PEDIATRICS INTERNATIONAL Official Journal of the Japan Pediatric Society

Pediatrics International (2016) **58**, 338–346 doi: 10.1111/ped.12845

Original Article

Pediatric extended spectrum β-lactamase infection: Community-acquired infection and treatment options

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Abstract ***Background:*** Infection caused by extended spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae* in pediatric patients has been increasing and spreading to the community, compromising the options for effective antibiotics. This retrospective study was conducted to identify which antibiotics ESBL-producing *Enterobacteriaceae* remain susceptible to. In addition, the prevalence of community-acquired infection caused by these organisms, and the possibility of association between these organisms and septic shock, were explored.

Methods: Antibiotic susceptibility of ESBL-producing and non-ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* strains isolated from pediatric patients were reviewed to determine the rates of susceptibility to various antibiotics. A chart review was performed to clarify the prevalence of community-acquired infection and the severity.

Results: Of 849 strains analyzed, 40% were ESBL positive. Apart from cephalosporins, ESBL-producing strains were also less likely to be susceptible to other antibiotics, such as quinolones, gentamicin, netilmicin, and cotrimoxazole, more than 90% of which were still susceptible to amikacin, carbapenems, colistin, and tigecycline. Around 20% of community-acquired infections in the present study were caused by ESBL-producing strains. ESBL-producing strains found in the community were more likely to be susceptible to gentamicin, netilmicin, and cefepime than those found in hospital. Infection caused by ESBL-producing strains was not significantly associated with septic shock.

Conclusion: The increase in infection caused by ESBL-producing *Enterobacteriaceae* limits the availability of effective antibiotics. Given that carbapenems are necessary for treating serious infections, amikacin, cefepime, and piperacillin/tazobactam are possible options for consolidative therapy or for non-serious infection.

Key words β-lactamase, community-acquired infection, drug resistance, *Enterobacteriaceae*, prevalence.

The emergence of extended spectrum β-lactamase (ESBL)-producing organisms is a growing problem in general pediatric practice.[1] This limits the options of previously effective antibiotics, resulting in poorer outcome.[2] Given that the production of ESBL confers resistance to most cephalosporins, the choice of antibiotics used in infection caused by these organisms relies mostly upon carbapenems.[3,4] Frequent or inappropriate use of these drugs, however, poses the risk of resistance development. Many studies have shown that other antibiotic classes show promise in the treatment of infection caused by ESBL-producing organisms.[5] It is therefore important to know which antibiotics remain active against these organisms.

There has been accumulating evidence showing that ESBL-producing organisms have also emerged in community settings.[6–9] This would have an impact on the decision on which empirical antibiotics should be used in community-acquired infections. Information on the prevalence of pediatric infections caused by ESBL-producing organisms in the community, and antibiotic susceptibility, remains scarce. Another issue to be addressed is whether ESBL-producing organisms are associated with more severe presentations, such as septic shock. If this is the case, infection caused by these organisms will not only create difficulties in selection of appropriate antibiotics but also in supportive care. The aims of this study were the following: (i) to determine the prevalence of infections caused by ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* in pediatric patients, in particular community-acquired infection; (ii) to compare rates of antibiotic susceptibility between non-ESBL- and ESBL-producing organisms using the new criteria from the Clinical and Laboratory Standards Institute (CLSI 2014)[10] to indicate treatment options; and (iii) to compare the severity of infections at presentation caused by non-ESBL- and ESBL-producing organisms, using septic shock as the surrogate marker.

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Received 13 July 2015; revised 2 September 2015; accepted 21 October 2015.

Methods

Study design and patients

This study was performed at the Department of Pediatrics, Ramathibodi Hospital, a tertiary care university hospital in Bangkok. The Department of Pediatrics services 150 inpatient

beds, and 200 outpatients daily. This study was performed in a 20 month period between January 2012 and October 2013, and was approved by Ramathibodi Hospital Ethics Committee.

The positive culture records for *E. coli* and *K. pneumoniae* from patients aged 0–15 years old were obtained from the microbiology laboratory. They contained information regarding drug susceptibility, minimum inhibitory concentration (MIC), the presence or absence of ESBL, and sites from which samples were obtained. Samples were considered to be repeated when collected from the same episode of infection and drug susceptibility patterns between those samples were the same, or when the MIC difference was < twofold for tested drugs. Patient demographic data, site of infection, severity of infection, and treatment information in each episode of infection were obtained from electronic chart review.

