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Background. Enterobacteriaceae infections resistant to extended-spectrum β-lactams are an emerging problem in children. We used a large database of clinical isolates to describe the national epidemiology of extended-spectrum β-lactamase (ESBL)–producing and third-generation cephalosporin-resistant (G3CR) Enterobacteriaceae.

Methods. Antimicrobial susceptibilities of Klebsiella pneumoniae, Escherichia coli, and Proteus mirabilis reported to ~300 laboratories participating in The Surveillance Network (TSN) between January 1999 and December 2011 were used to phenotypically identify G3CR and ESBL isolates cultured from patients <18 years. Bi-annual trends in the prevalence of each phenotype were stratified by species, patient location, culture site, age, and region. Children of age 0–1 years were excluded from analysis as data were only available from 2010 onwards.

Results. Out of 368,398 pediatric isolates, 1.97% (7255) were identified as G3CR, and 0.47% (1734) as ESBL producers. The prevalence of both phenotypes increased, respectively, from 1.39% and 0.28% in 1999–2001 to 3% and 0.92% in 2010–2011. Trends were significant across all demographic and age groups, including outpatients, with the highest proportion of isolates in the 1–5-year-old age group. The majority of G3CR and ESBL isolates were E. coli (67.8% and 65.2%, respectively). Among ESBLs, resistance to ≥3 antibiotic classes was 74%. The lower regional prevalence of ESBL-producing bacteria in the upper Midwest relative to the rest of the country is consistent with recent local data.

Conclusions. Rates of G3CR and ESBL infections in children are increasing in both inpatient and ambulatory settings nationally. The identification of host factors and exposures leading to infection in children is essential.

Key words. antibacterial agents; child; drug resistance; epidemiology; Enterobacteriaceae infections; β-Lactamases.

Antibiotic resistance in Gram-negative bacteria has increased at an alarming pace over the last 2 decades. Of particular concern is emergence of Enterobacteriaceae resistant to third-generation cephalosporins and aztreonam. This resistance profile is commonly associated with the expression of extended-spectrum β-lactamases (ESBLs), a family of enzymes first identified in the mid-1980s that confer resistance to nearly all β-lactam antibiotics except carbapenems and cephamycins [1]. Genes encoding ESBLs are typically found on plasmids that also carry other antibiotic resistance genes, often rendering ESBL-producing strains multidrug-resistant [2]. In addition to ESBLs, resistance to extended-spectrum β-lactams in Enterobacteriaceae is increasingly mediated by other plasmid and chromosomally
encoded enzymes, such as carbapenemases and AmpC cephalosporinas [3–5]. This changing molecular landscape where multiple resistance mechanisms are carried on mobile genetic elements and are expressed at once further complicates the already difficult task of detecting ESBL producers in the clinical setting [6]. Due to the limitations and variability of testing and reporting practices across laboratories [7, 8], resistance to third-generation cephalosporins is often used as a more reliable indicator that avoids underreporting the true prevalence of ESBLs and other β-lactamases.

A recent report by the Centers for Disease Control and Prevention (CDC) ranking antibiotic resistance threats in the United States labels ESBLs as a “serious concern [that] requires prompt and sustained action to ensure the problem does not grow” [9]. The CDC National Healthcare Safety Network (NHSN) reports that 4% of pathogens reported from all healthcare-associated infections were extended-spectrum cephalosporin-resistant Escherichia coli or Klebsiella spp. [10]. Infection with these organisms has been associated with prolonged hospital stays, higher hospitalization costs, and increased mortality [11–14].

Despite the rising relevance of antibiotic-resistant Enterobacteriaceae infections in the United States [15–17], there are few studies describing their epidemiology in pediatric populations. In the present study, we used a large national database of antimicrobial susceptibility results reported between 1999 and 2011 to analyze resistance prevalence trends, demographic and isolate characteristics of pediatric clinical isolates exhibiting third-generation cephalosporin resistance (G3CR), and ESBL resistance patterns. Our primary objective was to describe the national and regional epidemiology of ESBL and G3CR phenotypes in children.

