Extended Spectrum Beta-Lactamases In Escherichia Coli & Klebsiella Spp - Prevalence, Associated Risk Factors And Clinical Outcome In Hospitalized Patients.

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Abstracts: **Objective:** Infection by extended spectrum beta-lactamase (ESBL) producing strains of *Escherichia coli* and *Klebsiella spp.* is variably associated with presence of co-morbid conditions, predisposing factors and poor outcome. Objective of this study was to determine the prevalence of ESBL producing strains along with the outcome and risk factors in patients infected with such strains. **Materials and Methods:** This observational study was conducted on 6910 clinical samples. *E coli* & *Klebsiella spp.* were identified with detection of ESBL production according to Clinical and Laboratory Standards Institute (CLSI) guidelines. Patients' clinical and demographic details along with risk factors and co-morbid conditions, type of response to antimicrobial therapy, length of hospital stay and mortality were collected. **Results:** 69.62% out of 563 *E.coli* and 62.80% out of 342 *Klebsiella spp.* were isolated from 6910 samples were ESBL producers respectively. Male:Female ratio was 1.36:1 and 2.37:1 for *E coli* and *Klebsiella spp.* respectively. Blood Stream Infection (p=.006), soft tissue infections (p=0.08), genital tract infections (p=0.03) and admission in intensive care units were significantly associated with risk of infection by *Klebsiella spp.* Immunosuppressive therapy (p=0.02) and diabetes mellitus (p=0.04) were significant comorbid conditions in ESBL producing *E coli* infections. The mean duration of hospital stay for ESBL producing *E coli* and *Klebsiella spp.* was 13.65 ± 12.6 and 17.89 ± 14.76 days with mortality of 8.6% and 13.34% respectively. **Conclusions:** Several co-morbid conditions and invasive devices were significantly associated with infection by ESBL-producing, strains of *E. coli* and *Klebsiella spp.* with longer duration of hospital stay and increased mortality in comparison to ESBL non-producers.[Singh S et al NJIRM 2014; 5(2) :75-81]

Key Words: ESBL prevalence, risk factors, clinical outcome

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Introduction Fight between men and microbe have been existing since beginning and would persist forever. Infection by multidrug resistant Gram negative organisms like *Escherichia coli* and *Klebsiella* spp. are the predominant causes of morbidity and mortality in hospitals.[1] Extensive spread of extended spectrum beta lactamase (ESBL), is a global challenge as it confers resistance to beta lactam antibiotics except carbepenems leaving very little therapeutic options for the treating physician.

This challenge of multidrug resistance due to ESBL producing strains of *E coli* and *Klebsiella spp.* has been of interest to many investigators worldwide including India. On literature survey it has been found that risk factors for acquiring such infections and its impact on patient's outcome is variable.[2] Thus a study to find out the prevalence, risk factors and outcome of patients with infection by highly antibiotic resistant strains of *E coli* and *Klebsiella* species in a tertiary care hospital was conducted.

Material and Methods: This is a cross-sectional study duly approved by institutional human research ethics committee. The study was conducted on a total number of 6910 clinical samples received and processed from indoor patients admitted in Shree Krishna Hospital, Karamsad, Gujarat, India. Informed consent was taken from patients when detailed clinical history was required. The isolates were identified to species level using standard tests and antimicrobial sensitivity was performed by Kirby Bauer disc diffusion method on Muller Hinton agar according to revised Clinical and Laboratory Standards Institute (CLSI) guidelines.[3] *Klebsiella. pneumoniae* ATCC 700603 and *E.coli* ATCC 25922 were used as positive and negative control strains for ESBL detection respectively.

Isolates, that were found resistant to any of the 3rd generation cephalosporins, were considered as potential ESBL producers, confirmation of ESBL production was done by using three different methods i.e. disk approximation, inhibitor potentiated disc diffusion method according to

CLSI guidelines and ESBL E test strips (AB BIODISC Sweden). Isolate was labeled as indeterminate for ESBL production when no inhibition zone was formed around cefotaxime/ cefotaxime clavulanic acid (CT/CTL) or ceftazidime/ ceftazidime clavulanic acid (TZ/TZL) combination disc with minimum inhibitory concentration (MIC) more than the MIC range (CT>16 µg/ml and CTL>1 µg/ml and TZ>32 µg/ml and TZL>4 µg/ml).

Patients from whom multiple organisms were isolated were included only once. Patients were grouped in two categories; one included patient with infection by ESBL producing strains and other with infection by ESBL non -producing strains.

Patient's clinical and demographic details were collected from the case files as well as by history taking and physical examination as and when required. Data like age, sex, date of admission, date of culture isolate, presence of risk factors (age, sex, indwelling devises, duration of hospital stay, prior exposure to antibiotics) and co-morbid conditions (liver dysfunction, renal insufficiency, surgery/ invasive procedure in last 30 days, immunosuppressive therapy particularly steroids, chronic lung disease, diabetes mellitus and heart disease), type of antibiotics given and response to therapy were collected. The co-morbid conditions were considered as per the clinical diagnosis with supporting laboratory data. Clinical outcome was evaluated in terms of length of hospital, stay after the diagnosis of infection, response to therapy and mortality. Death was considered due to infection when it occurred within two weeks from the diagnosis of infection with evidence suggestive of active infection and absence of any other fatal event. Patients were followed till discharged from the hospital. The results were analyzed using the MedCalc and Statistical Package for the Social Sciences (SPSS) for windows (version 15.0; SPSS Inc, Chicago, IL, USA). Continuous variables were expressed as mean values ± Standard deviation (SD). Categorical variables were expressed as percentage. Comparisons at the univariate level were done using the student's t test/$\chi 2$ test as applicable. Levene's Test for Equality of Variances was also applied.
All test of statistical significance were 2-tailed. *p* value of < 0.05 at 95% Confidence interval (CI) was considered statistically significant. Analysis of risk factors and co-morbid conditions was done by using comparison of difference in proportions and binary logistic regression using stepwise backward elimination.

Results: A total of 6910 clinical samples were received and processed from indoor patients with a culture positivity rate of 3616 (52.32%). *E.coli and Klebsiella spp.* were isolated from 563 and 342 (15.56% & 9.45%) samples. Out of these 52 (9.25%) isolates of *E coli* and 62 (18.14%) isolates of *Klebsiella spp*. were labelled as indeterminate for ESBL production. Major findings of the study are shown in table 1 and 2. ESBL positivity for *E coli and Klebsiella spp.*, was 69.62 and 62.87% respectively.

Overall male to female ratio was 1.5:1. This was 1.36:1and 2.37:1 for *E coli & Klebsiella spp.* respectively.) .. Patients less than a year and in the age group of 41 to 50 years had more than 85% ESBL positive isolates in comparison to 68% in other age groups but these were not statistically significant.

Urine was the major sample from which *E coli* was isolated i.e. 226/ 511 (44.2%) followed by pus 117 (22.9%), respiratory samples 73 (14.3%) and blood 43 (8.4%) whereas for *Klebsiella spp.* respiratory samples were the major sample 92/280 (32.9%) followed by blood 75 (26.8%), pus 60 (21.4%) and urine 31 (11.1%).

ESBL positivity for *E coli* was maximum in respiratory samples i.e. 82.2% where as for *Klebsiella spp.* blood showed maximum ESBL positivity of 85.3%. *Klebsiella spp.* isolated from urine showed lowest ESBL positivity of 58.1%, which was 73% in *E coli* isolates.

Urinary tract infection was the most common clinical condition in *E coli* (23.9% with 70.5% ESBL producers) followed by blood stream infections (17.22% with 79.55% ESBL producers) whereas in *Klebsiella spp.* blood stream infection (33.21% with 87% ESBL producers) was most common followed by respiratory tract infection i.e. 21.1% with an ESBL positivity of 67.8% .

It was found that blood stream infections (p=.0063, 95% CI= 7.768-30.652), soft tissue infections (p=0.0844, 95%CI=2.148-14.032) and genital tract infections (p=0.0372, 95% CI=-0.725 to 11.225) were significantly associated with risk of infection with ESBL producer strains of *Klebsiella spp*. But none of the clinical conditions were significantly associated with ESBL producer *E coli* infections.

