Empiric Antimicrobial Treatment of Pediatric Patients with Liver Failure and/or Early Post-Liver Transplantation

BACKGROUND:

Diagnosis and management of infection in patients with liver failure is challenging in children as in adults. Causes of liver failure, indications for liver transplantation, and epidemiology of infections differ in pediatric vs. adult patients. Some pediatric liver transplant recipients are comparatively ?antibiotic-naïve? and thus at lower risk for multi-drug resistant (MDR) infections. For those patients at risk for MDR organisms due to significant healthcare exposure, antimicrobial resistance patterns differ in pediatric vs. adult sites of care.

It is important to match the empiric antimicrobial coverage to the patient?s risk factors, such that the most likely and most serious pathogens are covered, but harm is avoided as much as possible. Potential harm of overly broad-spectrum antibiotic therapy includes development of antimicrobial resistance, *Clostridium difficile* infection, and invasive candidiasis. The normal intestinal flora also provide resistance against colonization and invasive infection with pathogens, and emerging data in immunocompromised hosts show that disruption of this flora can be associated with increased risk for subsequent bacteremia.

GUIDELINES:

The following algorithms were developed specifically for pediatric patients receiving care at UCSF Benioff Children?s Hospital San Francisco. Separate algorithms have been developed for adults with end stage liver disease (ESLD). Management algorithms are focused on patients with newly recognized acute liver failure, patients with ESLD (primarily due to biliary atresia in the pediatric population) and those in the early (< 2 month) post-transplant period. Management of patients presenting > 2 months from initial liver transplantation should be individualized according to patient risk factors, immunosuppression and clinical presentation. Empiric antimicrobial therapy should be modified as needed based on the patient?s known history of prior microbiologic isolates (e.g. including coverage of prior resistant organisms).

Empiric antimicrobials according to these guidelines should be considered for patients presenting with signs or symptoms of systemic infection including fevers, leukocytosis, or otherwise unexplained physiologic instability. Empiric antimicrobials can be
considered for acute onset or progression of hepatic encephalopathy without a known non-infectious cause.

Individual patients may not strictly "fit" a particular algorithm. Clinical judgment is recommended. ID consultation is encouraged when individualized management may be more appropriate.

**Empiric Treatment of Suspected Infection in a Previously Healthy Neonatal/Pediatric Patient with Acute Liver Failure** [1]

**Empiric Treatment of Suspected Infection in Pediatric Patients with End-Stage Liver Disease/Biliary Atresia** [2]

**Empiric Treatment of Suspected Hospital-Onset Infection in Pediatric Patients with Acute Liver Failure or Early Post-Liver Transplantation** [3]

Patients for whom a clear source of infection is identified should be treated according to BCH Empiric Antimicrobial Therapy Guidelines [4].

**RATIONALE:**

*Infectious complications in pediatric patients with acute liver failure*

Acute liver failure (ALF) in children confers increased risk for infection, partly due to directly impaired immune function, with additional risk added by healthcare exposure and invasive support devices. Certain treatable infections (particularly HSV) may be the primary cause of ALF. In a multi-site study of viral testing in infants and children with acute liver failure, HSV was identified in 25.2% of tested patients aged 0-6 months, and 5.6% of tested patients aged > 6 months [1]. The most commonly identified non-viral sources of infection in children with ALF include bloodstream infection (9%), lower respiratory tract infection (7%), and urinary tract infection (12%) [2]. Causative organisms vary depending on setting and duration of hospitalization and include aerobic Gram-negative bacteria, Gram-positive bacteria, and *Candida* species, though infections due to *Candida* have been noted to occur later than those due to bacteria [2,3].

Though some centers have utilized prophylactic antibiotics in patients with ALF, antibiotic prophylaxis has not been shown to improve outcome of patients with ALF and is not routinely recommended in consensus guidelines of the American Association for the Study of Liver Diseases (AASLD), or the European Association for the Study of the Liver (EASL), or the Pediatric Gastroenterology Chapter of the Indian Academy of Pediatrics (which were developed specifically for children with ALF) [4-6].
Infectious complications in pediatric patients with biliary atresia

Biliary atresia is the most common cause of chronic liver failure in children and the most common indication for pediatric liver transplantation. It is associated with risk for ascending cholangitis, predominantly caused by Gram-negative bacteria (7,8). Initial episodes tend to occur with more drug-susceptible organisms, but patients may develop infections with drug-resistant organisms with subsequent episodes and with long-term antibiotic prophylaxis (typically trimethoprim-sulfamethoxazole) (7,8). Patients approaching transplantation with prior history of recurrent cholangitis may be highly antibiotic-exposed and with known prior history of MDR infections.

Infectious complications in pediatric liver transplant recipients

Pediatric liver transplant recipients are at highest risk for bacterial and fungal infection during the first month following transplantation. Known risk factors include pre-existing biliary atresia, young recipient age (< 1 year), small body size (<10kg), and surgical complexity (intra-operative transfusion requirement, cold ischemia time) (9-11). The most frequently identified focal source is intra-abdominal infection (9-12). Microbiology differs by center, but frequently identified organisms include *Enterococcus* species, *Staphylococcus* species, *E. coli*, *Klebsiella*, *Pseudomonas*, and *Candida* species (9,11-13).

