Pediatric community-acquired methicillin-resistant *Staphylococcus aureus* infection and colonization: trends and management

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Purpose of review

The scourge of community-acquired methicillin-resistant *Staphylococcus aureus* in pediatrics continues unabated. This review provides information on changes in epidemiology, therapeutic considerations, and measures to control the epidemic.

Recent findings

The epidemiology and clinical manifestations of methicillin-resistant *S. aureus* have undergone important changes that pose challenges in recognition, diagnosis, and treatment for the pediatrician. Community-acquired methicillin-resistant *S. aureus* used to be predominantly associated with localized disease among previously healthy children; however, there are recent reports of more invasive and severe diseases with some fatalities. The antibiotic susceptibility pattern is also changing with some community-acquired methicillin-resistant *S. aureus* having resistance patterns indistinguishable from that of hospital-acquired methicillin-resistant *S. aureus*. Thus the choice of antibiotics is becoming even more challenging in pediatrics, with an already-limited armamentarium of antibiotics. The management of common skin diseases such as furunculosis and boils now requires close collaboration between the general pediatrician and the infectious diseases specialist.

Summary

As the burden of community-acquired methicillin-resistant *S. aureus* disease continues to increase, pediatricians must have a high index of suspicion and must institute appropriate antimicrobial therapy based on community or regional antibiotic susceptibility of community-acquired methicillin-resistant *S. aureus*. There is an urgent need for effective infection control programs, including active surveillance components, to help curb the epidemic.

Keywords

colonization, community-acquired MRSA, hospital-acquired MRSA, infection, *Staphylococcus aureus*, treatment

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Abbreviations

CA-MRSA	community-acquired methicillin-resistant *Staphylococcus aureus*
HA-MRSA	hospital-acquired methicillin-resistant *Staphylococcus aureus*
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-susceptible *Staphylococcus aureus*
PVL	Panton–Valentine leukocidin
RF-HAI	risk factor for healthcare-associated infections
SCC	staphylococcal chromosomal cassette

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Introduction

Staphylococcus aureus is an important human pathogen that causes multifocal infections, often with high morbidity and mortality. These infections could be sporadic or in association with family or community-based outbreaks [1]. The epidemiology of the emerging community-acquired methicillin-resistant *S. aureus* (CA-MRSA) strains, including their origins, effective treatment, and control measures, has not been well characterized. Clinicians are being overwhelmed on a daily basis with increasing incidence and severity and in some cases fatalities from CA-MRSA. The main objectives of this review are to describe the epidemiology of CA-MRSA in children, and provide insights into current trends in management and control.

Epidemiology

Methicillin-resistant *S. aureus* (MRSA) was first identified in the United Kingdom and subsequently in the US in the late 1960s [2,3]. The first cases of CA-MRSA infections in children without any predisposing risk factors were reported in 1998 [4]. Since then, the dissemination of CA-MRSA in communities among otherwise healthy children has become a global problem [5,6].

MRSA originated by the introduction of the mobile genetic element, staphylococcal chromosomal cassette (SCC) carrying the *mecA* gene, into at least five phylogenetically distinct strains of methicillin-susceptible *S. aureus* (MSSA). The *mecA* gene encodes an altered penicillin binding protein, PBP2a (or PBP2′), making these isolates resistant to methicillin and all other β-lactam antimicrobials. There are five types of SSC*mec* elements: SCC*mec* I, II, III, IV, and V.

The classification of MRSA, into hospital-acquired (HA-MRSA) and CA-MRSA, has not been standardized [7••]. Classification has been based on several criteria: time to isolation, which is based on the US Centers for Disease Control and Prevention guidelines for nosocomial infections [8] with CA-MRSA including all isolates cultured from outpatients or from hospitalized patients within 72 h of admission and HA-MRSA including all isolates obtained after 72 h of admission; host risk-factor profile, with the patient with CA-MRSA lacking exposure to a healthcare facility and a patient with HA-MRSA having been exposed to a healthcare facility; antibiotic drug susceptibility, with generally CA-MRSA being resistant to two or fewer classes of antibiotics while HA-MRSA is resistant to three or more classes; and molecular characteristics of the isolate, including the SCC*mec* type or pulsed-field gel electrophoresis type.

