# Pharmacologic Resistant Microorganisms: A Modern Day Plague

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Pharmacologic Resistant Microorganisms: A Modern Day Plague

## Purpose

The purpose of this pharmacologic resistant microorganism: a modern day plague course is to alert, and provide health care providers on the importance of pharmacological resistant microorganisms. This course will provide the reader with the understanding on how microbial infections have been a leading cause of morbidity and mortality throughout history, and the effects on health care today. Antibiotic resistance is a public health problem of increasing magnitude, and health care providers should understand the importance of collaborating efforts for finding effective solutions to address this problem. This course will outline how microbial resistance occurs, list the importance, and how to select the proper antibiotic therapy for certain microorganisms.

## Objectives

## Pharmacologic Resistant Microorganisms

1. Understand the history of drug resistant microorganisms.
2. Describe how pharmacological microbial resistance occurs.
3. List the major pharmacological resistant microorganisms.
4. Understand the importance of selecting the proper antibiotic therapy.
5. List the treatment options for pharmacologic resistant microorganisms.
6. Understand Culture and sensitivity and how physician drug choice and
7. Describe the health care considerations pharmacologic resistant microorganisms
8. Discuss the importance of standard universal precautions when caring for a patient with a pharmacologic resistant microorganisms

 

## Introduction

Microbial infections have been a leading cause of morbidity and mortality throughout history. Instances of widespread bacterial infection are documented as far back as 541 A.D., with the first recorded *Yersinia pestis* (plague) pandemic in Egypt (Perry and Fetherston, 1997). Countless medical advancements have been made since, with one of the most important being the development of antibiotics to treat infection causing pathogens. The first antibiotic was marketed in the early 1900s and designed specifically to fight the bacterium responsible for syphilis infection, *Treponema pallidium.* This first antimicrobial drug, Salvarsan, held the standing of most widely prescribed medication until the development of sulfonamides and penicillin in the 1930s and 1940s. Over the next few decades, the 1950's to 1970's became the golden era for the discovery of new antimicrobial classes, with few additional classes encountered since then (Aminov, 2010). Antibiotics have greatly improved the medical field, saving inestimable lives. However, these wonder drugs are only effective when used sparingly. Unfortunately the overuse and mismanagement of antibiotics have been factors in the emergence of our own modern day plague – pharmacological resistant microorganisms (drug resistant microorganisms).

## History of Drug Resistant Microorganisms

Microbes are living organisms whose primary function is to multiply, spread, and survive. They reproduce quickly and evolve over time, allowing generations of genetic modifications to occur in a short period. This natural process of evolution sets

the stage for inevitable drug resistance (Glover, 2000). Numerous organisms have adapted to become resistant to antibiotics, some of the most common and widely known are methicillin resistant *Staphylococcus aureus* (MRSA) and Vancomycin resistant enterococci. These pathogens have some similar epidemiological considerations, but their biology and history are quite different. Each organism has its own distinct evolutionary pathway; this section details how these two veterans to drug resistance emerged to become the threat we know them as today.

*Staphylococcus aureus* is one example of a bacterium that is both dynamic and adaptable. It leads the pack as the most notorious of the pharmacological resistant microorganisms. Staphylococci reside on the skin, mucous membranes, intestinal and genitourinary tracts. Staphylococcus infections can usually be avoided with intact skin, and any disruption to skin integrity allows for potential infection (Glover, 2000). *S. aureus* was first identified in the 1880's, responsible for painful skin and soft tissue infections as well as potentially fatal pneumonia and bacteremia (NIH, 2008). In the early 1940's the treatment of choice for *S. aureus* was penicillin, which promptly lowered the mortality rate for these infections. By the mid 1940's, however, strains of penicillin resistant *S. aureus* were detected in hospitals, and by 1960 penicillin resistant strains were found widespread in both the community and hospital settings. The introduction of a new antibiotic, methicillin, a penicillinase-resistant semi-synthetic penicillin, temporarily solved the problem. By 1961, less than a year later, the first methicillin resistant strain of *S. aureus* (MRSA) was discovered (Corriere and Decker, 2007). Over the next 30 years MRSA prevalence slowly increased, mostly in hospital associated

cases. Distinct community associated strains emerged in the 1990's (Lin and Hayden, 2010). A study highlighted MRSA as the single most identifiable cause of skin and soft tissue infections among patients who presented to emergency departments in 11 U.S. cities in 2006 (Corriere and Decker, 2007).

A second common drug resistant bacteria in healthcare, vancomycin-resistant enterococci (VRE), has quite a different history from its predecessor MRSA. Enterococci, previously known as group D Strep, are Gram-positive, anaerobic oval cocci that form chains. They are durable and versatile, with a unique capability to survive under harsh conditions, such as high salt concentrations. Additionally, enterococci can withstand a wide range of temperatures spanning from 10 - >45 degrees Celsius. They are tolerant to heat, chlorine and some alcohol preparations as well, which may be why these organisms are widely spread throughout hospital settings (Arias and Murray, 2012). Enterococci reside in the gastrointestinal tract and female genital tract. Poor personal hygiene can lead to skin contamination (Glover, 2000). Enterococci are generally considered to display a low level of virulence as they are natural colonizers of the human body and have been used for several years as probiotics in both humans and farm animals (Arias and Murray, 2012). Major infections caused by enterococci in general include urinary tract, wound, and intra-abdominal infections secondary to a perforated viscous. Enterococci are also prevalent in postoperative infections, cholecystitis, bacteremia, endocarditis, and less commonly meningitis (Rubinstein and Keynan, 2013). The first description of an enterococcal infection was in 1899 and noted to be infective endocarditis (Arias and Murray, 2012). While penicillin and methicillin resistance

developed quickly in *S. aureus*, resistance to vancomycin in enterococci was not appreciated until thirty years after its introduction (Lin and Hayden, 2010).

The first VRE isolates were reported in 1988 in the U.K. and France, belonging to the species Enterococci faecium (VREm). VREm colonization in the community was high, and hospital outbreaks were rare (Cattoir and Leclercq, 2012). The presence of VREm in Europe was driven by the use of glycopeptide antibiotics, including avoparcin, as an additive to the food of farm animals for growth promotion (Rubinstein and Keynan, 2013). As Vancomycin is also a glycopeptide antibiotic, there is considerable evidence that the use of avoparcin selected for vancomycin-resistant organisms in these animals. Furthermore, the transmission of these organisms to humans through the food chain seemed very likely. Both the human and animal strains of VREm remained generally susceptible to ampicillin (Cattoir and Leclercq, 2012). These findings subsequently resulted in the banning of the use of avoparcin by the European Union (Rubinstein and Keynan, 2013). This decision was followed by a European ban on all other antimicrobials used as growth promoters in the 2000s. So far, however, this ban has not been adopted by nations outside of the European Union. Carriage rates of VREm steeply declined in the animal population, and initially the situation in European hospitals was reassuring, with only a few outbreaks in high-risk areas such as intensive care. A few years later, some European countries experienced an increase in reported VRE and large hospital outbreaks. Furthermore, these strains differed from the previous animal isolates, with emphasis on high resistance to ampicillin (Cattoir and Leclercq, 2012).

