

## Mupirocin resistance: clinical implications and potential alternatives for the eradication of MRSA

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Mupirocin 2% ointment is used either alone or with skin antiseptics as part of a comprehensive MRSA decolonization strategy. Increased mupirocin use predisposes to mupirocin resistance, which is significantly associated with persistent MRSA carriage. Mupirocin resistance as high as 81% has been reported. There is a strong association between previous mupirocin exposure and both low-level and high-level mupirocin resistance. High-level mupirocin resistance (*mupA* carriage) is also linked to MDR. Among MRSA isolates, the presence of the *qacA* and/or *qacB* gene, encoding resistance to chlorhexidine, ranges from 65% to 91%, which, along with mupirocin resistance, is associated with failed decolonization. This is of significant concern for patient care and infection prevention and control strategies as both these agents are used concurrently for decolonization. Increasing bacterial resistance necessitates the discovery or development of new antimicrobial therapies. These include, for example, polyhexanide, lysostaphin, ethanol, omiganan pentahydrochloride, tea tree oil, probiotics, bacteriophages and honey. However, few of these have been evaluated fully or extensively tested in clinical trials and this is required to in part address the implications of mupirocin resistance.

### Background

*Staphylococcus aureus* is a leading cause of healthcare-associated infections worldwide and is associated with increased morbidity, mortality and higher healthcare costs, including infections caused by MSSA and MRSA.<sup>1</sup> Colonization with MRSA increases the risk of adverse health outcomes and it is estimated that 10%–30% of carriers subsequently develop infection.<sup>2</sup> The nose as well as extranasal sites such as the throat and perineum, skin ulcers and skin lesions are frequently colonized.<sup>3–5</sup> A meta-analysis concluded that MRSA colonization conferred a 4-fold increased risk of infection as compared with MSSA colonization.<sup>6</sup> Eradication of MRSA carriage from the nose and other body sites forms an integral part of strategies to prevent and control MRSA in many countries.<sup>7–9</sup> Mupirocin is an important component in MRSA prevention and specifically for the eradication of nasal MRSA. However, reports of increasing mupirocin resistance (MR) are of serious concern.

This review aims to determine the prevalence of MR and its clinical consequences as well as measures to control MR. It also reviews the evidence supporting the use of new agents as potential therapeutic alternatives for the prevention and management of MRSA.

### Search strategy

The following databases were searched (date of last search: 30 March 2015): PubMed, CINAHL, Scopus and Web of Science. The search was limited to humans and English language publications from 1985 to March 2015. Search terms included multiple variants of the following terms: “*Staphylococcus aureus*, nose/nasal, colonisation/colonization, honey, infection control or prevention and control, wound, ulcer, surgical wound infection, topical, treatment, chlorhexidine, mupirocin and drug resistance” alone or in combination and/or ‘infection’. Medical subject headings (MeSH) terms where available were used. Additionally, the reference lists of retrieved articles were scanned to identify any further studies. The titles and abstracts identified were screened for relevance by one author. The list of potential articles was reviewed to remove duplicates and full-text versions were obtained. Further articles were eliminated following review. The original articles were obtained and assessed in detail for inclusion. Articles included in this review are those that addressed mupirocin, i.e. infections associated with *S. aureus*, MRSA, decolonization, resistance, surveillance reports, systematic reviews or meta-analyses where the search terms appeared in the article title or abstract. From a total of 499 articles initially found, after exclusion

for reasons of unsuitability or duplicates, 88 articles remained for inclusion, including those identified from reference lists. The search process is illustrated in Figure 1.