The limited resistance pattern and evolutional diversity of CA-MRSA as compared with HA-MRSA are attributed to the smaller size of type IV *SCCmec* and its lack of function other than those for methicillin resistance (*mecA*), and the movement of the element (*ccr* genes) [9]. Another genotypic characteristic of CA-MRSA is the possession of the *lukS-PV* and *lukF-PV* genes encoding the two subunits that comprise the Panton–Valentine leukocidin (PVL), a pore-forming toxin that is associated with deep-seated tissue infection and necrotizing pneumonia [10]. Notably, the PVL locus is found less commonly among HA-MRSA and hospital-acquired MSSA.

The rapid emergence of CA-MRSA as a cause of non-invasive and invasive infections in children was elegantly demonstrated by a 14-year study at Driscoll Children's Hospital, Corpus Christi, Texas, by Purcell and colleagues [11••]. A total of 1002 MRSA were identified from 1990 through 2003 of which 928 (93%) were CA-MRSA. The number of CA-MRSA cases ranged from none to nine per year from 1990 through 1999 and then increased exponentially from 36 in 2000 to 459 in 2003.

Zaoutis *et al.* [12••] in a 3-year retrospective cohort study at the Children's Hospital of Philadelphia also found that the proportion of MRSA out of all *S. aureus* infections rose from 15 to 40% ($P < 0.001$). Most of the infections were skin and soft tissue infections. A revealing aspect of this study was the epidemiologic characteristics of the group of children with risk factors for healthcare-associated infections (RF-HAIs), which included hospitalization during the past year, indwelling medical devices, or chronic medical conditions. The isolates from children with RF-HAIs had the same *SCCmec* type IV cassette as found in otherwise healthy children and the authors speculated that CA-MRSA strains might have become endemic within their pediatric healthcare facilities. Hulten *et al.* [13••] at Texas Children's Hospital also identified a third class of MRSA, which they referred to as community-onset healthcare-associated MRSA. Children with community-onset healthcare-associated MRSA had a similar risk profile to that of children with RF-HAIs identified by Zaoutis *et al.* [12••].

Li *et al.* [14••] in a retrospective study of isolates collected by the State of Hawaii Antimicrobial Resistance Project (SHARP) from 2000 to 2002 demonstrated an increase in prevalence of CA-MRSA in Hawaii over the study period especially among pediatric patients as compared with adults (24% versus 21%; $P < 0.01$). Also, 25% of all *S. aureus* infections from pediatric outpatients were due to MRSA.

Risk factors

CA-MRSA continues to be more prevalent in previously healthy children with no specific predisposition contrasting with HA-MRSA (Table 1). There have been CA-MRSA outbreaks in childcare centers, camps, and among participants of team sports [15]. Purcell *et al.* [11••] found that 89% of the children with CA-MRSA did not have any identifiable risk factor and only 11% had one or more known risks associated with MRSA. There are studies suggesting that non-white persons are more likely to have CA-MRSA [13••,16••,17••]. Graham *et al.* [18•] found that persons of black race and those of Mexican birth had a lower risk of *S. aureus* colonization. Further studies are needed to substantiate the link between race and *S. aureus* colonization and disease. In a retrospective study by Ochoa *et al.* [16••] patients with CA-MRSA were significantly younger than those with MSSA infections.

Clinical manifestations

Skin and soft tissue infections are the predominant manifestations of CA-MRSA disease. The incidence of severe and invasive diseases such as pneumonia, osteomyelitis, septic arthritis, bacteremia, pyelonephritis, and toxic shock syndrome, however, has been increasing recently. Miles *et al.* [19•] reported in a study in a pediatric intensive care unit in Auckland, New Zealand that 55 out of 58 children admitted to the intensive care unit with *S. aureus* infections were infected with community-acquired strains, and 12% were caused by MRSA. Among these infections, 79% presented with musculoskeletal symptoms, and pneumonia or empyema accounted for 78%. Two of the children had epidural abscesses, five had vascular thrombosis, and one child had endocarditis.

