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Special Antimicrobial Resistance Issue

Bad Bugs Including No ESKAPE—Antimicrobial Resistance in Hospitals and Communities Continues to Challenge

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Increased risk of antibiotic resistance continues to impact significantly our practices, while experts warn that antibiotic misuse and declining development of new medicines may render current antibiotics increasingly ineffective. Our patients and families are aware of some of our challenges [see "A Deadly Bug Invades Our Towns," in the December 7, 2008 *Parade Magazine* and "Battling Superbugs," the March 2009 AARP Bulletin series of articles addressing the methicillin-resistant *Staphylococcus aureus* (MRSA) epidemic and the rising threat of *Clostridium difficile*]. **It is in primary care practices that efforts to sustain the lifespan of current antibiotics must originate**.

The Infectious Diseases Society of America (IDSA) continues to view with concern the lean pipeline for novel therapeutics to treat drug-resistant infections. The IDSA's "Bad Bugs, No Drugs" initiative is focused on multidrug-resistant pathogens in the hospital and in the community coined the acronym ESKAPE bacteria – *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella* sp., *Acinetobacter baumanii*, *Pseudomonas aeruginosa*, and *Enterobacter* sp. representing two-thirds of all healthcare-associated infections.[1] **The following** discussion **relates the pragmatism of antimicrobial resistance to the** practitioner's **inpatient and outpatient** challenges **with a contemporary** epidemiologic and clinical perspective **of *Streptococcus pneumoniae* (SN), *Clostridium difficile* (CD), and community-associated methicillin-resistant *Staphylococcal aureus* (CA-MRSA).**

It is in primary care practices that efforts to sustain the lifespan of current antibiotics must originate.

ABSTRACT

The global burden of antibiotic resistance in 2010 occurs with limited future antimicrobial choices and with a need for the practitioner to make the most effective use of those antibiotics that are currently available to preserve their usefulness. Antibiotic selection for individual patients now impacts both inpatient and outpatient resistance, the carriage of more resistant and/or virulent bacteria, and more aggressive bacteria resulting in disease with increased complications, morbidity, and mortality.

This article addresses updated evidence, with an epidemiologic and clinical focus, pertaining to the new resistance and/or virulence challenges with *Streptococcus pneumoniae*, *Clostridium difficile,* and community-associated methicillin-resistant *Staphylococcus aureus* (MRSA). A pragmatic and clinical introduction to heteroresistant vancomycin-intermediate *Staphylococcal aureus* (hVISA) is accomplished and an important pharmacologic update on new vancomycin therapeutic guidelines is presented, with the clinical goal improved MRSA morbidity and mortality.

This special issue supplements earlier *Epi Notes* and DHEC website updates that address SN and CA-MRSA resistance challenges and outpatient clinical management.

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Over-Prescribing of Antibiotics: Truly Not a Benign Practice

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Patients with acute respiratory infections in the community seeking antibiotics typically emerge from an ambulatory care clinic or office rewarded for their visit with an antibiotic prescription in hand. Antibiotics are prescribed during nearly 1/5 of all outpatient physician visits annually.[1] Despite efforts to curb antibiotic prescribing, unnecessary antibiotic usage continues to be a widespread practice, as nearly 67% of adults with acute bronchitis received antibiotic therapy in 2005.[2] In considering acute respiratory tract infections in general, it has been estimated that 55% of antibiotic prescriptions are unnecessary.[3] Long-term effects of the over-prescribing of antibiotics such as the influence on local susceptibility rates and inherent pressures on emerging resistance patterns are well documented and usually stressed in outreach programs and professional communication meant to discourage unnecessary antibiotic use. Unfortunately, little attention has been paid to the negative short-term untoward effects of antibiotics, notably the **adverse drug effects (ADE)**, including allergic reactions. Overall, ADEs account for up to 2.8% of hospital admissions and are recognized as a leading cause of mortality in the United States.[4,5] ADEs secondary to antibiotics contribute greatly to these numbers and ultimately lead to an increase in office and emergency room visits, hospitalizations, healthcare costs and the potential for significant morbidity and mortality.

Stereotypically, antibiotics have been labeled by clinicians as a benign therapy with a consistently favorable risk: benefit profile. Emerging data does not support this notion, and in fact refutes it altogether. In an article published in June 2008, Shehab and colleagues describe an investigation of the rate and impact of ADEs secondary to antibiotics.[6] The authors reported that nearly 150,000 Emergency Department (ED) visits annually were due to adverse events associated with antibiotics. Approximately 80% of these adverse events were attributed to allergic reactions with beta-lactams, identified as the primary offenders.[6] Allergic-type reactions were typically mild in nature, however, significant life-threatening IgE-mediated anaphylactic reactions may occur in up to 1 in 5,000 to 10,000 patients posing a significant mortality risk.[7,8] Given the considerable availability of antibiotic samples and frequent “pharmacy shopping” among patients, allergy reporting is increasingly important, yet more cumbersome and less accurate, posing an even greater threat to the public.

Shehab and colleagues reported the number of ED visits to be highest in patients aged 15-44, comprising over 40% of all visits.[6] Pediatric patients (< 15 years) accounted for nearly 25% of all ED visits secondary to ADEs from antibiotics, with infants less than 1 year accounting for the highest overall ED visit rate of 15.9 ED visits per 10,000 outpatient prescription visits. Nearly 15% of visits were observed in the elderly population (> 65 years of age).[6] These rates of ADEs are concerning as, in these particularly vulnerable populations, significant morbidity may result from moderate-to-severe ADEs. Approximately 1% of all ED visits resulted in hospitalization.[6] The average cost of an admission secondary to an ADE is estimated to be $4000 - $6000 per admission – which should be considered avoidable costs.[4]

Which adverse drug effects are most common? Gastrointestinal complaints or symptoms are a common ADE associated with antibiotic therapy. Up to 25% of patients will develop antibiotic-associated diarrhea (AAD).[8] Although causing personal discomfort and anxiety, AAD is generally considered a mild side-effect carrying very low rates of morbidity and mortality. However, of significant concern is the development of *Clostridium difficile*- infection/diarrhea (CDI). Many believe use of antibiotics is the single greatest risk factor for developing CDI.[9] Although primarily a nosocomially-acquired pathogen, reports of community-acquired infections continue to accumulate. Clindamycin, 3rd generation cephalosporins and fluoroquinolones have been associated with the highest risk – but all antibiotics capable of altering the normal gastrointestinal flora should be considered associated risk factors for CDI.[9] CDIs can be associated with significant morbidity and sequelae, including prolonged hospitalization with attendant increased cost and the potential for death in high-risk patients.

