Prevalence of ESBL-Producing Enterobacteriaceae in Pediatric Bloodstream Infections: A Systematic Review and Meta-Analysis

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Abstract

Background

Pediatric bloodstream infections (BSIs) with Extended-Spectrum Beta-Lactamase- producing Enterobacteriaceae (ESBL-PE) are associated with worse clinical outcomes. We aimed to estimate the prevalence of and the mortality associated with ESBL-PE in this patient population.

Methods

A systematic review and meta-analysis using PubMed and EMBASE and included studies reporting the prevalence of ESBL-PE among confirmed BSIs in patients <19 years old.

Results

Twenty three (out of 1,718 non-duplicate reports) studies that provided data on 3,381 pediatric BSIs from 1996 to 2013 were included. The prevalence of ESBL-PE was 9% [95%CI (6, 13)] with an annual increase of 3.2% (P = 0.04). The prevalence was 11% [95%CI (6, 17)] among neonates, compared to 5% [95%CI (0, 14)] among children older than 28 days. The pooled prevalence was 15% in Africa [95%CI (8, 23)], 12% in South America [95%CI (5, 23)], 11% in India [95%CI (7, 17)], 7% in the rest of Asia [95%CI (0, 22)], 4% in Europe [95%CI (1, 7)] and 0% in Oceania [95%CI (0, 3)]. Importantly, the mortality in neonates with BSI due to ESBL-PE was 36% [95%CI (22, 51)], compared to 18% [95%CI (15, 22)] among all other neonates with BSI and this difference was statistically significant (P = 0.01).

Conclusions

In the pediatric population, the prevalence of BSI due to ESBL-PE is significant and is associated with increased mortality in neonates. Further studies are warranted to establish a high-risk group and the evaluation of preventive measures, such as antibiotic stewardship programs and infection control measures, in this population is urgently needed.
Introduction

Extended-spectrum beta-lactamases (ESBL) are enzymes produced by Enterobacteriaceae that hydrolyze most beta-lactams [1]. They are frequently encoded by plasmids that carry genes conveying resistance to other antibiotic groups, such as aminoglycosides and fluoroquinolones [1]. According to the 2013 report of the Centers for Disease Control and Prevention, ESBL-producing Enterobacteriaceae (ESBL-PE) were classified as a serious threat [2] and the prevalence of ESBL infections keeps rising [1,3]. In the pediatric population, bloodstream infections (BSIs) with ESBL-producing Enterobacteriaceae (ESBL-PE) are associated with longer hospital stays, increased healthcare costs and worse outcomes [4–7]. For example, the SENTRY Antimicrobial Surveillance Program in Europe, North and South America (1997–2002) reported that among <1 and 1–12 years old children, the prevalence of ESBL-producing isolates among Klebsiella spp. bloodstream pathogens was 41.7% and 31.3%, respectively [8].

Carbapenems are the mainstay of treatment of BSIs caused by ESBL-PE [9], and are not part of the established empiric therapy in most areas. Moreover, among adults with BSI due to ESBL-PE, failure to provide adequate antibacterial therapy within 72 hours of infection is an independent risk factor for mortality [10]. Given the clinical significance of these infections, we aimed to evaluate the burden of ESBL-PE among pediatric BSIs. More specifically, the purpose of this systematic review and meta-analysis is to estimate the prevalence and geographical distribution of BSI attributed to ESBL-PE among pediatric patients in non-outbreak settings. Furthermore, we evaluated the mortality associated with these infections.

Methods

Study selection

Three researchers (MF, MA, SK) searched the PubMed and EMBASE databases up to October 9th 2015 for studies eligible for inclusion. The exact term used was “[ESBL OR (extended spectrum beta lactamase)] AND (pediatric OR paediatric OR neonat* OR infant* OR child*)”. The articles were searched rigorously by abstract and title and potential publications in English, French and Spanish were accessed in full text. Additionally, the references of the accessed studies were searched for eligible studies. The authors of the papers were contacted, when needed, for clarification. This systematic review and meta-analysis was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11] (S1 Checklist).

Studies were considered eligible when they reported the number of all laboratory-confirmed BSI cases (discussed below under Definitions) and the number of cases attributed to ESBL-PE. The age limit of 19 was used to define pediatric cases and each child could have suffered from one or multiple bloodstream infections during the study period. We excluded the studies that did not differentiate between specimen contamination and laboratory-confirmed infections, as defined by the as defined by the Centers for Disease Control and Prevention (CDC) [12]. Case reports, case series, as well as conference abstracts were also excluded. Studies that reported outbreaks and studies that implemented stewardship intervention periods were excluded in effort to avoid possible over or underestimation of ESBL-PE prevalence.

