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Guidelines

European Society of Clinical Microbiology and Infectious Diseases/European Committee on infection control clinical guidelines on pre-operative decolonization and targeted prophylaxis in patients colonized by multidrug-resistant Gram-positive bacteria before surgery

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ABSTRACT

Scope: The aim of these guidelines is to provide recommendations for decolonization and perioperative antibiotic prophylaxis (PAP) in multidrug-resistant Gram-positive bacteria (MDR-GPB) adult carriers before inpatient surgery.
Methods: These European Society of Clinical Microbiology and Infectious Diseases/European Committee on Infection Control guidelines were developed following a systematic review of published studies targeting methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci, methicillin-resistant coagulase-negative *Staphylococci*, and pan-drug-resistant-GPB. Critical outcomes were the occurrence of surgical site infections (SSIs) caused by the colonizing MDR-GPB and SSIs-attributable mortality. Important outcomes included the occurrence of SSIs caused by any pathogen, hospital-acquired infections, all-cause mortality, and adverse events associated with the interventions, including resistance development to the agents used and the incidence of *Clostridioides difficile* infections. The last search of all databases was performed on 1 November 2023. The level of evidence and the strength of each recommendation were defined according to the Grading of Recommendations Assessment, Development, and Evaluation approach. Consensus of a multidisciplinary expert panel was reached for the final list of recommendations. Antimicrobial stewardship considerations were included.

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Recommendations: The guideline panel reviewed the impact of decolonization, targeted PAP, and combined interventions (e.g. decolonization and targeted PAP) on the risk of SSIs and other outcomes in MDR-GPB carriers, according to the type of bacteria and type of surgery.
We recommend screening for *S. aureus* before high-risk operations, such as cardiothoracic and orthopaedic surgery. Decolonization with intranasal mupirocin with or without a chlorhexidine bath is recommended in patients colonized with *S. aureus* before cardiothoracic and orthopaedic surgery and suggested in other surgeries. The addition of vancomycin to standard prophylaxis is suggested for MRSA carriers in cardiothoracic surgery, orthopaedic surgery, and neurosurgery. Combined interventions (e.g. decolonization and targeted prophylaxis) are suggested for MRSA carriers undergoing cardiothoracic and orthopaedic surgery. No recommendation could be made regarding screening, decolonization and targeted prophylaxis for vancomycin-resistant enterococci because of the lack of data. No evidence was retrieved for methicillin-resistant coagulase-negative *Staphylococci* and pan-drug-resistant-GPB. Careful consideration of the laboratory workload and involvement of antimicrobial stewardship and infection control teams are warranted before implementing screening procedures or performing changes in PAP policy. Future research should focus on novel decolonizing techniques, on the monitoring of resistance to decolonizing agents and PAP regimens, and on standardized combined interventions in high-quality studies. **Elda Righi, Clin Microbiol Infect 2024;30:1537**

Scope and context

Surgical site infections (SSIs) are important complications of surgical procedures associated with considerable morbidity, extended length of hospital stay, increased healthcare costs, and mortality [1–3]. Data from the European Centre for Disease Prevention and Control, including 7816 SSIs from 11 countries, showed that Gram-positive bacteria (GPB) were the most frequently isolated bacteria, except for open cholecystectomy and colon surgery-associated SSIs displaying Enterobacterales predominance [4]. In cardiothoracic and orthopaedic surgery, a relevant proportion of GPB-SSIs are caused by *Staphylococcus aureus* (SA), including methicillin-resistant SA (MRSA) [4–7]. In these high-risk surgeries, if not prevented, MRSA-SSIs can lead to long-term disability, hospital readmission, and reoperation [8,9]. Although SSIs represent the costliest hospital-acquired infections (HAIs), it is estimated that at least 60% of these infections can be prevented [8,10]. Therefore, SSI reduction is considered a goal for healthcare quality improvement. Several studies highlighted how GPB carrier status, such as SA nasal colonization and vancomycin-resistant enterococci (VRE) rectal colonization, can predispose to the development of SSIs caused by the colonizing agent [11–16]. Schweizer et al. [17] performed a meta-analysis to investigate the impact of decolonization, perioperative antibiotic prophylaxis (PAP), and bundles (e.g. combining both interventions) on SA-SSIs rates. The results showed that mupirocin (MUP)-based decolonization reduced both MRSA-SSIs (relative risk (RR) 0.30, 95% CI: 0.15–0.62) and methicillin-susceptible *Staphylococcus aureus* (MSSA)-SSIs (RR 0.50, 95% CI: 0.37–0.69). Compared with β-lactams, glycopeptide-based PAP was not associated with decreased GPB- or SA-SSIs but appeared protective against MRSA-SSI (RR 0.40, 95% CI 0.20–0.80) in observational studies. When bundled interventions, including the combination of decolonization and glycopeptide PAP, were analysed, a protective effect was shown for both MSSA-SSIs (0.45, 95% CI: 0.26–0.78) and MRSA-SSIs (0.22, 95% CI: 0.12–0.38) [17]. The meta-analysis, however, did not focus specifically on SA carriers and combined both randomized controlled trials (RCTs) and observational studies, emphasizing the lack of high-quality data deriving from patients colonized with multidrug-resistant GPB (MDR-GPB). In this patient population, previous guidelines highlighted that SSI reduction strategies should be based on surgical perioperative best practices such as infection surveillance, appropriate PAP and decolonization, effective temperature and glucose control, antiseptic techniques, and personnel education [18].

Objective

The objective of these European Society of Clinical Microbiology and Infectious Diseases/European Committee on Infection Control guidelines is to provide evidence-based recommendations for decolonization and PAP in adult inpatients with pre-operative MDR-GPB colonization, without restrictions on the type of surgery or associated comorbidities. Expected users of these guidelines include surgeons, anaesthetists, infection control and infectious diseases specialists, clinical microbiologists, hospital staff (e.g. clinical medical, nursing, and paramedical staff), and policy makers.

Questions addressed by the guidelines

The target MDR-GPB (listed in the subsequent section) and the following questions were selected by consensus during the first-panel meeting:

(a) Should patients be screened for MDR-GPB prior to surgery?
(b) Should decolonization be performed in MDR-GPB carriers before surgery?
(c) Should PAP be adapted in MDR-GPB carriers before surgery?
(d) Should combined (bundled) interventions be implemented in MDR-GPB carriers before surgery?

The recommendations are summarized in Table 1.

Methods

These guidelines were developed according to the European Society of Clinical Microbiology and Infectious Diseases guideline methodology and involved a multidisciplinary group of experts, including infectious disease specialists, clinical microbiologists, surgeons, and a guideline methodologist. The panel reviewed the articles and discussed the evidence-based tables, evidence certainty classification, and recommendation strength. The recommendations were revised until a consensus was reached through

discussion, and the final list of recommendations was approved by the whole panel.

Literature search and data extraction

A systematic review of the published literature was performed, including studies evaluating screening, decolonization, PAP, and combined interventions in adult inpatients (aged 18 years and older) before surgery.

The review protocol followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement and was registered in the International Prospective Register of Systematic Reviews (No. CRD42021170244) [19].

Data retrieved from outpatient and paediatric populations were excluded. The articles were identified through computerized literature searches using PubMed, Embase, and Cochrane databases, covering a period between January 1990 and December 2022. A focused search update for more recent relevant studies was performed on 1 November 2023. A combination of Medical Subject Headings and equivalent terms and keywords were used for each MDR-GPB, as detailed in Appendix S1. Screening was performed by two independent reviewers using a two-stage selection process. All retrieved abstracts were screened against the eligibility criteria and duplicates were discarded. Disagreements were resolved by discussion with a third reviewer. Flowcharts with detailed exclusion reasons are reported in Appendix S1. A standardized data extraction method was used to record the relevant features into an electronic database, including country and year of publication, study design, type of surgery, target bacteria, type of decolonization, culture-directed (here reported as targeted) PAP, and outcomes. Article references were also screened for further inclusion in the review.