Management algorithms were developed based on review of microbial isolates from pediatric patients at UCSF who underwent liver transplantation or were listed but not transplanted for acute liver failure from 2010-2015. Review focused on the 1 month preceding and 2 months following transplantation. Because the number of infection episodes was small, empiric treatment recommendations are also based on the BCH San Francisco hospital-wide antibiogram [5]:

**Evaluation of suspected infection**

- A careful physical examination is recommended with attention to sites of central venous catheters and other invasive devices, identification of focal sources of bacterial infection, or skin/mucosal lesions that may be seen with viral infection.
- For all patients? blood cultures from CVC sites and peripheral blood, urinalysis, with reflex to culture.
- For patients with changes in respiratory status, secretions, or increased ventilator requirements? endotracheal aspirate and chest X-ray, consider rapid RSV and flu PCR.
- For pediatric patients with newly recognized ALF, rapid HSV PCR of blood should be sent.
- For neonates with newly recognized ALF, HSV PCR of blood, + CSF if LP not contraindicated, + surface swabs (eyes, nose,
mouth, rectum) for PCR + vesicular lesions for PCR if present.

- Paracentesis is recommended if able to perform for patients with ascites.
- Full liver/comprehensive metabolic panel. For patients with biliary atresia or other conditions predisposing to ascending cholangitis, the diagnosis of ascending cholangitis is suspected based on elevation of bilirubin from baseline, combined with fever and abdominal pain/tenderness.
- Other evaluation should be directed based on suspected focus of infection. Therapy should also be modified based on suspected focal source.
- Note that other evaluation for viral etiologies of acute liver failure, and pre-transplant infectious evaluation, should be conducted concurrently in patients who are being initially evaluated for ALF, but is outside the scope of this guideline. Please refer to ?Pediatric Liver Transplant Evaluation? in the Liver Transplant Manual.

### Infections in previously healthy patients with acute liver failure

- Empiric therapy directed against community-onset etiologies of sepsis is recommended for newly admitted patients with suspected infection.
- Acyclovir should be routinely included for neonates with ALF, until HSV infection is excluded, as disseminated HSV is a common cause of ALF in this age group.
- Acyclovir should be considered, pending exclusion of HSV viremia, for pediatric patients with ALF who present with fevers and/or severe clinical illness. Although HSV is a less common cause of ALF in older children, it was found in 5.6% of tested patients between age 6 months – 18 years in a multicenter study (1).
- If the patient develops progression or new signs of infection while hospitalized, therapy should be broadened to cover healthcare-associated organisms, based on the BCH antibiogram. Management should switch to the hospital-acquired infection algorithm.

#### Empiric Gram-positive therapy

- Given the low rates of VRE among *Enterococcus* isolates at BCHSF, we do not routinely recommend empiric treatment with linezolid in pediatric patients, unless there is a known history of VRE, or decompensation despite empiric vancomycin treatment.

#### Empiric Gram-negative therapy

- Piperacillin-tazobactam is recommend as the mainstay of therapy for suspected sepsis and hospital-acquired infection in pediatric patients with ALF or post-transplantation.
- Therapy should be modified if the patient has known prior resistant infections, or if the patient develops progressive
decompensation despite empiric piperacillin-tazobactam treatment.

Empiric anaerobic therapy

- Antimicrobial therapy with anaerobic activity is recommended for suspected intra-abdominal infection.
- Piperacillin-tazobactam and meropenem both have excellent anaerobic activity.

Empiric antifungal therapy

- Empiric antifungal therapy with caspofungin is recommended in patients ALF or post liver transplantation if they develop evidence of severe sepsis or septic shock. When administered it should be dose-adjusted for hepatic dysfunction with Child-Pugh class B or greater.
- Caspofungin is not routinely recommended for fever alone without clinical sepsis, given the overall low rate of fungal infection observed in our pediatric liver failure/post-liver transplant patients.

Empiric antiviral therapy

- Empiric treatment with acyclovir is recommended for neonates with acute liver failure until disseminated HSV is excluded, and should be considered for pediatric patients with ALF who present with preceding fevers, severe clinical illness, or other features potentially concerning for disseminated HSV.
- Patients with suspected influenza-like illness during influenza season should receive empiric oseltamivir until influenza is excluded.
- Available testing for HSV and for influenza has good sensitivity and rapid turnaround time. In general, acyclovir can be discontinued based on negative HSV PCR testing. However, in neonates, ID consultation is recommended to ensure that the HSV evaluation is complete before discontinuing acyclovir.

DEVELOPMENT & REVIEW:

Initiated 2018. Content developed by Pediatric Antimicrobial Stewardship Program in collaboration with Pediatric Hepatology Service, reviewed by Pediatric ID, Liver Transplant Surgery, Pediatric Pharmacy representatives.

Approved by UCSF Committee on Pharmacy and Therapeutics 8/31/18. Please direct questions about guideline content to rachel.wattier@ucsf.edu [6].

REFERENCES:


