Prevalence and risk factors of extended-spectrum β-lactamases producing Enterobacteriaceae in a general hospital in Saudi Arabia

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ABSTRACT

Objective: To estimate the prevalence and associated risk factors of extended-spectrum β-lactamase producing Enterobacteriaceae (ESBL) in King Khaled General Hospital, Saudi Arabia.

Methods: A twelve-month retrospective study for the presence of ESBL producing Enterobacteriaceae infection was performed by using the Microbiology and Infection Control Departments’ database. For all the collected specimens, microbiological identification and antimicrobial sensitivity testing were done using MicroScan WalkAway system and then confirmed by API 20E and E-test respectively.

Results: The prevalence of ESBL producing Enterobacteriaceae infection among studied patients was 22%. The most common types of infections were urinary tract infections representing 59.2%. Previous use of antibiotics, urinary catheter, mechanical ventilation, previous hospitalization, previous intensive care unit admission and nosocomial origin of infection were significant risk factors for acquiring infection. Amikacin had the highest activity against ESBL producing isolates, whereas 20% of isolates were resistant to carbapenems.

Conclusions: The study revealed that prevalence of ESBL producing Enterobacteriaceae infection was relatively high. Our findings suggest that invasive devices, the use of antibiotics, prolonged hospitalization especially in the intensive care unit increases the risk of acquiring such infections. A strict antibiotic policy should be addressed especially with observed emergence of carbapenem resistance. Continuous review of need to invasive devices and strict compliance with basic infection control measures are mandatory to limit the spread of ESBL Enterobacteriaceae.

Key words: Enterobacteriaceae, extended-spectrum β-lactamase, prevalence, ESBL, resistant bacteria, risk factors

Suudi Arabistan’da bir genel hastanede genişlemiş spektrumlu β-laktamaz üreten Enterobacteriaceae prevalansı ve risk faktörleri

ÖZET

Amaç: Suudi Arabistan Kral Halid Hastanesi’nde genişlemiş spektrumlu β-laktamaz (GSBL) üreten Enterobacteriaceae prevalansı ve enfeksiyon gelişmesinde risk faktörlerin belirlenmesi


Bulgular: Çalışmaya alınan hastalarda GSBL üreten Enterobacteriaceae prevalansı % 22 olarak bulundu. En sık karşılaşılan enfeksiyon % 59,2 ile üriner sistem enfeksiyonu idi. Antibiyotik kullanımı, üriner kateterizasyon, mekanik ventilasyon, daha önce hastanede yatış, yoğun bakım ünitesinde tedavi görme ve enfeksiyonunun hastane kaynaklı olması GSBL üreten Enterobacteriaceae ile enfeksiyon gelişmesi için risk faktörleri olarak bulundu. GSBL üreten bakterlere karşı en etkin antibiyotik amikasinken, izolatların % 20’sinde karbapenemlere karşı direnç saptandi.

Sonuçlar: Bu çalışmanın sonuçları GSBL üreten Enterobacteriaceae oranının yüksek olduğunu göstermektedir. Bulgular; antibiyotik kullanımı, invaziv işlemler ve özellikle yoğun bakım ünitesine olmak üzere uzamış hastane yatışının GSBL üreten bakterilerle enfeksiyon gelişmesi riskini artırdığı göstermektedir. Gözlenen yüksek karbapenem direnç oranı antibiyotik kullanımla ilgili etkin politikalar oluşturulması gerektiği ortaya koymaktadır. GSBL üreten Enterobacteriaceae yayılmasının engellenmesi için kullanılan invaziv cihazlara ihtiyaçtan kaynaklanmasına ve temel enfeksiyon kontrol önlemlerine etkin şekilde uygulması gerekmektedir.