Thus, the prescribing of antibiotics should not be considered a benign practice with little downside or negative short-term impact. Immediate ADEs secondary to antibiotics are real, significant and largely avoidable given the recognized shift in risk: benefit ratio for the patient. Both potential ADEs and startlingly rising rates of bacterial resistance should give the care provider pause before prescribing antibiotics in dealing with a case with a less than convincing causative bacterial infection.

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A Message from DHEC's Bureau of Disease Control

James "Jerry" Gibson, MD, MPH, State Epidemiologist, Director, SC DHEC Bureau of Disease Control

The increasing problem of antimicrobial resistance in healthcare associated and community associated infections continues to challenge the practicing clinician and affect the public's health. Recognizing this serious public health problem has resulted in this unique edition of the DHEC *Epi Notes* focusing entirely on antibiotic resistance and the individual clinician's decision making with each patient. Decisions on antimicrobials will now determine who in our community carries or is infected with the new, more virulent *Strep pneumoniae* isolates, the more virulent CA-MRSA isolates, or who experiences GI infection with the new hyper-virulent *C. difficile* isolates.

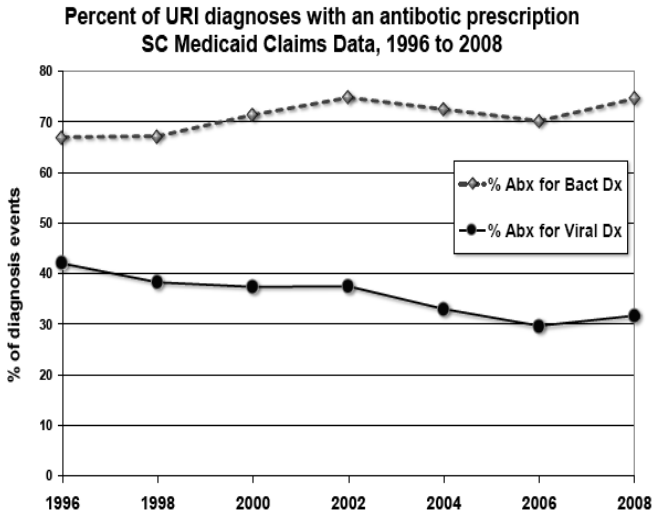
We hope the updated information in this *Epi Notes* issue will promote the most appropriate utilization of antimicrobials in your daily practice.

SC Careful Antibiotic Use (SC CAUse): Resources for the Practicing Clinician

Dixie F. Roberts, APRN, MPH, Director, Healthcare Infections and Antibiotic Resistance Section, SCDHEC Bureau of Disease Control

Antibiotics are essential and can be life-saving. However, antibiotic resistance is a major public health problem. Careful antibiotic use of antibiotics (stewardship) is critical to maintain their availability and to minimize any risks to individual patients. According to Centers for Disease Control and Prevention (CDC), more than ten million courses of antibiotics are prescribed each year for viral conditions, which do not benefit from antibiotics. It is recognized that these prescribing trends reflect the national downward trend over time; however, it is important that the antibiotic prescribing rates continue to decline. There is significant and growing evidence that a single prescription to an individual patient in the community or a broad spectrum antibiotic to a hospitalized patient now significantly affects each patient and the community.

DHEC collaborated with Pharmacy Professor, Dr. Mike Dickson, from the SC College of Pharmacy, Columbia to ascertain trends in antibiotic prescribing practices from SC Medicaid claims data for visits for common upper respiratory infections (URIs). Each visit was matched with the drug and the dose of the prescriptions filled. Evidence suggests that educational efforts by professional associations, public health, and other community efforts have been effective in decreasing over prescribing of antibiotics for viral URIs in South Carolina since 1998 *(as shown in the lower, solid line on the graphic.)* These data are available from the SC CAUse website.



The SC CAUse program has prepared resources for practicing clinicians in the community and in healthcare facilities to use in educating their patients about when antibiotics are not needed and to promote the judicious use of antibiotics in healthcare facilities (stewardship). SC Careful Antibiotic Use (CAUse) and Antimicrobial Stewardship information is available on the following websites:

- SC CAUse: www.scdhec.gov/sccause
- CDC Antimicrobial Resistance in healthcare facilities www.cdc.gov/ncidod/dhqp/ar.html
- CDC Get Smart About Antibiotics Campaign www.cdc.gov/getsmart/index.html

Get Smart About Antibiotics:
Because Sometimes the Best Medicine is No Medicine

DHEC SC CAUse is a partner with the CDC's Get Smart About Antibiotics Campaign and will be participating in the campaign for provider and community education throughout the year. This year, Get Smart About Antibiotics Week will coincide with Europe's community careful use education campaign to emphasize the global impact of antibiotic resistance. SC CAUse will be participating in Get Smart Week activities. We will be providing more information through our website.

Get Smart About Antibiotics Week - November 15 – 21, 2010

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The public and legislatures are becoming significantly aware of "superbugs," appropriate antibiotic use, and hand-washing in the hospital setting (healthcare workers clean their hands effectively only about half the time). On October 1, 2008, Medicare stopped paying for complications arising from certain infections and conditions that result from hospital care and are "reasonably preventable."

> Currently, there are no new classes of antibiotic entering late-stage clinical development. Since 2000, two new classes of antibiotics have been approved for use with none 1970-2000 compared with 10, 1930-1960.