Medical wards (28.7%) were the main location from where clinical samples were received followed by surgical wards (18.0%). Non intensive care units contributed to 55.54% (437/791) of ESBL producing clinical isolates, which was only 21.49% (170/791) from intensive care units though intensive care units had more percentage i.e. 87.62% of ESBL producers in comparison to 73.91% isolates being ESBL producers from non-intensive units. Thus location of patient in the hospital was found to be a significant risk for acquisition of infection by ESBL producing strains of *E coli* and *Klebsiella spp*..

The co morbidities and indwelling devises for *E coli* and *Klebsiella spp*. infections were observed to be more common in ESBL producer cases. Most of them were not found significant statistically except for immunosuppressive therapy (p=0.0273, 95% CI 2.657 to 11.523) and diabetes mellitus (p=0.0475, 95% CI 1.429 to 17.151) in ESBL positive *E coli* infections and mechanical ventilation in both *E coli* and *Klebsiella spp*.

Mean duration of hospital stay for patients infected with ESBL producing and non-producing strains was 15.15 ± 13.55 days and 10.89±8.74 days respectively which was statistically significant (p value <.001). The mean duration of hospital stay for ESBL producing strains of *E coli and Klebsiella spp.* was 13.65 ± 12.6 days and 17.89 ± 14.76 days respectively.

Overall mortality among patients infected with ESBL producing and non-producing strains was 13.34% Vs 1.6% (p<0.0001). This was 8.6% Vs 0.8% (p=0.0060) for *E coli* and 21.8% Vs 3.07% (p=0.001) for *Klebsiella spp.*

Discussion: *E coli* and *Klebsiella spp*. are the predominant gram-negative clinically significant pathogens isolated from human samples. We found *E coli* & *Klebsiella spp* in 15.56% and 9.45% of clinical samples. Similar results have been found by other investigators, ESBL producing *E. coli* has been isolated from 45- 82% followed by *K. pneumoniae* from 17-37.8% clinical samples.[4-7]

Indian cities have shown variable prevalence, ranging from 12% to 85.8% in various studies. [8,9] We found ESBL positivity of 69.62 and 62.87% in *E coli and Klebsiella spp.*, respectively. Similar findings have been reported from many Indian cities.[10-13]

Klebsiella spp. has been found to be a more potent ESBL producer as found by Superti SV *et al* but we had almost equal percentage of *E coli* and *Klebsiella spp.* (69.2 and 62.80 %) producing ESBL.[14] This is similar to the findings of Rao Shridhar PN *et al* (62.9 & 62.2%), Goyal A *et al* (63.6 & 66.7%), Shivprakash S *et al* (67.4 & 62.34%) and Mahesh E *et al* (66.78 & 60.27%).[10,11,13,15]

Age and sex of patients has been found to be variably associated with susceptibility to different kind of infections so is true for ESBL producer strains.[16] Tumbarello M *et al* and Khanfar HS *et al* found the mean age of patients infected with ESBL producer isolates significantly more in comparison to ESBL non-producer with a p value of <0.001.[17,18] We had 25.8% of patients with 80.9% ESBL positivity who were more than 60 yrs of age, similar to findings in literature.[17]

Mean age of infection in our study was 43.22 and 42.04 years for ESBL producer and non-producer cases and was similar to 42.02 yrs found by Goyal A *et al.* This is significantly less than 67.9±16.0 Vs 65.5±14.8 years in ESBL producers and non producers respectively as found by other investigators.[15,16]

Male to female ratio in our study was 1.5:1 with 28.69% females and 48.04% of male being ESBL producer which was similar to that of Goyal A *et al* who had M:F ratio of 1.86:1.[15] No association was found between ESBL status and gender in our study except for a significant value in the age group

of 11-20 and 21-30 yrs where female gender had significantly higher ESBL infections. The values for male and female in the age group of 11-20yrs were 2.6% Vs 7.4% (p=.0097; 95% CI: 1.04 to 8.56), and in 21-30 yr were 8.4% Vs 25.11% (p< 0.0001; 95% CI: 10.417 to 23.003). Such observations are not shared by other investigators except for Gudiol C *et al* who has reported female gender as independent risk factors for acquisition of infection by ESBL producing strains.[12]

Location of patients in intensive care units is a risk factor for acquisition of infection by ESBL producing strains as has been found in our as well as many other studies. Intensive care units have contributed to more than 50% of ESBL producers.[14,18,19] We had 21.49% patients from intensive care units with 87.62% of ESBL producer in comparison to 73.91% isolates being ESBL producer from non intensive care units.