Definitions

Clinically suspected BSIs were defined as cases where a blood culture was ordered based on symptomatology and clinical markers. Laboratory-confirmed BSIs (LCBSIS) were defined as clinically suspected cases where the blood culture showed significant pathogen growth that justified the need for treatment. Infections occurring in non-hospitalized children or within 48
hours of hospitalization were characterized as community-acquired, while those occurring after that time window were classified as nosocomial [13]. Healthcare-associated infections were defined as infections related to previous inpatient stay, indwelling medical devices, previous invasive procedures and surgeries and chemotherapy-induced neutropenia.[14]

Data extraction and quality assessment
The primary outcome was the prevalence of ESBL-PE in pediatric LCBSIs and it was calculated by dividing the number of ESBL-PE BSI cases by the total number of LCBSI cases. As a secondary outcome, we calculated the prevalence among clinically suspected BSIs by dividing the number of ESBL-PE BSI cases by the total number of clinically suspected BSI cases, when this data was available. We also estimated the impact of ESBL-PE in all-cause BSI mortality.

As noted above, data extraction was performed by three individual researchers (MF, MA, SK) and discrepancies between them were resolved by consensus. We developed a spreadsheet that included the following data: study midyear and study duration, whether the study was prospective or retrospective, country and continent, age group of patients, hospital setting of the study, characteristics of patients in studies that selected a subgroup of hospitalized children, or in studies that had separate subpopulations, number of LCBSI cases, number of ESBL-PE LCBSI cases, ESBL-producing isolated species, ESBL microbiological method of detection. For studies that did not report their time frame, we assumed that the study period was 2 years prior to publication.

We evaluated the methodological quality of all included studies with the Newcastle–Ottawa Quality Assessment Scale (NOS),[15] a “star-based” rating system that consists of three parts (selection, comparability, and outcome). Studies received “stars” based on the representativeness of the exposed cohort, ascertainment of exposure, assessment of outcome, adequacy of follow-up time or outcomes to occur, and adequacy of follow-up of cohorts. Included studies could obtain a maximum of 5 stars because the parameters “selection of the non-exposed cohort”, “demonstrated that the outcome of interest was not present at the start of the study”, and “comparability between cohorts”, were not pertinent to our analysis. Studies that received at least 3 stars were considered adequate in quality (S1 Table).

Data analysis
Since heterogeneity was expected because of the variable rates of ESBL-PE in different countries reported in the literature, the meta-analysis was performed using a random-effects model to estimate the pooled prevalence and the 95% confidence intervals (CI) [16]. To ensure proportionate weight distribution to studies presenting extreme prevalence (near 0 or 1), we applied the Freeman-Tukey arcsine methodology.[17] The heterogeneity of the studies was estimated by the tau-squared[18] and possible sources of heterogeneity were investigated by subgroup/sensitivity analysis following Knapp and Hartung approach.[19] We stratified the studies per region; due to aggregation of studies from India, these were separately analyzed from the rest of the Asian continent. The effect of small studies in publication bias was calculated by the Egger’s test.[20] The effect of ESBL-PE on mortality compared to non-ESBL-PE BSI cases was estimated using random effects meta-analysis and reported as unadjusted Risk Difference (RD) estimates and confidence intervals (95%CI). The time trend model for ESBL-PE infection was created by transforming the model coefficients to rates and plotting them against the midyear along with the observed prevalence rates [21]. Statistical analysis was performed using STATA v13 software package (STATA Corporation, College Station, TX). Statistical significance was set at 0.05 (two-tailed).
Results

The database search yielded 1,718 non-duplicate abstracts. Among them, 1,009 were removed by title and abstract screening and 709 were accessed in full text. Among the 686 excluded studies, 273 did not report extractable pediatric data, 328 did not report data for BSI or did not report the exact number of BSI cases, 48 described outbreaks, 21 were case reports or case series, 8 were reviews, 7 did not specifically mention the number of ESBL-PE cases and 1 included data after implementation of antibiotic restriction. Twenty three studies met the inclusion criteria and were included in this meta-analysis. Screening of the reference lists did not yield additional papers. All studies were deemed of high quality (≥3 stars). The review process is depicted in Fig 1.

The 23 included studies [14,22–43] reported data for a total 3,381 LCBSI cases, ranging from 1996 to 2013 (Table 1). Fourteen studies were prospective [14,23,25,26,28–30,32,33,35,37,40–42], whereas 9 were retrospective [22,24,27,31,34,36,38,39,43]. The pooled prevalence of ESBL-PE infection was 9% [95%CI (6, 13), \(\tau^2 = 0.09\)] with no evidence of small study effect across studies (Egger’s bias = -0.491, \(P = 0.440\)). Among them, 12 studies [22–25,29,32,34–36,40–42] provided data for 8,568 clinically suspected infections. Their pooled prevalence was 5% [95%CI (3, 7), \(\tau^2 = 0.03\), (Egger’s bias = 0.859, \(P = 0.133\))]. Regarding continent distribution, the pooled prevalence of LCBSIs was 15% in Africa (4 studies) [95%CI (8, 23)], 12% in South America (1 study) [95%CI (5, 23)], 11% in India (10 studies) [95%CI (7, 17)], 7% in the rest of Asia (5 studies) [95%CI (0, 22)], 4% in Europe (2 studies) [95%CI (1, 7)] and 0% in Oceania (1 study) [95%CI (0, 3)] (Fig 2). Interestingly, no studies from North America were identified. Comparing the rates from different regions did not yield statistically significant results (\(P = 0.081\)). The time trend plot we produced using the mid-years showed a statistically significant 3.2% annual increase in ESBL-PE LCBSIs (\(P = 0.04\)) (Fig 3). We have performed a sensitivity analysis, excluding a single study [29] that did not provide the timeframes of study conduction and found no significant time trend (\(P = 0.077\)).

