Staphylococcus aureus colonization and infection: optimizing MRSA decolonization and addressing challenges in S. aureus bacteremia management

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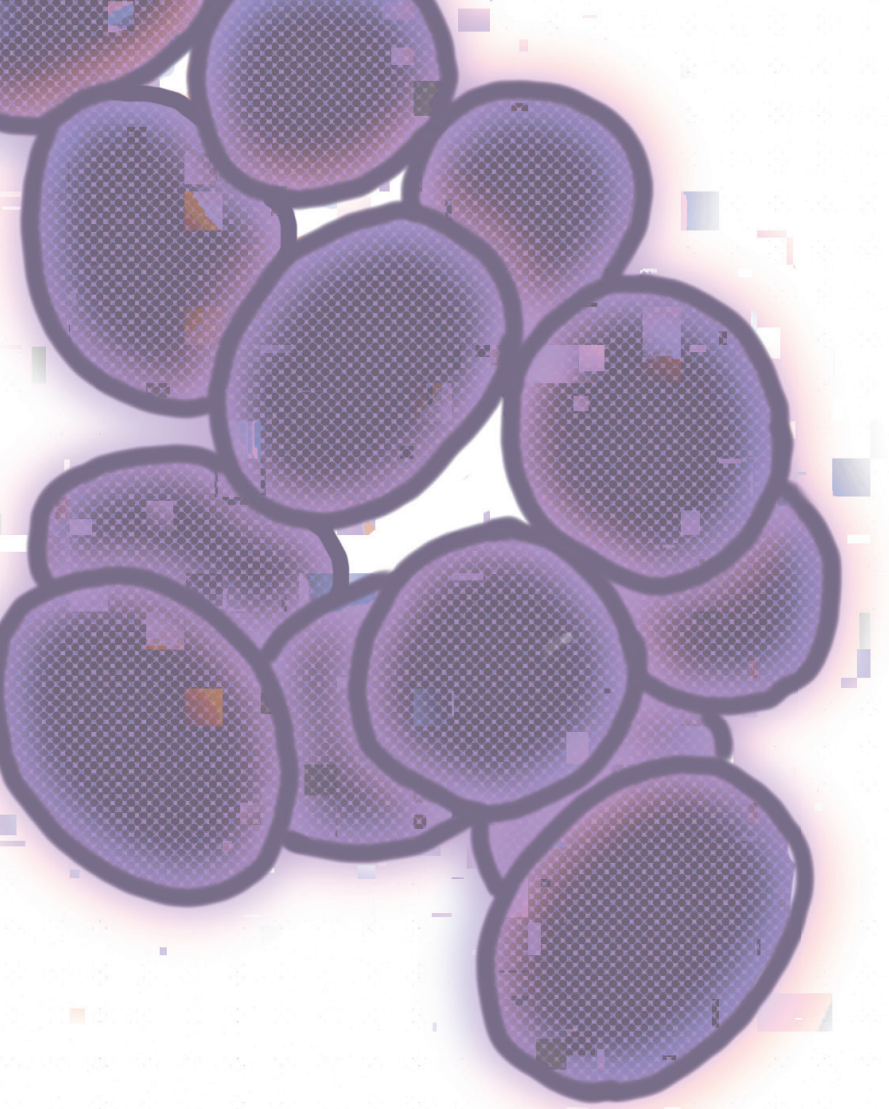

Chapter 11

Summary and general discussion

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Staphylococcus aureus colonizes millions of people, often without causing any symptoms. In contrast, when mucosal or skin barriers are broken, *S. aureus* becomes a frequent cause of hospital-acquired, healthcare-associated, and community-acquired infections in all age categories. *S. aureus* disease is highly variable, ranging from mild skin infections to catastrophic bloodstream infections with high mortality rates. Perhaps as a result of this heterogeneity, many questions remain with respect to risk factors, complications, and management.

The resistant variant of *S. aureus* is a major threat to global public health. Methicillin-resistant *Staphylococcus aureus* (MRSA) is a dominant actor in antimicrobial resistance. MRSA colonization increases infection risks, forming the basis for decolonization of MRSA carriers. This thesis addressed the optimization of MRSA decolonization strategies and frequently encountered challenges in *S. aureus* bacteremia management. The results of the studies described in chapters 2 through 10 will be briefly summarized and discussed in this chapter.