METHODS

Regional and national data were obtained from The Surveillance Network Database–USA (TSN, Eurofins-Medinet, Herndon, VA). The data have been used widely to characterize national antibiotic susceptibility trends [18–21]. The network includes close to 300 clinical laboratories that service 1 or more patient care facilities. Although the identity of laboratories and clinical sites cannot be revealed, participants in the network have been selected on the basis of geographic and demographic criteria to be representative of hospitals in each of 9 US Census Bureau regional divisions [21]. Laboratories are required to submit results from all routine antimicrobial susceptibility testing performed on site, after which data are electronically validated and merged into a central database. Categorical result interpretations are based on Clinical Laboratory Standards Institute (CLSI) criteria adopted by the reporting facilities at the time of testing and reflect susceptibilities as reported to clinicians [19].

The analysis considered all isolates from pediatric patients (ages 1–17) collected in outpatient (ambulatory), inpatient non-intensive care unit (ICU) (referred to as inpatient), ICU, and long-term care settings between January 1, 1999 and December 31, 2011 and identified as K. pneumoniae, E. coli, and Proteus mirabilis. Recommended detection of ESBLs in Enterobacteriaceae involves screening isolates for reduced susceptibility to third-generation cephalosporins, followed by a confirmatory test [22]. Because ESBL organisms may appear falsely susceptible to some β-lactams under routine testing procedures, CLSI guidelines specific to our analysis period have recommended the qualitative reporting of confirmed ESBL producers as “resistant” to most β-lactams, regardless of actual breakpoint reading [7, 8]. Based on these recommendations, we defined the G3CR phenotype to include all isolates that were nonsusceptible to 1 or more of the 5 agents recommended for ESBL screening (aztreonam, cefotaxime, ceftizoxime, ceftazidime, and ceftriaxone) [22]. The ESBL phenotype included those G3CR-positive isolates that were reported resistant to all β-lactams with the exception of carbapenems, cephamycins, and β-lactam–β-lactamase inhibitor combinations [2–4]. While data on the use of the ESBL confirmatory testing were not available in TSN, our rule for identifying presumed ESBLs is based on the above-mentioned CLSI reporting standard. The frequency of both phenotypes is reported as the proportion of positive isolates over all tested isolates included in the analysis.

Data from 287 clinical laboratories that reported results in the study period were filtered to retain isolates that were tested against at least 1 drug included in each phenotype definition. To avoid bias from duplicate cultures, we considered only the first isolate from a patient in a rolling 30-day period. Isolates from infants (age <1 years) were excluded from the analysis, as data were only available for 2010 onwards.

Individual susceptibility results were stratified by isolate source (blood, urine, wound, and respiratory), patient location (inpatient, ICU, outpatient), age (1–5, 6–12, 13–17), sex, and year. The site-level breakdown was collapsed into regions based on the location of the laboratory (West, Northeast, South Atlantic, South Central, East North Central and West North Central), and aggregated over bi-annual intervals in order to smooth trends. Available susceptibility information of G3CR and ESBL phenotypes to seven additional drug classes not included in the phenotype definitions was assessed, including fourth-generation cephalosporins (cefepime), aminoglycosides, carbapenems, fluoroquinolones, nitrofurantoin,
trimethoprim–sulfamethoxazole, and β-lactam with inhibitor combinations. Multidrug resistance was defined as resistance to 3 or more of the above-mentioned drug classes.

The χ² (Cochran-Armitage) test for linear trend was used to test the significance of bi-annual trends. A quadratic term was added to test for a nonlinear shape of the trend. If the parameter estimate for the square of the time variable was significant and positive [negative] (P < .05), that implied the trend was curvilinear and the frequency of resistance followed a [inverse] U-shape, or was changing at an increasing [decreasing] rate. Data were analyzed using Stata version 11 (StataCorp, College Station, TX).

