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Original Article

Methicillin-resistant *Staphylococcus aureus* (MRSA) infection in lower extremity amputations – A gigantic health-care problem or a false alarm?

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Abstract

Objectives: Methicillin-resistant *Staphylococcus aureus* (MRSA) poses not only an increasingly serious health-care problem but also a notoriously gigantic public issue. We aimed to evaluate whether MRSA infection is a significant negative predictive factor for amputation healing and morbidity, in comparison to non-MRSA infections.

Materials and Methods: A cross-sectional comparative study of all the lower extremity amputations during the 25-month study period to examine the influence of MRSA and non-MRSA infection on clinical outcome. Results were compared between MRSA- and non-MRSA-infected patients using Fisher's exact test.

Results: During the two-year period, 171 patients underwent lower limb amputations for acute or chronic limb ischemia. Sixteen (9.3%) had documented wound infection; including 10 MRSA (62.5%), 2 methicillin-sensitive *Staphylococcus aureus* (12.5%), 2 Pseudomonas aeruginosa (12.5%), 1 coagulase-negative staphylococci (6.2%) and 1 enterococcus (6.2%). Patients with MRSA and non-MRSA infections were well matched in demographics, indication & level of amputation, duration of operation, American Society of Anesthetists (ASA) grades, and wound classification ($p<0.05$).

There was no death or morbidity observed within 30 day post-operative period in all groups within the study. Over a 28 months median follow-up (range 16-50 months), an overall survival of 93% was observed. Twelve patients (7%) died including one in MRSA group and 11 in no infection group.

Conclusion: MRSA infection does not adversely affect the clinical outcome in patients undergoing lower extremity amputations. Regardless of presence of MRSA bacteria; common infection control measures, thorough wound debridement, careful wound surveillance and judicial administration of antibiotics should be routinely applied to all patients.

1. Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) was first isolated in a culture medium in Europe during the 1960's. [1] Now widespread throughout the world, infection with this organism has emerged as a major problem in surgical practice. [2] An audit by the Joint Vascular Research Group in Great Britain and Ireland demonstrated that the majority of documented wound and graft infections in vascular patients were secondary to MRSA. [3] The likelihood of developing morbidity and perioperative death was shown to be higher in patients with MRSA than those with the other bacterial infections.

MRSA colonization has been reported in 3-20% of vascular patients. [4] Many develop infective complications. Stump infection with MRSA increases time to wound healing, augments risk of revision amputation and hence duration of hospital stay.[5] Wound infections with other bacteria are not related with worse outcome.[4] Several reports and audits have been published suggesting that MRSA infection is associated with worse clinical outcome relative to other organisms.[6,7]

The clinical impact and attributable risks of MRSA infection on the vascular surgical patients undergoing lower extremity amputations remain unclear. We reviewed our clinical experience over two-year duration with 171 consecutive lower limb amputations, determining the incidence of MRSA as well as non-MRSA infections, with the objective of establishing relative effect on clinical outcomes.

2. Materials and Methods

The study was conducted at the Department of General Surgery, Royal Wolverhampton NHS trust hospital, Wolverhampton, UK, from November 2012 to December 2014. All the patients who underwent limb amputation in vascular unit during this time were identified through the hospital coding system as well as operation theatre register. 176 patients were identified but five had amputations of upper limb and these patients were excluded from this study. Records of remaining 171 patients with lower extremity amputation were reviewed for patient demographics, underlying disease condition, presenting symptoms and clinical indication for amputation. Wound class, American Society of Anesthetists (ASA) grade, operative details, hospital stay, and microbiology culture reports were also reviewed. Follow-up details, including time for stump healing, need for re-operation or revision, and postoperative complications were recorded.

The decision for type of amputation and need for any adjunctive revascularization was made by the consultant vascular surgeons. Patients with clinically non-salvageable extremities and chronically non-ambulatory individuals underwent primary amputation. Operative procedures included removal of all necrotic tissue, wide drainage of purulent collections, routine cultures of wounds, staged amputation for grossly septic wounds, and meticulous haemostasis. Intravenous antibiotics were routinely administered at the time of surgery. The type and duration of antimicrobial therapy were neither uniform nor standardized. Initial choice was based on the consultant's preference, though it was uniformly modified when culture results were available. Follow-up included regular wound examinations until discharge, followed by continued clinical evaluation until complete epithelialization of the stump wound was achieved.

Demographic variables, operative procedure, and clinical course of the MRSA-infected patients were compared with the non-MRSA-infected patients using Fisher's exact test. A p value of less than 0.05 was considered to be statistically significant.

