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Severe Sepsis in Pediatric Liver Transplant Patients: The Emergence of Multidrug- Resistant Organisms

Alicia M. Alcamo, MD, MPH^{1,2}, Lauren J. Alessi, MD^{1,2}, S. Noona Vehovic, CRNP-AC^{1,2}, Neha Bansal, MD³, Geoffrey J. Bond, MD⁴, Joseph A. Carcillo, MD^{1,2}, Michael Green, MD, MPH², Marian G. Michaels, MD, MPH², and Rajesh K. Aneja, MD^{1,2}

¹Department of Critical Care Medicine, UPMC Children's Hospital of Pittsburgh, University of Pittsburgh Medical Center, 4401 Penn Avenue, Faculty Pavilion, Suite 2000, Pittsburgh, PA 15224, USA,

²Department of Pediatrics, UPMC Children's Hospital of Pittsburgh, University of Pittsburgh Medical Center,

³Division of Pediatric Cardiology, Children's Hospital of Montefiore, Bronx, NY,

⁴Departments of Transplant Surgery and General and Thoracic Pediatric Surgery, UPMC Children's Hospital of Pittsburgh, University of Pittsburgh Medical Center

Abstract

Objective: To describe characteristics of liver transplant patients with severe sepsis in the pediatric intensive care unit (PICU)

Design: Retrospective descriptive analysis

Setting: Tertiary children's hospital PICU

Patients: Liver transplant recipients admitted Jan 2010 to Jul 2016 for pediatric severe sepsis

Interventions: None

Measurements and Main Results: Between Jan 2010 – Jul 2016, 173 liver transplants were performed, and 36 of these patients (21%) were admitted with severe sepsis (54 episodes total). Median age at admission was 2 y [1–6.5 y], 47.2% were male. Bacterial infections were the most common (77.8%), followed by culture negative (12.9%) and viral infections (7.4%). Fungal infections accounted for only 1.9%. Median time from transplant for viral and culture negative infections was 18 d [8.25–39.75 d] and 25 d [9–41 d], while 54.5 d [17–131.25 d] for bacterial infections. Bloodstream and intra-abdominal were the most common bacterial sites (45% and 22.5%, respectively). Multidrug-resistant organisms (MDROs) accounted for 47.6% of bacterial sepsis. Vancomycin resistant enterococcus and extended spectrum beta-lactamase producers were the most frequently identified MDROs. Patients with MDRO sepsis demonstrated higher admission PELOD scores ($P=0.043$) and were noted to have an odds ratio of 3.8 and 3.6 for mechanical ventilation and MODS, respectively ($P=0.047$ and $P=0.044$). Overall mortality was 5.5% (n=2 patients), with both deaths occurring in MDRO episodes.

Conclusions: We report that MDROs are increasingly being identified as causative pathogens for sepsis in pediatric liver transplant recipients and are associated with significantly higher odds for mechanical ventilation and higher organ failure. The emergence of MDRO infections in pediatric liver transplant patients has implications for patient outcomes, antibiotic stewardship and infection prevention strategies.

Keywords

pediatric severe sepsis; pediatric liver transplantation; multidrug-resistant organisms

Introduction

The Sepsis Prevalence, Outcomes and Therapies (SPROUT) study, a prospective cross-sectional study of approximately 7000 children in 26 countries, reported a severe sepsis prevalence rate of 8.2% and a mortality of 25%. Similar to other studies, children with comorbid conditions were noted to have a higher mortality than previously healthy children, e.g., children with solid organ or stem cell transplant had a mortality of 48.2%¹. Based on data retrieved from the Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients (OPTN/SRTR), approximately 600 pediatric liver transplants are performed annually, with the overall 5-year patient survival being 88%. Of note, infection was the leading cause of death followed by cardio/cerebrovascular complications in children with deceased donor transplant recipients². Thus, this cohort of immunosuppressed patients faces an increased risk of infection by common pathogens, as well as, opportunistic infections caused by less virulent microorganisms that are harmless in an immunocompetent host³⁻⁵.