RESULTS

Patient demographic characteristics associated with the pediatric K. pneumoniae, E. coli, and P. mirabilis isolates from the TSN database are described in Table 1. Of 363,398 isolates analyzed between 1999 and 2011, 7255 (2%) were G3CR, and 1734 (0.5%) exhibited the ESBL phenotype. From the age groups represented, tested samples tended to come from younger patients: 37.7% of all isolates were from children between 1 and 5 years of age, 32% from ages 6–12 years, and 30% from ages 13–17, and the median age was 8 years. The age distribution was more skewed toward young patients when looking at the resistant phenotypes, with 47.1% of G3CR and 50.5% of ESBL isolates coming from 1–5-year-olds, and the median age falling to 5 years for both phenotypes. The majority of tested isolates were from female children (85.6%), but the proportion of male patients increased more than twice when looking at G3CR and ESBL-positive isolates (32.4% and 39.2%, respectively). The majority of tested isolates were E. coli (85.2%), from urinary sources (90.5%), and isolated in the outpatient setting (82.1%). Among resistance phenotypes, the share of E. coli declined to 67.8% among G3CR and 65.2% among ESBL isolates, as the relative frequency of K. pneumoniae increased. The relative frequency of blood, respiratory, and wound isolates from ICU and

<table>
<thead>
<tr>
<th>Organism</th>
<th>Tested Isolates N = 368,398</th>
<th></th>
<th>ESBLa N = 1734/368,398 (0.47%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td>313,901 85.21%</td>
<td>4922 67.84%</td>
<td>1130 65.17%</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>28,628 7.77%</td>
<td>1836 25.31%</td>
<td>574 33.10%</td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
<td>25,869 7.02%</td>
<td>497 6.85%</td>
<td>30 1.73%</td>
</tr>
<tr>
<td><strong>Healthcare setting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inpatient</td>
<td>59,255 16.08%</td>
<td>2425 33.43%</td>
<td>646 37.25%</td>
</tr>
<tr>
<td>ICU</td>
<td>6690 1.82%</td>
<td>577 7.95%</td>
<td>198 11.42%</td>
</tr>
<tr>
<td>Outpatientb</td>
<td>302,453 82.10%</td>
<td>4253 58.62%</td>
<td>890 51.33%</td>
</tr>
<tr>
<td><strong>Isolate source</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>6232 1.69%</td>
<td>652 8.99%</td>
<td>208 12.00%</td>
</tr>
<tr>
<td>Respiratory</td>
<td>5843 1.59%</td>
<td>704 9.70%</td>
<td>205 11.82%</td>
</tr>
<tr>
<td>Urine</td>
<td>333,524 90.53%</td>
<td>4966 68.45%</td>
<td>1077 62.11%</td>
</tr>
<tr>
<td>Wound</td>
<td>20,284 5.51%</td>
<td>815 11.23%</td>
<td>218 12.57%</td>
</tr>
<tr>
<td>Otherc</td>
<td>2515 0.68%</td>
<td>118 1.63%</td>
<td>26 1.50%</td>
</tr>
<tr>
<td><strong>Patient age</strong>d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–5</td>
<td>138,810 37.68%</td>
<td>3417 47.10%</td>
<td>876 50.52%</td>
</tr>
<tr>
<td>6–12</td>
<td>118,326 32.12%</td>
<td>2124 29.28%</td>
<td>525 30.28%</td>
</tr>
<tr>
<td>13–17</td>
<td>111,262 30.20%</td>
<td>1714 23.63%</td>
<td>333 19.20%</td>
</tr>
<tr>
<td><strong>Patient gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>315,254 85.57%</td>
<td>4902 67.57%</td>
<td>1055 60.84%</td>
</tr>
<tr>
<td>Male</td>
<td>53,144 14.43%</td>
<td>2353 32.43%</td>
<td>679 39.16%</td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>East North Central</td>
<td>61,258 16.63%</td>
<td>946 13.04%</td>
<td>203 11.71%</td>
</tr>
<tr>
<td>West North Central</td>
<td>30,245 8.21%</td>
<td>713 9.83%</td>
<td>227 13.09%</td>
</tr>
<tr>
<td>Northeast</td>
<td>49,603 13.46%</td>
<td>1227 16.91%</td>
<td>271 15.63%</td>
</tr>
<tr>
<td>West</td>
<td>90,785 24.64%</td>
<td>1483 20.44%</td>
<td>311 17.94%</td>
</tr>
<tr>
<td>South Atlantic</td>
<td>75,549 20.51%</td>
<td>1606 22.14%</td>
<td>390 22.49%</td>
</tr>
<tr>
<td>South Central</td>
<td>60,958 16.55%</td>
<td>1280 17.64%</td>
<td>332 19.15%</td>
</tr>
</tbody>
</table>

Per centages represent column relative frequencies.

