Original Article

# *Escherichia coli* resistance patterns, empiric and targeted antibiotic prescriptions in children: a single center experience

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**Abstract.** *Background and aim:* Antibiotic resistance represents one of the major public health issues, due to the potential future ineffectiveness of available antibiotics. However, epidemiological studies on E. coli antibiotic resistance patterns in the pediatric population are limited. *Methods:* We conducted a retrospective analysis on children younger than 18 years of age admitted to the Department of Pediatrics from April 2016 to April 2018 with E. coli isolation on biological materials. *Results:* 205 subjects were included in the study (median 45 days, IQR 7-139 days). We found an overall low rate of resistance of E. coli isolates to amoxicillin/clavulanate (20%), cephalosporins (6.3%) and aminoglycosides (6.3%), while no isolates were resistant to carbapenems. Presence of invasive devices and intensive care admissions were associated with resistance to cephalosporines (P: < 0.001; OR 9.21, 95% CI 2.7 – 31.39) and aminoglycosides (P: < 0.004; OR 5.42, 95% CI 1.71 – 17.15), while no factors associated with resistance to the other antibiotics were found. *Conclusions:* Aminoglycosides and cephalosporins were frequently used as empirical therapy. On the other hand, once the antibiograms were available, targeted therapies aimed at sparing these classes of antibiotics were not always administered. Our study reports on local antimicrobial management in children and can guide the development of programs aimed at better use of antibiotics. (www.actabiomedica.it)

**Key words:** Escherichia coli, antibiotics resistance, antibiotic stewardship, children, resistance risk factors

## Introduction

Escherichia coli (E. coli) is the most frequently isolated Gram-negative bacterium. It is the cause of numerous infections during the pediatric age, such as gastroenteritis, urinary tract infections (UTIs), hospital-acquired pneumonia, cholecystitis, peritonitis, neonatal osteomyelitis, meningitis and sepsis (1).

Due to the selective pressure of antimicrobials, strains of E. coli with various mechanisms of antibiotic resistance, including the production of extended-spectrum-beta-lactamases (ESBLs), plasmid-mediated AmpC (pAmpC), carbapenemases, resistance to fluoroquinolones, aminoglycosides, trimethoprim-sulfamethoxazole and colistin (2), have spread around the world.

The global distribution of E. coli resistance is characterized by high geographic diversity and variation over the years (3-9).

However, epidemiological studies on E. coli antibiotic resistance are limited. In addition, to our knowledge in Italy researches about the pediatric population

are few. Antibiotic resistance represents one of the major public health issues, due to the potential future ineffectiveness of antibiotics (10), necessitating periodic studies to select the most effective empirical antibiotic treatment.

Consequently, we performed a retrospective study in order to evaluate the antibiotic sensitivity of E. coli isolates in our facility; to identify the risk factors for the presence of E. coli resistant to different classes of antibiotics; to assess empiric and targeted therapies used during the study period.

## Materials and Methods

We conducted a retrospective analysis on children younger than 18 years of age admitted to the Department of Pediatrics from April 2016 to April 2018 with E. coli isolation on biological materials [urine, bronchoalveolar lavage (BAL), blood, conjunctivae, cerebrospinal fluid, wounds].

Species identification was performed by the matrix-assisted laser desorption/ionization time-of-flight (MALDI) mass spectrometry using the Bruker Daltonics MALDI Biotyper® system (Bruker Daltonics, Bremen, Germany). To assess antimicrobial susceptibilities of E.coli , the MICs of amikacin, amoxicill-clavulanate, ceftazidime, cefotaxime, ciprofloxacin, ertapenem, gentamicin, meropenem, piperacillin-tazobactam, trimethoprim-sulfamethoxazole were determined by the VITEK® 2 system using AST cards, and results were interpreted according to EUCAST breakpoints (11). We further evaluated the susceptibilities to extended-spectrum cephalosporins and carbapenems by using panels manufactured by MERLIN Diagnostica GmbH (Bornheim, Germany).

We searched the computerized database of the clinical microbiology laboratory to identify all inpatient infections caused by E. coli isolates that were diagnosed between April 2016 and April 2018. We retrieved data from this database, which contains complete profiles for all the patients with positive culture results.

The study was approved by the Institution Review Board of our Department (DIPUSVSP-16-11-2095).

Medical record information included demographics (gender, age), cause and duration of hospitalization, intensive care unit (ICU) admission, antimicrobial susceptibility testing, comorbidities, antibiotic therapy during hospitalization.

