



Clinical and Diagnostic Significance of Methicillin-resistant *Staphylococcus aureus* Infection in Bangladesh: A Systematic Review

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Authors' contributions

This work was carried out in collaboration between all authors. Author MAY designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors AFMAS and ZHH managed the analyses of the study. Authors SR and AFMAS managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Accurate diagnosis of Methicillin-resistant *Staphylococcus aureus* (MRSA) is essential for the clinician. In Bangladesh MRSA creates a great problem for the treatment of infection.

Objective: The purpose of the present study was to observe the clinical and diagnostic significance of MRSA infection in Bangladesh.

Design: Systematic review of published articles in Bangladesh.

Data Sources: PubMed (Medline), Embase, Scopus, Web of Science, the Cochrane Library, and the World Health Organization (WHO) Regional Databases (African, eastern Mediterranean, Latin American and Caribbean, western Pacific, and southeast Asian regions) as well as Google Scholar, Banglajol, Asijol.

Review Methods: The search was restricted to full articles published from January 2000 (publication date of the first study identified by the research) to December 2013. Studies

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were excluded that did not provide appropriate data on the prevalence of MRSA. Only English language was applied.

Result: A total number of 125 studies were identified during systematic review which were relevant to the present research question and among these only 14 studies were met the criteria for analysis. The level of evidence and freedom from bias of these studies were generally low. MRSA was diagnosed phenotypic in most of the articles. Majority were isolated from skin wound. The isolation rate of MRSA among all culture isolates ranged from 4.8-78.7%. From all studies diagnosis of MRSA infection was done from hospital setting; however, only two studies had been reported from community settings though the CDC definition was not followed in either study.

Conclusion: Significance of methicillin-resistant *Staphylococcus aureus* infection in Bangladesh is very high leading to a huge clinical as well as laboratory burden in the health care facilities as well as in the community settings of Bangladesh.

Keywords: Methicillin-resistant Staphylococcus aureus; CA-MRSA; HA-MRSA; clinical significance; diagnostic significance; systematic review.

1. INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is very alarming pathogenic bacteria creating a huge clinical burden [1]. MRSA isolates are resistant to all available penicillins and other beta-lactam antimicrobial drugs [2]. It is commonly isolated from skin and soft-tissue infections, pneumonia, septic arthritis, endocarditis, osteomyelitis, foreign-body infections, and sepsis [3]. However these were confined largely to hospitals, other health care environments, and patients frequently visiting these facilities. On the contrary, there has been an outburst of MRSA infections reported for those populations who have lacking the risk factors for exposure to the health care system [4-5].

MRSA were reported in developed countries [6]. Previously, MRSA infections were confined to hospital outbreaks. Currently, MRSA was progressively created a burden as a nosocomial pathogen in the United Kingdom [7]. Nosocomial MRSA infections occurred in many cities in Australia [8] and Japan [9]. MRSA infections have remained rare even in the health care setting in Norway [10], Finland [11], Sweden [12], the Netherlands [13] and Denmark [14]. There has been a marked increase in the incidence of MRSA in India [15-17]. Khan et al [18] was reported the first documented MRSA isolates in Bangladesh. However, investigation into the epidemiology of MRSA was limited largely to the health care setting.

In this context Bangladesh is very vulnerable to develop CA-MRSA due to irrational use of antibiotics. This will create a huge burden to the physician as well as the patient. In this review it is tried to summarize the available information regarding community-acquired MRSA infections as well as the health care associated MRSA (HA-MRSA), emphasizing the characteristics that have prompted the emergence of MRSA in the community setting and the virulence factors associated with its typical clinical presentations and to find out the future burden of CA-MRSA and HA-MRSA in this country.