Among the 23 studies included in our analysis, 16 studies provided data stratified by age: 12 [14,22–24,27,29,30,35–37,40,42] reported 1,757 neonatal LCBSIs with a pooled prevalence of 11% [95% CI (6, 17)], 4 studies [14,31,33,39] reported 321 infections in children older than 28 days with a pooled prevalence of 5% [95%CI (0, 14)]. The difference was not statistically significant (\(P = 0.499\)). The prevalence of LCBSIs among patients hospitalized in Neonatal Intensive Care Unit (NICU) was 11% (12 studies)[95%CI (4, 20)],[14,22–24,27,29,30,35–37,40,42] in the Pediatric Intensive Care Unit (PICU) 7% (2 studies) [95%CI (3, 13)][28,38] and in the Emergency Department 4% (1 study) [95%CI (1, 15)] [32].

Five studies [14,26,28,30,38] provided data on 372 nosocomial LCBSIs with a pooled prevalence of 4% [95%CI (1, 9)], while 2 studies [14,32] provided data for 86 community-acquired BSI with a pooled prevalence of 2% [95%CI (0, 6)], with no statistically significant difference (\(P = 0.71\)). Moreover, 4 studies [14,31,33,39] reported 244 healthcare-associated LCBSIs with a pooled prevalence of 5% [95%CI (0, 12)]. Of note is that there was no statistically significant difference in the rates between studies that reported the microbiologic method of detection (either phenotypic ESBL confirmatory tests [14,22–26,29,31,32,34–37,40–43] (\(\tau^2 = 0.10\), or automatic methods [33],) and the studies that did not [27,28,30,38,39] (\(\tau^2 = 0.02\), (\(P = 0.574\)). Similarly, there was no statistically significant difference in rates between studies that specified that a single LCBSI case per patient was recorded [13%, 95%CI (8, 19)] [22,23,29,31,32,34–37,40–42] and those that did not address this point [(6%, 95%CI (2, 10)] [14,24–28,30,33,38,39,43].

Based on 3 studies [23,27,42] that recorded mortality data for 675 neonatal LCBSI cases, the pooled all-cause mortality rate among patients infected with ESBL-PE was 36% [95%CI (22,
Studies identified through PubMed and EMBASE (n=2,552)

Removal of duplicates (n=834)

Title and abstract screening (n=1,718)

Excluded studies (n=1,009)

Full text review (n=709)

Excluded studies:
- No extractable pediatric data (n=273)
- No data for BSI / no report of No of BSI cases (n=328)
- Outbreaks: (n=48)
- Case reports / case series: (n=21)
- Reviews (n=8)
- No report of No of ESBL-PE BSI cases (n=7)
- Implementation of antibiotic restriction (n=1)

Fig 1. PRISMA flow diagram.
doi:10.1371/journal.pone.0171216.g001

51), $\tau^2 = 0.04$, (Egger’s bias = 0.46, $P = 0.688$), compared to 18% among BSIs from all other pathogens [95%CI (15, 22), $\tau^2 = 0$, (Egger’s bias = 0.14, $P = 0.003$)], presenting a statistically
Table 1. Summary of the 23 included studies.