In our study urinary tract infection was the most common clinical condition (23.9%) with 70.5% ESBL producer isolates in *E coli* where as blood stream infections was more common in *Klebsiella spp.* accounting for 33.21% with 87% isolates being ESBL producers. This is similar to findings by Shiju MP *et al* who reported 92% of *E. coli* isolates from urine samples as ESBL producers.[20]

ESBL producers were more in comparison to ESBL non-producers in majority of the clinical conditions in our study but none of them were seen to be significantly associated with ESBL producer infections in *E coli* and only blood stream infection was found significantly more in *Klebsiella spp.* i.e. 37.67% Vs 18.46% (p=0.0063; 95% CI: 7.768 to 30.652).

None of the invasive devises were found to be significantly associated with infection by ESBL producing strains in our study, except for mechanical ventilation both in *E coli* infected case (p =0.0059, 95% CI: 4.721 to 13.179) and *Klebsiella spp.* (p=0.0016, 95% CI: 10.693 to 22.567). Urinary catheterization (p=0.0024, 95% CI: 8.341 to 35.599) was also found to be significantly associated with infection by ESBL producing strains of *Klebsiella spp.* on univariate analysis.

Ozgunes I *et al* from Turkey in their study found almost all indwelling devises i.e. Foley catheter (p<0.001), intravenous catheter (p<0.001), central venous catheter (p=0.002), intubation (p<0.001), surgery (p<0.001) and mechanical ventilation (p=0.002) to be significantly associated as risk factors for the acquisition of *E. coli* and *K. pneumoniae* with ESBLs.In a study conducted by Lee CI *et al,* the most significant factor that was found to predispose to infection by ESBL producing organisms was urinary catheter.They had 38.8% of patients with indwelling urinary catheters (p=0.03).[16,19] Presence of central venous catheters (p=0.08) and exposure to previous surgery (p=0.15) were not found to be as significant factors for development of infection by ESBL producing strains by them.

Tumbrello M et al also demonstrated that patients with infections by ESBL producing strains were more likely to have previous UTI (56% Vs 43%), invasive procedure (58% Vs 28%), mechanical ventilation (40% Vs 30%), and urinary catheterization (62% Vs 54%).[18] Goyal A et al found use of urinary catheter (4.280; 95% CI: 2.210-8.290; p<0.001), intravenous devises (3.041;95% CI: 1.668-5.545; p<0.001) and renal insufficiency (2.824;95% CI: 1.349-5.911; p=0.006) as significant risk factors whereas as use of ventilators and admission in intensive care units, diabetes mellitus, use of corticosteroids and malignancy was not found to be significantly associated.[15] We found presence of mechanical ventilation as significant risk factor both in E coli and Klebsiella spp. infection (p= 0.0059, 0.0016 respectively).

The co morbidities were observed to be more in ESBL cases but most of them were not found significant statistically except for immunosuppressive therapy (p= 0.0273) and diabetes mellitus (p= 0.0475) for *E coli* infection in our study. In a study by Lee CI *et al,* a number of co morbid conditions like diabetes mellitus (48.7% Vs 35.0%, p=0.02), liver cirrhosis (22.6% Vs 11.7%, p=0.02) and uraemia (21.7% Vs 11.7%, p<0.001) were found to be present significantly more in patient with infections by ESBL producing strains .[16] Some of the other conditions that were not found significantly associated were HIV and AIDS (1.7% Vs 1.2% p=0.72), haematological malignancy (3.5% Vs

5.5%, p=0.43), and steroid therapy (11.3% Vs 9.8%, p=0.69).[16]

One factor found to be strongly associated with acquiring infection with ESBL producing strains is prior exposure to antibiotics particularly 3GC.[9,15] We could not study this important aspect due to the lack of information regarding prior use of antibiotics because of uncontrolled prescribing habits and poor awareness status of our patient population.

