Brief Communication

Epidemiological Analysis of Extended-Spectrum Beta-Lactamase-Producing Bacterial Infections in Adult Live Donor Liver Transplant Patients

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Abstract

Introduction: Bacterial infections are a leading cause of morbidity and mortality in patients receiving solid-organ transplants. Extended-spectrum beta-lactamases (ESBL) pathogens are the most important pathogenic bacteria infecting these patients. **Aim:** This study aims to evaluate for the incidence and characteristics of ESBL-positive organism, to look for the clinical outcomes in ESBL-positive infected cases, and to evaluate and draft the antibiotic policy in posttransplant patients during the first 28 days posttransplant. **Materials and Methods:** This is a retrospective data analysis of liver transplant recipients infected with ESBL culture-positive infections. All the culture sites such as blood, urine, and endotracheal tube aspirates were screened for the first ESBL infection they had and noted. This data were collected till day 28 posttransplant. The antibiotic susceptibility pattern and the most common organism were also noted. **Results:** A total of 484 patients was screened and 116 patients had ESBL-positive cultures. Out of these, 54 patients had infections and 62 patients were ESBL colonizers. The primary infection site was abdominal fluid (40.7%), with *Klebsiella* accounting for most of the ESBL infections. Colistin was the most sensitive antibiotic followed by tigecycline. The overall mortality was 11.4% and 31 out of 54 ESBL-infected patients died. **Conclusions:** Infections with ESBL-producing organism in liver transplant recipients has a high mortality and very limited therapeutic options.

Keywords: Extended-spectrum beta-lactamases, *Klebsiella*, liver transplant recipients

Introduction

Bacterial infections are a leading cause of morbidity and mortality in patients receiving solid-organ transplants.[1-3] Liver transplantation is a standard lifesaving procedure for the treatment of many acute and chronic end-stage liver diseases. Although infections can occur at any time after transplantation,[4] their incidence is highest during the 1st postoperative month.[2,3]

Bacteria such as *Klebsiella pneumoniae*, *Escherichia coli*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, and related species are some of the most important pathogenic bacteria causing infection in transplant patients. It has been reported that these organisms had acquired a transmissible form of drug resistance conferred by-extended-spectrum beta-lactamases or (ESBLs). ESBLs are especially dangerous because they are plasmid/transposon associated, and the plasmids/transposons may be exchanged among a variety of bacterial species, thus adding to development and spreading of resistance in various species of organisms.[5,6]

More than 50 studies (describing in total >3000 patients) have been published in peer-reviewed medical literature utilizing molecular typing methods in the study of the epidemiology

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of nosocomial infections with ESBL-producing organisms. The main reason of treatment failure of ESBL-producing organisms is development of multidrug resistance (MDR). They often remain susceptible only to carbapenems and these agents remain the drugs of choice for treatment of infection in case of suspected and susceptible culture-positive cases.[7] With growing resistance against carbapenems and other classes of antibiotics, the antibiotic arsenal against these ESBL-producing organisms has been further compromised.

This study presents the retrospective analysis of culture-positive liver transplant patients that will help us in providing information regarding incidence of infection, possible source of infection, organisms causing infections, their sensitivity patterns, and expected mortality in infected population to formulate a consensus on the appropriate use of empiric and directed antibiotic therapy that can effectively curtail infection in these patients.

Materials and Methods

This retrospective analysis of cases of live donor liver transplant patients was conducted at a multispecialty tertiary care hospital situated at Gurgaon, Haryana, India. All the adult live donor liver transplant recipients in 2 years were studied. Patients showing signs of infection with culture positivity for ESBL-producing organism were included in the study. Data of patients were collected till 28 days posttransplant surgery.