| Author          | Country        | Midyear   | Duration | Study type | Age | Hospital setting | Patients | ESBL-PE | LCBSI Cases | Prevalence % | Isolates | ESBL detection |
|-----------------|----------------|-----------|----------|------------|-----|------------------|----------|---------|-------------|--------------|----------|----------------|
| Isendahl [32]   | Guinea-Bissau  | 2010      | 34       | Prospective| 0–5 years | Emergency department, tertiary hospital | N/A      | 2       | 46          | 4.35         | K        | VITEK 2, E test, Disk diffusion test (EUCAST) PCR, identification: VITEK 2 |
| Kayange [42]    | Tanzania       | 2009      | 9        | Prospective| 0–28 days | Neonatal units, tertiary hospital | N/A      | 36      | 149         | 24.16        | K, E and others | Screen: MacConkey agar CTX, Confirm: Double disk synergy test |
| Ballot [27]     | South Africa   | 2009      | 13       | Retrospective| 0–28 days | Neonatal unit, tertiary hospital | N/A      | 34      | 246         | 13.82        | K        | N/A |
| Ben Jaballah [28]| Tunisia        | 2004      | 24       | Prospective| 0–15 years | PICU, tertiary hospital | Admitted >48 hours | 7       | 41          | 17.07        | K        | N/A |
| Tariq [34]      | Afghanistan    | 2011      | 30       | Retrospective| 1 day-18 years | ICU and wards, Pediatric hospital | N/A      | 110     | 410         | 26.83        | K, E, EB, SR and others | Screen: CTX, CAZ Confirm: Disk diffusion test |
| Dimitrov [13]   | Kuwait         | 2009      | 96       | Retrospective| N/A     | Infectious diseases hospital | N/A      | 0       | 75          | 0            | N/A      | Screen: Disk diffusion test Confirm: E test |
| Latiff [39]     | Malaysia       | 1999      | 12       | Retrospective| 9 months-17 years | Pediatric haematology oncology unit | Febrile neutropenic | 4       | 25          | 16           | K        | N/A |
| Bhattacharjee [29]| India         | 2006      | 14       | Prospective| 0–28 days | NICU university hospital | N/A      | 26      | 117         | 22.22        | K, E, P, A | Screen: Mueller Hinton Agar CTX, CAZ, Confirm: Disk diffusion test (CLSI), MIC reduction method |
| Chandel [11]    | India          | 2004      | 36       | Prospective| 0–60 days | Multicentre: town hospitals and tertiary hospitals | N/A      | 42      | 478         | 8.79         | K, E    | Screen: CTX, CAZ, CFP Confirm: double disk synergy test CAZ, CTX±AMX/CLA |
| Chelliah [40]   | India          | 2011      | 18       | Prospective| 0–28 days | NICU, Tertiary hospital | N/A      | 33      | 110         | 30           | K, E and others | Screen: CTX, CAZ, Confirm: Disk diffusion test CAZ, CTX±CLA, MIC reduction, PCR |
| Gajul [22]      | India          | 2011      | 25       | Retrospective| 0–28 days | NICU, Tertiary hospital | N/A      | 2       | 114         | 1.75         | K       | Screen: CTX, CAZ, Confirm: Disk diffusion test CAZ, CTX±CLA, MIC reduction, PCR |
| Kumar [24]      | India          | 2002      | N/A      | Retrospective| 0–28 days | Multicenter: Neonatal Units | N/A      | 13      | 346         | 3.76         | K        | Double disk synergy test |
| Muley [36]      | India          | 2013      | N/A      | Retrospective| 0–28 days | NICU, Tertiary Hospital | N/A      | 7       | 48          | 14.58        | K, E    | Per CLSI criteria |
| Rao [33]        | India          | 2010      | N/A      | Prospective| 0–28 days | NICU, University hospital | N/A      | 48      | 280         | 17.14        | K, E, EB, C, A | Disk diffusion test: CAZ ±CLA |
| Roy [35]        | India          | 2008      | 5        | Prospective| 0–28 days | Neonatal nurseries, Tertiary hospital | N/A      | 18      | 177         | 10.17        | K, E    | Screen Etest: CRO, CAZ, FEP Confirm Disk diffusion test CAZ, CTX ±CLA |
| Tiwari [25]     | India          | 2009      | 12       | Prospective| 1 day-10 years | Pediatric wards, University hospital | N/A      | 3       | 32          | 9.38         | K, E    | Double disk synergy test |
| Shah [37]       | India          | 2011      | 2        | Prospective| 0–28 days | NICU, tertiary hospital | N/A      | 4       | 60          | 6.67         | N/A      | Per CLSI criteria |
| Grisaru-Soen [38]| Israel        | 2001      | 24       | Retrospective| N/A     | PICU, Tertiary Children’s Hospital | Admitted >48 h | 4       | 90          | 4.44         | K       | N/A |
| Al-Sweidan [31] | Jordan         | 2006      | 60       | Retrospective| 0–17 years | University hospital | Admitted with febrile neutropenia | 5       | 167         | 2.99         | N/A      | Disk diffusion test: CPD, CAZ, CTX±CLA |
| Crivaro [36]    | Italy          | 2008      | 60       | Prospective| 0–28 days | NICU, tertiary hospital | Admitted >48 hours, catheter associated | 3       | 60          | 5            | K        | N/A |
| Raymond J [26]  | Multinational  | 1996      | 6        | Prospective| N/A     | Multicenter: Pediatric and General hospitals | Admitted >48 hours | 4       | 131         | 3.05         | K        | Double disk synergy test: CAZ, CRO, CTX, ATM ± AMX/CLA |

(Continued)
significant difference in mortality risk ($P = 0.01$) [pooled RD = 16.5%, 95%CI = (3.9, 29.1), (Egger’s bias = 9.16, $P = 0.491$)] (Fig 4).

**Discussion**

We highlight the emergence of ESBL-PE in the pediatric patients with BSI. We found a considerable rate of 9% among all LCBSI cases; the incidence is even higher in Africa, South America and India and is increasing over time. Importantly, these infections appear to be more common among neonates while the mortality rate among neonates with BSI due to ESBL-PE was 36% and was significantly higher compared to those infected with other pathogens.