2. METHODOLOGY

2.1 Search Strategy

We developed a comprehensive search strategy that focuses the main subject areas of the review which were MRSA, screening, diagnosis and isolation and control of infection. We identified keyword and controlled vocabulary terms applicable to each of these concepts, then combined keywords in each database syntax. Studies conducted on humans were included. We searched the following databases, with no date or language restrictions: pubmed (medline) 2000-2013, embase 2000-2013, scopus, web of science, and the Cochrane library 2000-2013, the world health organization (who) regional databases (African, eastern Mediterranean, Latin American and Caribbean, western pacific, and southeast Asian regions), Google scholar 2000-2013, banglajol, asiajol. We also conducted hand searches through the reference lists of retrieved as well as the screened articles and published systematic reviews and did not find any additional articles. We also searched abstracts from key journals to verify the sensitivity of the search strategy. Index search terms included the medical subjects heading 'methicillin-resistant *Staphylococcus aureus* and Bangladesh' or 'community-associated methicillin-resistant *Staphylococcus aureus*' or 'CA-MRSA' or 'health-care associated methicillin-resistant *Staphylococcus aureus* and bangladesh' or 'HA-MRSA' or 'antibiotic resistant and community-associated methicillin-resistant *Staphylococcus aureus*' or 'community-associated methicillin-resistant *Staphylococcus aureus* and Bangladesh', 'MRSA and diagnosis', 'MRSA and . Articles which were published in Bangladesh retrieved in full text were included in the present study. No attempt was made to obtain information on unpublished studies. The animal studies, studies outside Bangladesh and studies with only abstract were excluded from these searches. Reviewed articles were maintained in a master log, and any reason for exclusion from analysis was documented in the rejected log.

2.2 Study Selection

At first abstracts were appraised by the reviewers. Full articles published in bangladesh were obtained if abstracts mentioned about MRSA infection. As the number of studies was far greater than anticipated, we revised the original article. We imposed the minimal requirement that accepted studies should include a component of prospective data collection or retrospective. Two investigators reviewed the papers independently, to confirm that they met the above criteria. We rejected studies not mentioning an isolation policy or without relevant MRSA related infection.

3. RESULTS AND DISCUSSION

A total number of 2405 articles were identified during literatures searching which were containing the research question. Among these articles 125 studies were taken into consideration and from the 125 articles 14 studies conducted in Bangladesh were met the criteria for systematic review analysis Table 1 and 2. The level of evidence and freedom from bias of these studies were generally low. MRSA was diagnosed phenotypic in most of the articles. Majority were isolated from skin wound. The isolation rate of MRSA among all culture isolates ranged from 4.8-78.7%. All studies had been reported from the hospital setting and only two studies had been reported from community settings though the CDC definition was not followed either study.

Table 1. Clinical infection of MRSA in Bangladesh

Authors name	Infection site	Name of specimen	Specimen number
Afroz et al. [26]	Skin infection, Suppurative infection	Pus, wound swab	49 specimens
Shahriar et al. [42]	Infections Not mentioned	purulent drainage, wound swabs, urine, ear swabs and blood	Not Mention
Haque et al. [43]	Infections Not mentioned	pus, blood, CSF, urine, throat swab, umbilical swab, sputum, prostatic, semen	Not Mention
Islam et al. [27]	Infections Not mentioned	Surgical wound swab, Burn ulcer exudates, Aural swab, Pus from skin infection, Diabetic ulcer exudates, Vaginal swab	100 specimens
Shamsuzzaman et al. [48]	Surgical infections	wound swabs	74 specimens
Begum et al. [49]	Several diseases with cough, fever, tonsillitis, wound, abscess	pus, urine, sputum and throat swab	50 specimens
Khan et al. [50]	Infections Not mentioned	pus, wound swabs, exudates of burn ulcer	550 specimens
Murshed et al. [51]	SSTI, UTI	Urine, wound swab	210 specimens
Ahmed et al. [53]	Puerperal Sepsis	Vaginal & cervical swab	50 specimens
Barai et al. [54]	ICU patients, Infections Not mentioned	blood, urine, respiratory secretions and pus/wound swab	1660 specimens
Kawsar et al. [55]	Infections Not mentioned	Pus, wound swab, urine, conjunctival swab, nasal swab	50 specimens
Iqbal et al. [56]	SSTI, UTI	Urine, wound swab	132 specimens
Haq et al. [57]	Wound Infection, UTI, RTI	pus, urine, sputum	3611 specimens