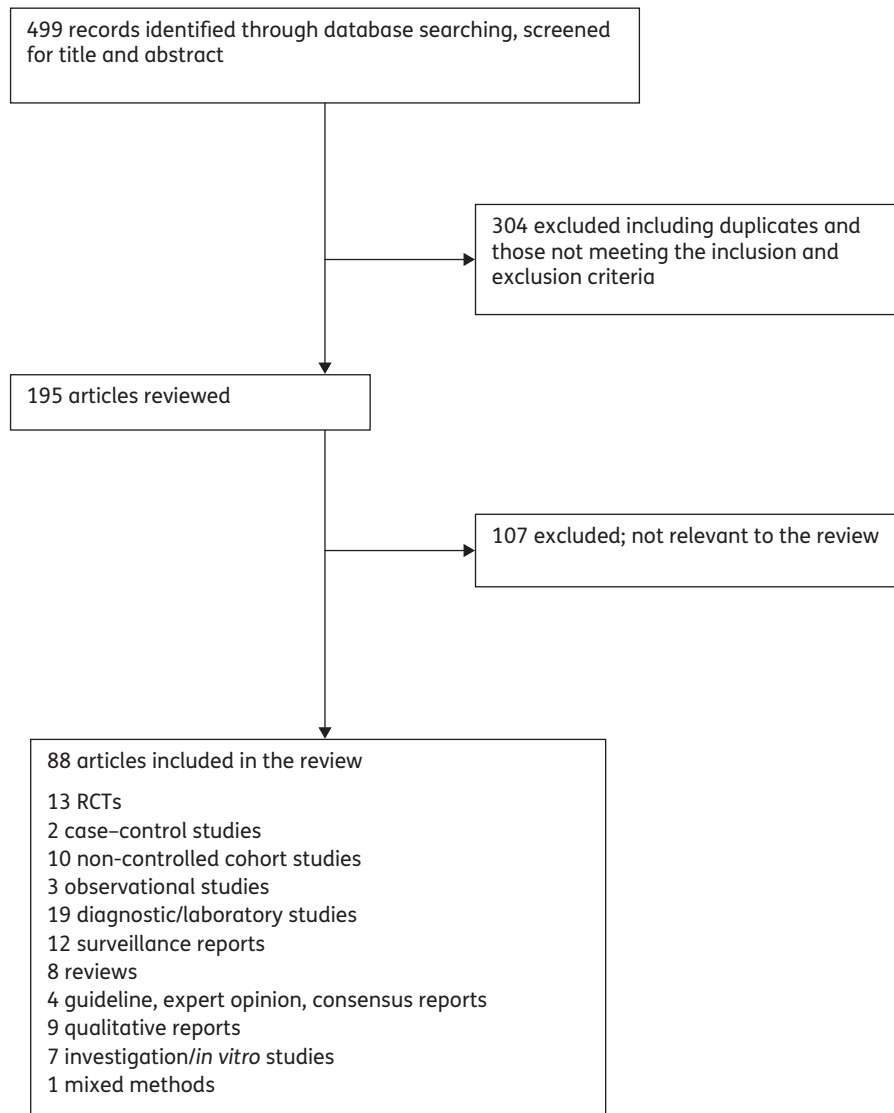
## Mupirocin use

The antibiotic mupirocin (pseudomonic acid A) is produced by the bacterium *Pseudomonas fluorescens*. Mupirocin calcium ointment was clinically introduced in the late 1980s and has proved to be one of the most successful topical antibiotics for the clearance of nasal *S. aureus*, both MSSA as well as MRSA.<sup>5,10–12</sup> Mupirocin is a competitive inhibitor of bacterial isoleucyl-tRNA synthetase and is active against most ‘Gram-positive’ and some ‘Gram-negative’ bacilli. Mupirocin-mediated inhibition of isoleucyl-tRNA synthetase impedes protein and RNA synthesis, ultimately leading to bacterial death. There is very little systemic absorption following the topical application of mupirocin. After systemic administration,

mupirocin has a short half-life (15 min) and is rapidly converted into inactive monic acid, which is excreted principally through the kidneys.

The therapeutic indication for mupirocin is the elimination of nasal carriage of staphylococci, including MRSA. The method of application is nasal ointment, usually 2%, applied to the anterior nares two to three times daily. Nasal carriage is then normally cleared within 5–7 days of commencing treatment.<sup>12,13</sup> A systematic review that included 23 trials concluded that mupirocin applied two or three times daily for 4–7 days to both nostrils showed excellent efficacy and eradicated *S. aureus* in 90% of patients as assessed 1 week after treatment.<sup>13</sup> A meta-analysis in 2008 concluded that mupirocin appears to be cost-effective only in those patients who are proven nasal carriers, where a significant and strong reduction in *S. aureus* infection was confirmed.<sup>12</sup>

A significant limitation to the use of mupirocin is resistance, which reportedly ranges from 1% to 81%.<sup>14–21</sup> Mupirocin is also used by some clinicians for the treatment of local skin and soft



**Figure 1.** Search process and the number of relevant references.

tissue infections caused by *S. aureus* and streptococcal species, which also contributes to MR.<sup>22</sup>

Mupirocin 2% ointment is used for nasal decolonization alone or as part of a comprehensive MRSA decolonization strategy along with skin antiseptics such as chlorhexidine. The impact of the application of mupirocin to the nose has been investigated by various researchers with varying success, in terms of immediate as well as medium- to long-term sustained nasal MRSA decolonization.<sup>5,23–25</sup> In a multicentre trial in care homes, intranasal mupirocin ointment was compared with a placebo among persistent carriers of *S. aureus* and MRSA ( $n=127$ ) with a follow-up period of 6 months. Mupirocin initially eradicated *S. aureus*, including MRSA in 60/64 (94%) compared with 54/63 (86%) in the placebo group, but after 90 days recolonization occurred in 39% of the mupirocin group.<sup>24</sup> In a study of 40 hospitalized patients, it was found that MRSA clearance was more common amongst patients with mupirocin-susceptible isolates (91%) than in those patients colonized with low-level MR (LLMR) and high-level MR (HLMR).<sup>25</sup> A double-blind, randomized, placebo-controlled trial in a tertiary healthcare facility evaluated the efficacy of mupirocin in eradicating nasal carriage of MRSA with body washing using chlorhexidine soap for other sites. At the end of follow-up, i.e. 4 weeks from the initiation of decolonization, 19/43 (44%) who received mupirocin were free of nasal MRSA compared with 11/44 (25%) in the control group.<sup>5</sup>

## Mupirocin resistance

MR is very important for infection prevention and control personnel who are engaged in MRSA control efforts and also in the management of individual patients such as before major surgery to minimize post-operative MRSA infection, as the presence of resistance significantly reduces the likelihood of MRSA eradication.