Definitions

Colonization episode was defined as the presence of organisms that did not cause any adverse symptoms and there was no specific treatment, or the treatment was discontinued <48 h after detection of the organisms.[11] An episode in which the attending physicians regarded the recovered organisms to be responsible for the patient's symptoms, and decided to treat, was designated as the true infection episode. A community-acquired episode was defined as an episode in which cultures were obtained at the time of admission or <48 h after hospitalization, in patients who had not been hospitalized or stayed in long-term care facility <1 year before culture collection, and who did not have any permanent indwelling catheters or percutaneous medical devices.[12] For infection episodes in patients <1 year old, community-acquired episodes were defined as hospital nursery stay <48 h following the delivery period, no permanent indwelling catheters, and not being admitted to hospital before the episode of infection began. Shock episode was defined as poor tissue perfusion or hypotension at first presentation before the results of cultures were available. If patients had more than one episode of true infection, there was a culture-negative interval separating each episode.

In vitro susceptibility and ESBL detection

The MIC for each sample was determined using the microbroth dilution technique (Sensititre, West Sussex, UK). The presence of ESBL was tested using the disk diffusion method: a ≥5 mm increase in a zone diameter for cefotaxime or ceftazidime in combination with clavulanic acid versus when tested alone confirmed ESBL-producing organisms. The interpretation of susceptibility was based on CLSI 2014 criteria.[10]

Statistical analysis

Comparison of proportions was performed using the chi-squared or Fisher exact test in SPSS version 16.0 (New York, USA). Statistically significant difference was defined as $P < 0.05$.

Given that one patient can contribute to more than one episode of infection, risk factors associated with shock were analyzed on multi-level logistic regression analysis using STATA version 13.1 (Texas, USA). The presence of ESBL was the main variable considered in multivariate logistic regression analysis. Presence of ESBL-producing organisms was analyzed for the statistically significant factors from the univariate analysis ($P < 0.1$). Risk factors with $P < 0.05$ on multivariate analysis were considered to be independent risk factors associated with septic shock.

Results

Sample selection

Of 1448 samples obtained during the defined period, susceptibility tests were performed on 1035. After repeated samples were excluded, there were 849 samples from 503 patients. The number of samples in each individual patient varied from 1–11 samples. Approximately 70% of the patients had only one sample, and approximately 90% of the patients had no more than 3 samples.

After the samples considered to cause colonization and those in which the clinical data could not be traced were excluded, there were 565 strains of organisms from 461 episodes, representing true infections from 349 patients. There were 277 patients (79%) who contributed to only one episode, and 52, eight, seven, and three patients who contributed to two, three, four, and five episodes, respectively. One patient contributed to six and one contributed to seven episodes. These two patients had genitourinary anomalies and recurrent urinary tract infection. The number of total strains and true infection episodes is summarized in Figure 1.

The demographic data for all 461 episodes are listed in Table 1. Around 45% of total episodes occurred in patients aged <1 year old. One-fourth of total episodes occurred in immunocompromised patients. Patients presenting with shock accounted for 105 episodes. The data regarding sites of infection are summarized in Tables 1,2. Urinary tract infection was the most common source of infection in the study, while bacteremia was the second most common. A total of 162 out of 461 episodes (35%) had ESBL-producing organisms as the causative agent.

There were 145 *E. coli* strains causing community-acquired infections, 31 of which (21.4%) were ESBL-producing strains. Only 37 *K. pneumoniae* strains causing community-acquired infection were identified in the present study, four of which (10.8%) were ESBL-producing strains. Thus, the prevalence of community-acquired ESBL-producing organisms in the present study was 19.2% (95%CI: 13.8–25.7). While most ESBL-producing organisms from the community were isolated from the genitourinary tract, two were isolated from blood and the other two were from wound (Table 2). Of note, immunocompromised patients had the highest prevalence of community-acquired ESBL infection compared with other groups (Table S1).

Presence of shock was used as a marker of severe episodes of infection in this study. Septic shock presented in 9.8% (95%CI: 7.2–12.8) of all infection episodes. Presence of ESBL did not confer a risk of developing shock, although the presence of ESBL-producing *K. pneumoniae* strains was significantly associated with shock on univariate analysis. Multivariate analysis was performed to determine whether the presence of ESBL strains or the presence of ESBL-producing *K. pneumoniae* strains was independently associated with shock, neither of which were. Only the presence of bacteremia and male sex remained associated with septic shock (Tables 3,4).

