

# Future Challenges in Pediatric and Neonatal Sepsis: Emerging Pathogens and Antimicrobial Resistance

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## Abstract

The incidence of severe infections caused by multidrug-resistant (MDR) pathogens is currently rising worldwide, and increasing numbers of neonates and children with serious bloodstream infections due to resistant bacteria are being reported. Severe sepsis and septic shock due to gram-negative bacteria represent a significant cause of morbidity and mortality, and contribute to high health care costs. Antimicrobial resistance among Enterobacteriaceae represents a major problem in both health care-associated and community-acquired infections, with extended-spectrum  $\beta$ -lactamases (ESBLs) and carbapenem-resistant Enterobacteriaceae (CRE) now presenting the main threat. These infections in adult populations have been associated with poor clinical outcomes, but very limited data have been published so far about risk factors and clinical outcome of ESBL-associated and CRE sepsis in the pediatric population. The treatment of these infections in neonates and children is particularly challenging due to the limited number of available effective antimicrobials. Evidence-based use of new and older antibiotics based on both strategic and regulatory clinical trials is paramount to improve management of these severe infections in neonates and children.

## Keywords

- ▶ sepsis
- ▶ pediatrics
- ▶ neonate
- ▶ drug resistance
- ▶ bacterial
- ▶ gram-negative bacteria

## Introduction

### Global Antimicrobial Resistance in Children and Neonates

In 2013, an estimated 6.3 million live-born children worldwide died before the age of 5 years. Among them, nearly half (51.8%) died of infectious causes, with sepsis accounting for 15% of overall under 5-year infection-related childhood deaths.<sup>1</sup>

The dramatic increase in antimicrobial resistance (AMR) among key human pathogens is likely to continue to emerge as one of the main global health care threats in the 21st century, requiring urgent actions at both national and international levels.<sup>2</sup> Deaths attributable to AMR are assumed to be due to delayed diagnosis and inappropriate treatment. The incidence of severe infection caused by multidrug-resistant (MDR) pathogens is currently rising not only in low-middle income but also in highly industrialized countries.<sup>3</sup>

Increasing numbers of neonates and children with serious bacterial infections due to resistant bacteria associated with considerable morbidity and mortality are being reported, and bloodstream infections (BSIs) are one of the most common serious bacterial infections in hospitalized children.<sup>4,5</sup> However, very limited data have been published so far on the global impact of AMR in childhood.

MDR gram-positive pathogens, such as Methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, and penicillin-non-susceptible *Streptococcus pneumoniae*, are responsible for community-acquired and hospital-associated infections, and are a recognized public health threat.<sup>6</sup> However, the spread of these severe infections is now being contained by the development of new antibiotics, improvement of infection control measures, and implementation of vaccine programs.<sup>7</sup>

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Conversely, AMR is still a major concern in gram-negative bacteria (GNB), with a global rise in the reported incidence of infections caused by MDR-GNB and very limited therapeutic options.<sup>8</sup> Several studies report GNB accounting for 30 to 55% of all BSIs detected in children in the past 20 years, depending on the age group, patient population, and geographical region.<sup>9,10</sup> Hospital data from low-middle income countries show that alarming proportions of pathogens causing infections in neonates < 28 days of age are resistant to the World Health Organization first-line recommended treatment regimen of ampicillin and gentamicin (43%) and to the second-line treatment with third-generation cephalosporins (44%).<sup>7</sup> High rates of resistance have also been reported in early-onset (presumably maternally acquired) neonatal infections.<sup>11</sup>

The treatment of these infections in neonates and children is particularly challenging due to the limited number of available effective antimicrobials and the pipeline for novel antibiotics in this population is virtually empty.