The reported prevalence of ESBL-PE in pediatric BSIs shows the global emergence of these resistant infections and our results are comparable to the rates of ESBL-PE among pediatric bloodstream Enterobacteriaceae, observed in different regions that range from 25% to 70% in endemic areas [6,8,44–48]. Moreover, we estimated that the annual increase is 3.2%. Interestingly, a study documenting 368,398 pediatric Enterobacteriaceae isolates revealed that the prevalence of ESBL-PE has tripled during the period between 1990 and 2011 [3]. Another study calculated the incidence of pediatric ESBL-PE among 2,697 *Escherichia coli*, and *Klebsiella* spp. to be 2.2 times greater in the last 2.5 years, compared to the first 30 months of the study period (2003–2007) [49]. Further studies are needed to evaluate the current burden as well as why current preventive measures are failing to control the dissemination of these important resistant pathogens. For example, their rise is associated with selective pressure exerted by antimicrobial agents [50], thus antimicrobial stewardship protocols might help control their spread and should be specifically evaluated in this patient population.
Regarding age distribution, ESBL-PE infections were frequently encountered in neonatal units. A recent case-control study involving 110 pediatric patients with BSIs from ESBL-PE found that newborns are more likely to suffer from ESBL-PE BSIs compared to older children, irrespectively of concomitant co-morbidities [7]. The neonatal immune system requires 5–7 days to develop and during this time, newborns depend on the innate immune response and passive immunization by the mother [51]. Moreover, ESBL-PE infections have been associated with prematurity [52], further underlining the role of immaturity of the immune system in these infections.

Importantly, our analysis showed a higher mortality among neonates infected with ESBL-PE. High fatality rates and have been observed in neonatal infections with ESBL-PE [47,53–55] and our analysis demonstrates this difference with statistically significant results. In a study performed at the NICU of a tertiary hospital higher mortality was documented among BSI cases with ESBL–PE (23.6 vs. 4.0%), though the difference was not statistically significant. [54] Also, in a prospective study that included 400 bloodstream pathogens, more than 60% of neonates infected with ESBL-PE died in contrast with 35.7% of those infected with other isolates [47].

![Fig 2. Prevalence of ESBL-PE among laboratory-confirmed bloodstream infections in pediatric patients: forest plot of included studies and geographical distribution.](https://doi.org/10.1371/journal.pone.0171216.g002)
Regarding strengths, our analysis included studies in 3 major languages and highlights the emergence of ESBL-PE in the understudied pediatric population. Regarding limitations of our meta-analysis, data on consumption of antimicrobial agents prior to blood culture were not provided in most studies and the use of antimicrobial agents has been associated with higher ESBL-PE rates [45]. Also, we found no significant difference between different hospital settings and this may be affected by the small sample of studies reporting stratified data on this parameter. Regarding mortality rates, data were available only for neonatal infections and further studies are needed to estimate rates in the other age groups. Further stratification to account for patient comorbidities and gestational age was not possible based on the available data.

Finally, five studies did not report the method used for ESBL isolation while ten studies did not report the exclusion of recurrent infections, but, as shown above, this did not significantly affect our results.

In conclusion, in the pediatric population, BSIs caused by ESBL-PE are increasing in frequency and, at least among neonates are associated with significantly higher mortality rates. Preventive and screening protocols, development of rapid diagnostics and the appropriate treatment of children at high risk should be evaluated. For this, studies are warranted to

Fig 3. Time trend of ESBL-PE laboratory-confirmed bloodstream infections (1996–2013) depicting annual increase of 3.2%. Circles illustrate the estimates from each study, sized proportionately to the precision of each estimate. The fitted regression line is represented by study midyear.

doi:10.1371/journal.pone.0171216.g003
identify potential risk factors and establish a well-demarcated high-risk group and address the lack of data from North America.

**Supporting Information**

**S1 Checklist.** PRISMA checklist.

(DOCX)

**S1 Table.** Quality assessment of eligible studies.

(DOCX)