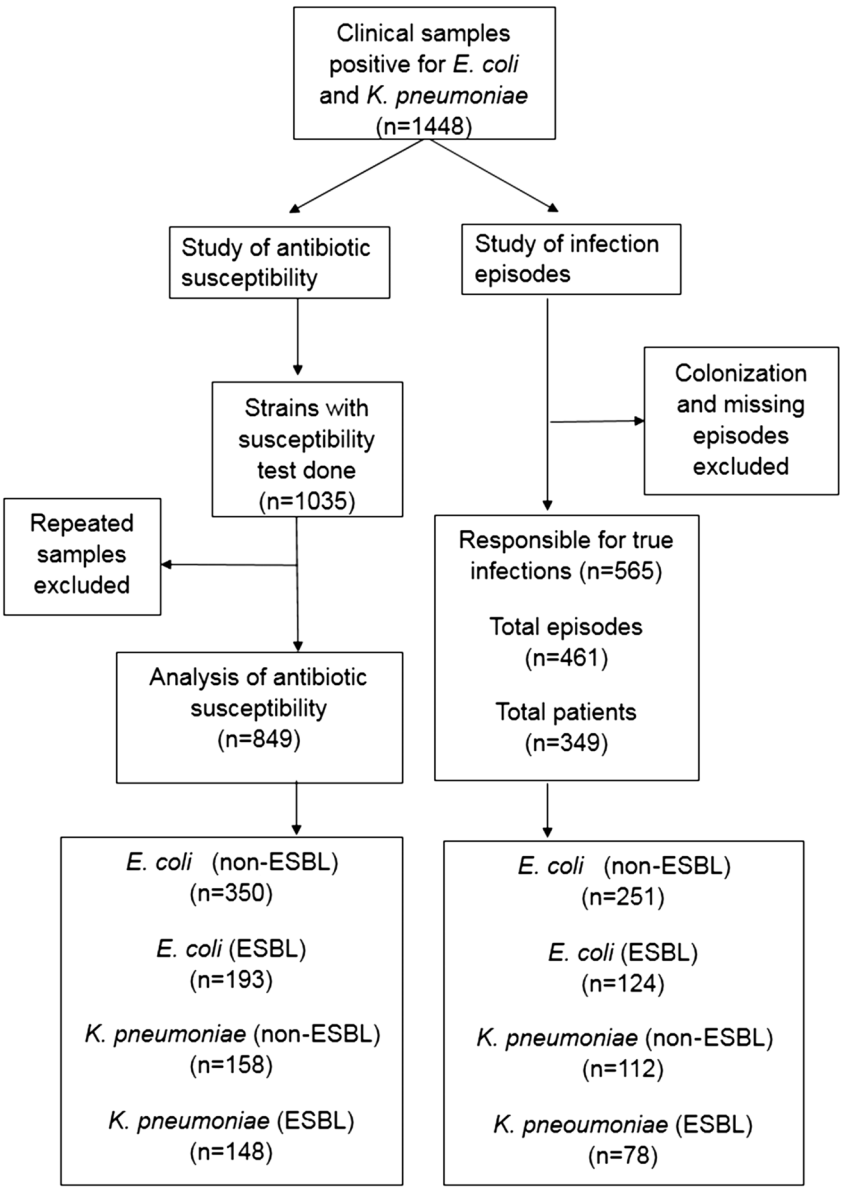

Fig. 1 Flowchart of the retrospective study: antibiotic susceptibility analysis (left), and true infection episode analysis (right). ESBL, extended spectrum β-lactamase.

Antibiotic susceptibility

Overall, 40% (341/849) of total strains (including those causing colonization and true infections) in the present study were ESBL positive, while 36% (193/543) of *E. coli* strains and 48% (148/306) of *K. pneumoniae* strains were ESBL producing. Table 5 lists the rates of *E. coli* and *K. pneumoniae* strains susceptible to antibiotics tested. ESBL production generally confers resistance to β-lactam antibiotics, especially cephalosporins, but ESBL strains of both organisms also had lower rates of susceptibility to amoxicillin/clavulanic acid, quinolones, gentamicin, netilmicin, and cotrimoxazole compared with their counterpart non-ESBL strains. The rates of susceptibility to these drugs in ESBL-producing strains were <50%. Furthermore, co-resistance to non-β-lactam antibiotics (levofloxacin, gentamicin, and cotrimoxazole) in the same strain was found in 26% of ESBL-producing *E. coli* and 13% of ESBL-producing *K. pneumoniae* strains. Resistance to all oral antibiotics (levofloxacin, ciprofloxacin, cotrimoxazole, and amoxicillin/clavulanic acid) was found in 15% of ESBL-producing *E. coli* strains and in 18% of ESBL-producing *K. pneumoniae* strains.