A population/participant, intervention, comparator/control, and outcome (PICO) framework was implemented defining the following elements:

- *Population*: Adult surgical inpatients with screening samples before surgery yielding one of the following MDR-GPB: MRSA, VRE, methicillin-resistant coagulase-negative *Staphylococci* (MR-CoNS), and pan-drug-resistant GPB (PDR-GPB).
- *Interventions*:
  (a) Screening is defined as the performance of cultures to check for colonization (e.g. nasal cultures to detect SA or rectal cultures for VRE).
  (b) Decolonization is defined as the practice of treating patients with an antimicrobial and/or antiseptic agent to suppress colonization.
  (c) Targeted PAP, defined as a regimen selected according to bacterial culture results and their susceptibility pattern (or predefined according to the effective antibiotic) to target the colonizing MDR-GPB.
  (d) Combined (bundled) interventions are defined as the association of decolonization practices and targeted PAP. Bundles often included additional practices such as enhanced disinfection protocols, personnel education, and infection control practices (IPC) such as patient isolation. Except for decolonization and targeted PAP, the other practices varied across the studies. For consistency, we decided to include the studies reporting both decolonization and targeted PAP, irrespective of additional protocols, and defined these interventions as 'combined interventions'.
- *Controls*: patients not receiving the intervention.
- *Outcomes*:
  (a) Critical: Occurrence of SSIs caused by the colonizing MDR-GPB; SSIs-attributable mortality.
  (b) Important: Occurrence of SSIs by any type of bacteria; any type of postsurgical infectious complication reported as HAIs such as bacteraemia, pneumonia, and urinary tract infections in patients colonized with MDR-GPB; all-cause mortality; length of hospital stay (LOS); and adverse events (including antibiotic toxicity, resistance development to antibiotics used for PAP, and *Clostridioides difficile* infections).

Because of the expected limited number of RCTs including MDR-GPB carriers, other types of studies were also reviewed, specifically: (a) RCTs including MSSA carriers, (b) RCTs including patients with unknown carrier status receiving PAP targeting MDR-GPB (e.g. glycopeptides that are active against MRSA), (c) Before/after studies including SA carriers and non-carriers undergoing combined interventions, and (d) Observational studies involving MDR-GPB carriers. MSSA carriers were considered in the recommendations even if MSSA does not belong to MDR-GPB because of (a) the high relevance of MSSA infections; considering that, in most situations where the intervention is applied, the majority of infections are caused by MSSA, the panel believed it was appropriate to include overall SA recommendations; (b) the effectiveness of certain interventions, for example, decolonization, on both MSSA and MRSA, therefore the evidence for the former can be applied to the latter, even if the evidence was retrieved for MSSA; and (c) the detrimental consequences of SA infections in a certain type of surgery (e.g. cardiothoracic and orthopaedic surgery), prompting recommendations that underline the importance of this pathogen.

No meta-analyses were performed because of the high study variability in terms of type of surgery, outcome assessed (SSIs or HAIs or SA infections), or agent used in the interventions.

Sampling techniques and microbiological practices were not reviewed or discussed because they were beyond the scope of these guidelines.

Quality assessment and grading recommendations

The risk of bias assessment of included studies was performed using the Cochrane Effective Practice and Organization of Care Review Group's criteria for RCTs, and the Newcastle-Ottawa Scale for observational studies (Appendix S1) [20,21]. The certainty of the evidence was classified as high, moderate, low, or very low, and the strength of recommendations was reported as strong or conditional (weak) according to the Grading of Recommendations Assessment, Development, and Evaluation system [22]. When no evidence was available, good practice statements were designated [23]. Evidence to Decision frameworks were used to decide on the direction and strength of recommendations [24].

Further research propositions and indications for IPC and antimicrobial stewardship were not developed formally and were therefore not graded.

Recommendations

The guidelines are reported according to the colonizing bacteria and by type of intervention. When appropriate, separate recommendations were issued according to the type of surgery. Each section describes the questions addressed, recommendations graded according to the available evidence, rationale for study inclusion, risks and benefits of each intervention, the studies' main characteristics and limitations, and suggestions for future studies. Each recommendation is followed by some brief remarks. A dedicated section for IPC and antimicrobial stewardship considerations is also included for each question.

No RCTs were retrieved comparing SSIs between MDR-GPB carriers and non-carriers receiving the intervention. No studies

Table 1
Summary of recommendations

Recommendation	Strength of recommendation	Level of evidence
Staphylococcus aureus		
Should patients be screened for Staphylococcus aureus prior to surgery?		
It might be good clinical practice to screen patients for methicillin-susceptible and methicillin-resistant *S. aureus* before elective cardiac and orthopaedic surgery, according to local epidemiology.	Ungraded good practice statement	Indirect evidence, not assessed with GRADE
Should Staphylococcus aureus carriers be decolonized prior to surgery?		
We recommend decolonization with mupirocin with or without chlorhexidine for methicillin-susceptible and methicillin-resistant *S. aureus* carriers before cardiac and orthopaedic surgery.	Strong	Moderate
We suggest decolonization with mupirocin with or without chlorhexidine for methicillin-susceptible and methicillin-resistant *S. aureus* carriers before other surgeries.	Conditional	Low
Should perioperative antibiotic prophylaxis be adapted in Staphylococcus aureus carriers before surgery?		
We suggest perioperative targeted prophylaxis for methicillin-resistant *S. aureus* carriers before cardiac, orthopaedic surgery, and neurosurgery.	Conditional	Low
There is insufficient evidence for or against targeted prophylaxis for methicillin-resistant *S. aureus* carriers undergoing other surgeries at the time of writing and therefore no recommendation can be issued.	No recommendation	
Should Staphylococcus aureus carriers receive combined interventions prior to surgery?		
We suggest combined interventions (decolonization and targeted prophylaxis) for methicillin-resistant *S. aureus* before cardiac and orthopaedic surgery.	Conditional	Very low
There is insufficient evidence for combined interventions (decolonization and targeted prophylaxis) for methicillin-resistant *S. aureus* carriers before other surgeries.	No recommendation	
Vancomycin-resistant enterococci (VRE)		
Should patients be screened for VRE colonization prior to surgery?		
There is insufficient evidence for or against screening for VRE carriers before surgery.	No recommendation	
Should VRE carriers be decolonized prior to surgery?		
There is insufficient evidence for or against decolonization for VRE carriers before surgery.	No recommendation	
Should PAP be adapted in VRE carriers before surgery?		
There is insufficient evidence for or against perioperative targeted prophylaxis for VRE carriers before surgery.	No recommendation	
Methicillin-resistant coagulase-negative staphylococci (MR-CoNS)		
Should patients be screened for MR-CoNS colonization prior to surgery?		
There is insufficient evidence for or against screening for MR-CoNS carriers before surgery.	No recommendation	
Should MR-CoNS carriers be decolonized prior to surgery?		
There is insufficient evidence for or against decolonization for MR-CoNS carriers before surgery.	No recommendation	
Should perioperative antibiotic prophylaxis be adapted in MR-CoNS carriers before surgery?		
There is insufficient evidence for or against perioperative targeted prophylaxis for MR-CoNS carriers before surgery.	No recommendation	
Pan-drug-resistant (PDR)-Gram-positive bacteria (GPB)		
Should patients be screened for PDR-GPB colonization prior to surgery?		
There is insufficient evidence for or against screening for PDR-GPB carriers before surgery.	No recommendation	
Should PDR-GPB carriers be decolonized prior to surgery?		
There is insufficient evidence for or against decolonization for PDR-GPB carriers before surgery.	No recommendation	
Should perioperative antibiotic prophylaxis be adapted in PDR-GPB carriers before surgery?		
There is insufficient evidence for or against perioperative targeted prophylaxis for PDR-GPB carriers before surgery.	No recommendation	

GRADE, Grading of Recommendations Assessment, Development and Evaluation.

were retrieved that targeted MR-CoNS and PDR-GPB, and therefore no recommendations could be made (Table 1).

1. Methicillin-resistant *Staphylococcus aureus* (MRSA)

Question 1.1: Should patients be screened for MRSA prior to surgery?

Recommendation

It might be good clinical practice to screen patients for MSSA and MRSA before elective cardiac and orthopaedic surgery, according to the local epidemiology (ungraded good practice statement).