The S.C. State Legislature in May 2006 passed the Hospital Infection Disclosure Act[2] designed to assure that the public has access to information on hospital acquired infections in each hospital along with recent legislation addressing resistance patterns within our state. **This is noteworthy in that all antimicrobial resistance problems come down to antimicrobial selective pressure and infection** control.[3]

Efforts to sustain the lifespan of current antibiotics are vital. Several major medical associations warn that antibiotic resistance is the number one problem facing the medical community. With most practices currently managing community infections successfully, experts worry providers will not have effective antibiotics to treat all patients in the future. One way to overcome antibiotic resistance would be to get more specific with treatment; for example, rapid *Streptococcus* pyogenes testing for sore throat /pharyngitis can reduce unnecessary antibiotic prescriptions by more than 50%. Another way for providers to address antibiotic resistance is to become educated about which drugs create the most antibiotic pressure, remembering that some are worse than others at driving resistance. This is especially the case when physicians use antibiotics at times much beyond what is needed (e.g., amoxicillin and amoxicillin clavulanate have much less of an effect on antibiotic pressure than macrolides and cephalosporins). Antibiotic usage at both patient and hospital levels correlates with the risk of multidrug-resistant bacteria, i.e., antimicrobial exposure increases the risk of MRSA acquisition 2-3 fold depending on drug class.[4]

Pneumococcus Epidemiology / Clinical Update

Asymptomatic nasopharyngeal (NP) carriage of pneumococci is an important factor in the development and transmission of pneumococcal disease, with carriage rates varying by serotype, ranging from 11-75% at any one time. Up to 54% of children carry pneumococci by one year of age.[5] NP carriage may occur in up to 60% of healthy preschool children and up to 30% of older children and adults.[6] Widespread use of pneumococcal conjugate vaccine (PCV7) resulted in decreases in invasive pneumococcal disease (IPD) among children and elderly persons with the incidence of pneumococcal disease caused by virulent clones of non-vaccine serotypes increasing.[73,74] **Significantly,** a more virulent appearing **non-vaccine serotype 19A has become the predominant cause of invasive disease in children**, (accounting for 44% of isolates in 8 children's hospitals)**.**[7,8,73] Massachusetts data over the recent half decade[9] have revealed non-vaccine serotypes as the etiology of 72-91% of invasive pneumococcal disease annually in children less than 5 years of age. Those same data demonstrate that the mortality from invasive pneumococcal disease in children less than one year of age is approximately ten times higher than for those aged 1-10 years – about 3% of whom develop invasive disease. Several studies have shown that nasopharyngeal carriage of 19A serotype has greatly increased (e.g., from 3.5% in 2000 to 19% in 2004) since the introduction of PCV7.[10,11] A recent study (sampling data was two-thirds noninvasive respiratory sources at 80 study sites) collected *S. pneumoniae* isolates from subjects < 14 years old with non-vaccine serotypes accounting for 89.1%, with serotype 19A most prevalent representing 30.5% of all isolates.[12]

> Clinical challenges grow with infections acquired in hospitals resulting in 99,000 patient deaths per year (hospital infections kill more Americans each year than AIDS, breast cancer, and automobile accidents combined).

Another study with *S. pneumoniae* tympanocentesis isolates revealed 40% were serotype 19A (the most common serotype isolated) with 23% of these resistant to multiple antimicrobial drugs including one otopathogen strain resistant to all FDA-approved antibiotics for treatment of acute otitis media in children.[13,14] Overall, the most recent literature suggests approximately 60-75% of *S. pneumoniae* otopathogen isolates are penicillin susceptible/intermediate in sensitivity. Recent epidemiology also suggests otopathogens in persistent,

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acute otitis media (AOM) and AOM treatment failure have changed with *H. influenza* (Hi) the predominant pathogen.[15] Three events are influencing *S. pneumoniae* epidemiologic trends – expansion of existing clones, introduction of new clones, and capsule switching. In 2005-2006, Pneumococcal macrolide resistance in the U.S. showed its first significant increase since 2000 with an increase from 34.1% to 39.4% with 50.4% resistance noted in respiratory isolates in children less than two years of age.[16] Because non-vaccine serotype replacement is significant, it appears prudent to continue a traditional approach to the management of the febrile young infant and child.[17]

Failure to achieve early bacterial eradication during antibiotic therapy for acute otitis media (AOM) increases clinical failure rates. Guidelines[18] for the treatment of AOM in children, including consideration of no treatment with select criteria, establish a clear hierarchy among the various antibacterials for treatment. The effect of treatment did not differ very much from one drug to another when AOM is caused by a penicillin-susceptible pneumococcus (range of failures 0-10% for all antibiotics studied). Major differences appear with non-susceptible pneumococci with cefdinir ineffective in eradicating most non-susceptible pneumococci. Azithromycin and trimethoprim are similar to placebo in eradicating resistant pneumococci. High doses of amoxicillin, amoxicillin/clavulanate, and 3 doses of ceftriaxone show significant efficacy in the eradication of non-susceptible pneumococci. One injection of ceftriaxone is insufficient against nonsusceptible pneumococci, with a bacteriologic failure rate of approximately 40%.[19]

The American Academy of Pediatrics guidelines[18] differentiate between the first episode of AOM or no AOM within the last 3 months, and recalcitrant, recurrent, or nonresponsive AOM. A limited choice of antibiotics is recommended. For first episode cases (simple, uncomplicated AOM), the choice is between regular and high doses of amoxicillin and amoxicillin/clavulanate. Cefuroxime or one injection of ceftriaxone (for those unable to take oral therapy) are additional alternatives. If the patient has received antibiotics for AOM during the last month or if he attends a child care center, recommendations are for a high dose of amoxicillin/clavulanate. A high dose of amoxicillin or amoxicillin/clavulanate or 3 doses of ceftriaxone are necessary for recurrent or nonresponsive AOM. **It is prudent to consider culturing otorrhea, from PE tubes or perforated tympanic membranes, given the changing epidemiology of SN, Hi, and CA-MRSA.** At Texas Children's Hospital, serotype 19A has become the most common pneumococcal serotype isolated from chronic or recurrent pneumococcal sinusitis and mastoiditis patients with 68% multidrug resistance noted in the latter, making physicians aware of a more aggressive and complicated infection to treat.[20,21,22]