More than 90% of the ESBL-producing strains were susceptible to carbapenems and amikacin. More than 90% of ESBL-producing *E. coli* were susceptible to piperacillin/tazobactam, while only 60% of ESBL-producing *K. pneumoniae* were. Although ESBL-producing Enterobacteriaceae are presumed to be resistant to cephalosporins, on MIC test 40% of ESBL-producing *E. coli* strains, and 20% of ESBL-producing *K. pneumoniae* strains were susceptible to ceftazidime, and around 20% of ESBL-producing strains of both organisms were susceptible to cefepime. From the new CLSI 2014 criteria for cefepime susceptibility,[10] organisms with

Table 1 Demographic data of true infection episodes

	Total (% of total episodes)	Community acquired (% of total episodes)
Total episodes	461 (100)	166 (36)
Age at infection		
<1 month	23 (5)	8 (35)
1 month – 1 year	208 (45)	86 (41)
1–5 years	76 (16)	32 (42)
6–10 years	77 (17)	26 (34)
11–15 years	77 (17)	14 (18)
Gender		
Male	211 (46)	80 (38)
Female	250 (54)	86 (34)
Underlying diseases		
Immunocompromised*	114 (25)	19 (17)
Immunocompetent	347 (75)	147 (42)
Catheter related		
Yes	125 (27)	0 (0)
No	336 (73)	166 (49)
Sites of infection		
Peritoneal cavity	21	2 (10)
Blood	68	11 (16)
Wound	47	14 (30)
Respiratory tract	40	2 (5)
Urinary tract	302	139 (46)
More than one site	16	2 (13)
Severity of infection		
Shock	45 (10)	6 (13)
No shock	416 (90)	160 (39)
Presence of ESBL-producing organisms		
Yes	162 (35)	31 (19)
No	299 (65)	135 (45)

*Immunocompromised group includes patients who were on immunosuppressive therapy and preterm infants. ESBL, extended spectrum β-lactamase.

an MIC 4–8 μg/mL are considered to be susceptible dose dependent, suggesting that optimizing the dose or the dosing interval could effectively eradicate organisms. In the study, 35.8% of ESBL-producing *E. coli* and 39.2% of ESBL-producing *K. pneumoniae* fell into this category. Adding to the number of susceptible strains, between 55% and 60% of ESBL-producing strains may be effectively treated by cefepime.

Of note, two strains of non-ESBL-producing *E. coli*, one strain of non-ESBL-producing *K. pneumoniae*, four strains of ESBL-producing *E. coli*, and eight strains of ESBL-producing *K. pneumoniae* were resistant to at least one carbapenem. One strain of non-ESBL-producing *E. coli*, and four strains of ESBL-producing *K. pneumoniae* were resistant to colistin. All *E. coli* strains were susceptible to tigecycline, but three strains of non-ESBL-producing and three strains of ESBL-producing *K. pneumoniae* were resistant to this antibiotic.

Although some ESBL-producing organisms remained susceptible to piperacillin/tazobactam, carbapenems, amikacin, and quinolones, there may be an MIC shift towards the resistance breakpoints. To explore this possibility, the rates of the susceptible strains with the lowest MIC for each antibiotic for ESBL-producing strains were compared with those for non-ESBL-producing strains (Fig. 2). The susceptible ESBL-producing strains had lower rates of the lowest MIC for amoxicillin/clavulanic acid, ciprofloxacin, and amikacin when compared with the susceptible non-ESBL-producing strains. This applied to both *E. coli* and *K. pneumoniae*, although the difference was more pronounced in the latter. This suggests that there is a tendency for MIC shifts in ESBL-producing organisms in many antibiotics, even though the organisms were still reported to be susceptible to the antibiotics. Of note, the rate of ESBL-producing strains with low MIC for carbapenems, and colistin was similar to those of non-ESBL-producing strains. The rate of ESBL-producing *E. coli* with low MIC for piperacillin/tazabactam was also similar to that of non-ESBL-producing strains (data not shown).

The antibiotic susceptibility patterns of hospital and community-acquired ESBL-producing *E. coli* strains were compared to discover any differences. As shown in Table 6, hospital-acquired strains had lower rates of susceptibility to gentamicin, netilmicin, and cefepime. If cefepime-susceptible dose-dependent strains were included, a total of 90% of community-acquired strains and 67% of hospital-acquired strains are potentially treatable with this drug. The rates of susceptibility to other antibiotics tested were not statistically different. Hospital-acquired strains of netilmicin-susceptible ESBL-producing *E. coli* also had lower rates of lowest MIC (≤2 μg/mL) when compared with community-acquired strains (50% vs 76% of total susceptible strains). A comparison of ESBL-producing *K. pneumoniae* strains was not performed because the sample size of community-acquired strains was small (n = 4). All of these four strains were susceptible to amikacin and all carbapenems. Only one out of four strains was resistant to piperacillin/tazobactam. No carbapenem-resistant strains of community-acquired ESBL-producing organisms were observed. Among 35 strains of community-acquired ESBL-producing organisms, seven (20%) were resistant to three other classes of antibiotics (levofloxacin, gentamicin, and cotrimoxazole) and three (8.6%) were resistant to all oral drugs (levofloxacin, ciprofloxacin, cotrimoxazole, and amoxicillin/clavulanic acid).