3. Results

During the two-year review, 171 patients underwent lower extremity amputation. Sixteen patients (9.3%) had documented wound infections confirmed through the bacterial cultures. These were

stratified into two groups: group 1 (n = 10) had positive MRSA cultures, while group 2 (n = 6) grew other bacterial flora. Table 1 outlines the patient demographics of the two groups along with comparison with the rest of the patients without any wound infection. No significant differences were noted in the clinical features and co-morbid conditions between the two groups. Most of the surgical procedures were performed electively by the consultant surgeons. Operating time varied depending upon the level of amputation and seniority of the operating surgeon, but there was no statistically significant difference between the operating times of the two groups (p = 0.19).

Table 1: Demographics of 171 patients undergoing lower limb amputations

Factor	No infection (n = 155) [n (%)]	Group 1 MRSA infection (n = 10)[n (%)]	Group 2 Non-MRSA infection (n = 6)[n (%)]	Statistical difference between MRSA & non-MRSA (p value)
Age in years (median ± SD)	75 ± 12.64	71 ± 11.09	68.5 ± 9.66	0.43
Gender frequency (Male: Female)	99:56	5:5	3:3	N/A
DM	92 (59.3)	7 (70)	4 (66.6)	0.43
HTN	113 (72.9)	9 (90)	5 (83.3)	0.88
Hyperlipidemia	52 (33.5)	3 (30)	2 (33.3)	0.16
Urgency frequency (Elective: Emergency)	125:30	8:2	5:1	N/A
Surgeon level frequency (Consultant: Registrar)	100:55	6:4	4:2	N/A
Operation duration in minutes (median ± SD)	60.0 ± 26	62.5 ± 58	77.5 ± 30	0.19

Fisher's exact test is used. Level of significance p ≤ 0.05
SD: standard deviation; DM: diabetes mellitus; HTN: hypertension; N/A: not applicable

All 171 patients underwent lower limb amputation for acute or chronic limb ischemia. Table 2 compares the levels of amputation between these groups. No significant differences were noted in the level of amputation between the groups. On analysis of American Society of Anesthetists (ASA) grades of patients developing MRSA & non-MRSA infections, 81.2% of patients belonged to ASA grade 3 (severe systemic disease), 12.5% to ASA grade 2 (mild systemic disease) and 6.3% to ASA grade 4 (incapacitating disease). None was seen in ASA grade 1 (no disease) or 5 (moribund).

Table 2: Comparison of level of amputation in MRSA- and non-MRSA-infected patients undergoing lower limb amputation

Level of amputation	No infection (n = 155) [n (%)]	Group 1 MRSA infection (n = 10) [n (%)]	Group 2 Non-MRSA infection (n = 6) [n (%)]	Statistical difference between MRSA & non-MRSA (p value)
Above-knee (AKA)	51 (32.9)	4 (40)	2 (33)	0.78
Below-knee (BKA)	38 (24.5)	3 (30)	3 (50)	0.09
Trans-metatarsal	7 (4.5)	0	0	N/A
Toe	59 (38.0)	3 (30)	1 (17)	0.57

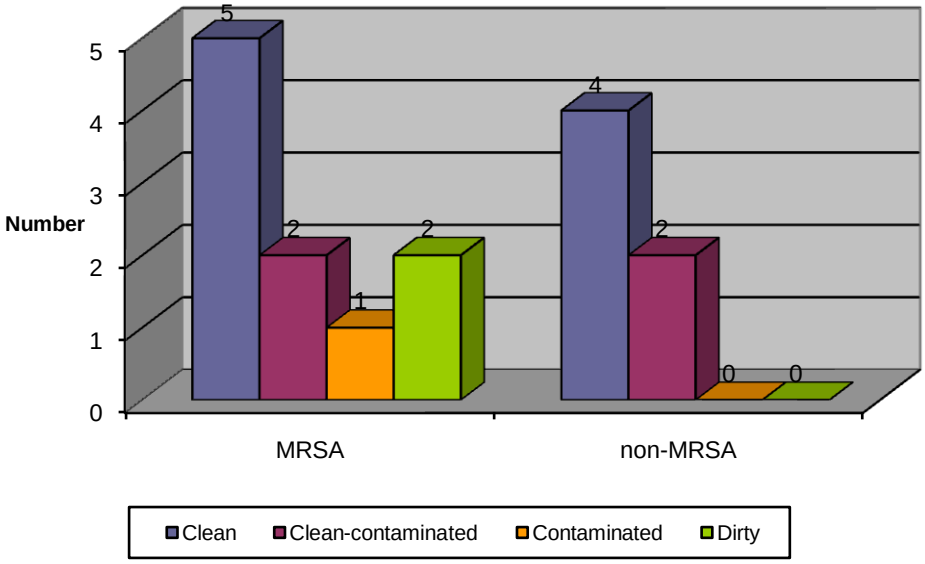
Fisher's exact test is used. Level of significance p ≤ 0.05
N/A: not applicable