Several factors predispose pediatric liver transplant recipients to a higher risk for colonization and infection with multidrug-resistant organisms (MDROs). These include frequent and prolonged hospitalizations, multiple rounds of antibiotics, and impairment of the immune system⁶. Recent data suggests that almost 25% of adult patients who are readmitted within 1 year following an MDRO infection had an MDRO isolated during the readmission⁷. Furthermore, the manifestations of sepsis in the immunosuppressed adult patient have been reported to be different with a slightly higher incidence of thrombocytopenia and organ failure, in contrast to non-transplant recipients⁸. Since there are important developmental differences between children and adults that can significantly impact the pathophysiology and outcome, we need to be cautious about extrapolating the results of adult studies to children. Therefore, it is imperative we understand if similar nuances exist in septic children who have previously received a liver transplant.

Since its inception in 1981, the pediatric liver transplantation program at UPMC Children's Hospital of Pittsburgh (CHP) has become a leading center for technical variant allografts and living-donor liver transplantation, reporting survival rates above the national average (1-year survival, 98% vs 95%)². Our expertise and relatively high volume in the field of pediatric organ transplantation has enabled us to perform this retrospective study. In this study, we aim to perform a descriptive analysis of pediatric liver transplant patients admitted to the pediatric intensive care unit (PICU) with severe sepsis.

Methods

This was an IRB approved retrospective chart review of all pediatric liver transplant recipients between January 1, 2010 to December 31, 2015. CHP is a 293-bed tertiary hospital that has performed more pediatric transplants than any other center in the United States. All episodes of severe sepsis requiring PICU admission after transplant were identified between January 1, 2010 and July 31, 2016. This study timeframe allowed for a six-month follow-up period for any patient who received their transplantation at the end of 2015. Using the electronic medical record, demographic data were obtained, as well as the time from transplant, mortality, degree of critical illness, and location and etiology of infection. After a training session for uniformity in data collection, three reviewers (AMA, LJA, SNV) abstracted the data using a standardized data collection form. If there was any uncertainty about classification of a clinical episode, the information was independently reviewed by three separate individuals, who were not involved with the initial data extraction, and the episode was classified per the majority opinion.

Bacterial infections were identified based on positive cultures from sites of infection (respiratory aspirates, blood, peritoneal fluid, urine, or wound cultures). Viral infections were identified with polymerase chain reaction testing for common respiratory tract viral pathogens, as well as, Epstein-Barr virus, cytomegalovirus, and adenovirus. Fungal cultures, as well as, *Aspergillus* antigen (galactomannan) testing were used to identify fungal infection. A multidrug-resistant organism (MDRO) was defined per the Centers for Disease Control and Prevention (CDC) guidelines as an organism resistant to one or more classes of antimicrobials. MDROs such as vancomycin resistant enterococcus (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA), and extended spectrum beta-lactamases (ESBLs) have been identified by the CDC to deserve special attention in healthcare⁹.

Bloodstream and urinary tract infections were classified as positive blood and urine cultures, respectively. Urinary cultures were considered positive if greater than 50,000 colony forming units of a single organism was identified in a specimen obtained via sterile catheterization. Urinalysis at the time of culture was also evaluated for the presence of pyuria (leukocyte esterase, nitrites, and/or white blood cells) or bacteria (organisms on gram stain)¹⁰. Diagnosis of a respiratory tract infection was based on clinical signs and examination, worsening chest radiograph, and/or the need for oxygen supplementation or ventilatory support (or increased ventilatory support in a ventilator-dependent patient or patient already intubated post-operatively)¹¹. Wound infections were denoted by positive wound cultures with consistent clinical signs and examination. Intra-abdominal infections (such as peritonitis or cholangitis) were based on clinical signs and symptoms, as well as, positive cultures. The classification of culture negative was provided to patients without an identifiable source of infection by cultures or physical examination, but whom had clinical signs of severe sepsis.

Severe sepsis was defined based on the criteria set by the International Pediatric Sepsis Consensus Conference. For episodes classified as severe sepsis, patients were identified to meet systemic inflammatory response syndrome (SIRS) criteria in the setting of presumed or confirmed infection with either cardiovascular dysfunction, respiratory distress syndrome, or

organ dysfunction of two or more systems. SIRS was determined by the presence of at least two of the four criteria: 1) hypothermia or fever, 2) age-appropriate tachycardia or bradycardia, 3) age-appropriate tachypnea or need for ventilator support, or 4) leukopenia or leukocytosis for age. Patients were identified to have septic shock if their presentation was consistent with severe sepsis and had evidence of cardiovascular dysfunction¹². Multiple organ dysfunction syndrome (MODS) was defined as dysfunction of two or more organ systems in the setting of severe sepsis^{13,14}.