Discussion

The present study highlights the impact of ESBL-producing organisms on antibiotic options available in pediatric patients infected with these organisms. Although the data represented the situation from one institution, this would be considered a reasonable pilot study for nationwide study in the pediatric population. According to the new CLSI 2014 criteria, which lowered the MIC breakpoint of most cephalosporins, most ESBL-producing organisms are considered to be resistant to first-, second-, and third-generation cephalosporins. These organisms were not only resistant to cephalosporins, but also to quinolones, gentamicin, netilmicin, and cotrimoxazole. In addition, one-fifth of the isolates were resistant to all non-β-lactam drugs (levofloxacin, gentamicin, and cotrimoxazole), indicating that acquisition of drug-resistant elements is not restricted to β-lactamase.[13] It is possible that drug resistance genes are co-located on the same mobile genetic elements[14,15] acquired under selective pressure from various

Table 2 Infection sampling sites

Sites of infection/organisms	Total strains	ESBL (% total strains)	Community acquired (% total strains)	ESBL in community acquired (% community acquired)
Peritoneal cavity				
E. coli	19	7 (37)	1 (5)	0 (0)
K. pneumoniae	16	6 (38)	1 (6)	0 (0)
Blood				
E. coli	41	15 (37)	8 (20)	2 (25)
K. pneumoniae	47	22 (47)	4 (9)	0 (0)
Wound/tissue				
E. coli	38	15 (40)	7 (18)	2 (29)
K. pneumoniae	28	6 (21)	8 (29)	0 (0)
Respiratory tract				
E. coli	17	6 (35)	2 (12)	0 (0)
K. pneumoniae	34	16 (47)	3 (9)	0 (0)
Urinary tract				
E. coli	268	84 (31)	129 (48)	27 (21)
K. pneumoniae	66	29 (44)	21 (32)	4 (19)
Summary				
E. coli	375[†]	124 (33)	145 (39)	31 (21)
K. pneumoniae	190[†]	78 (41)	37 (20)	4 (11)
Total	565	202 (36)	182 (32)	35 (19)

[†]Total number is lower than the sum of the strains from each site because some strains caused infection at more than one site. ESBL, extended spectrum β-lactamase.

Table 3 Univariate risk factors for shock (multi-level model for binary outcome)

Risk factor	Without shock n = 416 (%)	With shock n = 45 (%)	Univariate analysis	
			OR (95%CI)	*P*-value
ESBL	144 (35)	18 (40)	1.43 (0.61–3.37)	0.413
E. coli (ESBL)	102 (25)	6 (13)	0.44 (0.14–1.36)	0.154
K. pneumoniae (ESBL)	51 (12)	13 (29)	**3.62 (1.26–10.46)**	**0.017**
Age < 1 year	204 (49)	27 (60)	1.77 (0.73–4.31)	0.206
Immunocompromised	94 (23)	20 (44)	**4.29 (1.34–13.69)**	**0.014**
Bacteremia	40 (10)	28 (62)	**17.30 (4.72–63.34)**	**0.000**
More than one site of infection	11 (3)	5 (11)	**7.05 (1.28–38.84)**	**0.025**
Hospital acquired	256 (62)	39 (87)	**5.08 (1.69–15.21)**	**0.004**
Catheter	107 (26)	18 (40)	2.49 (0.99–6.24)	0.052
Male	183 (44)	28 (62)	**2.52 (1.02–6.24)**	**0.046**

ESBL, extended spectrum β-lactamase.

