

# UniNet Healthcare Network Continuing Medical Education

## Antimicrobial Stewardship Part I: Inpatient

**Update December 2011**

### **Program Objectives:**

- **Review basic components of successful antimicrobial stewardship programs**
- **Review ESKAPE pathogens: resistance patterns and treatment recommendations**
- **Summarize the risks associated with unrestrained antimicrobial use**
- **Review hospital management of various multi-drug-resistant bacteria**

**Prepared by Henry Sakowski, M.D., UniNet Medical Director and UniNet Healthcare Network's Education and Communication Committee. Edited by Kaye Bellino R.N.**

No individual involved in the preparation of this program has any significant relationship with any commercial company or organization whose products or services may be referenced in the program

### Accreditation Statement:

The Alegent Health Continuing Medical Education Department is accredited by the Nebraska Medical Association Commission of Medical Education (NMACME) to provide continuing medical education for physicians.  
The Alegent Health Continuing Medical Education Department designates this Enduring material for a maximum of 1.0 AMA PRA Category 1 Credit(s)<sup>™</sup> from January 1, 2012 to January 1, 2014. Physicians should only claim credit commensurate with the extent of their participation in this activity.

Alexander Fleming's discovery of penicillin in the late 1920s revolutionized modern medicine so much that by the 1950's, bacterial infections were no longer viewed as such a significant threat to health. In 1956 Dr. Ernest Jawetz wrote in his review of antimicrobial therapy, "The mortality and morbidity from bacterial diseases has fallen so low that they are no longer among the important unsolved problems of medicine."<sup>(1)</sup> William H. Stewart M.D. was the United States Surgeon General from 1965-1969 and although some question whether the following statement was made by him, it is frequently attributed to him and accurately reflects the thinking of the late 1960's: "It is time to close the book on infectious diseases and declare the war against pestilence won."<sup>(2)</sup> Although bacterial resistance to antibiotics was already evident at that time, new antimicrobial development was able to stay well ahead of the problem. Unfortunately, this is no longer the case.

The battle between man and microbe has shifted and resistance to nearly all antimicrobial classes continues to increase. Multi-drug resistant and pan-drug resistant pathogens have emerged while all of the so-called easily exploitable bacterial binding sites for antibiotics have been exhausted.<sup>(3)</sup> From 1983 to 2007, the number of systemic antibiotics approved by the Food and Drug Administration (FDA) has decreased by 75%.<sup>(4)</sup> With the antimicrobial armamentarium shrinking and the foe becoming more cunning, clinicians must adopt proven strategies to limit the onslaught of resistant organisms through antimicrobial stewardship and infection control programs.

This educational program focuses attention on efforts to control antibiotic use in the *inpatient* arena and presents current recommendations to empirically manage infections with the potential of various drug resistant pathogens. A second program (Part II Outpatient Antimicrobial Stewardship) will focus on the *outpatient* setting to identify common areas of inappropriate antibiotic use and discuss proper treatment for frequently encountered outpatient infections.

## The History of Antibiotic Resistance

Genetic plasticity and the ability to rapidly replicate make bacteria very adaptable and capable of overcoming environmental changes detrimental to their survival.<sup>(5)</sup> Even before penicillin became widely available in the 1940's, penicillin resistant *Staphylococcus aureus* was already detected. By the end of the decade, penicillin resistance was demonstrated in 50% of the *Staph aureus* that was isolated.<sup>(6)</sup> Methicillin was introduced in 1961 and followed a similar, but more prolonged pattern. With few exceptions, each introduction of a new antibiotic has been followed within a few years by the first cases of resistance.

The hospital ward has been the front line for the battle against resistance with approximately 40% of all hospitalized patients in the United States receiving antibiotics.<sup>(7)</sup> Patients in the hospital are frequently more susceptible to infections due to impaired immune systems, and are often exposed to microbes that have been continually exposed to antibiotics. In fact, one in every 20 hospitalized patients experiences a nosocomial infection.<sup>(8)</sup> That number jumps to 1 in every 3 for patients in the Intensive

Care Unit (ICU).<sup>(9)</sup> The majority of nosocomial bacterial infections are caused by what has been termed the “ESKAPE” pathogens. (See table 1) These microbes “escape” the effects of many common antibiotics making them difficult to eradicate.<sup>(10)</sup>

Table 1. **ESKAPE** pathogens:

<b>E</b> nterococcus faecium
<b>S</b> taphylococcus aureus
<b>K</b> lebsiella pneumoniae
<b>A</b> cinetobacter baumannii
<b>P</b> seudomonas aeruginosa
<b>E</b> nterobacter species

### **Categories of antibiotics according to their principal mechanism of action<sup>(11)</sup>**

- Antibiotics can be categorized according to their principal mechanism of action:
  - Interference with cell wall synthesis  
Ex: Penicillins, cephalosporins, carbapenems, monobactams, vancomycin, teicoplanin
  - Inhibition of protein synthesis  
Ex: Macrolides, clindamycin, linazolid, aminoglycosides, tetracyclines
  - Interference with nucleic acid synthesis  
Ex: Fluoroquinolones, rifampin
  - Inhibition of a metabolic pathway  
Ex: Sulfonamides

### **Developing Bacterial Resistance to Antibiotics**

The end result bacterial resistance is to render the antibiotic useless against the pathogenic microbes.