* CSF=cerebrospinal fluid; SSTI=Superficial & soft tissue infections; UTI=Urinary tract Infection; RTI=Respiratory tract Infection

3.1 Categorization of MRSA Infection

MRSA was highlighted in several times in many studies conducted in Bangladesh where the burden of MRSA was focused [1;18-20]; however, categorization of MRSA infection was not properly highlighted. MRSA are categorized into two broad classification which are community-associated MRSA (CA-MRSA) and hospital acquired-MRSA (HA-MRSA); these two strains have some genotypic, epidemiological as well as clinical differences [5]. MRSA infection diagnosed for an outpatient or within 48 hours of hospitalization if the patient lacks

the health care-associated MRSA risk factors like hemodialysis, surgery, residence in a long-term care facility or hospitalization during the previous year, the presence of an indwelling catheter or a percutaneous device at the time of culture, or previous isolation of MRSA from the patient is known as CA-MRSA [21-22]. All other MRSA infections were considered to be HA-MRSA. Unfortunately this classification did not follow any article published in Bangladesh. It is interesting that though the sample was collected from hospital of OPD of the hospital, the articles didn't mention about the classification. A third category of MRSA infections has been used by CDC investigators as "health care-associated, community-onset" MRSA (HACO-MRSA) infection [23]. In this category it includes cases that would be HA-MRSA infections by history of health care exposure though these have onset in the community. This tripartite classification scheme, HA-, CA-, and HACO-MRSA, still has limitations because a history of exposure to a health care setting does not exclude the possibility of MRSA acquisition and infection in the community [24]. The distinctions between CA-MRSA and HA-MRSA isolates have become increasingly blurred [25]. Defining a case as being community acquired is usually based on the timing of isolation of MRSA in relation to the time of hospitalization.

Table 2. Studies of MRSA in Bangladesh

Authors name	Year	Study type	Place of study	Number sample	Isolation rate
Dutta et al. [20]	2013	Original Article	Hospital	266	46.0%
Afroz et al. [26]	2008	Short Communication	Hospital	26	44.1%
Haque et al. [43]	2011	Original Article	Diagnostic centers	10	43.5%
Islam et al. [44]	2011	Original Article	Hospital	10	25.0%
Hossain et al. [46]	2002	Original Article	Hospital	70	42.5%
Rahman et al [47]	2002	Original Article	Hospital	12	47.2%
Shamsuzzaman et al. [48]	2007	Original Article	Hospital	571	22.0-42.0%
Begum et al. [49]	2011	Original Article	Hospital	50	0.0%
Khan et al. [50]	2007	Original Article	Hospital	79	50.6%
Murshed et al. [51]	2011	Original Article	Hospital	90	43.2%
Ahmed et al. [53]	2008	Original Article	Hospital	50	46.2%
Barai et al. [54]	2010	Original Article	Hospital	632	77.0%
Kawsar et al. [55]	2008	Original Article	Hospital	50	4.8%
Haq et al. [57]	2005	Letters to Editorial	Multicentre study	NM	32.0-63.0%