Remarks

- The interventions addressed (decolonization, targeted prophylaxis, and combined interventions) target patients whose carrier status is known. Therefore, these guideline recommendations apply only to centres where SA screening is feasible.
- Although there is evidence that decolonization can reduce SA-SSIs and is beneficial for surgeries at high risk for SA infections (e.g. cardiothoracic and orthopaedic surgery), as reported in the next section, current evidence does not assess the impact of screening as a single measure to reduce SA-SSIs, but rather as a screening-and-decolonize procedure.
- The decision to implement targeted screening based on a clinical risk assessment approach (e.g. past infection, SA colonization in sites other than the nose) vs. screening of all patients undergoing high-risk surgery for SA infections (universal screening) should be taken according to the local epidemiology, organization of work as well as personnel and economic resources.
- Rapid screening for SA, including MRSA, may represent a useful tool to obtain timely results in the pre-operative assessment [25].

Infection prevention and antimicrobial stewardship considerations

- Screening for SA may be useful for infection control purposes and to inform antibiotic policy (e.g. knowing MRSA rates drives antibiotic recommendations for empiric therapy).
- Before implementing pre-surgical recommendations, local costs and feasibility analyses should be performed.
- Standard operating procedures should be agreed upon according to national recommendations and the decision should be

based on local epidemiology, patient risk factors for SA acquisition, microbiological capacity, and financial resources available at the healthcare facility.

Review of the evidence

The rationale for study inclusion

There is a lack of studies supporting MRSA screening alone as a specific intervention to decrease MRSA infection in the surgical context. One prospective interventional study targeting MRSA screening was included.

Evidence from retrieved study

Harbarth et al. [26] reported that a universal, rapid MRSA admission screening strategy did not reduce nosocomial MRSA infections in a surgical department. The article referred to an area that is endemic for MRSA (5% surgical carriers) but with a relatively low incidence of MRSA infection (1.2 infections per 1000 patientdays). In addition, this study used the screening results for infection control measures and did not use decolonization when MRSA was found.

Other organizations, such as the WHO and the Infectious Diseases Society of America do not provide recommendations on the role of SA screening or the surgical patient population that should undergo screening [18,27]. Both guidelines, however, acknowledge that some trials demonstrated that pre-operative SA screening, combined with decolonization, was effective in reducing SSIs [28–35].

Evidence summary and additional considerations

One prospective study of moderate quality showed no benefits in the use of rapid MRSA screening for SSI reduction, however, there were several factors that could have contributed to this result [26]. Specifically, an overall lower MRSA infection rate compared with the expected may have contributed to a lack of statistical power [36]. Furthermore, nearly 60% of infected patients were MRSA-free on admission and acquired MRSA infection during hospitalization, showing that postoperative transmission may also play an important role in postoperative MRSA infections.

Question 1.2: Should MRSA carriers be decolonized before surgery?

Recommendation

We recommend decolonization with MUP with or without chlorhexidine (CHX) for MSSA and MRSA carriers before cardiac and orthopaedic surgery (strong recommendation and moderate certainty of the evidence).

We suggest decolonization with MUP with or without CHX for SA carriers for other surgeries (conditional recommendation and low certainty of the evidence).

Remarks

- The strongest evidence exists for MUP nasal ointment 2% twice daily for 5 days with or without combination with CHX gluconate soap, 40 mg/mL [28].
- Although limited evidence is available, we recognize that surgery in immunocompromised patients or interventions involving prosthetic material may benefit from decolonization more than others because of the high risk of SA-SSIs.
- Decolonization should be performed, and completed, as close as possible to the operation (e.g. 1–2 weeks before surgery).
- Patients whose 5-day course of nasal MUP decolonization is not completed preoperatively should complete it post-surgery.
- In elective surgery, postponing a procedure to complete decolonization might be considered, if feasible, and posing no additional risks for the patient.
- Unless tested in clinical trials, universal pre-operative decolonization without screening should be applied cautiously as it may lead to MUP resistance.

Infection prevention and antimicrobial stewardship considerations

- The implementation of decolonization procedures should follow a careful assessment of the local prevalence of SA colonization and infection among patients admitted or transferred to the surgical wards.
- Changes in decolonization policies should be based on local epidemiology, locally available financial resources, and patient risk factors for SA acquisition.
- Controlling for exogenous factors contributing to SSIs, such as lack of adherence to standard operating procedures, hand washing, and clean surgical techniques remains paramount.
- Policies should include monitoring of resistance to MUP in colonizing isolates and those causing infection.

Review of the evidence

The rationale for study inclusion

Only RCTs including SA carrier status were included. We agreed not to include as evidence: (a) RCTs not reporting patients' carrier status; (b) observational studies with unknown or MSSA carrier status only; and (c) studies reporting combined interventions. No evidence was found reporting outcomes in decolonized vs. non-decolonized MRSA carriers, likely because of a limited number of MRSA carriers enrolled in RCTs and because of the lack of a control group, as most MRSA carriers received decolonization. We assumed that decolonization works on both MSSA and MRSA [37,38], therefore its benefits can be translated to MRSA carriers.

Evidence from retrieved studies

We included nine RCTs (two from the Netherlands, two from Australia, and the others from the United States, Colombia, Canada, Portugal, and Switzerland) performed between 2002 and 2020 (Table 2) [28,30–33,35,39–41]. The main outcome retrieved was the rate of SSIs caused by any pathogen with a low risk of bias for all studies included. Three RCTs involved orthopaedic surgery, two cardiac surgery, two mixed surgeries, and two Mohs surgery for skin cancer.

The main study providing evidence for decolonization was performed by Bode et al. [28], enrolling 808 patients mainly undergoing cardiothoracic (48%) and orthopaedic (21%) surgery and using a rapid test to identify SA carriers. Decolonization with MUP plus CHX was beneficial for SA-HAIs (RR 0.41, 95% CI: 0.22–0.76) and for deep SSIs caused by any pathogen (RR 0.21; 95% CI: 0.07–0.62). Sequential analysis of the cumulative data between the treatment groups was significant (p 0.008). No baseline differences were reported except for higher rates of immunodeficiency in the placebo vs. decolonization group. The authors showed decreased LOS in the intervention arm but similar mortality, concluding that the study was underpowered to assess SA-associated mortality. A *post-hoc* analysis investigating long-term mortality in the RCT treatment arms showed that all-cause 1-year mortality was lower in MUP plus CHX vs. placebo among 666 patients undergoing clean procedures (3% vs. 7%, hazard ratio [HR] 0.38, 95% CI: 0.18–0.81) [29]. Perl et al. [33], including 891 patients undergoing mixed surgeries, showed that MUP reduced SA-HAIs [odds ratio (OR) 0.49, 95% CI: 0.25–0.92, p 0.02], whereas no difference was shown for SSIs or LOS. Kalmeijer et al. [32] compared SA-SSIs between 614 MUP decolonized and non-decolonized carriers receiving orthopaedic surgery. Endogenous SA infections were five times less likely to occur in the MUP group vs. placebo, however, the difference was

Table 2
Characteristics of studies comparing decolonization vs. non-decolonization in *Staphylococcus aureus* carriers