- Bacteria acquire resistance through one of the following
  - Spontaneous genetic mutations (vertical evolution) - OR
  - Acquiring new genetic material from resistant bacteria (horizontal evolution)
    - This exchange of genetic material can occur between strains of the same species or between different bacteria species
- Mechanisms for bacterial resistance to an antimicrobial agent
  - Altering the cell wall target protein to which an antibiotic binds
  - Altering the outer membrane protein channels (required by the antibiotic for cell entry)
  - Up-regulating pumps that expel the antibiotic from the cell
  - Producing enzymes that inactivate the antibiotic
    - i.e. Beta-lactamase

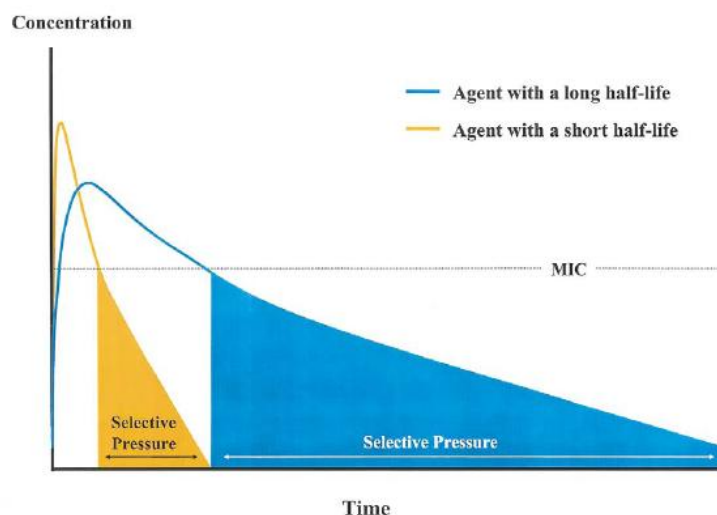
### **Controlling Resistant Bacterial Proliferation**

The ability of antibiotic-resistant bacteria to proliferate is dependent on several factors

- Exposure to antibiotics

- The more exposure a bacteria has to a given antibiotic, the greater the chance for microbes with resistant genetic material to be selected out
  - Up to 50% of antimicrobial usage in humans is inappropriate<sup>(12)</sup>
  - Reduction in the use of antibiotics has been shown to reduce antibiotic resistance<sup>(13,14)</sup>
    - Acquiring antibiotic resistance typically confers a biological fitness cost on bacteria
    - Bacteria with a genetic ability to develop antibiotic resistance maintain a survival advantage over other bacteria of the same species only if and when exposed to selective pressure from antibiotic exposure
    - In the absence of antibiotic exposure, these resistant bacteria lose any survival advantage
- Choice of antibiotic
  - Factors influencing an antibiotic's capacity to induce resistance include
    - Elimination half-life and pharmacodynamics
      - Use of antibiotics with long half-lives can result in extended periods of time during which drug concentrations dip below the Minimum Inhibitory Concentration (MIC) allowing the emergence of resistant strains (Figure 1)
      - Bacteriostatic antibiotics (sulfa, tetracyclines, Clindamycin, macrolides, etc.) may also be more likely to promote the development of resistant strains
      - Third-generation cephalosporins have been identified as agents whose use should be restricted because of their high propensity to induce extended-spectrum beta-lactamase (ESBL) expression in gram-negative bacteria and Vancomycin resistance in enterococcus<sup>(15)</sup>
      - Interventions in which fourth-generation cephalosporins are substituted for third-generation cephalosporins have shown significant reduction in the development of infections with resistant organisms<sup>(16)</sup>

**Figure 1**<sup>(17)</sup> Antibiotics with longer half-lives (e.g. azithromycin) will also have a larger window during which sub-therapeutic concentration (>MIC) that may allow for resistant organisms to develop.



## Adverse outcomes from Antibiotic Use

While antibiotics provide immense benefit, saving countless lives and reducing the morbidity of common bacterial infections, they are not without risks. Every antimicrobial agent carries risks and side-effects. Beta-lactams and sulfa antibiotics are the most common antibiotic culprits for the development of drug rashes, drug fever, serum sickness and anaphylaxis. They are also the most likely antibiotics to produce leucopenia or thrombocytopenia.

### **Clostridium difficile-associated Diarrhea (CDAD)**

CDAD illustrates one of the strongest arguments for antimicrobial stewardship. CDAD has always been the one of most common nosocomial infections, but in recent years it has surged in virulence creating significantly higher morbidity and mortality.<sup>(12)</sup> Studies have shown that hospitalized patients acquire *Clostridium difficile* through transmission from health care workers, other patients or environmental objects. Infection control measures such as patient isolation, strict hand hygiene, and environmental cleaning have been shown to help control the spread of the bacteria.<sup>(18)</sup> *Clostridium difficile* spores are not killed by alcohol-based disinfectants and can survive for months in the environment.