**Author Contributions**

**Conceptualization:** SK EM.

**Data curation:** MF MA.

**Formal analysis:** SK MF.

**Methodology:** MF SK EM.

**Software:** SK.
Validation: MF SK MA.
Writing – original draft: MF SK.
Writing – review & editing: MF SK MA EM.

References

1. Paterson DL, Bonomo RA (2005) Extended-spectrum beta-lactamases: a clinical update. Clin Microbiol Rev 18: 657–686. doi: 10.1128/CMR.18.4.657-686.2005 PMID: 16223952
2. Centers for Disease Control and Prevention Antibiotic resistance threats in the United States, 2013. Available from: http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf.
3. Logan LK, Braykov NP, Weinstein RA, Laxminarayan R (2014) Extended-Spectrum beta-Lactamase-Producing and Third-Generation Cephalosporin-Resistant Enterobacteriaceae in Children: Trends in the United States, 1999–2011. J Pediatr Infect Dis Soc 3: 320–328. doi: 10.1093/jpids/piu010 PMID: 26625452
4. Blomberg B, Jureen R, Manji KP, Tamim BS, Mwakagile DS, Urassa WK, et al. (2005) High rate of fatal cases of pediatric septicemia caused by gram-negative bacteria with extended-spectrum beta-lactamases in Dar es Salaam, Tanzania. J Clin Microbiol 43: 745–749. doi: 10.1128/JCM.43.2.745-749.2005 PMID: 15695674
5. Zaoutis TE, Goyal M, Chu JH, Coffin SE, Bell LM, Nachamkin I, et al. (2005) Risk factors for and outcomes of bloodstream infection caused by extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella species in children. Pediatrics 115: 942–949. doi: 10.1542/peds.2004-1289 PMID: 15805368
6. Kim Y-K, Pai H, Lee H-J, Park S-E, Choi E-H, Kim J, et al. (2002) Bloodstream Infections by Extended-Spectrum β-Lactamase-Producing Escherichia coli and Klebsiella pneumoniae in Children: Epidemiology and Clinical Outcome. Antimicrob Agents Chemother 46: 1481–1491. doi: 10.1128/AAC.46.5.1481-1491.2002 PMID: 11959586
7. Ndri A, Diop A, Faye PM, Cissé MF, Ndoye B, Astagneau P (2016) Epidemiology and Burden of Bloodstream Infections Caused by Extended-Spectrum Beta-Lactamase Producing Enterobacteriaceae in a Pediatric Hospital in Senegal. PLoS ONE 11: e0143729. doi: 10.1371/journal.pone.0143729 PMID: 26867226
8. Biedenbach DJ, Moet GJ, Jones RN (2004) Occurrence and antimicrobial resistance pattern comparisons among bloodstream infection isolates from the SENTRY Antimicrobial Surveillance Program (1997–2002). Diagn Microbiol Infect Dis 50: 59–69. doi: 10.1016/j.diagmicrobio.2004.05.003 PMID: 15002799
9. Paterson DL (2000) Recommendation for treatment of severe infections caused by Enterobacteriaceae producing extended-spectrum β-lactamases (ESBLs). Clin Microbiol Infect 6: 460–463.
10. Tumarello M, Sanguinetti M, Montuori E, Trecarichi EM, Posteroar B, Fiori B, et al. (2007) Predictors of Mortality in Patients with Bloodstream Infections Caused by Extended-Spectrum β-Lactamase-Producing Enterobacteriaceae: Importance of Inadequate Initial Antimicrobial Treatment. Antimicrob Agents Chemother 51: 1987–1994. doi: 10.1128/AAC.01509-06 PMID: 17387156
11. Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Medicine 6: e1000097. doi: 10.1371/journal.pmed.1000097 PMID: 19621072
12. Horan TC, Andrus M, Dudeck MA (2008) CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control 36: 309–332. doi: 10.1016/j.ajic.2008.03.002 PMID: 18538699
13. Laupland KB, Gregson DB, Church DL (2015) Validity of calendar day-based definitions for community-onset bloodstream infections. BMC Res Notes 8: 123. doi: 10.1186/s13104-015-1051-x PMID: 25889421
14. Raymon NJ, Blackmore TK, Humble MW, Jones MR (2006) Bloodstream infections in a secondary and tertiary care hospital setting. Intern Med J 36: 765–772. doi: 10.1111/j.1445-5994.2006.01213.x PMID: 17096739
15. Wells GA SB OCD, Peterson J, Welch V, Losos M, The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available from: http://www.ohri.ca/programs/clinical_epidemiology/nos_manual.pdf.
16. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7: 177–188. PMID: 3802833
17. Nyaga VN, Arbyn M, Aerts M (2014) Metaprop: a Stata command to perform meta-analysis of binomial data. Arch Public Health 72: 39. doi: 10.1186/2049-3258-72-39 PMID: 25810908

18. Rucker G, Schwarzer G, Carpenter JR, Schumacher M (2008) Undue reliance on I(2) in assessing heterogeneity may mislead. BMC Med Res Methodol 8: 79. doi: 10.1186/1471-2288-8-79 PMID: 19036172

19. Thompson SG, Higgins J. P. T. (2002) How should meta-regression analyses be undertaken and interpreted? Stat Med 21: 1559–1573. doi: 10.1002/sim.1187 PMID: 12111920

20. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ (Clinical research ed) 315: 629–634.