The pattern of VRE emergence differed in the U.S. from European routes. Avoparcin had never been legally available for use in U.S. food animals, and epidemiological surveys did not find VRE to be carried by community volunteers, food producing animals, or pets. However, oral and intravenous vancomycin was massively used in the U.S. to treat human infection. VRE was first reported in US hospitals by the end of 1989, shortly after its emergence in Europe. By 1993 almost one third of all enterococcal isolates in U.S. hospitals showed vancomycin resistance. Most were VREm with high level resistance to ampicillin (Cattoir and Leclercq, 2012).

Although VRE is less virulent than MRSA, it poses a danger to debilitated and immunocompromised patients, such as those in intensive care units. Colonization and perseverance are among VRE's key traits. This ability of VRE to endure poses a threat as the bacteria harbor vancomycin resistance genes that can potentially be transferred to more virulent microorganisms such as *S. aureus* (Lin and Hayden, 2010).

## How Pharmacological Microbial Resistance Occurs

As previously mentioned, the natural process of evolution allows for the development of drug resistance. The main purpose of bacteria is to reproduce and survive. Antibiotics are chemical compounds that interfere with fundamental processes to stop the spread of and/or kill bacterial cells. Antibiotics work by one of two main functions; they interfere with protein synthesis, or disrupt cell membranes (Glover, 2000). Resistance to antibiotics occurs when bacteria share genetic material, or when bacteria evolve to compensate from external environmental pressures – this can be hastened by both healthcare providers and patients with overuse and misuse of antibiotics.

Some microbes may also get genes from each other, including genes that enable the organism to be drug resistant (NIAD, 2011). This is how MRSA develops resistance (Glover, 2000). The emergence of high-level vancomycin resistant *S. aureus* (VRSA) has long been feared. The ability of S. aureus to acquire the *VanA* gene, which codes for vancomycin resistance, from enterococci was demonstrated *in vitro* in 1992. The first clinical isolate of VRSA was reported in 2002. A handful of VRSA cases have since been reported in the U.S., which were susceptible to other antimicrobials with no reported secondary cases. In most of these cases it was found that MRSA obtained the vancomycin resistance from a cocolonizing VRE strain (Calfee, 2012).

Most microbes reproduce by dividing every few hours, thus allowing for rapid evolution and adaptation. With so many replications taking place, mutations arise, some of which may help an individual microbe survive a particular antibiotic (NIAD, 2011). These resilient organisms may survive when antibiotics are used. This is the process in which antibiotic resistance occurs in a single organism or generation. Stronger antibiotics are subsequently used which perpetuates the cycle of antibiotic resistance. Resistance is more likely to develop in this manner if the antibiotic therapy is stopped prematurely (Glover, 2000).

The use of antimicrobials, even when used appropriately, creates a selective pressure for the development of resistant organisms. Societal pressures which contribute to accelerate the increase of antimicrobial resistance include the inappropriate prescription of antibiotics (NIAD, 2011).

Using one drug empirically for a specific type of infection can lead to development of resistance. An example of this would be prescribing sulfa antibiotics across the board for urinary tract infections (UTI), as UTI's are most commonly caused by *Escherichia coli*. Both Penicillin-resistant pneumococcus and multidrug resistant tuberculosis developed through this practice of using one antibiotic empirically to treat a specific type of infection (Glover, 2000).

Some healthcare providers inappropriately prescribe antibiotics for viral infections to placate patients. A common misperception by the public is that antibiotics can cure infections period – they do not always understand the difference between viral infections vs. bacterial infections. More often, providers are using incomplete or imperfect information to diagnose an infection and therefore prescribe an antibiotic just in case, or use a stronger broad spectrum antibiotic when a more specific antimicrobial may be more appropriate (NIAD, 2011). Other misuses of antibiotics include long term low-dose "suppression" antibiotics such as therapy for acne; prophylaxis antibiotics that are stronger than needed, and the use of prophylactic antibiotics for more than 48 hours postoperatively. Another area of misuse is the treatment of any positive culture, not just those with symptomatic infection. Bacteria are resident on the body and are essential to our health, a positive bacterial culture demonstrates that bacteria are present; it does not necessarily indicate infection (Glover, 2000).

Critically ill patients are often more vulnerable to infection, and as a result require the use of antimicrobials. Excessive use of antibiotics in these patients can put them at higher risk by selecting for drug resistant microorganisms. Hospitals create a fertile

 

environment for the spread of antimicrobial resistant germs with the extensive use of antibiotics and close contact among patients (NIAD, 2011).

Antibiotics that are used for purposes other than healthcare are also a large contributor to the rapid spread of microbial resistance. Much of this resistance development has been associated with the indiscriminate overuse of antibiotics in areas such as the meat industry by integrating antibiotics into the feed stocks to prevent infections in domestic or feedlot animals (Avner, Fialho, and Chakrabarty, 2012). More than half of the antibiotics produced in the United States are used for agricultural purposes (NIAD, 2011). As previously cited, agricultural antibiotic use has been directly linked to the initial emergence of VRE in Europe through the use of avoparcin to promote growth in feed animals.

The make-up of the antibiotics themselves may be yet another contributing factor to the development of drug resistance. Bacteria are constantly multiplying and changing. The use of antibiotics which focus on a single key step in their fundamental processes enable the cells to quickly change or switch off this single target, thereby becoming resistant. The pharmaceutical companies choose to use compounds that are effectively inhibitory to the crucial step in the growth of the pathogen, thereby promoting selective pressure. The perfect antibiotic would be one that could inhibit multiple steps in the disease progression pathways, but with less severity in these steps. Low levels of inhibition at multiple stages would together provide a formidable inhibitory effect, yet allow for little inducement of the bacteria to form a resistance (Avner, Fialho, and Chakrabarty, 2012).

 

There are no "perfect" antimicrobial agents on the horizon and all these contributory factors to add to the evolving resistance in microorganisms. It is more important than ever for all individuals to put in an effort to slow the progress of these dangerous pathogens in society. The first step in that process is to educate the public of what drug resistant microorganisms exist in the community.

## Pharmacological Resistant Microorganisms – The Major Players

MRSA and VRE have been widely publicized antimicrobial resistant organisms encountered in the hospital setting. There are, however, handfuls of others that have become noteworthy; with more still emerging every day. While there are too many drug resistant microorganisms to name, this next section will cover some of the most difficult to treat drug resistant infections that are problematic globally.