The CDC's Active Bacterial Core Surveillance Network ("ABC sites") documented rates of pneumococcal meningitis have decreased among children/adults since PCV7 was introduced. Although the overall effect of the vaccine remains substantial, a recent increase in meningitis caused by non-vaccine serotypes, including strains non-susceptible to select antibiotics is concerning[23]. Researchers studied pneumococcal meningitis rates 1998-2005 and compared years with baseline values from 1998-1999 (PCV7 introduced in 2000). Overall rates of PCV7-serotype meningitis decreased 73.3%, and PCV7 related serotype disease decreased 32.1%. However, rates of non-PCV7-serotype disease increased from 0.32 cases per 100,000 people to 0.51 cases per 100,000 people with significant increase in non-PCV7 serotypes 19A, 22F, 35B (2004-2005 pneumococcal meningitis incidence - 0.29 case per 100,000 people). Overall meningitis incidence rates in patients younger than 2 years decreased 64% and adults 64 years and older, rate decreased 54%.

> The increased parapneumonic empyema prevalence includes 61% with negative bacterial cultures with suspicion that non-vaccine pneumococcal serotypes are responsible, along with prior antibiotic therapy.[25]

Vanderbilt University and CDC researchers utilizing a nationwide data-base sampling 1997-2006 revealed pneumococcal conjugated vaccine (PCV7) remains effective against childhood pneumonia. Both 2005 and 2006 rates were 27% and 35% lower than baseline rate for all-cause pneumonia hospitalizations in children younger than two years including for 2006 36,300 fewer pneumonia hospitalizations.[24] Up to a five-fold increase in parapneumonic empyema has been found in the post-pneumococcal conjugate vaccine era.

Similar studies from eight children's hospitals[26] and Utah[27] identified the most prevalent pneumococcal serotypes isolated were 1, 3, 6, 14, and 19A, most all non-vaccine serotypes. **Empyemas that are culture-negative can be managed in a similar fashion to those that are known to be caused by *S. pneumoniae*.**

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In 2008, the Clinical and Laboratory Standards Institute (CLSI) and the FDA revised susceptibility breakpoints for penicillin and *Streptococcus pneumoniae* for non-meningeal infections in patients receiving intravenous penicillin (susceptible, intermediate, resistant) with the respective new breakpoints = 2, 4, and 8 mcg/ml. For meningitis, the figures change to 0.06 for susceptible and = 0.12 mcg/ml for resistant. The in vitro penicillin susceptibility of pneumococcal isolates = 0.06, 0.12, and = 2 mcg/ml respectively still pertain for patients being treated with oral penicillins as outpatients. The scientific basis for the revisions to the breakpoints was supported by microbiologic, pharmacokinetic and/or pharmacodynamic, and clinical data. **Clinicians, once again should feel comfortable prescribing penicillin for pneumococcal pneumonia and other pneumococcal infections outside the central nervous system.**[28] Beta lactams should be used cautiously in lung infections caused by pneumococci with minimum inhibiting concentrations (MICs) of 4 mcg/ml or more because therapeutic failures have been seen.[17]

"Use of narrow spectrum agents, such as penicillin, is encouraged to prevent the spread of antimicrobial-resistant *S. pneumoniae* and also the spread of methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile*, which can result from use of broader-spectrum antimicrobials. The changes in penicillin breakpoints for *S. pneumoniae* have the potential to allow clinicians to increase use of penicillin to treat penicillin-susceptible non-meningitis pneumococcal infections, instead of using broader-spectrum antimicrobials."(CDC)[29]

The 13-valent pneumococcal conjugate vaccine (PCV) had been granted fast-track status for the pediatric indication based on "an unmet medical need," with goal replacement of PCV7, with PCV13 using a technology that worked successfully with Prevnar. The 13-valent version contains the same 7 serotypes in Prevnar (4, 6B, 9V, 14, 18C, 19F, 23F) along with six new pneumococcal strains (1, 3, 5, 6A, 7F, 19A). In 2006, the proportion of invasive pneumococcal cases caused by the 7 strains in Prevnar was 2% in children less than 2 years of age and 4% in those aged 2-4 years. The proportion of invasive pneumococcal disease (IPD) cases caused by the 13 serotypes in the new version was 64% and 73% respectively, with half of the cases due to 19A. Data has shown a single dose of PCV13 will induce an immune response to the six new serotypes in more than 90% of children aged 12 months and older. Thus, potentially after completion of the primary three-dose series with PCV7, after age 12 months a child could receive simply the PCV13 as a booster. Final recommendations were published March 2010.[74,75]

Clostridium difficile Epidemiology/Clinical Update

The incidence of *Clostridium difficile* – associated disease (CDAD) is increasing in both **inpatients** and **outpatients** worldwide with an **accompanying increased severity.**[30] U.S. hospital discharge data reveals in less than a decade a doubling of CDAD.[31] Cases of CDAD at children's hospitals increased significantly between 2001 and 2006 with an annual rate increase of 53% including an 85% increase in cases among children ages 1-5 years.[32] Greater frequency and severity of CDAD have been linked to a previously uncommon and more virulent strain of *C. difficile*, identified as the BI/NAP1/027 strain. The incidence of CDAD is increasing in both inpatients and outpatients with more complications seen in the outbreaks caused by this hypervirulent strain, which produces more than 15 times toxins A and B than previously identified strains[33].

Community-associated CDAD is now occurring in persons who lack traditional risk factors, which included antibiotic use, advanced age, and severe underlying disease.

