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

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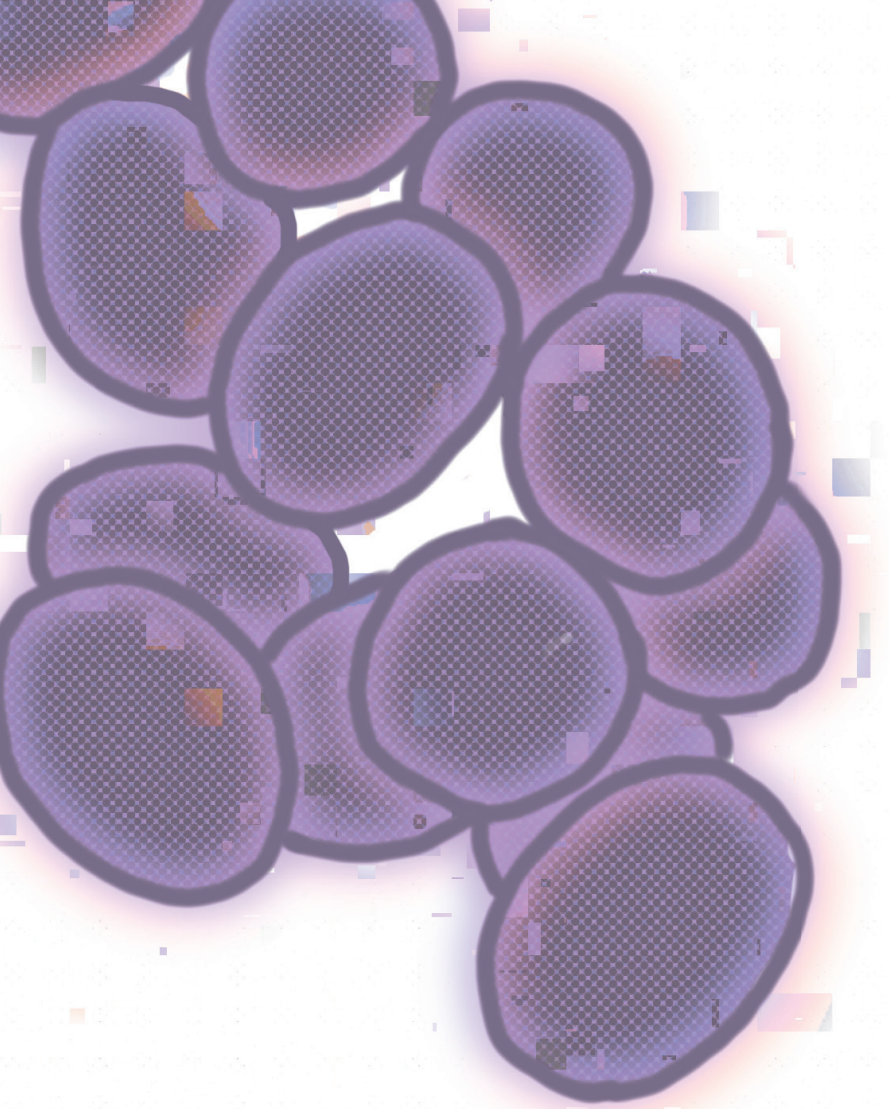

Chapter 1

Introduction and outline
of the thesis

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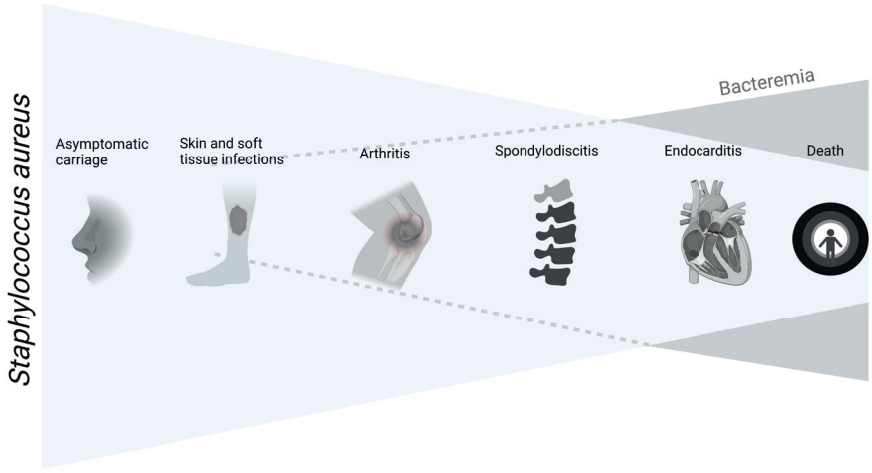
Staphylococcus aureus is a fascinating pathogen. The Gram-positive spherically shaped bacterium is generally considered as the most virulent member of the *Staphylococcus* genus [1]. It adopted its name in the 1880s from the combination of the Greek words *staphyle* (bunch of grapes), *kokkos* (berry), and the Latin word *aureum* (gold), representing the appearance of the colonies on blood agar plates [2, 3].

