

Mortality among Burned Colonized/Infected by *Staphylococcus aureus* Sensitive and Resistant to Methicillin: Meta-Analysis

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Abstract *Staphylococcus aureus* is a Gram-positive bacterium that colonizes the skin of 30% of healthy individuals. Although considered as a part of the human microbiota, in some conditions, especially in burned patients, *Staphylococcus aureus* can become pathogenic and cause a wide variety of infections, such as respiratory infections and skin and is responsible for several Infections Related to Health Care (HAI) and community. Therefore, it is necessary to identify the occurrence of methicillin-resistant/sensitive *Staphylococcus aureus* in burned patients, assessing the mortality related to cases of burn patients infected / colonized. **Results:** After bibliographic search of the literature presented in the databases 1519 studies were found. In the pre-selection 13 relevant studies were identified, which were discussed with the group of reviewers. Only two met the inclusion criteria of the study. The studies by Kaiser et al (2011) and Reardon et al (1998) were included in this review, addressing the colonization / infection by methicillin-resistant/sensitive *Staphylococcus aureus* and the mortality for each group. **Conclusion:** We found that colonization by methicillin-resistant *Staphylococcus aureus* is associated with burned body surface, so the higher the percentage burned, the greater the risk / colonization by oxacillin-resistant *Staphylococcus aureus*. Most patients who died were colonized by methicillin-resistant *Staphylococcus aureus*. The evidence obtained in this study suggests that the burns, especially those infected with methicillin-resistant *Staphylococcus aureus*, fall into a serious public health problem because of the difficult, and often unsuccessful treatment, which confirms an increase in morbidity and mortality in these patients. We emphasize the importance of this systematic review and meta-analysis of these data to allow the implementation of treatment protocols, improving the quality of preventive measures and reducing mortality rates by methicillin-resistant *Staphylococcus aureus*.

Keywords: Resistant *Staphylococcus aureus* and Methicillin Sensitive, Burn Units, meta-analysis

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1. Introduction

Staphylococcus aureus (*S. aureus*) is a Gram-positive bacterium that colonizes the skin of 30% of healthy individuals [1,2]. Although considered part of the human microbiota, in some conditions, especially in burned patients, *S. aureus* can become pathogenic and cause a wide variety of infections, such as respiratory and skin infections and is also responsible for several other Infections Related to Health Care (HAI) and community [3].

In the 60's in the United Kingdom, shortly after the introduction of methicillin in clinical practice, early strains *S. aureus* resistant to that antibiotic have been detected. A characteristic of these strains is not only to be resistant to

β -lactams, but also to a wide range of other antibiotics, which makes the treatment of infections with Methicillin-Resistant *S. aureus* (MRSA) difficult and economically challenging [4].

MRSA is currently the leading cause of HAIs, and its prevalence in community-acquired infections also continues to grow [5]. It is estimated that since the 90's, 2.9% of *S. aureus* were isolated methicillin-resistant. In 2000, the prevalence was 19%, and three years later, it was 62.4% [6].

In the hospital setting, the source of cross-transmission of MRSA is usually through infected or asymptomatic patients who may present colonization in the nose, pharynx, wounds, burns and chronic lesions of the skin [4]. The primary route of transmission within a hospital appears to be from patient to patient via the hands of health professionals. The risk of colonization/infection with

MRSA increases with the length of hospital stay, severity of underlying disease, number of surgeries, manipulations and previous exposure to antibiotics, among other factors [6].

Studies reveal that MRSA infections have a high mortality rate, much higher in relation to staphylococcal infections caused by non-resistant strains. Such episodes are triggered by the disruption of the skin barrier or weakened immune system [8].

Among the major causes of skin damage are burns, ranking second among the most common accidents that occur in the world, which are caused by direct or indirect action of the heat and the main causes are the direct flame, contact with boiling water or hot liquids, known as scalding, contact with electrical current and also by chemical and biological agents [8].

