BACTERIAL INFECTIONS IN PEDIATRIC LIVER TRANSPLANT PATIENTS BETWEEN 2016 AND 2021

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ABBREVIATIONS PAGE

CRE	Carbapenem-resistant Enterobacteriaceae
ESBL	Extended-spectrum beta-lactamase
LT	Liver transplant
MDR-GNB	Multi-drug resistant Gram-negative bacilli
UTI	Urinary tract infections
SOT	Solid organ transplant

ABSTRACT

Background: Immunosuppression predispose solid organ transplant recipients to clinically significant infectious complications. This paper sought to characterize the bacterial infections of pediatric liver transplant patients at a high complexity national referral center.

Method: A descriptive, retrospective study, included pediatric liver transplant recipients, was performed between July 2016 and 2020 at Fundación Cardioinfantil in Bogotá, Colombia. Data were collected on hospital admissions documenting bacterial infections from the time of transplant up to September 2021.

Results: A total of 126 patients were identified, 3 retransplanted and 316 infectious episodes; 65.07% were females, 51.94% were under one year old, and 53.17% had a diagnosis of biliary atresia. Altogether, 75.97% patients had at least one bacterial infection during the transplant hospitalization, and 76.98% had 1 to 14 hospitalizations with infections; intraabdominal infections were the most frequent 33.41%. A third of the infections occurred within the first month after transplant, with a reduction in infectious events in the subsequent six months. *Escherichia coli* and *Klebsiella pneumoniae* were the most frequent isolates; CRE were documented in 18 hospitalizations. The most used empirical treatment was ampicillin/sulbactam (24.21%) with a mean treatment period of 13.13 days; 55.80% had viral and/or fungal coinfections, and this group had a greater mortality, with a significant difference. The mean hospitalization time was 17.99 days. A total infection-related mortality recorded was 10.32% with 1.59% due to CREs.

Conclusion: Infections are a significant cause of morbidity among children receiving liver transplants in our setting.

Keywords: Bacterial infections, Liver transplant, pediatric liver transplant.

INTRODUCTION

Advances in solid organ transplants techniques and treatments have provided a growing survival benefit for patients who develop terminal organ dysfunction[1]. Specifically for liver transplantation, the morbidity and mortality of pediatric patients with various diseases has decreased very significantly over the last years.

Patients who receive solid organ transplants require prolonged immunosuppressant therapy for the transplanted organ to be accepted. However, the potential for surgical complications, together with the impact of immunosuppression, predisposes solid organ transplant recipients to clinically significant infectious complications[1]. There are pre as well as post-transplant interventions aimed at preventing these infections.

The most reported infectious complication following solid organ transplantation is bacterial infection [2]. Specifically, infections caused by resistant microorganisms can not only lead to increased morbidity and mortality but can also affect the graft. The implementation of clinical guidelines has helped optimize the prophylaxis strategies against the main opportunistic microorganisms [3].

It is essential to be aware of the bacterial infections which occur in pediatric patients after liver transplantation, as well as the infectious agents most frequently involved, which will allow prevention, care and treatment strategies to be designed. As far as we know, this is the first study on bacterial infections in this group of patients in Colombia and Latin America. Our objective is to characterize the bacterial infections which occurred in pediatric liver transplant (LT) recipients at a high complexity referral institution in Colombia.

MATERIALS AND METHODS

A chart review was performed for 126 pediatric patients with liver transplantation carried out between July 2016 and July 2020 at Fundación Cardioinfantil, collecting demographic data as well as data from the transplant hospitalization and all other hospital admissions in which a bacterial infection was found, up to September 2021.

The information was recorded in a Microsoft Excel database. Statistical analysis was performed using IBM® SPSS Statistics 22. Measures of central tendency and dispersion were used for quantitative variables, as well as absolute and relative frequencies of the bacterial infectious episodes. The Chi square statistical test was used to compare the distributions of qualitative variables. The study was approved by the institutional Research and Ethics Committees.

RESULTS

A total of 126 transplant patients were identified during the study period; of these, three were retransplanted and 316 infectious episodes were detected.