Factors to assess for degree of clinical illness included vasoactive requirement, mechanical ventilation, use of hydrocortisone, and presence of multiple organ dysfunction syndrome (MODS). Illness of severity was assessed using the pediatric logistic organ dysfunction (PELOD) score, which were calculated retrospectively using available chart data. Technical challenges and post-operative complications often lead to recurrent operative interventions and are a risk factor for development of sepsis^{15–17}. Therefore, we evaluated all obtained abdominal imaging (ultrasound, computed tomography, magnetic resonance imaging, or cholangiogram) for findings of hepatic artery thrombosis (HAT) or new biliary complications.

STATISTICAL ANALYSIS

Descriptive statistics performed for demographic data, infection etiology and site, and degree of clinical illness. Categorical variables were described using frequencies and percentages, while median and interquartile ranges (IQRs) were used to describe continuous variables. Fisher's exact test was used to evaluate the risk for MODS and mortality in patients who had an identified MDRO infection compared to those who did not have an identified MDRO infection. Wilcoxon rank-sum test was used to compare PICU and hospital length of stay. Statistical significance was defined as a *P*-value ≤ 0.05 . Statistical analysis performed using RStudio (Boston, MA).

Results

There were 173 liver transplants performed at CHP during the study period (average 28.8 liver transplants per year). Thirty-six patients (21%) were admitted to the PICU for a total of 54 severe sepsis episodes. There were 13 patients who had more than one episode of severe sepsis (9 patients with two and 4 patients with more than two episodes). Majority of patients received a deceased donor liver transplant (66.7%, *n*=24 patients). Primary indications for transplant are shown in Table 1. The median age for the septic patients was 2 y [1–6.5 y], and 47.2% were male. Time from transplant to sepsis for all episodes was 41 d [21.25–113 d]. Seventeen episodes (31.5%) in 16 patients were noted in the initial admission for transplant within a median of 8 days [4–13 d]. Overall mortality was 5.5% in the cohort of septic pediatric liver transplant patients (*n*=2 patients).

Etiology and site of infections for severe sepsis episodes shown in Table 2. Bacterial infections were the most commonly identified etiology for severe sepsis episodes (*n*=42 episodes; 27 patients). There were two episodes with simultaneous fungal co-infection where both the fungal and bacterial organisms were cultured either from the bloodstream only or in addition to the peritoneal fluid. One of these polymicrobial episodes also had

detection of a respiratory virus in addition to the bacterial and fungal isolates. Overall bloodstream infections accounted for 45% of these occurrences (n=18 episodes; 15 patients). Twelve episodes had multiple sites identified (28.6%), of which the majority included bloodstream involvement (n=9 episodes). The viral infections identified were respiratory in origin, and there were no concurrent Epstein-Barr virus or cytomegalovirus infections in this cohort. There was one isolated fungal infection diagnosed from a respiratory fungal culture.

A noteworthy finding was the presence of MDROs as the infecting organism in 47.6% of bacterial infections (n=20 episodes; 15 patients). Site of MDRO isolates are shown in Table 2. MDRO infections were more likely to involve multiple sites (n=9 episodes). Majority of these multi-site infections included bloodstream involvement (n=6 episodes). In comparison, there were more intra-abdominal and less multi-site infections identified for non-MDRO bacterial episodes. Bacterial, viral and culture negative infections occurred 54.5 d [17–131.25 d], 18 d [8.25–39.75 d] and 25 d [9–41 d] from transplant, respectively. The identified MDROs are shown in Table 3. Interestingly, methicillin-resistant *Staphylococcus aureus* (MRSA) was isolated in only one patient as being the causative organism.