The evaluation of the antibiotic therapy was carried out on the basis of the indications of Red Book (12), which, according to the principles of Antibiotic Stewardship, stated that they were empiric recommendations; specific option of antibiotic therapy should be led by the culture results (13). We also evaluated that the antibiotic had a good penetration in the system affected by the infectious disease.

### *Statistical analysis*

A descriptive statistical analysis was performed by constructing frequency tables (absolute and relative) for the categorical variables. We also performed an inferential statistical analysis: the univariate analysis to compare the frequency of antibiotic resistance with categorical variables through the Chi-square ($\chi^2$) test or Fisher Exact test; the Mann-Whitney test to compare numeric variables without normal distribution among the resistant and non-resistant group; the multivariate analysis with Odds ratio and 95% confidence interval. The P values $< 0.05$ were considered statistically significant. The analysis was performed with STATA v16.1.

## Results

### *Study population (Table 1)*

Two hundred and five subjects were included in the study. Eighty-four (41%) were females. The median age was 45 days (IQR 7-139 days): eighty-five (41.5%) were newborns, fifty-one (24.9%) were aged between 29 and 90 days and 69 (33.7%) were older. The antibiograms were performed on several clinical specimens: urine (87%), bronchoalveolar lavage (4%), blood (3%), conjunctiva (3%) and others (3%).
The most frequent reason for admission was an infectious disease (133, 64.9%), followed by neurologic disease (22, 10.7%), respiratory disease (16, 7.8%), prematurity (11, 5.4%), renal disease (7, 3.4%) and others (16, 7.8%).

**Table 1.** Characteristics of children included in the study

| Patients characteristics | N. (%) |
|---|---|
| Age (days) | |
| 0-28 | 85 (41.5) |
| 29-90 | 51 (24.9) |
| >90 | 69 (33.7) |
| Sex | |
| Male | 121 (59.0) |
| Female | 84 (41.0) |
| Comorbidities | 57 (27.8) |
| Hematology | 11 (5.4) |
| Gastrointestinal | 11 (5.4) |
| Infectious | 13 (6.3) |
| Renal | 9 (4.4) |
| Other | 13 (6.3) |
| Devices | 41 (20.0) |
| Intensive Care | 32 (15.6) |
| NICU | 15 (7.3) |
| PICU | 17 (8.3) |
| Specimen type | |
| Urine | 178 (86.8) |
| Bronchoalveolar lavage | 8 (3.9) |
| Blood | 6 (2.9) |
| Cerebrospinal fluid | 0 |
| Other | 13 (6.3) |
| Days of hospitalization (median; IQR) | 10; 6-22 |
| Reason for admission | |
| Suspected sepsis | 88 (42.9) |
| Fever | 7 (3.4) |
| Gastrointestinal | 11 (5.4) |
| Urinary Tract Infection | 52 (25.4) |
| Convulsion | 5 (2.4) |
| Respiratory | 6 (2.9) |
| Perinatal asphyxia | 10 (4.9) |
| Other | 26 (12.7) |
| N. of previous hospitalizations (median; IQR) | 3; 2-4 |

Abbreviations: N.= Number; NICU= Neonatal Intensive Care; PICU= Pediatric Intensive Care

Seventeen children (8.3%) needed Pediatric Intensive Care Unit (PICU) admission, while fifteen (7.3%) were admitted to the Neonatal Intensive Care Unit (NICU).

Fifty-six patients (27.3%) had comorbidities: hematologic (19.6%), gastrointestinal (19.6%), followed by infectious (23.2%), renal (16.1%) and others (21.4%).

Devices, such as central venous catheter, tracheostomy, urinary catheter, percutaneous endoscopic gastrostomy (PEG), arterial catheter, were present in forty-one patients (20%).

*Antibiotic resistance and use*

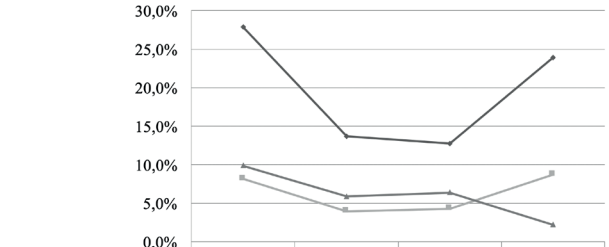
The overall antibiotic resistance of our population is reported in the Table 2. 97 (47.3%) and 41 (20%) patients had E. coli infection resistant to ampicillin and amoxicillin/clavulanate, respectively. Resistance to aminoglycosides and cephalosporins was present in 6.3% of cases. None of the isolated germs was resistant to carbapenems.