## Methicillin-Resistant *Staphylococcus Aureus* (MRSA)

MRSA has become the focus of media attention over the last decade, being termed the "super bug", responsible for more deaths in the U.S. in 2005 than AIDS (Corriere and Decker, 2008). One year mortality rates among patients with skin and soft tissue infections caused by MRSA have been reported as high as 22% with MRSA bloodstream infections as high as 33% (Johnson and Decker 2008). Surveillance data have revealed that MRSA has achieved an uninterrupted presence, or "endemic state" in ICUs in most countries, particularly in the United States. Asymptomatic carriage of MRSA is common among patients in a variety of health care settings. Recent studies of hospitals have shown that for every patient with positive MRSA cultures, there may be up to 10 additional patients who are asymptomatically colonized (Calfee, 2012). The

ecologic niche for MRSA in humans is skin and mucous membranes, most particularly the anterior nares, where it is adapted to multiply and reside (Lin and Hayden, 2010).

MRSA has become such a cause of fear to the American public that state legislatures in Maryland, Illinois, Pennsylvania, Florida, and New Jersey have proposed actions to target the spread of MRSA, including mandated use of surveillance cultures to screen hospitalized patients, and public reporting of MRSA infections (Corriere and Decker, 2008). And although MRSA has been historically considered a pathogen one might contract with increased exposure to health care, community associated MRSA strains are becoming more widespread. For example, the Center for Disease Control's (CDC) Active Bacterial Core surveillance (ABCs) system, a population-based active laboratory surveillance system, found that 85% of invasive MRSA infections had health-care related risk factors, but that more than two thirds of these infections had their onset in the community setting rather than in the hospital (Calfee, 2012).

## Vancomycin-Resistant *Enterococci* (VRE)

VRE is a close second to MRSA in notoriety to antimicrobial resistance. Seven types of resistance have been characterized in enterococci, and the transferability of these genes has likely facilitated the rapid dissemination of VRE (Lin and Hayden, 2010). In U.S. hospitals, enterococci are the second most common pathogens recovered from catheter associated infections of the blood stream and urinary tract and from skin and soft tissue infections (Arias and Murray, 2012). Colonization with VRE generally precedes infection, but not all individuals who become colonized will develop an active infection (Rubinstein and Keynan 2013). To an extent greater than that of MRSA, the ratio of

 

VRE colonized patients far exceeds those infected, often by a factor of 10 to 1. The gastrointestinal tract of patients is the largest reservoir, where the pathogen can persist asymptomatically for months to years. The environment of infected or colonized individuals can also serve as a source of infection, as VRE can survive on surfaces for months (Lin and Hayden, 2010). The increased use of antibiotics in hospitals worldwide has helped to facilitate increased colonization. Enterococci though common inhabitants of the human gastrointestinal tract, normally only constitute a small fraction of the gut microbiota. Exposure of hospitalized patients to antibiotic therapy results in significant changes which disrupt the balance of bacteria in the gut, thereby allowing colonization of the GI tract by VRE. Studies have shown that presence of VRE in the bloodstream of patients is preceded by VRE becoming the predominant species in the GI tract of these patients (Arias and Murray, 2012).

### ***Pseudomonas aeruginosa***

*Pseudomonas aeruginosa* is another primarily nosocomial pathogen that has become increasingly problematic due to its intrinsic resistance to many anti-microbial drugs and its ability to adapt quickly to defend against several others (Avner and Chakrabarty, 2012). *P. aeurginosa* was first observed as a blue discoloration on surgical wound dressings as early as 1850. It was later identified in 1862 that rod shaped organisms were the cause of this pigment, and in 1882 *P. aeurginosa* was successfully isolated in a pure culture from two patients with bluish-green pus (Lister, Wolter and Hanson, 2009). Although, P. aeurginosa is a Gram-negative bacillus found primarily growing in soil, this organism is also able to survive in the human body. It is largely

known as a healthcare associated infection, and is capable of infection at all body sites with particular affinity for the respiratory tract. P. aeurginosa is infamous as the most common respiratory pathogen in patients with cystic fibrosis, the second most common pathogen responsible for nosocomial pneumonia (Avner and Chakrabarty, 2012), and the leading cause of pneumonia among pediatric patients in the intensive care unit (ICU) (Lister, Wolter and Hanson, 2009). Even more alarming than the high prevalence of this organism in hospitals is its high mortality rate of 30-40% for pneumonia caused by P. aeruginosa (Avner and Chakrabarty, 2012). P. aeruginosa is rarely part of the normal human microbial flora, with typical colonization rates ranging from 0-2% for skin, 0-3.3% for nasal mucosa, 0-6% for the throat, and 2.6-24% for fecal samples. However, colonization rates may be greater than 50% during hospitalization, especially for patients with surgical sites, severe burns, or with exposure to in-dwelling medical devices such as mechanical ventilators/tracheostomy, and indwelling catheters (Lister, Wolter and Hanson, 2009).

P aeruginosa has been able to evade antimicrobial therapies with multiple strategies for resistance. Genes are acquired on mobile genetic elements (plamids), or mutational processes occur that can alter the expression and/or function of chromosomally encoded mechanisms. Both of these methods of developing resistance can seriously limit therapeutic options to treat acute infections (Lister, Wolter and Hanson, 2009). Resistance to fluoroquinolones is common worldwide. Even the most potent drug of this class, ciprofloxacin, was found to have resistance rates of 25-40% by 1999 (Avner and Chakrabarty, 2012). P aeurginosa has developed resistance to other

classes of antibiotics including aminoglycosides with Gentamicin at rates of 12-22% resistant, and lesser rates for tobramycin and amikacin. Not surprisingly, multidrug resistant strains (MDR), those resistant to three or more drug classes, are on the rise. MDR strains are more commonly found in nursing homes and ICU's, and were found in the highest prevalence in lower respiratory tract infections, such as pneumonias. In 1993 4% of P. aeurginosa isolates were found to be MDR, compared to 14% in 2002 (Lister, Wolter and Hanson, 2009). A global surveillance study done from 1997-1999 exhibited a widespread drop in the proportion of antibiotic susceptible isolates, and furthermore showed a statistically significant rise in resistance to nearly all antipseudomonal antibiotics in Europe. No single anti-pseudomonal drug was shown to be effective to greater than 90% of all isolates in this study. Moreover, no present day antibiotic exists to which resistant strains have not emerged (Avner and Chakrabarty, 2012). Picking the first line antibiotic to initiate therapy is crucial to facilitating good clinical outcomes, but this is further complicated by P. aeurginosa's ability to develop resistance to antibiotics even during the course of treatment (Lister, Wolter and Hanson, 2009).

**Antibiotic-Resistant *Mycobacterium tuberculosis* (TB)**

Tuberculosis, commonly known as TB, is an airborne disease caused by bacterial infection that can be severe and is highly contagious. In Western countries, such as the United States, popular belief is that TB is a disease of the past. Evidence of tubercular decay has been found as far back in history as ancient Egypt in the skeletons of mummies thousands of years old. TB was also common in ancient Greece and the Roman Empire. However, TB remains one of the leading infectious diseases as young adults succumb to

untimely deaths by TB worldwide. Some 2 billion people – one third of the global population – are thought to be infected with TB bacteria (NIAD, 2012).