## Emerging Pathogens in Children

### Extended-Spectrum $\beta$ -Lactamase-Producing Enterobacteriaceae

Antimicrobial resistance among the Enterobacteriaceae represents a major problem in both health care-associated and community-acquired infections. The extended-spectrum  $\beta$ -lactamases (ESBLs), first reported in Germany in 1983, are the result of a single nucleotide polymorphism in the *blaSHV* gene producing a family of enzymes able to hydrolyze the  $\beta$ -lactam ring.<sup>12</sup>

There are many phenotypic and genetic variants among  $\beta$ -lactamases, all leading to the inactivation of  $\beta$ -lactam anti-

biotics, such as early generation and extended-spectrum (e.g., ceftriaxone and ceftazidime) cephalosporins, monobactams, and penicillins.<sup>13</sup> ESBLs are inhibited by  $\beta$ -lactam inhibitors (clavulanic acid, tazobactam, and sulbactam).<sup>14</sup>

$\beta$ -lactamase genes in Enterobacteriaceae are mostly carried on mobile genetic elements, such as transposons or plasmids, frequently harboring other resistance genes.<sup>15</sup> These coresistance factors confer them associated-resistance to other antibiotic classes, such as fluoroquinolones, aminoglycosides, and trimethoprim-sulfamethoxazole, limiting the choice of alternative therapies.<sup>16</sup>

The most commonly encountered ESBLs are members of the SHV, TEM, and CTX-M (Ambler class A) families (**►Table 1**).<sup>13,17</sup> In 2010, the Clinical and Laboratory Standards Institute (CLSI) updated the guideline for phenotypic identification of ESBL-producing Enterobacteriaceae by lowering minimum inhibitory concentration (MIC) breakpoints, with MICs for cefotaxime and ceftriaxone now reported as resistant at  $\geq 4 \mu\text{g/mL}$ .<sup>18</sup> This reduction resulted in more isolates now defined as resistant to  $\beta$ -lactams, and therefore a relative increase in the rate of  $\beta$ -lactam-resistant infections reported.

Our understanding of the molecular epidemiology of ESBLs in Enterobacteriaceae has dramatically improved in the past 20 years, largely because of the advent of next-generation sequencing methods. The spread of CTX-M-type ESBLs, and particularly of *Escherichia coli* sequence type (ST) 131 bearing CTX-M-15, has been reported as particularly worrying because of its increased activity against cefotaxime. Furthermore, although in the last decade this highly resistant strain has been almost exclusively reported in the hospital setting, increasing numbers of cases are now being reported as community-acquired.<sup>19</sup>

**Table 1** Summary of resistance mechanisms, phenotypes, and therapeutic options for clinically important  $\beta$ -lactamases according to Ambler classification

Ambler classifications	Resistance mechanism	Representative enzymes	Genetic basis	Relevant organisms	Substrates	Therapeutic options
Class A	ESBLs	TEM, SHV, CTX-M	Plasmid	<i>Escherichia coli</i> , <i>Klebsiella spp.</i> , <i>Proteus mirabilis</i>	Penicillins, 3rd gen-cephalosporins	Carbapenems
	Carbapenemases	KPC	Plasmid	<i>Klebsiella pneumoniae</i> , <i>E. coli</i> , <i>Klebsiella oxytoca</i> , <i>Serratia marcescens</i> , <i>Enterobacter spp.</i> , <i>Citrobacter freundii</i>	All $\beta$ -lactams	Polymyxins, tigecycline
Class B	Carbapenemases, metallo- $\beta$ -lactamases	VIM, IMP, NDM-1	Plasmid	<i>K. pneumoniae</i> , <i>E. coli</i> , <i>K. oxytoca</i> , <i>S. marcescens</i> , <i>Enterobacter spp.</i> , <i>C. freundii</i>	All $\beta$ -lactams, except monobactams	Polymyxins, tigecycline, aztreonam + avibactam
Class C	Cephalosporinases	AmpC	Chromosomal	<i>K. pneumoniae</i> , <i>E. coli</i> , <i>Enterobacter spp.</i> , <i>Salmonella enteritidis</i> , <i>C. freundii</i> , <i>S. marcescens</i>	Cephamecins, 3rd gen-cephalosporins	Polymyxins, tigecycline
Class D	Carbapenemases	OXA	Plasmid	<i>Acinetobacter baumannii</i> , <i>Pseudomonas aeruginosa</i> , <i>E. coli</i> , <i>K. pneumoniae</i> , <i>P. mirabilis</i> , <i>C. freundii</i>	All $\beta$ -lactams	Polymyxins, tigecycline

Abbreviations: ESBL, extended-spectrum  $\beta$ -lactamase; IMP, Inosine-5'-monophosphate; KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo- $\beta$ -lactamase; VIM, verona integron-encoded metallo- $\beta$ -lactamase.