*NM= not mentioned

3.2 Diagnostic Significance of Genotypic Detection of MRSA

There are some clinical as well as diagnostic significance of CA- and HA-MRSA infection [24]. Diagnosis of MRSA has been done in phenotypic as well as genotypic way; however, few studies in Bangladesh have identified MRSA by detecting *mecA* gene [19;26-27]. Phenotypic detection of MRSA is easy, convenient as well as less costly [28]. Therefore, phenotypic confirmation has been done mostly. However, there are several ways of detection of MRSA. Only Afroz et al. [26] have identified the MRSA in multiple ways. In addition to that it has been highlighted the significance of diagnosis of MRSA in different ways. Furthermore, subdivision of MRSA was also mentioned by this study. However, the

sample size is small making this research work less weight. It is a vital need to detect the MRSA during isolation of bacteria from different clinical specimens. This is an important issue regarding the diagnosis of MRSA from different infection sites. It has been established that MRSA isolates can be categorized on the basis of their antimicrobial susceptibility profiles [2], DNA fragment patterns upon pulsed-field gel electrophoresis (PFGE) [29-30], protein A (*spa*) gene typing [31-32], carriage of PVL genes [33], multilocus sequence typing (MLST) [34] and the type of *SCCmec* element carried [35]. Definitions based on one or more of these isolate characteristics have been used to quantify the MRSA disease, clinical as well as diagnostic burden inside and outside the health care setting [1].

Genotypic detection of MRSA is important [1]. The gene that is responsible for development of MRSA is *mecA* gene [19]. Several other genes like *spa* gene, *coa* gene can be used for genotypic detection of MRSA [28]. Afroz et al. [26] have mentioned that all MRSA with type III *SCCmec* contains coagulase serotype IV, *coa*-repeat type C-6 and *Spa*-repeat type S-7. No other study has done such type of research. Interestingly Khan et al [36] has performed a diagnostic test by applying a panel of anti-sera against different coagulase enzymes. However, genotypic detection of MRSA was not performed and the study was only compared with phenotypic detection of MRSA. DNA fragment patterns upon pulsed-field gel electrophoresis (PFGE) are not mentioned to any study published in Bangladesh. The reason may be due to lack of facilities to perform this molecular test. In addition to that very few number of DNA sequencer is available in Bangladesh. Carriage of PVL genes in both MSSA and MRSA was done only Afroz et al. [26] in Bangladesh and reported that PVL gene is distributed to limited number of MRSA which were belonged to CA-MRSA. It has been established that methicillin resistance results from the production of an altered penicillin binding protein known as PBP2a and it has decreased affinity for most beta-lactam antibiotics [37-38]. The *mecA* gene encodes PBP2a and it is carried on a mobile genetic element known as the staphylococcal cassette chromosome (*SCC mec*) [39]. Zahan et al [19] have detected this gene for diagnosis of MRSA and highlighted the importance of *mecA* gene during diagnosis of MRSA. Besides the *mecA* gene itself, the *SCCmec* element contains regulatory genes, an insertion sequence element (IS431*mec*), and a unique cassette of recombinase genes (*ccr*) responsible for the integration and excision of *SCCmec* [39]. Afroz et al. [26] have detected this gene for the diagnosis of MRSA. Based on the class of *mecA* gene complex and the type of *ccr* gene complex, at least five types of *SCCmec* elements have been identified and are numbered from I to V [40]. Another *SCCmec* typing system has also been used by multiplex PCR assay to accurately identify types I-IV [41]. Molecular detection of this *SCCmec* gene was performed only by Afroz et al. [26]. Zahan et al [19] didn't perform this molecular detection. In another study Islam et al. [27] have detected the *mecA* gene by PCR and have found 25% of MRSA from clinical isolates of *S. aureus*.

3.3 Clinical Significance of MRSA Infection in Bangladesh

Studies [18-20;26-27;36;42-59] related to MRSA infection in Bangladesh is focused on the clinical burden of it. Burden of MRSA in the hospital settings were highlighted in these studies very well. However, it is very surprising that no study has mentioned about the burden of CA-MRSA in the community of Bangladesh. Afroz et al. [26] have mentioned about the relationship of CA-MRSA relating with the PVL gene though the research work was not defined it clearly. Shahriar et al. [42] have performed a study on 122 clinical isolates of *S. aureus* from different specimens from different hospitals, clinics and diagnostic centers in the Dhaka city; Interestingly all of them were identified as MRSA, as determined by susceptibility to methicillin discs and growth on CMCSA agar. In another study Haque et al.