The incidence of people suffering burns is very high, making it a public health problem, corresponding to the fourth cause of death by injury in the United States and, according to the World Health Organization (WHO), is the fifth leading cause of violent deaths worldwide and accounted for 322,000 deaths in 2002. In Brazil, it is estimated that at least 1,000,000 individuals burn up a year, with no restriction on sex, age, origin or social class. There is a strong economic impact, taking into account the long-term treatment [9,10].

Burns are the greatest traumas to which a human being can be exposed. No other type of trauma triggers such an intense a metabolic response and so many repercussions in virtually all organs and systems. In addition to the immediate repercussions resulting to burns, physical and emotional sequelae of the burn patient and his family remain throughout life [11,12].

However, recent advances in understanding the pathophysiology of the metabolic response to burns, wounds care, new surgical techniques and bioengineered skin have shown excellent results in the majority of burn patients who survive the trauma [11,12], since the sepsis is one of the most significant complications in burn patients and in many cases can lead to death.

The burn patient is more susceptible to infections due to immunosuppression and loss of skin coverage. Among the microorganisms involved in these patients, bacteria are the most common and major cause of death in burned patients is bacterial infection [13]. However, factors associated with the patient and the microorganism, such as age, extent of thermal damage, the depth of the burn, the type and number of microorganisms, production of toxins and enzymes, determines the probability of invasive infection of the wound [14,15].

It is understood that the characteristics of the resulting wound colonization of the burn change over time. Initially, the Gram-positive cocci are more frequent, mainly from the sebaceous glands and hair follicles [16] and the *S. aureus* are sensitive to oxacillin (MSSA), the increased occurrence of HAIs, the wounds caused by burns, is explained by the increase in the number of MRSA, their main causing agent [17].

Among the various studies for tracking and organizing data, such as control of infections in burn patients, the reduction of morbidity and mortality and increased efficiency in care of burn victims, emphasize the importance of this study secondary systematic review and meta-analysis.

Considering the above, and motivated by the importance of infections associated with burns, the present study aimed, through and meta-analysis and systematic review, to identify the occurrence of MSSA and MRSA in burn, evaluating mortality related to cases of MSSA and MRSA infected/colonized burned.

2. Materials and Methods

The study was conducted after approval by the Ethics Committee of the Foundation Hermínio Ometto - UNIARARAS under protocol 483/2012.

The study was conducted through meta-analysis and systematic literature review, an important resource for evidence-based practice, since the results are collected, categorized, evaluated and synthesized.

This meta-analysis and systematic review followed the steps proposed by the Cochrane Collaboration [18]. Studies were included regardless of the language or form of publication. For inclusion in this meta-analysis the studies should present the primary outcome: death among burn patients colonized or infected with MRSA or MSSA. Exclusion criteria were studies that did not assess relevant outcomes concerning this study.

2.1. Strategies for Identification of Studies

Relevant studies were identified through electronic search of the database of the Cochrane Library (including the Cochrane Controlled Trials Register - The Cochrane Controlled Trials Register, PubMed, Embase, LILACS, SciELO, CINAHL, and Web of Science databases: www.controlledtrials.com, abstracts of papers presented at conferences, references of review articles and systematic review, published and identified, and references of identified randomized clinical trials.

The main keywords for the search were: ("burns" [MeSH Terms] OR "burns"[All Fields] OR "burn" [All Fields]) AND ("Methicillin-resistant Staphylococcus aureus" [MeSH Terms] OR ("methicillin-resistant" [All Fields] AND "Staphylococcus" [All Fields] AND "aureus" [All Fields]) OR "Methicillin-resistant staphylococcus aureus" [All Fields] OR "MRSA"[All Fields]).

2.2. Selection of Studies

The studies were read by two independent reviewers (ALRZB and LAP) in order to ascertain whether the criteria for inclusion were met.

Reviewers were not blinded and evaluated the titles and abstracts of all the identified studies. Complete copies of all relevant articles were obtained. In case of doubt or disagreement, a third reviewer (MT) was asked whether the study should be included or not.

2.3. Assessment of Methodological Quality

Methodological quality was defined as the confidence that the design and reporting of the study are free of bias.

Two independent reviewers used the recommendations STROBE (Strengthening The Reporting of Observational Studies in Epidemiology Statement) [19] for the evaluation of 22 items related to the information that should be present in the title, abstract, introduction, materials and methods, results and discussion of scientific papers.