The hypervirulent strain of CDAD accounted for 10-38% of isolates of hospitalized children[34] with a complication rate of 29% versus 6% with other strains. Many authorities suspect additional contributing factors may include increased fluoroquinolone use in the community (most commonly used antimicrobials in N. America with BI/NAP1/027 strain highly resistant to quinolones) and an increase in proton pump inhibitor exposure.[30] **CDAD is an unintended consequence of antimicrobial use, now in the community (including otherwise healthy persons) and hospital settings. Vital to its prevention is judicious use of antibiotics and antimicrobial stewardship.**

Community-Associated Methicillin-Resistant *Staphylococcus aureus* Epidemiology/Clinical Update

Staphylococcal infections encompass a spectrum from relatively mild localized infections to rapidly fatal invasive infections. In the 1990s, new strains of MRSA emerged as a cause of infection among otherwise healthy people in

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the community, adding to the burden of community-associated *S. aureus* infections. Community-associated methicillin-resistant *S. aureus* (CA-MRSA) isolates have a distinct pathogenesis, epidemiology, and clinical manifestations that differ from those of healthcare-associated MRSA (HA-MRSA) isolates. The USA 300 clone, and to a lesser extent the USA 400 variant, have emerged as the predominant causes of CA-MRSA disease[35]. Epidemiologic models strongly suggest that the community-acquired strain will soon become the major MRSA strain in the hospital setting, surpassing and replacing the healthcare-associated MRSA (HA-MRSA) strain.

> Competitive exclusion of HA-MRSA by CA-MRSA (mainly USA 300 clone) will occur, with increased severity of CA-MRSA infections resulting in longer hospitalizations and a larger in-hospital reservoir of CA-MRSA.[36]

Also noted, hand hygiene has the greatest return of benefits, and if compliance is optimized, other strategies may have minimal added benefit.[36]

> Today, MRSA accounts for 50-70% of all *S. aureus* isolates with a $4.2 billion annual financial impact in the United States.[37]

It is also becoming clear that antimicrobial resistance is an increasing problem outside of hospitals. The CDC Active Bacterial Core Surveillance Network ("ABC sites") noted the estimated rate of invasive (bloodstream or other sterile site) MRSA infections in 2005 was 31.8 per 100,000 persons. This estimated rate of invasive MRSA infections was greater than the combined rate in 2005 of invasive pneumococcal disease (14.1 per 100,000), invasive group A streptococcal infection (3.6 per 100,000), invasive meningococcal disease (0.35 per 100,000), and invasive Haemophilus influenzae infection (1.4 per 100,000).[38] Among 5287 surveyed patients hospitalized with MRSA infection during 2005, 988 deaths occurred.

> Based on these data, it was estimated that there were 18,650 patients who died of invasive MRSA infection in the U.S. in 2005 – exceeding the total number of deaths attributable to HIV/AIDS in the U.S. during that year.[39]

A study from the CDC found that 6% of CA-MRSA infections were invasive[40] and a pediatric study noted 9% of children hospitalized in 2003 for CA-MRSA infection had invasive disease.[41]

CA-MRSA, a new pathogen for children and adults, may represent up to 50-80% of all *S. aureus* community isolates in various regions of the U.S. CA-MRSA is resistant to methicillin and to all other beta-lactam antibiotics that are FDA approved to date. In contrast to HA-MRSA, CA-MRSA usually does not have multiple antibiotic resistance genes. However, there are an undetermined number of pathogenicity factors that appear to make CA-MRSA more aggressive than methicillin-susceptible *S. aureus* (MSSA). Compared with MSSA, CA-MRSA appears to cause greater tissue necrosis, an increased host inflammatory response, an increased rate of complications, and an increased rate of recurrent infections. Response to therapy with non-beta-lactam antibiotics appears to be delayed. It is unknown whether higher dosages and longer courses of alternative agents needed for clinical cure are due to a hardier, better-adapted pathogen, or whether alternative agents are not as effective as beta-lactam agents were against MSSA. **No data are currently available to compare one antibiotic against another for CA-MRSA, let alone one combination against another.**

Transmission of CA-MRSA strains and infections to close contacts has frequently been reported. A prospective study of CA-MRSA infected patients showed that reports of new skin infection among household members in the 30 days after the initial infection was 13% for CA-MRSA patients but 4% for those who had CA-MSSA infections.[42] **In military recruits who were colonized on entry into boot camp, any antibiotic use during the previous 6 months was a risk factor for nasal colonization with CA-MRSA.** Nasal colonization resolved within weeks; however, subsequent infections developed in 38% of those with nasal colonization, compared with 3% of those without colonization.[43] The 2008 ICAAC/IDSA meeting had a recent three year study from the Chicago hospital system revealing patients with *S. aureus* (40% had MRSA) who had been treated with antibiotics within the past 3 months may be at increased risk for MRSA serious infections.

There are limited published data on MRSA in child care centers. Recent data from the 2008 Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and the Infectious Diseases Society of America (IDSA) noted that 7% of children were colonized, employee colonization was 3%, and among family members of children or staff found to carry MRSA, 35% were also colonized. Findings indicated children treated with a

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macrolide antibiotic in the past were at increased risk for MRSA colonization. Genetic analysis revealed many isolated strains were related implying that transmission of MRSA may be occurring in the child care setting. *S. aureus* cultured from nares did not match wound isolates in many children with skin infections with a 33% discordance.[44] The MRSA colonization rate in elementary school children was 0.5-0.9% over three years with an increase in CA-MRSA strains.[45]

To date, frank resistance to vancomycin is rare; however, true intermediate resistance (MIC 4-8 mcg/ml), vancomycin intermediate *S. aureus* (VISA), and vancomycin hetero-resistance (hVISA) are encountered. **Serious infections caused by hVISA/VISA strains are associated with poor clinical outcomes,[46] with a recent international cohort of patients revealing the hVISA phenotype occurring in more than one-quarter of MRSA ineffective endocarditis isolates and was associated with a higher frequency of complications, i.e., persistent bacteremia and heart failure.**[47]

Hetero-resistance refers to the presence, within a large population of fully antimicrobial-susceptible microorganisms, of subpopulations with lesser susceptibility. Current focus revolves around hetero-resistance to vancomycin. Hetero-resistant subpopulations of vancomycin-susceptible *S. aureus* (hVISA) were first described in 1997 shortly after the initial description of vancomycin intermediately susceptible strains (VISA). hVISA have minimum inhibitory concentrations (MICs) in the intermediately susceptible range and likely represent a step on the path to the development of a fully VISA population. Recent U.S. reports note hVISA having been identified among clinical isolates of MRSA with an 8-9% frequency and a recent international study with infective endocarditis isolates a prevalence of 13.9% (N. America), 35% (Europe), and 77.8% (Oceania).[47,48,49] Vancomycin hetero-resistance is present in both hospital and community strains of *S. aureus*. The proportion of MRSA isolates demonstrating hetero-resistance increases with increasing vancomycin MICs, but hetero-resistance is observed in strains with MICs as low as 1.0 mcg/ml. The phenomenon is inducible and may be either stable or unstable. **As compared with MRSA bacteremia, hVISA bacteremia may be associated with prolonged bacteremia duration, greater rates of complications, and emergence of rifampin resistance.**[50,51]