[43] has reported 43.48% methicillin resistant isolates. This study was carried out in the two largest private diagnostic centres at Dhaka city. For this reason it doesn't represent the whole country scenario about the prevalence of MRSA. Maree et al. [44] have reported the CA-MRSA among the people without the prior exposure of the hospital settings in outside Bangladesh. In Bangladesh Islam et al. [27] have reported MRSA in 25.0% of total isolated *Staphylococcus aureus*. However, in this study, author didn't mention the number of hospitals from where the human samples are collected. This gives a Berksonian bias to the result and thus it doesn't represent the actual burden of MRSA. By taking similar sample Islam et al. [45] was performed a study to determine the sensitivity pattern of MRSA. Hossain et al. [46] has done an antimicrobial susceptibility testing against *Staphylococcus aureus* isolated at a tertiary care hospital outside Dhaka and found a significant number of MRSA isolates. However, molecular detection was not performed. Rahman et al. [47] have reported the prevalence of β -lactamase producing methicillin-resistant *Staphylococcus aureus* isolated from different specimens and have found that very few isolates are resistant to β -lactam drugs. Shamsuzzaman et al. [48] have mentioned that the trend of prevalence of MRSA at a tertiary care hospital has been also reported here and have added that the MRSA isolates are 22.0% in 2001 which is increased to 42.0% in 2003. This is alarming to the health sector of Bangladesh. Begum et al. [49] has reported eight *Staphylococcus aureus* isolates and surprisingly has found no MRSA strains. The reason may be due to small sample size and the study was performed 14 years back. Khan et al. [50] have found 79 strains of *S. aureus* of which 40(62.6%) were identified as MRSA from multiple site infections. This is a significant number of isolates detected in the different specimens. The authors have mentioned that there is a history and evidence of long-term infections among these patients as well as didn't show any clinical response to multiple courses of antibiotic. This causes the high rate of isolation of MRSA. Murshed et al. [51] has compared the detection rate of MRSA between two tertiary care hospitals at Dhaka city and has found a high rate of MRSA in both hospitals. Shahidullah et al. [52] has found only 10.5% isolates of *Staphylococcus aureus* from different specimens in referral specialized cardiac hospital; however, MRSA was not detected. Ahmed et al. [53] has found 46.2% MRSA strains from the patients with puerperal sepsis. Interestingly the all strains are vancomycin sensitive. Barai et al. [54] analyzed 1660 different samples of ICU patients and have found that about 77.0% of isolated *Staphylococcus aureus* were methicillin resistant (MRSA). Kawsar et al. [55] has found 50 cases of *Staphylococcus* infection of which 42(84.0%) cases are *Staphylococcus aureus*. Interestingly out of 42 cases of *Staphylococcus aureus* only 2(4.8%) cases are methicillin resistant. There is only study that has been performed on CA-MRSA in Bangladesh which was done by Iqbal et al. [56] though the clear definition of CA-MRSA was not maintained. In that study it has been reported that CA-MRSA was present in the community in 25.0% causing the UTI and soft tissue infection. Interestingly, 40.0% MRSA causes UTI in the OPD of the hospital. Haq et al. [57] reported isolation rate of MRSA in the four hospitals ranged between 32.0% and 63.0%; however, it was 40.0% in OPD of Dhaka hospital. The origin of these communities acquired MRSA is not known, though clear cut definition of CA-MRSA was not mentioned that article. However, exact data regarding the proportion of patients with a history of hospital stay was not recorded and this multicentre study showed that there was a high incidence of MRSA in hospitals in four different regions of Bangladesh and in the community in Dhaka.