There are reports of increased severity, complications, and risk of mortality for patients with CA-MRSA as compared with community-acquired MSSA [16••,20]. The severity of the infection is trending toward being associated with virulence factors produced by

Table 1 Risk factors for methicillin-resistant *Staphylococcus aureus* in children

	Risk factor type
Hospital-acquired MRSA	
Previous hospitalization	
Intensive care unit	
Surgery	
Total parenteral nutrition/enteral feeding	
Mechanical ventilation	
Previous antibiotic therapy (e.g. Fluoroquinolones, β-lactams, vancomycin)	
Previous MRSA infection/colonization	
Dialysis patient	
Endotracheal/tracheostomy/nasogastric tube	
Community-acquired MRSA	
Previously healthy	Risk for traditional community-acquired MRSA
Recent contact with healthcare environment	Risk factors for healthcare-associated infections or community onset healthcare-associated MRSA
Chronic disease	Risk factors for healthcare-associated infections or community onset healthcare-associated MRSA
Documented MRSA colonization	Risk factors for healthcare-associated infections or community onset healthcare-associated MRSA
Previous antibiotic use	Risk factors for healthcare-associated infections or community onset healthcare-associated MRSA
Tympanostomy tube for recurrent otitis media	Risk factors for healthcare-associated infections or community onset healthcare-associated MRSA
Younger age	Risk factors for healthcare-associated infections or community onset healthcare-associated MRSA Risk for traditional community-acquired MRSA

MRSA, methicillin-resistant *Staphylococcus aureus*.

the CA-MRSA isolate, notably PVL [21]. In a survey by Diep *et al.* [22•] of 34 virulence genes, only PVL appeared to differentiate CA-MRSA from HA-MRSA. More studies are needed to clarify the clinical significance of these genes.

Children with risk factors apparent for MRSA at presentation are more likely to have invasive CA-MRSA infection [12••,13••].

Diagnosis

CA-MRSA should be considered as a possible etiological agent in patients having any of the consistent clinical presentations and all efforts should be made to establish a bacteriologic diagnosis. The microbiologic diagnosis of CA-MRSA is important because the first line treatment for skin and soft tissue infections caused by MSSA and streptococci is not vancomycin but β-lactam and other non-β-lactam agents. In localized infections where specimens cannot be obtained for culture, an option may be nasal and skin surface swabs to identify MRSA colonization. It is generally considered that colonization precedes infection [23•] and therefore may be helpful in guiding antibiotic choice.

Treatment

For presumed CA-MRSA infections the following factors should be considered in the choice of empiric antibiotics: site of infection; history or risk of MRSA acquisition; prevalence of MRSA in the community; and antibiotic susceptibility of MRSA in the community.

Site of infection

For children with localized CA-MRSA infections such as cellulitis and abscess and who appear clinically well and outpatient management is anticipated, trimethoprim-sulfamethoxazole may be the antibiotic of choice especially if the rate of inducible clindamycin resistance is high in the community (>15%) [11••,24•]. Incision and drainage for abscesses, including obtaining a specimen for culture, should be performed before beginning antibiotic treatment. The prevalence of inducible clindamycin resistance in the US varies from 8% of CA-MRSA in Houston, Texas to 94% of isolates in Chicago, Illinois [1,25]. In Europe the trimethoprim-sulfamethoxazole resistance rates to MRSA have been reported between 53 and 76% [26], and therefore the use of trimethoprim-sulfamethoxazole even for uncomplicated skin and soft tissue infections may not be appropriate. Alternative antibiotics are oral doxycycline, ciprofloxacin, and linezolid [27•,28]. It is important to stress that if an abscess is present, then incision and drainage remain the cornerstone of management. Lee *et al.* [29] showed that incision and drainage were associated with clinical improvement in most of the 69 immunocompetent pediatric patients, even those who did not receive antibiotics active against MRSA (abscess diameter <5 cm). Children hospitalized with non-life-threatening invasive and noninvasive infections and who are not toxic in appearance have responded well to intravenous clindamycin [30]. Intravenous clindamycin is not recommended to such patients in communities with high rates of inducible clindamycin resistance as treatment failures have occurred [25,31].

In children presenting with necrotizing fasciitis, pneumonia, osteomyelitis, and other life-threatening invasive conditions, it may be expedient to administer vancomycin until antibiotic susceptibilities of the isolate are known. Some have recommended using both vancomycin and antistaphylococcal penicillin in these instances pending culture results [32•]. Alternative antibiotics are intravenous linezolid, quinupristin–dalfopristin, and daptomycin [27•,33•,34].

