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Review

Vancomycin-resistant enterococci colonisation, risk factors and risk for infection among hospitalised paediatric patients: a systematic review and meta-analysis

Myrto Eleni Flokas [1], Spyridon A. Karageorgos [1], Marios Detsis, Michail Alevizakos, Eleftherios Mylonakis [*,2]

Infectious Diseases Division, Warren Alpert Medical School of Brown University, Rhode Island Hospital, Providence, RI, USA

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ABSTRACT

The objective of this study was to estimate the rate and significance of colonisation with vancomycin-resistant enterococci (VRE) among hospitalised children. The PubMed and EMBASE databases were systematically searched (last accessed on 29 May 2016) to identify studies evaluating VRE colonisation of the gastrointestinal tract of hospitalised children in non-outbreak periods. Of 945 non-duplicate citations, 19 studies enrolling 20 234 children were included. The overall and paediatric intensive care unit (PICU) rate of VRE colonisation were both 5% [95% confidence interval (CI) 3–8% overall and 95% CI 2–9% in the PICU] but was 23% in haematology/oncology units (95% CI 18–29%). Studies that were exclusively performed in haematology/oncology units reported significantly higher rates compared with all other studies in the univariate and multivariate analyses ($P = 0.001$). Previous vancomycin [risk ratio (RR) = 4.34, 95% CI 2.77–6.82] or ceftazidime (RR = 4.15, 95% CI 2.69–6.40) use was a risk factor for VRE colonisation. Importantly, VRE colonisation increased the risk of subsequent VRE infection (RR = 8.75, 95% CI 3.19–23.97). In conclusion, a high rate of VRE colonisation was found among hospitalised children in institutions that performed targeted screening. Importantly, colonised children were almost 9 times more likely to develop subsequent VRE infection. Judicious use of specific antibiotics along with intensification of infection control measures should be considered in high-prevalence institutions. Also, the high incidence of VRE colonisation among children with haematological/oncological diseases identifies a high-risk population.

1. Introduction

Vancomycin-resistant enterococci (VRE) constitute a major cause of healthcare-associated infections [1,2], with extensive resistance to multiple antimicrobial agents and the capacity to transfer resistance to other pathogens through plasmids [3]. Especially in the paediatric population, there is a concerning rise of VRE infections, as highlighted by a recent study that revealed a two-fold increase in VRE infections among hospitalised children in the USA between 1997 and 2012 [4]. These infections are also associated with increased hospital length of stay and hospitalisation costs [4]. In a recent meta-analysis, infections caused by VRE were also associated with increased mortality compared with vancomycin-sensitive strains [5]. However, it is still unclear whether this difference is due to delays in initiation of effective therapy to the increased virulence of *Enterococcus faecium* or to co-morbidities that burden VRE-infected patients [6–10].

The gastrointestinal system of hospitalised children has been recognised as a possible reservoir of VRE [11]. Given that prior VRE colonisation has been identified as a risk factor for VRE infection in other patient populations [12], we aimed to estimate the rate of VRE colonisation among hospitalised children, to identify pertinent risk factors and to evaluate the significance of colonisation on the development of subsequent VRE infections in the paediatric population.

2. Materials and methods

This systematic review and meta-analysis conforms to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-

* Corresponding author. Infectious Diseases Division, Warren Alpert Medical School of Brown University, Rhode Island Hospital, 593 Eddy Street, POB, 3rd Floor, Suite 328/330, Providence, RI 02903, USA. Fax: +1 401 444 8179.
E-mail address: emylonakis@lifespan.org (E. Mylonakis).
[1] These two authors contributed equally to this work.
[2] Present address: Infectious Diseases Division, Warren Alpert Medical School of Brown University, Rhode Island Hospital, 593 Eddy Street, POB, 3rd Floor, Suite 328/330, Providence, RI 02903, USA.

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Analysis) and MOOSE (Meta-analysis of Observational-Studies in Epidemiology) guidelines [13,14].

2.1. Search strategy and sources

The PubMed and EMBASE databases were searched for relevant publications in English, French and Spanish using the term '(VRE OR (vancomycin resistant enterocc*) OR (GRE) OR (glycopeptide resistant enterocc*)) AND (child* OR paediatric* OR pediatric* OR newborn* OR toddler* OR infant* OR neonat* OR adolescen*)'. The search was also supplemented with screening of the references of all included studies. The date of last search was 29 May 2016. Case series, case reports and conference abstracts were not eligible for inclusion. The authors of three studies [15–17] were contacted for clarification regarding secondary outcomes (see Results).

2.2. Study selection and outcomes of interest

Among the screened reports, studies that provided data on VRE gastrointestinal colonisation on admission and/or during in-hospital stay among patients aged up to 18 years were selected for inclusion. Colonisation was defined as the isolation of VRE from rectal, perirectal, faecal and meconium cultures, since VRE colonisation mostly commonly occurs in the gastrointestinal tract [18,19]. Studies that did not differentiate between VRE infection and colonisation were excluded. Studies conducted after major interventions aimed at eradicating VRE carriage as well as studies performed during outbreaks were not considered in an effort not to overestimate or underestimate the rate of VRE colonisation.

The primary outcome of interest was the rate of VRE colonisation on admission and during the hospital stay of paediatric patients. This rate was calculated by dividing the number of patients with positive VRE surveillance cultures by the total number of patients screened. As secondary outcomes of interest, risk factors for colonisation with VRE, the rate among patients hospitalised at different inpatient units were estimated, and the risk for infection of VRE-colonised versus non-colonised patients was evaluated.