Anahtar kelimeler: Enterobacteriaceae, genişlemiş spektrumlu β-laktamaz, prevalans. GSBL, dirençli bakteri, risk faktörleri

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INTRODUCTION

In the last twenty years, antimicrobial resistance especially extended-spectrum β-lactamases (ESBLs) have spread among Enterobacteriaceae, particularly Escherichia coli and Klebsiella pneumoniae.1 B-lactamases are enzymes that hydrolyse β-lactam ring thus destroying the activity of β lactam antibiotics. ESBLs were discovered in 1983 and they can hydrolyze oxyimino-cephalosporins, and monobactams, but not cephamycins or carbapenems.2 ESBLs together with resistance to other antibiotics such as chloramphenicol, trimethoprim, tetracyclines, sulphonamides and aminoglycosides are encoded by genes present on large plasmids.3 Majority of ESBL associated infections are resistant to various antibiotics, leaving only limited compounds as a therapy.4 Presently, carbapenems became the first line antimicrobials for the treatment of such infections.5 The spread of ESBLs has certain consequences such as hindering effective treatment, poor outcomes, prolonged hospitalization and increase treatment costs.6 Risk factors for ESBLs associated infections include patients’ prior comorbidities (such as diabetes mellitus, renal failure, immunosuppression, neoplastic diseases, etc.), long hospital stay, advanced age, use of mechanical interventions (urinary catheters, venous catheters, endotracheal tubes) and previous therapy with broad spectrum antimicrobials.6 The prevalence of ESBLs differs between countries and hospitals. In Saudi Arabia the prevalence of ESBLs varies greatly in different regions. It was shown to be 11% in eastern province whereas, in Abha (southern region) and Riyadh (central region) it was reported to be 27.5% and 36% respectively.5-9 This study was conducted to describe the prevalence of ESBLs among Enterobacteriaceae in our hospital over a period of one year and to identify risk factors for infections.

METHODS

The current study was conducted in King Khaled General Hospital (KKGH), Saudi Arabia between January and December 2012. KKGH is a 300-bed tertiary care facility with approximately 23,000 admissions per year. Microbiological results were reviewed retrospectively. Only positive cultures for Enterobacteriaceae in different specimens from inpatients were included. If two similar cultures from the same patient were encountered, only one was included. For analysis, we defined cases as those patients with isolates classified as ESBL producers, and controls as patients with isolates negative for ESBL production. For each patient, age, sex, previous hospitalization (last six months) or intensive care unit admission, nosocomial infection (any infection presented within 48 hours of admission and was not diagnosed at that time),10 use of invasive devices (more than 48 hours) during current hospital stay and previous antibiotic use (more than seven days) were recorded from infection control surveillance data. Type of specimen, species of bacteria and antibiotic sensitivity pattern were also recorded.

Microbiological methods

The identification of Enterobacteriaceae species, antibiotic sensitivity testing and ESBL production were done by MicroScan WalkAway 96 (Siemens, Sacramento, USA) with its panels (negative breakpoint combo42). Results were interpreted by Microscan software program, following Clinical and Laboratory Standards Institute (CLSI) guidelines.11 Confirmation of species identification and ESBL production were done by API 20E (bioMerieux, France) and two ESBL E test strips for ceftazidime and cefotaxime with and without clavulanate (AB Biodisk, Sweden) respectively. ESBL diagnosis was considered if MIC was reduced by ≥3 twofold dilutions with clavulanic acid.

Statistical analysis

The analysis was done using the statistical software Open Epi (Open Source Epidemiologic Statistics for Public Health) Version 3.01. The qualitative data were presented in the form of number and percentage. Two by two tables are used to evaluate the association between a possible risk factor (Exposure) and an outcome (Disease). The risk was estimated using odds ratio, 95% confidence interval and Chi-Square. Statistical value of p <0.05 was considered to be significant.

RESULTS

A total of 1870 patients with Enterobacteriaceae isolates were included in the study. Out of these, 412 (22 %) were ESBL producers. The mean age of the case group (± standard deviation) was 53.7 ± 17.5years, and (54.6%) of them were male. The mean age of the control group (± standard deviation) was 55.3 ± 16.9 years, and (53.4%) of them were male. E coli had the highest prevalence (61.2%) followed by Klebsiella pneumonia (22.8%) as demonstrated in Table 1.

The distribution of ESBL-producing Enterobacteriaceae in different type of specimens is shown in Table 2. The clinical characteristics and possible
risk factors for ESBLs related infections are demonstrated in Table 3 and the sensitivity rates of ESBL producing Enterobacteriaceae to antibiotics are demonstrated in Figure 1.