Main objectives of this study were to evaluate for the incidence and characteristics of ESBL-positive organism, to look for the clinical outcomes in ESBL-positive infected cases, and to evaluate and draft the antibiotic policy in posttransplant patients during the first 28 days posttransplant. Patient's data was screened and Age, Sex, type of microorganism, Site of Infection, antibiotic susceptibility pattern, history of previous hospitalization, antibiotics used as a part of empiric and directed antimicrobial therapy were recorded. First positive culture was registered as index infection and source recorded as primary source. If the same patient was positive for some additional organism, it was registered as secondary infection and source recorded as secondary source of infection.

All the cultures including blood, urine, drain fluid, and endotracheal tube aspirate were sent for first 5 days posttransplant and repeated as and when required. Blood culture was done using the BacTAlert™ 3D system, identification and susceptibility pattern of culture flashing positive was done on automated VITEK 2™ system using appropriate ID and antibiotic susceptibility testing cards. In case of cultures other than blood, conventional methods of culture were used. Species identification and sensitivity pattern were always done using VITEK 2 system. A total of 484 patients were included in the study, 146 of which were culture negative during the whole period of 28 days. Patients that developed culture positivity after the follow-up period of 29 days were 119 in number and thus excluded. A total of remaining 219 were culture-positive cases, of whom 103 patients were positive for non-ESBL-producing organisms with 45 being colonizers and 58 were infected. ESBL-producing organisms were positive in a total of 116 patients, out of these 116 patients 54 were infected and 62 showed no signs of infection [Figure 1].

Statistical methods

The analysis included profiling of patients on different demographic, source of infection, organism types, antibiotic susceptibility patterns, and mechanism of resistance. Cross tables were generated between types of organism and source of infection (primary and secondary). Mortality and survival details have been presented for each of the four different ESBL groups. Chi-square test was used for testing of significance of associations. Quantitative data relating to Intensive Care Unit (ICU) stay and model for end-stage liver disease (MELD) score have been presented in terms of means and standard deviation. Student's *t*-test was used for comparison of quantitative outcome parameters. $P < 0.05$ is considered statistically significant. SPSS software Version 23.0 was used for statistical analysis.

Results

Extended-spectrum beta-lactamases-producing organisms

Among the 54 patients (40 males and 14 females) in whom cultures were positive for ESBL-producing organisms, the youngest patient was 23-year-old female and oldest was 67-year-old female. As shown in Table 1, more male patients were affected than female patients.

Primary infection

The primary source of infection was abdominal fluid (40.7%) followed by sputum (27.7%), blood (24.07%), and urine (7.4%) [Table 2].

Among all the ESBL-producing organisms, *Klebsiella* spp. accounted for a maximum number of cases (51.85%) followed by *Pseudomonas* spp. (24.07%), *Acinetobacter* spp. (12.96%), and *E. coli* (11.11%) [Table 3].

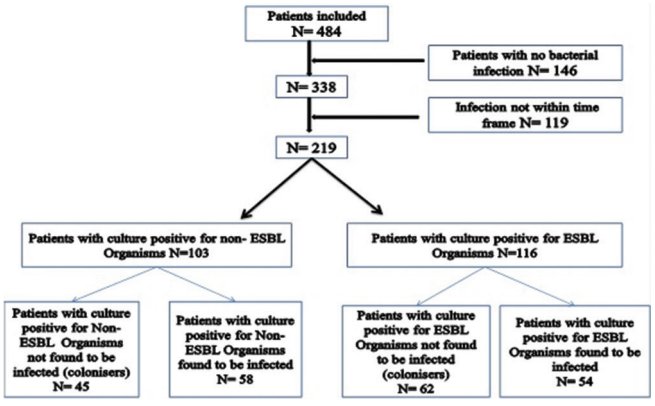

Figure 1: Summary of patient inclusion

Antibiotic susceptibility patterns

Culture sensitivity pattern of *Klebsiella* spp. showed that this ESBL-producing organism had resistance to carbapenems, other beta-lactams, quinolones, and tetracycline [Table 4]. ESBL *Klebsiella* was sensitive to colistin in almost all the cases. Sensitivity of *Klebsiella* was relatively preserved for amikacin (17/28) and tigecycline (8/28). *Pseudomonas* spp. was reported in 14 cases; 12 were sensitive to colistin and 2 were pan resistant. Sensitivity for carbapenems was 3/14 and 2/14 for piperacillin and tazobactam.