### Mechanisms

Phenotypically, MR is determined according to MIC breakpoints with susceptible being  $\leq 4$  mg/L, LLMR 8–256 mg/L and HLMR  $>512$  mg/L.<sup>21,26</sup> Mupirocin MICs of 8–64 mg/L are usually due to non-synonymous changes in the native isoleucyl-tRNA synthetase gene. *S. aureus* isolates with an MIC of 128 or 256 mg/L are uncommon but are considered to demonstrate LLMR; these isolates have acquired base changes in the native isoleucyl RNA synthetase gene, *ileS*.<sup>14,21,27</sup> MICs of  $\geq 512$  mg/L reflect HLMR and this is mediated by the acquisition of a conjugative plasmid containing *mupA* (*ileS2*), which encodes an alternative isoleucyl-tRNA synthetase.<sup>26,28</sup> Plasmid-mediated HLMR can spread clonally and horizontally, even between different staphylococcal species.<sup>29</sup> In addition to the *mupA* gene, another mechanism of HLMR, mediated by a novel locus (*mupB*), has been reported.<sup>30</sup> The *mupB* gene (3102 bp) shares 65.5% sequence identity with *mupA*, but only 45.5% with *ileS*. The resultant MupB protein shares 72.3% and 41.8% similarity with MupA and IleS, respectively. These findings support the presence of non-*mupA*-mediated HLMR as reported by others.<sup>21,30,31</sup> Molecular studies of MR in *S. aureus* populations indicate that nearly all *S. aureus* isolates with HLMR have the *mupA* gene.<sup>27</sup> However, low or non-expression of the *ileS2* gene has been described amongst LLMR isolates.<sup>32</sup> Although *ileS2* does not encode resistance to other antibiotics, the presence of *ileS2*-carrying plasmids has been associated with

resistance to antibiotics such as clindamycin, tetracycline, erythromycin and levofloxacin.<sup>33</sup> A recent review of the presence of *ileS2* in CoNS bloodstream infection (BSI) isolates found that the increase in the percentage of CoNS isolates carrying *ileS2* (8% in 2006 to 22% in 2011;  $P=0.01$ ) was correlated with increased mupirocin use in each of the corresponding years (3.6 kg/year in 2006 to 13.3 kg/year in 2010).<sup>34</sup> Widespread acquisition of MR following nasal decolonization with mupirocin among CoNS is reported from the Netherlands and higher MR among CoNS is reported from a prevalence survey in France.<sup>35</sup>

### Prevalence

Increased mupirocin use predisposes to both LLMR and HLMR.<sup>14,17,18,35–43</sup> Some of the larger studies are outlined in Table 1. In a Canadian study, the proportion of MRSA strains with HLMR increased from 1.6% in the first 5 years of surveillance (1995–99) to 7.0% (2000–04). The pattern of mupirocin use during the study periods is not described, but the investigators acknowledge the widespread use of mupirocin in their institution.<sup>14</sup> Another study in a tertiary care facility in the USA over 18 months reported MR amongst positive MRSA patients on hospital admission in 20/591 (3.4%); HLMR occurred in 0.62% and LLMR in 2.9%.<sup>36</sup>

A surveillance programme carried out over 2 years in a 24 bed surgical ICU between December 2002 and December 2004 in Missouri, USA, with a low level of mupirocin use, detected MRSA in 13.6% ( $n=338/2840$ ); 13.2% of 302 isolates were MR, 8.6% being HLMR and 4.6% LLMR.<sup>37</sup> A nationwide prospective study of MR amongst staphylococcal isolates in France between October 2011 and February 2012 reported a resistance rate of 10.3% amongst 708 isolates of CoNS, mainly HLMR (5.6%). Among the MRSA isolates, 2.2% ( $n=8$ ) were MR, of which 0.8% were HLMR and carried the *mupA* gene.<sup>35</sup> Another study compared MR during two time periods in a 500 bed tertiary hospital in Brazil. In the first period (1990–95), when mupirocin was used extensively including application to any skin wound comprising  $<20\%$  of body surface, 28/43 (65%) MRSA infections were caused by MR isolates, which decreased to 15% when mupirocin use was restricted to only patients colonized in the nose (1996–2000).<sup>38</sup> The effect of mupirocin ointment for nasal decolonization along with other infection prevention and control measures was evaluated in a study during an MRSA epidemic in a Canadian hospital. There was a significant increase in MR, from 2.7% to 65%, between the beginning of the first year at the onset of the epidemic (1990) and the end of the third year.<sup>39</sup> Similar findings have been reported from another study in Brazil in two tertiary care university hospitals, in one of which there was extensive use of mupirocin and where 72/114 (63%) of isolates were MR, compared with the second hospital in which mupirocin use was controlled and where only 3/49 (6.1%) were MR.<sup>18</sup>

The emergence of HLMR MRSA following the use of mupirocin for prophylaxis at intravenous exit sites to prevent local infection and BSI was reported in 3% of patients on a peritoneal dialysis unit after a 4 year period of continuous use.<sup>40</sup> In a screening programme in Shanghai and Wenzhou (China), 53/803 (6.6%) isolates that were MR MRSA over a 3 year period were HLMR with the *mupA* gene detected by PCR.<sup>41</sup> In a prevalence study in a tertiary care hospital in Singapore, HLMR was reported from 34/307 (11%) isolates; 14% from screening isolates and 10% from clinical

