style="list-style-type: none"> <li>• Resistance to metronidazole predictable</li> <li>• 125 mg vancomycin po q 6° x 10–14 days</li> <li>• 90% response rate</li> <li>• IV vancomycin</li> </ul>
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## Standard and Contact Precautions

The use of standard precautions is based on the principle that all blood, body fluids, secretions, excretions except sweat, non-intact skin, and mucous membranes may contain transmissible infectious agents. Therefore, first and foundationally, compliance with standard precautions for all patients is essential. Caregivers should wash their hands after touching blood, body fluids, secretions, excretions, and contaminated items. Hands should be washed immediately after gloves are taken off and before and between patient contacts. It might be necessary to wash hands between tasks and procedures on the same patient to prevent cross-contamination from one site to another. Caregivers should gown, glove and mask when exposed to body fluids, etc. Clean, non sterile gowns and gloves are typically adequate. These items must also be changed between patients and removed or changed immediately after a procedure is done, in order to prevent cross-contamination.<sup>14</sup>

Contact precautions apply where the presence of excessive wound drainage, fecal incontinence, or other discharges from the body suggest an increased potential for extensive environmental contamination and risk of transmission. Guidelines recommend:

- Place a patient in a private room. If not available, cohort, i.e. room the patient with another infected patient

- Limit the movement or transport of the patient to essential purposes only. If the patient is transported out of the room, ensure that precautions are maintained so that the risk of transmission of microorganisms to other patients, other areas of the hospital, or other equipment is minimized
- Ensure that patient-care items, bedside equipment, and frequently touched surfaces receive daily cleaning
- When possible, dedicate the use of non-critical patient-care equipment and items such as stethoscope, bedside commode, or thermometer to a single patient (or cohort of patients infected or colonized with MRSA) to avoid sharing between patients. Colonized or infected patients should not share dialysis machines.<sup>14</sup>

## Hand Washing

According to the CDC, the most important way to minimize the spread of infection and the development of resistance is good hand washing. Hand washing is the cornerstone of infection control and, unfortunately, still the “holy grail”. Compliance remains a serious issue. Studies report varying degrees of non-compliance with hand washing, but the bottom line is healthcare workers can service as vectors for infection transmission and the incidence of nosocomial infections could be reduced by up to half if caregivers simply and properly washed their hands.<sup>15</sup>

According to the Bloomberg Press, October 2008, hand washing occurs about 55 percent of the time. Each increase of 1 percentage point would save a hospital \$39,000 a year.

Using the Duke hospital’s average length of stay, and the number of visits to a user’s room each day, the researchers estimated that a patient who stayed in a hospital for 6.2 days would have eight encounters with a healthcare worker who had seen a MRSA positive patient and hadn’t washed his/her hands.

CDC guidelines recommend that healthcare workers

- Wash their hands with soap and water when they are visibly dirty or contaminated
- Use an alcohol-based hand rub when their hands are not visibly soiled

## Decreasing the Risk

In the home care and case management arenas there are ways to impact antimicrobial drug resistance as well.

Given the risk of LOS on the chances to develop a nosocomial infection, minimizing the total number of days in the hospital for appropriate patients is critical. This can be accomplished with appropriate discharge, that is not keeping patients in the hospital for any more days than necessary,

Hungarian physician Ignaz Philipp Semmelweis discovered in 1847 that hand washing was key to the prevention of puerperal fever. He insisted that physicians and medical students wash their hands in chlorinated solution before entering obstetric wards and again before examining each patient. His rule was much resented and opposed — but hundreds of mothers’ lives were saved.

avoiding hospital days totally with first-dosing at home and considering best site-of-care options—each to prevent or minimize risk.

Hospital avoidance lessens the risk of acquiring a nosocomial infection and all its consequences.

Therapies such as nutrition, pain management and antibiotics are types of infusions that can often be safely started in the home without the need for hospitalization. For example, you may have an oncology patient who needs to start TPN but has no other clinical reason to be hospitalized. Does this present an opportunity NOT to expose the patient to the risk of nosocomial, often resistant, infection?

With antibiotic agents, a patient can be sent home on a broad spectrum agent and await cultures and sensitivities for the narrow spectrum agent needed to fight the infection at home if no other co morbidities exist.