### Global Epidemiology of Extended-Spectrum $\beta$ -Lactamase in Children

Several studies have been conducted between 1999 and 2014 in many regions of the world on the prevalence of both community- and hospital-acquired invasive ESBL infections in children. The largest study conducted in the United States on more than 300,000 pediatric clinical isolates from 1999 to 2011 showed that the number of ESBL-producing Enterobacteriaceae more than tripled in 10-year time, rising from 0.28% of all *E. coli* and *Klebsiella pneumoniae* to 0.92% in 2010 to 2011.<sup>20</sup>

European data on 3,500 pediatric clinical isolates from the SENTRY study identified rates of ESBL production in 5.4% of *E. coli* and 24% of *Klebsiella* isolates.<sup>21</sup> Studies on the molecular epidemiology of ESBL-producing isolates in European children are limited to single-center cohorts. However, these small studies showed a similar trend to the spread of CTX-M type as has been globally observed.<sup>12</sup>

In Asian countries, the highest rate of ESBL-producing isolates in children has been reported in India.<sup>22</sup> In a retrospective analysis, 61% of 75 cases of GN neonatal sepsis were due to ESBL-producing strains. Other countries, like China and South Korea, have also reported increasing rates of ESBL invasive infections in children over the last decade.<sup>23,24</sup>

The first study on CTX-M-15-type emergence in African children was published in Tanzania in 2005 where 14% of 113 children with BSIs had an ESBL-positive isolate.<sup>25</sup>

### Risk Factors and Clinical Impact on Children

Risk factors for ESBL infections have been well documented in adult populations. Prior hospitalization, prolonged length of stay, antibiotic use, and indwelling devices have been reported as the main determinants.<sup>15</sup> Infections due to ESBL-producing Enterobacteriaceae in adults have been shown to have a significant impact on patient outcomes, resulting in prolonged hospitalization, high economic burden, and increased mortality rates.<sup>12</sup> However, there are few studies describing their clinical epidemiology and impact in pediatric populations outside of outbreaks.<sup>15,26,27</sup>

The early reports in children described mostly single-unit outbreaks in pediatric and neonatal intensive care units (PICUs and NICUs). In this context, *K. pneumoniae* was the most frequently implicated pathogen, and suboptimal hygiene standards, including understaffing, the most frequent risk factor for outbreaks.<sup>28</sup> In non-outbreak settings, health care-related risk factors independently associated with ESBL colonization and infection in neonates included prematurity, low weight at birth, prolonged hospitalization, invasive devices, and previous antibiotic use.<sup>12</sup>

The majority of studies performed in children beyond the neonatal period are case-control or single-center studies.<sup>26,27</sup> Recent health care exposure, gastrointestinal comorbidities, and underlying neurological conditions have been recently identified as potential risk factors in a two-center case-case-control study in children from Illinois aged 0 to 17 years.<sup>15</sup>

Like in adults, ESBL GN bacterial infections in children have been associated with negative outcomes, such as pro-

longed length of stay, secondary complications, and increased mortality, with a fatality rate ranging from 27 to 71%.<sup>23,25,27,29</sup> In particular, the clonal CTX-M *E. coli* often express extraintestinal pathogenic virulence factors that have been associated with severe systemic infections.<sup>30</sup>

### Carbapenem-Resistant Enterobacteriaceae

Due to the spread of highly resistant ESBL-expressing organisms, the use of carbapenems, such as ertapenem, meropenem, and imipenem, has increased in many clinical settings in the last 10 years. As a plausible consequence, carbapenem-resistant Enterobacteriaceae (CRE) have appeared and started to spread worldwide.<sup>31</sup> *K. pneumoniae* is most commonly reported as showing resistance to carbapenems, followed by *Enterobacter spp.*<sup>32</sup>

As surveillance and diagnostic methods for CRE detection have improved in the last decade, the rapid spread of these highly resistant organisms at a global level has become increasingly evident. Moreover, the recent emergence of carbapenemases carried on mobile genetic elements, such as transposons or plasmids, often harboring additional resistance genes that confer resistance to multiple classes of antibiotics, favored an efficient person-to-person and species-to-species spread.<sup>33</sup> Carbapenem resistance can result from the acquisition of various plasmid or chromosomal genes. According to the responsible resistance determinant, the dynamic of spread and the associated-resistance phenotype may be variable.<sup>34</sup>