Reference, year, country	SA carrier status; *N* included	Type of surgery	Intervention	Outcomes for intervention vs. placebo
Bode et al. [28], 2010 The Netherlands	18% of 6771 screened; 808	Cardiothoracic (48%), orthopaedic (21%), vascular (12%), general (13%), and gastrointestinal (6%)	MUP 2% q12 h + CHX OD 5 d vs. placebo	Lower deep SSIs (RR 0.21; 95% CI: 0.07–0.62) SA-HAIs lower for all surgeries, 17 (3.4%) vs. 32 (7.7%), RR 0.42, 95% CI: 0.23–0.7 and for cardiothoracic surgery, 3 (1.4%) vs. 15 (8.8%) RR 0.14, 95% CI: 0.04–0.51. P value NS for orthopaedic and vascular surgery. All-cause and SA-related mortality: p value NS Median LOS: 9 (7.5–12) vs. 10 (7–14) d, p 0.04 AE[a]: 9 (1.8%) vs. 8 (1.9%), p value NS
Cherian et al. [39], 2013 Australia	26% of 693 screened (9 MRSA); 179	Skin (Mohs)	MUP 2% q12 h + CHX 4% 5 d vs. cephalexin 2 g (pre-operative and at 6 h)	SSIs: 8 (9%) vs. 0 (p 0.03) AE: none reported
Garcia et al. [31], 2003 Colombia	34% carriers; 191	Elective cardiovascular	MUP 2% q12 h 5 d vs. no treatment	SA-HAIs lower but p value NS (RR 0.28, 95% CI: 0.04–1.71)
Kalmeijer et al. [32], 2002 The Netherlands	571 screened, 181 carriers	Elective orthopaedic (including prosthetic implant)	MUP 2% q12 h until surgery vs. placebo	SA-SSIs: 2 (0.6%) vs. 5 (1.7%) p value NS; Endogenous SA infections five times less likely for MUP (p value NS) for all patients enrolled[b] Mean LOS: 14.7 ± 7.3 vs. 15.0 ± 6.3 d, p value NS Resistance: 0/13 SA infections
Konvalinka et al. [30], 2006 Canada	UNK, 263	Elective cardiac	MUP 2% q12 h 7 d vs. placebo	SSIs: 18 (13.8%) vs. 11 (8.6%), OR 1.61 95% CI: 0.69–3.75, p value NS SA-HAIs: 5 (3.8%) vs. 4 (3.2%), p value NS Mortality: 4 (non-infection related) vs. 5 (1 pneumonia +1 SA BSIs), p value NS AE: none reported
Perl et al. [33], 2002 United States	3864 screened, 23% carriers; 891	Elective mixed: general, gynaecologic, neurologic, and cardiothoracic	MUP q12 h 5 d	SSIs 44 (9.9%) vs. 52 (11.6%), p value NS SA-HAIs: 17 (4.0%) vs. 34 (7.7%), OR 0.49; 95% CI: 0.25–0.92, p 0.02 LOS >8 d: 18 (4.1%) vs. 16 (3.6%), p value NS AE[a]: 4.8% in both groups Resistance to MUP in 6/1021 (0.6%) SA (from infection or nasal swab)
Rohrer et al. [40], 2020 Switzerland	1318 screened, 35% carriers (one MRSA), 465	Elective orthopaedic	MUP 5 d q12 h + CHX OD vs. no treatment	SSIs: 1 SA vs. 1 *Staphylococcus epidermidis* Mortality: 1 (non-SSI related) in no treatment group
Sousa et al. [41], 2015 Portugal	1028 screened; 228 (22%) colonized (8 MRSA)[c]	Elective orthopaedic (total hip or knee arthroplasty)	MUP 2% q12 h + CHX OD 5 d vs. no treatment	SA-SSIs: 2 (2.2%) vs. 3 (2.2%), p value NS
Tai et al. [35], 2015 Australia	738 screened, 38% carriers; 203	Skin (Mohs)	MUP 2% q12 h + CHX 4% OD 5 d vs. no treatment	SSIs: 4 (3.9%) vs. 11 (11.0%), RR 0.3, 95% CI: 0.1–1.0, p 0.05

AE, adverse events; BSI, bloodstream infection; CHX, chlorhexidine; HAIs, hospital-acquired infections; LOS, length of stay; MRSA, methicillin-resistant *Staphylococcus aureus*; MUP, mupirocin; NS, not significant; OD, once daily; OR, odds ratio; RR, relative risk; SA, infections.
Studies reported in alphabetical order (first author). Elective surgery is reported when indicated by the authors. If not reported, no MRSA carriers were identified.
[a] AE (adverse events): Bode: mild and local irritation; Perl: local, five patients discontinued (one MUP, four placebo).
[b] Results were provided for the SA carriers subgroup, however endogenous and exogenous infections were not provided for carriers.
[c] *N* = 8 (0.8%) MRSA carriers received vancomycin perioperative prophylaxis.

not significant (RR 0.19; 95% CI: 0.02–1.62). Garcia et al. [31] enrolled 191 patients undergoing cardiovascular surgery. Higher SA-HAIs were shown for placebo vs. MUP, however, the results were not significant (RR 0.28, 95% CI: 0.04–1.71) potentially because of the limited number of carriers included. Konvalinka et al. [30] enrolled 263 patients undergoing cardiac surgery showing similar rates for SSIs, SA-HAIs, and mortality between patients receiving MUP vs. placebo. The authors, however, reported an unexpectedly high rate of placebo patients clearing nasal colonization before surgery (46%), potentially affecting the results. Roher et al. [40] treated 465 carriers undergoing orthopaedic surgery either with MUP plus CHX or no treatment. The study was halted at interim analysis because of the low number of SSIs (one in each arm) and deemed unfeasible as the sample size recalculation to reach statistical power would have required 14 752 patients instead of the original 2690 enrolled. Sousa et al. [41] enrolled 228 SA colonized patients receiving orthopaedic surgery, however, 11% did not receive the intended treatment as culture results were not received in time. Similar rates were shown for SA-SSIs between groups in three RCTs [30,40,41]. Finally, two studies were retrieved for skin surgery using the Mohs technique [35,39]. Cherian et al. [39] compared decolonization using MUP plus CHX vs. antibiotic prophylaxis with oral cephalexin in 179 patients, showing higher infections in the prophylaxis group (9% vs. 0, p 0.003) leading to early study termination. Tai et al. [35] included 203 SA carriers showing significantly increased SSIs for those who were not decolonized (11%) vs. decolonized (4%), p 0.05.

Evidence summary and additional considerations

In summary, we did not retrieve data for critical outcomes but only for important outcomes. The overall study quality was good. Only 18 MRSA carriers were included from three different RCTs [39–41]. In the general population, mean nasal carriage rates ≤37% for SA are reported, however, the weighted cumulative incidence of SA-SSIs can be as low as 0.5–2% [11,32,40–42]. MRSA colonization is highly variable, and an overall decline in MRSA infections has been reported in recent years [43,44]. Decolonization impact on SA-HAIs was shown by three RCTs including cardiovascular and mixed surgeries [28,31,33] and on SSIs by three RCTs including mixed and skin surgeries [28,35,39]. None reported significant benefits for SA-

SSIs, likely because of the low and often variable rates of these infections [36]. In this scenario, the sample size needed to obtain significant power and demonstrate the benefit of the intervention would have to exceed 12 000 patients, as reported in the example in Appendix S2. Mortality and LOS appeared lower in the intervention group vs. placebo in one large RCT, however infection-related mortality and LOS were not investigated [38]. Overall, resistance to MUP and adverse effects appeared to be low (Table 2) [28,30–33,35,39–41]. Other benefits of decolonization should also be considered. Although the rates of infection after certain surgeries are low, SSI might result in significant morbidity or mortality (e.g. mediastinitis, cardiac device infections, and endocarditis) or prosthetic material infections (e.g. orthopaedic, vascular, and neurosurgery) leading to high-risk reoperation. In this context, the benefits and cost-effectiveness of the intervention should be taken into consideration, as topic decolonization is a low-cost and safe procedure. Van Rijen et al. [45] performed an investigator-blinded analysis comparing hospital costs of patients undergoing cardiothoracic or orthopaedic surgery ($n = 415$) in one of the participating centres of a previous RCT. Total costs included personnel, surgery, laboratory tests, radiological investigations, and functional assessments. Costs in the treatment arm were on average €1911 lower per patient vs. placebo (p 0.01).

Recommendation for further studies

Cost-effectiveness studies are recommended to investigate the impact of decolonization implementation, for example using rapid tests (e.g. polymerase chain reaction) to detect MRSA carriers in key populations such as immunocompromised patients, according to the local epidemiological scenario, resources, and type of surgery.

We recommend performing trials to assess the impact of universal decolonization (defined as decolonization in case of unknown carrier status) in high-risk surgery and immunocompromised patients. This approach may be useful, especially in centres with a high risk of SA-SSIs [46]. If this approach is investigated, thorough follow-up including monitoring for MUP resistance should be performed.

Because of reported MUP resistance, the efficacy of alternative decolonizing regimens (e.g. intranasal povidone-iodine, intranasal alcohol-based antisepsis, and phototherapy) characterized by anti-MRSA activity, good tolerability, and low potential for resistance should be investigated [18,47]. Other strategies currently under investigation, such as the use of probiotics, should be explored [48].

Question 1.3: Should MRSA carriers receive targeted PAP prior to surgery?

Recommendation

We suggest targeted prophylaxis for MRSA carriers before cardiac, orthopaedic surgery, and neurosurgery (conditional recommendation and low certainty of the evidence).