Initial empiric antibiotic choices were either piperacillin/tazobactam monotherapy or vancomycin and piperacillin/tazobactam combination therapy in over half of the episodes. This empiric therapy was appropriate in 52.4% of episodes, and if therapy needed to be modified, the length of delay to appropriate antimicrobial coverage was 2 d [0.5–4 d]. Such delay for appropriate antimicrobial coverage was more commonly observed in MDRO septic episodes, as compared to non-MDRO episodes (15 vs 5 episodes).

There were no identified occurrences of graft loss secondary to sepsis. Abdominal imaging was obtained in 42 episodes (77.8%). Five instances of HAT occurred within 8 d [3–10 d] after transplantation and only one was associated with an MDRO infection. In comparison, three patients were re-admitted to hospital with HAT occurring 24 d [20.5–109.5 d] after transplantation, all of which were associated with an MDRO septic episode. There were 10 new biliary complications (18.5%) that occurred 20.5 d [11.8–156 d] after transplantation. One third of the biliary complications occurred in the setting of an MDRO sepsis episode. Half of the biliary complications occurred concurrently with a diagnosis of HAT. In only one episode was it necessary to place a biliary drain for further management.

The level of support required for MDRO sepsis compared to remaining septic episodes is shown in Table 4. Significantly more MDRO septic episodes required mechanical ventilation and hydrocortisone therapy. No difference was noted in terms of vasoactive or extracorporeal membrane oxygenation (ECMO) support. Patient with MDRO sepsis had significantly higher admission-level PELOD scores as compared to the remaining episodes (11 [8.75–17.25] vs 9 [6.25–11]; $P=0.043$). MODS was significantly more prevalent in MDRO sepsis resulting in longer PICU and hospital length of stay (Table 5). Mortality was noted exclusively in the MDRO sepsis cohort (n=2 patients).

Discussion

Infection is known to be a significant cause for morbidity and mortality in the pediatric solid organ transplant patient, both in the early and late post-transplant period^{3,5,18–20}. To our knowledge, this is one of the first studies to provide insights into the epidemiology and outcomes of severe sepsis in pediatric liver transplant recipients, specifically as it relates to ICU admission and MDROs. Three main findings from our study include: 1) MDROs have emerged as a significant cause of severe sepsis for the pediatric liver transplant patient. 2) Higher acuity in pediatric septic transplant patients (i.e., need for mechanical ventilation and evidence of multi-system organ failure) associated with MDRO severe sepsis episodes. 3) In contrast to historical data, median time for bacterial infections was 54.5 days after transplant. Each of these findings merit further discussion, as below.

The most noteworthy finding of this study was the identification of MDRO as a significant cause of severe sepsis episodes in the pediatric liver transplant recipient. Select pediatric studies have noted the emergence of MDRO infections in pediatric oncology, hematopoietic stem cell transplantation, cystic fibrosis, and neonatal patients, but there are no such studies in pediatric liver transplant recipients^{21–24}. Studies in adult transplant recipients have noted history of prior hospitalizations, previous invasive temporary or permanent lines and multiple prior antibiotic exposures as factors determined to be associated with increased risk for MDRO colonization^{25–27}. We noted that only 40% of the patients with an MDRO septic episode had a previous MDRO-identified infection or documented colonization. Part of the challenge was that identification of such factors was limited given that many patients were referred to our hospital for their transplantation and thus, the majority of their pre- or peri-transplant care was at the referring institution. Similar to the adult studies, our results indicate vancomycin resistant enterococcus and extended spectrum beta-lactamase producing organisms are the most common^{25–27}. Further studies examining the prevalence of MDRO colonization need to be performed as this has implications for treatment of these children and their outcomes.

The association of MDRO septic episodes with outcomes was an important finding in this study. Patients with MDRO infections had more significant organ dysfunction and significantly longer hospital stays, as well as a trend toward longer PICU lengths of stay. These findings are similar to others studies which have shown an association of increased mortality, need for hospital readmission, longer lengths of stay, and increased hospital costs due to MDRO infections^{28,29}. In our study, median delay to appropriate antibiotic coverage was 2 days and more prevalent in patients with an identified MDRO, which may be a potential explanation for the observed worsened outcomes in that subset of patients. Early recognition of sepsis and prompt treatment of the underlying cause is a hallmark of the contemporary care delivered in pediatric emergency rooms and hospitals. The 2017 American College of Critical Care Medicine septic shock guidelines recommend administering empiric antibiotics within the first hour of treatment³⁰. Kumar *et al* have shown that there is an increase in mortality rate for every hour delay of effective antibiotic administration after the onset of septic shock in adults³¹. Similarly in pediatric sepsis patients, Weiss *et al* have shown that a three-hour delay for appropriate antibiotics is associated with an increased mortality and prolonged organ failure³². Given the potential for