Abbreviations: ESBL, extended spectrum β-lactamase; G3CR, third-generation cephalosporin resistant; ICU, intensive-care unit.

aG3CR, defined as nonsusceptible to one or more of the following drugs: aztreonam, cefotaxime, ceftizoxime, ceftazidime, ceftriaxone; ESBL producer includes G3CR-positive isolates that were reported resistant to all β-lactams with the exception of carbapenems, cephamycins, and combinations with β-lactamase inhibitors.

bIncludes 839 (0.22%) isolates recovered from patients in long-term care facilities.

cOther includes upper respiratory and skin cultures.

dData for patients <1 year old were not available for all years and were excluded from analysis.
inpatient areas also increased in the resistant samples. Of the 6 regions represented in the dataset, most tested G3CR and ESBL isolates came from West and South Atlantic regions, and the least from West North Central and East North Central.

The proportion of resistance phenotypes throughout the period was higher among females, 1–5-year-olds, E. coli isolates, and respiratory cultures (data not shown; see Supplementary Figures 1–4 for respective breakdowns).

Blood and respiratory cultures showed a higher proportion of G3CR and ESBL, rising in prevalence across patient settings, US regions, and pediatric age groups represented in the data \((P < .01)\); respiratory G3CR and ESBL prevalence increased from 7.01% and 2.2% in 1999–2001 to 16.2% and 6.3% in 2010–2011, respectively. Trends were different between males and females when comparing urinary isolates (which tend to be less common, but more resistant among males), and respiratory isolates (which are equally resistant, but more common among males).

When analyzing for linear and quadratic trends between 1999 and 2011, we found a significant increase \((P < .01)\) in the proportion of G3CR and ESBL isolates (Fig. 1). The overall prevalence of G3CR and ESBL phenotypes increased from 1.4% and 0.26% in 1999–2001 to 3% and 0.92% in 2010–2011, respectively, with the most significant increase seen in respiratory isolates. This correlated with a statistically significant increase in resistance phenotypes seen in all settings (Fig. 2) for G3CR \((P \leq .02)\) and in inpatient and outpatient (but not ICU) for ESBL isolates \((P < .01)\). Antibiotic susceptibilities to 7 drug classes were assessed (Table 2). The most common co-resistance to non-β-lactam antibiotics in both groups was trimethoprim/sulfamethoxazole \((G3CR 52.8\% \text{ and ESBL 66.1\%})\), followed by aminoglycosides \((G3CR 45.9\% \text{ and ESBL 64.5\%})\), and fluoroquinolones \((G3CR 32.8\% \text{ and ESBL 54.3\%})\). Although the majority of isolates tested carbapenem-susceptible \((G3CR 96.5\% \text{ and ESBL 94.2\%})\), multidrug resistance was common, with
46.8% and 74.4% of G3CR and ESBL isolates testing nonsusceptible to 3 or more drug classes (breakdown by species available in Supplementary Table 1).

Regional data are shown in Figure 3. In the early 2000s, G3CR isolates predominated in the Northeast, with ESBLs remaining uncommon in the pediatric population. By 2004–2007, G3CR began to rise in the West North Central and South Central regions. By 2008–2011, the increase in both G3CR and ESBL phenotypes continued throughout most of the United States. However, rates in the East North Central region remained consistently lower than other regions.