There is insufficient evidence for or against targeted PAP for MRSA carriers undergoing other surgeries at the time of writing and therefore no recommendation can be issued.

Remarks

- Patients with documented successful decolonization may not need MRSA-targeted PAP, however, eradication should be performed close to surgery (e.g. 1–2 weeks before surgery), as recolonization commonly occurs.
- Vancomycin, in association with a β-lactam, is suggested as the preferred targeted PAP for MRSA carriers; published data are most supportive of using 15 mg/kg 2 hours before surgery, however, each institution should develop its own guidance to optimize vancomycin use [18].
- Teicoplanin high dose (10–12 mg/kg) could be an alternative option and could be more practical to administer than vancomycin (e.g. as a bolus or 30-min infusion), however, the evidence for its efficacy remains limited.
- The addition of vancomycin can be considered in urgent high-risk procedures and for patients at increased risk for MRSA colonization or infection, even if carrier status is unknown. This may apply, for example, to patients with recent MRSA infections, those receiving haemodialysis, or nursing home residents. The evidence is poor and limited to observational studies [18,34,49,50].

Infection prevention and antibiotic stewardship considerations

- As per decolonization, the implementation of targeted PAP should follow a careful assessment of the local prevalence of MRSA colonization and infection among patients admitted or transferred to the surgical wards. Changes in PAP policies should be based on local epidemiology, locally available financial resources, and patient risk factors for MRSA acquisition.

Review of the evidence

The rationale for study inclusion

RCTs (including SA carriers or unknown carrier status) were included if the intervention consisted of the use of PAP that was effective on MRSA (e.g. glycopeptides). Observational studies investigating targeted PAP in MRSA carriers were also considered for inclusion. We agreed not to include as evidence observational studies with unknown or MSSA carrier status and studies reporting combined interventions.

Evidence from retrieved studies

We retrieved 16 RCTs and one observational study performed between 1993 and 2020 [14,51–66]. Five studies were from the United States, four from Italy, three from the United Kingdom, two from Greece and Finland, and one from Canada (Table 3) [14,51–66]. Six RCTs included cardiac surgery, six orthopaedic surgery, three neurosurgery, one cardiac and vascular surgery, and one only vascular surgery. Ten used vancomycin compared with a second-generation cephalosporin or a third-generation cephalosporin (Table 3) [14,51–66]. One study compared cefazolin combined with vancomycin vs. cefazolin alone [14]. Seven RCTs used teicoplanin as prophylaxis (Table 3) [14,15–66]. The main outcome retrieved was the rate of SSIs caused by any pathogen, with a low risk of bias for all studies except for one RCT and one observational study (Appendix S1).

Colonization status was reported in three studies and, of these, two included 4 and 54 MRSA carriers, respectively [14,51,66]. Saveli et al. [14] included patients receiving surgery for open fractures. Four (3%) and 25 (20%) patients were MRSA and MSSA carriers, respectively. No significant difference in SSIs rates was found between arms. Adapa et al. [51] performed a retrospective observational study enrolling 54 neurosurgical MRSA carriers. Carriers showed higher comorbidities compared with non-carriers. Targeted PAP was associated with lower SSIs vs. standard PAP (16% vs. 26%), however the difference was not significant. Interestingly, non-screened patients receiving vancomycin displayed higher SSIs vs. standard PAP (p 0.0001). Multivariate logistic regression showed no significant predictors of SSI, including PAP choice or comorbidity in the MRSA-colonized group. Three RCTs showed significant benefits for vancomycin compared with standard PAP [53,56,63]. Dhadwal et al. [53] showed lower sternal

Table 3
Characteristics of studies comparing glycopeptide-based vs. standard prophylaxis

Reference, year, country	SA carrier status; *N* included	Type of surgery	Intervention	Outcomes for intervention vs. placebo
Adapa et al. [51], 2020[a] United States	744 screened (7% MRSA carriers), 54	Neurosurgery	CEF 2 g or 3 g if > 120 kg vs. VANC 1 g or 1.5 g if > 80 kg; for skull base surgery 3 g ampicillin-sulbactam	SSIs: 12 (15.8%) vs. 44 (25.7%), p value NS
Finkelstein et al. [52], 2002 United States	UNK, 885	Cardiac	VANC 1 g q12 h for 24h vs. CEF 1 g q8h	SSIs: 43 (9.5%) vs. 39 (9.0%), p value NS GPB-SSIs: MSSA and CoNS 17 (3.7%) vs. 6 (1.3%), p 0.04 MRSA-SSIs: 2 (4.6%) vs. 7 (17.9%), p value NS HAIs (BSIs): 20 (4.4%) vs. 18 (4.1%), p value NS LOS: 8.7 ± 8 vs. 9.3 ± 11 d, p value NS
Dhadwal et al. [53], 2007 United Kingdom	UNK, 186	Cardiac (elective coronary artery bypass)	RIF 600 mg/GENT 2 mg/kg/ VANC 15 mg/kg preop + 7.5 mg/kg q12 h 3 doses vs. cefuroxime 1.5 g preop +750 mg q8h 3 doses	SSIs: 8 (9.2%) vs. 25 (25.2%), p 0.004 GPB-SSIs: 4 (5%) vs. 10 (10%), p value NS Mortality: 1 vs. 2, p value NS Median LOS 9.1 vs. 12.0 d, p value NS AE: no difference in renal dysfunction (RD 5.6%, 95% CI: −16% to 5%) Resistance: no VRS
Kester et al. [54], 1999 United Kingdom	UNK, 272	Vascular	TEIC 6 mg/kg vs. cephradine 1 g 3 doses + metronidazole	SSIs: 6 (4.4%) vs. 8 (5.9%), p value NS GPB-SSIs: 3 (2.2%) vs. 4 (2.9%), p value NS Mortality: 2 vs. 1, p value NS AE: none definitely related to the antibiotics
Kanellakopoulou et al. [55], 2009 Greece	UNK, 616	Orthopaedic (hip/knee arthroplasty)	TEIC 10 mg/kg vs. comparator (48% 2GC, 45% BLBLI, 7% ciprofloxacin)	SSIs: 2 (0.78%) vs. 11 (3.53%), p 0.025 AE: 1 vs. 1, p value NS
Maki et al. [56], 1992[b] United States	UNK, 221	Elective cardiac (73.4%) and vascular (26.6%)	VANC 1 g preop + 500 mg q6h for 48 h vs. CEF 1 g preop +1 g q6h for 48h	SSIs: 4 (3.7%) vs. 14 (12.3%), p 0.05; cardiac 0 vs. 6 (6.9%), p 0.04; vascular p value NS GPB-SSIs: 2 (1.9%) vs. 9 (7.9%), p value NS HAIs: 17 (15.9%) vs. 17 (14.9%), p value NS LOS: 10.1 vs.12.9 d, p < 0.01 AE[c]: no difference; *Clostridioides difficile* infections 0 vs. 2, p value NS Resistance: no VRE/VRS
Maki et al. [56], 1992[b] United States	UNK, 220	Elective cardiac (73.4%) and vascular (26.6%)	VANC 1 g preop + 500 mg q6h for 48 h vs. cefamandole 2 g preop +2 g q6h	SSIs: 4 (3.7%) vs. 13 (11.5%), p 0.05 GPB-SSIs: 4 (4%) vs. 9 (8%), p NS HAIs: 17 (15.9%) vs. 13 (11.5%), p NS LOS: 10.1 vs.11.0 (p < 0.01) AE[c]: no difference; no *C. difficile* infections Resistance: no VRE/VRS
Marroni et al. [56], 1999 Italy	UNK, 238	Elective prosthetic vascular	TEIC 400 mg vs. CEF 2 g	SSIs: 7 (5.9%) vs. 2 (1.7%), p value NS Mortality: 4 (3.4%) vs. 3 (2.5%), p value NS HAIs: pneumonia, BSIs, UTIs, p value NS AE: none reported
Periti et al. [58], 1999 Italy	UNK, 826	Orthopaedic (prosthetic joint)	TEIC 400 mg vs. CEF 2 g preop +1 g q6h 24 h	SSIs: 6 (1.5%) vs. 7 (1.7%), p value NS GPB-SSIs: 6 (1.5%) vs. 8 (1.9%), p value NS HAIs: 57 (13.5%) vs. 57 (13.4%), p value NS AE: rash/erythema 2 vs. 2, p value NS
Pons et al. [59], 1993 United States	UNK, 826	Neurosurgery	VANC 1g + GENT 80 mg vs. ceftizoxime 2 g	SSIs: 5 (12%) vs. 5 (12%), p value NS HAIs: 24 (5.9%) vs. 25 (5.9%), p value NS AE: 6 hypotension/flushing vs. 0, p value 0.03
Saginur et al. [60], 2000 Canada	UNK, 3027	Cardiac (elective coronary bypass)	TEIC 15 mg/kg vs. CEF 2 g preop +1 g q8h 48 h	SSIs: (a) Superficial 80 (5.3%) vs. 50 (3.3%), p 0.011 and (b) deep 36 (2.4%) vs. 19 (1.3%), p 0.024 GPB-SSIs: 84 (5.5%) vs. 60 (4.0%), p 0.05[d] HAIs: tracheobronchitis 82 vs. 54 (p 0.021), UTIs 122 vs. 34 (p 0.01)[d] Mortality: overall 32 (2.3%) vs. 35 (2.3%); with infection 14 (0.9%) vs. 12 (0.82%), p value NS LOS: 10.0 ± 7.9 vs. 9.5 ± 6.7 d, p value NS AE[c]: 79 (5.2%) vs. 78 (5.2%), p value NS Resistance: no TEIC resistance (*N* = 205)
Salminen et al. [61], 1999 Finland	UNK, 200	Elective cardiac	VANC 500 mg q6h for 48 h vs. 2 g ceftriaxone	HAIs: 10.7% vs. 13.4%, p value NS AE: none reported
Saveli et al. [14], 2013 United States	20% MSSA (*n* = 25), and 3% MRSA (*n* = 4), 130	Orthopaedic (elective open fractures)	CEF 1 g q8h and/or VANC (based on eGFR) for 24 h	SSIs: 8 (15%) vs. 9 (19%), p value NS SA-SSIs: 4/9 vs. 2/8, p value NS Mortality: 0 vs. 1, p value NS AE: none reported
Suter et al. [62], 1994 Italy	UNK, 236	Orthopaedic (elective total hip replacement)	TEIC 400 mg vs. cefamandole 2 g preop +1 g after surgery	SSIs (only superficial) 0 vs. 4 (1.6%), p value NS HAIs: 10% vs. 12%, p value NS Mortality 0 vs. 1, p value NS LOS: no difference AE: 1 suspected allergic reaction in each group
Tacconelli et al. [63], 2008[e] Italy	UNK, 176	Neurosurgery (elective cerebrospinal shunt placement)	VANC 1 g vs. CEF 1.5 g	SSIs: 4 (4%) vs. 12 (14%), RR 0.33 (95% CI 0.11–0.99), p 0.03 HAIs: pneumonia and UTIs, p value NS Mortality: 5 (6%) vs. 7 (8%) p value NS; SSIs 0 vs. 5 (p 0.02)

