Infection control and prevention measures to reduce the spread of vancomycin-resistant enterococci in hospitalized patients: a systematic review and meta-analysis

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Objectives: Vancomycin-resistant enterococci (VRE) represent a major problem in healthcare settings worldwide. It is still unclear which is the most effective infection control and prevention (ICP) measure to reduce the spread of hospital-acquired VRE.

Methods: Cochrane databases, MEDLINE, EMBASE and CINAHL were searched until June 2012 to find studies comparing wards/hospitals where ICP measures to prevent VRE transmission were investigated. In the absence of heterogeneity, a fixed-effects model was used to estimate the pooled risk ratio (RR). Study quality was assessed according to Cochrane Effective Practice and Organisation of Care (EPOC) criteria.

Results: The search strategy retrieved 549 studies and 9 studies (1 randomized clinical trial, 3 controlled clinical trials and 5 interrupted time series) with 30949 participants were included. The overall study quality was low. Implementation of hand hygiene was associated with a 47% decrease in the VRE acquisition rate (pooled RR 0.53, 95% CI 0.39–0.73, I² 26%) while contact precautions did not significantly reduce the VRE acquisition rate (pooled RR 1.08, 95% CI 0.63–1.83, I² 0%). Due to the low number of studies, meta-analysis was not applied for surveillance screening, environmental cleaning and antibiotic formulary interventions. No studies were available on the effectiveness of isolation and cohorting of patients and staff.

Conclusions: Available evidence on the ICP measures to reduce VRE spread in adult hospitalized patients is poor. This systematic review suggests a significant role for the implementation of hand hygiene. Further studies with appropriate study design are urgently needed to define ICP measures able to reduce the acquisition of VRE among hospitalized patients.

Keywords: hand hygiene, contact precaution, screening

Introduction

Vancomycin-resistant enterococci (VRE) were first identified as hospital-associated pathogens in Europe during the mid-1980s and have rapidly disseminated worldwide.1 In the USA, Enterococcus spp. and the vancomycin-resistant phenotype were responsible for 13% and 3%, respectively, of all healthcare-associated infections reported to the National Healthcare Safety Network during 2009–10.2 In Europe, from 2007 to 2011, most countries have reported an increasing trend of vancomycin resistance among Enterococcus faecium responsible for severe infections, with Greece and Ireland reaching proportions >25%.3

The first guidelines for the control of VRE infections in hospitals were published in 1994 by the Hospital Infection Control Practices Advisory Committee (HICPAC).4 The HICPAC suggested the following measures to reduce cross-transmission among hospitalized patients: restriction of vancomycin use; education of hospital staff and the promotion of handwashing with antiseptic soap or a waterless antiseptic agent; routine screening for vancomycin resistance among isolates from clinical samples; contact isolation
for patients with VRE colonization or infection; and rectal surveillance cultures. Guidelines from the Society for Healthcare Epidemiology of America emphasized all the previous interventions including routine use of active surveillance cultures. However, VRE is still endemic in many countries. Controversies remain about the most efficacious infection control and prevention (ICP) measures to reduce the rate of hospital spread. In addition, a few studies have evaluated the cost-effectiveness of these ICP measures. For example, Montecalvo et al.6 estimated that the net saving due to enhanced infection control strategies to reduce the transmission of VRE in an endemic hospital for 1 year was ~$190000. As it is unclear which is the most effective ICP measure to reduce the transmission of VRE among hospitalized patients, a systematic review of the literature and meta-analyses were performed.

Methods

Types of studies and participants

Studies comparing the impact of different intervention policies to prevent VRE transmission were planned to be included. The following interventions were investigated: hand hygiene measures; contact precautions; screening cultures to identify those individuals colonized or infected with VRE; isolation unit or ward; room isolation; cohorting patients, defined as physical segregation of a group of VRE-positive patients from patients not known to be VRE positive; cohorting patients and staff, defined as above plus nursing by designated staff; environmental cleaning interventions; antibiotic formulary interventions; and ward closure. Contact precautions were defined as standard precautions (i.e. hand hygiene, personal protective equipment guided by risk assessment and the extent of contact anticipated with blood and body fluids, or pathogens) plus gown and gloves upon room entry of a patient/resident colonized or infected with VRE and using disposable single-use or patient/resident-dedicated non-critical care equipment. Randomized clinical trials (RCTs), controlled clinical trials (CCTs), interrupted time series (ITSs) and controlled before-and-after studies were considered eligible for inclusion only. Data limited to adult patients (>18 years old) were retrieved. No restriction of language was applied.