21. Zacharioudakis IM, Zervoudis FN, Pliakos EE, Ziakas PD, Mylonakis E (2015) Colonization with toxigenic C. difficile upon hospital admission, and risk of infection: a systematic review and meta-analysis. Am J Gastroenterol 110: 381–390; quiz 391. doi: 10.1038/aig.2015.22 PMID: 25949057

22. Gajul SV, Mohite ST, Mangalgi SS, Wavare SM, Kakade SV (2015) Klebsiella Pneumoniae in Septicemic Neonates with Special Reference to Extended Spectrum \(\beta\)-lactamase, AmpC, Metallo-\(\beta\)-lactamase Production and Multiple Drug Resistance in Tertiary Care Hospital. J Lab Physicians 7: 32–37. doi: 10.4103/0974-2727.151689 PMID: 25732416

23. Rao YK, Midha T, Garg A, Garg J, Dwivedi GN, Singh N, et al. (2012) Neonatal septicemia in north india due to extended spectrum beta lactamase (ESBL) producing gram negative bacteria. Int J Pharma Bio Sci 3: B282–B290.

24. Kumar CS, Neelagund YF (2004) Extended spectrum of \(\beta\)-lactamase mediated resistance to third generation cephalosporins among klebsiellae pneumoniae in neonatal sepsis. Indian Pediatr 41: 97–99. PMID: 14767101

25. Tiwari DK, Golia S, K TS, C LV (2013) A study on the bacteriological profile and antibiotic of bacteremia in children below 10 years in a tertiary care hospital in bangalore, India. J Clin Diagn Res 7: 2732–2735. doi: 10.7860/JCDR/2013/6682.3701 PMID: 24551625

26. Raymond J, Aujard Y (2000) Nosocomial infections in pediatric patients: a European, multicenter prospective study. European Study Group. Infect Control Hosp Epidemiol 21: 260–263. doi: 10.1086/501755 PMID: 10782588

27. Ballot DE, Nana T, Sriruttan C, Cooper PA (2012) Bacterial bloodstream infections in neonates in a developing country. ISRN Pediatr 2012: 508512. doi: 10.5402/2012/508512 PMID: 22919509

28. Ben Jaballah N, Bouziri A, Mnif K, Hamdi A, Khaldi A, Kchaou W (2007) Epidemiology of hospital-acquired bloodstream infections in a Tunisian pediatric intensive care unit: a 2-year prospective study. Am J Infect Control 35: 613–618. doi: 10.1016/j.ajic.2006.09.007 PMID: 17980241

29. Bhattacharjee A, Sen MR, Prakash P, Gaur A, Anupurba S (2008) Increased prevalence of extended spectrum beta lactamase producers in neonatal septicaemic cases at a tertiary referral hospital. Indian J Med Microbiol 26: 356–360. PMID: 18974490

30. Crivaro V, Bogdanovic L, Bagattini M, Iula VD, Catania M, Raimondi F, et al. (2015) Surveillance of healthcare-associated infections in a neonatal intensive care unit in Italy during 2006–2010. BMC Infect Dis 15: 152. doi: 10.1186/s12879-015-0099-9 PMID: 25885702

31. Al-Sweedan SA, Hyajneh W, Al-Ostath A (2012) Patterns of bacteremia in cancer patient with febrile neutropenia at King Abdullah University Hospital—Jordan 2003–2008. J Pediatri Infect Dis 7: 15–20.

32. Isendahl J, Manjuba C, Rodrigues A, Xu W, Henriques-Normark B, Giske CG, et al. (2014) Prevalence of community-acquired bacteraemia in Guinea-Bissau: an observational study. BMC Infect Dis 14: 3859. doi: 10.1186/s12879-014-0715-9 PMID: 25526763

33. Cheguirian ML, Carvalaj LR, Ledesma EM, Enrico MC, Reale AL, Culasso C, et al. (2008) Prevalence and antimicrobial susceptibility patterns of microorganisms causing bacteremia in pediatric oncology patients. Rev Argent Microbiol 40: 111–115. PMID: 18705494

34. Tariq TM (2014) Bacteriologic profile and antibiogram of blood culture isolates from a children's hospital in Kabul. J Coll Physicians Surg Pak 24: 396–399. PMID: 24953929

35. Roy S, Gaind R, Chellani H, Mohanty S, Datta S, Singh AK, et al. (2013) Neonatal septicemia caused by diverse clones of Klebsiella pneumoniae & Escherichia coli harbouring bla(CTX-M-15). Indian J Med Res 137: 791–799. PMID: 23703349

36. Muley VA, Ghadage DP, Bhore AV (2015) Bacteriological Profile of Neonatal Septicemia in a Tertiary Care Hospital from Western India. J Global Infect Dis 7: 75–77.