The bacteriology culture results from the study population are analyzed in table 3. MRSA predominated (62.5%), followed by methicillin-sensitive *Staphylococcus aureus* (12.5%), *Pseudomonas aeruginosa* (12.5%), coagulase-negative *staphylococci* (6.2%) and *enterococcus* (6.2%). Comparison of MRSA and non-MRSA patients based on wound classification is shown in Figure 1. The wounds were categorized at the time of surgery into four classes; a clean wound is where there is no inflammation, clean-contaminated wound has mild inflammation, contaminated wound has non-purulent inflammation, and dirty wound contains purulent inflammation. No significant increase was seen in the risk of acquiring MRSA infection based on the type of surgical wound.

Table 3: Frequency of organisms isolated from bacterial cultures grown from patients undergoing lower limb amputation.

Organism	Incidence [n (%)]
Methicillin-resistant *Staphylococcus aureus* (MRSA)	10 (62.5)
Methicillin-sensitive *Staphylococcus aureus* (MSSA)	2 (12.5)
Pseudomonas aeruginosa	2 (12.5)
Coagulase-negative *Staphylococcus*	1 (6.2)
Enterococcus	1 (6.2)
Total	16 (100)

Figure 1: Comparison of MRSA- and non-MRSA-infected patients based on wound classification, with p=0.46 on student's t-test. Level of significance p ≤ 0.05



There was no death within 30 day post-operative period in all groups within the study. Two patients (20%) with documented MRSA infection (group 1) required an amputation to a higher level. In group 2, none required revised amputation, while 5 patients had a higher level amputation in no-infection group. Overall there was no significant difference observed between group 1 or 2 in 30-day morbidity rates. Over a 28 months median follow-up (range 16-50 months), an overall survival of 93% was observed. Twelve patients (7%) died including one in MRSA group and 11 in no infection group.

4. Discussion

MRSA poses not only a serious health-care problem but also a notorious public issue. Many studies have confirmed an increase in the prevalence of methicillin resistance among *Staphylococcus aureus.* [8] In a study of European intensive care units, 30% of all infections were attributable to S. *aureus* and 60% of these were MRSA. [9] This study also demonstrated that MRSA most commonly affected the ischemic limb in the vascular patients undergoing lower extremity amputation, although positive blood cultures were not uncommon.

Several studies have been published demonstrating that MRSA infection is associated with worse clinical outcome compared to the other organisms. [5-7, 10] Ibelings and Bruining found that patients with MRSA infections had lesser chances of survival than those with non-MRSA infections. [11] However, these reports and audits also observed that patients with MRSA infections often had an increased incidence of co-morbid conditions that may itself be associated with poor outcome. No significant difference has been shown in mortality between matched MRSA and non-MRSA infected patients. [12] del Rio-Sola and colleagues found no statistical difference in relation to morbidity, mortality, re-amputation rate and mean time of hospital stay between well matched MRSA and non-MRSA infected patients undergoing lower extremity amputations. [13] The two groups in our study were also similarly matched in demographics, indication & level of amputation, duration of operation, ASA grades, and wound classification. We did not find any statistical difference between co-morbid conditions amongst these two groups, including diabetes mellitus (p 0.43), hypertension (p 0.88) and hyperlipidemia (p 0.16). This explains the lack of significant differences in the 30-day morbidity or mortality rates between MRSA- and non-MRSA-infected patients reported by our study.

Despite the development of focused antibiotics against MRSA, the most effective approach to reduce MRSA infection involves minimizing spread, through infection control measures. [14] Introducing practices, such as thorough hand washing, patient isolation, and aggressive treatment of affected patients have been shown to reduce the transmission of active infection. A typical combination of oral rifampicin and fusidic acid should be used for nosocomial strains of MRSA. All serious MRSA infections should be treated with parenteral vancomycin, or if the patient is vancomycin allergic, teicoplanin, which remains the antibiotic of choice for initial empirical treatment. New antibiotics such as linezolid, pristinamycin and quinupristin have good anti-MRSA activity but are very expensive. [15-17]

5. Conclusion

Irrespective of the dangers commonly associated with MRSA infection, the results of this study suggest that patients undergoing lower extremity amputation infected by MRSA are at no more increased risk of complications than patients with non-MRSA infection with similar pre-operative co-morbid conditions. Therefore, no additional interventions seem necessary in patients with MRSA infection. We suggest that regardless of the presence of MRSA bacteria; common infection control measures, thorough wound debridement, careful wound surveillance and judicial administration of antibiotics be applied to all the patients.

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