Risk of methicillin-resistant *Staphylococcus aureus* acquisition

It is imperative to elicit from their history the risk of MRSA acquisition in all patients presenting with symptoms and signs that could be attributed to staphylococcal infection. The isolates from children with identifiable risk factors are more likely to be resistant to ciprofloxacin or clindamycin than isolates from healthy children [12••].

Methicillin-resistant *Staphylococcus aureus* in the community

It is prudent for all hospitals to establish the prevalence rate of MRSA in the community that they serve and have an ongoing active surveillance program to track any changes.

HA-MRSA and CA-MRSA have been distinguished traditionally by the antibiotic susceptibility pattern. In recent years, however, there are reports of emergence of strains that have arisen *de novo* in the community and this may have influence on the antibiotic susceptibility pattern [35]. It is therefore important to establish local antibiogram data to help guide choice of empiric antibiotic for suspected MRSA infections. There are reports from several studies in the US in children of high rates of clindamycin susceptibility of CA-MRSA isolates, ranging from 67 to 100% [36–38]. There are also, however, reports of clindamycin treatment failures due to inducible resistance. At Texas Children's Hospital in Houston, clindamycin is not considered as initial empiric treatment of invasive infections potentially caused by *S. aureus* especially in children with underlying conditions (except eczema or asthma) [13••]. Communities with high prevalence rates should consider routine performance of the D-test especially before prescribing clindamycin. An isolate that is susceptible to clindamycin but tests positive on D-test should be considered resistant to clindamycin [39]. *S. aureus* resistance to macrolides may be due to ribosomal target modification (macrolide–lincosamide–streptogramin B (MLS_B) resistance), usually encoded by *ermA* or *ermC* genes. MLS_B resistance is either constitutive or inducible following exposure to a macrolide. Induction test (D-test) utilizes closely approximated erythromycin and clindamycin disks on a Mueller–Hinton agar with the *S. aureus* isolate. As the erythromycin diffuses through the agar, resistance to clindamycin is induced, resulting in a flattening or blunting of the clindamycin zone of inhibition adjacent to the erythromycin disk, giving a 'D' shape to the zone [40,41•].

There are suggestions that in severe CA-MRSA infections where a toxin such as PVL is suspected to play a role drugs that shut down ribosomal translation of proteins, such as clindamycin and linezolid, could be of benefit [42,43•]. This hypothesis, however, remains to be tested *in vivo*.

Methicillin-resistant *Staphylococcus aureus* superinfection

Postinfluenza staphylococcal pneumonia has been reported in healthy adults during influenza pandemics and epidemics for the last century. During the 2003–2004 influenza season there were reports of severe complications after influenza virus infection, including pneumonia caused by both MSSA and MRSA, among previously healthy children and adults [44]. During periods of high influenza activity, regions with high prevalence of CA-MRSA may consider empiric therapy for pneumonia to include MRSA coverage.

A management algorithm for children with suspected or documented CA-MRSA infections (Fig. 1) is useful but should remain flexible to revisions to reflect changes in resistance patterns and new antibiotic options as they become available.

