Antibiotic susceptibility profiles of neonatal invasive isolates of *Escherichia coli* from a 2-year nationwide surveillance study in Germany, 2009–2010

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**Abstract** A nationwide 2-year surveillance study on invasive neonatal *Escherichia coli* infections in Germany was conducted. A total of 158 isolates were tested for antibiotic susceptibility. The empirical treatment regimen of ampicillin plus gentamicin for neonatal sepsis appears to remain effective, but emerging resistance needs to be closely monitored.

**Background**

*Escherichia coli* is the leading Gram-negative organism, causing neonatal sepsis and meningitis with high rates of morbidity and mortality, despite advances in neonatal intensive care [1, 2]. In *E. coli*, attention concerning antibiotic susceptibility has mainly been focused on the development of ampicillin resistance in early-onset sepsis (EOS) of preterm infants [3, 4], whereas few studies have systematically examined susceptibility to other classes of antibiotics in neonatal sepsis. We present the first nationwide surveillance data on the antibiotic susceptibility of neonatal invasive *E. coli* strains isolated in Germany.

**Methods**

Active surveillance for invasive *E. coli* infections in all neonates up to the age of 3 months was performed from January 2009 through December 2010. Monthly questionnaires were sent out by the Robert Koch Institute (RKI), Berlin, Germany, to all microbiological laboratories in Germany serving neonatal wards and willing to participate in the study.

Strains were considered to be definitely invasive when isolated from blood or cerebrospinal fluid (CSF) culture or from other sterile compartments. *E. coli* isolates from non-sterile material in a clinically septic infant were considered to be suspected invasive. The study design targeted laboratories directly and personal data protection did not allow for retrieval of the patients’ age at acquisition of the isolate nor any additional clinical information.

Antimicrobial susceptibility to piperacillin/tazobactam, cefuroxime, meropenem, ciprofloxacin, cotrimoxazole, tetracycline, and tigecycline was assessed using disk diffusion tests (bioMérieux, Nuertingen, Germany). The minimum inhibitory concentration (MIC) of ampicillin, piperacillin, cefotaxime, and gentamicin was determined using Etest strips (bioMérieux, Nuertingen, Germany). Susceptibility was defined as “susceptible”, “intermediately susceptible”, or “resistant” according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines.
Results

A total of 1,230 laboratories were identified as target laboratories. Of these, 128 (10.4 %) laboratories responded to serving neonatal wards and performing antibiotic susceptibility testing on neonatal E. coli isolates. During the 2-year study period, 93 laboratories continuously provided data and 18 provided data only for a limited period ranging from 8 to 20 months. The capture areas of the laboratories include all 16 federal states of Germany. A total of 180 E. coli strains were collected, of which 115 (63.9 %) were identified as definitely invasive and a further 43 (23.9 %) strains were considered to be suspected invasive pathogens, as defined above. The remaining 22 (12.2 %) strains were either identified as non-invasive or could not be evaluated and were, thus, excluded from the analysis. Of the 115 confirmed invasive strains, 95 (82.6 %) were isolated from blood, 16 (13.9 %) from CSF, 2 (1.7 %) from pleural effusion, and one from an intra-abdominal abscess. No significant differences in antibiotic susceptibility were found between invasive and suspected invasive isolates.

The resistance rates are shown in Table 1. The MIC of ampicillin ranged from 0.5 to >256 μg/ml, with an MIC50 of 3 μg/ml and an MIC90 of >256 μg/ml (Table 2). The MIC of piperacillin ranged from 0.038 to >256 μg/ml, with an MIC50 of 1.5 μg/ml and an MIC90 of 64 μg/ml. Six isolates (3.8 %) were resistant to cefotaxime, with MIC ranging from 0.016 to 128 μg/ml, an MIC50 of 0.047 μg/ml and an MIC90 of 0.094 μg/ml. Among these six isolates, two harbored the ESBL gene blaTEM and the remaining four harbored blaCTX-M-1, blaCTX-M-3, blaCTX-M-14, and blaCTX-M-15, respectively. Macrorestriction patterns (PFGE analysis) of the ESBL strains showed no genetic relationship except for the two TEM-52 producing E. coli that were isolated from two different patients in two different hospitals in the same geographic area (Fig. 1).

Gentamicin MICs ranged from 0.19 to 96 μg/ml, with an MIC50 of 0.5 μg/ml and an MIC90 of 1.0 μg/ml. All 158 isolates were uniformly susceptible to meropenem, piperacillin/tazobactam, and tigecycline.

Discussion

We present the first national surveillance study on antibiotic susceptibility in neonatal invasive E. coli strains conducted in Germany to date. Empirical treatment regimens for neonatal sepsis combine ampicillin with either an aminoglycoside or a cephalosporin of the cefotaxime group. The proportion of ampicillin resistance in this study was comparable to the published data of resistance rates of 40–65 % in E. coli EOS [3, 4], whereas susceptibility to gentamicin and cefotaxime was shown to remain high throughout Germany. However, 3.8 % of the strains proved to be resistant to the combination of ampicillin and gentamicin, likewise, 3.8 % were resistant to the combination of ampicillin and cefotaxime. The emergence of ESBL-producing strains needs to be closely monitored in the future, considering its potential impact on the choice of empirical therapy. Outbreaks of ESBL-producing E. coli strains in neonatal intensive care units did not occur during the study period, but have recently been reported from elsewhere in Europe [8, 9]. Few studies presenting nationwide susceptibility profiles of neonatal invasive E. coli in Europe have been published. A current publication from England showed a slightly higher rate of cephalosporin resistance of 5 %
in late-onset sepsis (LOS) E. coli strains [10]. The same study showed that 93 % of LOS E. coli strains remained susceptible to a combination of amoxicillin and gentamicin. In contrast, an English multicenter surveillance study found resistance rates to amoxicillin plus cefotaxime of approximately 16 % among E. coli LOS strains [11].

We recognize limitations to our study. Although we initiated a comprehensive recruitment of laboratories, we cannot claim to have a full coverage of all laboratories in question and we cannot assure full representativeness of the participating sample. Yet, we have no indication that our data are subject to a systematic recruiting bias. Since the design of this study targeted laboratories directly, clinical information could not be retrieved, making it impossible to differentiate susceptibility profiles between EOS and LOS.

In summary, susceptibility to aminoglycosides and cefotaxime among E. coli isolates causing neonatal sepsis in Germany remains high. Empirical therapy combining ampicillin with either an aminoglycoside or a cephalosporin of the cefotaxime group can, thus, still be considered effective. The emergence of ESBL-producing E. coli strains among the neonatal population should be closely monitored through future surveillance studies.

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Conflict of interest The authors declare that they have no conflict of interest.

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References