Table 3 (*continued*)

Reference, year, country	SA carrier status; *N* included	Type of surgery	Intervention	Outcomes for intervention vs. placebo
				LOS: 38 ± 37 d VANC vs. 54 ± 78 CEF, p 0.03 AE: none reported Resistance: no VRE
Tyllianakis et al. [64], 2010[e] Greece	UNK, 435	Orthopaedic (hip and knee arthroplasty)	Cefuroxime 1.5 g preop + 750 mg q8h 2 doses vs. VANC 1 g preop +1 g 12 and 24 h	SSIs: 6 (4.7%) vs. 6 (5.1%), p value NS GPB-SSIs: 5 (3.9%) vs. 3 (2.5%), p value NS HAIs: 6 (4.7%) vs. 4 (3.4%), p value NS
Vuorisalo et al. [65], 1998 Finland	UNK, 884	Cardiac (coronary bypass)	Cefuroxime 1.5 g prep + 750 mg q8h 3 doses vs. VANC 1 g preop +1 g 12h	SSI: 15 (3.5%) vs. 14 (3.2%), p value NS GPB-SSIs: 11 (2.5%) VANC vs. 14 (3.2%), p value NS Mortality: 2 vs. 3, p value NS LOS: 11 vs. 11 d, p value NS
Wilson et al. [66], 1998 United Kingdom	23% MSSA carriers, 314 (trial 1) and 271 (trial 2)	Cardiac	TEIC (trial 1: 400 mg preop + 200 mg 24h; trial 2: 400 mg for 3 doses) vs. flucloxacillin 500 q6h 5 d + tobramycin 80 mg 3 d	SSIs: coronary artery surgery (25.2%) vs. 10 (10.3%), p < 0.01; intracardiac surgery p value NS GPB-SSIs: Trial 1 32 (21.5%) vs. 13 (7.9%), p < 0.01; Trial 2 p value NS HAIs: UTIs (p < 0.001) and pneumonia (p < 0.05) higher in TEIC AE: higher nausea for comparator (p < 0.04) Resistance: no TEIC resistance

2GC, second-generation cephalosporins; AE, adverse events; BLBLI, β-lactam β-lactamase inhibitor; BSIs, bloodstream infections; CEF, cefazolin; GENT, gentamicin; GPB, Gram-positive bacteria; HAIs, hospital acquired; LOS, length of stay; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; NS, not significant; PAP, prophylaxis; RIF, rifampicin; SA, *Staphylococcus aureus*; SSIs, surgical site infections; TEIC, teicoplanin; UNK, unknown: UTI, Urinary Tract Infection; VANC, vancomycin.

Studies reported in alphabetical order (first author). Elective surgery is reported when indicated by the authors. If not reported, no MRSA carriers were identified.

[a] Observational study.

[b] Same study with two different standard PAP regimens, reported separately.

[c] AE (adverse events): Maki, no difference in rash (3 CEF, 1 VANC, 0 cefamandole) or serum creatinine; hypotension higher in VANC but p value NS; discontinuation were 3 VANC, 0 CEF, 2 cefamandole; Saginur TEIC vs. CEF nausea (30 vs. 22), vomiting (12 vs. 11), rash (4 vs. 3), hypotension (3 vs. 5), and anaphylactic shock (1 vs. 1).

[d] Results reported at 6 mo; 30-d follow-up showed SSIs p value NS while tracheobronchitis and UTIs were higher for TEIC vs. CEF.

[e] Both authors report high rates of methicillin resistance at their institutions but do not specify the study colonization rates.

wound infections in patients undergoing coronary bypass receiving vancomycin vs. cefuroxime (9 vs. 25%, p 0.004). Maki et al. [56] showed lower SSIs in the intervention group vs. comparator for both cefazolin (4 vs. 12%, p 0.05) and cefamandole (4 vs. 11%, p 0.05) as well as lower LOS. Tacconelli et al. [63] reported lower SSIs among neurosurgical patients receiving vancomycin vs. cefazolin (RR 0.33, 95% CI: 0.11–0.99, p 0.03). Mortality because of SSIs was lower with vancomycin vs. standard PAP (Table 1). In four RCTs (two including cardiac surgery, one orthopaedic, and one neurosurgery), no significant benefits were shown for vancomycin-based vs. standard PAP [59,61,64,65]. Conversely, Finkelstein et al. [52] showed increased SSIs because of MSSA and CoNS for vancomycin (4%) vs. cefazolin (1%) (p 0.04).

Teicoplanin-based PAP (using 15 mg/kg single dose and 400 mg followed by 200 mg or two 400 mg doses) was associated with increased postoperative infections in two RCTs involving cardiac surgery [60,66]. Conversely, Kanellakopoulou et al. [55] showed lower SSIs among patients undergoing total hip or knee arthroplasty receiving teicoplanin (1%) vs. standard PAP (4%), p 0.025. Patients in the teicoplanin arm were younger and received less knee vs. hip interventions. Four RCTs, two including patients undergoing orthopaedic surgery and two vascular surgeries, showed no differences in SSIs between arms [54,57,58,62].

Summary of the evidence and additional considerations

Several meta-analyses over the years have yielded controversial results on the benefit of glycopeptide PAP, however, most studies did not report carrier status or pooled together different surgeries showing high heterogeneity and high risk of bias [17,67–70].