As a human commensal, it colonizes more than half of the population, either intermittently or persistently [4]. Colonized persons are often asymptomatic and can be colonized in the anterior nares, throat, groin, skin, intestine, and other body sites. In only a minority, *S. aureus* causes disease – often caused by the individual's colonizing strain [5]. *S. aureus* is the causative agent of common and relatively benign infections such as folliculitis and impetigo. On the other end of the clinical spectrum, it is the causative agent of severe invasive infections such as endocarditis, spondylodiscitis, and bacteremia (Figure 1), and even the leading cause of mortality by bloodstream infections worldwide [6].

Figure 1. A glimpse of the spectrum of clinical manifestations of *Staphylococcus aureus*



The variability in both colonization and invasive infection of *S. aureus* is the result of a complex interplay between host, pathogen, and environment. Many aspects of these interactions are largely unexplained. Susceptibility of the host is, among other factors, influenced by age, immune response and genetic make-up. Although predisposing factors in the host have been identified, it remains impossible to predict who will be colonized, who will develop disease and in whom this disease will be severe.

Concerning the pathogen, *S. aureus* is capable of colonizing healthy individuals as well as causing catastrophic disease in many different animal hosts, including humans. It produces various virulence and immune evasion factors, interfering with the immune system of the host and preventing it from effectively warding off recurrent infections [7]. *S. aureus* has unique features, such as the ability to cause metastatic infections throughout the human body, mainly facilitated by the expression of surface proteins that mediate adhesion, and the tendency to persist in the bloodstream despite appropriate antibiotics. Besides, the pathogen has the ability to form biofilms leading to chronic device infections [8], and to produce multiple exotoxins, some of which are accountable for toxic shock syndrome and food poisoning [9]. Environmental factors are of influence on the variability of *S. aureus* as well, such as the prevalence in the community and the timely initiation of effective treatment.

A major additional complicating factor is the capacity of *S. aureus* to develop antimicrobial resistance.

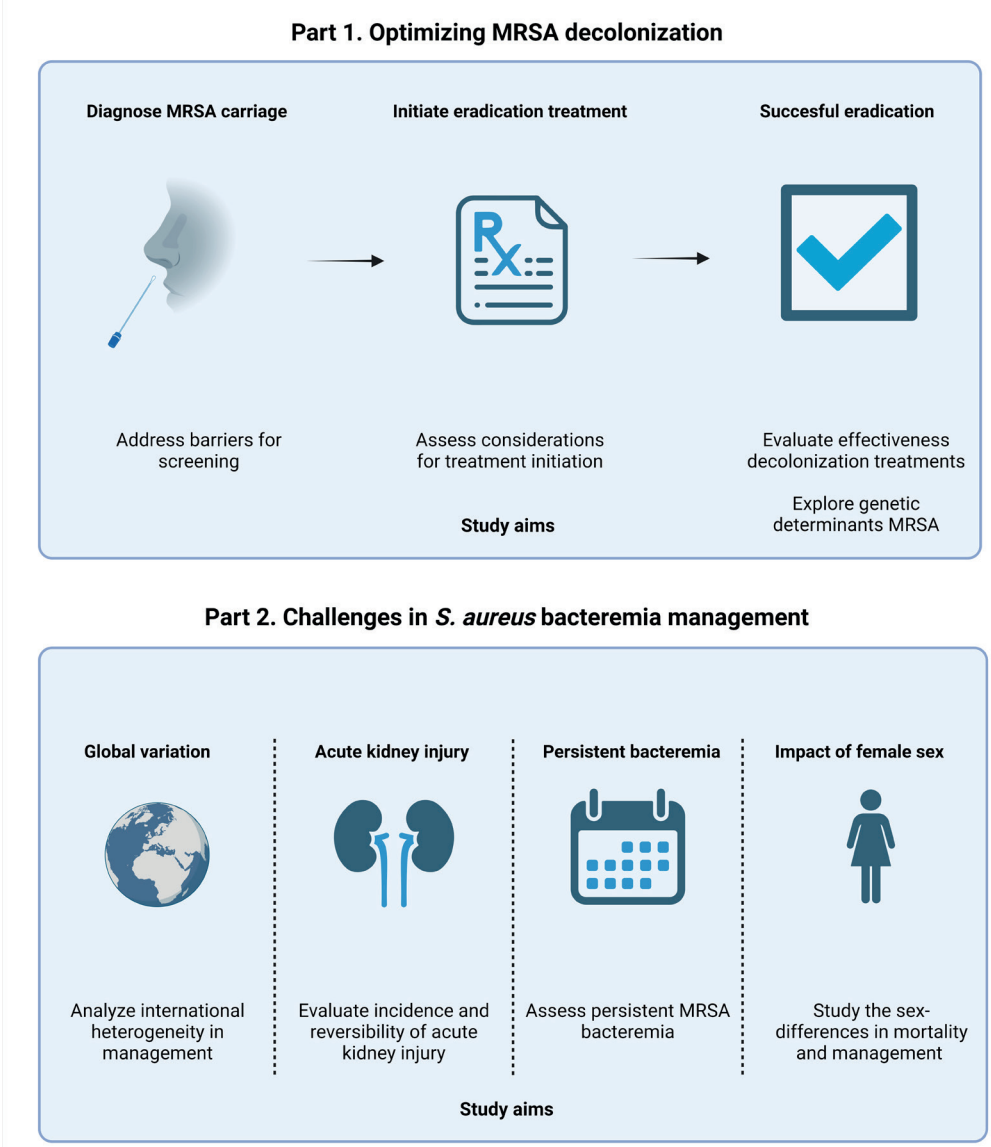
Antimicrobial resistance and *Staphylococcus aureus*