Though G3CR and ESBL phenotypes were not analyzed for age group 0–1 years due to lack of data before 2010, data from 2010 to 2011 were consistent with the levels of resistance seen in other age cohorts (data not shown, see Supplementary Table 2). Of 6574 isolates, 271 (4.1%)
were G3CR and 82 (1.25%) exhibited the ESBL phenotype. Of the G3CR and ESBL phenotypes, the majority of isolates were E. coli (72% and 81.7%, respectively), from males (57.9% and 53.7%, respectively), and from the urine (52% and 63.4%, respectively). Many of these children also presented in the outpatient setting (G3CR 37.6% and ESBL 48.8%); however, whether these children were previously hospitalized in the ICU or for prolonged periods is unknown.

**DISCUSSION**

We find that among children, the isolation of third-generation cephalosporin-resistant (G3CR) and presumed ESBL-producing *Enterobacteriaceae* is becoming more common across patient settings, US regions, and pediatric age groups. These findings are consistent with previous reports of the same data in adults, which also report an upward trend in extended-spectrum cephalosporin resistance in inpatient and outpatient settings, although the prevalence among adults was higher, ranging from 5% to 13% over the same period [18]. Using the largest sample of pediatric clinical isolates to date, we find that the prevalence of G3CR and ESBL phenotypes increased, respectively, from 1.39% and 0.28% in 1999–2001 to 3% and 0.92% in 2010–2011. Trends were significant across all demographic and age groups, including outpatients.

Increasing resistance in *Enterobacteriaceae* is an emerging public health threat, underscored by recent well-publicized outbreaks and national reports [23]. Resistance to third-generation cephalosporins is particularly worrisome when caused by ESBLs, as the spread of these enzymes is plasmid-mediated and can be transferred to other Gram-negative species [2–4]. ESBL infections are concerning for many reasons, including increased hospital costs, length of stay, and mortality rates [13, 24–26].

To date, ESBLs have been a more pronounced problem in adults, with children carrying a smaller share of the burden due to their limited healthcare exposure. Consistent with a prior analysis of adult TSN data, we find that ~70% of positive isolates are from urine, ~50% are from outpatients, and ~30% are from male patients [18]. Clinical risk factors for ESBL colonization and infection in children may also be similar to those for adults (such as prior hospitalization, prolonged length of stay, prior antibiotic use, and indwelling devices) [26–28]. However, data from US children are limited, mainly coming from single-center retrospective studies [15–17]. In our 2-center retrospective case–case–control study of Chicago children identified with ESBL infections between the years of 2008 and 2011, ESBL cases were 5.7 and 3.3 times more likely to have gastrointestinal (P = .001; 95% confidence interval [CI] 1.9–17.0) and neurologic comorbidities (P = .001; 95% CI 1.1–3.7), respectively, when compared to controls; however, gastrointestinal comorbidities may be a general risk factor for *Enterobacteriaceae* infection as cases of non-ESBL infections were also more likely to have a gastrointestinal condition (odds ratio 3.6; P = .014; 95% CI 1.2–10.1) (Logan et al. [29]).

We found high rates of multidrug resistance among G3CR and ESBL phenotypes in our study, which was a concern because resistance to trimethoprim/sulfamethoxazole, nitrofurantoin, β-lactam/β-lactamase inhibitor combinations and fluoroquinolones limit oral therapeutic options. Although carbapenem resistance in *Enterobacteriaceae* was rare in the national cohort, the prevalence of resistant isolates is increasing, even in children [18, 30]. Clinical trials of new antibiotics for the treatment of G3CR and ESBL-producing bacterial infections are conducted primarily in adults. Older oral drug options such as fosfomycin are available to children, but they are indicated primarily for the treatment of urinary tract infection [31].

The low national levels of ESBL among children (ranging from 0.26% to 0.92% over the study period), as well as the lower regional prevalence of resistant phenotypes in the upper Midwest compared to the rest of the country, are consistent with our local (Chicago) study, which found an ESBL infection prevalence of 1.7% that remained stable over the study period (2008–2011) (Logan et al. [29]). Nationally, 51.3% of subjects with ESBL-producing bacteria were outpatients; previous medical histories of these children are unknown. Locally, we found 30% of children presented in the outpatient setting, of whom 13% were considered to have community-acquired ESBL infection [14], which was similar to other pediatric studies (Logan et al. [29]). This means of acquisition may be increasing in children, as it is in adults [32–34]. The CTX-M-type ESBL is often referred to as the community-acquired ESBL, and results in multidrug-resistant infections in people with no significant history of healthcare exposure [33, 35]. While assessing the molecular epidemiology of isolates was outside the scope of this study, it is possible that the spread of CTX-M resistance accounts for the high numbers of children we found presenting in the ambulatory setting nationally.