Regarding demographic characteristics, 65.07% (82) were female and 34.92% (44) were male, 51.94% (67) were under one year old, 10.85% (14) between one and two years old, 13.95% (18) between two and five years old, 10.85% (14) between six and ten years old, and 12.40% (16) were over the age of ten. Forty-seven patients were from Bogotá, followed by 37 from the Andean region, and 30 from the Caribbean region. Most patients arrived from home; only 13 (10.32%) were referred from another healthcare center.

As to the underlying pathology, 53.17% (67) had biliary atresia, followed in frequency by hepatoblastoma 7.94% (10), familial intrahepatic cholestasis 6.35% (8) and autoimmune hepatitis 6.35% (8) (Table 1).

One hundred percent of the patients were started on immunosupresive treatment during transplantation, using methylprednisolone and tacrolimus, as established by the institutional protocol. Ninety-eight patients (75.97%) were diagnosed with at least one bacterial infection during the transplant hospitalization.

One hundred percent of the transplant patients received antimicrobial surgical prophylaxis. A combination of ampicillin + cefotaxime was used in 58 transplants (46.03%), followed by piperacillin/tazobactam in 26 (20.63%) and ampicillin/sulbactam + cefotaxime in 12 cases (9.52%). The mean duration of surgical prophylaxis was 3.90 days, although antimicrobial treatment was scaled up in 72.09% (93) of the patients in the first 72 hours after transplantation. Twenty-six patients (20.6%) had surgical complications. During the transplant hospitalization, fever and elevated acute phase reactants were the main reasons for beginning or scaling up antibiotic treatment (inpower 72.16% and 75.26% of the patients, respectively). No statistically significant relationship was found between surgical complications and the number of hospitalizations for bacterial infections after liver transplantation (X^2: 11,104, p: 0.269).

Of the 126 patients, 29 (23.02%) did not have infections after liver transplantation up to September 2021; 97 children (76.98%) had between 1 and 14 hospitalizations with at least one bacterial infection, with a mean of 8.78 hospitalizations. Of these, 33.65% (103) occurred during the first month after transplantation, with 14.15% (45) between 1 and 6 months, 35.53% (110) between 6 and 12 months, and 16.67% (53) more than 12 months after transplant.

In 74.84% of the hospital admissions the patients had a single infectious episode, 19.18% had two, 3.77% had three and 2.2% had four or more infections. Intraabdominal infections were the most common with at 33.41%, followed by pneumonias and urinary tract infections (UTI) in 12.35% and 12.11%, respectively. The most reported symptom was fever, followed by respiratory symptoms and diarrhea.

As shown in the Figure 1, intraabdominal infections occurred mainly in the first month after transplantation. Respiratory and skin and soft tissue infections were most

frequent between 6 and 12 months after transplant. A statistically significant relationship was found between the post-transplant period and the number of infections per hospitalization (x^2 = 15.561, p: 0.016).

Cultures were taken in 88.6% of the hospitalizations, with blood cultures being the most frequent, followed by urine cultures. The most common microbiological isolates were *Escherichia coli, Klebsiella pneumoniae* and *Enterococcus faecium* in blood; *Escherichia coli, Klebsiella pneumoniae* and *Proteus mirabilis* in urine*;* and *E. coli* and *Salmonella spp.* in stool cultures. Likewise, *E. faecium, K. pneumoniae* and *Pseudomonas aeruginosa* were the most frequent in peritoneal fluid, *E. coli* and *E. faecium* the most common in bile, and *Staphylococcus aureus* and *K. pneumoniae* were the most common in secretions (orotracheal, tracheal, superficial, abscesses, etc.) No bacteria were isolated in 61.3% (195) of the hospital admissions.

Carbapenem-resistant enterobacteriaceae (CRE) isolates were recorded in 18 hospitalizations, with *K. pneumoniae* being the most frequently microorganism found (11). Patients who had received or not carbapenems within the three months prior were compared in regard to CRE infections after transplant, finding a statistically significant difference (X^2= 215.271; p=<0.001). (Table #2).

The most frequently used empirical treatment was ampicillin/sulbactam as monotherapy (n: 77, 24.21%), followed by piperacillin/tazobactam (n: 63, 19.81 %) and the combination of meropenem + vancomycin (n: 32, 10.06%). In 21.07% of the hospitalizations, the patients received a minimum of three different antimicrobial schemes. The overall mean duration of antibacterial treatment was 13.13 days (range: 1-107)., A carbapenem was ordered as treatment in 35.22% of the hospitalizations, and the mean duration was 14.25 days (range: 1 – 50).