Table 4 Multivariate risk factors for shock (multi-level model for binary outcome)

Risk factors	Multivariate analysis		Risk factors	Multivariate analysis	
	OR (95%CI)	*P-value*		OR (95%CI)	*P-value*
ESBL	0.93 (0.51–2.43)	0.844	***K. pneumoniae* (ESBL)**	1.89 (0.82–4.4)	0.138
Immunocompromised	1.11 (0.51–2.43)	0.793	Immunocompromised	1.18 (0.54–2.57)	0.683
Bacteremia	**13.25 (6.08–28.84)**	**0.000**	Bacteremia	**12.89 (5.91–28.12)**	**0.000**
More than one site of infection	0.93 (0.26–3.29)	0.912	More than one site of infection	0.92 (0.25–3.3)	0.893
Hospital acquired	2.18 (0.77–6.15)	0.14	Hospital acquired	1.8 (0.63–5.11)	0.271
Catheter	1.48 (0.67–3.26)	0.331	Catheter	1.51 (0.68–3.34)	0.310
Male	**2.26 (1.10–4.63)**	**0.026**	Male	**2.24 (1.09–4.60)**	**0.029**

ESBL, extended spectrum β-lactamase.

Table 5 Antibiotic susceptibility: Non-ESBL- vs ESBL-producing strains[†]

Drugs	*E. coli* (% of susceptible isolates)		*K. pneumoniae* (% of susceptible isolates)	
	Non-ESBL	ESBL	Non-ESBL	ESBL
Ampicillin	16.6	0.5*	2.5	0.7*
Amoxicillin/clavulanic acid	80.2	59.6*	85.4	25.9*
Piperacillin/tazobactam	97.1	94.3	94.3	62.6*
Cephalothin	60.9	1.6*	74.7	0.7*
Cefuroxime	91.6	4.7*	87.3	9.5*
Cefoxitin	93.4	82*	88.6	86.5
Cefotaxime	93.1	4.7*	89.2	4.7*
Ceftriaxone	93.1	3.1*	89.9	2*
Ceftazidime	95.1	42*	92.4	19.6*
Cefepime[‡]	97.7	26.9*	96.2	19.6*
Imipenem	100	99	99.4	100
Meropenem	100	98.4*	99.4	97.3*
Doripenem	99.7	99	100	99.3
Ertapenem	99.7	97.9*	99.4	95.3*
Levofloxacin	70.9	44*	86.7	70.3*
Ciprofloxacin	69.1	45.1*	81.5	50.7*
Gentamicin	78	36.3*	86.1	37.8*
Amikacin	99.4	96.4*	98.7	97.3
Netilmicin	92.8	54.2*	97.5	65.5*
Cotrimoxazole	39.4	24.6*	66.5	27.7*
Colistin	99.7	100	100	97.3
Tigecycline	100	100	98.1	98

*P <0.05 vs non-ESBL strains (chi-squared test or Fisher exact test). [†]Intermediate susceptibility was regarded as non-susceptible. [‡]Dose-dependent susceptibility for cefepime was not regarded as susceptible. ESBL, extended spectrum β-lactamase.

antibiotics. This implies that inappropriate use of one class of antibiotic poses the chance of producing multidrug-resistant organisms. Although these ESBL-producing organisms were still susceptible to amikacin, the MIC of the drug tended to be higher. It is probable that more selective pressure on this drug would lead to a higher chance of the organisms becoming resistant to this drug in the near future. The shift of MIC also has an impact on the dose administered, given that the killing mechanism of amikacin is concentration dependent. Higher MIC would need higher concentration to achieve maximum killing. The shift in MIC did not happen only with amikacin but with other antibiotics, such as ciprofloxacin, and netilmicin. For *K. pneumoniae*, the shift also involved amoxicillin clavulanic acid, piperacillin/tazobactam, and tigecycline. The fact that MIC of tigecycline has shifted should be very concerning, because tigecycline is now considered to be an option for treatment of infections caused by carbapenem-resistant organisms. Shifting of MIC would imply that the effectiveness of the drug is decreasing.

There are many types of β-lactamase enzymes circulating in *E. coli* and *K. pneumoniae*.[16] The limitation of the present study was that molecular identification was not performed to determine which type predominated in the present patients. Approximately 40% and 20% of ESBL-producing *E. coli* and *K. pneumoniae*, respectively, however, were susceptible to ceftazidime, and they were more likely to be susceptible to piperacillin/tazobactam. These strains may harbor CTX-M β-lactamases, which usually confer resistance to cefotaxime but not to ceftazidime, and can be inhibited by β-lactamase inhibitors.[17] This type of β-lactamase has been proven to be widespread among these organisms.[8,13]