While only a small proportion (0.22%) of national inpatient isolates were from long-term care facilities, this might be an under-recognized source of antibiotic resistance in children. Recent studies suggest multidrug-resistant *Enterobacteriaceae* are commonly carried by children in long-term care facilities, but often go undetected, posing significant infection control challenges when these patients are transferred to acute-care centers [36]. Long-term care facilities are a well-described reservoir in adults [37, 38].
Though ESBL and G3CR phenotypes were not analyzed for age group 0–1 years due to lack of data before 2010, data from 2010–2011 were similar to the levels of resistance seen in other age cohorts. However, whether these children were previously hospitalized in the neonatal ICU or otherwise differed from the other represented groups is unknown. Of note, in our case-case-control study of Chicago children, the median age of ESBL cases was 1.06 years [29]. Future studies should focus on the prevalence of multidrug-resistant infections in that special population, as recent reports suggest that long-term fecal carriage of ESBLs is found in colonized neonates (median 12.5 months after hospital discharge), which facilitates intra-household transmission [39].

Our study has several limitations. As our national data are from laboratory surveillance, we cannot account for patient clinical characteristics, or distinguish between confirmed infection and colonization. This limits our ability to compare results with studies such as the Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) program and NHSN, which focus exclusively on pathogenic isolates. Second, patient location entered in laboratory information systems may not correspond to the clinical setting where patients ultimately received care (eg, culture specimens obtained in the emergency department may be counted as outpatient cultures, even if the patient was ultimately admitted to the ICU). Third, although all TSN laboratories apply CLSI methods, susceptibility testing was not centralized. Unfortunately, minimum inhibitory concentrations or the test methods used by TSN laboratories were not available. If local discrepancies in susceptibility testing do affect our data, they would also likely have affected the results of other large-scale surveillance studies, most of which do not rely on centralized testing [20]. Fourth, interpretive susceptibility breakpoints for cephalosporins were lowered in January 2010 [22]; the new breakpoint revisions could be expected to increase cephalosporin resistance (G3CR) for the same isolates after that date. However, the adoption of revised criteria has been slow to occur in most laboratories [40], and even so, the trend of increasing resistance appears to have occurred prior to the new breakpoints. Fifth, the analyzed data do not include Klebsiella oxytoca, which is often reported alongside K. pneumoniae [10]. In the latest NHSN, results for the 2 organisms are pooled, thus limiting comparisons. However, earlier NHSN reports that separate the organisms show that, while K. oxytoca is less resistant, it is also is four-to-five times less common, which should not drastically affect our results [41]. Finally, we based the ESBL phenotype on reported susceptibility results, as our data set did not report results of ESBL clavulanate synergy confirmatory testing [22]. To add robustness to our results, we present the G3CR results. Resistance to ceftazidime or ceftriaxone is commonly used by large surveillance studies to proxy for β-lactamase production in E. coli, Klebsiella, and Proteus spp., making our results comparable to other published data [42, 43].

CONCLUSIONS

ESBL infections in children remain uncommon, but appear to have increased in the United States during recent years, with the majority of isolates displaying multidrug resistance. Presentation in the ambulatory setting is common. Additional studies in children to assess risk factors for acquisition, prevalence in ambulatory and long-term health care facilities, and the molecular epidemiology of ESBL-producing bacteria are warranted.

Supplementary Data

Supplementary materials are available at the Journal of the Pediatric Infectious Diseases Society online (http://jpids.oxfordjournals.org). Supplementary materials consist of data provided by the author that published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

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Potential conflicts of interest. All authors: no conflict.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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