2.3. Data extraction and quality assessment

Two authors (MEF and SAK) screened and extracted information from the text, tables and figures of eligible articles. Information and data of included studies were then summarised in different spreadsheets using Microsoft Excel 2010 (Microsoft Corp., Redmond, WA) and discrepancies were discussed until consensus (Table 1).

The Newcastle–Ottawa Scale (NOS) was used to assess the quality of included studies [36], with the assignment of a star for each of the following pertinent parameters: 'representativeness of the exposed cohort'; 'ascertainment of exposure'; 'assessment of outcome'; 'follow-up long enough for outcome to occur'; and 'adequacy of follow-up of cohorts'. Studies that received a minimum of 4 out of 5 stars met the standards for inclusion (Appendix Table S1).

2.4. Data synthesis and analysis

A random-effects meta-analysis was conducted to estimate the pooled rate and 95% confidence interval (CI) using DerSimonian and Laird methodology [37]. The Freeman–Tukey arcsine method was used to stabilise the variance of proportions [38]. The Egger's test (ET) was performed to assess for publication bias due to small study effect [39]. Heterogeneity between the studies was evaluated with the τ^2 statistic [40], and univariate as well as multivariate meta-regression analyses were implemented to explore for potential heterogeneity sources [41]. For production of the time trend graph, the midyear of each eligible study was determined, the estimated coefficients were transformed to rates and the fitted values were plotted against the midyear of each study, respectively [42].

In a secondary analysis, the risk for infection was calculated based on studies providing data on VRE infection in prior colonised and non-colonised patients. To further evaluate the effect of VRE colonisation on infection with VRE, a diagnostic accuracy meta-analysis was performed. The bivariate random-effects model was used, which accounts for correlation between studies to determine pairs of logit-transformed sensitivity and specificity and their 95% CI [43,44]. The positive and negative likelihood ratios (LRs), diagnostic odds ratio and their 95% CI were also calculated. To estimate whether VRE colonisation changes the probability for development of VRE infection, positive LR values were interpreted by the method described by McGee [45].

Potential risk factors for VRE colonisation in the paediatric population were assessed if three or more studies provided data on the same factor. Pooled relative effects were measured using random-effects meta-analysis and were reported as unadjusted risk ratio (RR) estimates and 95% CI. Heterogeneity was measured by Cochran's *Q*.

STATA v.14 software package (Stata Corp., College Station, TX) was used to perform the statistical analysis. The statistical significance threshold was set at 0.05.

3. Results

Nineteen studies [15–17,20–35] that provided data on 20 234 paediatric patients were included the meta-analysis, all of which were of high quality (≥4 stars in the NOS). The review process is shown in Fig. 1. The main characteristics of the included studies are summarised in Table 1. The pooled rate of VRE gastrointestinal tract colonisation was 5% (95% CI 3–8%; $\tau^2 = 0.03$) without a small study effect (ET = 0.62, $P_{ET} = 0.162$) (Fig. 2). In the analysis of time trend plot, a stable trend in VRE colonisation among paediatric patients was found (annual rate = –0.01%, $P = 0.349$) (Appendix Fig. S1).

Seven studies were conducted in Asia (six in Turkey [27–32] and one in Pakistan [15]) with a pooled rate of 6% (95% CI 3–10%; $\tau^2 = 0.03$; ET = 0.95, $P_{ET} = 0.386$). Six studies were conducted in North America (all in the USA) [16,21–25] with a pooled rate of 6% (95% CI 2–13%; $\tau^2 = 0.06$; ET = 1.42, $P_{ET} = 0.230$). Two studies were performed in Europe (one in Germany [33] and one in the UK [34]) with a pooled rate of 7% (95% CI 5–9%), two in South America (one in Argentina [17] and one in Brazil [26]) with a pooled rate of 14% (95% CI 8–21%), and one study each was conducted in Oceania (New Zealand) [35] and Africa (Nigeria) [20] and both of these single studies reported a 0% rate. In the univariate meta-regression sensitivity analysis, the reported rate was not associated significantly with the region where studies were conducted (coefficient = 0.90, $P = 0.138$).

Regarding the unit distribution of the included patients, four studies reported the colonisation status of 2110 patients hospitalised in the neonatal intensive care unit (NICU) with a pooled rate of 4% (95% CI 0–15%; $\tau^2 = 0.06$; ET = –1.20, $P_{ET} = 0.284$) [27,28,32,33], whilst five studies that included 3251 patients were performed in the paediatric intensive care unit (PICU) with a pooled rate of 5% (95% CI 2–9%; $\tau^2 = 0.02$; ET = 0.054, $P_{ET} = 0.960$) [15,23,24,26,30]. Three studies reported data for 263 haematology/oncology patients with a pooled rate of 23% (95% CI 18–29%; $\tau^2 < 0.001$; ET = –1.29, $P_{ET} = 0.616$) [16,17,22]. In the univariate meta-regression sensitivity analysis, it was found that studies that were exclusively performed in haematology/oncology units reported statistically significant different rates compared with studies that were not (coefficient = 0.61, $P = 0.001$).

As a sensitivity analysis, the VRE colonisation rate in studies that conducted screening cultures only once (point prevalence) were compared with the reported rate in studies that conducted screening multiple times. The prevalence was 3% (95% CI 0–8%; $\tau^2 = 0.1$;