***Washing hands with soap and water is recommended to prevent the spread of CDAD because *Clostridium difficile* spores are not killed by alcohol-based hand wash.<sup>(18)</sup>***

A clinical infection of *C. difficile* (colitis with diarrhea) is almost uniformly associated with using antibiotics in the hospital setting. Almost any antibiotic may induce *C. difficile* infections, but second- and third-generation cephalosporins, clindamycin, and broad spectrum penicillins are most frequently implicated. A recently recognized hyper-virulent strain of *C. difficile* is resistant to fluoroquinolones, and use of this class of antibiotic may carry the highest risk for inducing CDAD.<sup>(19)</sup>

Good antimicrobial stewardship has been consistently shown to decrease the incidence of *C. difficile* infections through:<sup>(18)</sup>

- Avoiding inappropriate prescribing
- Restricting the use of high-risk antibiotics
- Reducing unnecessary multi-drug regimens
- Avoiding superfluous long-term therapy

Recent studies have also implicated proton pump inhibitors (PPI) for the increased incidence of pseudomembranous colitis. PPI use was associated with a tripling of the risk for developing *C. difficile* colitis at one hospital.<sup>(20)</sup>

## Inpatient Antimicrobial Stewardship

Studies have shown that effective antimicrobial stewardship is commensal with reducing the infections and associated mortality caused by resistant organisms.<sup>(16, 21)</sup> Antimicrobial stewardship involves selecting the most appropriate drug at its optimal dosage and duration of therapy to eradicate an infection while minimizing side effects and pressures for the

selection of resistant strains.<sup>(22)</sup> Making an appropriate antimicrobial choice starts with knowledge of infectious diseases and the possible pathogens involved in particular infections, as well as understanding which organisms are susceptible to a given antimicrobial agent (local patterns of resistance) and whether that agent is capable of reaching the infection site.<sup>(23)</sup> An over-reliance on antimicrobial chemotherapy has led to the consequent emergence of antimicrobial resistance. To be successful, inpatient antimicrobial stewardship must work in concert with a strong infection control program to reduce nosocomial infections and limit inappropriate antibiotic use.

### **Reducing nosocomial infections**

The role of personal and institutional hygiene must be re-emphasized by using well-known methods for preventing the spread of infectious agents.<sup>(23)</sup> UniNet facilities are taking this call to action seriously through:

- Staff education
- Monitoring factors contributing to the transmission of infection from person to person
- Using contact and/or respiratory isolation for patients with highly resistant pathogens
- Implementing computer software to monitor the identification and management of resistant pathogens
- Compliance with hand hygiene recommendations
- Monitoring compliance with care bundles for central line insertion, ventilator management

### **Empiric Antibiotic Selection**

While it may take days to properly identify an infecting microbe and determine antimicrobial sensitivity, patients with serious infections require prompt treatment with appropriate empiric coverage. Failure to properly cover offending agents with empiric antibiotics increases morbidity and mortality in these critically ill patients.<sup>(24-26)</sup>

- Select empiric antibiotics that cover the most-likely offending agents
- Identify patients at risk for resistant pathogens<sup>(27,28)</sup>
  - Previous hospitalization (in the past year)
  - Long-term hemodialysis
  - ICU admission
  - Broad spectrum antibiotics in the past 90 days
  - Tube feeding
  - Nursing home or long term care resident
- De-escalate the antibiotic regimen based on culture results, selecting the narrowest feasible antibiotic spectrum to effectively treat the infection

Inadequate treatment of infection is the most important risk factor for hospital mortality.<sup>(29)</sup>

### **Duration of Treatment Considerations**

- Ineffective antibiotics must be quickly discontinued after cultures identify the infecting bacteria
- Unnecessary continuation of broad spectrum empiric coverage increases a patient's risk of CDAD and yeast infections, while promoting bacterial resistance

- Continuation of treatment despite a negative infectious work-up adds to selective pressure without providing evidence of patient benefit<sup>(30)</sup>
- Duration of therapy with an antimicrobial should be defined in accordance with national guidelines because efforts to appropriately limit the duration of treatment are associated with reduced resistance without a reduction in efficacy<sup>(31)</sup>

### **Antibiotics around Surgery**

Studies have shown that continuing prophylactic antibiotics beyond 24 hours after surgery is associated with the development of vancomycin-resistant Enterococcus, cephalosporin-resistant Enterobacteriaceae, and MRSA<sup>(32,33)</sup>

- In recent years, national quality organizations have joined the war on antimicrobial resistance by monitoring proper use of prophylactic antibiotics in surgery
  - Core measures for quality documentation required by The Joint Commission for the Accreditation of Hospitals (JCAHO) and the Centers for Medicare and Medicaid (CMS) have had a significant impact on reducing unnecessary or inappropriate antibiotic use in surgical patients<sup>(34)</sup> through attention to:
    - 1) Antibiotic selection
    - 2) Timing of dose prior to surgery
    - 3) Discontinuation of antibiotics within 24 hours (48 hours for cardiac surgeries)
- It is estimated that 1 in every 10 surgical patients develops a health care-associated infection<sup>(35)</sup>

### **Surgical Site Infections (SSI)**

- Most are caused by organisms that reside on the skin, i.e., Staphylococcus aureus, coag negative Staphylococcus and Enterococcus species
- Resistance to the antibiotics commonly used for surgical prophylaxis has been observed in these organisms
- Surgical site infections with resistant organisms are associated with worse patient outcomes
  - A study published in 2003 reported a 12-fold increase in 90-day mortality in patients with MRSA surgical site infections (SSI) compared to patients without an SSI
- Risk factors for SSI include obesity, advanced age, diabetes mellitus, malnutrition, prolonged preoperative stay, infection at a remote site, duration of surgery, surgery technique, presence of drains, inappropriate use of antimicrobial prophylaxis, perioperative temperature, and poor postoperative glycemic control
- Preventing SSI
  - Preoperative skin antisepsis has been shown to reduce SSI
  - Studies suggest a 30-40% reduction in SSI with chlorhexidine compared with iodine<sup>(36,37)</sup>
  - Peri-operative temperature and glucose control (in cardiac surgeries) have also been shown to reduce SSI<sup>(38,39)</sup>

