Impact of MRSA on the Military Medical Service and Diagnostic Point-of-Care Options for the Field Setting

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Methicillin-resistant *Staphylococcus aureus* (MRSA) poses an infection risk for international military deployments. In the presented mini-review, the history of MRSA in the medical service and modern warfare is highlighted. To allow rapid diagnosis, various molecular diagnostic point-of-care solutions are available. Most evaluation studies, however, are focused on screening swabs rather than clinical materials and evaluation data from harsh environments are widely lacking. Accordingly, studies with complex sample materials under difficult environmental conditions, e.g., in the desert or in the tropics, are desirable to close this gap of knowledge regarding the diagnostic reliability of such modern molecular point-of-care devices.

Keywords: MRSA, molecular detection, molecular point of care testing, military medicine, transmission prevention

Impact of Methicillin-Resistant *Staphylococcus aureus* on the Military Medical Service

Methicillin-resistant *Staphylococcus aureus* (MRSA) has been a menace to the military medical service for decades. As early as in the 1980s, an outbreak of MRSA was described in a British Royal Navy hospital [1]. After this, multiple publications on this issue followed, including reports from deployment sites. For example, during an assessment of 2242 US casualties from Operation Iraqi Freedom and Operation Enduring Freedom in the first decade of the present century, MRSA was among the three most frequently isolated multidrug-resistant pathogens associated with nosocomial infection rates less than 5% [2].

Nosocomial transmission of MRSA in military settings is of particular relevance in very constricted environments, e.g., on board of seagoing military vessels. Onboard of US American warships, prevalence of 3.5% (17/400) MRSA colonization was observed. No specific risk factors were identified, suggesting that the environment itself might be a problem. Also, 198 (49.5%) soldiers were colonized with methicillin-sensitive *S. aureus* (MSSA) [3].

Similarly, limited living conditions exist in military barracks. In case of staff skin lesions in military barracks, however, the differential diagnosis of MRSA infections is often neglected and alternative hypotheses like spider bites seem more plausible to soldiers [4].

Especially, strains which are positive for Panton–Valentine leukocidin (PVL) showed a clear tendency of progression from colonization of the skin to soft tissue infections in US soldiers [5]. Thereby, PVL is an epidemiological marker for strains with pronounced invasiveness which are associated with severe wound infections. Nevertheless, PVL is not the exclusive cause of increased pathogenic potential. Instead, various factors including phenol-soluble modulins (PSM) have an equal or even bigger role in this process [6–10]. Anyway, wound infections are highly relevant in military deployment settings, resulting in a variety of studies in this field.

Thereby, MRSA infections are rarely observed in early post-surgical wound infections. In particular, only 2 out of 49 cases of very early wound stages in casualties in Iraq were associated with MRSA detection [11]. Such results make nosocomial transmission highly likely.

MRSA prevalence is regularly monitored by the US armed forces also in their home country. In the USA, community-acquired MRSA is infrequently detected at military training units. The frequency ranges between 27 and 32 MRSA infections per 1000 soldiers [12]. Mupirocin-based eradication is effective but neither prevents recolonization nor does it reduce the infection rate in soldiers [13]. Next to military training camps, community-acquired MRSA strains were also infrequently (9 out of 67 [13.4%] total MRSA cases) observed in patients without identified risk factors in a US military hospital [14]. Generally, community-acquired colonization with MRSA in US soldiers was shown to be associated with previous antibiotic therapy [5].

The high relevance of MRSA for military deployments makes rapid diagnostic detection an issue of importance. Rapid and easy-to-apply molecular diagnostic options are therefore detailed in the following.

Diagnostic Point-of-Care Solutions for Potential Use on Deployment

Rapid MRSA detection is in the focus of molecular RDT (rapid diagnostic test) approaches. Rapid identification of MRSA using the Xpert MRSA/SA (Cepheid) RDT system was recently shown to contribute to optimized antimicrobioal management in a small proof-of-principle study with positive blood cultures in obstetric patients [15]. In a recent evaluation from Denmark with screening swabs and a culture-based gold standard including broth enrichment, sensitivity, specificity, positive and negative predictive

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value of the Xpert MRSA Gen 3 system were 88.2%, 97.9%, 62.5%, and 99.5%, respectively, with hands-on time of 8.8 min and mean laboratory turnaround time of 2.9 (1–6) hours [16]. Similarly good results for the Xpert MRSA assay were shown by an Irish study with sensitivity, specificity, and positive and negative predictive values of 95%, 98%, 90%, and 99%, respectively, for nasal swabs and 90%, 97%, 86%, and 98%, respectively, for swabs from nose, throat, and groin/perineum sites. Throat swabs scored worst with 75% sensitivity. The limit of detection (LOD) was estimated to be 610 cfu (colony forming units)/mL or 58 cfu per swab [17].

When applying MRSA PCR on swabs, however, one has to bear in mind that there is the risk of deodorant/anti-perspirant-induced invalidation of axillary PCR samples as observed in an evaluation of the Xpert SA Nasal Complete PCR by the US military [18]. In addition, a French study group reported sensitivity problems of the Xpert MRSA/SA Nasal system in association with a sample collection which contained phenotypic MRSA isolates with the *mecA* homologue *mecALGA251* [19].

An evaluation of the Xpert MRSA/SA technique for the detection of coagulase-negative staphylococci in periprosthetic joint infections showed sensitivity, specificity, positive and negative predictive value of 36%, 98%, 90%, and 74%, respectively, so the approach had to be dropped due to poor sensitivity [20].

In a study with positive-blood-culture broths, the Xpert MRSA/SA BC system showed sensitivity of 98.1% (range, 87.5%–100%) and specificity of 99.6% (range, 98.3%–100%) for the identification of MRSA [21]. Similarly good results for blood culture materials were detected by other authors [22–25].

The commercial loop-mediated amplification (LAMP)-based eazyplex MRSA assay (AmplexDiagnostics) showed sensitivity of 83.3% and specificity of 97.8% for *S. aureus* detection in pleural and synovial fluid with an LOD of 6.4×10^3 cfu/ml for *S. aureus* and 1.0×10^4 cfu/mL for MRSA [26]. Of note, the eazyplex system was also designed to target *mecC*-based resistance.

The Filmarray system (BioFire Diagnostics, Inc., Salt Lake City, UT, USA), another molecular tool for potential use in the field, includes an option for the detection of MRSA from blood cultures in its blood culture identification panel. In detail, three resistance genes (*mecA*, *vanA/B*, and bla_{KPC}) are targeted and allow for the detection of *mecA*-associated MRSA strains. In an eight-center trial with 2207 positive aerobic blood culture samples, sensitivity and specificity were 98.4% and 98.3% for *mecA* gene detection, respectively [27]. In a South African study, consistency with the reference methods was even as good as 100% [28].

Conclusions

Various molecular point-of-care approaches for the diagnosis of MRSA are available and potentially suitable for use on deployment. Nevertheless, there is still some evaluation work to be done. Evaluation data from deployment sites with harsh environmental effects, e.g., in the desert or in the tropics, are scarcely available. Furthermore, most of the evaluations have focused on swabs, which usually detect mere colonization rather than real infections. Therefore, broader evaluations with more complex sample matrices and under more difficult environmental conditions are desirable to estimate the use of devices for molecular point-of-care detection of MRSA for military medical purposes.

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Conflicts of Interest

The author declares that there is no conflict of interest regarding the publication of this article.

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