Mortality associated with community-acquired cephalosporin-resistant *Escherichia coli* in patients admitted to a district hospital in a resource-limited setting

Gerardo Alvarez-Uria,[1]
Uvummala Priyadarshini,[2]
Praveen K. Naik,[1] Manoranjan Midde,[1]
Raghuprakash Reddy[2]

[1]Department of Infectious Diseases;
[2]Department of Microbiology, Rural Development Trust Hospital, Bathalapalli, Anantapur district, AP, India

Abstract

Studies performed in developed countries have shown that infections by third generation cephalosporin resistant *Escherichia coli* (G3CREC) are associated with increased mortality, but data from developing countries are scarce. In this observational study, we collected clinical and microbiological information of 194 patients admitted to a district hospital in India who had community-acquired isolation of *Escherichia coli*. The proportion of patients with G3CREC was 79.4%. In a multivariable logistic regression analysis, factors associated with 21-day mortality were isolation from a normally sterile site, HIV infection and isolation of G3CREC. Strains of *Escherichia coli* isolated from normally sterile sites had lower levels of resistance to quinolones and beta-lactam antibiotics. The proportion of meropenem and ciprofloxacin resistance was 11.1% and 80.9% respectively. The high proportion of G3CREC in the community and the association of G3CREC with 21-day mortality indicate that G3CREC is a major public health problem in developing countries.

Introduction

Rapid development of antimicrobial resistance by common bacteria is a major concern worldwide. Studies from developed countries have shown that infections produced by resistant microorganisms are associated with increased mortality and increased cost for health care systems.[1] Developing countries bear most of the common bacterial infection burden worldwide,[2] but data from resource limited settings are scarce.[3]

Recent studies have predicted a shift in the burden of antimicrobial resistance from Gram positive to Gram negative infections.[1] *Escherichia coli* is the most common cause of urinary tract infections and one of the leading cause of blood stream infection worldwide.[4] For *Escherichia coli*, third generation cephalosporin resistance is associated with resistance to other antimicrobials and can be used as a marker of multidrug-resistance. In Europe, third generation cephalosporin resistant *Escherichia coli* (G3CREC) has shown to increase mortality and hospital stay in patients from tertiary hospitals with blood stream infection.[5] India is a highly populated country with nearly 69% of people living in rural areas.[6] Previous studies have shown high levels of G3CREC in India.[7] However, the majority of these studies were performed in tertiary hospitals in urban areas, so the results of these studies may reflect local prevalence of resistant bacteria related to high antibiotic pressure in these sites. The prevalence of antibiotic resistant *Escherichia coli* in the community of rural areas of India is not well known. The aim of this study is to describe the prevalence of G3CREC and to investigate the effect of G3CREC on the mortality of patients admitted to a district hospital in a rural area of India.

Materials and Methods

Setting

The study was performed in the Bathalapalli Rural Development Trust Hospital, a non-profit private district hospital in Andhra Pradesh, India. The hospital belongs to a non-governmental organization that provides free consultation and medicines at reduced cost to people of low socio-economic status. The hospital is fully computerized and, as a routine, clinical and microbiological information of the patients is introduced in a hospital database.

Study design

For this study we selected cases admitted to the hospital with isolation of *Escherichia coli* from any clinical specimen from 24th March 2011 to 18th March 2012. Of this group, patient who met criteria for having a community-acquired isolation of *Escherichia coli* were included in the study: isolation in the first 48 h of admission and no previous hospital admission in the last 90 days.[8] Antimicrobial susceptibilities were performed in the Microbiology Laboratory of the hospital using disk diffusion testing according to recommendations of the Clinical Laboratory Standard Institute.[9] All strains where tested for extended spectrum beta-lactamase (ESBL) production by double disk synergy test. G3CREC was defined when the antibiogram shown resistance to cefotaxime.[10] The primary end-point of the study was to compare the 21-day mortality of patients who had G3CREC with patient who had a cephalosporin-susceptible *Escherichia coli* isolation. Blood, bone marrow, cerebrospinal fluid, ascitic fluid and pleural fluid were considered as normally sterile site (NSS) isolations.

Statistical analysis

Confidence intervals for proportions were estimated utilizing the Wilson method.[11] Variables that could be related to increased mortality as age, sex, HIV infection and NSS isolation were introduced in a multivariable logistic regression analysis model to assess the effect of having G3CREC isolation on 21-day mortality. We used Kaplan-Meier survival curves to describe the mortality of patients with and without G3CREC. Time was measured from the date of admission to the date of death in patients who died, or from the date of admission to the last visit date or the date of discharge, whatever occurred last. Statistical analysis was performed using Stata Statistical Software (Stata Corporation. Release 11. College Station, TX, USA).