TB is a chronic bacterial infection, most people who are infected with the bacterium harbor it without symptoms (latent TB), but some will develop active TB disease. Those with active TB infection can spread the pathogen through the air in microscopic droplets via coughing, sneezing, speaking, laughing, or singing (NIAD 2012). Anti-tuberculosis drug resistance is a major public health problem that threatens advancements made in the care and control of TB worldwide. Drug resistance develops due to improper use of antibiotics in treatment of drug-susceptible TB patients (WHO, 2012). With appropriate treatment, TB can be cured in most patients, but successful therapy demands close cooperation between patients and healthcare providers, and individuals who are compliant with their treatment regimen. Treatment usually involves taking several antibiotics for a minimum of 6 months and up to 2 years depending on the type of infection (NIAD, 2012). Both patients and healthcare providers play a role in the development of drug resistance. Patients who do not take their medications regularly or who do not complete the full course of therapy may develop drug resistant TB. Healthcare providers can further exacerbate resistance by prescribing the wrong treatment, wrong dose, or wrong duration of therapy. In areas where drug supply is unavailable or of poor quality resistance is more likely to occur (CDC, 2014). Drug resistance essentially arises in areas with weak TB control programs, due to improper treatment regimens, and failure to ensure patients complete their whole course of treatment (WHO, 2012).

 

Multidrug resistant TB (MDR TB) is a form of TB in which the bacteria are resistant to at least the antibiotics, isoniazid (INH) and rifampin (RIF), the most potent TB drugs which are used to treat all persons with susceptible TB (CDC, 2014). Consequently, this form of TB is more difficult to treat and requires up to 2 years of multidrug therapy. In 2010 the World Health Organization (WHO) estimated that more than 650,000 people have MDR TB (NIAD, 2012). Extensively Drug-resistant TB (XDR TB) is a less common type of MDR TB that is resistant to isoniazid, rifampin, plus any fluoroquinolone and at least of one of three injectable second-line drugs (i.e, amikacin, kanamycin, or capreomycin). As the most potent TB drugs are ineffective against XDR TB, patients are left with fewer and inferior treatment options. XDR TB is of particular concern to individuals with Human Immunodeficiency Virus (HIV) infection or who are otherwise immune-compromised; these patients are more likely to develop active disease and have higher mortality rates (CDC, 2014). The WHO estimates 11.4 million people worldwide are infected with TB and HIV, with TB being the primary cause of death among this population. In the U.S. health experts estimate that 20% of all TB infected people also have HIV. Patients with MDR TB and HIV appear to have a more rapid and lethal progression than those with MDR TB alone. If medications are not available, as many as 80% of those infected with both diseases die, often within months after diagnosis (NIAD, 2009).

## *Neisseria gonorrhoeae* (Gonorrhea)

Gonorrhea, the second most commonly reported infectious disease in the United States, has begun to emerge in drug resistant form. Gonorrhea is a sexually transmitted disease, caused by the bacterium *Neisseria gonorrhoeae* (NIAD, 2012). Gonorrhea represents 88 million of the 448 million new cases of curable sexually transmitted infections (which include syphilis, Chlamydia, and trichomoniasis) that occur globally each year (WHO, 2011). Areas typically affected include the reproductive tract including the cervix, uterus, and fallopian tubes of women, and in both sexes it can occur in the urethra, mouth, throat, eyes and anus (NIAD, 2012). Gonococcal infections have serious consequences, especially to reproductive, maternal and newborn health. Gonorrhea is associated with a five-fold increase of HIV transmission, infertility, ectopic pregnancy, first trimester abortion, pelvic inflammatory disease, and severe neonatal eye infections that may result in blindness (WHO, 2011).

The *N. gonorrhoeae* bacterium is exceptionally good at picking up pieces of DNA from other bacteria; in doing so it alters its genetic makeup, resulting in new ways to evade antibiotics (NIAD, 2012). Inherent genetic mutations within the organism along with overuse and misuse of antibiotics have played a role in the development in this pattern of resistance. Additionally, extra genital infections – such as anorectal and pharyngeal – affect key populations such as men who have sex with men. This may play a significant role in the progression of resistant strains of *N. gonorrhoeae*, as this allows for the communication and exchange of genetic material with other bacterial species in these anatomical sites (WHO, 2011).

Although antibiotics have been successfully used to treat gonorrhea for decades, the bacteria has grown resistant to every drug used to treat it (CDC, 2013). Antimicrobial resistance in gonorrhea became evident early after antimicrobials were introduced into clinical practice. The evolution of this bacteria has continued with the emergence of resistant strains to tetracyclines, macrolides (including azithryomycin), sulfonamide and trimethoprim combinations (WHO, 2011), penicillin, and most recently fluoroquinolones. In 2007 the CDC revised its gonorrhea treatment guidelines and longer recommends fluoroquinolones due to widespread resistance. This leaves only one class of antibiotics available for defense against gonorrhea, broad spectrum cephalosporins – which include the oral antibiotic cefixime, and the injectable antibiotic ceftriaxone (CDC, 2013). In recent years susceptibility to these currently recommended first-line antimicrobials, the extended spectrum cephalosporins, has decreased globally. For several years cefixime treatment failures have been identified in Japan, and more recently failures have also been confirmed in Europe (Ohnishi et al, 2011). There is mounting concern that *N. gonorrhoeae* may become resistant to all available antibiotics, resulting in untreatable gonorrhea (NIAD, 2012).

**Selection of proper antibiotic therapy**

One of the leading contributors to the emergence of drug resistant organisms is the misuse of antibiotic therapy. Therefore, it is of critical importance that the correct medications are chosen to initiate treatment. Antimicrobial susceptibility testing is used to establish which particular antibiotics a specific bacteria or fungus is sensitive to. Susceptibility testing usually goes along with a culture and Gram stain, which are

 

resulted more quickly. Results are normally reported as the minimal inhibitory concentration (MIC) (Street and Staros, 2014). The MIC is defined as the lowest dilution of an antimicrobial that will inhibit the visible growth of a microorganism after incubation overnight (Journal of Antimicrobial Chemotherapy, 2001). Reports commonly contain a quantitative result expressed in ug/mL as well as a qualitative interpretation. A high qualitative value means a higher concentration of drug is required to affect the organism's function or reproduction, whereas a lower value means less drug is needed. The quantitative interpretation usually classifies each result as susceptible (S), intermediate (I), resistant (R), sensitive-dose dependent (SD), or no interpretation (NI). Antimicrobial susceptibility testing can guide the physician in drug choice and dosage for infections that are difficult to treat (Street and Staros, 2014). MBC, or minimum bactericidal concentrations, may be of use in the treatment of certain infections, particularly those causing endocarditis. MBC is defined as the lowest concentration of antimicrobial that will prevent the growth of a pathogen after it is subcultured onto antibiotic-free media (Journal of Antimicrobial Chemotherapy, 2001). Bactericidal antibiotics normally have an MBC equal to or similar to the MIC, whereas bacteriostatic antibiotics usually have an MBC that is considerably higher than the MIC (Street and Staros, 2014).