**Table 1.** Larger studies on the prevalence of MR

Author	Year	Country	Study description	Patient population	No. of patients/no. of isolates	Molecular methods used	Prevalence (%)		
							LLMR	HLMR	overall
Miller <i>et al.</i> <sup>39</sup>	1990–93	Canada	LS	hospital	231/310	NA	NA	NA	2.7–65
Vivoni <i>et al.</i> <sup>38</sup>	1990–95	Brazil	LS	hospital	43/43	PCR, PFGE	NA	NA	65
Vivoni <i>et al.</i> <sup>38</sup>	1996–2000	Brazil	LS	hospital	89/108	PCR, PFGE	9	6	15
dos Santos <i>et al.</i> <sup>18</sup>	1995–2004	Brazil	PS	hospital	62/114	NA	NA	NA	6.1–63
Simor <i>et al.</i> <sup>14</sup>	1995–99 <sup>a</sup>	Canada	LS	hospital	NA/4980	PCR	6.4	1.6	NA <sup>a</sup>
	2000–04 <sup>b</sup>						10	7	NA <sup>b</sup>
Jones <i>et al.</i> <sup>37</sup>	2002–04	USA	PS	hospital, SICU	338/302	PCR	4.6	8.6	13.2
Liu <i>et al.</i> <sup>41</sup>	2005–07	China	LS	hospital	NA/803	PCR	0	6.6	6.6
Babu <i>et al.</i> <sup>36</sup>	2008	USA	PS	hospital	948/591	NA	2.9	0.6	3.4
Choudhury <i>et al.</i> <sup>17</sup>	2010	Singapore	PS	hospital	NA/307	PCR	0	11	11
Park <i>et al.</i> <sup>42</sup>	2011	Korea	PS	hospital, NICU	101/101	PFGE	0	47 CA/79 HA	73
Walker <i>et al.</i> <sup>19</sup>	2004	USA	LS, 5 eras	hospital, mixed population	50–100 isolates per era, random	PCR	28	31	67
Caffrey <i>et al.</i> <sup>16</sup>	2010	USA	retrospective case–control	hospital	310/40 cases MR and 270 controls mupirocin susceptible	NA	NA	NA	NA
Cadilla <i>et al.</i> <sup>15</sup>	2011	USA	LS	hospital	837 isolates (191 MDR and 646 non-MDR)	PCR	0	6.8 MDR	NA
Lee <i>et al.</i> <sup>20</sup>	2011	Switzerland	nested case–control	hospital, acute	150/75 cases and 75 controls; HLMR was excluded from the study	Etest, PCR	NA	NA	9–81
Desroches <i>et al.</i> <sup>35</sup>	2013	France	PS	hospital, national surveillance	NA/367	PCR, PFGE, microarray	1.4	0.8	2.2

LS, laboratory surveillance; NA, not available; PS, prospective surveillance; SICU, surgical ICU; NICU, neonatal ICU; CA, community acquired; HA, hospital acquired.

<sup>a</sup>Period 1.

<sup>b</sup>Period 2.

isolates during 2009–2010.<sup>17</sup> HLMR was also reported from a neonatal ICU in Korea where 101/223 (45%) of admissions were MRSA positive; of these, 79% of healthcare-associated MRSA isolates and 47% of community-acquired MRSA were HLMR.<sup>42</sup>

A multicentre study in care homes involving 3806 residents in the USA over 30 months detected MR in 101 (12%) isolates; HLMR in 78 (9%) isolates and LLMR in 23 (3%) isolates.<sup>43</sup> In a review of 240 MRSA isolates recovered over 20 years from patients who had failed decolonization, MR was identified in 63% of the isolates.<sup>44</sup>

In a matched case–control study of 40 cases with MR MRSA and 270 controls without MR MRSA during 2004–08, prior exposure to mupirocin in the preceding year was the most significant independent predictor for both LLMR and HLMR.<sup>16</sup>

In the Netherlands, widespread acquisition among CoNS of MR following nasal decolonization with mupirocin has been reported.<sup>34,45</sup> In the first study (2012), among the 238 CoNS BSI isolates, *Staphylococcus epidermidis* was most prevalent [150 isolates (63%)] and it was also the most common species amongst HLMR isolates, i.e. 25 isolates. In the latter report, a nasal decolonization study (2015), among the 607 CoNS isolates collected from 469 patients post-decolonization with mupirocin, 588 (97%) were HLMR. *S. epidermidis* was most prevalent with 568 isolates (94%).<sup>45</sup> A review of the clinical implications of MR among *S. aureus* suggests that unrestricted over-the-counter use and treatment of wounds and pressure sores with mupirocin are strongly associated with resistance.<sup>22</sup>

### Associated chlorhexidine resistance

In most MRSA infection prevention programmes, chlorhexidine is a major component and is often used in various forms as part of oral care, skin antisepsis prior to intravascular device placement, before surgical procedures, during patient bathing and as a component of some antimicrobial-impregnated catheters and dressings. As with any antimicrobial or antiseptic agent, increased use raises concerns about emerging chlorhexidine resistance and its implications for MRSA decolonization strategies. Chlorhexidine is a biguanide cationic bactericidal agent that is rapidly taken up by *S. aureus*.<sup>46,47</sup> Chlorhexidine gluconate (CHG) is a topical antimicrobial agent with broad-spectrum activity, including against *S. aureus*. At low concentrations it disrupts the integrity of the cell wall and membranes, resulting in leakage of the intracellular contents; at high concentrations, chlorhexidine causes coagulation of the intracellular contents. Significant reductions in central line-associated BSI were observed when CHG was used for procedural skin preparation.<sup>48</sup> Bacterial resistance to chlorhexidine was initially reported in 1995.<sup>47</sup> Resistance to chlorhexidine is conferred by two gene families, *qacA/B* and *smr*.<sup>49</sup> These plasmid-mediated *qacA/B* genes encode proton-dependent multidrug efflux pumps, expression of which results in high-level resistance to antiseptics, whereas the *smr* gene confers low-level resistance.<sup>20,47,50</sup> MRSA isolates carrying the *qacA/B* gene initially belonged to a single clone, but the *qacA/B* gene has been detected in MRSA isolates belonging to seven different clones from different countries.<sup>20,43,44,51–53</sup>

Concomitant resistance to other antiseptics and systemic antibacterial agents presents additional challenges in terms of decolonization strategies. For example, a strong association has been reported between HLMR and resistance to at least four non- $\beta$ -lactam antimicrobial classes.<sup>15</sup> In that study, the investigators

also identified that *mupA* was significantly more likely to be carried by isolates resistant to gentamicin, rifampicin or trimethoprim/sulfamethoxazole ( $P < 0.0001$ ) in comparison with erythromycin-, clindamycin- or ciprofloxacin-resistant isolates ( $P = 1.00$ ,  $P = 0.30$  and  $P = 0.07$ ), respectively.