Ten healthcare-associated infections (HAIs) were identified. In 178 hospitalizations (55.80%), the children had viral, fungal, parasitic or mycobacterial coinfections, with greater mortality in patients with coinfections (a statistically significant difference [X^2= 133.191 p= 0.000]). Acute rejection was documented in 15.82% of the hospitalizations.

The mean length of hospitalization was 17.99 days (SD 17.91), with a statistically significant relationship between post-transplant period and days of hospitalization ($X^{2:}$ 277.177, p= <0.001).

Overall, infection-related mortality was 10.32% and CRE mortality was 1.59% of all hospitalizations.

Discussion

In our description, the distribution by sex was similar to that reported by Schwake et al. in 2020, as it was the mean age at transplant, which was 41.08 ± 52 months [1], with most patients were under one year of age. The disease leading to

transplantation was biliary atresia (53.17%), which coincides with the rest of the published pediatric case series [1,2].

In a study of 235 bacterial infections in 162 pediatric liver transplant patients, the maximum number of bacterial infections per patient was six [1]. This is a much lower value than one found in our cohort in which, in addition, the mean number of hospitalizations for bacterial infections after transplant was 8.78, with the possibility of a hospitalized patient having more than one infection, which would make this figure even greater.

Immunosuppression in this population includes an induction regimen at transplantation and a maintenance regimen to prevent rejection [4]; these may vary according to the center and transplanted organ. In our center, induction is done with high-dose corticosteroids, which are also used for maintenance therapy and for treating rejection, due to their anti-inflammatory and immunosuppressant effects [4]. Calcineurin inhibitors (tacrolimus and cyclosporine) are one of the pillars of immunosuppressant maintenance scheme. As already mentioned in the institutional protocol, 100% of patients received methylprednisolone during the transplant, followed by tacrolimus. The most frequently used maintenance regimen was prednisolone + tacrolimus in varying doses.

Twenty percent of the patients had surgical complications, with a statistically significant relationship between surgical complications and the number of infections during the liver transplant hospitalization (X^2: 10.123, p: 0.018), but this was not associated with the number of hospitalizations for bacterial infections. Surgical complications have been associated with up to 75% of infectious episodes [5], and have been widely described [6].

The most frequently reported symptom was fever and, specifically in the early postoperative period, fever and elevated acute phase reactants were the main reason for scaling up antimicrobial treatment (72.16% and 75.26%). A high incidence of fever in the first 48 hours after transplant has already been reported, which motivates early initiation of empirical broad spectrum antibiotic treatment and low rates of microbiologically confirmed infection [7].

In our series, follow up of hospitalizations for bacterial infections was carried out for at least one year after transplant in all the included patients, finding that 76.98% of the patients had at least one suspected bacterial infection after transplant. This is a much higher percentage than that of Mueller et al. who reported that 39% (1,086/2,761) of solid organ transplant (SOT) recipients had bacterial infections [8].

One third of the hospitalizations occurred within the first month after transplant, with a subsequent reduction in the number of infectious events in the following one to six months. Likewise, the patients had a greater number of bacterial infections per hospitalization in the first 30 days after transplant, with statistically significant evidence ($x^2 = 15.561$, p: 0.016), as reported by similar studies in this population [6,8].

Other studies in both children and adults show that the incidence of all bacterial infections in LT recipients is higher in the early period, decreasing throughout the first year after transplant [8,9], when viral and fungal infections tend to occur [4,6]. An expected finding was that the less time elapsed since the LT, the greater the length of hospitalization, with a statistically significant association ($X^{2:}$ 277.177, p= <0.001).

It is interesting to note the increase in hospitalizations for bacterial infections between 6 and 12 months after transplant in our cohort. In this stage, the differential diagnosis of infectious syndromes includes graft rejection, persistent infection from the peri-surgical period, surgical complications such as anastomotic leaks, empyema, cholangitis, or infected hematoma, versus opportunistic infections caused by *Pneumocystis jiroveci*, *L. monocytogenes*, or *Nocardia* (none found in our patients, who received trimethoprim & sulfamethoxazole prophylaxis), which also includes *T. gondii*, *Aspergillus*, endemic fungi, or viral infections [6]. It is worth investigating which factors played a part in this case, or the characteristics such as changes in immunosuppression due to graft rejection, which could explain this event.