## Recap: Key Components of Inpatient Antimicrobial Stewardship

1. Develop and utilize hospital-approved guidelines for antibiotics to help insure the appropriate selection of empiric treatment
  - Refer to hospital antibiograms and local resistance patterns to help guide empiric antibiotic choice
  - Standard order sets for pneumonia have been shown to reduce excessive use of antibiotics and length of stay<sup>(40)</sup>
    - Standardized order sets have been implemented in all UniNet hospitals for treatment of pneumonia and sepsis as well as guidelines for the appropriate use of vancomycin and aminoglycosides
2. Obtain cultures to maximize the chances of identifying the responsible pathogen
  - Insure proper collection and handling of specimens
3. Discontinue unnecessary empiric antibiotics after culture results are known
  - Reevaluate the need for antibiotics after 48-72 hours if cultures are negative<sup>(41,42)</sup>
  - Empiric coverage of MRSA and gram-negative enterics should be discontinued if diagnostic tests fail to identify their presence in patients with nosocomial pneumonia<sup>(42)</sup>
  - Consider non-infectious causes of fever and leukocytosis
4. Cover pathogens identified on cultures with the narrowest possible spectrum of antibiotics
5. Employ multi-drug coverage only in specifically necessary instances
  - The American Thoracic Society (ATS) / Infectious Diseases Society of America (IDSA) guidelines recommend combination therapy to broaden empiric therapy and insure adequate coverage<sup>(43,44)</sup>
  - Switching to a single drug to treat the specific pathogen is usually possible according to culture and sensitivity information, **EXCEPT** for the following:
    - **Pseudomonas** infections - dual coverage has been shown to reduce mortality in treating serious infections<sup>(45)</sup>
      - May help prevent the development of resistance during treatment
    - Active **tuberculosis**
      - At least two drugs – both with demonstrated mycobacterium susceptibility
    - **Helicobacter pylori induced-gastric ulcer**
    - **Endocarditis**<sup>(46)</sup>
  - Although synergism has been shown for many antibiotic combinations and bacterial species (including Klebsiella, Enterobacter, and E. coli), clinical benefit has not been demonstrated except for pseudomonas
6. Avoid unnecessarily prolonged course of treatment
  - a. 3-days for uncomplicated urinary tract infection in women<sup>(47)</sup>
  - b. 5 days for mild-moderate community-acquired pneumonia if afebrile for 48-72 hours and no more than one sign of clinical instability<sup>(48)</sup>

***Empiric antibiotic coverage must be modified once a pathogen (or no pathogen) is identified in order to limit unnecessary exposure of antibiotics***

Hospitals have implemented a variety of strategies trying to provide effective antimicrobial stewardship. However, according to the medical literature, the **only** programs that have

demonstrated a real impact on antimicrobial utilization have been prospective interventional programs using<sup>(49, 50)</sup>

- ✓ Prior authorization
- ✓ Formulary restrictions
- ✓ Concurrent review with feedback

## **On the Horizon: Procalcitonin**

Current diagnostic tests for bacterial infections are limited by their low sensitivity (e.g. blood cultures), low specificity (e.g. sputum cultures) and the time delay to get results. Specificity is also low with inflammatory markers like C-reactive protein and erythrocyte sedimentation rates. Procalcitonin has recently stimulated interest as a potentially more specific marker for bacterial infections. Procalcitonin is produced in the presence of bacterial endotoxins and proinflammatory mediators released in response to bacterial infections. Procalcitonin levels correlate with the extent and severity of bacterial infections, and are not attenuated by corticosteroids. Levels increase within 6-12 hours of an infection and halve daily when the infection is properly treated.<sup>(51)</sup> Up-regulation of procalcitonin is attenuated by interferon- $\gamma$  (a cytokine released in response to viral infections) making it an effective aid for differentiating between viral and bacterial infections.<sup>(52)</sup> Procalcitonin has been studied as a diagnostic tool and a guide to antibiotic therapy with a variety of bacterial infections. The strongest evidence supporting the use of procalcitonin is in upper- and lower-respiratory tract infections and in severe sepsis.<sup>(53)</sup> Used as part of treatment algorithms, procalcitonin has been shown to reduce antibiotic use by documenting the resolution of infection.<sup>(54)</sup>

## **Bad Bugs in the House**

### **I. Methicillin-resistant Staphylococcus aureus (MRSA)**

Staphylococcus aureus could be the poster (child) bacteria for the antimicrobial stewardship cause. This ubiquitous pathogen has demonstrated the capacity to evade all major antibacterial drug classes, either through horizontal transfer of genetic material conveying resistance from other bacteria, or through mutation of existing genetic material.

As noted above, resistance to penicillin was observed soon after the drug was released for widespread use. By the 1960s, 80% of Staph aureus was resistant to penicillin.<sup>(55)</sup> Released in 1959, Methicillin was the first of many penicillinase-fast penicillins brought to market, which provided a brief reprieve from the staph onslaught. Methicillin-resistant Staphylococcus aureus was rarely seen during the 1960's, but became the most prominent nosocomial-associated pathogen by the late 1970's.