Very high prevalence of *qacA* and/or *qacB* MRSA isolates has been reported from Taiwan where chlorhexidine has been used for >20 years for hand hygiene; of 240 isolates obtained during 1990–2005, the proportion of MRSA isolates with a chlorhexidine MIC of  $\geq 4$  mg/L was 1.7% in 1990, 50% in 1995, 40% in 2000 and 46.7% in 2005. Among these isolates, 46/83 (55.4%) carried the *qacA/B* gene. In addition, *qacA* and/or *qacB* were identified in 91% of MRSA isolates from patients who had failed decolonization.<sup>44</sup> Similar findings were reported from a secondary and tertiary hospital in Korea over 4 years among the MR MRSA isolates; the *qacA/B* and *smr* genes were detected in 65% of isolates.<sup>51</sup> A nested case–control study of MRSA decolonization found that combined LLMR and the presence of chlorhexidine resistance significantly increased the risk of persistent MRSA carriage.<sup>20</sup> However, the investigators reported that chlorhexidine resistance alone did not predict persistent carriage, suggesting that the combination of LLMR and chlorhexidine resistance may be necessary for clinical failure, i.e. persistent colonization. In practice, both these agents (mupirocin and CHG) are often administered concurrently as part of MRSA decolonization regimens. Studies evaluating chlorhexidine resistance and MRSA and the clinical significance are outlined in Table 2.

### Controlling MR

In controlling MR, Patel *et al.*<sup>21</sup> proposed three approaches. First, additional studies are needed to quantify the efficacy and unintended consequences of mupirocin use as a prevention strategy. Second, a strategy for monitoring the prevalence of resistance should be developed and implemented whenever mupirocin is routinely used. Third, monitoring should not only focus on MR itself, but also should help determine whether mupirocin use might amplify the spread of other MDR via its linkage to other resistance determinants.<sup>21</sup> There may be a benefit in incorporating MR surveillance as part of ongoing surveillance programmes such as EARSS-Net, which monitors antibiotic resistance amongst invasive isolates of MRSA, i.e. in BSI. While these do not represent isolates from the nose or other carriage sites, they are representative of isolates responsible for serious infection throughout Europe and from a population in which many have had or will be undergoing MRSA decolonization.

The assessment of mupirocin susceptibility amongst isolates of MRSA varies. While most centres determine and report mupirocin susceptibility when MRSA is initially isolated from an individual patient, the ongoing testing of repeat isolates from the same patient varies. For persistent MRSA carriers, mupirocin MIC testing should be repeated to assist in informed decision making and provide the potential opportunity to impact on the control of resistance. Point prevalence surveillance in centres where mupirocin is widely used and/or resistance is reported is also indicated.

Control of mupirocin use, i.e. targeted decolonization in selected patients based on risk assessment rather than the decolonization of all MRSA-positive patients, has proved an effective strategy to combat MR. For example, in the ICU there may be little point in attempting to eradicate upper respiratory tract

**Table 2.** Studies evaluating MR and chlorhexidine resistance and their clinical significance

Author	Year	Country	Study design	Patient population	MRSA/MSSA	No. of patients/isolates	Molecular method	Follow-up	Prevalence of MR	Prevalence of <i>qacA/B</i> , <i>smr</i>	Comments
Wang <i>et al.</i> <sup>44</sup>	2008	Taiwan	longitudinal analysis	hospital	MRSA	240 BSI and clinical isolates	MLST	NAP	NA	1.7% (1990), 46.7% (2005)	83/240 had high CHX MIC >4 mg/L, 55.4% carried <i>qacA/B</i>
Vali <i>et al.</i> <sup>53</sup>	2008	UK (Scotland)	longitudinal analysis	hospital	MRSA	120 clinical isolates	PCR	NAP	NA	8.3% ( <i>n</i> = 10) <i>qacA/B</i> , 44.2% ( <i>n</i> = 53) <i>smr</i>	high resistance to AMX, GEN, OXA, CTX, CXM and CIP; low resistance to TET; none resistant to VAN
Lee <i>et al.</i> <sup>20</sup>	2011	Switzerland	nested case-control	hospital	MRSA	150: 75 cases and 75 controls	PCR	2 years	LLMR present in all <i>qacA/B</i> -positive isolates	91% cases ( <i>n</i> = 68), 68% controls ( <i>n</i> = 51) <i>qacA/B</i>	HLMR excluded
Longtin <i>et al.</i> <sup>46</sup>	2011	Canada	longitudinal analysis	hospital ICU	MRSA	234 isolates	PCR	NAP	NA	2% ( <i>n</i> = 7) <i>qacA/B</i> , 7% ( <i>n</i> = 23) <i>smr</i>	
McDanel <i>et al.</i> <sup>43</sup>	2013	USA	longitudinal analysis	nursing homes ( <i>n</i> = 26)	MRSA	3806 patients, 829 MRSA isolates	PCR	NAP	3% ( <i>n</i> = 23) LLMR, 9% ( <i>n</i> = 78) HLMR	0.6% ( <i>n</i> = 5) <i>qacA/B</i>	all five were resistant to CLI, ERY, LVX, TET, SXT and GEN
Lee <i>et al.</i> <sup>51</sup>	2013	Korea	longitudinal analysis	hospital ( <i>n</i> = 2)	MRSA	456 isolates	MLST, PCR	NAP	12% ( <i>n</i> = 53) LLMR, 2% ( <i>n</i> = 9) HLMR	65% ( <i>n</i> = 40) <i>qacA/B</i> , 71% ( <i>n</i> = 44) <i>smr</i>	all MR isolates resistant to ERY, CLI, GEN and CIP; none resistant to VAN
Fritz <i>et al.</i> <sup>52</sup>	2013	USA	longitudinal analysis	hospital	MSSA and MRSA	1089 patients/696 isolates	PCR	NAP	2.1% ( <i>n</i> = 23) at baseline to 4.5% ( <i>n</i> = 31)	0.9% ( <i>n</i> = 10) at baseline to 1.6% ( <i>n</i> = 11) <i>qacA/B</i>	isolates resistant to CLI were more likely to be MR compared with CLI-susceptible isolates; CHX resistance was not associated with resistance to other systemic antibiotics