The effects of these increasing rates of carbapenem resistance among Enterobacteriaceae need to be studied comprehensively in terms of both clinical features and molecular epidemiology. Unfortunately, defining the extent of the global CRE epidemic is challenging for several reasons, including conflicting definitions of carbapenem resistance, methodological limitations in distinguishing carbapenemase production from other resistance mechanisms, and incomplete reporting of CRE isolates worldwide.<sup>35</sup>

### Mechanisms of Carbapenem Resistance

Resistance to carbapenems can be the result of enzymatic or nonenzymatic mechanisms. Enzymatic mechanisms imply the production of carbapenemases, enzymes able to break down the  $\beta$ -lactam ring of carbapenems. Bacteria that produce carbapenemases are also able to hydrolyze other  $\beta$ -lactam antibiotics including penicillins, cephalosporins, and monobactams.<sup>33</sup> Nonenzymatic mechanisms involve the production of ESBLs and/or AmpC cephalosporinases together with reduced membrane permeability due to alterations or loss of porins, a family of proteins that allow the diffusion of many substrates, including antibiotics, across the bacterial membrane.<sup>35</sup> Deletions or mutations of porin genes commonly cause resistance in GNB.<sup>33</sup>

Carbapenemase-producing Enterobacteriaceae (CPE) are considered to be responsible for the rapid global spread of CRE, favored by the easy transfer of mobile genetic elements encoding for carbapenemase genes. In contrast, reduced membrane permeability is frequently associated with a loss in fitness and reduced transmissibility.<sup>36</sup> Considering

this, from the epidemiological point of view, it is very important to distinguish CPE from other non-CP CRE, since for the latter routine contact precautions are generally recommended, while the former may require more intensive infections control interventions, such as targeted active surveillance.<sup>37</sup>

#### Definition and Classification of Carbapenemases

As for ESBL-producing Enterobacteriaceae, in 2010, the CLSI updated the guideline for phenotypic identification of CRE. The result was a decrease in the MIC breakpoint for imipenem and meropenem from  $\leq 4$  to  $\leq 1$   $\mu\text{g/mL}$  and from  $\leq 2$  to  $\leq 0.5$   $\mu\text{g/mL}$  for ertapenem.<sup>18</sup> As mentioned above, this reduction increased sensitivity, but also led to a higher proportion of CRE reported.

In the United States, in 2015, the Centers for Disease Control and Prevention (CDC) revised the definition for CRE as organisms resistant to imipenem, meropenem, doripenem, or ertapenem, or documentation of carbapenemase production (CPE).<sup>38</sup> Compared with the previous definition, this increased the sensitivity by including ertapenem resistance, as a small subset of *K. pneumoniae* carbapenemase (KPC)-producing organisms are susceptible to all carbapenems apart from ertapenem. Additionally, the new definition does not require anymore that the isolate exhibits resistance to all third-generation cephalosporins to be defined as CRE. This is to account for some OXA-48-type carbapenemases that can be susceptible to third-generation cephalosporins.<sup>39</sup>

Molecular classification of carbapenemases includes Ambler class A, B, and D, distinguished by the site of the hydrolytic mechanism (–Table 1).<sup>36</sup> Whereas class A and D necessitate serine at their active site, class B carbapenemases, the metallo- $\beta$ -lactamases (MBLs), are zinc dependent.<sup>33</sup> Class A include chromosomally as well as plasmid-encoded carbapenemases, such as KPC, IMI, SME, GES, and NMC-A enzymes. Among them, the KPC gene, *blaKPC*, most commonly found on *K. pneumoniae*, is associated with a mobile transposon Tn4401 particularly adept at clonal expansion, such as ST 258, largely responsible for the epidemiologic success of KPC-producing organisms.<sup>36,40</sup> Class B carbapenemases include Verona integron-encoded MBL (VIM), inosine-5'-monophosphate, and the recently added New Delhi MBL (NDM) genes.<sup>41</sup> Lastly, class D OXA-carbapenemases, so-called because of its ability to hydrolyze oxacillin, are commonly found in *Pseudomonas aeruginosa* and *Acinetobacter spp.*, but have been reported also in Enterobacteriaceae.<sup>42</sup>