We confirmed that community-acquired infections by ESBL-producing organisms do exist in pediatric patients and that the prevalence is of concern, because it accounted for one-fifth of all community-acquired infections. Furthermore, invasive infections such as bacteremia could also occur in this setting. Information regarding prevalence of community-acquired infections caused by ESBL-producing organisms in pediatric patients is very scarce. The current prevalence is similar to that in the Qin *et al.* study, conducted in Seattle.[9] The prevalence in the general population varies from as low as 1%[18] to as high as 70%.[19] In the present study, we categorized patients with community-acquired infections as the ones who had not been hospitalized <1 year before the cultures were collected. This would strictly include only patients with real community-acquired, not community-onset infections.[16] This may, however, underestimate the real prevalence of community-acquired infections, suggesting that the burden of infections in the community should be higher than the present estimate. We could observe a difference in antibiotic susceptibility pattern between community- and hospital-acquired ESBL-producing strains. The rates of susceptibility to gentamicin, netilmicin, and cefepime were higher in community-acquired strains. This may be because these strains experience less selection pressure from these drugs in the community, given that the injected drugs are not as easily accessed in the community as oral drugs such as fluoroquinolones and cotrimoxazole. The prevalence of resistance to these drugs was not different between community- and hospital-acquired strains. Widespread use of antibiotics in domestic animals[16] in the community may also account for the rise in infections caused by ESBL-producing organisms.

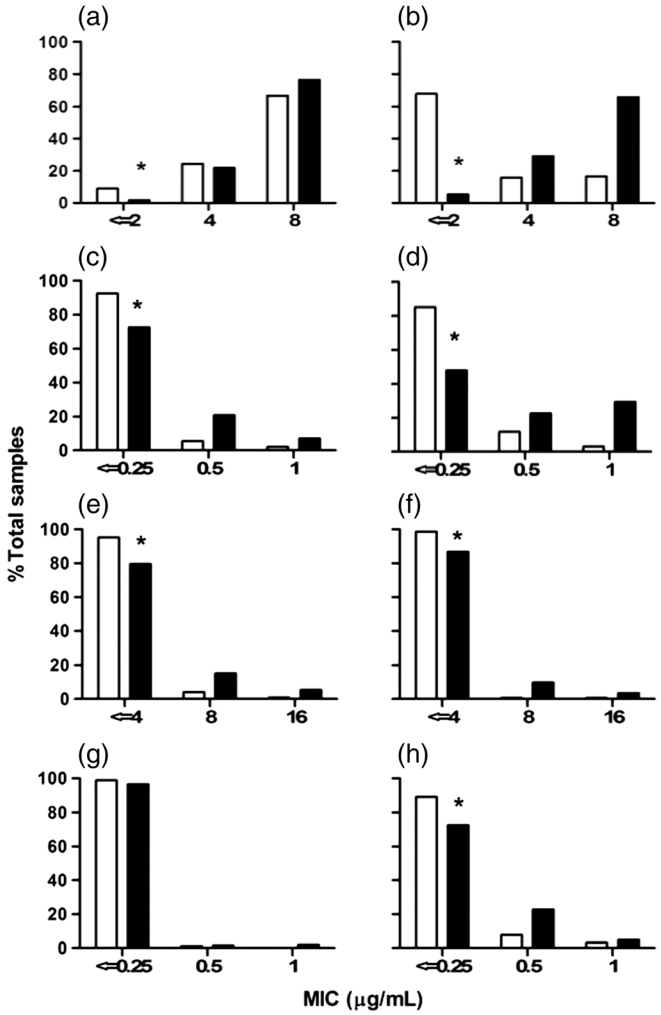

Fig. 2 Percentage of antibiotic-susceptible strains vs minimum inhibitory concentration (MIC) for (a,c,e,g) *Escherichia coli* and (b,d,f,h) *Klebsiella pheumoniae*. Antibiotics tested: (a,b) Amoxicillin/clavulanic acid; (c,d) ciprofloxacin; (e,f) amikacin; (g,h) tigecycline. (□) Non-extended spectrum β-lactamase (ESBL) strains; (■) ESBL strains. *$P < 0.05$ vs the non-ESBL strains (chi-squared test or Fisher exact test).