E. coli was reported in six cases. *E. coli* was sensitive to amikacin in 4/6 cases, to gentamicin in 3/6 cases, to imipenem and meropenem in 3/6 cases, to tigecycline 5/6 cases, and was sensitive to colistin in all the cases.

Acinetobacter spp. was positive in five cases, all of which were sensitive to colistin and tigecycline and was resistant to all other class of drugs including carbapenems.

Table 1: Distribution of patients according to age and gender

Age group (years)	Number of males	Number of females
0-30	0	2
31-60	32	10
61-70	8	2
Total	40	14

Table 2: Primary source of infections

Source of infection	Number of patients (%)
Sputum	15 (27.7)
Blood	13 (24.07)
Urine	4 (7.4)
Abdominal fluid	22 (40.7)

Table 3: Primary source organisms

Name of organisms	Number of patients (%)
Klebsiella spp.	28 (51.85)
Pseudomonas spp.	13 (24.07)
Escherichia coli	6 (11.11)
Acinetobacter spp.	7 (12.96)

Secondary infection

A total of 17 patients developed secondary infection. Source of infection in maximum number of cases was abdomen (52.9%) followed by blood (23.5%), sputum (17.6%), and urine (5.8%) [Table 5].

Klebsiella (52.9%) was predominant in cases of secondary infection followed by *Pseudomonas* spp. (23.5%) and *Acinetobacter* spp. (23.5%) [Table 6].

In case of secondary infection, *Klebsiella* was sensitive to colistin in all the cases followed by tigecycline (5/9), amikacin (3/9), and meropenem (1/9) cases. *Pseudomonas* spp. was sensitive to colistin in all cases, was relatively sensitive to aminoglycosides (amikacin 3/5, gentamicin 3/5, and tobramycin 2/5 cases), ciprofloxacin 3/5 cases, and was resistant to other class of drugs.

Acinetobacter spp. was reported in five cases. Out of them three were sensitive to both Colistin and Tigecycline, one was sensitive to Colistin only and one case was pan resistant Acinetobacter spp. [Table 7a].

While evaluating for mechanism of resistance beta-lactamases production, impermeability and efflux pumps were the

Table 4: Antibiotic susceptibility patterns

	Klebsiella spp.	*Pseudomonas* spp.	*Escherichia coli*	*Acinetobacter* spp.
Amikacin	12	5	4	0
Ampicillin	0	0	0	0
Ampicillin/sulbactam	1	0	0	0
Aztreonam	0	0	0	0
Cefazolin	0	0	0	0
Ceftriaxone	0	0	0	0
Ciprofloxacin	1	1	0	0
Cefepime	0	1	0	0
Ertapenem	1	0	2	0
Gentamicin	3	2	3	1
Imipenem	1	3	3	0
Meropenem	1	2	3	0
Moxifloxacin	1	-	1	0
Piperacillin/tazobactam	1	2	1	0
Tigecycline	8	0	5	5
Tobramycin	1	2	0	0
Trimethoprim/sulfamethoxazole	1	0	0	0
Cefoperazone/sulbactam	1	0	0	1
Colistin	27	12	6	5

predominant factors. Impermeability was associated in almost all the cases in both primary and secondary infections.