#### Global and Molecular Epidemiology of Carbapenem-Resistant Enterobacteriaceae in Children

Noteworthy, published data show that CPE are no longer confined to the hospital environment, but are currently reported also in the community and among livestock.<sup>43,44</sup>

Several studies have been published reporting on the ongoing spread of CRE worldwide. After the worldwide dissemination of KPC producers, it seems that OXA-48 and NDM-positive strains are now expanding globally.<sup>45</sup> Moreover, although *K. pneumoniae* and *E. coli* still remain the

predominant strains carrying these genes, the *blaKPC*, *blaNDM*, and *blaOXA-48* gene variants are now being reported in a wide variety of Enterobacteriaceae.<sup>43</sup> Conversely, even if reported in several enterobacterial species, the *blaVIM* and *blaIMP* genes seem to be still confined to their original foci (Mediterranean and Far East regions, respectively).<sup>45</sup>

KPC-producing strains account for up to 80% of carbapenem resistance in the United States and an increasing proportion of CRE worldwide. The United States, Israel, Greece, Poland, Italy, China, Columbia, Brazil, and Argentina represent highly endemic areas.<sup>46</sup> NDM-1, endemic to the Indian region where it accounts for nearly half of isolated CRE, has now been also identified across Europe, the rest of Asia and Africa, as well as in the United States, often as a result of individuals traveling in endemic regions.<sup>36</sup> Ambler class D carbapenemases, such as OXA-48, are most commonly identified in *Acinetobacter spp.* However, the OXA-48 carbapenemase has now been increasingly reported in *K. pneumoniae* and *E. coli* isolates. This CRE was originally reported in the Middle East and North Africa, and is still endemic in Turkey. Nevertheless, it has now being reported in several regions worldwide, including the United States.<sup>41</sup> Considering the increase of international migration and medical tourism, it is likely that the geographic distribution of the various carbapenemases genes will be widespread soon.<sup>35</sup>

Despite this increased global attention to CRE, limited data have been published so far on the epidemiology of these severe infections in the pediatric population. CRE in children are still isolated infrequently, and currently available data are largely limited to case reports, small case series, and few narrative reviews. Available data, however, suggest that CRE epidemiology, risk factors, and outcomes in children are broadly comparable with the trends observed in adults.<sup>35</sup> In the United States, a recently published study reported that the frequency of carbapenem resistance increased from 0% in 1999 to 2000 to 0.47% in 2010 to 2011 among Enterobacteriaceae in children.<sup>47</sup> The frequency of meropenem-resistant *K. pneumoniae* and *E. coli* pediatric isolates is now being reported as approximately 4 and < 1% worldwide.<sup>48</sup> Nosocomial outbreaks have been reported in NICUs and PICUs, and the geographic distribution is generally comparable with the one reported in adults.<sup>33</sup>

#### Risk Factors and Clinical Impact on Children

Infections due to CRE in adult populations have been associated with poor clinical outcomes, with fatality rates as high as 65% reported in some populations despite antibiotic therapy.<sup>49</sup> However, the real impact of risk factors for CRE infections has not been defined completely, with conflicting results reported so far likely due to the high heterogeneity in study populations and frequent methodological limitations.<sup>50</sup> Long-term exposure to health care facilities have been recognized as a significant risk factor for CRE, as well as previous antibiotic exposure, indwelling medical devices, admission to intensive care units, solid organ transplant, and renal failure.<sup>51</sup>

Far less is known about the risk factors for CRE in children. Pediatric long-term care facilities have been reported as a significant risk factor for CRE similarly to the situation in adults.<sup>52</sup> Other risk factors at a patient level in children include underlying diseases, invasive devices, prolonged hospitalizations, previous use of antibiotics, neonatal age, and travel from endemic regions.<sup>35</sup> Although mortality rates in children with CRE have been reported as very variable, neonates seem to be the group most at risk.<sup>53,54</sup>

## Managing Severe Sepsis in Children

Severe sepsis and septic shock due to GNB represent a significant cause of morbidity and mortality, and contribute to high health care costs.<sup>8</sup> Clinical presentation varies depending on the age of the child, with neonates and infants usually presenting with nonspecific signs and symptoms and older children often presenting with features of a systemic inflammatory response syndrome.<sup>55,56</sup> In all age groups, if not promptly treated, sepsis can rapidly progress and the patient may develop severe sepsis or septic shock.