## Treatment Options for Drug Resistant Microorganisms

In lieu of the widespread emergence of drug resistant organisms, presently there are still treatment options available for even the cleverest pathogens. With careful monitoring and judicious use of antibiotics, hopefully we can prolong the development of

total drug resistant organisms long enough to invent some novel therapies against these pathogens.

## MRSA

Vancomycin, which inhibits cell wall synthesis, has been the primary drug to treat severe MRSA infections for over 40 years (Johnson and Decker, 2008). Researchers have noticed a MIC creep, or an increase in the proportion of MRSA isolates with Vancomycin MIC levels at the high end of the susceptible range by the Clinical Laboratory Standards Institute (CLSI) guidelines. Multiple studies have demonstrated that infections due to such organisms have poorer outcomes when treated with vancomycin than infections whose isolates had lower MIC values. A meta-analyses of 22 studies found that higher vancomycin MIC is associated with treatment failure and mortality (Calfee, 2012).

Vancomycin is not, however, the only treatment option for MRSA infections. Instead of using one antibiotic to treat all varieties of MRSA infection, the type of infection (local vs. invasive) and strain of MRSA (community vs. hospital acquired) need to be considered before making a choice of therapy. For example, localized infections of the skin and soft tissue such as abscesses and furuncles typically respond well to incision and drainage alone, although antibiotics are usually prescribed in conjunction. Additionally, community associated MRSA can be susceptible to different antibiotics than hospital associated infections. Agents that have proven successful against MRSA other than vancomycin include trimethoprim-sulfamethoxazole, linezolid, daptomycin, and tigecycline (Johnson and Decker, 2008).

 

Trimethoprim-sulfamethoxazole (TMP-SMX) is most commonly used for outpatient MRSA infections along with clindamycin (Johnson and Decker, 2008). TMP-SMX is a combination of a methoprim and a sulfonamide, which work together synergistically to inhibit folate synthesis (U.S. National Library of Medicine, 2015). TMP-SMX has demonstrated rapid bactericidal action in both community and hospital associated MRSA infections when compared to other antibiotics, however fared less than optimal against Group A Streptococcus. Statistics from 2005 revealed a 97% susceptibility of community associated MRSA isolates to TMP-SMX (Johnson and Decker, 2008).

Linezolid is an oxazolidinone antibiotic that works to inhibit protein synthesis at the 50s ribosome. It has demonstrated bacteriostatic capacity against almost all community associated MRSA strains as well as Group A Streptococcus (Johnson and Decker, 2008). Like all therapies linezolid has both benefits and disadvantages. Linezolid has already established a potential for resistance. The drug was introduced in 2000, and the first report of resistance was only a year later. Other shortcomings of this therapy include expense, hematologic side effects (thrombocytopenia, and anemia), and contraindication for use with selective serotonin reuptake inhibitors (SSRI's). The intrinsic monoanimine oxidase inhibitor activity of linezolid raises concern for the development of serotonin syndrome in patients who take SSRI's. Finally, there is an apprehension to use linezolid against MRSA endocarditis due to the lack of bactericidal activity (Johnson and Decker, 2008).

On the other hand, linezolid has the potential to change outcomes in the treatment of MRSA ventilator associated pneumonia (VAP) infections. Success rates of treatment with vancomycin for MRSA VAP have been reported as low as 35-57%. Linezolid penetrates lung tissue well in the setting of active pneumonia and inflammation. A retrospective analysis of two double-blinded studies found that linezolid had a higher overall survival and clinical cure rate than vancomycin in the treatment of hospital associated MRSA pneumonia (Johnson and Decker, 2008).

Two additional antibiotics for use against MRSA include daptomycin and tigecycline. Daptomycin is a cyclic lipopeptide semi synthetic antibiotic. Daptomycin works as a bactericidal agent by causing bacterial cell wall depolarization. First available in 2003 for skin and soft tissue MRSA infections, resistance to daptocycline was reported two years later. Daptomycin was proven non-inferior to vancomycin in 2006 for use against MRSA bacteremia and endocarditis. Considerations for daptomycin are; inactivation by surfactin and therefore not suitable to treat pneumonia, and the need for monitoring due to potential myopathy. Serum creatinine kinase (CK) levels must be monitored at least weekly. Therapy should be discontinued if the patient is symptomatic, or if the patient is asymptomatic with CK elevations above 1000 u/L (Johnson and Decker, 2008).

Tigecycline is a minocycline derivative which inhibits protein synthesis by binding to the 30s ribosome. It has been FDA approved to treat local infections, such as, MRSA complicated skin and soft tissue infections and methicillin sensitive staphylococcus aureus (MSSA) complicated intra-abdominal infections. Due to a large

volume of distribution, considerable trepidation exists about the use of tigecycline in the setting of more global infection such as MRSA bacteremia (Johnson and Decker, 2008).

With so many options for MRSA treatment available prescribers need to use caution in choosing the correct one. In addition to traditional antibiotic therapy, new treatments are on the horizon. Vaccine development for MRSA has begun with a *Staphylococcus aureus* polysaccharide which demonstrated protective immunity in patients receiving hemodialysis. However, in Phase-III trials of the vaccine no long term immunity was demonstrated. Successful vaccine development with long term efficacy may greatly reduce the incidence and acuity of MRSA infections in the future (Gleeson, 2008).

**VRE**

Many of the fist line antibiotics used to treat VRE are the same ones described for use against MRSA. Linezolid, as described earlier, is a bacteriostatic synthetic oxazolidinone which affects protein synthesis at the 50s ribosome. Available in both oral and intravenous forms, linezolid has proven effective in the treatment of various VREm infections (Cattoir and Leclercq, 2012). Results of linezolid use have been varied. In one study of 500 patients with VRE, linezolid yielded an 81% cure rate. Another study of organ transplant recipients with severe VRE and bacteremia reported a 63% cure rate. The development of resistance during treatment has been associated with treatment failure. Linezolid resistance is associated with heavy use, but enterococci isolates with linezolid resistance have been obtained from patients without previous exposure to the antibiotic (Rubinstein and Keynan, 2013). Ribosomal mutations usually cause resistance

 

patterns. However, the worrisome account of plasma-mediated resistance to linezolid in E. faecalis of animal and human origin implies the likely spread of further resistance (Cattoir and Leclercq, 2012). In addition to the development of resistance, the same considerations previously mentioned for linezolid use against MRSA infections also apply: adverse hematologic effects, and contraindication to use with SSRI's.