For staph to develop resistance to Methicillin, it must accrue a large genetic cassette. Detailed genetic studies have demonstrated that this variation has occurred only a few times, which means that the world-wide dissemination of MRSA has come from only a few clonal types, rather than being the result of frequent formations.<sup>(9,56)</sup>

Because the genes conveying methicillin-resistance also reduced virulence and fitness, MRSA bacteria were initially capable of infecting only susceptible hospitalized patients and others with weakened immune systems. However, in the past decade more virulent strains of MRSA have emerged which have successfully infected healthy victims and created a sustained presence in the community i.e., Community-acquired MRSA (CA-MRSA).<sup>(57)</sup>

- CA-MRSA represents the majority of staph infections outside the hospital and is becoming more prevalent within hospitals
- Up to 90% involve skin or soft tissues (e.g. furuncles, carbuncles), although necrotizing pneumonias (especially post-influenza), septic arthritis and bacteremia/sepsis have been reported

### **Spreading MRSA**

- Patient-to-patient contact is thought to be the primary mode of transmission for hospital-acquired MRSA, primarily via the hands of health care workers<sup>(23)</sup>
- Colonization with MRSA has been shown to precede the development of overt infections in many hospitalized patients<sup>(58)</sup>
- Colonization with CA-MRSA is a major risk factor for the development of subsequent infection
  - Direct skin-to-skin contact plays a major role in the transmission of CA-MRSA

### **Strategies to prevent the spread of MRSA within hospitals**

1. Aggressive environmental cleaning
2. Patient isolation and contact precautions
3. Hand hygiene among caregivers
4. There have been calls for surveillance cultures to screen all patients admitted to the hospital because up to 80% of colonized hospitalized patients will not be identified from clinical cultures<sup>(59)</sup>
  - Cultures of the anterior nares will correctly identify 80% of patients colonized with *Staphylococcus aureus*<sup>(60)</sup>
    - Efforts to decolonize patients who are found to harbor MRSA in their anterior nares have achieved only marginal success and universal decolonization is not recommended
    - No standard regimen has been identified
    - A 5-10 day course of intranasal mupirocin, and 2% chlorhexidine washes or dilute bleach baths is recommended if decolonization is warranted<sup>(64)</sup>
      - Oral antibiotics are not routinely recommended for decolonization because of concerns regarding resistance<sup>(64)</sup>
        - Resistance to mupirocin has been observed as a result of wide scale decolonization programs
      - This strategy may be appropriate for colonized patients with<sup>(23, 61)</sup>
        - recurrent skin or soft tissue infections
        - surgical implant(s)
        - liver and stem cell transplant
        - dialysis
5. Decontaminating stethoscopes - Staph has been shown to survive for long periods of time on a variety of surfaces including stethoscopes<sup>(62)</sup>

***Stethoscopes should be decontaminated between patients by using either 1) an alcohol wipe or 2) an ethanol-based hand cleanser (while cleaning hands)<sup>(63)</sup>***

### **Treatment**

- For simple abscesses or boils, incision and drainage alone is likely to be adequate<sup>(64)</sup>
- Empiric coverage for MRSA is appropriate in patients with nosocomial infections
  - First line – Vancomycin
    - IV only
  - Linazolid (Zyvox) may be a better choice in patients with MRSA pneumonia, but is not indicated in patients with catheter-related bacteremia or endocarditis<sup>(65,66)</sup>
    - Available in IV or oral formulations
  - Ceftaroline (Teflaro)
    - Beta-lactam safety
    - IV only
  - Tigecycline (Tygasil)
    - Bacteriostatic versus MRSA
    - No clinical trials for bacteremia
  - Daptomycin also has activity against MRSA and is indicated for skin and soft tissue infection and bacteremia with resistant staphylococcus
    - May be inactivated by surfactant, and therefore should **not be used for pneumonia**
    - Not recommended as part of empiric treatment
- Empiric coverage for CA-MRSA to manage outpatient skin and soft tissue infections include:
  - (off label agents, non FDA approved) Trimethoprim-sulfamethoxazole, clindamycin, doxycycline, or minocycline<sup>(64)</sup>
  - Linazolid

## **II. Vancomycin-resistant Enterococcus (VRE)**

- Incidence of VRE
  - Enterococcus is the third most frequent cause of hospital-acquired bloodstream infections in the United States<sup>(67)</sup>
    - Enterococcus faecalis remains susceptible to a variety of antibiotics (except Synercid)
    - Enterococcus faecium has acquired resistance to most common antibiotics including vancomycin
      - 66% of E. faecium isolates in UniNet hospitals were resistant to vancomycin in 2008
  - Enterococci contain transposons and plasmids that allow for transfer of genetic material to other bacteria
    - VRE has been identified as the source for vancomycin resistance found in the first cases of vancomycin resistant Staphylococcus aureus<sup>(68)</sup>
- **Recommended Treatment of VRE**
  - If VRE is a suspected pathogen, alternative agents such as linezolid, daptomycin or Synercid should be considered as part of empiric therapy<sup>(69)</sup>

- 97% of isolates from UniNet facilities in 2010 demonstrated sensitivity to linazolid and Synercid