Figure 1 describes the trends in antibiotic resistance over time for E. coli isolates. We reported a reduction in resistance to amoxicillin/clavulanate, cephalosporins and aminoglycosides between 2016 and 2017. However, the trend was again increasing in the second semester of 2017, with the exception of aminoglycosides.

Figures 2 summarizes antibiotics used as empiric and targeted therapy. We did not report substantial differences in the use of amoxicillin/clavulate, cephalosporins and aminoglycosides, while we noted less use

**Table 2.** Resistance profiles of E. coli to the main antibiotics tested

| Antibiotics | Resistance |
|---|---|
| Fluoroquinolones | 26 (12.7%) |
| Ampicillin | 97 (47.3%) |
| Amoxicillin/clavulanate | 41 (20.0%) |
| Cephalosporins | 13 (6.3%) |
| Piperacillin/tazobactam | 13 (6.3%) |
| Carbapenems | 0.0% |
| Aminoglycosides | 13 (6.3%) |




| | First semester 2016 | Second semester 2016 | First semester 2017 | Second semester 2017 |
|---|---|---|---|---|
| AMOXI/CLAV | 27,9% | 13,7% | 12,8% | 23,9% |
| CEPHALOSPORINS | 8,2% | 3,9% | 4,3% | 8,7% |
| AMINOGLICOSIDES | 9,8% | 5,9% | 6,4% | 2,2% |

**Figure 1.** Distribution of resistance patterns of amoxicillin/clavulanate, cephalosporins and aminoglycosides over the years analyzed by the study

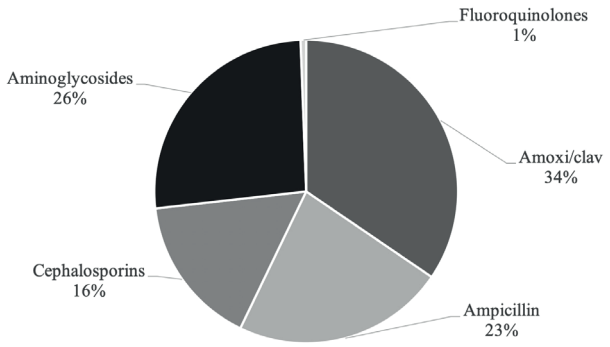



**Figure 2A.** Antibiotics before the antibiogram

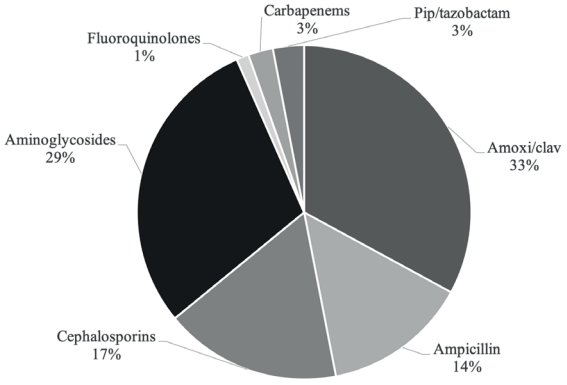



**Figure 2B.** Antibiotics after the antibiogram

of ampicillin and greater administration of piperacillin/tazobactam and carbapenems after viewing the antibiogram.

*Amoxicillin/clavulanate*

Forty-one E. coli isolates (20%) were resistant to amoxicillin/clavulanate. Fifty-eight patients (28.3%) were empirically treated with amoxicillin/clavulanate; ten of them (17.2%) subsequently demonstrated resistance to this antibiotic. As a result, 7 of them (70%) switched therapy. No clinical or epidemiologic data significantly associated with resistance to amoxicillin/clavulanate have emerged (table 3).

*Cephalosporins*

We tested third generation cephalosporins, in particular cefotaxime.

Thirteen E. coli isolates (6.3%) were resistant to cephalosporins.

Twenty-seven (13%) were treated with cephalosporins. Five of the treated patients (18.5%) were resistant to cephalosporins: two of them changed therapy for this reason. Twenty-three of the treated E. coli (85.2%) were also sensitive to amoxicillin/clavulanate, but only two patients (8.7%) changed therapy with a down switch to amoxicillin/clavulanate.

A previous admission to an intensive care unit setting (P: 0.01) and presence of devices (P: < 0.001) were significantly associated with an E. coli resistant to cephalosporins. On multivariate analyses, the presence of devices remained significant (P: < 0.001; OR 9.21, 95% CI 2.7 – 31.39) (table 4).