> It is impossible to ignore reports of rising vancomycin MICs and the effect that higher vancomycin MICs within the susceptible range seem to have on treatment outcomes.
>
> There is also some evidence that exposure to subtherapeutic concentrations may tend to select for reduced susceptibility to vancomycin. Also under selective pressure from vancomycin, a series of sequential mutations are selected for as an organism transitions from full susceptibility to hVISA to VISA.

Challenges, but vancomycin remains a drug of choice, the standard treatment for serious MRSA infections and serious MSSA infections in patients with B-lactam allergies. To date, most clinical trials have not demonstrated superiority of new agents.[52] However, vancomycin resistance is a growing concern as data from several reports suggests a correlation between increased MICs, and treatment failure. Generally, current glycopeptides (e.g. vancomycin) are less efficacious than B-lactams against MSSA. **However, vancomycin is still a gold standard against severe MRSA infections, until proof is found of newer anti-MRSA drugs.**[53]

Increases in serious invasive CA-MRSA infections continue with many patients with endemic disease, particularly children, having no discernible risks. Several trends of CA-MRSA infections have been associated with some clinical manifestations of *S. aureus* infections, such as deep venous thromboses (DVT), pyomyositis, and neonatal disease that had not been seen commonly while there are relatively few existing data on effective therapy with these infections. There is a paucity of literature examining the epidemiology of CA-MRSA infections, especially skin infections. Skin and soft tissue infections (SSTI) account for approximately 85-95% of CA-MRSA infections[54] in children and adults with SSTI caused by CA-MRSA more severe than those caused by CA-MSSA isolates.[55] Recurrent skin infections are encountered in about 10% of patients with SSTI.[56] **Basics apply, with incision and drainage and obtaining cultures used to assess for MRSA with uncomplicated SSTI.**

Medical management of SSTI with antimicrobials has been addressed in previous publications and mailings by the SC DHEC Bureau of Disease Control (see "Outpatient Management of Skin & Soft Tissue Infections in the Era of Community-Associated MRSA," April 2008 – available from http://www.scdhec.gov/health/disease/acute/mrsa.htm). Necrotizing pneumonia (especially with influenza), empyema, sepsis syndrome, purpura fulminans, Waterhouse-Friderichsen syndrome, and necrotizing fasciitis have all been associated with CA-MRSA. Musculoskeletal infections such as osteomyelitis and

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pyomyositis are also increasing in prevalence. **Patients with CA-MRSA experience longer duration of fever, prolonged hospital stays, and more complicated clinical courses when compared with patients with CA-MSSA[55], especially if the isolate contains genes encoding for Panton-Valentine leukocidin (PVL) toxin.**

Osteomyelitis accounted for 7.5% of all MRSA infections (CA-MRSA or HA-MRSA) among all age groups by CDC reported surveillance of invasive MRSA infections for the ABC sites.[38] Musculoskeletal infections are the most common invasive infections caused by CA-MRSA in children. Osteomyelitis with CA-MRSA had greater inflammation with increased white blood cell count, ESR, CRP, greater frequency of positive blood cultures, greater admission to intensive care units, greater frequency subperiosteal intraosseous abscesses, prolonged bacteremia, increased frequency surrounding myositis, and a tendency more often for multiple sites of infection, 15%.[57] Optimal antibiotic therapy duration has yet to be established but can range from 6-10 weeks. CA-MRSA complications include chronic osteomyelitis or an associated deep venous thrombosis, adjacent to the infected bone. Venous thrombophlebitis leading to septic pulmonary emboli and other sites of dissemination occurs more commonly with CA-MRSA isolates, especially the USA 300 clone. There are increasing reports of osteomyelitis in adults involving USA 300 CA-MRSA strains with complications of septic emboli or pathologic fractures as seen in children.[58]

Multiple sites of myositis/pyomyositis and/or osteomyelitis can develop in a patient with disseminated *S. aureus* infection necessitating careful exams of patient daily to detect areas of infection and/or abscesses that may not have been appreciated even the previous day with a necessity often of repetitive MRI studies.

CA-MRSA pyomyositis in adult reports includes postpartum women.[59] MRI is the most sensitive modality for early diagnosis of musculoskeletal infections. It can demonstrate the bone changes consistent with osteomyelitis and identify bone and subperiosteal abscesses, myositis/pyomyositis (an elevated creatine kinase, CK, may be seen in some cases), and most venous thromboses (ultrasound utilizing Doppler flow diagnostic modality of choice). Bone scans may be useful when the site(s) of infection is not clearly localized.[60]

Complicated pneumonias with empyema with CA-MRSA isolates have become common with some children's hospitals with CA-MRSA the most common pathogen with pleural empyema. Lung involvement may be a severe pulmonary syndrome with a rapidly progressing necrotizing pneumonia usually preceded by flu-like symptoms (classically hemoptysis, leukopenia, lung necrosis radiologically) with a mortality rate 76%.[61] Necrotizing pneumonia patients may not have positive *S. aureus* blood cultures but sputum cultures or bronchoalveolar lavage will usually be *S. aureus* positive.

Lung involvement is an important feature of the sepsis syndrome. Pulmonary manifestations are diverse including pulmonary emboli, necrotizing pneumonia, lung abscess, and empyema among the most significant.[62] In patients who present with osteomyelitis and shortness of breath, respiratory distress, or chest pain, pulmonary emboli from an endovascular source (DVT) should be sought.