Table 5: Secondary source of infection

Source of infection	Number of patients (%)
Abdominal fluid	9 (52.9)
Blood	4 (23.5)
Sputum	3 (17.6)
Urine	1 (5.8)
Total	17 (100)

Table 6: Secondary source organisms

Organism	Total, *n* (%)
Klebsiella	9 (52.9)
Pseudomonas spp.	4 (23.5)
Escherichia coli	0
Acinetobacter spp.	4 (23.5)
Total	17 (100)

Efflux pump overfunction was detected in *Klebsiella*, *Acinetobacter*, and *Pseudomonas* in primary infection. This mechanism was found in *Pseudomonas* in secondary infection. Carbapenemases were detected in all the cases of *Klebsiella*, *E. coli*, and few cases of *Pseudomonas* in primary infection. In case of secondary infection, carbapenemases were detected in all the cases of *Klebsiella*, *Acinetobacter*, and *Pseudomonas*. No carbapenemases were detected in *E. coli*-infected patients [Table 7b].

Mortality

Overall mortality [Tables 8 and 9] in the study population was 11.4%. Mortality in noninfected patients was 5.4%. Ten out of 58 patients died, which was slightly higher than the noninfected group. Mortality was highest in patients infected with ESBL-producing organisms (31/54). Of all the ESBL-producing organisms infected patients, highest number of patient died were those infected with ESBL-producing *Pseudomonas* spp. (51%) followed by *Klebsiella* (50%), *Acinetobacter* spp. (55.7%), and *E. coli* (50%).

Table 7a: Antibiotic susceptibility patterns

	Klebsiella	*Pseudomonas* spp.	*Escherichia coli*	*Acinetobacter* spp.
Amikacin	03	3	0	0
Ampicillin	0	0	0	0
Ampicillin/sulbactam	0	1	0	0
Aztreonam	0	0	0	0
Cefazolin	0	0	0	0
Ceftriaxone	0	1	0	0
Ciprofloxacin	0	3	0	0
Tetracyclin	0	1	0	0
Cefepime	0	2	0	0
Ertapenem	0	0	0	0
Gentamicin	0	3	0	0
Imipenem	0	1	0	0
Meropenem	1	1	0	0
Moxifloxacin	0	0	0	0
Piperacillin/tazobactam	0	1	0	0
Tigecycline	5	0	0	3
Tobramycin	0	02	0	0
Trimethoprim/ sulfamethoxazole	0	0	0	0
Cefoperazone/sulbactam	0	1	0	0
Colistin	9	5	0	4
Levofloxacin	0	1	0	0

Table 7b: Mechanism of resistance

	Primary source				Secondary source			
	Beta-lactamases	Carbepenemases	Impermeability	Efflux pump	Beta-lactamases	Carbepenemases	impermeability	Efflux pump
Klebsiella	28	28	28	3	9	9	9	0
Acinetobacter spp.	7	0	7	2	4	4	4	0
Escherichia coli	4	4	4	0	0	0	0	0
Pseudomonas spp.	12	2	12	4	5	5	5	4

Table 9 shows mortality in ESBL-producing organisms was highest in *Acinetobacter* spp. in primary and *Klebsiella* in secondary infections. Other organisms that followed were *Pseudomonas* spp., *Klebsiella*, and *E. coli* in primary while *Pseudomonas* spp. and *Acinetobacter* spp. in secondary infection.

Nonextended-spectrum beta-lactamases organisms

Of all the 58 patients infected with non-ESBL organisms, majority were isolated from blood (43%) followed by abdominal fluid (36.2%), sputum (10.34%), urine (5.1%), pus (3.4%), and throat swab (1%) [Table 10].

Organisms isolated in majority of the cases were *Staphylococcus* species (39.6%) (three were *Staphylococcus aureus* out of which one was methicillin-resistant *S. aureus* [MRSA]). The second most common infection was with *Candida* which was isolated in 25.86% of the cases positive for non-ESBL cases. Other organisms that followed were *Enterococcus* (18.9%), *Stenotrophomonas maltophilia* (6.8%), *Salmonella* paratyphi (3.4%), *Sphingomonas paucimobilis* (1.7%), *Burkholderia cepacia* (1.7%), and *Streptococcus* (1.7%). Of all non-ESBL infections, highest number of patients died of *Candida* infection (20%) and *Staphylococcus* infections (17.39%) [Table 11].