The evidence we retrieved mainly focused on SSIs or HAIs caused by any pathogen rather than SA-SSIs. RCTs mainly included unknown carrier status. As reported in the decolonization section, even if SA is a common pathogen after surgery, the overall rates of MRSA carriers and SA/MRSA-SSIs can be low, therefore requiring very high numbers of patients to reach statistical power. In this context, and considering that SSIs can lead to increased morbidity, mortality, and risk of reoperation, the benefits and cost-effectiveness of the intervention are important. Risks associated with glycopeptide-based PAP include potential adverse effects, emergence of resistance to the antibiotics used as PAP, and costs. Nevertheless, low rates of toxicity and resistance were reported, and costs may be limited by the frequency of their use (usually single-dose administration for glycopeptides). Glycopeptides should be administered with a β-lactam to avoid an increase in postoperative MSSA infections [52] and their use should be considered carefully in non-carriers. A recent RCT showed that the addition of vancomycin to cefazolin PAP was not superior to a placebo for the prevention of SSIs in arthroplasty among patients without known MRSA colonization [71].

Recommendation for further studies

We recommend monitoring the emergence of resistance to glycopeptide (e.g. post-surgery VRE colonization and/or infection rates) in trials including glycopeptide-based PAP. Trials using high doses of teicoplanin (e.g. 10 mg/kg or higher) are also recommended [55]. Studies targeting cardiac surgery should be performed to investigate the optimal PAP regimen to reduce sternal wound infections. The results of a meta-analysis suggested that β-lactams should be administered for 48 hours instead of 24 hours or less to reduce sternal wound infections, however, trials comparing PAP duration are lacking [69]. As shown by Elliot et al. [72], the cost-effectiveness of glycopeptide-based PAP should be further explored in economic models targeting the prevention of MRSA infections after surgery.

Question 1.4: Should a combined intervention (decolonization and targeted prophylaxis) be used in patients colonized with MRSA before surgery?

Recommendation

We suggest combined interventions (decolonization and targeted prophylaxis) for MRSA carriers before cardiac and orthopaedic surgery (conditional recommendation and very low certainty of the evidence).

Table 4
Characteristics of studies with combined interventions in MRSA carriers

Reference, year, country	Carrier status	Type of surgery	Intervention[a]	Outcomes for post- vs. pre-intervention
Hadley et al. [73], 2010 United States	351 (21.4%) SA, 58 (3.5%) MRSA carriers	Orthopaedic (elective total hip/knee replacement)	MUP 5 d + CHX shower preop; MRSA carriers also VANC	SSIs: decrease of 13%, 21 (1.28%) vs. 6 (1.45%), p value NS
Lok et al. [74], 2010 Hong Kong	UNK, 527 included	Orthopaedic (elective hip fracture)	CHX bath 1 d before surgery + VANC if MRSA carrier + extra disinfection protocol	SSIs: 9 (3.2%) vs. 17 (7.0%), p 0.04 MRSA-SSIs: 1.05% vs.1.65%, p value NS
Mallet et al. [75], 2018 France	74 (22.4%) MSSA, one MRSA carrier	Adolescent scoliosis	SA carriers received MUP 5 d + CHX 4% 5 d (+ VANC 15 mg/kg for MRSA)	SA-SSIs: 5.1% vs. 1.3%, $p < 0.05$
Saraswat et al. [76], 2017 United States	56 (1.4%) MRSA carriers	Cardiac	SA carriers MUP + 5 d CHX; MRSA carriers also VANC + CEF	SSIs: decreased (adjusted OR 0.58, 95% CI: 0.39–0.86), p 0.007
Schweizer et al. [34], 2015 United States	UNK, 38 049 included	Cardiac and orthopaedic	SA carriers had MUP 5 d + CHX 5 d (+ VANC and CEF/cefuroxime for MRSA)	SA-SSIs: decreased in orthopaedic, adjusted RR 0.48 (95% CI: 0.29–0.80), cardiac surgery NS LOS: 3 vs. 3 d, p value NS AE: $N = 4$ mild skin irritation associated with CHX bathing Resistance: 1 MUP and 1 CHX within 36 SA isolates
Sporer et al. [15], 2016 United States	$N = 1443$ (2.9% MRSA, 25.1% MSSA carriers)	Orthopaedic	SA carriers MUP + CHX 5 d + VANC for MRSA carriers	SSIs: 1.11% vs. 0.34%, $p < 0.05$
Sun et al. [77], 2022 China	131 (4.6%) SA and 33 (1.2%) MRSA carriers	Cardiac	MRSA carriers MUP + CHX + VANC + cefuroxime	SA-HAIs: 10 (0.35%) vs. 9 (1.13%), RR 0.31, 95% CI: 0.13–0.77, p 0.02 MRSA-HAIs: 6 (0.21%) vs. 6 (0.76%), RR 0.28, 95% CI: 0.09–0.87, p 0.03
Walsh et al. [16], 2011 United States	56 (2.2%) MRSA carriers	Cardiothoracic	MUP 5 d; MRSA VANC + CEF (unless urgent procedures)	SSIs: 20 (0.8%) vs. 59 (2.1%), $p < 0.001$ MSSA-SSIs: decreased by 56%, 2 (0.08%) vs. 5 (0.18%), p value NS MRSA-SSIs: decreased by 93%, 2 (0.08%) vs. 32 (1.16%); RR 0.069, 95% CI 0.02–0.29; $p < 0.001$ Resistance: no VRE

AE, adverse effects; BSIs, bloodstream infections; CEF, cefazolin; CHX, chlorhexidine; HAIs, hospital-acquired infections; LOS, length of stay; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; MUP, mupirocin; NS, not significant; OR, odds ratio; RR, relative risk; SA, *Staphylococcus aureus*; SSIs, surgical site infections; UNK, unknown; VANC, vancomycin, VRE, vancomycin-resistant enterococci.
Studies reported in alphabetical order (first author). Elective surgery is reported when indicated by the authors. If not reported, no MRSA carriers were identified.
[a] Full details of bundled interventions are reported in Appendix S2.
Hadley, Lok, Mallet, Sporer, Sun, Walsh: unadjusted data; Saraswat, Schweitzer: risk-adjusted data.

There is insufficient evidence for combined interventions before other types of surgeries at the time of writing and therefore no recommendation can be issued.

Remarks

- Each institution should update or enhance its own combined interventions according to the local needs, type of surgery, and SA-SSIs surveillance data.

Review of the evidence

The rationale for study inclusion

We agreed not to include as evidence RCTs and observational studies with unknown carrier status. No RCTs reporting SA carrier status, however, were found. We retrieved only before/after studies reporting data before the intervention in patients with unknown carrier status. All studies combined decolonization and, among MRSA carriers, targeted PAP (Table 4) [15,16,34,73–77]. The interventions were usually associated with other practices that varied across the studies (e.g. screening for carriers, enhanced disinfection, personnel education, etc.). As reported in the Methods section, we included the studies reporting a combination of decolonization and targeted PAP irrespective of additional protocols. Details of bundled interventions for each study are reported in Appendix S2.

Evidence from retrieved studies

Eight before-after studies were included during the period 2010–2022 [15,16,34,73–77]. Five studies were performed in the United States, two in China, and one in France. Three included orthopaedic surgery, three cardiac surgery, and one both orthopaedic and cardiac surgery (Table 4) [15,16,34,73–77].

In six studies (four orthopaedic and two cardiac surgery) SSIs significantly decreased in the intervention group [15,16,34,74–76]. Only two studies performed risk adjustment [34,76]. Mallet et al. [75] showed a significant decrease in SA-SSIs after intervention in spine surgery. Schweizer et al. [34] showed decreased SA-SSIs after bundled intervention in orthopaedic (adjusted RR 0.48, 95% CI: 0.29–0.80) but not in cardiac surgery. In a study including patients undergoing cardiothoracic surgery [16], MRSA-SSIs but not MSSA-SSIs decreased after the intervention (Table 4) [15,16,34,73–77]. Sun et al. [77] showed lower SA-HAIs in the intervention group vs. baseline (RR 0.31, 95% CI: 0.13–0.77) in cardiac surgery; MRSA-HAIs were also lower in the intervention group (0.21%) vs. baseline (0.76%, p 0.03).