37. Shah AJ, Mulla SA, Revdiwala SB (2012) Neonatal sepsis: high antibiotic resistance of the bacterial pathogens in a neonatal intensive care unit of a tertiary care hospital. J Clin Neonatol 1: 72–75. doi: 10.4103/2249-4847.96753 PMID: 24027694
38. Grisaru-Soen G, Sweed Y, Lerner-Geva L, Hirsh-Yechezkel G, Boyko V, Vardi A, et al. (2007) Nosocomial bloodstream infections in a pediatric intensive care unit: 3-year survey. Med Sci Monit 13: Cr251–257. PMID: 17534230

39. Latiff Z, Zulkifli SZ, Jamal R (2002) Risk assessment and microbiological profiles of infections in paediatric cancer patients with febrile neutropenia. Malays J Pathol 24: 83–89. PMID: 12887165

40. Cheillah A, Thyagarajan R, Katragadda R, Leela KV, Babu RN (2014) Isolation of MRSA, ESBL and AmpC—beta-lactamases from Neonatal Sepsis at a Tertiary Care Hospital. J Clin Diagn Res 8: Dc24–27. doi: 10.7860/JCDR/2014/8597.4512 PMID: 25120982

41. Chandel DS, Johnson JA, Chaudhry R, Sharma N, Shinkre N, Parida S, et al. (2011) Extended-spectrum beta-lactamase-producing Gram-negative bacteria causing neonatal sepsis in India in rural and urban settings. J Med Microbiol 60: 500–507. doi: 10.1099/jmm.0.027375-0 PMID: 21183602

42. Kayange N, Kamugisha E, Mwizamolya DL, Jeremiah S, Mshana SE (2010) Predictors of positive blood culture and deaths among neonates with suspected neonatal sepsis in a tertiary hospital, Mwanza-Tanzania. BMC pediatrics 10: 39. doi: 10.1186/1471-2431-10-39 PMID: 20525358

43. Dimitrov TS, Panigrahi D, Emara M, Al-Nakkas A, Awini F, Passadilla R (2005) Incidence of bloodstream infections in a speciality hospital in Kuwait: 8-year experience. Med Princ Pract 14: 417–421. doi: 10.1159/000088115 PMID: 16220016

44. Dramowski A, Cotton MF, Rabie H, Whitelaw A (2015) Trends in paediatric bloodstream infections at a South African referral hospital. BMC pediatrics 15: 33. doi: 10.1186/s12887-015-0354-3 PMID: 25884449

45. Ariffin H, Navaratnam P, Mohamed M, Arasu A, Abdullah WA, Lee CL, et al. (2000) Ceftazidime-resistant Klebsiella pneumoniae bloodstream infection in children with febrile neutropenia. Int J Infect Dis 4: 21–25. PMID: 10689210

46. Zaki Mel S (2007) Extended spectrum beta-lactamases among gram-negative bacteria from an Egyptian pediatric hospital: a two-year experience. J Infect Dev Ctries 1: 269–274. PMID: 19734604

47. Jain A, Roy I, Gupta MK, Kumar M, Agarwal SK (2003) Prevalence of extended-spectrum beta-lactamase-producing Gram-negative bacteria in septicemic neonates in a tertiary care hospital. J Med Microbiol 52: 421–425. doi: 10.1099/jmm.0.04966-0 PMID: 12721319

48. ARSP Working Group TSLOCM (2013) A multi centre laboratory study of Gram negative bacterial blood stream infections in Sri Lanka. Ceylon Med J 58: 56–61. doi: 10.4038/cmj.v58i2.5680 PMID: 23817934

49. Blaschke AJ, Korgenski EK, Daly JA, LaFleur B, Pavia AT, Byington CL (2009) Extended-spectrum beta-lactamase-producing pathogens in a children’s hospital: a 5-year experience. Am J Infect Control 37: 435–441. doi: 10.1016/j.ajic.2008.09.019 PMID: 19155096

50. Hawkey PM (2008) The growing burden of antimicrobial resistance. J Antimicrob Chemother 62 Suppl 1:i–9.

51. Wynn JL, Levy O (2010) Role of innate host defenses in susceptibility to early-onset neonatal sepsis. Clin Perinatol 37: 307–337. doi: 10.1016/j.clp.2010.04.001 PMID: 20569810

52. Linkin DR, Fishman NO, Patel JB, Merrill JD, Lautenbach E (2004) Risk factors for extended-spectrum beta-lactamase-producing Enterobacteriaceae in a neonatal intensive care unit. Infect Control Hosp Epidemiol 25: 781–783. doi: 10.1086/502477 PMID: 15484805

53. Vijayakanthi N, Bahl D, Kaur N, Maria A, Dubey NK (2013) Frequency and characteristics of infections caused by extended-spectrum beta-lactamase-producing organisms in neonates: a prospective cohort study. Biomed Res Int 2013: 756209. doi: 10.1155/2013/756209 PMID: 24175299

54. Sehgal R, Gaidn R, Chellani H, Aganwal P (2007) Extended-spectrum beta lactamase-producing gram-negative bacteria: clinical profile and outcome in a neonatal intensive care unit. Ann Trop Paediatr 27: 45–54. doi: 10.1179/146532807X170501 PMID: 17469732

55. Stapleton PJ, Murphy M, McCallion N, Brennan M, Cunney R, Drew RJ (2016) Outbreaks of extended spectrum beta-lactamase-producing Enterobacteriaceae in neonatal intensive care units: a systematic review. Arch Dis Child Fetal Neonatal Ed 101: 72–78.