NAP, not applicable; NA, not available; CHX, chlorhexidine; AMX, amoxicillin; GEN, gentamicin; OXA, oxacillin; CTX, cefotaxime; CXM, cefuroxime; CIP, ciprofloxacin; TET, tetracycline; VAN, vancomycin; CLI, clindamycin; ERY, erythromycin; LVX, levofloxacin; SXT, trimethoprim/sulfamethoxazole.



colonization, including nasal carriage, in a patient who is intubated and ventilated given the presence of an endotracheal tube or a tracheostomy to which the bacteria will adhere and form a biofilm. Targeted decolonization therefore involves an antimicrobial stewardship programme, healthcare worker education and refresher training, surveillance, feedback and electronic alerts.<sup>19</sup> There was a precipitous decline in the number of isolates with HLMR (from 31% to 4%) and also LLMR (from 26% to 10%) after measures were introduced to control or limit the use of mupirocin over 2 years in a mixed healthcare setting that included acute, domiciliary and nursing home care.

Similar reductions in MR following the control of mupirocin use were reported from a neonatal unit in the Netherlands by Zakrzewska-Bode *et al.*<sup>54</sup> where the routine application of mupirocin to central vascular catheter insertion sites was discontinued. Finally, in Western Australia, susceptibility testing of *S. aureus* isolates was mandated from 1993 and restricted mupirocin use led to similar reductions, where MR decreased from 6.4% ( $n=16$ ) in 1994 to 0.3% ( $n=3$ ) in 1997.<sup>55</sup>

Recent years have seen an emphasis on horizontal infection prevention and control approaches, i.e. applying measures to a whole population rather than to those at risk. An example of this is the use of mupirocin and chlorhexidine applied to all patients in an ICU compared with their use in those patients screened and found to be positive for MRSA. The case for the universal decolonization approach in ICU settings may inevitably contribute to higher MR as well as resistance to chlorhexidine.<sup>56</sup> The independent effect of mupirocin could not be distinguished from the combined mupirocin/chlorhexidine effect in the same study. The downside of universal decontamination is the unnecessary use of mupirocin in 70%–80% of the patients not carrying *S. aureus*, potentially enhancing resistance in CoNS and creating a reservoir of MR for *S. aureus*.<sup>22</sup> A systematic review on chlorhexidine body washing reports that evidence is lacking that it reduces carriage or infections with antimicrobial-resistant bacteria.<sup>57</sup> Consequently, if this practice becomes more widespread, it will be essential to monitor for the emergence and spread of both MR and chlorhexidine resistance.

In a multicentre, cluster-randomized, non-blinded crossover trial, the effect of daily bathing with chlorhexidine-impregnated washcloths on the acquisition of MDR organisms and the incidence of hospital-acquired BSI was evaluated.<sup>58</sup> The overall rate of hospital-acquired BSI was 4.78 cases per 1000 patient-days with chlorhexidine bathing versus 6.60 cases per 1000 patient-days with non-antimicrobial washcloths ( $P=0.007$ ), a 28% lower rate with chlorhexidine-impregnated washcloths. However, when analysed by individual organism, there were no significant reductions in MRSA acquisition or *S. aureus* BSI. In a similar trial, paediatric ICU patients demonstrated a 36% reduction in BSI with 2% CHG bathing, which failed to achieve significance in the ITT analysis. In that study, the incidence of BSI was lower in patients receiving CHG bathing compared with standard practices.<sup>59</sup>

## Other antimicrobial agents

Bacitracin ointment, usually in combination with polymyxin B and neosporin (e.g. polysporin), has been studied as a potential decolonization strategy for MRSA and the results have not been as encouraging as those for mupirocin. In a double-blind,

randomized controlled trial (RCT), bacitracin was compared with mupirocin and all the patients received daily CHG body washes. Only 15/49 (30.6%) patients in the polysporin arm were MRSA negative at all sites at 48 h, compared with 35/54 (64.8%) of those given mupirocin.<sup>60</sup>

Retapamulin is a pleuromutilin (a new class of antibiotic) that exhibits activity against various skin bacteria including MSSA and MRSA and is used for the treatment of impetigo. An *in vitro* study assessed susceptibilities amongst various MSSA and MRSA strains from acute and chronic wounds to commonly used topical antimicrobial agents. The investigators found that mupirocin treatment was the most effective antimicrobial, with areas of inhibition ranging from 30.34 to 61.70 cm<sup>2</sup> ( $P<0.05$ ), as compared with the next most effective, retapamulin, with areas of inhibition ranging from 11.97 to 23.54 cm<sup>2</sup>.<sup>61</sup> Another study reported that retapamulin had good activity against 15/16 (94%) of MR isolates.<sup>62</sup> A recent double-blind RCT concluded that the clinical success rate in the treatment of secondarily infected traumatic lesions amongst patients with MRSA was significantly lower with retapamulin compared with linezolid.<sup>63</sup>