Optimization of MRSA decolonization

In the Netherlands, we are proud of having one of the world's lowest rates of MRSA. Less than 5% of invasive *S. aureus* isolates in our country are resistant to methicillin, compared to up to 25% in our neighboring countries [1]. Yet, given the rising MRSA prevalence in our surrounding countries, the immigration of people from high-endemic areas, and the travelling of Dutch citizens towards these regions, it requires our continuous attention. The 'search and destroy' policy targeting MRSA is executed in the Netherlands since 1988 and has since been proven to be cost-effective [2, 3].

However, the effectiveness of the 'search and destroy' policy as a whole, depends on several consecutive steps. Analogous to the renowned cascade of care for persons living with HIV, that has been frequently used to identify culprits in the uptake of antiretroviral therapy [4, 5], we constructed a cascade of care for MRSA decolonization. Each consecutive step of this conceptual cascade is crucial, since individuals may be lost in every step. The first steps include identification of carriers and the initiation of treatment, and were analyzed in **chapter 2**. We surveyed 114 general practitioners about their familiarity with the 'search and destroy' policy and evaluated barriers in the uptake of MRSA eradication care. Remarkably, the majority of the responding general practitioners were not familiar with the policy. Moreover, they often refrained from starting eradication treatment, for various reasons including lack of recommendation in a general practitioners' guideline, patients' burden and

out-of-pocket costs. The most apparent improvements in these steps therefore lie in expanding familiarity with the 'search and destroy' policy and incorporating it in a general practitioners' guideline. In addition, treatment initiation should be made as accessible as possible, for example by facilitating easy referrals and eliminating costs for the individual patient.

It is essential to realize that the aforementioned study focuses specifically on the Dutch situation and is not necessarily applicable to the rest of the world. MRSA endemicity varies widely around the globe, significantly impacting the rationale behind decolonization treatments, as described in **chapter 3**. Due to the high risk of recolonization in the setting of high MRSA prevalence in the community, the likelihood of successful long-term decolonization is low. In this setting, a standard 'search and destroy' policy is not likely to attribute to lowering its prevalence in the population as a whole. Short-term bacterial load reduction aiming at prevention of nosocomial infections and transmission might be appropriate in countries where MRSA is endemic. Nevertheless, a broader approach with nationwide infection control programs is able to reduce the high prevalence of MRSA in healthcare settings drastically, as demonstrated in the United Kingdom at the beginning of this century [6]. Furthermore, individual risk factors for treatment failure contribute to likelihood of successful eradication. Thus, both likelihood of successful durable eradication and treatment goal should guide the eligibility for community-onset MRSA decolonization treatment of the individual patient.

The last step in the MRSA cascade of care concerns the effectiveness of decolonization treatments. In **chapter 3**, we describe the effectivity of different decolonization treatments. The combination of mupirocin and antiseptic body wash is highly effective in decolonization of nasal MRSA carriage but appears to be insufficient in patients with extra-nasal MRSA colonization. Most evidence supports topical therapy combined with rifampin and a second antimicrobial agent for extra-nasal MRSA eradication. However, the clinical applicability of many studies on MRSA decolonization is hampered by the lack of reporting of the carrier status of household contacts and long-term follow-up cultures. Also, the MRSA colonization rate in the population varies between studies and is believed to be a major driver of recolonization. In this respect, it is of importance that strain genotype is often not reported in case of positive follow up cultures, which makes differentiating between treatment failure and recolonization impossible. Future studies should include these factors, to accurately determine the most effective treatment and the real risk of recolonization in low and high prevalent settings.