Daptomycin is another antibiotic that works both against MRSA and VRE. Daptomycin is a lipopeptide antimicrobial with bactericidal activity against VRE in vitro through depolarization of the cell membrane. Although there are few clinical studies for the efficacy of daptomycin, retrospective studies have shown a success rate of 87-90% against VREm bacteria (Cattoir and Leclercq, 2012). Patients should be monitored for myopathy and have serial creatine phosphokinase (CPK) levels at least weekly. Treatment should be discontinued for symptomatic patients with a CPK greater than or equal to 5x the upper limit of normal CPK, or for asymptomatic patients with greater than or equal to 10x the upper limit of normal. Resistance to daptomycin has been reported in enterococci, including samples from patients who never received daptomycin therapy in the past (Rubinstein and Keynan, 2013).

Quinupristin-dalfopristin, an injectable streptogramin antibiotic has been available for use against VRE since 1999. However, it is not widely used in clinical practice due to several limitations (Cattoir and Leclercq, 2012). One such constraint is that central venous access is required for administration of quinupristin-dalfopristin. In addition, the drug has only been approved for *E. faecium* infections, as it has demonstrated poor activity against *E. faecalis*. Side effects such as metabolic interactions, severe myalgias,

nausea and hyperbilirubinemia further limit its use (Rubinstein and Keynan, 2013). Resistance to quinupristin-dalfopristin is reported in 1-2% of enterococci isolates (Cattoir and Leclercq, 2012). The low number of resistant isolates may be due to the fact that this antibiotic has not been widely used. Due to the many disadvantages of this drug it may not always be the first line therapy – but it serves as a good back up for strains with multidrug resistance.

Tigecycline, previously described for use against MRSA, works by inhibiting protein synthesis. Although not approved by the FDA for use against VRE, tigecycline has in vitro activity against many gram positives, gram negatives, anaerobes and atypical species. Certain concerns were raised in clinical trials of tigecycline, which showed higher mortality rates when compared to the control group for patients with; skin and soft tissue infections, pneumonia, and intra-abdominal infections. VRE seems to be susceptible to tigecycline based on in vitro and animal models (Rubinstein and Keynan, 2013). As with quinupristin-dalfopristin, tigecycline may not be a first line treatment candidate. It may, however, be an option for patients with VRE who are intolerant of other agents, or who are co infected with additional tigecycline susceptible pathogens. In combination with daptomycin, tigecycline has been used successfully to treat severe non-responding VRE infections (Rubinstein and Keynan, 2013).

### *Pseudomonas aeruginosa*

When a pseudomonal infection is suspected, an aggressive attempt to retrieve a pathogen for culture prior to the first dose of antibiotic therapy is recommended. The use of one antibiotic regimen across the board for these infections is no longer considered a

 

rational approach. The postponing of treatment, however, pending sampling from the respiratory tract may not necessarily be advised. The delay of antibiotic therapy has been linked to higher mortality rates, even when a patient is assessed to be clinically stable (El Solh and Alhajhusain, 2009). If culture is obtained, it may be difficult to choose an initial therapy while awaiting results. Some options include using national surveillance data, studying the susceptibility profile from recently isolated pathogens, and determining the patient's risk profile (previous healthcare/antibiotic exposure) (El Solh and Alhajhusain, 2009).

One of the most effective anti-pseudomonal classes of antibiotics are the polymixins. Polymyxins are cyclic, positively charged peptide antibiotics derived from different species of Paenibacillus (Bacillus) polymyxa. These antibiotics have a detergent-like effect that interrupts the cell membrane causing leakage of cellular contents. This mechanism of action shelters them from cross-resistance with other antipseudomonal agents, and protects them from the rapid development of resistance. Colistin has been one of the most widely used polymyxin since their reintroduction during the last several years. Colistin has been used as mono or combination therapy against multidrug resistant strains of pseudomonal pneumonia, and the efficacy of this drug, especially when it is a last resort, outweighs its risk of nephrotoxicity and neurotoxicity. Other antimicrobials have been used in combination with colistin, but data fails to show improved outcome over monotherapy in clinical studies (El Solh and Alhajhusain, 2009).

Doripenem, is a new carbapenem, which binds to penicillin-binding proteins, causing cell wall damage and has bactericidal properties. Doripenem has shown promising activity *in vitro*; where the MIC of doripenem was lower than all other comparative agents against pseudomonas isolates. This drug is cleared by the kidneys and dosing would need to be adjusted based on renal function. To date clinical studies have shown improved outcomes with doripenem as compared to other treatment regimens, but they have not been statistically significant. Further studies are ongoing with different dosage regimens to establish the full potential for this antibiotic as well as multiple others including other carbapenems, cephalosporins and fluoroquinolones (El Solh and Alhajhusain, 2009).

## Drug Resistant Tuberculosis

Tuberculosis differs from some of the other drug resistant microorganisms in that there is a vaccine available in much of the world to prevent TB infection. The bacilli Calmette-Guerin vaccine, or BCG is used in many countries with high instances of TB infection to prevent childhood complications of TB such as meningitis. BCG is not however typically recommended for use in the United States due to several factors. Namely, there is a low risk of infection with *Mycobacterium tuberculosis* in the U.S., but also because of the variability of protection the vaccine provides against adult pulmonary TB as well as the potential for the vaccine to produce false positives with tuberculin skin testing (CDC, 2011).

High mortality rates are associated with MDR and XDR TB but many cases can be treated with the right combination of medications (Caminero, Sotgiu, and Migliori,

2010). Drug resistance is confirmed through drug-susceptibility testing, but this can take weeks to complete. An empirical treatment regimen should be initiated based on expert advice as soon as MDR TB is suspected. The course of therapy should then be adjusted once results are complete (CDC, 2012). The World Health Organization guidelines recommend treatment regimens consisting of an intensive phase of 8 months and a total duration of treatment of 20 months for most patients with MDR TB. These guidelines were based on an analysis of more than 9,000 cases treated in observational studies (WHO, 2012).

An example of one such regimen is a combination of at least four drugs to which the *M. tuberculosis* isolate is susceptible. The drugs used in therapy are chosen in a stepwise selection process through five separate groups on the basis of their efficiency, safety and price. The first group includes the oral first-line drugs high-dose isoniazid, pyrazinamide and ethambutol. The second group consists of fluoroquinolones, with high-dose levofloxacin preferred as the first choice. Next are the injectables in the following order: capreomycin, kanamycin then amikacin. Fourth, the second-line drugs are considered in the following order: thioamides, cycloserine, then aminosalicylic acid. The last group includes drugs which are not very effective or for which there are limited data. Drugs in the final group are to be used in order as follows: clofazimine, amoxicillin with clavulanate, linezolid, carbapenems, thiocetazone, then clarithromycin (Caminero, Sotgiu, and Migliori, 2010). Several drugs belonging to new classes of anti-mycobacterial agents are under development, but have yet to be shown effective in properly conducted clinical trials (WHO, 2012).