Specifically related to bacteremias, we found that 57.1% occurred in the first month after transplant, while a study of bloodstream infections in pediatric liver and kidney transplant patients reported that 83% of the cases occurred after the first post-transplant month [9]. Other authors concur with our findings, but with a smaller percentage difference in the first period [8].

The frequency of UTI typically remains the same in all the periods following LT, which is confirmed in our findings [4]. Intra-abdominal infections predominate in the reported cohorts of adult and pediatric liver transplant patients [8], as opposed to ours in which they made up a third of all infections.

As shown in Figure 1, intra-abdominal infections occurred mainly in the first month after transplant. Respiratory, skin and soft tissue infections had their greatest incidence between 6 and 12 months after transplant, mimicking the most frequent infections in the general pediatric population.

Cultures, most frequently blood cultures, were taken in 100% of the hospitalizations with systemic involvement, isolating *E. coli*, *K. pneumoniae* and *E. faecium*. Altogether, 52.73% of the positive blood cultures were identified in the first month after transplant, with a significant decrease in their positivity in the second period (Figure 3). Lee J et al. described a statistically significant difference in the incidence rate of positive cultures between 1-2 weeks after transplant, which decreased up to week 4 and then increased between weeks 4-12 [5].

Regarding the microbiological description of the infections in our group of patients, we coincide in the predominance of enterobacterial infections, regardless of the type of culture [8]. *Pseudomonas* isolates were mainly related to intra-abdominal infections, as has been described, with predominance in the first month after transplant [10]. Figure 2 shows the distribution of microorganisms according to the SOT period in

which they were isolated, finding, for example, that *E. coli* isolates were frequent in all stages, while *H. influenzae* was detected more than 12 months after transplant, which would be expected in this stage according to the prevalence of typical childhood infections[6].

In most hospitalizations there was no microbiological confirmation by culture, which leads us to consider and propose a work window for programs aimed at the control and rational use of antimicrobials [1].

Viral, fungal, parasitic, or mycobacterial coinfections were common (55.80%) and related to a greater mortality (X^2 = 133.191 p= 0.000), which could be due to the fact that the presence of other coinfecting agents entails greater systemic involvement.

Likewise, although rejection rates at 3, 12, 24 and 36 months have been reported at 44.8%, 52.9%, 59.1% and 60.3% [4], respectively, in our series we only recorded cases in which acute rejection was diagnosed during hospitalization, obtaining a rate of 15.82%, with no statistically significant relationship with mortality. It would be worthwhile to obtain more information on the patients who experienced chronic rejection, which would probably produce higher rates.

Regarding CRE infection, these isolates were recorded in 15.6% of the hospitalizations, with *K. pneumoniae* being the most frequently identified bacteria. Half of these isolates were from blood, in contrast to what Leth Moller reported, in whose series of patients with bloodstream infections there was only one extended-spectrum beta-lactamase (ESBL) producing enteric bacterium and no cases of CRE [9]. One study showing the incidence and factors associated with multi-drug resistant Gram-negative bacilli (MDR-GNB) infections following pediatric liver transplantation reported that 25% of the patients developed at least one MDR-GNB infection in the 25 days after transplant [2], most of which were due to ESBL producing enteric bacteria (34 isolates, 58.6 %) and CREs (17.2%), a figure similar to our findings. Prior exposure to broad spectrum antibiotic treatment, prolonged operative time and length of ICU stay are associated with a greater risk of resistant GNB infection [2,4], suggesting the implementation of screening with a rectal culture prior to transplant, contact isolation for colonized patients, strict surveillance of at-risk patients after LT and the rational use of antibiotics as the main measures for preventing infections with resistant bacteria.

In our study, 75.19% of the patients had a rectal culture prior to liver transplantation, but rectal colonization prior to transplant was not statistically significantly related to subsequent CRE infections. However, we found a significant relationship between the use of carbapenems in the three months prior and CRE infections after transplant (X^2= 215.271; p=<0.001). We agree that programs for the rational use of antimicrobials play an essential role in preventing and reducing antimicrobial resistance, and specifically CRE infections [4], which in our center had an associated mortality of 1.59%.