Studies have demonstrated that patients with infection with ESBL producing strains were more likely to have longer hospital stay along with more of healthcare associated infections, longer hospitalizations and it associated cost.[18] Similar to adult patients, 'length of stay in NICU' was found as the single independent factor associated with ESBL-acquisition as reported by Shakil S *et al*.[21]

The duration of hospital stay has been found to be significantly more in infection with ESBL producing strains in comparison to ESBL non-producer cases. The mean duration of hospital stay in ESBL non-producer Vs producer cases in our study was 15.15 ± 13.55 days Vs 10.89 ± 8.74 days (p value <.001). This was nearly the same mean duration of hospital stay (15 and 16.95 days) as that found by Goyal A *et al*.[15] Schwaber MJ *et al* reported comparatively less number of hospital stay (11 Vs 5 days) while Superti SV *et al* had it on the higher range i.e. 26±20 Vs 16±16 days (p=0.002).[22,23] Lee CI *et al* found the infections with ESBL producing strains to be of higher severity with resultant longer duration of hospital stay (51.1 Vs 31.9 days p=0.007).[16]

Infection with ESBL producing strains has been consistently associated with poor outcome. Tumbarello M *et al* have reported mortality of 52% in blood stream infections caused by ESBL producers in comparison to only 29% in ESBL non-producer infection. [18] Similarly Lee CI *et al* and Gudiol C *et al* also found significantly higher mortality in cases with ESBL producing infections (34.8% Vs 23.9%; p=0.03) and (37.5% versus 6.5%; p = 0.01) respectively.[9,16] We had overall mortality of 13.34% Vs 1.6% (p<0.0001). This was 8.6% Vs 0.8% (p=0.0060) for *E coli*, 21.8% Vs 3.07% (p=0.001) for *Klebsiella spp.* in ESBL producing and non-producing strains respectively.

Conclusion: Thus, several studies have tried to find out the risk factors for acquiring infections by ESBL-producing organisms with different results. Out of a number of probable risk factors investigated; prior surgery, immunosuppressive therapy and instrumentation particularly mechanical ventilation have been found to be consistently associated with infection by ESBL-producing *E. coli* or *Klebsiella spp.* as was found in our study. A longer duration of hospital stay and increased mortality in comparison to ESBL non-producer cases as found by us was also found in other studies thus adding strength to the association.

Number of factors dependent on the host, the infecting organism as well as the promptness and correctness of therapy influence the outcome of infection. The baseline health status, age, presence or absence of chronic disease like diabetes, hypertension, renal failure, malignancy, immunosuppressive therapy etc can have significant influence on the outcome of infection. These conditions can act synergistically with the infecting organisms and complicate the infection. Thus, infection by highly drug resistant isolates can influence outcome, but it is very difficult to ascertain the impact due to a number of confounding factors beyond the control of investigators.

References:

1. Janda JM and Abbott SL. The Enterobacteria 2nd edition 2006:13-60. Published by Lippincott Raven Philadelphia/ New York.
2. Zahar JR, Lortholary O, Martin C, Potel G, Plesiat P, Nordmann P. Addressing the challenge of extended spectrum beta-lactamases. Curr Opin Investig Drugs. 2009;10:172-80.
3. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial disk tests; Approved Standards, 9th ed. CLSI Document M2- A9;26 (1). Wayne PA: 2006
4. Khanfar HS, Bindayna KM, Senok AC, Botta GA Extended spectrum beta-lactamases (ESBL) in *Escherichia coli* and *Klebsiella pneumoniae*:

trends in the hospital and community settings. J Infect Dev Ctries. 2009;3:295-99.
5. Ali AM, Rafi S, Qureshi AH Frequency of extended spectrum beta lactamase producing gram negative bacilli among clinical isolates at clinical laboratories of Army Medical College, Rawalpindi. J Ayub Med Coll Abbottabad. 2004;16:35-37.
6. Babypadmini S, Appalaraju B. Extended-spectrum β -lactamases in urinary isolates of *Escherichia coli* and *Klebsiella pneumoniae* - prevalence and susceptibility pattern in a tertiary care hospital. Indian J Med Microbiol 2004;22:172-74
7. Tankhiwale SS., Jalgaonkar SV., Ahamad S & Hassani U Evaluation of extended spectrum beta lactamase in urinary isolates Indian J Med Res 2004;120: 553-56
8. Menon T, Bindu D, Kumar CP, Nalini S, Thirunarayan MA. Comparison of double disc and three dimensional methods to screen for ESBL producers in a tertiary care hospital Indian J Med Microbiol. 2006;24:117-20.
9. Gudiol C, Calatayud L, Garcia-Vidal C, Lora-Tamayo J, Cisnal M, Duarte R *et al* Bacteraemia due to extended-spectrum β-lactamase-producing *Escherichia coli* (ESBL-EC) in cancer patients: clinical features, risk factors, molecular epidemiology and outcome J Antimicrob Chemother 2010; 65:333-41.
10. Mahesh E, Ramesh D, Indumathi V.A, Punith K, Kirthi R and Anupama H.A, Complicated Urinary Tract Infection in a Tertiary Care Center in South India. Al Ameen J Med Sci 2010;3 :1 2 0 - 2 7
11. Shivaprakasha S., Radhakrishnan K., Gireesh A. & Shamsul K P. Routine Screening for ESBL Production, a Necessity of Today. The Internet Journal of Microbiology. 2007; 3
12. Piroth L, Aube H, Doise JM, Martin MV. Spread of ESBL - producing *K. pneumoniae*. Are - lactamase inhibitors of therapeutic value? Clin Infect Dis 1998;27:76-80
13. Rao Sridhar PN, Basavarajappa KG, Krishna GL. Detection of extended spectrum beta-lactamase from clinical isolates in Davangere. Indian J Pathol Microbiol 2008;51:497-9
14. Superti SV, Augusti G, Zavascki AP Risk factors for and mortality of extended-spectrum-beta-lactamase-producing *Klebsiella pneumoniae* and *Escherichia coli* nosocomial bloodstream infections. Rev Inst Med Trop Sao Paulo. 2009 ;51:211-16
15. Goyal A, Prasad KN, Prasad A, Gupta S, Ghoshal U, Ayyagari A. Extended spectrum beta-lactamases in *Escherichia coli* & *Klebsiella pneumoniae* & associated risk factors. Indian J Med Res 2009;129:695-700
16. Lee CI, Lee NY, Yan JJ, Lee HC, Ko NY, Chang CM *et al* Extended-spectrum beta-lactamase-producing phenotype signifies a poor prognosis for patients with cefpodoxime-resistant *Escherichia coli* or *Klebsiella pneumoniae* bacteremia. J Microbiol Immunol Infect 2009; 42:303-9.
17. Khanfar HS, Bindayna KM, Senok AC, Botta GA Extended spectrum beta-lactamases (ESBL) in *Escherichia coli* and *Klebsiella pneumoniae*: trends in the hospital and community settings. J Infect Dev Ctries. 2009;3:295-99.
18. Tumbarello M, Sali M, Trecarichi E M, Leone F, Rossi M, Fiori B, *et al* Bloodstream Infections Caused by Extended-Spectrum β Lactamase-Producing *Escherichia coli*: Risk Factors for Inadequate Initial Antimicrobial Therapy Antimicrob Agents Chemother. 2008;52:3244–52.
19. Ozgunes I, Erben N, Kiremitci A, Kartal ED, Durmaz G, Colak H *et al*. The prevalence of extended-spectrum beta lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* in clinical isolates and risk factors. Saudi Med J 2006; 27:608-12.
20. Shiju M P, Yashavanth R, Narendra N. Detection of extended spectrum beta-lactamase production and multidrug resistance in clinical isolates of *E.coli* and *K.pneumoniae* in Mangalore. Journal of Clinical and Diagnostic Research. 2010; 4:2442-45
21. Shakil S, Ali SZ, Akram M, Ali SM, Khan AU. Risk factors for extended-spectrum beta-lactamase producing Escherichia coli and Klebsiella pneumoniae acquisition in a neonatal intensive care unit. J Trop Pediatr. 2010; 56:90-6.
22. Kang CI, Kin SH, Kim DM, Park WB, Lee KD, Kim HB, *et al.* Bloodstream Infections Due to Extended-Spectrum_-Lactamase-Producing *Escherichia coli* and *Klebsiella pneumoniae*: Risk Factors for Mortality and Treatment Outcome, with Special Emphasis on Antimicrobial

Therapy. Antimicrob Agents Chemother. 2004;48: 4574–81.

23. Schwaber MJ, Navon-Venezia S, Kaye KS, Ben-Ami R, Schwartz D, Carmeli Y. Clinical and economic impact of bacteremia with extended-spectrum-beta-lactamase-producing Enterobacteriaceae. Antimicrob Agents Chemother. 2006;50:1257-62.

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