Proper management of sepsis in children first requires a timely recognition. Prompt diagnosis and appropriate treatment represent the main determinants of patients' outcome.<sup>56</sup> However, these interventions must be made before a definitive etiological diagnosis is available.<sup>57</sup> Empiric antibiotic therapy for suspected sepsis should be initiated with broad spectrum antibiotics according to age group and local epidemiology, and administered in doses able to achieve a bactericidal concentration in the blood. Once a pathogen has been identified, the antibiotic regimen should be narrowed and targeted to the isolated bacteria.

The global increase in the reporting of AMR among pediatric isolates is a crucial issue, and the clinical impact of these MDR organisms is now significant in many countries, both resource-rich and resource-poor.<sup>3</sup> This situation has several clinical implications because it exposes children to higher risk of treatment failure and it backs clinicians into an "escalation corner."

Noteworthy, several hemodynamic and metabolic changes occur in septic children who are critically ill, such as higher cardiac output and glomerular hyperfiltration. These alterations significantly affect the pharmacokinetic and pharmacodynamics parameters of antibiotics, and may be responsible for subtherapeutic concentrations therefore worsening clinical outcomes.<sup>58</sup> Moreover, other therapeutic interventions, like hemodynamically active drugs, mechanical ventilation, or hemodialysis, may potentially increase the volume of distribution and then alter drug's clearance.<sup>59</sup>

## Treating Multidrug-Resistant Gram-Negative Infections in Children

Children are particularly at risk for MDR-Enterobacteriaceae due to the lack of broad-spectrum antibiotics approved for pediatric use. Data reporting the use of  $\beta$ -lactam- $\beta$ -lactamase inhibitors (BL/BLIs) for the treatment of ESBL infections is still inconsistent, due to the fact that many organisms are

able to produce multiple ESBLs simultaneously, therefore reducing the effectiveness of the inhibitor.<sup>19</sup> The pediatric literature is currently limited to small observational studies comparing treatment with BL/BLIs and carbapenems in neonates with ESBL-producing Enterobacteriaceae with no difference in clinical outcomes.<sup>60</sup> However, carbapenems showed excellent in vitro activity against ESBL-producing organisms and are currently considered the treatment of choice for invasive ESBL infections in children.<sup>61</sup>

Data on optimal treatment regimens for CRE infections are lacking due to the absence of randomized trials evaluating the efficacy of different therapeutic approaches. Existing recommendations are based on single case reports, small case series, and highly heterogeneous cohort studies.<sup>62</sup> Combination therapy with at least two agents seems to significantly reduce mortality compared with single agents.<sup>45</sup> However, these data are not consistent enough to recommend a particular combination treatment, and antibiotic regimens should be driven by local epidemiology and clinical source of infection.<sup>35</sup>

The vast majority of CPE isolates are resistant to the most used antibiotic classes,  $\beta$ -lactams and aminoglycosides. Colistin and tigecycline have become the first-line options, even if the increasing prevalence of CPE strains exhibiting reduced susceptibility to these drugs is concerning.<sup>45</sup> Moreover, colistin is associated with significant renal toxicity, with rates of acute kidney injury reported in around 40 to 60% of adult patients.<sup>35</sup> Mortality has been reported to be higher in adult patients with CRE infections treated with colistin monotherapy compared with those receiving colistin-containing combinations.<sup>63</sup>

Few studies have been published so far about the use of colistin in pediatric patients. Furthermore, none of them were specifically focused on children with infections caused by CRE. Some pharmacokinetic studies have been conducted in children aged 8 to 11 years treated with tigecycline for serious bacterial infections, but phase III clinical trials are still necessary to evaluate its efficacy and safety profile in children of different age.<sup>64</sup> Older drugs, such as fosfomycin, are now being reconsidered for the treatment of urinary tract infections especially due to KPC. However, the appropriate dosing of intravenous fosfomycin in children still needs to be defined.<sup>65</sup>

As of June 2018, 42 antibiotics are listed on the Pew Charitable Trusts Antibiotic Pipeline.<sup>66</sup> Some of them, such as meropenem + vaborbactam and plazomicin, specifically target infections caused by CRE.<sup>67</sup> At the moment, there is one study currently ongoing on the use of meropenem + vaborbactam in pediatric subjects with serious bacterial infections.<sup>68</sup>

Prevention of transmission and definition of highest-risk patients, together with targeted surveillance programs, seem to be the major determinants of CRE spread control among children. At the same time, it is necessary that high-quality clinical trials of both new and old antibiotics will be selectively conducted in the pediatric population to allow the definition of the currently best available treatment and doses.