Objectives and outcome measures

The primary objective was determining the effects of different ICP measures on the incidence of VRE colonization/infection in adult hospitalized patients. Therefore, the primary outcome was the calculation of the risk of VRE colonization and/or infection defined as the number of patients with newly acquired VRE colonization or infection (i.e. not present at study inclusion).

The secondary objectives were to determine the effects of different ICP measures aimed at minimizing the spread of VRE on the risk of death at 30 days follow-up, prolonged hospitalization, adverse effects and hospital costs. Studies reporting a different primary outcome were excluded.

Search methods for identification of studies

We searched the following electronic databases for relevant studies: Cochrane Wounds Group Specialised Register (searched 15 June 2012); the Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library 2012, issue 6); Ovid MEDLINE (1950 to May Week 5 2012); Ovid MEDLINE (In-Process & Other Non-Indexed Citations; 13 June 2012); Ovid EMBASE (1980 to 2012 Week 23); and EBSCO CINAHL (1982 to 14 June 2012). The search strategy is available as Supplementary data at JAC Online. The references of retrieved articles were checked for additional relevant articles not identified by the search strategy. The study authors were contacted in case of missing data. The studies were excluded if authors provided no reply or insufficient data to reliably confirm inclusion.

Selection of studies, data extraction and management

The abstracts of all papers identified by the search were appraised for eligibility independently by two members of the review team. Full copies of articles were obtained for all papers meeting (or appearing to meet) the inclusion criteria. Members of the review team were not permitted to appraise or review any paper on which they had been an author at any stage of the appraisal process. Data were independently extracted by two review authors. The data extraction was discussed in case of disagreement and the justification for excluding studies from the analysis was documented.

Assessment of risk of bias in included studies

We assessed the risk of bias of included studies according to the detailed criteria developed by the Cochrane Effective Practice and Organisation of Care (EPOC) group.7 The risk of bias was assessed independently by two reviewers without blinding to the journal or study authorship. Discrepancies were resolved by discussion or involvement of a third review author if required.

Assessment of heterogeneity

We assessed both clinical and statistical heterogeneity. In the absence of clinical and statistical heterogeneity, we applied a fixed-effects model to pool data. If evidence of significant ‘extra’ variability was identified between a sufficient number of studies to inform the distribution of effects (at least four), a DerSimonian and Laird random-effects model was applied. The overall consistency between trials was measured by the statistic.8 Substantial heterogeneity was considered for values >50%. Publication bias was measured by the Begg funnel plot.9

Data synthesis

We compared the results for intervention and control groups and analysed the data using ReviewManager 5. We presented the results with 95% CIs and reported estimates for dichotomous outcomes as risk ratio (RR) and for continuous outcomes as difference in means. Data from studies with different design were not combined.10 We calculated cluster-adjusted effect sizes using the inverse variance method.11 None of the included studies provided an estimate of the intracluster correlation coefficient (ICC) that was therefore derived from the available literature.12,13 In the absence of specific data for the outcome of interest (VRE acquisition), since the range of ICCs of studies in primary care is estimated to be between 0.01 and 0.1, a value of 0.05 was considered the most appropriate.

Results

Results of the search

The search strategy retrieved 549 records. After deduplication and examination of the titles and abstracts, all but 136 studies were eliminated and excluded from further review (Figure 1). Full-text copies of the remaining studies were obtained and subjected to further evaluation. One hundred and twenty-five of these studies were excluded and the reasons for their exclusion were noted. Finally, nine publications met the eligibility criteria and were selected for review.16–22