MELD scores were higher and statistically significant for ESBL infection but were not statistically significant when compared to patients who were culture negative.

Patients with ESBL infections have longer duration of ICU stay. Longest ICU stay being 28 days and shortest being 2 days [Table 12].

Table 8: Mortality in all 484 patients (infected and noninfected)

Study group	Total	Alive	Deaths	*P**
ESBL-producing infected patients	54	23	31	<0.001**
Non-ESBL-producing infected patients	58	48	10	0.19
ESBL-positive noninfected patients	62	56	6	0.81
Non-ESBL-positive noninfected patients	45	40	5	0.848
Nonculture-positive noninfected patients	146	138	8	0.01***
Total patients enrolled	484	429	55	NA

*Chi-square test with Yates correction, **Highly significant $P<0.001$, ***Significant $P<0.05$. NA: Not applicable; ESBL: Extended-spectrum beta-lactamases

Table 9: Percentage mortality in patients with primary and secondary infection

Organisms	Mortality in patients with primary infection		Mortality in patients with secondary infection	
	Total	Deaths (%)	Total	Deaths (%)
Klebsiella	28	14 (50)	9	7 (77.77)
Pseudomonas spp.	13	8 (61.53)	4	3 (75)
Acinetobacter spp.	7	6 (85.71)	4	2 (50)
Escherichia coli	6	3 (50)	0	0

Table 10: Nonextended-spectrum beta-lactamases organisms: Source of infection

Source	Number of patients (%)
Blood	25 (43.1)
Urine	3 (5.1)
Body fluid	21 (36.20)
Sputum	6 (10.34)
Throat swab	1 (1.7)
Pus	2 (3.4)
Total	58 (100)

Discussion

Bacterial infections are a leading cause of morbidity and mortality in liver transplant patients and incidence of infection is highest during the 1st postoperative month.[2-4] Factors including severity of underlying illness at the time of transplant, other comorbidities, persisting infections, colonization, breaches in mucocutaneous barrier resulting from surgery, immunosuppression, volume of blood products transfused, bilio-entertic anastomosis, hepatic artery thrombosis, graft dysfunction, and *Cytomegalovirus* infection make a patient more prone to infections, and thus increase ICU stay and postoperative mortality.[2,8-16]

Emergence of MDR pathogens has made the treatment challenging and in turn has increased mortality in posttransplant patients following infection.[17-24] Bacteremia has been the main cause of morbidity and mortality during the 1st month.[8] Primary and secondary sources of infection at our center in majority of cases were abdominal fluid followed by sputum, blood, and urine.

In contrast to Western countries where the incidence of Gram-positive infections is highest, majority of infections in our study were caused by Gram-negative bacteria followed by Gram-positive bacteria and fungi. Among Gram-negative bacteria, majority were ESBL-producing organisms. Mortality among patients infected with ESBL-producing organisms was higher as compared to those not infected and those infected with non-ESBL-producing organisms. Mortality among those with colonization only and noninfected patients was comparable, which was contrary to the findings of Giannella *et al*. probably because no culture-positive patients were taken for transplant surgery.[25] ESBL-producing *Klebsiella* accounted for highest number of culture-positive infections in both primary and secondary infections with very high mortality, *Klebsiella* was followed by *Pseudomonas* spp., *Acinetobacter* spp., and *E. coli*.[26,27] In non-ESBL culture-positive cases, major source was blood followed by ascitic fluid, sputum,

urine, throat swabs, and pus. *Staphylococcus* accounted for highest number of cases with a high mortality rate of 17.39% (three *Staphylococcus aureus* cases out of which two were MRSA). *Candida* infections were a close second with a mortality rate of 20%. Other infections included *Enterococcus*, *Streptococcus*, *Stenotrophomonas*, *Sphingomonas*, *B. cepacia*, and *Salmonella* paratyphi. ESBL-positive infections (57.4%) caused significantly high mortality as compared to noninfected patients and patients infected with non-ESBL-producing organisms. Patients infected with ESBL-producing organisms had longer ICU stay and had higher mortality. Patients with higher MELD score were more prone to infections with ESBL-producing organisms but was not statistically significant when compared to noninfected patients, Similar findings have been reported in numerous number of studies done earlier.[14,27,28]