To optimize available drugs while limiting the spread of AMR, effective antimicrobial stewardship programs are necessary. Empiric broad-spectrum antibiotics for patients known to be at risk of MDR GN infections should be followed by timely de-escalation and efforts to minimize the duration of antimicrobial treatment, whenever possible.<sup>69</sup>

## Unanswered Questions and Future Perspectives

Many questions are still unanswered about significant determinants and real impact of CRE infections in children. Further targeted studies need to be conducted selectively in the pediatric population, even if the low prevalence of these infections can hamper the quality of results.

The correlation between genotype, antimicrobial susceptibility profile, and clinical outcome is still debated, and a direct association between resistance genes and adverse clinical outcome has not been clearly demonstrated. Clarifying this correlation will provide evidence to define particularly virulent pathogens as well as virulence determinants, and will make it possible to define if resistant phenotype or MDR genotype (or both) are the major determinants of patients' outcome. This will allow setting up targeted surveillance programs and may be used for selecting anti-infective therapies and improve infection prevention and control practices.

Patients at risk may exhibit gut colonization by ESBL-producing GNB and CRE that, under certain conditions, can cause infections by gaining access to usually sterile body sites like bladder, lungs, or bloodstream. However, the actual mechanisms leading from colonization to infection have not been clarified yet. By demonstrating the actual correlation between highly resistant GNB bowel colonization and development of infection, it will be possible to define the best strategies for infection prevention and control (e.g., through cohorting of patients during hospital outbreaks) and the appropriate antibiotic treatment (by selecting babies really needing broad-spectrum antibiotics at individual patient level).<sup>70</sup>

Targeted surveillance programs collecting neonatal/pediatric AMR data and clinical outcomes are critical to design properly targeted interventions. Future studies need to focus on defining the global burden of invasive MDR GN infections in children and neonates and to define the impact of associated risk factors on patients' outcome.

Some initiatives have already been put in place to gain evidence on the extent of this issue among children, and to improve current knowledge about these life-threatening infections. The Innovative Medicines Initiative-funded project EURECA (*EUropean prospective cohort study on Enterobacteriaceae showing REsistance to CARbapenems*) is a prospective, multicenter, observational study currently ongoing in 50 hospitals in South and East Europe aiming to collect high-quality data about clinical management, risk factors, and outcome determinants of MDR GN severe infections in adults and children.<sup>71</sup>

The *Multi-Site Gram-Negative Bacilli Surveillance Initiative* (MuGSI) is part of the CDC's Emerging Infections Program

(EIP) Healthcare-Associated Infections Community Interface (HAIC) activity aiming to evaluate the population-based incidence of carbapenem resistance in *Enterobacteriaceae* and *Acinetobacter baumannii*, and describe resistance mechanisms among CRE.<sup>72</sup>

The *Global Antimicrobial Resistance, Prescribing, and Efficacy among Neonates and Children* (GARPEC) project is a global surveillance network specifically focused on the collection of data on neonatal and pediatric antimicrobial prescribing and resistance by using a clinically based surveillance platform.<sup>73</sup>

Studies on MDR GN severe infections in neonates and children are limited. Moreover, the few available studies often focus on epidemiological aspects, without proper investigation of infection mechanisms and outcome determinants. Consistent surveillance systems are urgently needed to harmonize susceptibility testing methods, improve alert for emerging resistance mechanisms, compare resistance levels, and improve the control of AMR in the pediatric population. Evidence-based use of new and older antibiotics through both strategic and regulatory clinical trials is mandatory to define the best available treatment and improve management of these severe infections in neonates and children.

### Conflict of Interest

None declared.

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