Results

During the period of the study, *Escherichia coli* was identified in 219 specimens from 194 patients admitted to the hospital. Antimicrobial resistance to antibiotics by specimen type is

presented in Table 1. Nitrofurantoin (only tested in urinary specimens), amikacin, chloramphenicol, meropenem and gentamicin had low levels of resistance. The proportion of specimens with G3CREC was 78.1% (95% confidence interval [CI], 72.1-83.1). The proportion of meropenem and ciprofloxacin resistance was 11.1% (95% CI, 7.6-16) and 80.9% (95% CI, 75.1-85.6) respectively. Colistin was tested only for 17 isolations and all of them were susceptible. Compared to other sites, isolations from NSS had lower levels of resistance to ciprofloxacin (P=0.019), cefotaxime (P=0.003), ceftazidime (P=0.004), cefepime (P=0.011) and piperacillin-tazobactam (P<0.001).

The proportion of patients with G3CREC was 79.4% (95% CI, 73.1-84.4) and the global 21-day mortality was 13.4% (95% CI, 9.3-18.9). 21-day mortality was 5% (95% CI, 1.4-16.5) in patients with cephalosporin susceptible *Escherichia coli* and 15.6% (95% CI, 10.7-22.1) in patients with G3CREC. Among the 154 patients with G3CREC, 126 (81.8%, 95% CI 75-87.1) had an ESBL producing *Escherichia coli*. Baseline characteristics of the patients and multivariable analysis of factors associated with 21-day mortality are presented in Table 2. Factors significantly related to 21-day mortality were HIV infection, isolation from a NSS and isolation of G3CREC. Kaplan Meier survival curves of patients with and without G3CREC are presented in Figure 1.

Discussion

The results of this study show the high proportion of resistance to quinolones, penicillins and cephalosporins in strains of *Escherichia coli* isolated from the community. Other Indian studies have shown high levels of ESBL producing *Escherichia coli*, ranging from 63% to 79% in different settings and specimen types.[12–14] However, the rise of G3CREC is not an exclusive Indian phenomenon. In a study that involved 31 European countries, it was predicted an exponential increase in the number of bacteraemias produced by G3CREC in Europe.[1] Reports of resistant *Escherichia coli* have also been recently described in Africa.[15,16] Genes that encode third generation cephalosporin resistance are easily spread within health-care facilities,[17] but also among travelers to countries with high levels of G3CREC.[18,19] G3CREC is now a major public health problem in India, but we will probably see a rapid spread of G3CREC in other parts of the world in the near future.

Our results indicate that there is an association between isolation of G3CREC and 21-day mortality in patients admitted to a district hospital in India. Not surprising, the odds ratio for mortality found in this study was higher than the odds ratios for mortality found in other

Table 1. Percentage of antibiotic resistance by clinical specimen.

Antibiotic	Urine (N=113)	NSS (N=21)	Pus (N=42)	Sputum (N=11)	Others (N=32)	Total (N=219)
Nitrofurantoin	0.9	-	-	-	-	0.9
Amikacin	1.8	0.0	4.8	9.1	6.3	3.3
Gentamicin	22.5	9.5	19.0	18.2	15.6	19.4
Chloramphenicol	6.4	0.0	16.7	0.0	20.0	9.5
Ciprofloxacin	86.2	61.9	73.8	90.9	81.3	80.9
Cotrimoxazole	79.6	61.9	65.0	80.0	70.0	73.7
Cefotaxime	85.0	52.4	71.4	90.9	75.0	78.1
Ceftazidime	83.6	52.4	71.4	90.9	74.2	77.2
Cefepime	82.6	55.0	73.8	90.9	75.0	77.6
Piperacillin-tazobactam	100.0	57.1	70.0	90.0	77.4	83.9
Amoxicillin-clavulanate	92.9	81.0	82.9	100.0	90.6	89.9
Meropenem	8.1	14.3	19.5	0.0	12.5	11.1

NSS, normally sterile site (blood, bone marrow, cerebrospinal fluid, ascitic fluid and pleural fluid).

Table 2. Baseline characteristics and factors associated with 21-day mortality.