Regarding treatment, enteric bacteria and the *Enterococcus spp*. group have been identified as responsible for most infections in liver transplant patients [8], against which empirical antibiotic coverage should be directed. We found that the most frequently used empirical treatment in our study was ampicillin/sulbactam as monotherapy (24.13%), followed by piperacillin/tazobactam 63 (19.81%). This coincides with the institutional recommendation for intra-abdominal infections, which were the main cause of bacterial disease in the study patients. The next most frequent empirical combination was meropenem + vancomycin (10.06%), observing that an antimicrobial regimen including vancomycin was used in 52.71% of the hospitalizations.

It is interesting to note Shoji et al.'s report which concludes that the standard dose of vancomycin was not sufficient to achieve an AUC/MIC of 400 in pediatric liver transplant patients, suggesting that a higher dose may be needed and that this would depend on the MIC of vancomycin, creatinine clearance and days elapsed since the LT. In our study, we did not evaluate the used dose of vancomycin, but it would be worthwhile to expand this information in future studies [10].

In 35.22% of the hospitalizations, a carbapenem was ordered for treatment and the mean duration was 14.25 days. Bio LL et al. described the impact of the standardization of antimicrobial use in the early postoperative period following liver transplantation in a pediatric liver transplant center in the United States. The result of the intervention was a significant reduction in individuals who received broad spectrum antibiotics for Gram negatives for more than 48 hours after surgery, going from 76% prior to the intervention to 44% after the intervention ($P = 0.01$), and the use of postoperative vancomycin going from 50% prior to the intervention to 7.4% after the intervention ($p < 0.001$), with no statistically significant differences between the groups in postoperative fever, positive cultures and length of hospital stay [7].

Conclusions: This is the first study to attempt to characterize bacterial infections in pediatric liver transplant patients in our setting. Post-transplant bacterial infections are an important cause of morbidity and mortality in this group of patients. This study is limited by its retrospective nature; new studies are needed to expand the information on bacterial infections and risk factors, to implement prevention strategies.

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Table #1: Demographic characteristics

Sex	**N**	**%**
Female	82	65.07
Male	44	34.92
Age		
<1 year	67	51.94
1-2 years	14	10.85
2-5 years	18	13.95
6-10 years	14	10.85
>10 years	16	12.40
Region of origin		
Bogotá	47	37.30
Andean Region	37	29.37
Atlantic Coast	30	23.81
Foreigners	5	3.97
Eastern Plains	4	3.17
Pacific Coast	3	2.38
Origin		
Referral	13	10.32
Home	113	89.68
Underlying disease		
Biliary atresia	67	53.17
Hepatoblastoma	10	7.94
Familial intrahepatic Cholestasis	8	6.35
Autoimmune hepatitis	8	6.35
Inborn error of metabolism	6	4.76
Caroli syndrome	6	4.76
Congenital fibrosis	5	3.97
Other	4	3.17
Alagille syndrome	3	2.38
Wilson’s disease	3	2.38
Cirrhosis secondary to a Choledochal cyst	2	1.59
Budd Chiari	1	0.79
Cryptogenic cirrhosis	1	0.79
Hemangiomatosis	1	0.79
Cholestatic hepatitis	1	0.79
Retransplantation		
Yes	3	2.38
No	123	97.62

Infections during hospitalization of transplant		
No infection	31	24.03
Infection	98	75.97
Number of infections during hospitalization		
0	31	24.03
1	60	46.51
2	26	20.16
3	7	5.43
4 or more	5	3.88
Type of infections		
Intra-abdominal	138	33.58
Pneumonia	51	12.41
UTI*	50	12.17
Bacteremia	49	11.92
Gastrointestinal	44	10.71
Skin and soft tissues	28	6.81
Sepsis of unknown origin	26	6.33
Upper respiratory	17	4.14
Other	5	1.22
Endocarditis	2	0.49
Meningitis	1	0.24

*UTI: urinary tract infections

Table #2: Multivariate analysis result

	P
Relationship Post-transplant period and days of hospitalization	<.001
Relationship between coinfections and mortality.	0.000
Relationship between the use of carbapenems in the three months prior and CRE infections.	<.001
Relationship Surgical complications and the number of infections in one month.	0.018