**Table 3.** Factors affecting resistance to amoxicillin/clavulanate

| | **Amoxicillin/clavulanate Resistance N. (%)** | **Amoxicillin/clavulanate Sensitivity N. (%)** | **P-value** |
|---|---|---|---|
| Age days | | | |
| 0 – 28 | 20 (9.8) | 65 (31.7) | 0.519 |
| 29 – 90 | 8 (3.9) | 43 (21.0) | |
| >90 | 13 (6.3) | 56 (27.3) | |
| Male | 21 (10.2) | 100 (48.8) | 0.256 |
| Intensive Care | 5 (2.4) | 27 (13.2) | 0.501 |
| Prev. hospitalizations | 12 (5.9) | 57 (27.8) | 0.506 |
| Comorbidities | 14 (6.8) | 43 (21.0) | 0.311 |
| Devise | 7 (3.4) | 34 (16.6) | 0.6 |

**Table 4.** Factors affecting resistance to cephalosporins

| | Cephalosporins Resistance N. (%) | Cephalosporins Sensitivity N. (%) | P-value |
|---|---|---|---|
| Age days | | | |
| 0 – 28 | 3 (1.5) | 82 (40.0) | 0.089 |
| 29 – 90 | 2 (1.0) | 49 (23.9) | |
| >90 | 8 (3.9) | 61 (29.8) | |
| Male | 21 (10.2) | 117 (57.1) | 0.032 |
| Intensive Care | 5 (2.4) | 27 (13.2) | 0.019 (OR 3.82 IC 1.16-12.54) |
| Prev. hospitalizations | 6 (2.9) | 63 (30.7) | 0.325 |
| Comorbidities | 6 (2.9) | 51 (24.9) | 0.127 |
| Devise | 8 (3.9) | 33 (16.1) | <0.001 (OR 7.71 IC 2.37-25.05) |

*Aminoglycosides*

Thirteen E. coli isolates (6.3%) were resistant to aminoglycosides. Forty-four patients (21.4%) were treated with this antibiotic as empiric therapy. Five children (11.4%) were subsequently found to be resistant to aminoglycosides; four (80%) changed therapy. Thirty-two patients (72.7%) treated with aminoglycosides were also sensitive to amoxicillin/clavulanate, but only one patient shifted therapy to this drug. A previous admission to an intensive care unit setting (P: < 0.01) and presence of devices (P: < 0.004) were significantly associated with an E. coli resistant to aminoglycosides. On multivariate analyses, the presence of devices remained significant (P: < 0.004; OR 5.42, 95% CI 1.71 – 17.15) (table 5).

*Fluoroquinolones*

Twenty-six E. coli isolates (12.7%) were resistant to fluoroquinolones. Only one patient was treated with fluoroquinolones (0.6%).

*Carbapenems*

None of the E. coli strains were resistant to carbapenems. Four patients, after the results of the antibiogram, shifted their therapy to carbapenems: in these cases, E. coli strains were resistant to ampicillin, amoxicillin/clavulanate, aminoglycosides, cephalosporins and fluoroquinolones.

These patients were admitted to the NICU, with comorbidities or device.

**Table 5.** Factors affecting resistance to aminoglycosides

| | Aminoglycosides Resistance N. (%) | Aminoglycosides Sensitivity N. (%) | P-value |
|---|---|---|---|
| Age days | | | |
| 0 – 28 | 4 (2.0) | 81 (39.5) | 0.715 |
| 29 – 90 | 4 (2.0) | 47 (22.9) | |
| >90 | 5 (2.4) | 64 (31.2) | |
| Male | 6 (2.9) | 115 (56.1) | 0.330 |
| Intensive Care | 5 (2.4) | 27 (13.2) | 0.019 (OR 3.82 IC 1.16-12.54) |
| Prev. hospitalizations | 5 (2.4) | 64 (31.2) | 0.325 |
| Comorbidities | 6 (2.9) | 51 (24.9) | 0.127 |
| Devise | 7 (3.4) | 34 (16.6) | 0.004 (OR 5.42 IC 1.71-17.15) |

## Discussion

In this study, we assessed E. coli antibiotic resistance patterns and antibiotic use in a large cohort of pediatric patients. Overall, we found that the rate of resistance to amoxicillin/clavulanate, cephalosporins and aminoglycosides was low, and no isolates were resistant to carbapenems. Conversely, we found that aminoglycosides and cephalosporins were frequently used as empiric therapy, whereas targeted therapies aimed at sparing these classes of antibiotics once antibiograms were available have not always been established.