## Gonorrhea

As previously mentioned, due to extensive multi drug resistance, broad spectrum cephalosporins (oral cefixime, and injectable ceftriaxone) are the only available defense left against gonorrhea (CDC, 2013). With decreasing susceptibility and emerging reports of treatment failures cefixime is no longer recommended by the Centers for Disease Control (CDC) as an effective oral treatment. This leaves the injectable ceftriaxone to be used in combination with one of two oral antibiotics – azithromycin, or doxycycline, as the primary treatment for gonorrhea (CDC, 2013). It is important, however, in this time of rising antibiotic resistance that more than one type of treatment is available. This practice safeguards against infections that may be resistant to one drug, leaving other options available (NIAD, 2012). Ceftriaxone is more potent than cefixime, and by combining it with an additional oral antibiotic the progression of resistance may be delayed. Cefixime may be used as an alternative treatment in some cases. For example, if ceftriaxone was not readily available, cefixime may be prescribed along with another oral antibiotic as a dual therapy. If a severe allergy to cephalosporins exists, azithromycin may be used alone. However, if one of these alternative treatments is prescribed a test of cure should be performed in one week (CDC, 2013).

Providers need to play a role in preventing the spread of further resistance by closely monitoring for ceftriaxone treatment failure. Furthermore, every effort needs to be made to evaluate and treat all sex partners of patients within the last 60 days (CDC, 2013).

The National Institute of Allergy and Infectious Diseases (NIAD) is studying new ways to treat cephalosporin resistant gonorrhea by combining existing antibiotic therapies such as gentamycin and azithromycin, or gemifloxacin and azithromycin. The vital need for new and improved therapeutics would be alleviated with the development of a safe vaccine against gonorrhea. An investigator for the NIAD is studying two proteins as potential targets for vaccine development. The proteins help the bacteria to utilize iron and have been identified in all strains of gonorrhea. If essential for survival of the pathogen, these proteins would likely be suitable vaccine targets. A vaccine targeted to knock out these two particular proteins and prevent the progress of this bacterium would be a great success for researchers in both the gonorrhea and antimicrobial resistance field (NIAD, 2012).

## Healthcare Considerations

As previously cited the misuse and overuse of antibiotics has been an exacerbating factor in the emergence of drug resistant microorganisms. To help prevent history from repeating itself, most healthcare institutions have committees that develop guidelines for antibiotic use. Some practices involve monitoring of antibiotic therapy with peak and trough levels, reviewing antibiotic use based on culture results, recommending the use of narrow spectrum antibiotics until culture reports are complete, suggesting combination antibiotic therapies, and restricting the use of certain antibiotics empirically for prophylaxis (Glover, 2000). This overt use of antibiotics, although significant, is only one of many areas in healthcare that leave room for improvement when it comes to infection control.

 

### *Hand Hygiene*

Hand washing is the single most effective way to decrease the spread of infections. Healthcare workers who come into contact with a MRSA colonized patient or their contaminated environment carry the microorganism transiently on their hands, clothing, and equipment. These workers then unknowingly act as a vector for patient to patient spread of the pathogen. A seemingly insignificant contact with patient skin or their environment can result in significant hand contamination (Johnston and Bryce, 2009). Since transmission occurs via transiently contaminated hands of health care workers, strict adherence to standard precautions would result in lower rates of MRSA and VRE transmission (Lin and Hayden, 2010). Standard precautions are defined by the CDC as the minimum infection prevention practices that apply to all patient care. These guidelines including hand hygiene before and after patient care, after coming into contact with surfaces in the patient environment, after coming into contact with body fluids, excretions or wound dressings, and after removal of gloves. The use of personal protective equipment such as gloves, masks, gowns and eye protection for potential exposure to blood, body fluids, mucous membranes, non-intact skin, or contaminated equipment is also described as part of standard precautions (CDC, 2015).

Soap and water hand washing is recommended for visibly soiled hands or for contact with patients that have a known infectious diarrhea. Otherwise, the use of alcohol based hand rubs are recommended as the primary mode of hand hygiene in the health care setting by the CDC. This is encouraged due to the alcohol based hand rub's ability to protect against a broad spectrum of pathogens and to make hand hygiene more

accessible at the bedside, to increase compliance (CDC, 2015). Studies have demonstrated that in hospitals with alcohol based waterless antiseptics, with a campaign to promote hand hygiene as a center of patient care, rates of MRSA and VRE have declined. Compliance in hand hygiene, however, has been reported as low as 48-66% in various studies (Johnston and Bryce, 2009). Programs that can foster hand washing compliance can improve rates of MRSA and VRE colonization and transmission. Emphasis needs to be made, however, that gloving is not an alternative to proper hand hygiene. In a study of healthcare workers caring for VRE infected patients, 29% of clinicians' hands were contaminated with VRE after glove removal (Lin and Hayden, 2010).

### *Environmental Reservoirs*

Equally as important as hand hygiene is the establishment and maintenance of a clean and orderly health care environment. High touch areas, especially those in close proximity to infected or colonized individuals are frequently contaminated with bacteria and need special attention. Several studies have indicated that environmental cleaning and disinfection in many hospitals is insufficient. One such observational study looked at 16 intensive care units reporting that only 57.1% of standardized environmental sites were cleaned after patients were discharged. Areas neglected were of high risk for contamination including toilet handle bars, light switches and door knobs (Lin and Hayden, 2010). MRSA and VRE have been isolated from charts, doorknobs, keyboards, toilets, tubs and furniture in patient rooms. One might argue that cleaning will never truly eliminate all microorganisms from the environment, but routine disinfecting will

decrease the microbial burden on high touch areas and shared clinical equipment (Johnston and Bryce, 2009).

One study looked at healthcare workers who cared for VRE positive patients in an intensive care unit. Two groups of workers were observed – those that had contact with the patient directly, and those who came into contact with only the patient's environment. The study found that the workers who did not come into direct contact with the patient, but touched only surfaces in the patient environment were less likely to wear gloves or clean their hands. Both groups were found to have high levels of hand contamination. MRSA can survive on inanimate surfaces for days to weeks, and VRE can persist in the environment for months. MRSA and VRE can both be removed from these surfaces by disinfectants routinely used in hospitals. Non-adherence to cleaning protocols along with continuous recontamination of surfaces seems to be responsible for persistence of these pathogens in the environmental reservoir (Lin and Hayden, 2010).

To prevent the further spread of resistant microorganisms such as MRSA and VRE time and sufficient staffing need to be devoted to proper cleaning. Ultimately all healthcare workers need to be conscientious to maintain a clean environment – it is not merely a "housekeeping" issue (Johnston and Bryce, 2009).

