

Guideline/Protocol Title:	Empiric Antimicrobial Treatment of Pediatric Patients with Liver Failure and/or Early Post-Liver Transplantation
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Approving committee(s):	BCH SF Medications Committee (2/16/22), BCH Oakland P&T (2/8/22), UCSF P&T (3/9/22)
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PURPOSE/SCOPE:	These guidelines were developed for pediatric patients receiving care at UCSF Benioff Children’s Hospitals. Management algorithms are focused on patients with newly recognized acute liver failure, patients with end stage liver disease (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 microbiological isolates (e.g. including coverage of prior resistant organisms).
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EXECUTIVE SUMMARY	
<p>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. Pediatric infectious diseases consultation is encouraged when individualized management may be more appropriate.</p> <p>Patients for whom a clear source of infection is identified should be treated according to BCH Empiric Antimicrobial Therapy Guidelines (https://idmp.ucsf.edu/guidelines-for-empiric-therapy-pediatrics). Management algorithms were developed in 2017-2018 based on review of microbiological isolates from pediatric patients who underwent liver transplantation or were listed but not transplanted for acute liver failure at UCSF from 2010-2015. Review focused on the 1 month preceding and 2 months following transplantation. This information was re-reviewed for 2016-2020 and results were similar (available upon request). Because the number of infection episodes was small, empiric treatment recommendations are also informed by overall UCSF inpatient multidrug-resistant organism (MDRO) incidence data (available upon request).</p>	

Evaluation of suspected infection

- For all patients, 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.
- Follow the algorithms below (Appendix 1-3) for diagnostic testing that is generally recommended based on the patient's scenario.
- Other evaluation should be directed based on suspected focus of infection. Therapy should also be modified based on any suspected focal source of infection.

Empiric treatment for suspected infection in previously healthy patients with acute liver failure (ALF)

- 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 herpes simplex virus (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.
- Available testing for HSV 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.
- 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 antibiograms. Management should switch to the hospital-acquired infection algorithm.

Empiric gram-positive therapy

- The frequency of vancomycin-resistant *Enterococcus faecium* (VRE) in the BCH population including pediatric patients with ALF or liver transplant recipients is substantially lower than in the adult population. Therefore, empiric treatment with linezolid is not routinely recommended in pediatric patients, unless there is a known history of VRE, or decompensation despite empiric vancomycin treatment.
- Use of vancomycin concurrently with piperacillin-tazobactam is associated with an increased risk for nephrotoxicity compared to use of vancomycin concurrently with other broad spectrum beta-lactam antibiotics (e.g. cefepime). This difference in risk is not observed during short durations of concurrent therapy (≤ 72 hours). Therefore, when vancomycin is empirically started, it should be discontinued within 48 hours if no resistant gram-positive infection is identified. If vancomycin is indicated for a longer duration, the remaining regimen should be reviewed to either discontinue concurrent piperacillin-tazobactam, if no longer indicated, or switch to an alternative beta-lactam antibiotic.
- If therapy is broadened due to decompensation but an antimicrobial resistant organism is not identified, the antimicrobial choice should be re-evaluated within 48-72 hours to plan de-escalation.

Empiric gram-negative therapy

- Because it is usually active against the isolated pathogens in the BCH patients with ALF or following liver transplantation, piperacillin-tazobactam is recommended 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.
- If therapy is broadened due to decompensation but an antimicrobial resistant organism is not identified, the antimicrobial choice should be re-evaluated within 48-72 hours to plan de-escalation.

Empiric anaerobic therapy

- Antimicrobial therapy with anaerobic activity is recommended for suspected intra-abdominal

infection.

- Piperacillin-tazobactam and meropenem both have excellent anaerobic activity, therefore addition of other antibiotics for this purpose is not recommended.

Empiric antifungal therapy

- Empiric antifungal therapy with an echinocandin (micafungin or caspofungin) is recommended in patients ALF or post liver transplantation if they develop evidence of severe sepsis or septic shock.
- An echinocandin is not routinely recommended for fever alone without severe sepsis or septic shock, given the overall low incidence of fungal infection.

Empiric antiviral therapy

- In addition to recommendations provided above for specific patients with ALF to undergo evaluation for HSV and empiric treatment with acyclovir, patients with suspected influenza-like illness during influenza season should receive empiric oseltamivir until influenza is excluded.

BACKGROUND / INTRODUCTION

Appropriate use of antimicrobial therapy is especially important for pediatric patients with liver failure and following liver transplantation (LT) because of their increased risk for infection and related complications. In particular, infections with multidrug resistant organisms (MDROs) are increasingly reported among children with liver failure or following LT and are associated with higher complication rates. Antimicrobial stewardship including selection of empiric treatment based on local antimicrobial susceptibility data, following consistent pathways, and appropriately targeting treatment to the cause of infection has been identified as a priority for solid organ transplantation practice [1,2].

Local guidelines adapted specifically for pediatric patients and are necessary because pediatric patients with liver failure or post-LT differ from their adult counterparts. Causes of liver failure, indications for LT, and epidemiology of infections differ in pediatric vs. adult patients. Some pediatric LT recipients are comparatively “antibiotic-naïve” and thus at lower risk for MDROs. For those patients at risk for MDROs due to significant healthcare exposure, antimicrobial resistance patterns differ in pediatric vs. adult sites of care. Antimicrobial selection should account for these differences to avoid further selection of MDROs and minimize the burden of antimicrobial-related adverse events and development of breakthrough infections such as *Clostridioides difficile* infection and invasive candidiasis.

SUPPORTING EVIDENCE

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.

- Viral infections: Certain treatable infections (particularly herpes simplex virus, 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 [3]. American Gastroenterological Association guidelines recommend testing for HSV in the setting of ALF and treatment if infection is identified [4]. In the context of the coronavirus disease 2019 (COVID-19) pandemic it is also important to recognize that SARS-CoV-2 infection has been associated with development of ALF in individuals with previously compensated chronic liver disease, so should be incorporated into testing approaches [5]. Other viruses potentially associated

with ALF are incorporated into a separate and well-established diagnostic algorithm for new ALF evaluation.

- **Bacterial and fungal infections:** The most commonly identified non-viral sources of infection in children with ALF include bloodstream infection (9%), lower respiratory tract infection (7-15%), and urinary tract infection (12-16%); in one study most infections were found to be nosocomially acquired [6,7]. 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 [6,8].
- **Antimicrobial prophylaxis:** 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 (developed specifically for children with ALF) [9–11].

Infectious complications in pediatric patients with biliary atresia

Biliary atresia (BA) is the most common cause of chronic liver failure in children and the most common indication for pediatric liver transplantation.

- **Ascending cholangitis:** Children with BA are at risk for ascending cholangitis, predominantly caused by gram-negative bacteria [12,13]. Initial episodes tend to occur with more antimicrobial-susceptible organisms, but patients may develop infections with antimicrobial-resistant organisms with subsequent episodes and with long-term antibiotic prophylaxis [12,13]. