THE ROLE OF ADVANCED PRACTICE NURSING IN COMMUNITY-ACQUIRED MRSA INFECTION: IMPLICATION FOR PRACTICE AND COMMUNITY HEALTH

by

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ABSTRACT

In the last 10-15 years community-acquired methicillin-resistant Staphylococcus aureus (CA-MRSA) has become increasingly recognized as a significant, worldwide health problem. CA-MRSA causes skin and soft tissue infections as well as more serious, sometimes life-threatening, pneumonias in otherwise healthy people. Outbreaks of CA-MRSA infections have occurred in unexpected groups. Some CA-MRSA strains are particularly virulent and have achieved ecological stability, raising concern that those strains of CA-MRSA could become endemic in certain areas of the country and within certain populations. No generally accepted diagnostic, treatment, or prevention guidelines for practitioners currently exist for CA-MRSA as there are for hospital-acquired MRSA infections (HA-MRSA). This paper reviews currently available pathophysiological, epidemiological, and historical information from various journals and texts, as well as current diagnostic and treatment approaches. The treatment guidelines and algorithm presented here are designed to aid practitioners in their clinical decision-making and interventions when addressing potential CA-MRSA infections.
CHAPTER 1 PURPOSE AND SIGNIFICANCE

Introduction

The advent of antibiotics brought a new era in the treatment of infectious diseases and in the ability of health care providers to care for their patients. Antibiotics are a double-edged sword because the organisms we treat can mutate and develop resistance to the various actions of the antibiotics. Staphylococcus aureus (SA) has been recognized as a challenging organism in human infections since the development of germ theory and never more so than now, in the 21st century, because of SA’s ability to develop resistance to the currently available antimicrobial arsenal. Currently Methicillin Resistant Staphylococcus Aureus (MRSA) infections present such a major health care concern (Chini, Petinake, Foka, Paratiras, Dimitracopoulos, & Spiliopolou, 2006; Crisostomo, Westh, Tomasz, Chung, Oliviera, & deLencastre, 2001; Hulten et al., 2006; Ribeiro et al., 2005; Vandenesch et al., 2003), that they may constitute a worldwide health care crisis. MRSA has become endemic in many health care institutions (approximately 50% prevalence in the U.S. and approximately 20% in Europe) and new MRSA strains are developing in the broader community that are affecting people without recognized risk factors for nosocomial MRSA infection (Appelbaum, 2006; Carelton, Diep, Charlebois, Sensabaugh, & Perdreau-Remington, 2004; Henderson, 2006; Naimi et al., 2003; Salgado, Farr, & Calfee, 2003).

Problem Statement

Staphylococcus aureus (SA) has been a leading cause of infection in humans since bacteria were identified as a cause of illness and death. With the advent of antibiotics morbidity and mortality from SA has drastically decreased; however, SA has shown a remarkable ability to develop resistance to the antibiotics used against it. This ability to
develop resistance to anti-microbial agents has led, since the early 1990's, to a worldwide epidemic of drug resistant SA. Methicillin, introduced into clinical use in 1960 to replace penicillin (PCN), which had become ineffective in treating SA infections, rapidly fell prey to SA’s ability to develop drug resistance: Within a year of methicillin’s introduction resistant strains of SA had already been identified, with additional resistance rapidly developing to streptomycin, tetracycline and in some cases erythromycin (Livermore, 2000; Schito, 2006; Oliveira, Tomasz, & deLencastre, 2002; Rice, 2006). In 2006 Methicillin resistant SA (MRSA) is a worldwide problem involving multi-drug resistant infections, increasing levels of morbidity and mortality, and costing millions of healthcare dollars every year. Since the 1990's MRSA infections have moved out of the health care inpatient setting into previously unaffected populations in the community. The combination of SA’s ability to rapidly develop resistance to antibiotics and its spread into the larger, healthy community makes MRSA infections a concern for patients, practitioners, public and community health workers, and governmental leaders.

Purpose of project

No current guidelines exist for primary care and family practitioners for the diagnosis and treatment of community-acquired methicillin-resistant (CA-MRSA) infections in the community. A review of Cochrane, DARE and the ACP Book Club databases for the years 2000 through 2006 revealed no current published guidelines available for practitioners. Many recent articles have reviewed pathophysiology, epidemiology, diagnosis and treatment in specific populations or with specific types of infections. However, no general guidelines are currently available for practitioners to use in general practice to diagnosis and treat the variety of CA-MRSA infections presented to them. Additionally, information about CA-
MRSA infections is not readily available to primary care and family practitioners in forms they can access or readily use. This paper will present both diagnosis and treatment guidelines and decision-making algorithms derived from currently available scientific literature.

**Background and Significance**

Staphylococcus aureus has been a constant in human history, associated with infections of the skin, wounds, respiratory system, central nervous system, urinary tract, and blood stream (Enright, Robinson, Randle, Feil, Grundman, & Spratt, 2006; Oliveira et al., 2002; Sabol, Eshevarria, & Lewis, 2006). *S. aureus* has the ability to colonize humans without causing symptoms until the immune system is unable to control bacterial growth. *S. aureus*’s “versatility of pathogenic strategies, number of virulence factors, and capacity to survive and multiply in a wide range of environments…is unsurpassed by any other human pathogen” (Oliveira, p. 181). *S. aureus* has multiple mechanisms to rapidly develop resistance to drugs: use of plasmid borne penicillinase to degrade the antibiotic before it can reach its target; alteration in cell wall antibiotic binding sites that prevent drug binding; protein A and proteases that alter IgG antibody function and effectiveness; and superantigens that bind to major histocompatibility factors and moderate host immune function (Projan & Novick, 1997, pp. 55-75).

MRSA infections were initially a hospital based problem associated with defined risk factors: compromised immune system, indwelling invasive devices, serious chronic illness, extended hospitalization (especially in intensive care units), use of multiple broad spectrum antibiotics, and surgical procedures (Lewis, Salyers, Taber, & Was, 2002; Vandenesch et al., 2003). These hospital-associated MRSA (HA-MRSA) infections were associated with a small
number of S. aureus clones strains, with defined genetic identifiers, and were frequently
multi-drug resistant (Oliveira et al., 2002; Ribeiro et al., 2005). Methicillin resistance in S.
aureus is mediated primarily by chromosomal coding (mec DNA) for an altered penicillin-
binding protein (PBP2a) with lowered binding affinity for beta-lactam antibiotics (Lewis, p.
332). HA-MRSA is now considered endemic in many hospitals worldwide and has spread to
long-term and extended care facilities (Fridkin et al., 2005; Vandenesch). In more recent
years, MRSA infections have been isolated in patients without previously identified risk
factors for HA-MRSA; the MRSA strains for these CA-MRSA infections are distinct from
and unrelated to HA-MRSA strains (Chen, Huang, Chiu, Su, & Lin, 2005; Fridkin; Ribeiro).
CA-MRSA strains have spread worldwide and been responsible for outbreaks of mild to
moderate skin and soft tissue infections as well as fatal respiratory infections in healthy
adults and children (Charlebois et al., 2003; Cohen, 2005; Francis et al., 2005; Frazee, Salz,
Lambert, & Perdreau-Remington, 2005; Fridkin; Hageman et al., 2006; Hulten et al., 2006;
MMWR, 1999). Outbreaks of CA-MRSA infections have occurred in athletic teams, prison
populations, military recruits, medically underserved urban poor, and in relatively isolated
native American populations (Cohen; Ellis, Hospenthal, Dooley, Gray, & Murray, 2004;
Fridkin; Gilbert et al., 2006; MMWR; MMWR, 2003; Stemper, Shulka, & Reed., 2004; Young
et al., 2004) causing significant costs to individuals as well as the communities: direct health
care costs, lost work or school time, altered quality of life, and increased institutional
manpower and resource costs (Muto et al., 2003; Pittet et al., 2006; Wagstaff, 2006).
Definitions
The following definitions are used in this paper:

1. Community-acquired (associated) methicillin-resistant s. aureus (Carleton et al,
2004; Gorwitz et al., 2006; Kowalski, Berbari, & Osmon, 2005; Moran et al., 2006; Salgado et al., 2003)

-S. aureus strains isolated from hospitalized patients <24 hours after admission that are resistant to methicillin (oxacillin) and have limited resistance to other antibiotic classes

-S. aureus strains carrying the SCCmec IV(a) gene, and (frequently) associated with additional virulence factors such as Panton-Valentine leukocidin

-MRSA strains that have limited resistance to antibiotics other than beta-lactam agents and isolated outside the hospital

-MRSA strains with above characteristics in patients that have no identified risk factors for HA-MRSA infections

2. Hospital-acquired methicillin-resistant S. aureus (Charlebois et al., 2002; Hulten et al., 2006; Naimi et al., 2003)

-MRSA isolates collected from hospitalized patients >24-48 hours after admission that are multi-drug resistant

-MRSA strains carrying SCCmecI-III genes

-MRSA strains with above characteristics that are associated with identified risk factors (for example, recent hospitalization, frequent/multiple antibiotic use, serious chronic illness, indwelling invasive devices)

3. Beta-lactam antibiotics: class of antibiotics with a fused beta-lactam ring structure that inhibits bacterial growth by altering synthesis of the cell wall.
These antibiotics include natural and semisynthetic penicillins, extended spectrum penicillins, cephalosporins, imipenem, and aztreonam. (Craig, 2004, p. 180; Spencer, Nichols, Lipkin, Sabo, & West, 1986).

4. Tetracyclines: broad spectrum antibiotics with a four fused benzene structure that are bacteriostatic; divided into 3 groups: short-acting, intermediate-acting, and long-acting compounds. Examples are tetracycline, doxycycline, minocycline (Williams, 2004, pp. 208-209).

5. Macrolides and clindamycin: different chemical structures but having similar antimicrobial activity, mechanism of resistance, and action on bacteria. They inhibit protein synthesis in bacteria and are bacteriostatic. Examples are erythromycin, clarithromycin, azithromycin (Forrest & Oldach, 2004, p. 213).


7. Aminoglycosides: antibiotics containing two or more amino sugars in glycoside linkage with a hexose nucleus, that are bacteriocidal (Spencer, 1986, p. 216) Examples are gentamicin, streptomycin, kanamycin, and neomycin.


9. Multilocus-sequencing type (MLST): sequencing-based technique that is based on the DNA sequencing on the internal fragments of seven unlinked housekeeping genes (Oliveira et al., 2002)

Summary

S. aureus infections have progressed from the hospital environment where they developed methicillin resistance and moved into the community with this antibiotic resistance. CA-MRSA is becoming as significant a health care problem as HA-MRSA. However, no guidelines for diagnosis, treatment, and prevention of transmission of CA-MRSA have been developed to date, leaving primary care practitioners searching about for the safest, most effective, and most cost effective clinical interventions. Such guidelines are necessary for practitioners that treat CA-MRSA infections on a limited basis, and who may have limited diagnostic resources. Reviewing current evidence based information is a necessary first step in treatment guideline development.
CHAPTER 2 THEORETICAL FRAMEWORK AND LITERATURE REVIEW

Introduction

Nursing theories and models direct the practice of nursing for individual nurses and for health care organizations (Andrews & Roy, 1991). Practitioners work toward insuring that nursing practice is evidence based, using guidelines derived by reviewing the most current related scientific literature. Nursing theory also elucidates the interactions between the phenomena of nursing—environment, health, person and nursing—and promotes understanding of underlying relationships and interactions that broaden the art and science of nursing (Andrews & Roy). Roy’s Adaptation Model (RAM) provides a theoretical basis for assessing the relationships, establishing priorities, and developing practice guidelines for advanced practice nursing in response to CA-MRSA. The review of literature in this chapter includes pathophysiology, epidemiology, current treatment approaches, and areas for further research.

Theoretical framework

RAM as described by Roy is a Grand Nursing Theory that serves as a framework for nursing practice and research (Roy, 2004). RAM is derived partly from Von Bertalanffy’s 1968 general system's theory and Helson's 1964 adaptation level theory (Andrews & Roy, 1991, p. 5). For Roy RAM is applicable to any nursing setting by directing the way nurses think about people and their environment, by aiding the development of patient care priorities, and by moving nurses from the level of focus on survival to that of transformation (Andrews & Roy, p. xviii). RAM focuses on the individual's response to environmental stimuli (internal and external), that is, the individual's ability to adapt; these responses can
either promote integrity towards the individual's goals (adaptive response) or not contribute to that integrity (ineffective response) (Andrews & Roy, p. 4).

The Roy Adaptation Model is a complex, comprehensive nursing theory and as such includes a number of major concepts. McEwen and Wills (2002) identify 12 major concepts of RAM, while Andrews and Roy (1991) identify 16 major concepts. These concepts are grouped around the “four major scientific and philosophical perspectives” (Andrews & Roy, p. 5): systems theory, adaptation-level theory, humanism and veritivity. For Roy, “a person is an adaptive system, a whole comprised of parts that functions as a unity for some purpose” that is influenced by its internal and external environment via stimuli: focal stimuli (most immediately confronting the person), contextual stimuli (stimuli in a situation that contribute to the focal stimuli), and residual stimuli (factors whose influence is not clear) (Andrews & Roy, pp. 4-5). A person’s responses to these stimuli or behavior (internal and external actions) can be adaptive (promote integrity towards the human system’s goals) or ineffective (not contributing to the system’s integrity or goals) (Andrews & Roy, p. 4). A person’s responses to the changing environment are seen as coping mechanisms, which are either innate or acquired; these coping mechanisms are subdivided into the cognator subsystem (cognitive-emotive channels: perceptual/information processing, learning, judgment, and emotion) and the regulator subsystem--neural, chemical and endocrine systems (Andrews & Roy, p. 4). For Roy, health is “a state and a process of being and becoming an integrated and whole person” and the goal of nursing is “the promotion of adaptation in each of the four modes, thereby contributing to the person’s health, quality of life, and dying with dignity” (Andrews & Roy, p. 4). Finally, the two major philosophical concepts of humanism and veritivity are defined: humanism is “the broad movement in
philosophy and psychology that recognizes the person and subjective dimensions of the
human experience as central to knowing and valuing”, and veritivity is “a principle of human
nature that affirms a common purposefulness of human existence” (Andrews & Roy, 1991,
p. 6).

Health is “a state and a process of being and becoming an integrated and whole
person” (Andrews & Roy, 1991, p. 4) and is dependent on adaptation in the human system.
Nursing, for Roy and Andrews, is “a health care profession that focuses on human life
processes and patterns, and emphasizes promotion of health for individuals, families,
groups, and society as a whole” (1999, p. 4). Finally, the environment is seen as including
internal and external factors and “all conditions, circumstances, and influences surrounding
and affecting development and behavior or persons and groups with particular consideration
of mutuality of person and earth resources” involving “three kinds of stimuli: focal,
contextual, and residual” (Roy & Andrews, p. 18).

Roy weaves the themes of systems theory, holism, and adaptation throughout the
RAM. She directly connects the RAM with goals, interventions and evaluations (Andrews &
Roy, p. 28). She particularly emphasizes the need for nursing diagnoses to guide this
process. The RAM incorporates six steps in the nursing process for patient care:
assessment of behavior; assessment of stimuli; nursing diagnosis; goal setting; interventions;
and evaluation (Andrews & Roy, p. 28). Each step of this process is performed in
collaboration with the patient and often carried out simultaneously (Andrews & Roy, pp. 28-
29).

MRSA infections impact individuals and groups on many levels. The physical impact
of the infection can be mild or severe and affect the individual's external integrity and ability
to adapt to the environmental stimuli. MRSA infections involve significant time and cost, and some infections can be recurrent. In addition to the physical impact, there are also significant emotional and psychosocial stimuli. Skin and soft tissue infections, as well as more deep seated infections, can negatively impact an individual's self image and limit social interactions, usual role functions, and participation in activities. Health care workers can label and stigmatize individuals with MRSA. Physical isolation of these patients can lead to social isolation and may negatively impact the quality of care received and the satisfaction with that care. Community spread of MRSA carriage or infections can also lead to emotional and psychosocial stress for affected individuals and their families.

Roy's themes of holism, inter-connectedness and adaptation are used here to guide the investigation of MRSA spread, its impact on the individual and community, and the individual and community's adaptation to MRSA. The RAM facilitates assessment of stimuli, development of areas of focus (nursing diagnoses), and goal setting (e.g., limiting spread of CA-MRSA, appropriate treatment of infections, etc). The guidelines described later in this paper define the interventions. Evaluation of these guidelines will be an ongoing, interdisciplinary, multi-agency effort. The RAM also helps identify areas for further research and investigation.

Review of Literature

Pathophysiology

Understanding the structure, cellular processes, virulence factors, and pathogenicity of an organism is necessary to effectively limit its threat to humanity. This section reviews the basic pathophysiology of S. aureus and its relation to human morbidity and mortality.
Staphylococcus Aureus (SA) is a gram-positive coccus bacterium that is coagulase positive: able to clot blood plasma. SA has a unique cell membrane peptidoglycan in which the interpeptide bridge contains multiple glycine residues, making it susceptible to lysostaphin (Wilkinson, 1997). The cell membrane peptidoglycan is O-acetylated, which has “a significant influence on the biologic properties of peptidoglycan in the host parasite relationship” (Wilkinson, p. 8). SA peptidoglycan allows for a semi-rigid, cross-linked, multilayered cell membrane structure capable of withstanding high internal cell pressures (Wilkinson, pp. 8-10). The cell membrane of SA typically contains four penicillin binding proteins (PBPs) probably representing transpeptidase or carboxypeptidase enzymes; strains of SA, such as MRSA, can thrive with a reduced number and altered structure of PBPs (Wilkinson, pp. 10-11). The SA genome “consists of a single circular chromosome plus prophages, plasmids, transposons, insertion sequences, and other incompletely characterized variable accessory genetic elements” (Wilkinson, p. 4), which contribute to cell maintenance, growth, and adaptation to a variety of environments.

In humans, SA is frequently associated with asymptomatic colonization of the mucous membranes (especially the anterior nares), skin, and skin glands; at any time approximately 20% of the general population may be colonized for varying periods of time with SA (Oliveira et al., 2002; Rice, 2006; Sheretz et al, 1996). SA also frequently colonizes and infects other mammals especially dogs, cats and horses. SA produces a number of extra cellular toxins and enzymes (e.g., coagulase, protease, pyrogenic exotoxins, leukocidin, beta-lactamase, hemolysins, nuclease, hyaluronidase, exfoliatin) that act as virulence factors, tissue invasion factors, and bacterial defense mechanisms to evade host immune responses (Projan & Novick, 1997, pp. 55-69). SA is associated with infections of the skin, wounds,
respiratory system, central nervous system, urinary tract system, and the blood stream; it is also associated with infections related to invasive devices, procedures and foreign bodies (Diep et al., 2006; Oliveira; Projan and Novick, pp. 55-81). SA’s “versatility of pathogenic strategies, number of virulence factors, and capacity to survive and multiply in a wide range of environments...is unsurpassed by any other human pathogen” (Oliveira, p. 181). SA has multiple mechanisms to rapidly develop resistance to drugs: use of plasmid borne penicillinase to degrade the antibiotic before it can reach its target; alteration in cell wall antibiotic binding sites that prevent drug binding to SA cell wall; Protein A and proteases that alter IgG antibody function and effectiveness; and superantigens that bind to major histocompatibility factors and moderate host immune function (Projan & Novick, pp. 55-81).

SA possesses an unsurpassed ability in the world of human bacterial pathogens to rapidly develop antibiotic resistance. Within a decade of benzylpenicillin’s initial use to treat SA infections, high level resistance isolates were identified because of SA’s acquisition of plasmid associated penicillinase that degraded the antibiotic before it could bind to PBPs (Oliveira et al., 2002). Methicillin was introduced into clinical use around 1960 in Europe and within a year SA strains resistant to methicillin were found (Oliveira). The mechanisms that SA uses to evade chemotherapy are complex. According to Oliveira et al.:

The introduction of vast quantities of structurally diverse antimicrobial agents into the human environment during the past 60 years has presented a new set of challenges to bacterial pathogens such as S. aureus. Effective lineages of contemporary pathogens must excel in several capacities: they must be able to acquire resistant genes and to construct regulatory mechanisms that can adjust resistance levels to increasing concentrations of the antimicrobial agent. In the environment, the resistance-related determinants must find their way into genetic backgrounds that assure the capacity to compete with other bacteria. Pathogens
must be able to spread, establish ecological reservoirs, colonies and cause disease (p. 182).

Large amounts of antimicrobials in the environment drive MRSA's accelerated evolution (Oliveira). MRSA's process of evolution involves acquisition of DNA foreign to SA (mec element or staphylococcal chromosomal cassette [SCCmec]) into a larger DNA section of SA, the mecA gene, which is at a site specific location (Oliveira). This mecA gene encodes for an altered PBP (PBP2A), which then manipulates cell wall biosynthesis, and allows limited binding of beta-lactam antibiotics to the altered PBPs (Oliveira). Extensive study of historical SA isolates suggests that the acquisition of the mecA gene occurred in Danish Methicillin susceptible SA (MSSA) isolates preserved from 1957 to 1970; these isolates belong to the phage III group or the related 83A complex, and the early MRSA isolates from the UK and Europe also belonged to this phage group and shared similar antibiotic resistance patterns: resistance to penicillin, streptomycin, tetracycline and occasionally erythromycin (Oliveira). The recently identified Iberian pandemic MRSA clone shares the same genetic background as the early Danish isolate with additional elements coding for multiple antibiotic resistance (Oliveira). To date five pandemic MRSA clones have been identified worldwide (Iberian, Brazilian, Hungarian, New York/Japan, and pediatric clones) representing clonal lineages that can successfully cause infection; persist in the environment; and spread geographically—in some cases inter-continentally (Oliveira). Using MLST, two genetic backgrounds (A and B) were identified for the five pandemic clones. Studies on available isolates suggest that the Iberian, Hungarian and Brazilian clones share closely related genetic backgrounds (A), while the New York/Japan and pediatric
clones share related genetic backgrounds (B) that are distinct from the other three pandemic clones (Oliveira).

The SCCmec element has been further broken down into four types: alleles I-IV, and closely related offshoots (e.g., IA, IIIA, IVA). SCCmec I-III alleles are associated with HA-MRSA strains, while SCCmec IV is associated with CA-MRSA strains (Oliveira et al., 2002). For the five pandemic MRSA clones the mec element types have been identified: Type I/IA: Iberian and archaic clone; Type II: New York/Japan clone; Type III/IIIA: Brazilian and Hungarian clones; Type IV/IVA: pediatric clone (Oliveira). The data suggest that the mec element has been incorporated into S. aureus species at “multiple, yet restricted and independent occasions” (Oliveira, p. 187) with expansion of clonal lineages, rather than by horizontal transfer of the mec element between different SA lineages, which occurs much less frequently (Oliveira). Where the mec element originated is unclear, possibly from coagulase negative staphylococcal strains (Oliveira). What is clear is that the SCCmec type IV element (associated with CA-MRSA strains) appears to have greater mobility (possibly due to its smaller size compared with types I-III), to have persistence in the environment, and to associate frequently with additional factors which increase its virulence and pathogenicity (Oliveira) such as the Panton-Valentine leukocidin (PVL) toxin that increases CA-MRSA's virulence by causing tissue necrosis and leukocyte destruction (Appelbaum, 2006; Kluytmans-VandenBergh & Kluytmans, 2006).

HA-MRSA has specific associated risk factors: recent reports of CA-MRSA have no such similar or identified associated risk factors. HA-MRSA infections have been classified into four distinct clones named for the areas where they were isolated (Iberian, Brazilian, Hungarian, and New York/Japan), all sharing the staphylococcal chromosomal cassette
SCCmec alleles I-III polymorphism. CA-MRSA isolates also share the SCCmec polymorphism with the additional association with a type IV allele and the Panton-Valentine leukocidin (PVL) virulence factor (Oliveira et al., 2002). HA-MRSA infections are generally multi-drug resistant, probably due to the high multi anti-microbial environment in the inpatient setting. CA-MRSA infections tend to be susceptible to many anti-microbial agents while retaining their resistance to beta-lactams. HA-MRSA infections are associated not only with skin and soft tissue structures, but also with bacteremia, pneumonia, endocarditis, urinary tract infections, septic joint infections, osteomyelitis, ophthalmic infections, meningitis, toxic shock syndrome, enterocolitis, and staphylococcal scalded skin syndrome (Crossley and Archer, 1997, pp. 310-311). CA-MRSA infections are primarily skin and soft tissue infections (Fridkin et al., 2005; MMWR, 2003; Ribeiro et al., 2005; Young et al., 2004), although more serious, and sometimes fatal, infections have also been reported (Chen et al., 2005; Fridkin; MMWR, 1999; Young et al., 2004). CA-MRSA isolates are also found to have a faster growth rate compared to HA-MRSA isolates, which may enhance CA-MRSA's fitness and spread in the environment (Kluytmans-VandenBergh & Kluytmans, 2006; Rice, 2006). HA-MRSA infections have been intensively studied for many years with identification of specific patterns. CA-MRSA infections are continually being isolated in differing populations and in various areas of the world with no specific pattern so far identified.

A new wrinkle in the story of MRSA is the development of MRSA strains that have reduced susceptibility to or are resistant to vancomycin. Vancomycin is a glycopeptide antimicrobial that inhibits synthesis of the SA cell membrane (Appelbaum, 2006). Vancomycin has been in use since 1958 and has become the mainstay of HA-MRSA and
some CA-MRSA infections since the 1990's (Schito, 2006). The first reports of reduced susceptibility to vancomycin (vancomycin intermediate SA—VISA) came in the late 1990's from Japan in 1996 or 1997, followed by reports in other areas of the world including the USA (Appelbaum, 2006; Appelbaum, 2006; Shito, 2006). The year 2002 witnessed the first completely vancomycin resistant strains of SA (VRSA): a chronically ill 40 year old Michigan man was infected with MRSA, vancomycin-resistant Enterococcus faecalis (VRE), and Klebsiella oxytoca. He had received ongoing antibiotic treatment and had an indwelling catheter, which was subsequently cultured (Appelbaum). A second case was identified in 2002 in PA, a third case in New York in 2004, and a fourth case in Michigan 2005 (Appelbaum; Schito). Common dominators in these cases include: older age, compromise of peripheral circulation to the lower extremities (associated with hypertension, peripheral vascular disease, and diabetes), chronic foot ulcers, and history or prior treatment with vancomycin (Appelbaum; Tenover, 2006). SA's mechanism of resistance to vancomycin is thought to be though genetic material transfer that codes for thickening of the SA cell wall; increased production of peptidoglycan with increased quantities of D-alanyl-D-alanine residues that bind and sequester vancomycin molecules extracellularly; and slowing of metabolic pathways resulting in slow cell growth (Appelbaum; Schito; Tenover, 2006). The development of VRSA is thought to occur in the presence of high vancomycin pressure from long term vancomycin therapy (Appelbaum) in the presence of VRE, debilitating chronic medical conditions, impaired lower extremity circulation with chronic ulcers and older age (Appelbaum; Howe, Monk, Wootton, Walsh, & Enright, 2004; Whitener et al., 2004). However, in one of these VRSA isolates, vancomycin use was not a relevant factor: the patient had developed a vancomycin allergy 5 years prior to culturing VRSA (Whitener,
VISA strains are thought to acquire resistance by altering peptidoglycan synthesis and changes in metabolic pathways that slow cell growth (Tenover); but VRSA strains are thought to acquire genetic material from other vancomycin resistant bacteria, such as VRE, via transfer of the vanA gene (Appelbaum; Schito; Tenover). VRSA had been reported in rare, isolated cases in the United States (Appelbaum; Howe et al., 2004; Whitener); however, more VISA strains have been emerging over the past decade, and the concern with reduced vancomycin susceptibility, and reduced susceptibility to all glycopeptides, has been growing worldwide (Appelbaum; Schito).

The development of MRSA clones, especially HA-MRSA, has been associated with high antibiotic selection pressure in the environment causing methicillin susceptible SA (MSSA) strains to acquire the SCCmec gene from other bacteria in the environment (via transduction by bacteriophages [Livermore, 2000]) and through horizontal transfer of the mec element between various lineages of SA (Oliveira et al., 2002) mediated by transposons and plasmids (Livermore). However, the ability of S. aureus to develop resistance to environmental stressors cannot be explained solely by high antimicrobial pressure. Studies of bacteria have found that several determinants of antibiotic resistance probably originated in bacteria that autonomously produce antibiotics as a protective mechanism against other bacteria, even before the advent of antibiotic use by man (Alonso, Sanchez, & Martinez, 2001). Additional bacterial pressure would select in favor of these resistant strains (Alonso, 2001), as is the case with SA and its ability to rapidly develop antibiotic resistance soon after the introduction of new antibiotics into clinical use (Livermore; Oliveira; Schito, 2006). Antimicrobial pressure on bacteria including SA occurs in the hospital setting as well as in the community environment: antibiotics used for humans, animals and in agriculture are
introduced into the environment (water and soil) because of direct use to prevent or fight infections or as additives to feed (in cattle, chicken, pig and fish raising industries), and in agriculture to fight plant infections and pests (Cabello, 2006; Greenlees, 2003; van den Bogaard & Stobberingh, 2000).

Antibiotic resistance can also develop in bacteria in the outside environment as well as in clinical settings via the process of co-selection. Bacteria develop mechanisms to resist stressors in the environment from contaminants such as metals (e.g., copper, silver, mercury, cadmium, zinc), chemicals (such as quaternary ammonium compounds), defouling agents, and detergents (Baker-Austin, Wright, Stepanauskas, & McArthur, 2006; Stepanauskas et al., 2006). These mechanisms take the form of efflux mechanisms to pump toxins out of the cell; mechanisms to reduce cell membrane permeability; release of enzymes to inactivate toxins; and mutation of cellular targets (Baker-Austin). The results of a study by Stepanauskas and colleagues suggest that such bacterial exposure to human introduced metals into the environment is a more important environmental selection factor for antibiotic resistance than antibiotic pressure (2006). While these studies involved different human pathogens than S. aureus and an aquatic environment, they provide compelling evidence that the mechanisms by which bacteria develop antibiotic resistance, as well as survive and flourish in many different environments, are more complex than was previously thought.

**Epidemiology**

In less than a decade, MRSA has evolved from a nosocomial problem into a community and health care institution problem. The deaths of four children between 1997 and 1999 in Minnesota and North Dakota from CA-MRSA infections (MMWR, 1999)
without traditional risk factors for MRSA infections accelerated the investigation into the origins, prevalence, and health implications of CA-MRSA infections (Appelbaum, 2006).

This section will describe the current epidemiological information about CA-MRSA.

MRSA first emerged as significant health care issue in 1963 with the first MRSA outbreak in Europe and has since spread throughout the world in successive outbreaks (Oliveira et al., 2002). In the United States, nosocomial MRSA infections have increased from a 4% infection rate to 50% or more, with similar statistics in the England and many European countries (Oliveira). Efforts to identify the evolutionary spread of MRSA worldwide have identified two major genetic backgrounds (A and B) from which the five early “pandemic clones” of MRSA worldwide have originated (Oliveira; Enright et al., 2006). At least two additional genetic backgrounds have subsequently been identified (C and D). CA-MRSA strains evolved from the B genetic background, while most pandemic HA-MRSA strains evolved from genetic background A (Oliveira); epidemic MRSA (EMRSA) strains identified in the UK and Germany evolved from genetic backgrounds C--EMRSA-16--and D--EMRSA-15 (Oliveira). Genetic backgrounds A1-4 share closely related genetic backgrounds “and evolved from a common ancestor with a genotype very similar to the archaic MRSA” (Oliveira, p. 187). The mec element responsible for methicillin resistance has most likely evolved from methicillin susceptible SA strains in the environment that have “imported” the mec element either vertically from other organisms in the environment or via horizontal transfer between different strains of MRSA (Oliveira). Both mechanisms have occurred many times in the last 40 years to account for the diversity of sequence types (ST) and clonal complexes (CC) that have so far been isolated, primarily in CA-MRSA strains (Crisostomo et al., 2001; Enright, 2002). The ultimate origin of the mec element has not
been identified so far but could have involved coagulase negative staphylococcal (CN-S.) species (Enright; Oliveira). In a sampling of MRSA clonal complexes from 22 different countries, Enright found close association and similarities between SCCmec I and IV (SCCmec I being the most frequent clonal complex), and found the presence of SCCmec I in early MRSA isolates and CN-S. species, leading to the conclusion that SCCmec IV in CA-MRSA strains may be related to a possible precursor of the mec element (2006).

CA-MRSA strains have evolved from genetic backgrounds A, B, and D and share the SCCmec IV and IVa elements (Oliveira et al., 2002), similar antibiotic susceptibilities--resistant to beta-lactams but susceptible to most other antimicrobial classes (Carleton et al., 2004; Crisostomo et al., 2001; Diep et al., 2006; Gilbert et al., 2006); similar propensity for causing skin and soft tissue infections (Fridkin et al., 2005; Gilbert; King et al., 2006; Stemper et al., 2004; Young, 2004); and increased incidence of acquiring additional virulence factors than HA-MRSA strains (Diep; Oliveira). The most common CA-MRSA strains isolated in North America are ST1-MRSA-IV (MW2/USA 400) and ST8-MRSA-IV (USA 300) (Allen, 2006; Diep; Ellis et al., 2004; Gilbert et al., 2006; Hulten et al., 2006; King, Humphrey, Wang, Kourbatova, Ray, & Blumberg, 2006; Moran et al., 2006; Stemper). While these CA-MRSA strains are primarily associated with SSTIs, ST8-MRSA-IV (USA300) is the more virulent strain causing severe, and sometimes fatal, cases of MRSA pneumonia (Francis et al., 2005; Frazee et al., 2005; Hageman et al., 2006). The ST8-MRSA IV (USA 300) strain has acquired an unusual genetic element called the "arginine catabolic mobile element" (ACME) that appears to provide a selective growth and survival advantage compared to other MRSA strains, and making it better adapted to "establish and maintain cutaneous colonization that do other staphylococcal strains" (Grayson, 2006).
Outbreaks of CA-MRSA infections have been noted in athletic team members (Cohen, 2005; Weber, 2005); military recruits (Ellis, 2004); urban poor, homeless, and drug users (Charlebois et al., 2002; Gilbert, 2006; Kowalski et al., 2005; Young et al., 2004); children, especially in day care settings (Chen et al., 2005; Hulten; Kluytmans-VandenBergh and Kluymans, 2006; Kowalski et al., 2005; Zaoutis et al., 2006); native populations (Stemper et al., 2004; Weber, 2005); closed or semi-closed communities (Salgado et al., 2003); correctional inmates (MMWR, 2003); and in increasing numbers in emergency departments nationwide (Fleming, Brown, & Tice, 2006; Moran et al., 2006). Risk factors vary between different populations and different geographical areas but include recent/frequent antibiotic use; recent hospitalization or contact with health care system; underlying medical conditions; depressed and crowded living conditions; pediatric age group; and African American or Native American groups (see tables 1 and 2). The individual and group characteristics that increase susceptibility to MRSA carriage and/or infection are unknown and no research is available that investigates the interactions of the above listed risk factors. Much available research investigates the microbiological and genetic details of MRSA and its susceptibility to anti-microbials and disinfectants, but this research does not evaluate the interactions of CA-MRSA infections with individual and population characteristics.

A number of factors make it difficult to determine the scope of the CA-MRSA problem. One obstacle is the lack of a consistent, generally accepted definition of what constitutes CA-MRSA. In a meta-analysis of CA-MRSA prevalence and risk factors Salgado et al. (2003) found 8 different definitions used in the research reviewed. The definitions used some or all of the following aspects: temporal analysis (MRSA isolate cultured <48-72
hours after hospital admission); microbiological analysis (e.g., PFGE or MLST) to determine sequence typing (ST) and clonal complexes (Enright et al., 2002) such as USA 300 or MW2 often with additional virulence factors such as PVL); antibiotic susceptibility; presence or absence of health care associated risk factors; and type of presenting infection (e.g., skin and soft tissue infections [SSTIs] (Salgado). Alternatively, CA-MRSA infections are defined by exclusion: MRSA infection or carrier state without identified characteristics of HA-MRSA (Cohen, 2005; Naimi et al., 2003; Sattler, Mason, & Kaplan, 2002).

The precise timing and location of MRSA acquisition is usually difficult to determine. MRSA carriage may be transient or persist for long periods of time (Salgado et al., 2002). MRSA carriage rates vary from 0.26% (Shopsin et al., 2000) to 1.5% in the general healthy population (Ali, Sykes, Flock, Hall, & Buchan, 2005; Maudsley et al., 2004), with rates of 20% or higher among some health care workers, residents in institutions/long term care facilities, and residents in closed communities (Charlebois et al., 2002; Graham, Lin, & Larson, 2006; Salgado; Kampf, Adena, Ruden, & Weist, 2003). Little is known about factors involved in the transmission of MRSA from the carrier state to subsequent development of infection. Recent evidence points to intra-familial transmission, as well as inter-species transmission from companion pets (Stemper et al., 2004; Salgado; Loeffler et al., 2005; Manian, 2003; Strommenger et al., 2005; Wagenvoort, DeBrauwer, Sijstermans, & Toenbreker, 2004; Weese et al., 2006). The community pool of MRSA carriers is probably far larger than most estimates determine. The distinctions between CA-MRSA and HA-MRSA are beginning to blur: CA-MRSA clonal strains are being isolated in hospitalized patients, and HA-MRSA strains are being isolated in patients in the community without specific health care associated risk factors (Appelbaum, 2006; Carleton et al., 2004; Hulten et
al., 2006; Kluytmans-VandenBergh and Kluytmans, 2006; Saiman et al., 2003). Other confounding factors are race, socioeconomic status and living conditions, and geographic location (Gilbert et al., 2006; Graham et al., 2006; King et al., 2006; Naimi et al., 2003; Sattler, Mason, & Kaplan, 2002; Stemper; Young et al., 2004).

Slightly different CA-MRSA definitions have been proposed by Carleton et al. (2004) and Salgado et al. (2002) and Said-Salim and colleagues (2003). Both Carleton and Salgado advocate using “community onset” as the designation for non-nosocomial MRSA acquisition (CO-MRSA), which highlights the ambiguity of MRSA acquisition time and location. This seems more technically accurate when combined with other indicators of community acquired MRSA. Alternatively, Said-Salim and colleagues (2003) and Salgado divide CA-MRSA in to two categories: CA-MRSA with risk factors and CA-MRSA without risk factors. While this latter designation seeks to identify true community acquisition of MRSA, it doesn’t acknowledge the complex interactions between individuals and their internal and external environments. We have yet to identify all the factors that constitute risk factors for individuals or communities. The use of CO-MRSA or community “associated” MRSA with or without risk factors is a reasonable compromise. A generally accepted, interdisciplinary definition of MRSA in the community is needed (Salgado; Said-Salim). The CA-MRSA definition used here is: MRSA carriage or infection with identified SCCmec IV/A element, with genotype matching already identified non-HA-MRSA strains, with antibiotic susceptibility to most non-beta lactam antibiotics (varying with geographical area), not associated with recognized HA-MRSA risk factors, and isolated <24 hours after hospital admission.
Naming of MRSA strains or genotypes has provided ambiguity and confusion. MRSA nomenclature differs in different countries and depending on the genotyping techniques used—examples are PFGE and MLST (Enright et al., 2002). Additionally, MRSA strains differentiated by the PFGE technique as distinct genotypes are found to be indistinguishable using the MLST (Enright). Five major MRSA genotypes have been identified from international isolates that account for the majority of MRSA genotypes, ST-5, ST-8, ST-22, ST-30, and ST-45 (Enright), identified as causing disease worldwide (Crisostomo et al., 2001; Enright; Oliveira et al., 2002). CA-MRSA strains have evolved from all five of the major genotypes (Enright). Enright has proposed a standardized nomenclature for MRSA clones using MLST designations and taking into account that MRSA clones may have evolved in different places on different occasions having the same genetic background. He proposes naming MRSA clones by their genotypes (ST-sequence type/allelic profile) and the SCCmec type: examples are ST8-MRSA-IV--aka EMRSA-2 and 6, and USA 300 clones (Diep et al., 2004; Enright). This system would decrease nomenclature confusion and standardize MRSA definitions that could be used internationally.

MRSA is transmitted via direct contact either with an infected individual or a contaminated object (Huws et al., 2006; Romero, Treston, & O’sullivan, 2006; Turabelidze, Lin, Wolkoff, Dodson, Gladbach, & Zhu, 2006), primarily via the hands of health care workers (Pittet et al., 2006), and most probably, via family members and contact with infected individuals. What is not clear is how individuals become transient carriers of MRSA. Personal hygiene and hand washing habits are key elements in MRSA transmission (Carrico & Niner, 2002; Muto et al., 2003; Pittet; Romero et al., 2006; Turabelidze).
However, this is not the only means of MRSA transmission. Research has been conducted for many years on airborne MRSA. When MRSA carriers infected with rhinovirus, influenza, or possibly, seasonal allergies sneeze, MRSA is expelled into the environment as airborne particles (Bischoff et al., 2006; Sheretz et al., 1996). Sneezeing, not coughing, is the key; and proximity to the carrier is necessary to receive the airborne MRSA particles. Amoebae in the environment (especially health care environments) can ingest MRSA and then reintroduce the bacteria back into the environment, either as airborne particles or onto environmental surfaces (Huws). The old advice to cover your sneeze and wash your hands applies now more than ever. This airborne MRSA transmission could be a confounding factor in determining where and how individual MRSA contact occurred.

**Current Treatment**

Across much of the US, the community treatment of SSTIs currently relies on the use of beta-lactam antibiotics as first line agents (Kowalski et al., 2005). The rates of CA-MRSA infections (mainly SSTI’s) vary greatly across the country (tables 1 and 2), and in much of the country, the CA-MRSA prevalence is unknown. Much of the information available involves outbreaks of CA-MRSA infections in specific groups where treatment failures resulted and cultures were obtained. In many communities, CA-MRSA infections may be treated without cultures, and subsequent treatment failures were attributed to factors other than CA-MRSA.

Current recommendations for the treatment of out patient CA-MRSA infections involve appropriate antibiotic therapy based on culture results, drainage of abscesses, combination therapy, and frequent follow-up. For most areas of the country, clindamycin, trimethoprim-sulfamethoxazole (TMP-SMX), and doxycycline have been effective as
monotherapy (Kowalski et al., 2005; Moran et al., 2006). Additional agents such as erythromycin, cipro, gentamicin and tetracycline have also been used effectively in some areas (tables 1 and 2). Varying rates of clindamycin resistance during treatment have been found making this agent a second choice in some areas (Hulton et al., 2006; Kowalski), and special laboratory testing should be used on strains resistant to erythromycin but susceptible to clindamycin when clindamycin is being used as monotherapy (King et al., 2006; Kowalski). Combination therapy with rifampin has been recommended because most CA-MRSA isolates remain susceptible to rifampin (Cohen, 2005; Fleming et al., 2006; Hulton); however, some studies have questioned the synergistic benefit of rifampin (Cunha, 2005; Ellis and Lewis, 2005). Monotherapy with rifampin is not recommended because of its ineffectiveness with Gram-positive bacteria and because of problems with inducible resistance (Livermore, 2000; Moran; Romero et al., 2006). Sabol et al. (2006) recommend TMP-SMX as the first line treatment for confirmed CA-MRSA infections because of its high bioavailability and bactericidal activity, with clindamycin, doxycycline, and monocytecline as alternative agents. For patients with more serious infections that require hospitalization, vancomycin, alone or in combination with other agents is recommended (Kowalski; Livermore; Moran). Newer agents are also available with good in vitro results against CA-MRSA, such as linezolid, teicoplanin, and daptomycin; however, these agents are significantly more expensive, have less availability for outpatient use, and have more significant adverse reactions associated with their use (Kowalski; Sabol). In children, antibiotic treatment recommendations are similar to those for adults, with the exception of tetracyclines because of potential tooth damage: clindamycin is recommended as a first line
agent, with TMP-SMX, and linezolid as alternative agents (Hulton; Hussain et al., 2000; Marcinak and Frank, 2003; Sattler et al., 2002).

Some CA-MRSA infections, such as abscesses and furunculosis, can be treated with incision and drainage, either as monotherapy or in combination with antibiotic therapy (Cohen, 2005; Fridkin et al., 2005; King et al., 2006; Romero et al., 2006; Young et al., 2004). No clinical trials comparing incision and drainage alone, incision and drainage with antibiotic therapy, and antibiotic therapy alone are available. However, the experience of some urban centers treating high volumes of SSTIs suggests that incision and drainage is an effective treatment alone or in combination with antibiotics, even with those antibiotics that were ineffective against CA-MRSA alone (King; Young). Clinician judgment is important in determining where incision and drainage is appropriate and when combination therapy with antibiotics is necessary.

Research is ongoing to find new agents that are effective against gram positive bacteria such as MRSA. Some exciting work is being done with bacterial transforming agents (BTAs) that enhance the activity of antimicrobials that attach to the bacterial cell wall because of their action in altering the cell's synthesis of peptidoglycan in the cell wall where methicillin resistance is found (Carey and Dancer, 2006). These BTAs are not antimicrobials but would be used in conjunction with beta-lactam agents to preserve the beta-lactams activity against MRSA (Carey and Dancer). In addition to BTA research, studies are being done to re-engineer beta-lactam agents so they could bind to the PBP2' site on the MRSA cell wall and thereby interfere with the cell wall stability; Ceftobiprole is such an agent that is currently in phase III trials in Europe and producing promising results against MRSA (Livermore, 2006). Quinupristin/dalfopristin, a semi-synthetic streptogramin agent that has
potent bacteriocidal activity against S. aureus, is currently being studied for use in mediating the toxicity of S. aureus toxins and virulence factors in host cells, at doses lower than used for bacteriocidal activity (Koszczol et al., 2006). A new fluoroquinolone agent is being studied for use against gram positive bacteria, including MRSA, and may provide an additional antibiotic agent if it passes clinical trials (Kwon et al., 2006). Tigecycline is a glycylcycline agent now available in the U.S. for MRSA caused SSTIs that is as effective as vancomycin, but it is only available as a parenteral agent and has limited experience in use against CA-MRSA infections (Ellis and Lewis, 2005). Finally, two lipoglycopeptide agents, dalbavancin and telavancin, are currently in clinical trials and showing promise in treating gram positive bacteria such as MRSA; however, their use for CA-MRSA infections hasn't been determined (Ellis and Lewis). As with many other new antimicrobial agents, the newer agents mentioned here are generally more expensive, have limited data concerning adverse reactions, and often have limited formulations available; all of which make their general use in treating CA-MRSA infections unlikely. In the current state of health care in the US many beneficial antimicrobial agents may be potentially available but out of reach in practice if not covered by Medicare/Medicaid, commercial and private insurers.

Areas for Further Research

There is much that is not known about CA-MRSA. We don’t understand why some healthy individuals are prone to CA-MRSA carriage and/or infection; what effect race and other risk factors have on CA-MRSA susceptibility; and how the complex interaction of individual and environmental factors affects CA-MRSA transmission. We also don’t know the true prevalence of CA-MRSA in any one area at a particular time: how stable is the prevalence rate, what factors affect rates of transmission, and what effect do control
measures have on CA-MRSA rates in different populations? Listed below are a sampling of research suggestions gleaned from various CA-MRSA research articles, highlighting the depth and breadth of needed scientific information.

1. Epidemiology

   a. research CA-MRSA to identify adequate risk factor analysis (Salgado et al., 2003)

   b. research MRSA of different mec types/clinical isolates to predict which would assist empirical therapy (Graham et al., 2006)

   c. research commonalities and differences in epidemiological subgroups of patients (Hulton et al., 2006)

   d. research to determine specific risk factors associated with acquisition for the purpose of establishing preventive measures in Native American communities (Stemper et al., 2004)

   e. research association between race and CA-MRSA (King et al., 2006)

   f. research to identify prevalence of MRSA in various locations, follow trends in antimicrobial susceptibilities, and identify optimal therapy (Moran et al., 2006)

   g. research to assess prevalence of MRSA in hospice and of associated morbidity, including risk of and source of infection within units: colonized patients and staff (Dand, Fyvie, Yee, & Sykes, 2005)

   h. research simultaneously in various locations the proportion of community-acquired pneumonia caused by MRSA (Frazee et al., 2005)
2. Economics

Research economic aspects: increased diagnostic expenses may be compensated by more effective therapy (Jappe, Petzoldt, & Wendt, 2004)

3. Microbiology

a. research to include multicenter and standardized studies to enable an extended comparison and further investigate the nature and origin of aminoglycoside susceptible MRSA (Lescat, Dupeyron, Faubert, & Mangeney, 2003)

b. research to identify worldwide trends in CA-MRSA: mechanisms, findings, and similarities (Charlebois et al., 2004)

c. research to extend understanding of the relationship between the antibiotic treatment, emergence of resistance, and clinical outcomes (Young et al., 2004)

d. research to further define the epidemiological and microbiological characteristics of MRSA in the community setting (Allen, 2006)

e. research the exact nature of the selective advantage conferred by the observed combination of genetic traits (Vandenesch et al., 2003)

f. research the role of staphylococcal toxins and internalization in the pathogenicity of this organism (Ferens and Bohack, 2000)
g. research the prevalence and role of antibiotic resistance genes, putative
virulence factors and genes that enhance bacterial fitness
(Holden et al., 2004)

h. research and follow up of HA-MRSA patients returning to the
community with the goal of identifying the selective loss or gain
of resistance genes responsible for resistance to agents other than
methicillin (Charlebois, 2002)

4. Risk factors
   a. research identifying risk factors for MRSA carriage to predict resistant
      SA carriage on hospital admission and thereby identify persons who
      require empirical MRSA coverage (Shopsin et al., 2000)
   b. research and continued surveillance, identification of risk factors, and
      evaluation of other antibiotics such as TMP-SMX and linezolid for
      treatment of minor as well as invasive CA-MRSA infections in the
      pediatric age group (Marcinak & Frank, 2003)

5. Surveillance
   a. research and active surveillance for CA-MRSA infection and
      colonization, and for molecular studies of virulence factors
      critical to a complete understanding of the epidemiology of
      CA-MRSA (Saiman et al., 2003)
   b. research into directed screening of patients most at risk to assess the
      extent of the VISA and VRSA problem (Appelbaum, 2006)
c. research reliable mechanisms for the routine surveillance of antibiotic resistant organisms in the general community in the UK (Abudu, Blair, Fraise, & Cheng, 2001)

6. Transmission

a. research animals as a source of infection and as a potential subsequent reservoir of infection; surveillance and control measures; and evaluation (Maniam, 2003; Weese et al., 2005)

b. research developing risk analysis studies to determine whether veterinarians and people living or working with companion animals are categories at risk for MRSA carriage (Loeffler et al., 2005)

c. research route of infection in animals; cross contamination (Strommenger et al., 2005)

d. research importance of the clinical setting compared with the intrinsic biology of MRSA isolates (Hussain, Boyle-Vavra, Bethel, & Daum, 2000)

e. research to ascertain whether other viruses cause similar airborne release patterns of MRSA (Bischoff et al., 2006)

7. Treatments

a. research to recommend empiric antibiotic therapy of SA acquired in the community where CA-MRSA prevalence is increasing (Sattler et al., 2002)

b. research and evaluate oral TMP-SMX therapy as the sequential therapy (Chen et al., 2005)
c. research use of older anti-microbial agents (including combinations) in prospective analyses for CA-MRSA infections (Ellis and Lewis, 2005)

d. research bacterial transforming agent (BTA) 19976a at different concentrations and its effect on vancomycin susceptibility in SA (Carey & Dancer, 2006)

e. research to correlate microbiological outcomes based on pharmocokinetics/pharmacodynamic (PK/PD) data and clinical outcomes in patients (Metlay, Powers, Dudley, Christiansen, & Finch, 2006)

Summary

The study of CA-MRSA infections in humans is a complex example of the ongoing adaptability of nature and humans in their interactions with each other. Bacterial infections have been a serious health problem for all of human history. While efforts to prevent and treat infections and to eradicate bacteria in our environment have led to longer and better lives, bacteria (especially S. aureus) have proven they can persist and adapt to treatment and control measures. Antibiotics are the main weapon against S. aureus infections; yet, S. aureus strains have developed resistance to every antibiotic discovered. MRSA infections have moved from hospital to the community, affecting healthy people without recognized risk factors for infection. Despite enormous focus and research, we do not fully understand the pathophysiology of CA-MRSA and its transmission in different communities or the risk factors predisposing portions of our population to infection. Roy’s Adaptation Model is used in this paper to guide the investigation of CA-MRSA and to develop appropriate interventions to use in our response to this stimulus in our environment.
An in depth literature search reveals enormous gaps in basic understanding of a serious, looming epidemic in every field or perspective of research: epidemiology of CA-MRSA, economics, microbiology, transmission, treatment, surveillance and risk factors.
CHAPTER 3 IMPLICATIONS FOR PRACTICE AND COMMUNITY HEALTH

Introduction

Guidelines are currently available for preventing nosocomial MRSA transmission (Muto et al., 2003) but not for CA-MRSA. A review of hospital MRSA isolation policies is also available in the Database of Abstracts of Reviews of Effects (DARE) (2006). The Arizona Health Sciences Library online databases (Medline, CINHAL, Cochrane, ACP Bookclub and DARE) for the years 1994 to 2006 were reviewed and no published guidelines or database reviews were found for CA-MRSA: for preventing transmission, diagnosing and treating infection, and monitoring surveillance of carriage and chronic infections.

The only sources found apart from the AHSL databases were the Centers for Disease Control and Prevention (CDCP) in an expert panel summary on CA-MRSA management (Gorwitz et al., 2006) and clinical practice guidelines for the Federal Bureau of Prisons (FBOP) for management of MRSA in the federal prison system (August 2005). The CDCP strategies provide concise and practical information for practitioners addressing skin and soft tissue CA-MRSA infections. The expert panel also suggests additional research studies on the epidemiology, microbiology and pathophysiology of CA-MRSA so that optimal prevention and treatment strategies can be developed (Gorwitz), agreed on, and implemented by the health care community. While the FBOP clinical guidelines are specific for a prison system environment, much of the information may be applicable for community health concerns with homeless shelters, psychiatric or drug rehabilitation group homes, homeless camps, and other situations with crowded and depressed living conditions.

Consistent strategies are needed for CA-MRSA not only to effectively treat active infections.
in individuals and groups (outbreaks) but also to address the growing problem of increasing bacterial resistance to available antimicrobials. Not all communities have access to routine and timely diagnostic tests and must therefore rely on clinical judgment and evidence based guidelines. Below are suggested guidelines for practice at the individual level and at the community health level.

*Implications for Advanced Practice Nursing*

Based on literature review implications for management of CA-MRSA in Advanced Practice Nursing are as follows:

*General guidelines*

1. Practitioners should be familiar with trends in their community of practice including: prevalence of infections/diseases in specific populations; prevalence of drug resistant infections in the community; specific patterns of resistance to individual or classes of antibiotics; and outbreaks of infections in their community (Gorwitz et al., 2006)

2. Practitioners should maintain a high index of suspicion for CA-MRSA and thoroughly investigate risk factors, contacts, and exposure (Holcomb, 2006; Romero et al., 2006)

3. Practitioners should focus on patient and family education when treating suspected CA-MRSA infections (Holcomb; Romero)

4. Practitioners should practice antimicrobial stewardship (Fishman, 2006): evidence based empiric prescribing of antibiotics, use of culture and sensitivity results to guide ongoing treatment (Fishman; Holcomb; Romero)
5. Practitioners should maintain consistent practice of routine, high quality infection control habits, routine cleaning of equipment including stethoscopes (Hill et al., 2005; Holcomb; Nicolle, 2006), and effective hand hygiene using alcohol based hand cleansers (Holcomb; Muto; Nicolle).

6. Practitioners should maintain frequent and consistent assessment of treatment, post infection monitoring, and follow-up care (Gorwitz; Holcomb; Lipsky et al., 2004).

*Diagnosis and Treatment Algorithm.* See Appendix A

The CA-MRSA algorithm is designed to be used in conjunction with the algorithm supplement and the CA-MRSA focused history tool. Together these tools assist practitioners to recognize and plan interventions, and follow up for patients presenting with potential CA-MRSA infections. A major focus of the algorithm is on timely and repeated re-evaluation of patient response to treatment, the need for potential alterations in treatment, and determining the need for higher levels of care.

*Outpatient antibiotic therapy*

Low risk of CA-MRSA:

Beta-lactam agents are appropriate for the initial treatment of suspected S. aureus infections where CA-MRSA is not suspected: semi synthetic penicillin, first or second generation oral cephalosporins, macrolides, or clindamycin (Gorwitz et al., 2006; Stevens et al., 2005).

Frequent wound reassessment, follow-up, and close monitoring are important to assess efficacy, and if no improvement or worsening is noted,
changing to an agent effective against CA-MRSA is appropriate
(Gorwitz, 2006; Grayson, 2006; Lipsky et al., 2004; Stevens).

High risk of CA-MRSA

Adult: a 7-10 day course of antibiotic therapy is recommended with the following agents: TMP-SMX, Clindamycin, Monocycline or Doxycycline, or Linezolid. Of 15 articles reviewed, TMP-SMX was recommended first by 7 authors and as a second agent by 3 authors. Clindamycin was recommended as an initial agent by 4 authors with TMP-SMX listed second by 3 authors; individual patient medication allergies would alter the available choices (Blumberg et al., 2006; Cohen, 2005; Graham et al., 2006; Grayson, 2006; Holcomb, 2006; Johnson, 2006; King et al., 2006; Kleper & Bush, 2006; Kowalski, Berbari, & Osmon, 2005; Marcinak & Frank, 2003; Moran et al., 2006; Nicolle, 2006; Sabol et al., 2006; Sattler, Mason, & Kaplan, 2002).

Recent CDCP experts’ recommendations include using Clindamycin, Tetracyclines (tetracycline, doxycycline, minocycline), TMP-SMX, Rifampin in combination with other agents, and Linezolid (Gorwitz et al., 2006).

Pediatric: a 7-10 day course of antibiotic therapy is recommended with the following agents: TMP-SMX, Clindamycin and Linezolid (Marcinak; Sattler). Tetracycline agents are not recommended under age 8 because of the risk of damage to tooth enamel (Gorwitz; Sabol; Stevens). CDCP recommendations are similar: Clindamycin, TMP-SMX, Rifampin
in combination with other agents, and Linezolid (Gorwitz).

**Outpatient parenteral antibiotic therapy (OPAT)**

For some patients who may not be able to tolerate oral medications or where IV antibiotics may be more appropriate, OPAT may be a viable option and is being used more frequently every year. OPAT may be appropriate for stable patients requiring long term antibiotic therapy for SSTIs, cellulitis, infected wounds, complicated SSTIs, or osteomyelitis to avoid hospitalization and reduce the costs of treatment (Tice et al., 2004; Wynn, Dalovisio, Tice, & Jiang, 2005).

Wynn studied the safety and efficacy of OPAT agents for MSSA infections and found that Vancomycin and Clindamycin were equally effective but that Vancomycin had more adverse reactions; Linezolid was not included in this study. No studies were found on the safety and efficacy of OPAT treatment for CA-MRSA infections; however, Wynn’s results are helpful because Vancomycin and Clindamycin are currently used frequently as parenteral agents for MRSA infections (Blumberg; Romero; Stevens). Other OPAT agents available are TMP-SMX, Linezolid, Daptomycin and Gentamycin. For serious SSTIs, Lee et al (2006) recommends initial use of broad spectrum parenteral agents in combination with antibiotics targeting MRSA to achieve maximum bactericidal effect; however, some of these agents or combinations would require either hospitalization or treatment in an outpatient infusion center (Lee).
The CDCP recommends starting with Vancomycin for severe S. aureus infections; other agents recommended are Clindamycin, Daptomycin, Linezolid, Quinupristin-Dalfopristin, tigecycline, and TMP-SMX (Gorwitz).

Implication for Community Health

CA-MRSA infections are a concern for many vulnerable groups in our society: the chronically ill with serious health problems; underprivileged, marginalized individuals (individuals with no consistent shelter and limited access to sanitary facilities, with chronic psychiatric illness, with serious drug abuse problems, with inadequate income and crowded living conditions); and those individuals who have been recently imprisoned (Allen, 2006; Charlebois et al., 2002). These individuals may have access to initial diagnosis and treatment of infections but may not have the financial resources available to afford or finish a recommended course of treatment, or may lack the physical or psychological resources to consistently follow a treatment plan. These individuals, singly or in cohorts, could act as a potential reservoir of CA-MRSA infection that could negatively impact an already stressed health care system as well as the individual communities affected (Allen, 2006). The fragmented public health system in the US makes coordinated, interagency response to outbreaks difficult and sharing of critical information nearly impossible (Ransom & Joseph, 2005).

Some common threads are found in recent CA-MRSA outbreaks. Poor personal hygiene, crowded living conditions, sharing of contaminated personal items, and frequent direct skin contact are factors implicated in CA-MRSA transmission within groups and close personal contacts (Allen, 2006; Carrico & Niner, 2002; Ransom, 2005; Turabelidze et al., 2006). For marginalized groups, education and access to resources are necessary to prevent
and treat infections while limiting spread. Ransom advocates use of traditional public health strategies such as improved and comprehensive disease and risk factor surveillance and intensive outreach and public education. Additional public health strategies include “developing active integrated active surveillance systems; developing and sustaining strategic partnerships with public health laboratories, hospitals, correctional facilities, nursing homes, and child care centers; enhancing outreach and public education and policy activism” (Allen; Ransom, p. 262). Allen also advises including veterinary facilities as part of a concerted public health effort.

The current U.S. healthcare approach to infectious diseases relies heavily on antimicrobial therapy: Antibiotics are the second most commonly prescribed medications in the US and 45% of those prescriptions are in outpatient settings (Fishman, 2006). While this approach has worked well for many years, the specter of increasing multi drug resistance in bacteria looms ever greater while the availability of newer medications has not kept apace with the need (Fishman; Metlay et al., 2006; Ransom, 2005). Judicious, targeted use of antimicrobials that is guided by evidence based clinical judgments, culture and sensitivity testing, assessment of epidemiological effects of antibiotic use in reducing disease and drug resistance, and the use of antibiotic protocols in the community is a reasonable approach to minimize drug resistance (Bell, 2001; Fishman; Levin, 2001). In order for antibiotic stewardship (Fishman) to be effective, professional and regulatory buy-in is essential, as is intensive and ongoing educational programs for practitioners (Bell; Fishman; Levin; Ransom).

A new threat developing on the horizon is vancomycin intermediate and resistant S. aureus (VISA and VRSA), presumed to have developed in MRSA via transfer of the vanA
gene from VRE species. VISA strains have been isolated worldwide and one study found that 18% of MRSA isolates had reduced susceptibility to vancomycin (Appelbaum, 2006). Four VRSA cases have been reported in the US since 2002, primarily in debilitated patients with multiple serious medical problems (Appelbaum); however, one recent case of VRSA has been reported in a patient that had no exposure to vancomycin for the previous 5 years (Whitener et al., 2003). Vancomycin has been the mainstay of treatment for serious gram positive infections and the loss of this medication (and probably the entire glycopeptide class) could seriously hamper effective treatment of these infections and thereby increase pressure on the use of newer drugs that do not have established track records. Additionally, the introduction of CA-MRSA strains into the inpatient environment with subsequent nosocomial transmission of CA-MRSA, even with short lengths of stay (Saiman et al., 2003), raises concern that CA-MRSA strains could acquire genes for multidrug resistance (MDR) from HA-MRSA strains via horizontal transfer. A new level of community health concern would then develop when addressing CA-MRSA strains with high virulence, stability in the environment, and resistance to multiple antibiotics (Wagenvoort et al., 2004).

The distinction between HA-MRSA and CA-MRSA is becoming blurred. Some CA-MRSA strains have been transmitted to short term hospital in-patients, possibly from a family contact or health care worker contact who was a CA-MRSA carrier, and then re-introduced into the community (Saiman, 2003). Some CA-MRSA strains acquired antibiotic resistance genes, in addition to the SCCmec gene for methicillin resistance, which makes them half hospital and half community MRSA (FIGURE 1); this could be the next step in the evolution of MRSA resistance (Said-Salim et al., 2003). This could signal further resistance in CA-MRSA: A merger of HA-MRSA strains with CA-MRSA could produce
HA-MRSA strains with higher virulence and CA-MRSA strains with increased drug resistance. With such constant interactions between the community environment and the health care environment, plans to control CA-MRSA infections must include ongoing institutional efforts at HA-MRSA control, and vice versa (Levin, 2001).

The Tucson metropolitan area is at potentially high risk for outbreaks of CA-MRSA infections because of several factors. There are county, state and federal prisons in and around the city of Tucson. Tucson has a large transient and homeless population often associated with psychiatric disorders and/or alcohol and drug abuse problems. Tucson is home to a large university with extensive dormitory housing and several semi-professional sports teams. There are two Native American reservations in and around Tucson with extensive interaction between reservation residents and Tucson residents. For its size, Tucson has a disproportionately large, elderly population with many long term care facilities and skilled nursing facilities, as well as general and specialized care homes. Any aforementioned example raises a risk for CA-MRSA outbreaks that could stress an already overloaded health care system. Addressing the problems of CA-MRSA transmission, identifying and treating infection outbreaks, and minimizing intermingling of HA-MRSA and CA-MRSA strains is a complex problem involving many community stakeholders. These stakeholders all need to unite to provide a consistent, comprehensive, cost-effective community response to MRSA, not only in the community, but also within the institutional environments.

Summary

Diagnostic and treatment guidelines, algorithms, and protocols guide the clinical decision-making and interventions of health care practitioners. Guidelines for treatment and
prevention of transmission are available for HA-MRSA infections and inpatient settings but not for CA-MRSA and community health care settings. Effective patient care must be evidenced based and guided by the most current information available. CA-MRSA infections can be treated without antibiotics; however, if antibiotic therapy is needed, then antibiotic resistance must be considered. CA-MRSA infections can affect individuals and groups that have no identifiable risk factors for infection, and outbreaks of infection can occur in groups with close physical contact, groups sharing personal items, and groups living in crowded or economically depressed conditions. Essential public health strategies, such as education of consumers, health care practitioners and the community, are inescapable for prevention of CA-MRSA transmission, identification of infection and outbreaks, and proper treatment and follow-up. Because of its vulnerable populations, Tucson metropolitan area is at risk for increasing incidence CA-MRSA.
CHAPTER 4 EVALUATION

Introduction

Evidence based patient care is the gold standard for health care professionals: treating on the basis of primarily scientific knowledge (Garau, 2006). Ongoing evaluation of the protocols, algorithms, and the clinical judgments that guide patient care also require knowledge, ongoing evaluation of efficacy and research to continually validate, update, and improve patient care approaches and fill in gaps in our knowledge (Garau, 2006; Price, 2006). Education at all levels (consumers, practitioners, health care policy makers, and governmental policy makers) is critical. The algorithm and guidelines presented here are based on currently available scientific information and are intended to provide practical tools and suggestions that apply to a variety of advanced practice settings. Each individual practitioner, however, must evaluate the appropriateness and applicability of these guidelines to their own patient populations.

Plans for Evaluation

In order to evaluate the tools provided here, the following implementation and evaluation plan is suggested: 1) request review of the material by groups of practitioners; if approved, define a study period for using the guidelines (for example 6-12 months); 2) put tools into use in different practice settings in different geographical areas; 3) at the end of the study period, elicit feedback from the participants in the areas of: applicability, ease of use, patient outcomes, and suggestions for improvement or change—this could be done using the AGREE instrument as an objective measure of guideline quality (Cluzeau and Burgers, 2001); 4) re-evaluate: review and implement appropriate suggestions. Other on-going
evaluation strategies that could be used, depending on the setting and resources, are peer reviews; chart reviews; and retrospective analyses.

_Strengths of project_

The information presented here is gleaned from a wide variety of scientific sources authored by health care practitioners, pharmacists, microbiologists, and epidemiologists to name a few. The sources used are current; most journal articles are within the last 6 years. The information is relevant to health care practitioners at all levels and in all different types of community practice. This information also has practical implications for consumers, community leaders, health departments, and government policy makers.

Roy’s Adaptation Model has been used throughout this project to highlight the relationships between the internal and external environmental processes (of patients, institutions, and communities) and the ongoing process of adaptation to changing stimuli. CA-MRSA epitomizes this process of adaptation on the micro level, while the process of investigating CA-MRSA and determining individual and community responses highlights the process of adaptation on a macro level.

_Limitations of project_

This paper is not meant to be a comprehensive investigation of CA-MRSA. There remains a wealth of specific, detailed information on many aspects of CA-MRSA that are outside the scope of this paper. The sources cited here are found online or in print at the Arizona Health Sciences Library (AHSL). Many sources could not be accessed through AHSL and were therefore not considered. While this may limit somewhat the information available, AHSL does have a large fund of sources covering a great variety of scientific
disciplines so that the information from unavailable sources is most likely duplicated in those sources available through AHSL.

