Late-onset bacteremia in uncomplicated pediatric liver-transplant recipients after a febrile episode

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Abstract The aim of this study was to analyze the incidence and risk factors of bacteremia after a febrile episode in uncomplicated pediatric recipients more than 2 months after liver transplantation, which has not previously been studied. This cross-sectional study was conducted over a 4-year period. Patients with known risk factors for sepsis at the time of admission were excluded from the study. Seventy-one patients were hospitalized on 128 occasions, with bacteremia occurring in the case of 11 admissions (8.6%). No laboratory tests were predictive of bacteremia. The bacteremic group most frequently presented with ill appearance ($P < 0.001$), lethargy ($P < 0.01$), decreased physical activity, and a history of early-onset bacteremia after transplantation and segmental graft ($P < 0.05$). This study identified a significant incidence of bacteremia in uncomplicated patients many months after liver transplantation.

Keywords Biliary strictures · Imunosuppression · Segmental graft

Introduction

Bacterial infections and bacteremia are an important cause of morbidity and mortality in the solid-organ transplant recipient during the first 2 months after surgery. The incidence of infection occurring during the immediate period following a liver transplantation (LTx) ranges from 25% to 85%, with an associated mortality rate of 10%–25% [3, 5, 8, 9, 11, 12, 13, 18, 19, 22, 23]. During this period, the incidence of bacteremia is approximately 30% [13, 20, 22, 23]. For the first 2 months after solid-organ transplantation, risk factors associated with infections have been well described, including: male recipients, encephalopathy, thrombocytopenia, prolonged prothrombin time, hyperbilirubinemia, prolonged intensive care unit (ICU) stay, ventilatory support, urgency of LTx, chronic lung disease, prior colonization or latent infection, prolonged antibiotic therapy before LTx, diabetes mellitus, renal failure, use of central venous catheter (CVC), prolonged operating time, massive transfusions, allograft failure, infected donor organ, acute-rejection treatments and immunosuppression, intra-abdominal bleeding, re-operation, and vascular or biliary complications [5, 8, 15, 18, 19, 21, 22, 24].

Infections 2–6 months after solid-organ transplantation are usually due to opportunistic micro-organisms or viral infections such as herpes viruses, adenovirus, and hepatitis B and C [3, 7, 17, 24]. By 6 months after solid-organ transplantation, the risk of bacterial infection for the uncomplicated adult patient has been reported to be at the level of the general population [6, 7, 11, 24]. Since most of these studies are on adults or mixed-age groups with an adult predominance, the long-term incidence of bacteremia in the uncomplicated child after solid-organ transplantation has not been defined well [3, 5, 8, 11, 12, 13, 22, 23]. In addition, children in the general population who are younger than 3 years of age are at an increased risk of incurring bacterial infections [1, 2, 10], adding to the concern that the post-transplant child is particularly at risk of developing bacteremia. The aim of this study was therefore to investigate the clinical
outcome of uncomplicated post-LTx children who were admitted to our institution with a febrile episode more than 2 months after LTx and to identify predictive risk factors and guidelines for clinical management.

**Patients and methods**

In this cross-sectional study, we reviewed the charts of all children who were admitted to UCLA Medical Center with fever at least 2 months after LTx between July 1993 and June 1997. We excluded patients with known risk factors for sepsis and/or recurrent fever such as CVC, known biliary strictures and/or drain tubes, chronic allograft rejection, end-stage liver disease, and known active viral infections or chronic hepatitis at the time of admission. Since an increased risk of bacteremia has only been described for children during the first 2 months post-LTx [9, 14, 18], we defined early-onset bacteremia as episodes that occurred within that time period. We also defined late-onset bacteremia as such that were documented in patients more than 2 months after transplantation.

We obtained data from the hospital stay for the febrile episode, and from the pre- and post-transplant period. The following parameters were collected for each patient: gender, date of birth, race, age at LTx, type of graft, indication for LTx, ICU days after LTx, LTx-related complications (hepatic artery thrombosis, portal vein or inferior vena cava thrombosis, intra-abdominal bleeding or abscesses, biliary stricture or leak, intestinal obstruction or perforation, peritonitis, diaphragmatic palsy, pleural effusion, pneumonia, atelectasis, and re-operation and/or re-transplantation), Epstein-Barr virus (EBV) status, cytomegalovirus (CMV) status, herpes simplex (HSV) status, renal failure before and after LTx, CVC before and after LTx, pre-LTx cultures, bacteremia and infection after LTx, and rejection episodes within the 1st 2 months after surgery.