## Alternative approaches to decolonization

The increasing prevalence of MR and associated chlorhexidine resistance means that alternative agents to decolonize patients with MRSA need to be considered. In 2009, Coates *et al.*<sup>12</sup> discussed alternatives that were in various stages of development with a diversity of mechanisms, but had yet to be proved efficacious in clinical trials. While considering the alternatives, the investigators were of the opinion that a more bactericidal antibiotic than mupirocin is needed, on the grounds that it might reduce the relapse rate and so clear the patient of MRSA for a longer period of time than mupirocin.<sup>12</sup> Oral antimicrobials for decolonization of MRSA carriage may be considered in certain populations (e.g. multiple sites of colonization) or under specific circumstances (e.g. prior to surgery); however, the risk of resistance to oral therapy or systemic side effects must be carefully considered. This is beyond the scope of this review and below we focus on emerging promising topical agents.

### Octenidine dihydrochloride

Decolonization of the nose and other body sites has been investigated using octenidine dihydrochloride body wash along with the intranasal application of 2% mupirocin. The efficacy was highest in the nose, where decolonization was successful in 28/32 (87.5%), and in the decolonization of extranasal sites it was successful in 18/32 (56.3%) of patients.<sup>64</sup>

### Polyhexanide

The efficacy of polyhexanide (Prontoderm<sup>®</sup>) Gel Light nasal ointment, body foam and mouthwash was retrospectively compared with the success rate achieved with a chlorhexidine and mupirocin regimen. Persistent MRSA was identified among 51/72 (71%) of those who underwent the Prontoderm<sup>®</sup> regimen compared with 20/44 (45%) of those who underwent the chlorhexidine and mupirocin regimen.<sup>65</sup>

### Ethanol

The bactericidal activity of 70% ethanol combined with emollients and a preservative (Nozin Nasal Sanitizer), when applied to the nasal vestibules of *S. aureus*-colonized volunteers, was compared with a placebo. The nasal application was performed at 0, 4 and 8 h during the course of a normal workday. The researchers reported a significant reduction in nasal vestibular carriage of both *S. aureus* and other cultivable bacteria in the antiseptic group. The reductions were very consistent, with a median decrease in the antiseptic-treated group of 98.8% at the end of the normal (10 h) workday. The investigators claim that the ethanol-based antiseptic provides a unique opportunity for regular daily use over prolonged periods by patients and staff in long-term care environments as it is unlikely to contribute to bacterial resistance.<sup>66</sup>

### Sodium hypochlorite

Sodium hypochlorite (bleach) was originally described in 1915 by Dakin and has since been used extensively as a topical antimicrobial for the treatment of wounds and burns. IDSA guidelines recommend nasal mupirocin and dilute bleach baths for 15 min twice weekly for 3 months as treatment for patients with refractory MRSA skin and soft tissue infections.<sup>67</sup> An RCT comparing various decolonization regimens using mupirocin, chlorhexidine and bleach on patients with community-based skin and soft tissue infections and multisite *S. aureus* colonization revealed that the highest rate of successful *S. aureus* eradication (71%) in patients occurred with a combination of nasal mupirocin and daily bleach baths.<sup>68</sup>

### Lysostaphin

Lysostaphin is a glycylglycine endopeptidase that cleaves the cross-linking pentaglycine bridges in the cell walls of staphylococci. In an animal model, a single application of 0.5% lysostaphin cream eradicated MSSA and MRSA from the nares of animals more effectively than mupirocin.<sup>69</sup> In 24 h time-kill studies, lysostaphin has also been found to be superior to mupirocin and tea tree oil.<sup>70</sup> However, to date, there have been no studies in humans and its potential remains to be confirmed.

### Omiganan pentahydrochloride

Omiganan pentahydrochloride is a novel topical cationic peptide active against a broad spectrum of bacteria and yeast. An *in vitro* study has demonstrated potent activity against *S. aureus* regardless of the underlying resistance mechanism. The observation that omiganan remains equally active against all isolates of *S. aureus* at a level significantly below the clinical formulation concentration (1% gel) is promising and warrants further studies.<sup>71</sup>

### Natural honey

Honey is of interest to healthcare practitioners involved with wound management and reduces the numbers of MRSA in open wounds.<sup>72-76</sup> An *in vitro* study of four types of honey, three sourced from Northern Ireland and one from Suisse Normande, France, found that they reduced the bacterial count of community-

acquired MRSA isolates.<sup>77</sup> Similar findings are reported elsewhere when medical-grade honey was applied to chronic wounds.<sup>76,78</sup> The antibacterial properties of honey vary between different geographic regions and floral species.<sup>79</sup>