Table 11: Nonextended-spectrum beta-lactamases organisms infection

Organism	Number of patients	Percentage in non-ESBL spp.	Number of patients died	Percent mortality
Candida spp.	15	25.86	3	20
Enterococcus	11	18.9	1	9.1
Staphylococcus spp.	23	39.6	4	17.39
Streptococcus spp.	1	1.7	0	-
Stenotrophomonas maltophilia	4	6.8	1	25
Sphingomonas paucimobilis	1	1.7	0	-
Burkholderia cepacia	1	1.7	1	100
Salmonella paratyphi	2	3.4	0	-
Total	58	100	10	17.24

ESBL: Extended-spectrum beta-lactamases

Culture sensitivity pattern showed ESBL organisms to have developed resistance to carbapenems where beta-lactams, fluoroquinolones, aminoglycosides, and tetracycline but were sensitive to colistin in almost all the cases. Two cases of MDR *Acinetobacter* spp. resistant to all including colistin were reported.

Mode of resistance for carbapenems and other classes of antibiotics in ESBL-producing Gram-negative organisms is generally because of production of ESBLs, carbepenemases, impermeability of outer membrane, and overexpression of efflux pumps. In our study, mode of resistance to carbapenems is due to the production of carbepenemases. Impermeability of outer membrane was present in almost all carbapenemase-producing bacteria. Impaired penetration to antibiotics and development of efflux pump has resulted in resistance to wide range of antibiotic. *Pseudomonas* spp. was found to have developed overexpression of efflux pumps in addition to impermeability in 42% of the cases. All the patients with efflux pump were resistant to all classes of antibiotics except colistin.

Conclusions

Infection is the major cause of mortality and morbidity after liver transplantation and in turn adds to the cost of treatment. Pertaining to the above culture sensitivity patterns and mode of resistance, empirical therapy with carbapenems/beta-lactamase inhibitors does not sound foolproof. The high mortality observed with these infections reflects very limited therapeutic options.

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Nil.

Table 12: ICU stay and MELD score in ESBL vs non ESBL groups

Case	ESBL-producing infected patients (Group 1) (n=54)	Non-ESBL-producing infected patients (Group 2) (n=58)	ESBL-positive noninfected patients (Group 3) (n=62)	Non-ESBL-positive noninfected patients (Group 4) (n=45)	Nonculture-positive noninfected patients (Group 5) (n=146)
ICU stay	13.20±8.08	7.51±4.19	6.79±3.140	7.13±2.23	6.83±2.27
MELD score	19.16±6.57	18.48±5.02	16.61±5.22	16.22±3.85	17.65±5.94
Comparison			***P***		
			ICU stay		**MELD score**
Group 1 versus Group 2			0.0001*		0.538
Group 1 versus Group 3			0.0001*		0.022*
Group 1 versus Group 4			0.0001*		0.009*
Group 1 versus Group 5			0.0001*		0.123
Group 2 versus Group 3			0.287		0.048*
Group 2 versus Group 4			0.583		0.014*
Group 2 versus Group 5			0.138		0.349
Group 3 versus Group 4			0.536		0.672
Group 3 versus Group 5			0.918		0.233
Group 4 versus Group 5			0.437		0.131

P-value significant $P<0.05$. MELD: Model for end-stage liver disease; ICU: Intensive Care Unit; *Statistically significant

Conflicts of interest

There are no conflicts of interest.

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