Characteristics of the included studies

The main characteristics of the studies included are shown in Table 1. Seven studies were carried out in the USA,14,15,17–21 one
in the UK\textsuperscript{16} and one in Canada.\textsuperscript{22} All studies were performed in university hospitals. Baseline VRE prevalence was defined as the proportion of positive patients at the perirectal area on admission and/or periodically during the hospitalization in the majority of the studies.\textsuperscript{14 – 20} VRE colonization at hospital admission ranged from 0.5% to 58%. One study was a cluster RCT,\textsuperscript{18} three were CCTs\textsuperscript{15,20,22} and five were ITSs.\textsuperscript{14,16,17,19,21} The oldest studies were published in 1996\textsuperscript{20} and 1999,\textsuperscript{16,21} following in 2006,\textsuperscript{17,19} 2007,\textsuperscript{15} 2009,\textsuperscript{22} 2010\textsuperscript{14} and 2011.\textsuperscript{18} The main intervention was different among studies and was always included in a multifaceted approach, which represents a more complex strategy including two or more single interventions. The following ICP measures were evaluated: environmental cleaning;\textsuperscript{17,22} handwashing measures;\textsuperscript{16,19} contact precautions;\textsuperscript{14,15,20} and antibiotic formulary intervention.\textsuperscript{16,21} One study evaluated the efficacy of screening cultures in association with contact precautions.\textsuperscript{18} No studies evaluated the efficacy of unit/ward closure and cohorting patients or staff. Studies describing the age\textsuperscript{16,18,20,21} and gender\textsuperscript{16,20} of the study population did not show any significant difference between intervention and control groups. In the cluster RCT,\textsuperscript{18} eligible intensive care units (ICUs) were randomly assigned to the intervention or to existing practice. In the three CCTs, the unit of randomization was represented by beds,\textsuperscript{20} by the whole medical ICU\textsuperscript{15} or by rooms previously occupied by VRE-positive patients.\textsuperscript{22} The overall quality of the studies was poor (see Figure 2).

### Effects of interventions

#### Primary outcome: VRE acquisition rate

Eight studies investigated the impact of the intervention on the VRE acquisition rate.\textsuperscript{14 – 20,22} The study by Weiss et al.\textsuperscript{21} was limited to the evaluation of the impact of the intervention on the VRE surgical site infection (SSI) rate and therefore was not included in the analysis of primary outcome.

#### Efficacy of contact precautions in preventing VRE acquisition

Four studies\textsuperscript{14,15,18,20} evaluated the effect of contact precautions in preventing VRE acquisition. One study\textsuperscript{16} was not included in the meta-analysis because of a different study design (ITS). Contact precautions did not significantly reduce the VRE acquisition rate (pooled RR 1.08, 95% CI 0.63–1.83; fixed-effects model) (Figure 3). No statistical heterogeneity was detected among studies.

#### Efficacy of hand hygiene measures in preventing VRE acquisition

Two studies\textsuperscript{16,19} were included in the analysis. The implementation of hand hygiene measures was associated with a significant decrease in the VRE acquisition rate (pooled RR 0.53, 95% CI 0.39–0.73; fixed-effects model). Low heterogeneity was detected between studies ($I^2 = 26\%$) (Figure 4).
Efficacy of environmental cleaning in preventing VRE acquisition. Two studies\(^{17,22}\) were included in the analysis. The implementation of environmental cleaning did not significantly reduce the VRE acquisition rate in both studies. The results were not combined in a meta-analysis because of different study designs (CCT and ITS).

Efficacy of antibiotic formulary interventions in preventing VRE acquisition. Two studies evaluated the effect of antibiotic formulary interventions in preventing VRE acquisition.\(^{16,21}\) Since the two studies evaluated different VRE outcomes (VRE acquisition rate and VRE SSIs), they were not combined in a meta-analysis. In one study,\(^{16}\) during the intervention period, the VRE acquisition rate progressively decreased. However, a return to ceftazidime in a post-intervention period, despite maintaining hand hygiene teaching and surveillance, was associated with a new increase in the VRE acquisition rate. In the second study,\(^{21}\) during the 3 year intervention period, no SSIs due to VRE were observed, while 2.4\% of SSIs were caused by VRE in the post-intervention period.

Efficacy of screening cultures in preventing VRE acquisition. Only one study\(^{18}\) evaluated the effect of screening cultures to detect unknown colonized patients (at hospital admission, weekly and at discharge) in association with expanded use of contact precautions as compared with standard of care on the incidence of VRE colonization and infection in adult ICUs. In control ICUs, screening cultures were performed but the ICU staff was not informed about the results. The intervention was not effective in reducing the incidence of VRE colonization and infection.

Secondary outcomes: length of hospitalization, mortality, costs and adverse effects
The duration of hospitalization was evaluated in five studies.\(^{14,15,17,18,20}\) The implementation of contact precautions\(^{15,20}\) was not associated with a decreased length of stay (Figure 5). In one study,\(^{17}\) the implementation of environmental cleaning did not have a significant impact in decreasing the duration of hospitalization. One study\(^{20}\) evaluated 30 day all-cause mortality, which showed no difference in ICU and in-hospital mortality between intervention and control groups. Possible adverse effects of interventions and costs were not evaluated by any of the included studies.

Publication bias
Publication bias was assessed using a funnel plot of all studies, which showed a slight asymmetry around the pooled point estimate, although the limited number of studies does not allow the exclusion of publication bias.