Based on the recommendations of the STROBE, the evaluation of this meta-analysis was divided into three categories: A - the studies fulfill a value equal to or greater than 80% of the criteria, B - compliance between 80 and 50% of the criteria and C - if the compliance corresponded to less than 50% of the criteria established by the STROBE.

2.4. Data Extraction and Statistical Analysis

The studies were initially statisticalized according to the kinds of designs and subsequently compared to outcomes following the methodology Cochrane [18].

Review Manager 5.1 [20], provided by The Cochrane Collaboration was used for statistical analysis.

Dichotomous variables, odds ratio (OR) with respective confidence interval (CI) of 95% were calculated using fixed and random model and chi-square Mantel-Haenzel and index of heterogeneity were used to calculate the heterogeneity (I²).

3. Results

After literature search performed using the described presented in databases, 1486 studies found in PubMed, SciELO and 20 in 13 in Medline, totaling 1519 studies In the pre-selection; 13 relevant studies were identified, which were discussed with the group of reviewers. Only two met the inclusion criteria of the study (Figure 1).

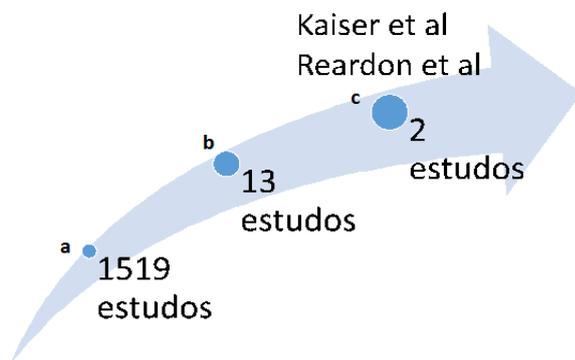


Figure 1. Organization chart of study selection a. 1519 studies found by descriptors; b. In the pre-selection were identified 13 relevant studies; c. Only two met the inclusion criteria of the study

The studies by Kaiser et al (2011) [21] and Reardon et al (1998) [22] were included in this review, that addressing the colonization/infection by oxacillin-resistant/sensitive *Staphylococcus aureus* and the mortality for each group.

The study by Kaiser et al (2011) [21] entitled "Epidemiology and risk factors for Hospital-Acquired Methicillin-Resistant *Staphylococcus aureus* among patients burn" was a retrospective study in California, which evaluated 752 patients were 70 cases (MRSA) and 682 controls (MSSA) and 14 died. Interventions were: nasal swab on admission and weekly, other areas were analyzed, including the lesion itself (burning), sputum and blood. The main findings were: surveillance cultures and contact precautions were effective for the prevention of MRSA among burn patients. Older patients, prolonged hospitalization, burned body surface area (Body Surface Area - BSA) and inhalation injury were considered risk factors.

The study by Reardon et al (1998) [22], entitled "Methicillin-Resistant *Staphylococcus aureus* in Burns patients - why all the fuss?", a Iso a retrospective study conducted in the UK had 207 participants, but only 86 were studied, 40 cases (MRSA) and 46 controls (MSSA) and four died. Interventions were: skin and nasal swabs on admission and at each dressing checking colonization of *S. aureus*. The main findings were: infection with *S. aureus* causes prolongation of hospitalization and at any moment of the hospitalization patients will be colonized with *S. aureus*. The isolation of the entire area of the Burn Care Unit (UTQ) is suggested.

Both studies are retrospective cohort studies. The analysis of methodological quality was performed using STROBE instrument [19], and both obtained concept A in this assessment instrument, i.e., a percentage of ≥ 80% in most items, including: title and abstract, introduction, materials and methods, results and discussion.

Figure 2 shows that patients colonized with MRSA were those with the highest death event compared with those who were colonized by MSSA. The odds ratio or possibilities (AB) is greater in the study by Kaiser et al [21] because it has the largest number of patients exposed, as well justified the increased number of deaths.

Figure 2 shows that patients colonized with MRSA were those with the highest death event compared with those who were colonized by MSSA.