MDRO septic episodes in this population, thoughtful empiric antibiotic management should be guided by each patient's infectious history, as well as, local bacterial epidemiology. Furthermore, these findings may have important implications for hospital quality improvement efforts, infection prevention, and antibiotic stewardship programs to decrease antibiotic usage and MDRO prevalence.

The identified viruses in this study were all common respiratory viral infections and not opportunistic or latent viral reactivations. These viral infections were also determined as early post-transplant sepsis etiologies, occurring a median of 18 days following transplantation. We suspect that improvement in laboratory techniques and technology have allowed for more accurate and faster detection of viral infections, making it more feasible to detect such etiologies for severe sepsis episodes^{33–35}. Historically, it has been shown that infections following transplantation occur in a temporal and predictable pattern, with bacterial infections occurring within the first 30-days after the transplant^{36,37}. In our study, the median time for bacterial infections was approximately 55 days, suggesting that bacterial infections can occur even after the 30-day period following transplantation. Several factors can explain these findings and include increasing patient complexity, complicated post-operative surgical courses, and in-dwelling medical devices. However, in this retrospective review, we were unable to verify these factors as it was difficult to obtain supporting data. Another striking finding was the association of HAT with severe sepsis episodes, suggesting a potential link to surgical complexity and complications, similar to previous reports^{38,39}. Almost all patients in our study had received imaging to assess for potential surgical complications, a practice that should be “standard of care” for any septic liver transplant recipient, especially in the early transplant period.

There are several limitations to this study. As this is a retrospective, single-center study, it is difficult to draw definitive conclusions regarding the epidemiology and risk factors of sepsis within this specific cohort. Particularly, there are limitations to exploring the landscape of antibiotic exposure for each patient to facilitate further understanding of the relationship of MDRO severe sepsis and prior antibiotic administration. Also, the small sample size limited our ability to perform multi-variate analyses to further assess MDRO severe sepsis, therefore our conclusions are suggestive of associations and need further evaluation in a multi-center setting. It is important to state that as a referral hospital for pediatric liver transplantation, our institution performs many complex and high-risk transplantations, therefore it is plausible that our patients may have different risk factors for pediatric severe sepsis following transplant compared to other centers, thus potentially limiting generalizability of our data. Lastly, the follow-up time after transplant varied for each patient evaluated, hence we may have missed some late sepsis episodes for patients who received their transplant at the end of the inclusion criteria. Despite these limitations, we feel that this unique dataset does allow inferences to be drawn, specifically highlighting the necessity for evaluation of antimicrobial practices in severe sepsis episodes for this population, as well as reexamining antibiotic stewardship and infection prevention practices given the emergence of MDROs.

Conclusion

Infection is a significant cause of morbidity and mortality in the pediatric liver transplant recipient, specifically in the early transplant period. Due consideration of MDROs as a causative agent should be made when these patients present with sepsis. Thus, initial antibiotic choices may differ for this population based on the patient's history and institutional antimicrobial resistant patterns. Larger prospective studies are needed to assess post-transplant severe sepsis outcomes to identify modifiable risk factors and to develop specific treatment guidelines for this unique patient cohort.

Conflicts of Interest and Source of Funding:

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Table 1.

Patient Demographics and Characteristics

Characteristic	Patients with Severe Sepsis (n=36)
Age at time of admission (median, IQR) *	2 y [1–6.5 y]
Gender (n, % male)	17 (47.2%)
Reason for Transplant (n, %)	
Acute Liver Failure	2 (5.6%)
Biliary Atresia	8 (22.2%)
Inborn Error of Metabolism/Metabolic	7 (19.4%)
Inherited/Intrinsic Liver Disease	11 (30.6%)
Malignancy	5 (13.9%)
Secondary Liver Disease	3 (8.3%)
Donor Status (n, %)	
Living	12 (33.3%)
Deceased	24 (66.7%)
Time from transplant (median, IQR)*	41 d [12.25–113 d]

IQR=interquartile range;

*
total of 54 admissions

Table 2.