Baseline characteristics	21-day mortality		21-day mortality multivariable analysis	
	N (%)	No (N=168) N (%)	Yes (N=26) N (%)	aOR	P-value
Age (years)	35.3 (25-50)*	35 (24-50)*	40 (32.7-49)*	1.03 (1-1.07)	0.072
Female	72 (37.1)	65 (38.7)	7 (26.9)	0.78 (0.28-2.19)	0.643
HIV infection	80 (41.2)	59 (35.1)	21 (80.8)	10.89 (3.26-36.42)	<0.001
Isolation from a NSS	19 (9.8)	13 (7.7)	6 (23.1)	11.96 (2.47-57.97)	0.002
G3CREC	154 (79.4)	130 (77.4)	24 (92.3)	8.24 (1.19-57.28)	0.033

*, Median (interquartile range); aOR, adjusted odds ratio; NSS, normally sterile site; G3CREC, third generation cephalosporin resistant *Escherichia Coli*.
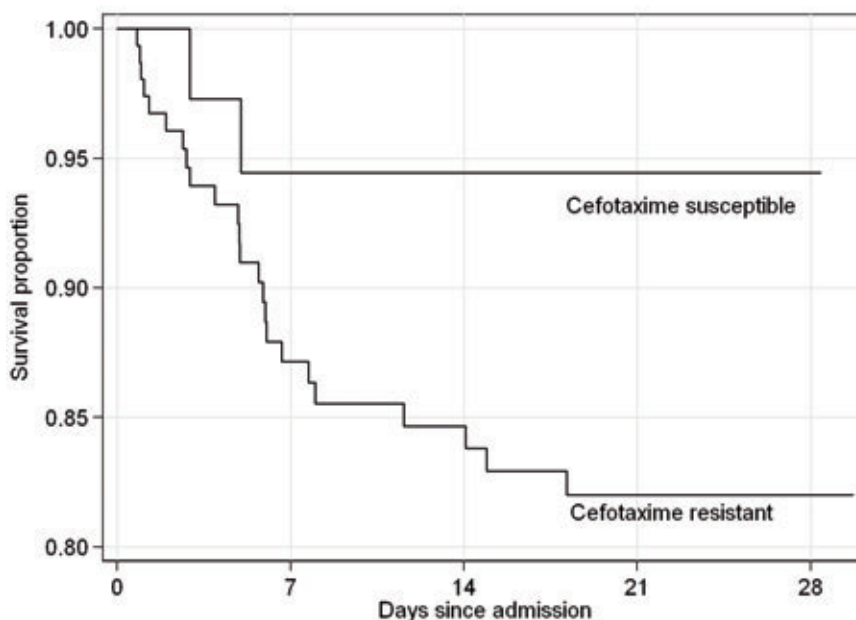

Figure 1. Kaplan Meier survival curves of patients admitted to the hospital with *Escherichia coli* isolation.

studies from tertiary hospital in Europe and in South Korea where resources are not so limited.[5,20] Although the spread G3CREC affects both developed and developing countries, it will cause higher mortality in resource-limited settings because of the scarcity of laboratories capable of providing antimicrobial susceptibilities and the high cost of effective antibiotics against G3CREC.

Interesting, isolations from NSS had lower proportion of antibiotic resistance to ciprofloxacin and beta-lactam antibiotics. It has been described that the development of antibiotic resistance by common bacteria bears a cost in terms of reduced fitness and virulence.[21] The lower proportion of G3CREC in specimens from NSS could be explained by the loss of virulence of *Escherichia coli* strains that develop resistance to these antibiotics.[21]

The spread of G3CREC should have important implication for the management of urinary tract infection and suspected *Escherichia coli* blood stream infections. The most commonly used antibiotics in non-complicated urinary tract infections (cotrimoxazole, fluoroquinolones, aminopenicillins and cephalosporins) are frequently not effective against G3CREC.[7] In our study, nitrofurantoin and chloramphenicol were more frequently susceptible than other antibiotics because they are not commonly used, so these antibiotics could be utilized for the treatment of non-complicated urinary tract infection. Aminoglycosides and carbapenems should preferably be reserved for empirical treatment of severe infections. However, there is an important concern about the future therapeutic options for *Escherichia coli* infections because of the scarcity of new antibiotics for treating Gram negative bacteria in the pipeline.[22]

The study has some limitations. We did not collect clinical data for distinguishing infection from colonization in some of the isolations from non-sterile sites. In addition, we did not collect clinical information of present morbidities at the moment of admission. It is possible that patients with G3CREC had unknown risk factors not included in the multivariable model that could modify the results of the study. However, the possibility of confounders related to having G3CREC isolation is unlikely, because the study was performed in a rural area, where referrals from other health-care centers are rare, and we excluded isolations performed after 48 h of admission and patients admitted in the previous 90 days.

Conclusions

The results of this study indicate that a high proportion of community-acquired isolations of *Escherichia coli* are resistant to multiple antibiotics and having G3CREC isolation is associated with higher risk of death in this Indian setting. If these findings are confirmed by other studies in resource-limited setting, the emergence of G3CREC could be a major public health threat in developing countries.

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