### Tea tree oil

Tea tree (*Melaleuca alternifolia*) oil has also been investigated as an antimicrobial and anti-inflammatory agent. Edmondson *et al.*<sup>80</sup> investigated the efficacy of tea tree oil for the decolonization of wounds positive for MRSA in 12 patients and concluded that although wounds in most cases showed signs of healing, they remained persistently colonized with MRSA. In another study, a tea tree oil-based regimen was compared with standard treatment consisting of mupirocin, chlorhexidine or silver sulfadiazine.<sup>81</sup> Of the patients who received standard treatment, 56/114 (49%) were cleared of MRSA carriage. Of the patients who received the tea tree oil regimen, 46/110 (42%) were cleared. Mupirocin was significantly more effective at clearing nasal carriage than tea tree cream (78% versus 47%;  $P=0.0001$ ). However, tea tree oil treatment was more effective than chlorhexidine or silver sulfadiazine in clearing superficial skin sites and skin lesions of MRSA. A Phase 2/3 RCT in two ICUs evaluated the effect of daily washing with tea tree oil (Novabac 5% skin wash) compared with standard care with a baby soft wash (Johnson's Baby Softwash) on the incidence of MRSA colonization. There was no statistical difference between the two approaches. The investigators therefore did not recommend tea tree oil as an effective means of MRSA decolonization.<sup>82</sup> Tea tree oil has been reported to cause allergic dermatitis in addition to gynaecomastia, probably owing to its oestrogenic and antiandrogenic properties, and should therefore be used with caution.<sup>71</sup>

### Probiotics

The potential of probiotics as agents for MRSA decolonization was investigated by Sikorska *et al.*,<sup>83</sup> who reported that many strains of lactobacilli and bifidobacteria isolated from a variety of sources inhibited *in vitro* the growth of *S. aureus* including clinical isolates of MRSA, suggesting that further research is warranted including clinical trials.

### Silver

The successful topical application of silver agents (Acticoat 7<sup>®</sup>, Smith & Nephew) in treating MRSA surgical site infection ( $n=2$ ) without systemic antibiotics as well as with gentian violet (0.5%) for skin lesions ( $n=28$ ) and for the eradication of nasal carriage ( $n=9$ ) has been described.<sup>84</sup>

### Bacteriophages

Bacteriophage therapy could also be an alternative to antibiotics for the treatment of chronic MRSA infections, as success has been reported both in treating infections ( $n=6$ ) as well as eradication of MRSA carrier status in a healthcare worker.<sup>85</sup> The potential for an engineered *Staphylococcus*-specific phage lysin (ClyS) to be used for topical decolonization was investigated in a mouse model.<sup>86</sup> ClyS eradicated a significantly greater number of MSSA and MRSA with a 3 log reduction compared with a 2 log reduction



with mupirocin. The use of ClyS also demonstrated a decreased potential for the development of resistance amongst MRSA and MSSA compared with mupirocin *in vitro*. Another agent, P128, a chimeric protein that combines the lethal activity of two enzymes, consists of a phage tail-associated muralytic enzyme of phage K and the staphylococcal cell wall-targeting domain (SH3b) of lysostaphin. Using the broth microdilution method, the investigators found that P128 was active against *S. aureus* clinical strains including MRSA, MSSA and MR MRSA. MBCs and MICs of P128 (1–64 mg/L) were similar across the 32 *S. aureus* strains tested, demonstrating its bactericidal nature. In time–kill assays, P128 reduced cfu by 99.99% within 1 h and inhibited growth up to 24 h.<sup>87</sup> Evidence that phages can effectively combat experimentally induced *S. aureus* infections in animals warrants further study in clinical trials.<sup>88</sup>

Overall, there is a paucity of studies on alternative agents for eradication of MRSA, such as alcohol-based agents, omiganan pentahydrochloride, lysostaphin, honey, bacteriophages and other agents. Clinical trials are warranted to confirm their potential before such agents can be routinely used for MRSA decolonization.

## Conclusions

Nasal carriage of MRSA is a recognized risk factor and a precursor for invasive infection. Clinical trials report that of all the various topical treatments used for the eradication of MRSA from the nose, mupirocin is the most effective. Increasing MR, either alone or combined with chlorhexidine resistance, means that ongoing monitoring of resistance is necessary, especially where there is widespread and even indiscriminate use of decolonization regimens. Before application, LLMR is significantly associated with persistent MRSA carriage and in addition there is a strong association between previous mupirocin exposure and both LLMR and HLMR. An association exists between HLMR (*mupA* carriage) and MDR. The presence of *qacA* and/or *qacB* and MR is another factor associated with failed decolonization.

The emergence of HLMR in CoNS isolates indicates an expanding reservoir of plasmids encoding MR, which can be transferred to other CoNS strains as well as to *S. aureus* including MRSA. HLMR and resistance to other antibiotics amongst CoNS may result in a reduction in oral antibiotic options for prolonged treatment of prosthetic infections with CoNS. Mupirocin should be used with caution if at all in patients with chronic extranasal colonization and should be limited to one or two 5 day courses of nasal application to reduce the emergence of resistance. However, the outcome following repeated courses of mupirocin application in the same patient is not explicit in the studies evaluated. We may eventually reach a point, or have done so already in some centres, where the benefits from mupirocin use are restricted to a minority of patients. Persistent colonization in the setting of MR may still be associated with reduced numbers of colonizing bacteria after attempts at decolonization, thus helping to reduce the risk of infection compared with patients colonized with MRSA who have not undergone decolonization of any kind. New antimicrobial therapies either on their own or in combination with alternative therapies are needed. There are very few antibacterial agents with new mechanisms of action under development to meet the challenge of MDR. The EU identifies a widening gap between the

burden of infections due to multidrug antibacterial resistant organisms and the development of new systemic agents as a key priority.<sup>89</sup> This also applies to topical agents used in decolonization. Tea tree oil, medical-grade honey, bacteriophages and other natural agents with antiseptic and antibacterial properties show promise but need to be further evaluated. Many of these have been initially developed in the academic sector or by small commercial enterprises, neither of which usually has the resources to develop the agents further and to carry out the necessary clinical trials to confirm or not their usefulness in the clinical arena. Consequently, there is a need for national and international agencies to sponsor further studies and evaluations.

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