Sepsis syndrome, occurring in all age groups, has increased with CA-MRSA and is seen most often in children less than 4 years of age and in adolescents. Most patients had musculoskeletal infections (2-10 sites in some series), bacteremia, and pulmonary involvement with common complications vascular thrombosis, multiple areas pyomyositis, subcutaneous nodules, and purpura fulminans. Clinical features include leukopenia (initial white blood cell count may be normal), neutropenia, profound tachycardia, lactic acidosis, and thrombocytopenia and/or disseminated intravascular coagulation. Leukocytosis or leukopenia may be seen in patients, with leukopenia indicating a more ominous prognosis. With osteomyelitis involvement, higher CRP and ESR admission levels have been associated with a higher likelihood of complications.[63]

Most patients with *S. aureus* sepsis syndrome have more than one positive blood culture. Prolonged bacteremia is common and suggests an un-drained focus of infection or an endovascular source (i.e., DVT or endocarditis) rather than an antibiotic failure. Patients with severe sepsis syndrome should have echocardiography assessment.

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CA-MRSA infections are being recognized more commonly in the otherwise healthy neonate less than 30 days of age, with the most common manifestation pustulosis.[64] Most cases of localized pustulosis appear to be adequately treated with topical treatment, mupirocin. Blood culture is recommended for diffuse pustulosis but treatment could be an oral antibiotic such as clindamycin.[65] Abscesses, cellulitis, and other invasive infections, although less common, can be associated with bacteremia and more severe illness. **Any infant with symptoms or with fever related to potential *S. aureus* infection**, **should undergo a complete evaluation including blood, urine, and CSF analysis and culture,**[55,65] **and hospitalization assessment.**

Rapid institution of appropriate antimicrobial therapy is critical in the treatment of severe *S. aureus* infections, as delay in therapy has been associated with increased mortality.[68] The American Academy of Pediatrics (AAP) Red Book recommends a combination of vancomycin, nafcillin (more rapidly bactericidal than vancomycin for MSSA isolates including adult clinical data for treatment of bacteremic pneumonia secondary to MSSA), and gentamicin for the initial empiric treatment of severe and critically ill/life-threatening *S. aureus* infections.

Poorer outcomes are associated with MRSA versus MSSA infections with a significant health care burden in terms of morbidity, mortality, and economic cost associated with the disease**. A meta-analysis of 31 cohort studies (1980-2000) determined that a significant increase in mortality was specifically associated with MRSA bacteremia.**[66] Also, patients with MRSA have higher inpatient costs, and longer hospital stays compared to patients with MSSA.[67]

However, no data support any one combination of therapy as being more efficacious than another. Pediatric patient recommendations are based on adult bacteremia and endocarditis data and on clinical experience accumulated with treatment of severe infections in pediatric hospitals. **If bacteremia/septicemia, endocarditis/endovascular, or CNS infection may be involved, vancomycin is the mainstay of therapy.** Clindamycin remains an important option for treating serious non-endovascular infections in children due to susceptible isolates.

New recommendations for targeting and adjustment of vancomycin therapy resulted from updated and existing evidence regarding vancomycin dosing and monitoring of serum concentrations, patient outcomes, and vancomycin's pharmacokinetic, pharmacodynamic, and safety record. The relationship between serum concentrations and treatment success or failure in serious *S. aureus* infections has recently been established.

New practice guidelines for therapeutic monitoring of vancomycin treatment for *S. aureus* infections in adult patients were reviewed by an expert panel of the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists.[69]

Failure rates exceed 60% for *S. aureus* with a vancomycin MIC value of 4 mcg/ml and recently studies established a relationship between vancomycin treatment failures and infections in patients with MRSA with MIC of 2mcg/ml. Vancomycin's (concentration independent activity against *S. aureus*) primary predictive pharmacodynamic parameter for efficacy is the area under the concentration curve (AUC) divided by the MIC with data supporting an AUC/MIC value of 400 the pharmokinetic – pharmacodynamic target. **To achieve this target, larger vancomycin doses and high trough serum concentrations are required. The following is a summary of therapeutic vancomycin dose adjustment (better prognosis with initial dosage therapeutic levels) and drug monitoring.**

Initial vancomycin dosages should be calculated based on actual body weight (including for obese patients) with subsequent dosages based on actual serum concentrations to achieve targeted therapeutic concentrations. Continuous infusion regimens are unlikely to substantially improve patient outcome. Trough serum concentrations (most accurate and practical for monitoring vancomycin effectiveness) should be obtained just before the fourth dose at steady state conditions. It is recommended that trough serum vancomycin concentrations always be maintained at > 10 mcg/ml to avoid the development of resistance **(evidence suggests *S. aureus* exposure to < 10 mcg/ml troughs can produce strains with VISA-like characteristics)**.

This trough level range should achieve a targeted AUC/MIC > 400 for most patients if the MIC is < 1 mcg/ml. The targeted AUC/MIC is not achievable with conventional

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Trough serum vancomycin concentrations of 15-20 mcg/ml are recommended with the potential to improve penetration, to increase the probability of optimal target serum concentrations, and to improve clinical outcomes of complicated infections such as *S. aureus* bacteremia, endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia.

dosing methods if the vancomycin MIC is = 2 mcg/ml for a patient with normal renal function (alternative therapies should be considered). Vancomycin dosages of 15-20 mg/kg (actual body weight) given every 8-12 hours are required for most patients with normal renal function to achieve the suggested trough serum concentrations when the MIC is < 1 mcg/ml. To achieve rapid attainment of target concentration for seriously ill patients, a loading dose of 25-30 mg/kg can be considered. When individual doses exceed 1 gram (1.5 and 2g), the infusion period should be extended to 1.5-2 hours.