The following data were collected for each admission: age, time since LTx, and immunosuppressive therapy. We also obtained information regarding history of recent rejection episodes (previous 6 months), antibiotic therapy prior to admission, occurrence and reason for a previous hospitalization that occurred within 8 weeks of admission, days with fever and symptoms, weight loss, ill contacts, symptoms of upper respiratory infection (URI), abdominal pain, vomiting, diarrhea, bleeding, dysuria, urination frequency, cyanosis, headache, and decrease of physical activity. We also recorded physical examination data. Appearance was classified by review of initial admission notes as healthy, ill, or toxemic.

Normal capillary perfusion was considered to be less than 3s. Fever was defined as a temperature of or more than 38 °C at home and/or the emergency room. Appearance was defined as ill when the child appeared irritable, had a decreased activity level, or showed evidence of hyper- or hypoventilation. Appearance was defined as toxemic if the child appeared ill and had lethargy and/or cyanosis. Lethargy was defined as poor or absent eye contact, or as failure of the child to recognize its parents or to interact with persons or objects in its environment [2].

Laboratory evaluation at the time of admission included: complete blood count (CBC) with differential, platelet count, liver function tests, electrolytes, creatinine, blood urea nitrogen (BUN), tacrolimus or cyclosporine level, urinalysis, urine, blood, and other cultures, and chest X-ray. White blood cell bandemia was defined as an absolute band count of more than 1.0×10^10/cm^3 [2]. Low absolute neutrophil count (ANC) was defined as fewer than 1.5×10^10/cm^3, and high ANC was defined as more than 10×10^10/cm^3 [10]. C-reactive protein and erythrocyte sedimentation rate were not consistently available.

Blood cultures were done upon admission for aerobic as well as anaerobic pathogens before any antibiotic therapy was begun. Patients were not systematically started on empiric antibiotic therapy. Antibiotics were started at the discretion of the attending physician and, in most cases, a third-generation cephalosporin was used. All patients with ill or toxemic appearance were started on antibiotic therapy upon admission. For all children, subsequent blood cultures were done if there were temperature spikes of or more than 38 °C up to three times or more, based on clinical progress.

In this study, the unit of analysis was both child and specific hospitalization for the febrile episode. We performed a univariate analysis of all variables. We used the Z-test and two-sample t-test for statistical analysis. Finally, multiple regression analyses were done to relate late-onset bacteremia with statistically significant variables. A P value of less than 0.05 was considered statistically significant.

**Results**

A total of 71 patients was admitted to the hospital on 128 occasions, and there were no deaths. One patient from whom coagulase-negative *Staphylococcus* was grown from a blood culture was excluded from the study because the isolate was considered to be a contaminant. Bacteremia was identified in 11 admissions (8.6%) and included *Streptococcus pneumoniae* (four), *Escherichia coli* (two), *Klebsiella pneumoniae* (two), *Enterobacter aerogenes* (two), and *Staphylococcus aureus* (one). In specific patients, the pathogens that were identified at the time of admission for late-onset bacteremia were different from those that were isolated during the immediate post-transplant period (n=6). Several patients were admitted more than once, but no patient had more than one episode of bacteremia. While bacteremia was identified in patients who were several years post-LTx, 73% of the episodes occurred within the 1st 3 years of surgery. Five patients (46%) who developed bacteremia were between 2 and 12 months post-LTx. Three episodes (27%) of bacteremia occurred between 2 and 6 months after LTx (Fig. 1).

The infections identified in patients without bacteremia are shown in Table 1. CMV and EBV infections were supported by serology, culture, immunoperoxidase stain from affected tissue and/or polymerase chain reaction analysis from affected tissue or blood. The comparisons between bacteremic and non-bacteremic children are provided in Tables 2, 3, 4, and 5. Patients in the bacteremic group most frequently presented with an illness occurring 2 days after receiving immunosuppressive therapy (P<0.001), lethargy (P<0.01), decreased physical activity, and history of early-onset bacteremia after LTx and split or living-related (segmental) graft (P<0.05) (Tables 2, 3, 4). In addition, complications associated with LTx were equally distributed between bacteremic and non-bacteremic groups (data not shown). Three patients (two in the non-bacteremic group) had hepatic artery thrombosis complicating their immediate post-LTx period. No patient had had a splenectomy before the febrile episode.