### III. Multi-drug resistant gram-negative bacteria

Gram-negative bacteria are significant causes of health care-associated infections. They survive exposure to a constant barrage of antibiotics, especially in the intensive care unit, by acquiring the ability to resist the effects of most antibiotics. The Enterobacteriaceae family has flourished in this setting through the accrual of genes capable of producing extended-spectrum beta-lactamases (ESBL) and include

- Escherichia coli
- Klebsiella
- Enterobacter species

ESBL enzyme inactivates penicillins, cephalosporins and aztreonam. To make matters worse, the genes that confer the production of ESBL are frequently found on the same plasmid as genes that encode resistance to aminoglycosides and sulfonamides.<sup>(69)</sup>

#### Recommended Treatment

- Carbapenems (meropenem or doripenem) have been considered to be the preferred agents for treatment of serious infections caused by ESBL-producing Enterobacteriaceae<sup>(70)</sup>
  - Resistance to this class of antibiotics has emerged in a number of Enterobacteriaceae such as:<sup>(71)</sup>
    - Klebsiella
    - Citrobacter
    - E. coli
    - Salmonella
  - Colistin or tigecycline are recommended treatment for carbapenem resistant strains<sup>(72)</sup>
- Many Enterobacteriaceae have also developed high-level resistance to quinolones, making adequate empiric coverage difficult if not impossible to achieve
- Infections with multi-drug resistant gram-negative bacteria are associated with increased mortality, length of stay and overall cost of care compared with infections with susceptible organisms<sup>(73, 74)</sup>

Like MRSA, multi-drug resistant gram-negative bacteria have spread beyond the hospital walls and are now seen in community-acquired urinary tract infections.<sup>(70)</sup>

### Conclusion

The development of antimicrobial medications was one of the great advances in health care in the past century, transforming previously lethal infections into treatable conditions. However, microbes have not given up the fight and have continued to find new ways to withstand the attack. At this point, multi-drug resistant organisms threaten to reverse nearly a century of success and return us to an era depicted in Sir Samuel Luke Fildes'

painting “*The Doctor*,” in which a dedicated, but weary, physician sits at a child’s bedside, helpless to combat the infection that threatens the little girl’s life.

Physicians today must show the same dedication to patients by avoiding inappropriate use of antimicrobial agents and thus preserving the antibiotics still available to combat potentially life-threatening infections.



## References

1. Jawetz E. Antimicrobial chemotherapy. *Ann Rev Microbiol* 1956;10:85-114.
2. Spellberg B. Dr. William H. Stewart: mistaken or maligned? *Clin Infect Dis*. 2008 47(2): 294. doi: 10.1086/589579 Accessed December 2, 2011 at: <http://cid.oxfordjournals.org/content/47/2/294.1.full>
3. Owens R. Antimicrobial stewardship: concepts and strategies in the 21<sup>st</sup> century. *Diagn Microbiol Infect Dis* 2008;61:110-128.
4. Boucher H, Talbot G, Bradley J, Edwards J, et al. Bad bugs, no drugs: No ESCAPE! An update from the Infectious Disease Society of America. *Clin Infect Dis* 2009;48:1-12.
5. Spellberg B, Guidos R, Bradley J, et al. The epidemic of antibiotic-resistant infections: A call to action for the medical community from the Infectious Diseases Society of America. *Clin Infect Dis* 2008;46:155-164.
6. Barber M, Rozwadowska-Dowzenko M. Infection by penicillin-resistant staphylococci. *Lancet* 1948;252:641-644.

7. Tamma P, Cosgrove S. Antimicrobial Stewardship. *Infect Dis Clin N Am* 2011;25:245-260
8. Klevens R, Richards C, Horan T, et al. Estimating health care-associated infections and deaths in U.S. hospitals, 2002. Accessed December 2, 2011 at: [http://www.cdc.gov/ncidod/dhqp/pdf/hicpac/infections\\_deaths.pdf](http://www.cdc.gov/ncidod/dhqp/pdf/hicpac/infections_deaths.pdf)
9. Rice L. Federal funding for the study of antimicrobial resistance in nosocomial pathogens: no ESKAPE. *J Infect Dis* 2008;197:1079-1081.
10. Paskovaty A, Pflomm J, Myke N, Seo S. A multidisciplinary approach to antimicrobial stewardship; evolution into the 21<sup>st</sup> century. *Int J Antimicrob Agents* 1997;24:471-485.
11. Tenover F. Mechanism of Antimicrobial Resistance in Bacteria. *Am J Med* 2006;119:S3-S10.
12. Hillier S, Roberts Z, Dunstan F, et al. Containing antibiotic resistance: demonstration of decreased antibiotic resistant coliform urinary tract infections with reduction in antibiotic prescribing by general medical practices. *Br J Gen Pract* 2007;57:785-792.
13. Cohen R, Levy C, de La Rocque F, et al. Impact of pneumococcal conjugate vaccine and of reduction of antibiotic use on nasopharyngeal carriage of nonsusceptible pneumococci in children with acute otitis media. *Pediatr Infect Dis* 2006;25:1001-1007.
14. Owens R, Rice L. Hospital-based strategies for combating resistance. *Clin Infect Dis* 2006;42:S173-S181.
15. Du B, Chen D, Liu D, et al. Restriction of third-generation cephalosporin use decreases infection-related mortality. *Crit Care Med* 2003;31:1088-1093.
16. Carling P, Fung T, Killion A, et al. Favorable impact of a multidisciplinary antibiotic management program conducted during 7 years. *Infect Control Hosp Epidemiol* 2003;24:699-706.
17. Anon J, Jacobs M, Poole M. et al. Sinus and Allergy Health Partnership Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. *Otolaryngol Head Neck Surg* 2004;130:S1-S45
18. Vonberg R, Kuijper E, Wilcox M, et al. Infection control measures to limit the spread of clostridium difficile. *Clin Microbiol Infect* 2008;14(Suppl. 5): 2-20.
19. Pepin J, Saheb N, Coulombe M, et al. Emergence of fluoroquinolones as the predominant risk factor for clostridium difficile-associated diarrhea: a cohort study during an epidemic in Quebec. *Clin Infect Dis* 2005;41:1254-1260.
20. 51<sup>st</sup> Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC): Abstract K-201. Presented September 17, 2011.
21. Fishman N. Antimicrobial Stewardship. *Am J Med* 2006;119:S53-S61.
22. Humphreys H, Grundmann H, Skov R, et al. Prevention and control of methicillin-resistant Staphylococcus aureus. *Clin Microbiol Infect* 2009;15:120-124.
23. Harbarth S, Garbino J, Pugin J, et al. Inappropriate initial antimicrobial therapy and its effect on survival in a clinical trial of immunomodulating therapy for severe sepsis. *Am J Med* 2003;115:529-535.
24. Dupont H, Mentec H, Sollet J, Bleichner G. Impact of appropriateness of initial antibiotic therapy on the outcome of ventilator-associated pneumonia. *Intensive Care Med* 2001;27:355-362.
25. Valles J, Rello J, Ochagavia A, et al. Community-acquired bloodstream infection in critically ill adult patients. *Chest* 2003;123:1615-1624