Most cephalosporins could not be used for ESBL-producing *Enterobacteriaceae*. The data suggested that carbapenems, amikacin, and piperacillin/tazobactam were good alternatives. Although amikacin showed good activity against most ESBL-producing organisms, its poor tissue penetration, and potential nephrotoxic property would limit its use except in urinary tract infection. According to the present data, amikacin is a good option for empirical therapy of community-acquired infections presenting without signs and symptoms of sepsis in the situation where the prevalence of community-acquired ESBL-producing organisms is increasing. Most community-acquired infections were urinary tract in origin, and all ESBL-producing strains originating from the community were still susceptible to this antibiotic. Piperacillin/tazobactam was still active against all ESBL-producing *E. coli* originating in the community, and against nearly 95% of all ESBL-producing *E. coli*. Its activity against ESBL-producing *K. pneumoniae*, however, was mediocre. This was consistent with a previous study.[20] In the most recent report, this drug could be used for treatment of non-bacteremic urinary tract infections caused by ESBL-producing organisms.[21] Cefepime is also promising given that nearly 60% of the present tested ESBL-producing strains were cefepime susceptible or cefepime susceptible dose-dependently. In community-acquired infections, the rate was as high as 90%. Many studies indicated that cefepime is inferior to carbapenems for treatment of bacteremia caused by ESBL-producing organisms,[22–24] but it is useful in non-bacteremic infections such as nosocomial pneumonia.[25] Given that it is excreted unchanged at high concentration in urine,[26] it has also been proved to be effective in urinary tract infection.[27] One of the reasons why piperacillin/tazobactam and cefepime are not effective in bacteremia is because of the inoculum effect, which is the rise of MIC when the organism burden is high.[28] After initial effective treatment and when the patient's clinical condition has improved, consolidate therapy with these agents is possible. Another worrisome issue is that a small proportion of ESBL-producing strains were susceptible to at least one oral antibiotic. This proportion is even lower if strains with higher MIC of amoxicillin/clavulanic acid are excluded. Treatment of urinary tract infection caused by ESBL-producing organisms with MIC for this agent at 4–8 μg/mL is associated with treatment failure.[29] If these strains are disregarded, there would be 39% of ESBL-producing *E. coli* and 21% of ESBL-producing *K. pneumoniae* strains that could not be treated by any oral antibiotics. This means that i.v. antibiotics are needed for the entire course of treatment, generating a higher medical cost.

Table 6 *E. coli* (ESBL) antibiotic susceptibility: Community- vs hospital-acquired infection[†]

Drugs	*E. coli* (ESBL) (% of susceptible isolates)	
	Community	Hospital
Ampicillin	0	1.1
Amoxicillin/clavulanic acid	74.2	68.8
Piperacillin/tazobactam	100	97.8
Cephalothin	0	3.2
Cefuroxime	3.2	7.5
Cefoxitin	90.3	80.6
Cefotaxime	0	7.5
Ceftriaxone	0	4.3
Ceftazidime	54.8	50.5
Cefepime[‡]	45.2	28*
Imipenem	100	100
Meropenem	100	100
Doripenem	100	100
Ertapenem	100	98.9
Levofloxacin	45.2	45.2
Ciprofloxacin	45.2	46.2
Gentamicin	64.5	33.3*
Amikacin	100	98.9
Netilmicin	83.3	53.8*
Cotrimoxazole	29	20.4
Colistin	100	100
Tigecycline	100	100

*$P < 0.05$ vs community-acquired strains (chi-squared or Fisher exact test). [†]Intermediate susceptibility was regarded as non-susceptible. [‡]Dose-dependent susceptibility for cefepime was not regarded as susceptible. ESBL, extended spectrum β-lactamase.

Regarding infection severity, ESBL-producing organisms did not pose a greater risk of septic shock, consistent with the previous study.[30] This implies that genetic elements of virulence factors might not be co-transferred with those of drug resistance. Further molecular identification would help to clarify this. Infection with ESBL-producing organisms leads to difficulty in selection of appropriate antibiotics. but they do not place infected patients at higher risk for more severe disease if appropriate antibiotics have been chosen.

In conclusion, pediatric infections caused by ESBL-producing organisms have spread to the community. They were not only resistant to cephalosporins but also to non-β-lactam antibiotics, compromising the choice of antibiotics used. A high proportion of ESBL-producing organisms were still susceptible to carbapenems, amikacin, colistin, and tigecycline. Colistin and tigecycline should be reserved for carbapenem-resistant organisms. Although ESBL-producing *Enterobacteriaceae* were resistant to many antibiotics, they were still not associated with more severe clinical presentation compared with non-ESBL-producing strains. Some antibiotic options other than carbapenems still remain for patients suspected to have non-bacteremic infection caused by ESBL-producing *Enterobacteriaceae*. Piperacillin/tazobactam and amikacin are examples of good options. Cefepime can also be considered for community-acquired infections. The efficacy of these drugs for treatment of infections caused by ESBL-producing organisms in the pediatric population, however, is still unknown. Further studies are needed before widespread implementation. Limitation of carbapenem use would halt the expansion of carbapenem-resistant organisms.

Acknowledgment

We thank the staff in the microbiology division for assistance with data acquisition.

Disclosure

The authors declare no conflict of interest.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Table S1 Prevalence of ESBL infections among patients with different underlying diseases.