Antimicrobial resistance has significantly increased over the past decades, and is now in the top ten public health threats facing humanity, as declared by the World Health Organization (WHO) [10]. As a natural evolutionary response to antimicrobial exposure, bacteria develop resistance to antibiotics through multiple different mechanisms [11]. For *S. aureus*, the most relevant resistance mechanism is by acquiring a *mecA* gene through horizontal transfer of a mobile genetic element designated staphylococcal cassette chromosome *mec* (SCC*mec*), leading to methicillin resistance. The *mecA* gene encodes for a specific penicillin binding protein (PBP2a), which crosslinks bacterial peptidoglycans and has low affinity for beta-lactam antibiotics, causing resistance to almost all antibiotics within this class [12]. Methicillin-resistant *S. aureus* (MRSA) was first described in the early 1960s, shortly after the introduction of the antibiotic methicillin [13]. However, modern molecular phylogenetics suggest that MRSA emerged already by natural selection in the pre-antibiotic era and was further selected for by the widespread use of penicillin since the 1940s. Methicillin only provided better selective pressure for the bacterium to spread [14, 15].

Responsible for over 100,000 deaths in 2019, MRSA is currently the leading cause of mortality attributable to antimicrobial resistance in the world [16]. As a major actor in the field of antimicrobial resistance, MRSA also serves as an indicator for antimicrobial resistance in the global sustainable development goals of the United Nations [17].

Despite the high prevalence and global burden of *S. aureus*, many questions remain unanswered with respect to the management and risk factors of both colonization and invasive infection. Research is continuously ongoing in order to unravel the complexities of this extraordinary pathogen and the diseases it causes in humans. This thesis aims to address the optimization of MRSA decolonization and some of the frequently encountered challenges in *S. aureus* bacteremia management (Figure 2).

Figure 2. Graphical summary of thesis



Outline of the thesis

Optimization of MRSA decolonization

Colonization with *S. aureus* is a risk factor for developing subsequent infections. For bloodstream infections, this results from an endogenous infection source, reflected by identical isolates cultured from the blood and nares of patients with *S. aureus* bacteremia. Colonization with MRSA increases infection risk even more than colonization with methicillin-susceptible *S. aureus* (MSSA), in both patients and healthy individuals [18-21]. Decolonization therapy has been proven to reduce *S. aureus* infections, although the evidence for infection reduction outside of hospital settings is limited [22-24].

In the Netherlands, the MRSA prevalence is one of the lowest in the world [25]. This low prevalence is, next to the restricted use of antibiotics, to a large part ascribed to our 'search and destroy' policy [26, 27]. The policy consists of screening and preemptive isolation of patients at risk for MRSA carriership when hospitalized, and subsequent decolonization treatment when persistent carriership is found [28]. The aim of this policy is to minimize MRSA colonization in order to prevent transmission and infection.

The effectiveness of the 'search and destroy' policy depends on several consecutive steps. First of all, MRSA carriers need to be identified. The second step includes the initiation of eradication treatment. We evaluated barriers in these first steps of MRSA eradication care in **chapter 2**.

The third and final step involves the effectiveness of decolonization treatments, and is addressed in the next two chapters. Despite being notorious for nosocomial transmission and hospital outbreaks, MRSA with onset in the community has emerged over the past decades and has become endemic in large parts of the world [29, 30]. In **chapter 3**, we reviewed the evidence on individual decolonization strategies for MRSA, with particular emphasis on community-onset MRSA.

The Dutch guideline for MRSA eradication distinguishes between uncomplicated and complicated carriership [31]. Complicated carriership is defined as extra-nasal MRSA colonization, colonization with active skin lesions, foreign body material with connection to exterior, or previous failure of eradication treatment. Active skin lesions are recommended to be treated and foreign body material with connection to exterior to be removed before initiation of eradication treatment. Extra-nasal MRSA carriership is recommended to be treated with the combination of topical therapy and two systemic antimicrobial agents. However, which combination of systemic anti-staphylococcal antibiotics is most effective in MRSA eradication has not been clarified yet [32]. In **chapter 4**, the effectiveness of different MRSA decolonization

treatments for complicated MRSA carriage is analyzed.

Another potential influencing factor on effective decolonization is the genetic composition of the MRSA strain, as well as the host [33]. The complex genetic host-pathogen interaction in MRSA decolonization is relatively undiscovered, but is starting to gain interest as a result of the rapid developments in the field of molecular biology, especially whole genome sequencing. **Chapter 5** describes an explorative study on genomic characteristics of MRSA isolates that are associated with decolonization failure.

Challenges in *Staphylococcus aureus* bacteremia management

S. aureus bacteremia (caused by both MSSA and MRSA) is a highly variable disease affecting a heterogenous patient population. Consequently, the disease course varies greatly, ranging from transient uncomplicated bacteremia to disseminated infection, metastatic infections or persistent bacteremia despite appropriate antimicrobial therapy. All combined, the incidence of *S. aureus* bacteremia is estimated at 30 per 100,000 person years, and the overall 90-day mortality amounting to 20-30% [34, 35]. In the past decades the disease has been extensively studied, learning us that infectious disease consultation, follow-up blood cultures, and routine echocardiography all improve patients' outcomes [36, 37]. However, many challenges in the optimal management of *S. aureus* bacteremia remain. Different strategies are practiced throughout the world regarding optimal antibiotic regimen, oral switch therapy, treatment duration and defining persistence. **Chapter 6** describes the results of a survey of over 2,000 clinicians from 71 countries and 6 continents, about their treatment practices. It focuses on identifying global variation in management, diagnostics, and definitions of *S. aureus* bacteremia.

In clinical practice, a frequent complication in patients with *S. aureus* bacteremia is acute kidney injury. The complexity of this phenomenon lies in the combination of the diverse etiology – including prerenal, toxic/drug-related, immune-mediated, tubulointerstitial nephritis, and postrenal pathophysiology – and the lack of diagnostic tests to differentiate between them. Moreover, acute kidney injury has a significant impact on patient management and outcome [38]. Still, knowledge on acute kidney injury in *S. aureus* bacteremia is limited. In **chapter 7**, we evaluated the incidence, reversibility and risk factors for the development of acute kidney injury in patients with *S. aureus* bacteremia.

As mentioned before, *S. aureus* has the ability to persist in the bloodstream despite adequate antimicrobial treatment. Persistent bacteremia has been associated with increased mortality compared to those whose bacteremia promptly resolves [39, 40].

Although very rare in countries with low MRSA prevalence such as the Netherlands, persistent MRSA bacteremia is relatively common in the United States [41]. A variety of host and pathogen factors are potentially associated with persistence, and few alternative therapeutical options for persistent bacteremia have gradually evolved over time. We reviewed the literature on persistent MRSA bacteremia in **chapter 8**.

S. aureus bacteremia affects both males and females around the globe. Females have a lower *a priori* risk of acquiring *S. aureus* bacteremia compared to males, and represent approximately 40% of the *S. aureus* bacteremia population [42]. Although less frequently affected, some previous studies reported an increased mortality risk of up to 30% in females with *S. aureus* bacteremia as compared to males [43, 44]. However, other studies did not find a sex inequality in mortality, or even a higher mortality in males in a subgroup of patients with more comorbidities [45, 46]. Thus, the impact of female sex on outcome among patients with *S. aureus* bacteremia remained unclear. **Chapter 9** describes our study on sex-differences in mortality, patient characteristics, disease aspects and management, in a large cohort of over 3,000 *S. aureus* bacteremia patients. In **chapter 10**, a systematic review and meta-analysis was conducted to determine the true association of female sex and mortality in *S. aureus* bacteremia.

The results of this thesis are summarized and discussed in **chapter 11**.

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