Discussion
A number of strategies have been studied for the prevention of VRE spread among adult hospitalized patients. Our meta-analysis, including nine studies (one cluster RCT, three CCTs and five ITSs) for a total of 30949 patients, showed that the implementation of hand hygiene measures was associated with a 47\% decrease in the VRE acquisition rate. In contrast, we could not demonstrate that the implementation of contact precautions, isolation unit or ward, single-room isolation, cohorting patients and/or staff and ward closure significantly reduce the VRE acquisition rate in hospitalized patients.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Study design</th>
<th>Setting</th>
<th>Description of the intervention</th>
<th>Compliance with the intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bearman 2010(^{14})</td>
<td>USA</td>
<td>ITS</td>
<td>surgical ICU</td>
<td>contact precautions versus universal gloving with emollient-impregnated gloves without contact precautions</td>
<td>67% (contact precautions) versus 78% (universal gloving)</td>
</tr>
<tr>
<td>Bearman 2007(^{15})</td>
<td>USA</td>
<td>CCT</td>
<td>medical ICU</td>
<td>contact precautions versus universal gloving without contact precautions</td>
<td>75.7% (contact precautions) versus 87% (gloves) not reported</td>
</tr>
<tr>
<td>Bradley 1999(^{16})</td>
<td>UK</td>
<td>ITS</td>
<td>haematology unit</td>
<td>piperacillin/tazobactam replaced ceftazidime as first-line treatment of febrile neutropenia plus enhanced infection control measures</td>
<td>not reported</td>
</tr>
<tr>
<td>Hayden 2006(^{17})</td>
<td>USA</td>
<td>ITS</td>
<td>medical ICU</td>
<td>educational intervention to improve environmental cleaning</td>
<td>87% (intervention period) versus 48% (pre-intervention period)</td>
</tr>
<tr>
<td>Huskins 2011(^{18})</td>
<td>USA</td>
<td>cluster RCT</td>
<td>medical-surgical ICU</td>
<td>active surveillance; pre-emptive universal gloves; universal gloves and gown for VRE-positive patients</td>
<td>not reported</td>
</tr>
<tr>
<td>Lai 2006(^{19})</td>
<td>USA</td>
<td>ITS</td>
<td>medical ICU</td>
<td>use of alcohol-based, waterless hand antiseptic in place of plain and antimicrobial soap</td>
<td>not reported</td>
</tr>
<tr>
<td>Slaughter 1996(^{20})</td>
<td>USA</td>
<td>CCT</td>
<td>medical ICU</td>
<td>universal use of gloves and gowns versus universal gloving alone</td>
<td>79% (gloves and gowns) versus 62% (gloves)</td>
</tr>
<tr>
<td>Weiss 1999(^{21})</td>
<td>USA</td>
<td>ITS</td>
<td>surgical unit</td>
<td>antibiotic restriction policies</td>
<td>not reported</td>
</tr>
<tr>
<td>Williams 2009(^{22})</td>
<td>Canada</td>
<td>CCT</td>
<td>all hospital except ICU</td>
<td>terminal cleaning and visual inspection versus terminal cleaning, environmental culture and closing of the room pending negative results</td>
<td>not reported</td>
</tr>
</tbody>
</table>
Handwashing has been proven to be an important component of interventions for the control of hospital-acquired pathogens, including methicillin-resistant Staphylococcus aureus (MRSA). Two studies were included in this meta-analysis. In the first one, the introduction of alcohol-based waterless antiseptic alone was effective in reducing the transmission rate of VRE in a medical ICU. However, the study was observational and hand hygiene compliance was not monitored before and after the intervention. In the second study, the authors performed an intensive education programme to improve hand hygiene compliance with alcoholic chlorhexidine hand rub or gel and observed a decrease in the VRE incidence. The intervention also included a change in antibiotic policy for febrile neutropenia, so the effect of hand hygiene promotion as a single measure cannot be demonstrated. In addition, no measure of hand hygiene compliance and no clear hand hygiene promotion after the intervention period were performed.

The implementation of contact precautions on the incidence of multidrug-resistant microorganisms in hospitalized patients have been assessed in many studies with heterogeneous results. One of the major limitations of these studies is that the self-reported rate of compliance with contact precautions usually exceeded that observed by the study personnel monitoring compliance. In the RCT by Huskins et al., the authors observed that the use of barrier precautions by healthcare workers (HCWs) was less than that required. Slaughter et al. were not able to show a positive effect of universal gloving added to universal gloving in endemic situations. The lack of a no-gloves–no gowns control group limited the conclusion concerning the importance of the use of gloves as a contact barrier.