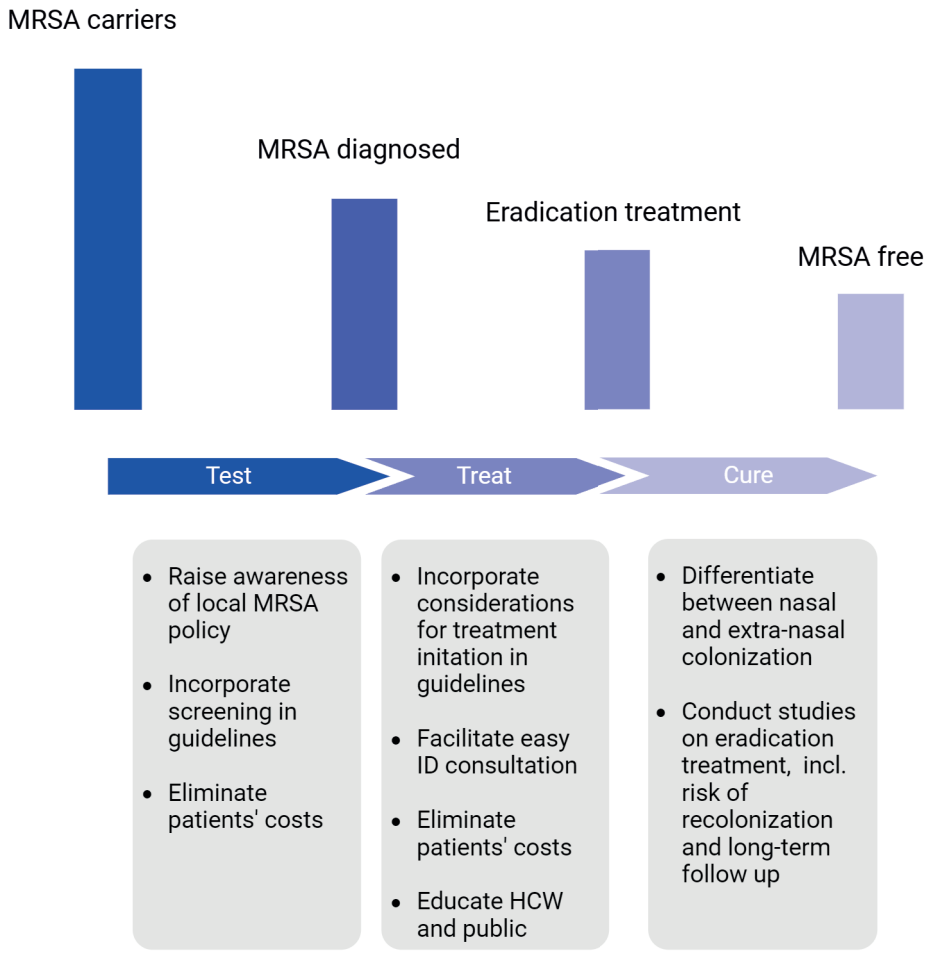
In order to provide insight in the situation in our region, we evaluated the efficacy of decolonization treatments in complicated MRSA carriership in five Dutch hospitals in **chapter 4**. We found an overall high success rate, and a trend towards a higher

success rate in patients treated with oral rifampin and doxycycline. Due to the retrospective design of the study and the small sample size, the causal relationship of this antimicrobial regimen with the higher success rate is not yet indisputably proven. To evaluate this further, we are currently conducting the CLEANEST study, a multicenter cluster-randomized trial comparing rifampin-doxycycline with rifampin-trimethoprim for the treatment of complicated MRSA colonization.

Apart from recolonization risks and individual risk factors for treatment failure, differences in genetic characteristics of the MRSA isolates may play a role in the probability of successful eradication. In **chapter 5**, we performed an explorative study on genetic determinants of MRSA isolates and their association with decolonization treatment outcome. We found a higher eradication failure rate in complicated MRSA carriers with ciprofloxacin-resistant MRSA lineages, which are mostly healthcare-associated. Although limited by a small and heterogenous patient population, this study suggests an effect of pathogen-associated factors on the success rates of MRSA eradication treatments as well. These pathogen-associated factors potentially interact with host factors, and this complex host-pathogen interaction adds to the likelihood of successfully eradicating individual MRSA carriers, in addition to the effectivity of the antimicrobial eradication treatment. A more individualized treatment approach could potentially be achieved with a deeper understanding of the genetic determinations and host-pathogen interaction.

In conclusion, there is room for improvement in every step of the cascade of MRSA care, in order to optimize the continuity of the cascade (Figure 1). These different targets at different levels underscore the importance of taking a comprehensive view when addressing potential healthcare improvements, and applying it to the local situation.

Figure 1: The cascade of MRSA care with potential targets for improvement



Legend. ID =infectious diseases, HCW = healthcare workers

Challenges in *Staphylococcus aureus* bacteremia management

The management of patients with *S. aureus* bacteremia is a complex challenge for healthcare professionals. Once the pathogen has entered the bloodstream, *S. aureus* has the potential to cause devastating damage to the human body. Uncomplicated *S. aureus* bacteremia does exist, but is very difficult to distinguish from an early phase of complicated disease and probably less prevalent than previously thought [7]. Many uncertainties need to be addressed to make decisions in diagnostic- and treatment paths. While managing uncertainties is inherent to practicing medicine, the erratic course of *S. aureus* bacteremia can amplify the usual burden of unpredictability. Even with the best available treatments, complications such as kidney injury or persistent bacteremia frequently occur in these patients. The mortality risk is high and has not substantially decreased in the past decades [8]. For equally lethal diseases such as coronary artery disease, mortality has significantly decreased following largely standardized management by guidelines, based on data from randomized controlled trials [9, 10]. Unfortunately, no such thing has happened yet for *S. aureus* bacteremia.