![Figure 1. Antimicrobial Susceptibility rates of ESBL Producing Enterobacteriaceae.](image)

**Table 1.** Distribution of ESBLs isolates according to species

<table>
<thead>
<tr>
<th>ESBL producing species</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esherichia coli</td>
<td>252 (61.2)</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>94 (22.8)</td>
</tr>
<tr>
<td>Enterobacter aerogenes</td>
<td>25 (6.1)</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>21 (5.1)</td>
</tr>
<tr>
<td>Klebsiella oxytoca</td>
<td>9 (2.2)</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>9 (2.2)</td>
</tr>
<tr>
<td>Citrobacter spp.</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Total</td>
<td>412 (100)</td>
</tr>
</tbody>
</table>

**Table 2.** Distribution of ESBL producing isolates according to type of the specimen

<table>
<thead>
<tr>
<th>Clinical Specimen</th>
<th>ESBL producers (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine</td>
<td>244 (59.2)</td>
</tr>
<tr>
<td>Blood culture</td>
<td>28 (6.8)</td>
</tr>
<tr>
<td>Others</td>
<td>52 (12.6)</td>
</tr>
<tr>
<td>Wound swab</td>
<td>72 (17.5)</td>
</tr>
<tr>
<td>Sputum</td>
<td>16 (3.9)</td>
</tr>
<tr>
<td>Total</td>
<td>412 (100)</td>
</tr>
</tbody>
</table>

**Table 3.** Clinical features and potential risk factors for ESBLs producing Enterobacteriaceae infections

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>No. of ESBL (%) (n=412)</th>
<th>Non-ESBL (%) (n=1458)</th>
<th>OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>225 (54.6)</td>
<td>778 (53.4)</td>
<td>1.05 (0.84-1.3)</td>
<td>0.35</td>
</tr>
<tr>
<td>Old age (≥65 years)</td>
<td>208 (50.4)</td>
<td>760 (52)</td>
<td>0.94 (0.75-1.17)</td>
<td>0.3</td>
</tr>
<tr>
<td>Nosocomial origin of infection</td>
<td>277 (67)</td>
<td>900 (62)</td>
<td>1.27 (1.0-1.6)</td>
<td>0.024</td>
</tr>
<tr>
<td>Indwelling urinary catheter</td>
<td>298 (72)</td>
<td>976 (67)</td>
<td>1.29 (1.01-1.64)</td>
<td>0.022</td>
</tr>
<tr>
<td>Central venous catheter</td>
<td>242 (58.7)</td>
<td>798 (54.7)</td>
<td>1.18 (0.94-1.47)</td>
<td>0.083</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>139 (33.7)</td>
<td>354 (24.3)</td>
<td>1.59 (1.25-2.01)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Previous antibiotic use</td>
<td>378 (92)</td>
<td>1278 (88)</td>
<td>1.6 (1.07-2.30)</td>
<td>0.01</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>324 (79)</td>
<td>1069 (73)</td>
<td>1.34 (1.03-1.74)</td>
<td>0.02</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>182 (44)</td>
<td>546 (37)</td>
<td>1.32 (1.06-1.65)</td>
<td>0.01</td>
</tr>
<tr>
<td>Recent operation</td>
<td>185 (44.9)</td>
<td>683 (46.8)</td>
<td>0.92 (0.74-1.15)</td>
<td>0.26</td>
</tr>
<tr>
<td>Previous hospitalization (B6 months)</td>
<td>282 (68.4)</td>
<td>878 (60.2)</td>
<td>1.43 (1.14-1.81)</td>
<td>0.001</td>
</tr>
<tr>
<td>Previous ICU admission</td>
<td>217 (52.7)</td>
<td>694 (47.6)</td>
<td>1.22 (0.99-1.53)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

