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Colonisation with extended-spectrum β-lactamase-producing Enterobacteriaceae and risk for infection among patients with solid or haematological malignancy: a systematic review and meta-analysis

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ABSTRACT

Cancer patients are vulnerable to infections, including those with extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-PE), and most of these infections are associated with colonisation of the gastrointestinal tract. The aim of this study was to estimate the prevalence of gastrointestinal colonisation with ESBL-PE cancer populations and to determine the risk for subsequent bloodstream infection (BSI) with these pathogens. PubMed and EMBASE databases were searched from 1 January 1991 to 1 March 2016 to identify studies regarding ESBL-PE colonisation among patients with malignancies. Ten studies (out of 561 non-duplicate articles) were included, providing data on 2211 patients. The pooled prevalence of ESBL-PE colonisation was 19% [95% confidence interval (CI) 8–32%]. Stratifying per region, the pooled prevalence in Europe was 15% (95% CI 10–21%), whereas in Asia the pooled prevalence was 31% (95% CI 4–69%). In addition, the pooled prevalence was 15% (95% CI 7–24%) among patients with haematological malignancy, whereas no studies were identified that included solely patients with solid tumours. Notably, cancer patients with ESBL-PE colonisation were 12.98 times (95% CI 3.91–43.06) more likely to develop a BSI with ESBL-PE during their hospitalisation compared with non-colonised patients. We found that, overall, one in five patients with cancer is colonised with ESBL-PE and the incidence can be as high as one in three in Asia. This is important because colonisation was associated with an almost 13 times higher risk for developing BSI with ESBL-PE. Screening measures should be evaluated to identify their clinical benefit in patients with malignancy.

1. Introduction

Extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-PE) are a global emerging threat [1–3]. Originally described in the early 1960s, ESBL-PE have over the last decades been increasingly identified worldwide as causative agents both in community and nosocomial infections [4]. In the clinical setting, detection of ESBL-PE is suggested by the non-susceptibility of isolated microbes to indicator oxyimino-cephalosporins and is subsequently confirmed by the ability of β-lactamase inhibitors to block this resistance [5]. These pathogens cause a broad range of infections that are difficult to treat and these infections are often associated with increased morbidity, mortality and healthcare costs [4,6]. Patients with malignancies, in particular, are especially susceptible to ESBL-PE infections, most commonly bloodstream infections (BSIs), which in turn increase mortality in this patient population [7,8].

Colonisation with ESBL-PE, most commonly of the gastrointestinal tract (GIT) [9], has been linked to subsequent infection with these resistant pathogens [10]. This is particularly concerning in the setting of cancer, as cytotoxic chemotherapy alters the gut microbiome and destroys the mucosal barrier [11], facilitating translocation of colonising microbes into the bloodstream [12].

In addition, use of quinolone prophylaxis has also been linked to increased isolation of ESBL-PE pathogens [13]. Thus, given the severity of ESBL-PE infections in cancer patients and the relationship of these infections to colonisation status [10], we performed a systematic review and meta-analysis to estimate the burden of colonisation with ESBL-PE and to evaluate the link between colonisation and BSI in this population.

2. Materials and methods

This systematic review and meta-analysis was conducted according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines [14].

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2.1. Data sources and searches

The term (ESBL OR (extended-spectrum beta-lactamase) OR (extended-spectrum β-lactamase)) AND (tumor OR cancer OR carcinoma OR sarcoma OR neoplasia OR malignancy OR leukemia OR leukaemia OR lymphoma OR oncolog* OR hematolog* OR haematolog* OR neutropen*) was used to search the PubMed and EMBASE databases for studies published from 1 January 1991 to 1 March 2016 in order to identify studies reporting the prevalence of colonisation with ESBL-PE among patients with solid or haematological malignancy. Two authors (MA and SK) independently screened the titles and abstracts to identify relevant studies, and discrepancies were resolved by consensus. Duplicates were removed prior to study selection and each database was examined separately. The search was supplemented by screening of the reference lists of all eligible studies and relevant reviews. Abstracts from conference proceedings were excluded from the analysis.

2.2. Study selection

Studies were considered eligible if they reported extractable data on the prevalence of ESBL-PE carriage in the GIT among patients with solid tumours or haematological malignancies. Both inpatient and outpatient populations were included. The GIT was focused on as it is the main reservoir of ESBL-PE [9]. Colonisation was defined as isolation of ESBL-PE from a rectal or faecal sample without evidence of gastrointestinal infection. Only studies which stated that collection of samples was performed as part of surveillance practices, and not as part of a search for an infection source, and that provided the timing at which these surveillance cultures were performed were included in the analysis. Also, to avoid duplicate samples, studies were included if the number of isolates per case was clearly reported. In studies that applied a specific intervention on the study population, only the pre-intervention period was included. Another inclusion criterion was that studies should state the microbiological method for ESBL-PE identification, which should be in accordance with standard practice as per Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations [5,15]. Both adult and paediatric studies were included and a restriction for English language literature was imposed.