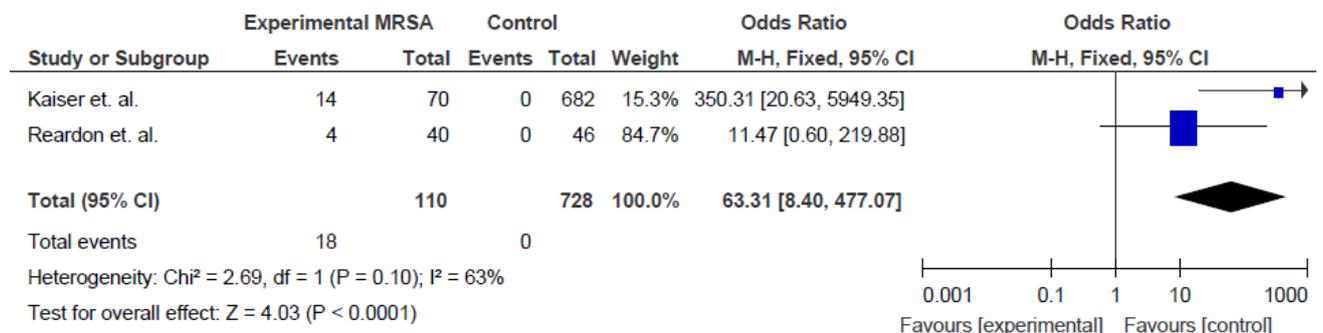


Figure 2. Deaths among burned colonization with MRSA versus MSSA

Heterogeneity was identified, but not statistically significant among the included studies (I² = 63%, p = 0:10). Odds ratio of 63.31 (8.40 to 477.07) and confidence interval of 95%).

The methodology of this systematic review and meta-analysis rigorously followed the recommendations of the Cochrane Collaboration [18] and STROBE [19] and the

whole process was carried out by two independent reviewers (ALRZB and LAP).

4. Discussion

To perform a systematic review it is essential to follow the appropriate methodology with all the necessary scientific rigor, avoiding biases and inaccuracies, which makes it different from the narrative and traditional literature review [23].

The best way to control bias in a systematic review is to include randomized controlled trials, which was not possible in this review.

An alternative to minimize biases of the study is subject was using the STROBE [19] instrument to assess the methodological quality of observational studies, which brings recommendations for critical analysis and transparent reporting of data from this type of study and evaluate the results which can be included in a systematic review [23,24]. Through meta it is possible to improve the statistical power because data from more than one study are combined, increase the sample size and thus statistical power, thereby reducing the possibility of incorrect acceptance or rejection of the null hypothesis [25]. The prevalence of resistant strains during treatment is a serious problem for infection control in the hospital environment. Therefore, MRSA is a major challenge for health professionals and especially for patients with burns, since they have a high chance of causing significant morbidity and mortality [26]. This bacterium is easily acquired and comprises a potential factor to become resistant to the antibiotics routinely used.

The present study found that the mortality of burn patients colonized with MRSA had higher mortality events than those with MSSA, according to data from the included studies (Table 1).

Table 1. Data extracted from the studies included

Given	Kaiser et al	Reardon et al
Number of patients studied	752	86
Number of events (MRSA)	70	40
Number of controls (MSSA)	682	46
Number of deaths	14	4

Thus, it can be observed that the odds ratio (OR) is greater in the study by Kaiser et al (2011) [21] having a greater number of patients exposed, thereby increasing the number of deaths.

5. Conclusion

It was found that MRSA colonization is associated with the burned body surface area (BSA), so the higher the percentage burn, (the) greater the risk of MRSA colonization. Most patients who died were colonized with MRSA. The evidence obtained in this study suggests that the burns, especially those infected with MRSA, fall into a serious public health problem because of the difficult, and often unsuccessful treatment, which confirms an increase in morbidity and mortality in these patients, in addition to excessive cost to health services.

Thus, we emphasize the importance of this meta-analysis for the organization of these data that facilitates the implementation of treatment protocols, improving the quality of preventive measures and reducing mortality rates for MRSA.

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