VRE are known to contaminate and survive in the hospital environment, to be extremely resistant in the environment and routine cleaning with bleach-based products was often not associated with effective cleaning. The risk of transmission of VRE from contaminated environments to patients depends on several factors, such as the density of VRE in stools, cleaning practices, patient comorbidities and the intensity of medical care. Huang et al. showed, in a retrospective cohort study, that the risk of acquiring MRSA and VRE is higher in patients admitted in rooms where an MRSA- or VRE-positive patient has been admitted before. One study included in our review observed that obtaining environmental samples before room entry of a new patient did not significantly decrease the risk of VRE transmission when compared with visual inspection. As a limitation, adherence to terminal cleaning procedures was not measured. The second retrieved study found that enforcing cleaning measures was associated with a decrease in environmental contamination but not VRE acquisition among inpatients. It is possible that the short periods of observation (58 days each) limited the possibility to observe any effect of the intervention.

Antibiotic use has been identified as one of the most important risk factors for VRE acquisition. In case–control studies, colonization and infection with VRE have been associated with exposure to vancomycin, third-generation cephalosporins, antibiotics active against anaerobes, ciprofloxacin and aminoglycosides. In a prospective cohort study including 864 patients starting antibiotics, the incidence of colonization by antibiotic-resistant bacteria, including VRE, for 1000 days of therapy was 14 for carbapenems, 9 for glycopeptides and 6 for third-generation cephalosporins and
A systematic review of 13 quasi-experimental studies on the efficacy of vancomycin restriction on VRE acquisition rate showed results ranging from a reduction of 82.5% to an increase of 475%. In our review, a meta-analysis was precluded by the heterogeneity of the two included studies. In one study, the authors changed antibiotic policy by replacing ceftazidime with piperacillin/tazobactam and, in the other, the authors restricted the use of vancomycin, ceftazidime, imipenem, aztreonam and ciprofloxacin. A significant reduction of the VRE acquisition rate was documented by Bradley et al., while Weiss et al. did not observe any change in VRE SSIs. In the study by Bradley et al., the intervention was combined with hand hygiene promotion. The study by Weiss et al. was not designed to test the intervention specifically on VRE acquisition and no data on antibiotic usage were reported.

The main limitation of this review was the impossibility to evaluate studies reporting on a single intervention. However, the meta-analysis showed a clear impact of hand hygiene in reducing the incidence of VRE colonization and infection and should be taken into consideration when designing bundles for infection control and prevention of VRE in the hospital setting. Due to the heterogeneity of interventions, it was impossible to clearly define the impact of other single interventions on VRE acquisition. The overall quality of the papers was low. The control group was usually not clearly defined, nor were the applied ‘standard precautions’. All but three studies were performed in ICUs, limiting the generalizability of the results. In addition, as we did not search for unpublished data or the grey literature, we recognize the possibility of missing information regarding outcomes and other variables that could be considered key to the interpretation of the results.

The research agenda needs to move to multicentre studies applying well-defined multifaceted interventions, including hand hygiene implementation, using a randomized study design with randomized allocation to interventions. This would provide better evidence as well as the power to measure cost-effectiveness and exclude important bias. If observational designs are preferred, study protocols should be clearly designed to guarantee the quality of data analysis and reporting. Sample size calculation should clearly state the hypothesis according to different levels of endemicity to avoid inconclusive results. The main outcome should be clearly described and calculated. The efficacy of interventions and their sustainability remain poorly defined because of the heterogeneity in study design and insufficient study quality to enable adequate causal inference. Notably, evidence is needed to show that interventions do not have possible adverse effects. Antimicrobial stewardship studies should consider multiple outcomes including both Gram-positive (VRE and MRSA) and Gram-negative bacteria (extended-spectrum β-lactamase or carbapenemase producers) and Clostridium difficile. In particular, we believe that there is an urgent need for studies on ICP measures including both Gram-positive and Gram-negative bacteria. More attention should be paid to the efficacy of prevention of VRE transmission in non-ICU wards. Trials assessing the hospital costs of such measures are also needed.

**Figure 4.** Efficacy of hand hygiene measures in preventing VRE colonization/infections. M–H, Mantel–Haenszel.

**Figure 5.** Impact of contact precautions on reducing duration of hospitalization. IV, inverse variance.

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This study was carried out as part of our routine work.

### Transparency declarations

None to declare.
Supplementary data

The search strategy is available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References