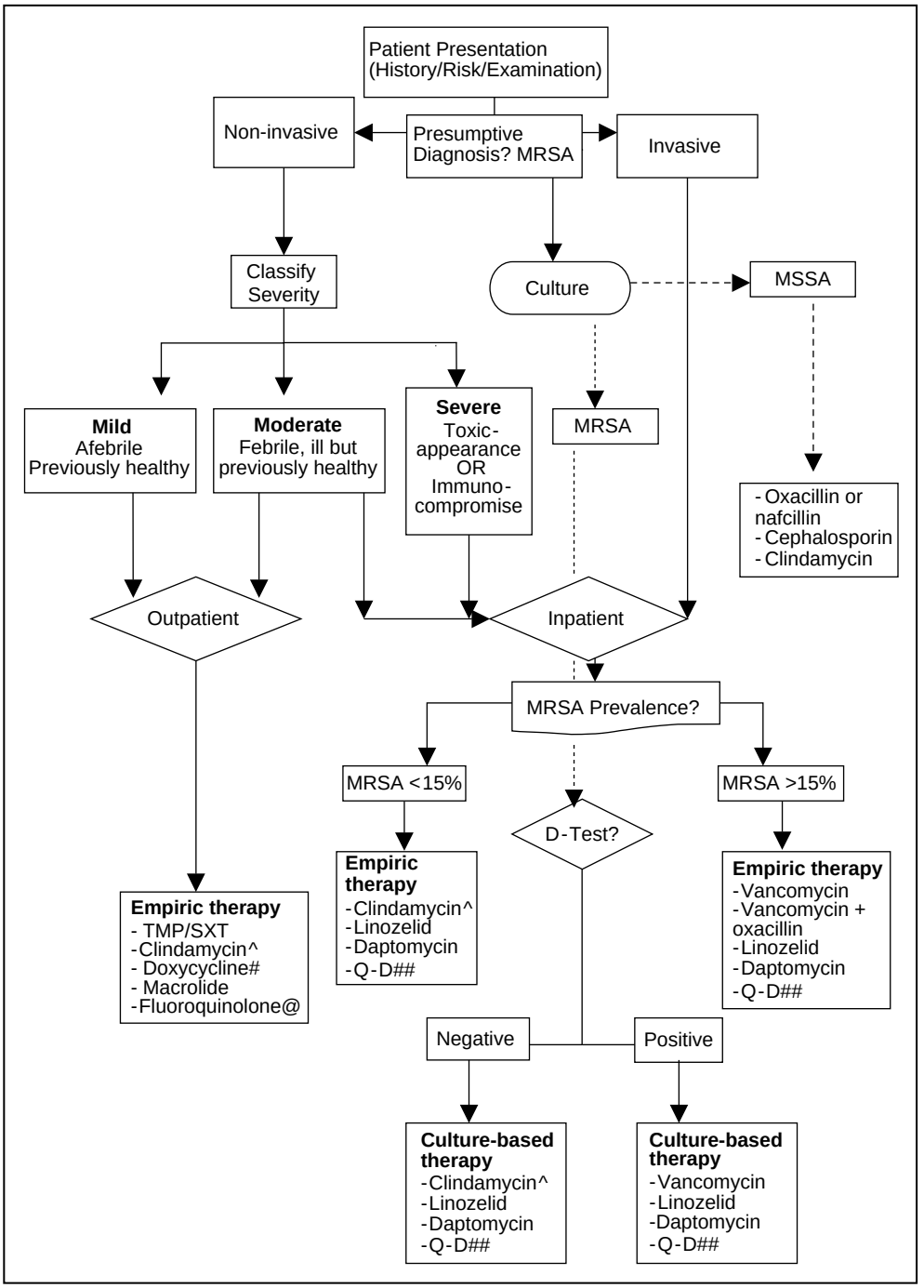
Management of colonization

In a cross-sectional analysis of nasal MRSA colonization in healthy children in Nashville, Creech *et al.* [23•] demonstrated a significant increase (10-fold) over a 3-year period. As colonization typically precedes infection, increased colonization may be a major factor in the emergence of CA-MRSA and therefore efforts at controlling the epidemic should have eradication of colonization as a component. Historically MRSA eradication protocols have not achieved favorable outcomes in either clinical practice or controlled trials. There are also various protocols in both Europe and USA. Protocols combining skin and hair disinfection and treatment of the nose with mupirocin ointment tend to be more successful then either disinfection or nasal treatment alone [45••,46,47•]. There have been reports of emergence of resistance to mupirocin [48]. A modified protocol consisting of skin disinfection and nasal mupirocin treatment [49] appears to be effective in decolonization and prevention of recurrent infections (Fig. 2).

Controlling the epidemic

There is a large gap between infection control policies and practices in most healthcare facilities. A survey of consultants in infectious diseases in US hospitals indicated that although over 70% supported and

Figure 1 Treatment algorithm for children with community-acquired methicillin-resistant *Staphylococcus aureus* infections



^Assume ≥90% prevalence of 'D' test negative, erythromycin-resistance CA-MRSA strains. #For patients over 8 years of age. @For patients ≥18 years of age. ##Quinupristin–dalfopristin. MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*. Adapted and modified with permission from the American Academy of Pediatrics suggested management of children with suspected CA-MRSA skin and soft tissue infections (Baker CJ, Frenck RW Jr. Change in management of skin/soft tissue infections needed. AAP News, Sep 2004; 25:105–117).

practiced contact precautions to control MRSA at their institution, only 30% benefited from any routine surveillance cultures to identify colonized patients [50]. A survey in European hospitals showed that a formal infection control program existed in 72% of the hospitals and that there was marked disparity between the policies and implementation in most of the hospitals [51].