OR: odds ratio, CI: confidence interval
DISCUSSION

The rate of ESBLs in bacterial species differs greatly all over the world, and rapidly changing from time to time. The prevalence of ESBLs was reported to be over 10% in east Europe, 3.5% in a Canadian study and 20-48.8% in Asia. Within the Arabian Gulf region, ESBL prevalence ranged from a low of 7.5% in Kuwait to as high as 41% in United Arab Emirates. In Saudi Arabia ESBL detection was reported to be 27.5% in K. pneumoniae and 36% in Enterobacteriaceae. In other studies, it was 15.8% and 8.9% in blood cultures and urinary isolates, respectively. In our study the prevalence of ESBL was (22%) in Enterobacteriaceae. When compared to regional and international data, the ESBL prevalence in our institution tends to be towards the higher limit. This can be attributed to availability of broad spectrum antibiotics, the haphazard use of many of them with lack of strict antibiotic policy to control their use. Their spread cannot be prevented by improper isolation of patients with ESBL producing strains.

ESBL-producing E. coli is of concern as an important community-acquired pathogen. Community acquired ESBL associated infections are mostly urinary tract infections (UTIs), however some patients suffer from intra-abdominal infections and bacteremia. In our study (33%) of ESBL associated infections were acquired within two days of admission. Similarly, Ben Ami et al. showed that the prevalence of community acquired ESBL associated infections was 34.6%. On the other hand, in a study conducted in the eastern region of Saudi Arabia, only 37.9% of the bacteremia due to ESBL producing isolates were hospital acquired. Also, in a nationwide study conducted in Spain, 51% of ESBL-producing E. coli strains were isolated from outpatients.

In our study E coli had the highest prevalence (61.2%) among ESBL producers followed by K. pneumoniae (22.8%) and most ESBL isolates were detected in urine samples (59.2%). The same findings were observed in other studies and explained by the fact that hospitalized patients suffer frequently from UTIs, and Enterobacteriaceae (mainly E. coli) are the most common isolated organisms in these infections. In our study, amikacin was quite active against ESBL isolates, which was reported also by Rubio-Perez et al. and attributed it to the reduction of aminoglycosides usage to avoid renal toxicity.

In the current study high level of carbapenem (20%) resistance has been observed among ESBL isolates. Carbapenems are the first line of treatment of these organisms and, until recently, carbapenems resistance was rare among Enterobacteriaceae. Carbapenem resistance can be due to production of carbapenemases, the poor binding of carbapenems to penicillin-binding proteins present in the bacteria, the over-expression of multidrug efflux pumps by the bacteria or lack of porins in the bacterial cell membrane. A combination of resistance mechanisms can result with a significant rate of resistance. In our facility the high rate of carbapenem resistance could have been predisposed by the wide use of carbapenems as empirical treatment because its broad spectrum, activity against ESBL isolates and relatively less side effects compared to amikacin.

Based on our results, antibiotics usage particularly cephalosporins and fluoroquinolones were significantly associated with ESBL associated infections. Antimicrobial exposure is considered to be an important risk factor for ESBL related infections as it allows resistant mutants to become the dominant strains. Cephalosporin and fluoroquinolone exposure was reported as risk factor for multidrug resistant bacteria infections, previously.

In conclusion, this study suggests there is a high prevalence of ESBL associated infections, mechanical ventilation and urinary catheter were both considered as risk factors. Similar findings were reported by other studies.

Previous hospitalization, and nosocomial origin of infection were significantly associated with ESBL acquisition which was described by other authors. In our study although central venous catheter was not considered as risk factor for ESBL producing Enterobacteriaceae infections, mechanical ventilation and urinary catheter were both considered as risk factors. Similar findings were reported by other studies.

Our study has limitations. As noted, high rate of carbapenem resistance has been observed but since it was a retrospective study, the exact rate and mechanism of this resistance could not be confirmed.

In conclusion, this study suggests there is a high prevalence of ESBL associated infections in our setting, which can be attributed to prolonged un-reviewed invasive interventions, unrestricted use of antibiotics, prolonged and probably unnecessary hospital stay. These isolates pose a special therapeutic challenge especially with the growing resistance to carbapenems. Therefore, strict antibiotic policy, continuous review of the need to in-
vasse devices, minimizing duration of hospital stay together with strict compliance to infection control precautions would serve as the most efficient way of preventing the spread of these organisms. We also recommend that carbapenem resistance should be thoroughly investigated by further research to know the magnitude and mechanism of such resistance.

REFERENCES