In **chapter 6**, we conducted a survey on the management of *S. aureus* bacteremia. This study illustrated the strength of using social media and being part of a professional network to understand global medical practices: within 20 days, over 2,000 physicians from 71 countries responded to the survey. In terms of content, the study showed that even the most basic aspects of treating patients with this disease differ profoundly between geographic regions. Differences existed in first-choice antibiotics for methicillin-susceptible *S. aureus* (MSSA) bacteremia, addition of rifampin for prosthetic device infections, the use of a 18F-FDG PET/CT scan, and route of antibiotic administration. Moreover, the definition of 'persistent SAB' varied widely between continents, ranging from two days to over seven days of positive blood cultures.

The lack of a global standard in the management of *S. aureus* bacteremia could be a result of the limited clinical trials with robust data. Despite its frequent occurrence, fewer than 3500 patients have been enrolled in published *S. aureus* bacteremia randomized trials over the past 20 years [11]. Apart from scarcity of clinical evidence, other factors such as cultural differences, type of healthcare insurance, (out-of-pocket) costs, and availability of resources also potentially influence the heterogeneity of management. Multinational clinical trials such as the *Staphylococcus aureus* Network Adaptive Platform (SNAP) are thus essential to standardize clinical definitions, identify treatment strategies, and improve patient outcomes of this common and frequently lethal infection [11]. Identifying a broadly accepted definition of persistent *S. aureus* bacteremia would not only be helpful in clinical decision-making, but also in harmonizing the terminology and outcomes used in clinical research.

In **chapter 7**, we focused on acute kidney injury in patients with *S. aureus* bacteremia. The main finding of the study was the high overall incidence of acute kidney injury. Furthermore, we observed an early development of kidney injury with a median time to peak creatinine of three days after first positive blood culture. Reversibility occurred in the majority of patients and was mostly seen in the first seven days. The early onset and swift recovery of renal insufficiency suggest that hemodynamic deterioration early in the disease plays an important role, and makes toxicity of antibiotic therapy as the primary cause of renal failure less likely. Insight in the pathogenesis of acute kidney injury in *S. aureus* bacteremia has important diagnostic and therapeutic consequences. Currently, kidney injury is often incorrectly ascribed to beta-lactam-induced tubulointerstitial nephritis, triggering an antimicrobial switch to a less potent agent. Prospective studies that focus on the different causal mechanisms of acute kidney injury in patients with *S. aureus* bacteremia are warranted to minimize unnecessary deviation from optimal therapy. Urine biomarkers potentially have additional value herein, and are a current subject of research. Different biomarker profiles may reflect prerenal or structural renal damage, and subsequently guide the clinician in the decision to change antibiotic treatment or focus on hemodynamic optimalization.

As a result of the low MRSA carriage prevalence in the Netherlands, MRSA bacteremia is exceptional in our country. However, in endemic regions such as the United States, MRSA bacteremia is common. Consequently, persistence of MRSA bacteremia despite appropriate antimicrobial treatment is also more frequently encountered. **Chapter 8** reviewed the literature on persistent MRSA bacteremia, addressing relevant host and pathogen factors. Clinical risk factors in persistent MRSA bacteremia include the retention of implanted devices and presence of metastatic infection. Potential host genetic variation and biomarkers indicative of MRSA bacteremia have recently been identified and show promise for future diagnostic options. Key genetic and phenotypic characteristics of *S. aureus* that have been associated with persistent SAB are accessory gene regulator dysfunction, variation in virulence factor production and phenotypes, antibiotic tolerance and reduced vancomycin susceptibility [12-14]. Considering treatment, vancomycin was the only recommended therapy for MRSA bacteremia for decades. Due to unfavorable safety profiles, many combinations of antibiotics have not been able to replace vancomycin. Since 2011, daptomycin is included in the guideline for MRSA bacteremia in the United States, but not in Europe. Although high-quality data is lacking, high-dose daptomycin (with a second antibiotic agent to prevent treatment-induced resistance), and the addition of ceftaroline, are currently regarded as 'best practice treatment' in persistent MRSA bacteremia [15]. Future therapeutical options may include ceftobiprole, dalbavancin, or non-antibiotic therapies such as bacteriophages.