There are limited data suggesting a direct causal relationship between toxicity and specific serum vancomycin concentrations. The safety of higher trough vancomycin concentrations over a prolonged period continues to be studied. Monitoring of trough serum concentrations to reduce nephrotoxicity is best suited for patients receiving aggressive dose targeting (for sustained trough serum concentrations of 15-20 mcg/ml) or who are at risk of toxicity (patients with concurrent treatment with nephrotoxins). Monitoring is also recommended for patients with unstable renal function and for patients with prolonged courses of therapy (>3-5 days). Exact frequency of monitoring is often a matter of clinical judgment with recommendations frequent trough concentrations in hemodynamically unstable patients (sometimes daily) and when a 15-20 mcg/ml vancomycin concentration is desired, once weekly, measurements of trough concentration for hemodynamically stable patients. Frequent monitoring for short course therapy (less than 5 days) or for lower intensity dosing (trough concentration < 15 mcg/ml) is not recommended.

It is unknown whether recommended vancomycin dosing regimens for children achieve an adequate AUC/MIC value and unfortunately, the response to therapy using standard vancomycin dosing (40 mg/kg/day) in treating CA-MRSA strains has not been as predictably good as in the past. Retrospective and modeling data indicate standard dosing does not achieve the pharmacodynamic target over 24 hours of AUC/MIC = 400 for optimally treating MRSA isolates with a MIC of 1.0 mcg/ml or greater.[70]

Recommendations of a more effective increased starting dosage, to maintain a range of trough concentration 15-20 mcg/ml, can be made for children with normal renal function and suspected or proven invasive MRSA infections (60 mg/kg/d – 15 mg/kg intravenously every six hours). With a higher treatment dose, one needs to follow renal function, but children appear to tolerate this higher dosage much better than do adults.

SUMMARY

An analysis published last year noted a return to pre-antibiotic conditions may occur as a result of antibiotic abuse and declining development of new medicines. Currently there are no new classes of antibiotics entering late-stage clinical development. ***Are we entering a post-antibiotic era?*** Resistance trends may be moving at a faster pace, in both hospital and community settings, than previously believed.[71]

People need to know that antibiotic overuse may put them at increased risk for a more virulent *C. difficile* disease and more invasive resistant infections in the future including *S. pneumoniae*, MRSA, vancomycin-resistant *Enterococcus*, and other ESKAPE organisms in a nosocomial setting.

With additional media coverage now addressing increased carriage of more resistant and virulent pneumococcus and MRSA, the public demand for antibiotics may decrease with resistance education and viable alternatives to antibiotics. Additional media exposure includes coverage addressing the internet purchase of antibiotics, the significant impact of adverse effects of antibiotics, and the potential relationship to increased childhood asthma and the use of antibiotics in the first year of life, with the risk increasing with the number of courses of antibiotics prescribed.[72]

Efforts to sustain the lifespan of current antibiotics are vital and must originate in primary care practices. One cannot be expected to change decades of patient behavior overnight and patients cannot be expected to limit their antibiotic use to promote the greater common good of resistance prevention. **However, after decades of antibiotic use and abuse, contemporary data now permit health care providers to highlight real risks for**

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individual patients expecting antimicrobials for viral syndromes. This may permit an improvement in judicious use of antibiotics for upper respiratory infections with earlier addressed guidelines on the SC DHEC website (in SC, patients receiving antibiotics for the common cold has decreased in the past few years from 42 to 29%). We hope that this *Epi Notes* update will help clinicians continue to take the necessary steps for their patients to reduce the impact of antimicrobial resistance in a changing inpatient and outpatient clinical environment.

Read more about CAreful Use of antibiotics (CAUse): http://www.scdhec.gov/health/disease/sccause/index.htm.

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Year-to-Date Summary of Reportable Conditions ‡
January 1, 2010 to March 15, 2010

Reportable Condition	Confirmed	Probable	Total
Animal Bites – PEP recommended	28	*	28
Arboviral Neuroinvasive Disease (includes West Nile Virus)	0	0	0
Brucellosis	0	0	0
Campylobacter enteriditis	39	0	39
Cryptosporidiosis	7	0	7
Cyclosporiasis	0	0	0
Ehrlichiosis	0	0	0
Enterohemorrhagic E. Coli (includes O157:H7)	1	0	1
Giardiasis	17	0	17
Haemophilus influenza	26	0	26
Hemolytic uremic syndrome	0	0	0
Hepatitis A, acute	9	0	9
Hepatitis B, acute	10	1	11
Hepatitis B, chronic	12	87	99
Hepatitis C, acute	0	0	0
Hepatitis C, chronic or past	666	3	669
Influenza, positive virus culture isolates (not Novel)	19	0	19
Influenza, Novel Influenza A Virus Infections (H1N1)	147	0	147
Legionellosis	1	0	1
Listeriosis	2	0	2
Lyme disease	3	0	4
Malaria	1	0	1
Measles (rubeola)	0	0	0
Meningitis, aseptic	23	0	23
Meningococcal disease	4	0	4
Mumps	1	0	1
Pertussis	36	3	39
Psittacosis	0	0	0
Rocky Mountain Spotted Fever	0	0	0
Rubella (includes congenital)	0	0	0
Salmonellosis	81	0	81
Shigellosis	17	0	17
Staphylococcus aureus, vancomycin-resistant (VRSA/VISA)	0	0	0
Streptococcus group A, invasive disease	25	0	25
Streptococcus group B, age < 90 days	18	0	18
Streptococcus pneumoniae, invasive	164	0	164
Varicella (only outbreak associated or hospitalized cases are reportable)	44	0	44
Vibrio infections (non-cholera)	1	0	1
Yersiniosis	3	0	3

‡ *To save space, several conditions with zero reported cases in 2010 were omitted from this list.*

* *Probable cases status is not allowed for this condition.*

Epi Notes
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DISEASE REPORTING:

For immediately or urgently reportable conditions, call your local health department or, after hours, call 1-888-847-0902.

Routine disease reports may be phoned in to your local health department or mailed on a completed DHEC DISEASE REPORTING CARD (DHEC 1129.) Contact the Division of Acute Disease Epidemiology (803-898-0861) regarding electronic submission of disease reports.

Local health department numbers are on the DHEC List of Reportable Conditions. For a copy of the current List of Reportable Conditions, call 803-898-0861 or visit www.scdhec.gov/health/disease.index.htm.

THE EPI NOTES NEWSLETTER IS AVAILABLE ONLINE AT
www.scdhec.gov/health/disease/index.htm.

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