There is mounting evidence from Australia, Europe and North America that the current MRSA epidemic can be

Figure 2 Methicillin-resistant *Staphylococcus aureus* eradication protocol

Stressing on the need to follow routine personal hygiene;

• Keeping fingernails short

• Changing sleepwear, underwear, towel and washcloth daily

Take cultures before given treatment; specimen from nares, axillae, and perianal area

Hexachlorophene bath (I table-spoon/gallon of water) daily for 7 to 10 days

Mupirocin application to the anterior nares two or three times a day for three weeks

Repeat surveillance cultures a week after treatment

If surveillance cultures are negative no further treatment; successful eradication. Repeat protocol if infection requires

If cultures are positive repeat skin/hair disinfection and nasal treatment as above, may repeat twice

controlled by an effective infection control program with an active surveillance component [45••,52–55,56•]. The Netherlands has maintained an MRSA prevalence rate of over 1% over the last decade due to their low tolerance infection control policy, in effect a 'search and destroy' policy for MRSA (Fig. 3). Details of the guidelines used in the Netherlands can be accessed online (www.wip.nl/UK/free_content/Richtlijnen/MRSA(1).pdf). In Australia, the MRSA control program is termed Operation Clean Start (OCS), consisting of MRSA screening of patients, healthcare workers, and environment; feedback of results; and introduction of a series of specific interventions, which

Figure 3 Search and destroy infection control approach

The figure illustrates the six main components. Details of the guidelines used in The Netherlands can be accessed online at (www.wip.nl/UK/free_content/Richtlijnen/MRSA(1).pdf). MRSA, methicillin-resistant *Staphylococcus aureus*. Adapted from the Netherlands guidelines for MRSA control [45••].

I: Identified MRSA carriers are treated in single rooms with barrier precautions.

II: High-risk patients (previously identified MRSA carriers or those transferred from endemic settings) are screened for MRSA colonization upon admission and precautionarily isolated.

III: All patients in a single ward are screened for MRSA colonization in case of an unexpected finding of MRSA colonization (i.e., in a patient not treated in isolation).

IV: In addition to measure III, all Healthcare workers (HCWs) in the affected ward are screened for MRSA colonization, and colonized HCWs are furloughed from working until decontamination has been achieved.

V: Wards are closed for new admissions when there is evidence of MRSA transmission among patients (>1 MRSA carrier) and remain closed until isolation capacity is sufficient for all carriers.

VI: MRSA colonization is eradicated at the end of hospitalization.

were supported by a detailed educational and promotional package [45••]. In a simulation model to predict control of MRSA in both low and high endemic areas, Bootsma *et al.* [57] demonstrated that isolation of MRSA carriers identified by clinical cultures is insufficient to control MRSA. Combined with a proactive search of high-risk patients on admission or contacts of index patients, however, prevalence levels could be maintained at under 1%. The implementation of such a policy will require a change in attitude among care providers, infection-control specialists and microbiologists so as to recognize the epidemiologic importance and preventability of MRSA; convincing hospital administrators that investing the necessary resources to develop an active surveillance and control program will reduce the health and financial costs of uncontrolled spread of MRSA in their own and neighboring care facilities; and raising awareness about this threat at the level of national public health authorities and mobilizing political, financial, regulatory and organizational support for the deployment of surveillance and control programs for MRSA and other relevant resistant pathogens [58]. An important cost reduction measure will be the implementation of rapid diagnostic testing for MRSA by hospitals. There are PCR-based assays that can identify MRSA from nasal swabs in 2–3 h. This will expedite the decision to put one on contact precautions or to discontinue such precautions and in the long run may be cost-saving.

Conclusion

With the current exponential increase in MRSA in hospitals and communities, the fusion of the epidemiologic and genotypic characteristics between healthcare and community isolates is bound to occur. This will lead to increased disease burden, severity, and therapeutic dilemmas. There is also an urgent need for establishment of functional infection control programs with active surveillance component to help curb the epidemic. An important consideration will be the use of geographic information system (GIS) software [59•] to map out hot spots of CA-MRSA and resistance pattern in communities to aid clinicians in the choice of appropriate empiric antibiotics.

Acknowledgements

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 120).

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