3.4 Antibiotics Sensitivity Profiles of MRSA Isolates in Bangladesh

Antibiotics sensitivity profiles of MRSA isolates in Bangladesh are highlighted in a serious way. Haque et al. [43] has identified the pattern of aerobic bacteria with their antibiotic susceptibility isolated from infected patients in one of the surgical units at a tertiary care

hospital outside Dhaka and reported that out of 74 clinical samples, *Staphylococcus aureus* was found in 8 cases. Majority (61.5%) of culture positive results were found in wound swabs. Over 87.0% strains of *S. aureus* were resistant to penicillin but sensitive to erythromycin whereas, 100% of those strains were sensitive to cloxacillin. Islam et al. [45] has detected the MIC of cloxacillin against 10 MRSA strains and has found 100.0% resistant to penicillin as well as amoxicillin. However, this 10 MRSA are 100.0% sensitive to vancomycin, ciprofloxacin, erythromycin, fusidic acid and rifampicin. Interestingly ceftriaxone (20%) and cephadrine (40%) are also resistant to MRSA. Rahman et al. [47] has reported similar result. In another study, Shamsuzzaman et al. [48] has reported about the trend of increase resistant of *Staphylococcus aureus* which has been markedly increase in resistance against almost all antibiotics even against ciprofloxacin (17% to 43%; $p < 0.05$) and ceftriaxone (28% to 83%; $p < 0.001$) except co-trimoxazole (55% to 57%); on the other hand, oxacillin resistance increased from 22% to 42% but no resistance against vancomycin was noted during this period. Begum et al. [49] was found reduced sensitivity pattern to some important antibiotics. Khan et al. [50] has performed antimicrobial susceptibility testing and coagulase typing of *Staphylococcus aureus* isolates, with particular emphasis to MRSA among strains isolated from various types of specimens. The study included 79 strains of *S. aureus* and of those, 40 were identified as MRSA on the basis of resistance to oxacillin discs. All MRSA were sensitive to vancomycin (MIC < 4mg/L). The rate of resistance pattern of *S. aureus* was 88.6% to penicillin and 48.1% to oxacillin. Over 90.0% of all *Staphylococcal* isolates from all regions were resistant to penicillin and ampicillin. However, none of the isolates showed vancomycin resistance. Both MRSA and non-MRSA strains were found belonging to coagulase type VI. The reason of disproportionate rate of MRSA isolation is due to the sample collection from the diabetic patients. The study reported that 77.0% strains were penicillin and ampicillin resistant which is very alarming; however, cloxacillin resistant was in 37.2% cases. Iqbal et al. [56] has documented the incidence of ciprofloxacin-resistance among MRSA patients. In this study clinical isolates from outdoor patients were tested to see the ciprofloxacin resistance among MRSA strains, using *In vitro* susceptibility tests by standard disk diffusion technique. Results show significantly high incidence of ciprofloxacin resistance among MRSA isolates in these patients. In another study Shamsuzzaman et al. [58] has reported that 52 wound swabs, 18 pus and 4 urine samples were analyzed and found that over 87% strains of *S. aureus* were resistant to penicillin but sensitive to erythromycin. On the other hand 100% of those strains were sensitive to cloxacillin. Interestingly this study didn't mention about the MRSA. In another study Shamsuzzaman et al. [59] has reported that over 87% strains of *S. aureus* were resistant to penicillin but sensitive to erythromycin; while 100% of those strains were sensitive to cloxacillin. Over 50% of all isolates were sensitive to gentamicin but resistant to cefalexin and cotrimoxazole.

Finally it is very clear from the above discussion that the MRSA has a clinical as well as the diagnostic significance in the context of Bangladesh. This resistant bacterium creates a great problem to the health care setting of this country. Every articles published on MRSA in Bangladesh has highlighted the serious burden due to the MRSA infection. Irrational use of antibiotic should be stop to prevent the development of MRSA. In the community, there is far less evidence to support the use of these approaches.

4. CONCLUSION

MRSA have created a huge clinical burden in the hospital settings as well as in the community. Clinicians and the health care workers of this country must be aware of the wide

and unique spectrum of disease caused by MRSA. Increased vigilance should be employed in the diagnosis and management of suspected and confirmed Staphylococcal infections.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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