### *Active Surveillance and Decontamination*

Along with hand hygiene and environmental decontamination, many facilities are instituting practices of active surveillance and decolonization to further prevent the spread of microorganisms. Active surveillance is the process of screening asymptomatic patients for colonization of microbes such as MRSA and VRE. Patients are swabbed at

one or more body sites (anterior nares most commonly for MRSA, and rectal/peri-rectal for VRE) (Lin and Hayden, 2010). The transmission of VRE has been decreased by the use of active surveillance in outbreak settings or in high risk units such as ICU's. Legislation has been introduced in several states mandating surveillance cultures to screen all patients for MRSA and VRE. Carriers are to be treated or offered treatment, and in some states are segregated from patients who test negative (Rubinstein and Keynan, 2013).

The separation of infected or colonized patients is part of contact isolation precautions. With contact precautions health care providers work under the assumption that the patient, the environment, or both are colonized or contaminated with bacteria in the absence of blood, body fluids, excretions, secretions or visible soiling. Contact precautions dictate that gloves and gowns should be worn when entering a patient's room and when in direct contact with the patient and their potentially contaminated environment (Johnston and Bryce, 2009). Colonized or infected patients may be placed into private rooms, or cohorted with similarly colonized patients. Additionally, cohorting healthcare workers can help to further prevent the transmission of microbes (Lin and Hayden, 2010).

Negative consequences have been associated with patients in isolation. These patients have less contact with healthcare workers, decreased examination, and as a result higher rates of preventable adverse events. Furthermore, isolation patients suffer from increased depression and anxiety compared to patients not on isolation. Due to the negative stigma and social isolation they have a greater incidence of dissatisfaction with

 

treatment (Johnston and Bryce, 2009). The workload for isolation patients is greater, and therefore should be taken into consideration when staffing assignments are created (Lin and Hayden, 2010).

Once patients are identified as carriers of bacteria, in some instances they can be decolonized. Colonization suppression is the process of reducing the burden of bacteria on a patient's skin by regular treatment with antiseptic agents, particularly chlorhexadine gluconate (Rubinstein and Keynan, 2013). Chlorhexadine is a topical antiseptic with a broad spectrum of activity, durability of effect, and is safe for routine use. Decolonization is possible in patients who are colonized with MRSA; for VRE carriers a method for decolonization does not yet exist (Lin and Hayden, 2010). Decolonization treatments for MRSA vary, but usually include the application of topical mupirocin ointment to the interior nares twice daily for five days in addition to chlorhexadine bathing (Gleeson, 2008). Although no specific treatment for VRE decolonization exists, a study in a medical ICU looked at the difference between regular soap and water bathing vs. daily chlorhexadine bathing on VRE. The chlorhexadine bathing was associated with less VRE on patients' skin, lower rates of VRE contamination of healthcare workers' hands, less VRE contamination in the patient environment, and decreased VRE acquisition by patients (Lin and Hayden, 2010).

The most favorable implementation of active surveillance has yet to be defined in healthcare. Many questions remain as to the best use of this process. Should cultures be performed only on admission, or at regular intervals throughout a patient's stay? Should patients be isolated initially, pending results of their cultures? Knowledge of risk factors

for exposure to microorganisms may help limit surveillance testing to high risk patients until the efficacy of more widespread monitoring can be established (Lin and Hayden, 2010).

### *Additional Considerations*

Inadequate staffing is another risk of increased incidence of patient to patient microbial spread. Healthcare workers caring for excessive numbers of patients have greater patient contacts, less cohorting, and lower levels of adherence to standard precautions. Understaffing has been associated with: VRE and MRSA transmission, increased rate of MRSA infection, prolonged ICU stays, increased incidence of central venous catheter associated bloodstream infections, late onset ventilator associated pneumonia, and other infections in the critically ill (Lin and Hayden, 2010).

## Conclusion

Drug resistance in microorganisms is out of control and has created major problems in health care delivery in the U.S. and worldwide (Avner, Fialho, and Chakrabarty, 2012). Antibiotic medications fail to perform over time due to microorganism resistance development. This property of becoming ineffective is unique to antibiotics and is not observed in other drug groups such as cardiovascular or anti-inflammatories. The future of modern medicine depends on effective antibiotics, yet only two new classes have been added to the antimicrobial arsenal since 1962 (Coates, Halls, and Hu, 2011). One factor hindering the development of new antibiotic medications is that the process is expensive and lengthy. It can take approximately 10 years to market a new antibiotic and cost roughly 300 million dollars (APUA, 2014). To make matters

worse, after all the time, effort and money that go into creating a new drug, resistance development follows almost immediately. Resistance can usually be observed within two years of marketing, even for new classes of compounds (Coates, Hall, and Hu, 2011). With so few novel antibiotic classes being developed, and the rapid emergence of resistant strains of microorganisms, a new approach needs to be taken globally, before options run out.

One important step to break the cycle of antibiotic resistance is to break the cycle of the release of a new compound, followed a few years later by the development of resistance. Treatments against TB have addressed this issue with the use of combination therapies. However, since the prevalence of MDR TB is on the rise, it is obvious that although this method can slow resistance development, it will not stop it (Coates, Hall, and Hu, 2011). Another strategy to address resistance is to modify existing antibiotics instead of creating new ones. The risk and cost of analogue development is much lower than that of creation of new classes. Possibilities include strengthening existing antibiotics so bacterial enzymes that can cause resistance are unable to attack. "Decoy" molecules have been used with some antibiotics. These work by enticing the bacteria to attack the decoy molecule instead of the antibiotic. Some examples include clavulanic acid and sulbactam which block the beta-lactamase enzymes that destroy penicillin (APUA, 2014).

Public education regarding appropriate hand hygiene and proper use of antibiotics should be emphasized worldwide. In some countries antibiotics can be purchased over the counter, whereas other countries require a physician's prescription. Other countries

allow the purchase of antibiotics via the internet – where there is little government regulation, and these products extend to reach international borders (APUA, 2014).

Existing antibiotics need to be preserved by avoiding careless use by medical professionals as well as the general public. They should be used only for bacterial infections, prescribed at the correct dose, and taken for the proper duration. Furthermore, narrow spectrum antibiotics should be used whenever possible to avoid affecting normal flora. Additionally, non-therapeutic uses of antibiotics, such as in agriculture, should be done away with. Food animals for human consumption are commonly given long-term, low-levels of antibiotics to help produce growth. Industrialized countries use a large percentage of antibiotics in agriculture. Some governments restrict which antibiotics can be used on animals in order to preserve the most potent drugs for human disease management (APUA, 2014).

While there are many strategies available to interrupt transmission of microbes and prevent infection, compliance rates are far from optimal (Calfee, 2008). Experts agree that a global tracking system for resistance in antibiotics is necessary. This type of surveillance could highlight "hot spots" of activity, and trend data to determine which methods and strategies are most effective in controlling resistant strains of microorganisms (APUA, 2014). Furthermore, global incentives are needed to motivate individuals as well as nations to take this looming threat seriously. Apart from monetary incentives, a global understanding needs to be shared that the infections of which drug resistant microorganisms play a part kill more people worldwide than heart attacks or strokes (Coates, Halls, and Hu, 2011).

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