Unfortunately, National and International Surveillance Data (http://atlas.ecdc.europa.eu/public/index.aspx) usually report general data of antibiotic resistance, while pediatric-focused data are rarely available. Moreover, pediatric practice encompasses a large range of different groups of patients, both on a clinical and epidemiologic point of view. Newborns or young infants significantly differ among each other and from older children and adults. For this reason, our analyses add important data on antibiotic resistance patterns in the pediatric population.

The largest recently published European study estimating the burden of infections with antibiotic-resistant bacteria does not mention the pediatric population (14). While this study provided useful information for public health decision-makers, similar pediatric studies are not available. However, overall antibiotic use in children is significant and how this may have long-term impact on antibiotic resistance in adults is unknown, but theoretically an inappropriate antibiotic exposure in childhood could affect antibiotic resistance in adulthood (15).

Comparing our data with those published in Italy by the National Surveillance of Antibiotic Resistance (16), we observed a lower resistance of E. coli to the most used antibiotics. In particular, while 47.3% of E. coli strains are resistant to ampicillin, only 20% and 6.3% are resistant to amoxicillin/clavulanate and aminoglycosides respectively. Consequently, in our patients, given its oral availability, amoxicillin/clavulanic acid can be safely used as first-line antibiotic to treat E. coli infections, or as a first-line empiric agent for diseases for which E. coli is the most likely pathogen, such as urinary tract infections (17).

Antibiotic resistance to second-line drugs, such as cephalosporins, fluoroquinolones and carbapenems, was rare in our cohort.

Interestingly, children with devices and ICU admission were more likely to have infections from E. coli isolates resistant to cephalosporins and aminoglycosides. In these categories of patients, therefore, a high index of suspicion is necessary and early use or shift to other classes of antibiotics in case of worsening during therapy or severe/life-threatening infections should be considered.

We divided the patients into 4 subgroups based on age: infants (0-28 days), suckling (29-90 days), infants (91-1095 days) and child (> 1095 days), due to the different characteristics of the immune system (18). However, due to the low number of patients enrolled in the different age groups, we did not have statistically significant results. In fact, our research is a more clinical than epidemiological study and it is infrequent for a patient over 3 years of age to be admitted to hospital. We analyzed the differences between the antibiotic used before (empiric) and after the antibiogram results (targeted). Our study demonstrates that, in case of antibiotic resistance, the pediatrician generally adjusts the therapy by choosing a sensitive drug.

Instead, in case of empiric use of a second-line antibiotic (e.g., cephalosporin or carbapenem), we found that not always the attending physician switched to a sensitive first-line antibiotic (e.g., amoxicillin/clavulanate), thus suggesting that adherence to strict antimicrobial stewardship practices may be improved. The reasons for this behavior may be multiple, such as fear of change, custom, good response to the antibiotic used. However, it is important to continue programs that reduce the use of high-cost and broad-spectrum antibiotics (19), in order to fight antibiotic resistance, a worldwide cause of mortality and morbidity (20).

Our study has several limitations. First, the retrospective investigation may have been influenced by several methodological shortcomings. Surveillance studies should be carried out over longer periods of time and with a larger population. Previous antibiotic therapies, which this study could not evaluate due to

its retrospective nature, should also be investigated in the future. However, our cohort still provides a comprehensive overview of antibiotic susceptibility of E. coli in children and antibiotic usage.

In conclusion, the increasing resistance of E. coli in various countries over the past decades constitutes an increasing concern for the treatment of E. coli disease. In our region of central-southern Italy, although E. coli represents one of the most frequent local pathogens, there are not many data on its antibiotic resistance in pediatric age. Our paper, therefore, suggests empirical antibiotic therapy appropriate to the target areas for the study, as well as offers pediatric reference data for future monitoring of the development of resistance.

Our study showed that E. coli antibiotic resistance is relatively rare in our setting, and those patients with a history of ICU admission or the presence of devices are at higher risk. However, we also pointed out that adherence to antimicrobial practices was not always appropriate, highlighting the need for better education on this topic for pediatricians and neonatologists. Antimicrobial resistance is a major public health concern and a broader focus on the pediatric population should be considered. Epidemiological studies to better understand the burden of antibiotic resistance in children and the long-term impact of antibiotic exposure in childhood on future development of resistance are urgently needed.

**Conflict of Interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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