Etiology and Site of Severe Sepsis Episodes

Type of Infection	All Episodes (total n = 54) (n, %)	MDRO Bacterial Episodes (total n = 20) (n, %)	Non-MDRO Bacterial Episodes (total n = 22) (n, %)	Time from Transplant [*] , median [IQR]
Any Bacterial Component	42 (77.8%)	20	22	54.5 d [17–131.25 d]
Bacterial	40 (74.1%)	19	21	
Bloodstream (n, %)	18 (45%)	7 (36.8%)	11 (52.4%)	
Urinary (n, %)	1 (2.5%)	1 (5.3%)	--	
Respiratory (n, %)	1 (2.5%)	1 (5.3%)	--	
Wound (n, %)	1 (2.5%)	--	1 (4.8%)	
Intra-abdominal (n, %)	9 (22.5%)	2 (10.5%)	7 (33.3%)	
Multiple sites (n, %)	10 (25%)	8 (42.1%)	2 (9.5%)	
Polymicrobial	2 (3.7%)	1	1	
Multiple sites (n, %)	2 (100%)	1 (100%) [†]	1 (100%) ^{††}	
Viral[‡]	4 (7.4%)	--	--	18 d [8.25–39.75 d]
Fungal[‡]	1 (1.9%)	--	--	444 d[¶]
Culture Negative	7 (12.9%)	--	--	25 d [9–41 d]

IQR=interquartile range;

^{*}
for all sepsis episodes;[†]
bacterial and fungal co-isolates;^{††}
bacterial, fungal and viral co-isolates;[‡]
respiratory site of infection(s);[¶]
reflective of one fungal-only episode

Table 3.

Identified MDROs as Causative Agents

Organism	% of MDRO episodes (n=20)
Vancomycin Resistant Enterococcus (VRE)	45% (n=9)
ESBL producers (E. coli or Klebsiella)	25% (n=5)
<i>Klebsiella pneumonia</i> carbapenemases (KPCs)	5% (n=1)
<i>Stenotrophomonas maltophilia</i>	5% (n= 1)
<i>Burkholderia cepacia</i>	5% (n=1)
<i>Acinetobacter baumannii</i>	5% (n=1)
More than 1 MDRO	10% (n=2) *

* one episode includes identification of methicillin-resistant *Staphylococcus aureus* (MRSA)

Table 4.

Measures for Degree of Critical Illness

Level of Support	All Episodes (total n=54) (%, n)	MDRO Episodes (n=20) (%, n)	Remaining Episodes (n=34) (%, n)	OR
MV	50% (n=27)	70% (n=14)	38.2% (n=13)	3.7 (CI 1.01–14.9), <i>P</i> =0.047*
Vasoactive Support	35.2% (n=19)	45% (n=9)	29.4% (n=10)	1.94 (CI 0.53–7.18), <i>P</i> =0.376
HCT	61.1% (n=33)	75% (n=15)	52.9% (n=18)	2.6 (CI 0.7–11.4), <i>P</i> =0.046*
ECMO	5.6% (n=3)	10% (n=2)	2.9% (n=1)	3.57 (CI 0.17–222.4), <i>P</i> =0.551

MV=mechanical ventilation, HCT=hydrocortisone, ECMO=extracorporeal membrane oxygenation

Table 5.

Clinical Outcome Measures

Outcome	MDRO Episodes (n=20 episodes, 15 patients)	Remaining Episodes (n=34 episodes, 21 patients)	<i>P</i>
MODS (% , n)	60% (n=12 episodes)	29.4% (n=10 episodes)	3.5 (CI 0.98–13.5), <i>P</i> =0.04*
Hospital LOS (median, IQR)	47.5 d [38.5–55.3 d]	28 d [11.3–47.5 d]	<i>P</i> =0.04*
PICU LOS (median, IQR)	15.5 d [2.8–37.5 d]	5.5 d [3–16 d]	<i>P</i> =0.15

MODS=multiple organ dysfunction syndrome, LOS=length of stay