26. Kollef M, Sherman G, Ward S, Fraser V. Inadequate antimicrobial treatment of infections. *Chest* 1999;115:462-474.
27. Shorr A, Zilberberg M, Micek S, Kollef M. Prediction of infection due to antibiotic-resistant bacteria by select risk factors for health care-associated pneumonia. *Arch Intern Med* 2008;168:1393-1399.
28. Shindo Y, Sato S, Maruyama E, et al. Health-care associated pneumonia among hospitalized patients in a Japanese community hospital. *Chest* 2009;135:633-640.
29. Aarts M, Brun-Buisson C, Cook D, et al. Antibiotic management of suspected nosocomial ICU-acquired infection: does prolonged empiric therapy improve outcome? *Intensive Care Med* 2007;33:1369-1378.
30. Marra A, Maria de Almeida S, Correa L, et al. The effect of limiting antimicrobial therapy duration on antimicrobial resistance in the critical care setting. *Am J Infect Control* 2009;37:204-209.
31. Harbarth S, Samore M, Lichtenberg D, et al. Prolonged antibiotic prophylaxis after cardiovascular surgery and its effect on surgical site infections and antimicrobial resistance. *Circulation* 2000;101:2916-2921.
32. Evans H, Sawyer R. Preventing bacteria resistance in surgical patients. *Surg Clin N Am* 2009;89:501-519.
33. Improving America's Hospitals. The Joint Commission's Annual Report on Quality and Safety, 2011. Accessed December 2, 2011 at: [http://www.jointcommission.org/2011\\_annual\\_report/](http://www.jointcommission.org/2011_annual_report/)
34. Engemann J, Carmeli Y, Cosgrove S, et al. Adverse clinical and economic outcomes attributable to methicillin resistance among patients with Staphylococcus aureus surgical site infections. *Clin Infect Dis* 2003;36:592-598.
35. Vazquez-Aragon P, Lizan-Garcia M, Cascales-Sanchez P, et al. Nosocomial infection and related risk factors in a general surgery service: a prospective study. *J Infect* 2003;46:17-22.
36. Darouiche R, Wall M, Itani K, Otterson M, et al. Chlorhexidine-alcohol versus povidone-iodine for surgical-site antisepsis. *NEJM* 2010;362:18-26.
37. Lee I, Agarwal R, Lee B, Fishman N, Umscheid C. Systematic review and cost analysis comparing use of Chlorhexidine with use of iodine for preoperative skin antisepsis to prevent surgical site infection. *Infect Control Hosp Epidemiol* 2010;31:1219-1229.
38. Kurz A, Sessler D, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. *NEJM* 1996;334:1209-1215.
39. Zerr K, Furnary A, Grunkemeier G, et al. Glucose control lowers the risk of wound infection in diabetics after open heart operations. *Ann Thorac Surg.* 1997;63:356-361.
40. Marrie T, Lau C, Wheeler S, et al. A controlled trial of a critical pathway for the treatment of community-acquired pneumonia. *JAMA* 2000;283:749-755.
41. Kaiser J, Casset J, Lewno M. Should antibiotics be discontinued at 48 hours for negative late-onset sepsis evaluations in the neonatal intensive care unit? *J perinatology* 2002;22:45-447.
42. Singh N, Rogers P, Atwood C, et al. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. *Am J Respir Crit Care Med* 2000;162:505-511.