Challenges in the management of *S. aureus* bacteremia can also arise in the form of identifying which patients are more at risk for dying than others. Ideally, in such a heterogenous disease, risk factors for mortality are known for every individual patient, guiding treatment plans and communication with patients and their relatives. Previously identified risk factors for mortality in patients with *S. aureus* bacteremia include increasing age, infective endocarditis, hemodialysis dependence and persistent bacteremia [16]. On top of these, female sex has been suggested as risk factor for mortality in several studies, even with reports of an increased mortality risk of 30% in females relative to males [17-19]. However, other studies did not find any sex-related mortality difference [20, 21]. Hence, the true influence of female sex on mortality remains unknown. Perhaps, the historical tendency to include fewer female patients in scientific studies has contributed to this knowledge gap. In **chapter 9**, we analyzed sex-differences in a large prospective cohort of *S. aureus* bacteremia patients in the United States. We found no difference in mortality between females and males. However, other characteristics differed significantly. For example, females were more often black, hemodialysis dependent, more likely to have implanted foreign material, and more likely to have used corticosteroids in the past month compared to males. Females were also more often infected with MRSA (as opposed to MSSA), compared to males. Although the aforementioned differences between females and males are interesting, they are pre-existing upon entry and therefore not potential targets for improvement.
This in contrast to differences in disease management, which were also notably present. Transesophageal echocardiography was performed less often in females. Furthermore, females were treated with a shorter median duration of antibiotics compared to male patients. The interpretation of these differences in disease management is complex, since males were also shown to have higher rates of metastatic infections, and different directions of causality are therefore plausible. More invasive diagnostic tests (i.e., transesophageal echocardiography) in males could have led to more frequent identification of complicated disease, and subsequently longer courses of antibiotics. Conversely, males could have truly had more complicated disease and therefore more often a true indication for transesophageal echocardiography. A sex-driven bias in management is therefore not downright proven in our study, but the findings warrant additional research to identify the underlying mechanisms of these discovered differences.

Given the contradictory reports in literature with regard to female sex as risk factor for mortality, we assessed all studies reporting mortality in *S. aureus* bacteremia stratified by sex in **chapter 10**. In this systematic review and meta-analysis, 89 studies with a total of 132,582 patients with *S. aureus* bacteremia were included. An increased odds of death of 18% in females relative to males was identified in this study. This difference remained when only studies that adjusted mortality for

patient and disease characteristics were included. Although almost entirely based on observational studies with a different primarily aim than assessing sex-differences, and with a risk of publication bias (inherent to meta-analyses), the sex-difference in mortality found in this study calls for further investigation.

Underlying causes of the higher mortality in females with *S. aureus* bacteremia were not addressed in our study, but it is tempting to speculate on the variety of potentially contributing factors. A biological survival disadvantage in females with *S. aureus* bacteremia is not immediately apparent, as males have generally worse outcomes in sepsis. However, female mice were more susceptible to lethal toxic shock caused by *S. aureus* enterotoxin B than male mice [22]. On a social level, a delay in health-seeking has been described in women with myocardial infarction [23], and could be present in *S. aureus* bacteremia as well. Differences in response to treatment may play a role, since both pharmacokinetics and pharmacodynamics are generally subject to sex influences [24]. Most disturbing would be a gender bias in healthcare delivery, which has been reported for example in women with septic shock, who experienced delays in antibiotic treatment relative to men [25]. Taking the results from chapter 9 in consideration, a gender bias in healthcare delivery is not yet excluded as a potential explanation for the sex difference in mortality in patients with *S. aureus* bacteremia.

Concluding remarks

Decolonization of MRSA carriership can be optimized on the levels of identification of carriers, treatment initiation, and treatment efficacy. Treatment goal and likelihood of successful prolonged eradication – driven by individual risk factors for treatment failure and risk of recolonization in the environment – should guide the eligibility for MRSA decolonization treatment in the individual patient. Future research would gain clinical applicability from reporting the carrier status of household contacts, long-term follow-up cultures, and reporting genotyping in case of failure. In order to maintain a low MRSA prevalence, the potential leakages of the MRSA cascade of care should be addressed. The details of this cascade may vary between countries, but the impact of MRSA extends beyond borders.

Large practice variations for *S. aureus* bacteremia exist throughout the world, emphasizing the complex challenge of managing this heterogeneous disease. Complications such as acute kidney injury and persistent bacteremia frequently occur in patients with *S. aureus* bacteremia, and their management is for a large part based on clinical experience rather than robust data. Female sex is a risk factor for mortality in *S. aureus* bacteremia, and the underlying cause should be unraveled. In a disease as common and frequently lethal as *Staphylococcus aureus* bacteremia, it is essential to internationally standardize clinical definitions and identify treatment strategies in order to improve patient outcomes.

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