2.3. Outcomes of interest

The main outcome of interest was the prevalence of ESBL-PE colonisation of the GIT among patients with malignancies. This was calculated as the number of patients with a positive ESBL-PE screening result divided by the number of screened patients. As a secondary outcome, the risk of subsequent ESBL-PE BSI among colonised and non-colonised patients was examined. In addition, the prevalence of ESBL-PE colonisation among different study subgroups was assessed and the temporal trend of ESBL-PE colonisation was examined.

Individual characteristics of each study were extracted and the Newcastle–Ottawa Scale (NOS) was used to assess the methodological quality of the included studies [16]. Since the fields 'selection of the non-exposed cohort', 'demonstration that the outcome of interest was not present at the start of the study' and 'comparability between cohorts' were not applicable to this analysis, each study could receive a maximum of 5 'stars'. Studies that were awarded 4 or 5 stars out of the 5 maximum were considered to be of high quality.

2.4. Data synthesis and analysis

A random-effects meta-analysis was carried out to estimate the pooled prevalence and 95% confidence interval (CI) using the approach of DerSimonian and Laird [17]. The variance of the raw proportions was stabilised using Freeman–Tukey arcsine methodology [18]. Egger's test was used to identify publication bias due to small study effect [19], and the τ^2 statistic was calculated to assess the between-study heterogeneity [20]. Studies were grouped by geographical continent, and a supplemental grouping of studies according to their respective continent subregion was performed. For time trends, the median year of each study was used as the index year, and the model coefficients were then transformed to rates and plotted against the index year along the observed prevalence rates. In cases where the study period was not provided, it was assumed that the study period was 2 years prior to the year of publication.

Meta-regression analysis was also implemented to perform subgroup analysis and to account for potential sources of heterogeneity and confounding. The effect of covariates on ESBL-PE prevalence was examined through univariate random-effects meta-regression using Knapp–Hartung modification. Finally, the effect of ESBL-PE colonisation on subsequent ESBL-PE BSI was explored. The pooled relative risk for BSI between colonised and non-colonised patients was measured using random-effects meta-analysis and was reported as unadjusted risk ratio estimates and 95% CIs. Heterogeneity was measured by Cochran's *Q*. Statistical analysis was performed using Stata v.13 software package (StataCorp LP, College Station, TX). The statistical significance threshold was set at 0.05.

3. Results

The database search yielded 847 studies. After removing 266 duplicate studies, 581 studies were identified and screened by reading through their title and abstract; 196 studies were considered eligible for full-text review. From these studies, 10 studies coded from 11 articles met the inclusion criteria [21–31], with 2 articles including overlapping data [21,31]. Among the 185 excluded studies, 100 studies were excluded due to not providing gastrointestinal colonisation data, 23 studies were reviews, 20 studies did not provide the total number of screened patients, 16 studies did not include cancer patients, 16 studies were published in non-English language, 5 studies had mixed infection and colonisation data, 4 studies concerned isolates without relating them to patients and 1 study was performed at a nursing home. No additional studies were added by reviewing the reference list of the included studies. The review process is shown in the PRISMA flowchart (Fig. 1). And all included studies were considered to be of high quality, being awarded 4 or 5 stars on the NOS (Appendix Table A1). The individual characteristics of the included studies are presented in Table 1.

Overall, the 10 studies provided data on 2211 patients with malignancy. All studies were prospective and were performed in the years 2001–2015. The duration of the included studies ranged from 3 weeks [29] to 30 months [24]. All studies included inpatients, and only one study [30] also included outpatients. The majority of the studies were conducted in Europe (two in Germany [25,27], two in the Czech Republic [22,23], one in Spain (coded from two articles [21,31]), one in Ireland [26] and one in Greece [24]), whereas the remaining studies were conducted in Asia (one in India [30], one in Japan [28] and one in Malaysia [29]). All studies identified ESBL production by performing double-disk diffusion tests, in accordance with the respective recommendations of the CLSI and EUCAST [5,15]. All studies utilised faecal or rectal samples for ESBL-PE detection. The population samples in the included studies ranged from 28 [29] to 618 patients [30]. Eight studies were conducted in adult populations [23–29,31], whereas two studies concerned paediatric patients [22,30]. None of the studies employed gastrointestinal decolonisation protocols.