43. Mandell L, Wunderink R, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007;44:S27-S72.
44. American Thoracic Society; Infectious Diseases Society of America (2005) Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005;171:338-416.
45. Safdar N, Handelsman J, Maki D. Does combination antimicrobial therapy reduce mortality in gram-negative bacteremia? A meta-analysis. *Lancet Infect Dis* 2004;4:519-527.
46. Baddour L, Wilson W, Bayer A, et al. Diagnosis, antimicrobial therapy, and management of complications: A statement for health care professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association Executive Summary. *Circulation* 2005;111:3167-3184.
47. Milo G, Katchman E, Paul M, et al. Duration of antibacterial treatment for uncomplicated urinary tract infection in women. *Cochrane Database Syst Rev* 2005;(2):CD004682.
48. Mandell L, Wunderink R, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007;44:S27-S72.
49. Carling P, Fung T, Coldiron J. Parenteral antibiotic use in acute-care hospitals: a standardized analysis of 14 institutions. *Clin Infect Dis* 1999;29:1189-1196.
50. Lesprit P, Brun-Buisson C. Hospital antibiotic stewardship. *Curr Opin Infect Dis* 2008;21:344-349.
51. Becker K, Procalcitonin and the calcitonin gene family of peptides in inflammation, infection, and sepsis. A journey from calcitonin back to its precursors. *J Clin Endocrinol Metab* 2004;89:1512-1525.
52. Linscheid P, Seboek D, Nylen E, et al. In vitro and in vivo calcitonin I gene expression in parenchymal cells: A novel product of human adipose tissue. *Endocrinology* 2003;144:5578-5584.
53. Schuetz P, Albrich A, Mueller B. Procalcitonin for diagnosis of infection and guide to antibiotic decisions: past, present and future. *BMC Med* 2011;9:107-116.
54. Schuetz P, Chiappa V, Briel M, Greenwald J. Procalcitonin algorithms for antibiotic therapy decisions. *Arch Intern Med* 2011;171:1322-1321.
55. Appelbaum P. Microbiology of antibiotic resistance in *Staphylococcus aureus*. *Clin Infect Dis* 2007;45: S165-170.
56. Kreiswirth B, Kornblum J. Evidence for a clonal origin of methicillin resistance in *Staphylococcus aureus*. *Science* 1993;259:227-230.
57. Miller L, An Diep B. Colonization, fomites and virulence: Rethinking the pathogenesis of community-associated methicillin-resistant *Staphylococcus aureus* infection. *Clin Infect Dis* 2008;46:752-760.
58. Williams R. Healthy carriage of *Staphylococcus aureus*: its prevalence and importance. *Bacteriol Rev* 1963;27:56-71.
59. Mutto C, Jernigan J, Ostrowsky B, et al. SHEA guidelines for preventing nosocomial transmission of multi-drug-resistant strains of *Staphylococcus aureus* and *Enterococcus*. *Infect Control Hosp Epidemiol* 2003;24:362-386.

60. Que T, Ho P, Yip K, et al. Three-year study of targeted screening for methicillin-resistant *Staphylococcus aureus* at hospital admission. *Eur J Clin Microbiol* 2003;22:268-270.
61. Simor A, Daneman N. *Staphylococcus aureus* decolonization as a prevention strategy. *Infect Dis Clin N Am* 2009;23:133-151.
62. Williams C, Davis D. Methicillin-resistant *Staphylococcus aureus* fomite survival. *Clin Lab Sci* 2009;22:34-38.
63. Lecat P, Cropp E, McCord G, Nairmeen A. Ethanol-based cleanser versus isopropyl alcohol to decontaminate stethoscopes. *Am J Infect Control* 2009;37:241-243.
64. Liu C, Bayer A, Cosgrove S, Daum R, et al. Clinical Practice guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus aureus* Infections in Adults and Children. *Clin Infect Dis* 2011;52:e18-e55.
65. Wunderink R, Rello J, Cammarata S, et al. Linezolid vs vancomycin: analysis of two double-blind trials of patients with methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia. *Chest* 2003;124:1789-1797.
66. Food and Drug Administration Information for Healthcare Professionals: Linezolid (marked as Zyvox) Silver Springs, MD. March 16, 2007. Accessed December 2, 2011 at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientandProviders/ucm101503.htm>
67. Wisplinghoff H, Bischoff T, Tallent S, et al. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. *Clin Infect Dis* 2004;39:309-317.
68. Chang S, Seivert D, Hageman J, et al. Infection with vancomycin-resistant *Staphylococcus aureus* containing the *vanA* resistant gene. *NEJM* 2003;348:1342-1347.
69. Volles D, Branam T. Antibiotics in the intensive care unit: Focus on agents for resistant pathogens. *Emerg Med Clin N Am* 2008;26:813-834.
70. Paterson D. Resistance in gram-negative bacteria: Enterobacteriaceae. *Am J Med* 2006;119:S20-S28.
71. Moellering R, Graybill J, McGowan J, Corey L. Antimicrobial resistance prevention initiative - an update: Proceedings of an expert panel on resistance. *Am J Med* 2007;120:S4-S25.
72. Peleg A, Hooper D. Hospital-acquired infections due to gram-negative bacteria. *NEJM* 2010;362:1804-1813.
73. Shorr A. Review of studies of the impact of gram-negative bacterial resistance on outcomes in the intensive care unit. *Crit Care Med* 2009;37:1463-1469.
74. Cosgrove S. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. *Clin Infect Dis* 2006;42:S82-S89.