Once in the home, infection control measures and precautions can be reiterated to the patient and family to prevent the spread or transmission of further infection. Case managers and the home care nurses are familiar with the practices of standard and contact precautions and use them in the instruction of infusion administration.

## Home Infusion Reimbursement

Implementation of Medicare Part D legislation in 2006 added more challenges to the reimbursement environment for the home infusion industry. Medicare Part D covers intravenous and injectable drugs, but not supplies, equipment, and pharmacy and nursing care, each needed to successfully and

safely administer the drugs. The legislation contains language that is confusing to many as to when drugs are covered under Part D and when they might be covered under Medicare Part B. This confusion can lead to one patient being covered for drugs, supplies, and services under Medicare Part B while another patient, who is covered under Medicare Part D, receives payment for only that drug and no coverage for services, supplies, and equipment needed to deliver the drug.

## Summary

Infection resistance is clinical and economically costly. Risk factors can be fairly generalized, which also supports screening. Resistance can—and must—be prevented, with hand hygiene as an essential component of that prevention!

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## Self-Assessment Quiz: Resistance

### LEARNING GOAL

To appreciate the impact of resistant pathogen, both clinically and economically.

### LEARNING OBJECTIVES

After reviewing this publication, each participant should be able to:

1. Discuss emerging issues surrounding antibiotic resistance
2. Identify risk factors and treatment considerations for resistant bacteria strains
3. Describe Standard and Contact precautions
4. Discuss hand hygiene

### SELF-ASSESSMENT QUESTIONS

**In the Quiz Answers section on the next page, fill in the correct answer for each question. To obtain two (2.0) contact hours toward CE credit, the passing score is 100%.** Return your Self-Assessment Quiz to Coram via email or fax. See the next page for details on how to return your quiz. Please allow approximately seven days to process your test and receive your certificate upon achieving a passing score.

1. A primary reason for resistance is the overuse of antibiotics.
  - a. True
  - b. False
2. The more exposure a pathogen has to an antibiotic, the more likely it is to evolve to resist the way that antibiotic works.
  - a. True
  - b. False
3. Staph. aureus is the most common pathogen cultured from nosocomial infections
  - a. True
  - b. False
4. About a third of enterococcus infections are resistant to vancomycin
  - a. True
  - b. False
5. Acinetobacter is highly virulent, contagious and a frequent cause of infection.
  - a. True
  - b. False
6. Which of the following statements is NOT true about C. difficile
  - a. Should be suspected in any adult with antimicrobial-associated diarrhea
  - b. Is not likely to be the cause of diarrhea if antibiotic treatment was completed days or weeks prior to symptom development
  - c. Is difficult to eradicate
  - d. Is resistant to stomach acids
  - e. Can recur
7. According to the CDC, effective hand washing is the most important way
  - a. To minimize the spread of infection
  - b. To minimize the development of resistance
  - c. Both a and b
8. CDC guidelines recommend that healthcare workers
  - a. Wash their hands with soap and water when they are visibly dirty or contaminated
  - b. Use antimicrobial soap with all hand washes
  - c. Use an alcohol-based hand rub when hands are not visibly soiled
  - d. A and C
  - e. B and C
  - f. All of the above
9. Hospital avoidance lessens the risk of acquiring a nosocomial infection and all its consequences
  - a. True
  - b. False
10. Medicare Part D covers
  - a. Intravenous and injectable drugs
  - b. Most supplies and equipment
  - c. Pharmacy and nursing care
  - d. A and B only
  - e. A and C only
  - f. All of the above

# Healthline

VOLUME 3

Coram<sup>®\*</sup> Continuing Education Program

## Resistance

### QUIZ ANSWERS

Fill in the key below with the correct answers to receive 2.0 Continuing Education credits.\*

1. (a) (b) (c) (d) (e) (f) (g)
2. (a) (b) (c) (d) (e) (f) (g)
3. (a) (b) (c) (d) (e) (f) (g)
4. (a) (b) (c) (d) (e) (f) (g)
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8. (a) (b) (c) (d) (e) (f) (g)
9. (a) (b) (c) (d) (e) (f) (g)
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