Summary of the evidence and additional considerations

Three before-after studies in cardiac surgery showed the benefit of combined interventions in reducing postoperative infections by any pathogen and/or MRSA/SA [16,76,77]. Four before-after studies in orthopaedic surgery showed a benefit in reducing postoperative infections [15,34,74,75]. Study quality was mainly moderate or low (Appendix S1). The main limitations included the observational nature of the studies retrieved, the limited number of MRSA carriers enrolled, and the analysis comparing patients with unknown carrier status with SA carriers. No mortality data were reported. Only one study reported low MUP resistance [35] and one study showed no VRE infections after combined interventions [16].

Recommendation for further studies

We recommend high-quality, multicentric studies using standardized combined protocols including MRSA-colonized patients to investigate the impact on MRSA-SSIs. We suggest monitoring

prospectively the development of resistance to the agents used in the combined interventions (e.g. MUP and glycopeptide resistance) and the impact of the drugs on the intestinal and pulmonary microbiome. The differences in the impact of combined interventions on MRSA carriers vs. MSSA carriers should also be investigated.

2. Vancomycin-resistant enterococci (VRE)

Question 2.1: Should patients be screened for VRE prior to surgery?

Recommendation

There is insufficient evidence to recommend rectal screening for VRE before surgery at the time of writing and therefore no recommendation can be issued.

Question 2.2: Should target PAP be used to reduce SSI in VRE carriers vs. standard prophylaxis?

Recommendation

There is insufficient evidence for or against targeted perioperative antibiotic prophylaxis for VRE carriers before surgery at the time of writing and therefore no recommendation can be issued.

Remarks

- In liver transplant (LT) recipients, VRE screening may be considered for epidemiological purposes or for implementing IPC practices, however, further studies should be performed to understand the benefits of screening on VRE-SSIs.

Infection prevention and antibiotic stewardship considerations

- Studies implementing targeted PAP in VRE should assess the risk of the emergence of resistance to the agents used for PAP.

Review of the evidence

The rationale for study inclusion

No RCTs were found analysing critical or important outcomes for VRE carriers undergoing screening or targeted PAP. Observational studies including VRE carriers were also reviewed. No evidence was found reporting the benefits of VRE rectal screening in reducing SSIs or HAIs. This may be related to the fact that there are currently no established interventions, such as decolonization, that can effectively eradicate VRE. Only three observational studies were found analysing targeted PAP in VRE carriers before surgery [78–80]. Of these, one using daptomycin [79] was excluded as there were only two patients in the control group.

Evidence from retrieved studies

Five observational studies, all including LT recipients, showed that post-transplant infections were higher in VRE carriers vs. non-carriers [78,81–84]. Study characteristics are summarized in Appendix S2. Two small retrospective studies [78,79] performed in the United States compared targeted vs. non-targeted PAP in VRE carriers undergoing LT. Viehman et al. [78] included 65 VRE carriers, showing no difference in deep SSIs for tigecycline (4/21, 19%) vs. ampicillin/sulbactam (9/44, 20%). In this study, pre-transplant VRE colonization was a risk factor for VRE-SSIs (OR 6.41, 95% CI: 1.84–22.26, p 0.003). Mak et al. [80] compared PAP between 19 patients receiving one dose of daptomycin (average dose 7.1 mg/kg) and 17 receiving piperacillin/tazobactam. VRE infections were higher with non-targeted vs. targeted PAP, respectively, within 14 days (24% vs. 0%, p 0.04) but not at 90 days post-LT (29% vs. 16%).

Evidence summary and additional considerations

Only two small retrospective studies with a high risk of bias were found showing no clear benefits in the use of targeted vs. standard PAP in LT carriers of VRE.

Recommendation for further studies

We recommend well-designed studies to assess the impact of rectal screening on VRE infections in high-risk surgeries and to assess the impact of VRE colonization status on critical outcomes. VRE decolonization has been explored using faecal transplantation [85], however, additional studies should be performed to understand its potential impact on surgical populations. We suggest designing trials of targeted PAP in VRE carriers undergoing LT and other high-risk surgical procedures (e.g. hepatobiliary surgery) to evaluate the effectiveness, applicability, and safety following antimicrobial stewardship principles, specifically:

- Clinical trials of targeted PAP should be designed considering rectal culture results.
- Post-transplant colonization should also be monitored as it may impact VRE infections following transplantation.
- Resistance monitoring should be performed through the detection of emerging resistance to the regimens used for targeted PAP. In SSIs, the clonal relationship between MDR bacteria detected after surgery and pre-operative colonizing bacteria should be determined, and both short- and long-term post-surgical colonization investigated.

Discussion and research needs

Our review of interventions to limit SSIs in MDR-GPB carriers undergoing surgery identified important knowledge gaps and limitations. Specifically, limited to no data were retrieved targeting patients colonized with MDR-GPB. For this reason, we used as evidence also the studies performed in MSSA carriers or patients with unknown carrier status. Furthermore, data on SSIs caused by any pathogen rather than specific MDR-GPB-SSIs were mainly retrieved. Although two interventions, decolonization, and targeted MRSA PAP, appeared to be beneficial in reducing SSIs, no high-quality studies were found confirming the positive impact of combining both interventions on MRSA-SSIs. Real-world studies appear to favour bundled interventions that have been previously beneficial in preventing MRSA infections in other HAIs [86–88], however, the evidence was very low, and practices are often inconsistent both within and across hospitals. Further research to standardize effective MRSA-SSIs bundles and overcome barriers to the implementation of combined interventions should be pursued. Interventions aiming at preventing MRSA infections should focus on high-risk surgical patient groups to achieve increased efficacy. These include patients undergoing surgeries at increased risk of SA-SSIs, such as cardiac, orthopaedic, and neurosurgery, especially when prosthetic material or shunt positioning is involved. In these groups, infection risks and associated costs likely exceed the benefits and costs of the interventions.

Future studies should aim to fill these gaps, however, the lack of feasibility of trials requiring tens of thousands of participants to reach statistical power should be acknowledged. Specifically, there is limited possibility of performing studies including high numbers of MDR-GPB carriers undergoing surgery or developing MDR-GPB-SSIs. This could be highly relevant among immunocompromised

patients who are burdened by high rates of resistance, as shown for VRE infections in LT recipients.

Further research should focus on investigating MUP resistance and alternative decolonization strategies, teicoplanin efficacy and its optimal dosing to impact SSIs, and interventions to limit VRE-SSIs in high-risk patients, including solid organ transplant recipients.

Finally, as reported in other international guidelines, the reduction of SSIs can be achieved only through a multidisciplinary and comprehensive approach. Surgeons, perioperative personnel, patients, and their families should be educated about SSIs prevention measures [18]. Best surgical practices, including infection risk assessment, antiseptic techniques, and antibiotic use according to stewardship principles should be put in place together with management of patient comorbidities, minimization of surgical operative time, and optimization of sterile techniques to limit SSIs [8,18].

Author contributions

ER: wrote the study protocol, chaired and supervised the work of the panel, selected and voted for PICO questions, performed a literature search, and drafted the manuscript. NTM: wrote the study protocol, selected and voted for PICO questions, performed a literature search, and critically revised and approved the manuscript. XG, MDT, CE, AWF, MG, JK, EP, GS, CT: selected and voted for PICO questions and other relevant decisions, reviewed the literature, critically revised, and approved the manuscript. ELAC, EC, AV: voted for PICO questions, performed literature search and data extraction, and approved the manuscript. ET and JK: chaired the panel, supervised the work of the panel, selected and voted for PICO questions and other relevant decisions, and critically revised and approved the manuscript. ET, JK: made equal contributions to the guidelines.

Transparency declaration

XG reports receiving a grant from 3M, consulting fees from Pfizer, and speaker fees from Pfizer, Johnson & Johnson/Ethicon, MSD, and Astra Zeneca. MG reports speaker fees from MSD, Shionogi, and Pfizer. EC reports speaker fees by Pfizer, Gilead, GSK, Menarini, and MSD. CE reports speaker fees from Advanz, Menarini, Pfizer, and Shionogi. NTM, ER, MDdT, JK, EP, AWF, ELAC, AV, GS, CT, and ET have nothing to disclose. This guideline was supported by the European Society of Clinical Microbiology and Infectious Diseases.

Updating

The guideline will be updated according to European Society of Clinical Microbiology and Infectious Diseases recommendations.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2024.07.012.

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