Significance

The volume of sources cited here speaks to the interest and significance that CA-MRSA has generated, not only in this country, but worldwide as well. Everyone in the world will be affected at some time in their lives, directly or indirectly, by bacterial infections and by bacteria’s increasing resistance to antibiotics. CA-MRSA provides a prime example of a growing health problem that could grow to crisis proportions if appropriate action is not taken. Science and technology provide many useful tools to improve our lives; however, nature adapts to science’s advances. We must recognize that we can’t fully control our environment, either internally or externally, and that our attempts at control have significant consequences. There are also many places in the world where advances in medical treatment, information, and technology are unavailable and resources are limited. Greater access to travel has effectively shrunk the world so that health problems in one corner can quickly spread worldwide—as evidenced by the worldwide spread of HA-MRSA and CA-MRSA infections. In the U.S., financial limitations already affect the health care decision of millions of consumers and their practitioners. New medications and treatments might be developed and be unavailable to most people because they cannot afford them or their insurance coverage denies payment. The health care community must be educated to the problems and unite to formulate a practical, efficacious approach to bacterial infections and antibiotic resistance.
FIGURE 1 Evolution of MRSA
<table>
<thead>
<tr>
<th>Year</th>
<th>State</th>
<th>Population Based</th>
<th>Surveillances</th>
<th>Age Groups</th>
<th>HQM &amp; VMSA</th>
<th>HIV Epidemic</th>
<th>Non-Reported Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>CA</td>
<td>65% of pop.</td>
<td>2.5% of pop.</td>
<td>21-59</td>
<td>0.3%</td>
<td>5.0%</td>
<td>12%</td>
</tr>
<tr>
<td>2006</td>
<td>CA</td>
<td>65% of pop.</td>
<td>2.5% of pop.</td>
<td>21-59</td>
<td>0.3%</td>
<td>5.0%</td>
<td>12%</td>
</tr>
<tr>
<td>2009</td>
<td>CA</td>
<td>65% of pop.</td>
<td>2.5% of pop.</td>
<td>21-59</td>
<td>0.3%</td>
<td>5.0%</td>
<td>12%</td>
</tr>
<tr>
<td>2005</td>
<td>CA</td>
<td>65% of pop.</td>
<td>2.5% of pop.</td>
<td>21-59</td>
<td>0.3%</td>
<td>5.0%</td>
<td>12%</td>
</tr>
<tr>
<td>2008</td>
<td>CA</td>
<td>65% of pop.</td>
<td>2.5% of pop.</td>
<td>21-59</td>
<td>0.3%</td>
<td>5.0%</td>
<td>12%</td>
</tr>
</tbody>
</table>

Note: Table 1
<table>
<thead>
<tr>
<th>Year</th>
<th>Location</th>
<th>Study Description</th>
<th>MDR prevalence (%)</th>
<th>MDR websites studied</th>
<th>Study type</th>
<th>Number of subjects studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>VA Med. Ctr.</td>
<td>2000</td>
<td>12.7</td>
<td>307</td>
<td>Prospective cohort</td>
<td>1000</td>
</tr>
<tr>
<td>2000</td>
<td>Chicago</td>
<td>2000</td>
<td>12.7</td>
<td>307</td>
<td>Prospective cohort</td>
<td>1000</td>
</tr>
<tr>
<td>2000</td>
<td>Hudson &amp; al.</td>
<td>2000</td>
<td>12.7</td>
<td>307</td>
<td>Prospective cohort</td>
<td>1000</td>
</tr>
<tr>
<td>2000</td>
<td>NYC. NY</td>
<td>2000</td>
<td>12.7</td>
<td>307</td>
<td>Prospective cohort</td>
<td>1000</td>
</tr>
<tr>
<td>2001</td>
<td>About 60 adults, Preventive Survey</td>
<td>2001</td>
<td>12.7</td>
<td>307</td>
<td>Cross-sectional</td>
<td>1000</td>
</tr>
<tr>
<td>2002</td>
<td>San Francisco</td>
<td>2002</td>
<td>12.7</td>
<td>307</td>
<td>Prospective cohort</td>
<td>1000</td>
</tr>
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<td>2004</td>
<td>San Francisco</td>
<td>2004</td>
<td>12.7</td>
<td>307</td>
<td>Prospective cohort</td>
<td>1000</td>
</tr>
<tr>
<td>2006</td>
<td>Winnipeg, Manitoba, Canada</td>
<td>2006</td>
<td>12.7</td>
<td>307</td>
<td>Prospective cohort</td>
<td>1000</td>
</tr>
</tbody>
</table>

**Notes:**
- MDR: Multi-drug resistant.
- MDR prevalence: Percentage of patients with MDR.
APPENDIX A: CA-MRSA ALGORITHM

[Flowchart diagram of CA-MRSA algorithm]
APPENDIX A: CA-MRSA ALGORITHM SUPPLEMENT

1. Risk factors for CA-MRSA
   a. history of MRSA infection or carriage
   b. serious chronic health condition: DM, immunocompromised, PVD, ESRD with HD, Cancer/chemotherapy/radiation therapy, HIV/AIDS, IVDA, chronic skin conditions
   c. frequent or long term antibiotic use in last 6 months
   d. hospitalization in last 6-12 months
   e. living in crowded/depressed conditions, homeless, living in a group home/LTCF/SNF, incarceration in last 6-12 months
   f. close contact with someone that has MRSA
   g. close contact with health care worker or vet care worker or work in health care facility or vet care facility

2. Common presentation of CA-MRSA infections: (Cohen, 2005; Fridkin et al., 2005; Gilbert et al., 2006; Kluymans-VandenBergh and Kluymans, 2006; Kowalski et al., 2005; Moran et al., 2006; Nicolle et al., 2006; Romero et al., 2006)
   a. SSTIs: especially infections slow to respond to beta-lactam agents
      - abscess with or without surrounding cellulitis
      - cellulitis
      - folliculitis
      - impetigo
      - infected wound; cellulitis with purulent drainage—upper extremities-
29%, lower extremities-27%, torso-17%, perineum-14%,

Head and neck-13% (Moran)

-single or multiple abscesses

-multiple tender erythematous fluctuant abscess with surrounding
  Cellulitis. Most frequent regions: axillary region, buttocks, Labia majora, face (Cohen, 2005).

-SSTIs accompanied by fever, swelling pain, purulent drainage or Warmth—lower extremities-58%, upper extremities-16%; Furnuncles-33%, abscesses-27%, open wounds-24% (Romero et al., 2006)

b. septic arthritis: short history of hot, swollen, tender joint(s) with restriction of movement with or without fever (Weston and Coakley, 2006)

c. diabetic foot ulcer: “any inframalleolar infection in a person with diabetes mellitus…aerobic gram-positive cocci (especially S. aureus) are the predominant pathogens in diabetic foot ulcers” (Lipsky et al., 2004, p. 891)

d. infections of particular concern include necrotizing fascitis, pyomyositis, empyema, severe pneumonia, and multiple cutaneous abscesses (Holcomb; Nicolle; Romero)

3. Factors to consider in using antibiotic therapy

  a. patient's general health

  b. presence of an immunocompromised condition

  c. surrounding cellulitis

  d. fever (Romero)
e. severity and rapidity of progression of the SSTI or the presence of associated cellulitis
f. signs and symptoms of systemic illness
g. associated patient co-morbidities or immune suppression
h. extremes of patient age
i. location of the abscess in an area that may be difficult to drain completely or that can be associated with septic phlebitis of major vessels (e.g., central face)
j. lack of response to initial treatment with incision and drainage alone (Gorwitz et al., 2006).

4. Supportive care of SSTI
   a. warm compresses and/or soaks
   b. rest
   c. elevation
   d. good basic personal hygiene especially consistent hand washing
   e. keep draining wounds covered
   f. avoid sharing equipment or personal items (razors, towels)
   g. avoid contact sports, common whirlpools or saunas
      (Gorwitz; Holcomb; Nicolle, Romero).

5. Use of Decolonization regimens—efficacy data are lacking; consider use when:
   a. an individual has multiple documented recurrences of MRSA infection
   b. ongoing MRSA transmission is occurring in a well-defined, closely associated group (e.g., a household)
c. use after standard prevention measures are unsuccessful at interrupting MRSA transmission

d. general decolonization measures include: nasal mupirocin and antiseptic body washes (e.g., chlorhexidine) for patients and their close contacts. (Gorwitz).

6. Considerations for hospitalization

a. toxic appearing patient/presence of systemic infection: high fever, hypotension, tachycardia, altered mental status

b. rapid spread of infection

c. no improvement or worsening despite treatment

d. significant co-morbidities: for example, immunosuppression

e. severe infection in patients at extremes of age

f. suspected septic arthritis, endocarditis, necrotizing fasciitis

g. need for parenteral antibiotic therapy and/or surgical intervention

(Ellis and Lewis, 2005; Francis et al., 2004; Gorwitz et al., 2006; Kowalski et al., 2005; Stevens et al., 2005)

7. Outpatient antibiotic treatment recommendations

Low risk of CA-MRSA:

Beta-lactam agents are appropriate for the initial treatment of suspected S. aureus infections where CA-MRSA is not suspected: semi synthetic penicillin, first or second generation oral cephalosporins, macrolides, or clindamycin (Gorwitz et al., 2006; Stevens et al., 2005).

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APPENDIX A: CA-MRSA FOCUSED HISTORY TOOL

A history taking tool for high risk patients

1. Have you been hospitalized in the last 6-12 months?
   - diagnosis__________  Length of stay__________  
   - treatment__________

2. Have you taken antibiotics in the last 6-12 months?
   - Which antibiotics?___________________
   - For what problem (diagnosis)?_____________
   - For how many days/weeks?_______________

3. Do you have close contact with someone who has MRSA?

4. Do you work as or live with someone who works in these fields:
   Health care worker?____________
   Veterinary care worker?____________

5. What is your living situation?
   live alone_____  live with family or roommates_______
   live in crowded living conditions________
   homeless_______  live in a shelter________
   live in a group home or long term care facility________
   incarcerated

6. Where do you live:
   - City__________  Suburban______________  Rural area__________
   Native American reservation_____________
   Closed or semi-closed community_____________
7. Do you have any chronic health conditions?

- Diabetes________
- Peripheral vascular disease (PVD)________
- Kidney failure (dialysis)_______
- Cancer________
- HIV/AIDS_______
- chronic skin problems________
- chronic MRSA or VRE infections________
- Organ transplant________
- Drug abuse________

8. Have you been incarcerated in the last 6-12 months?

9. Do you have a recent history of possible spider bite?

10. Do you regularly play sports on a team or are you in military training?

   - What type of sport team?_____________________
   - Frequent physical contact?___________
   - Do you share equipment with other team members?______________
REFERENCES


http://www.cmaj.ca/cgi/content/short/175/2/161.


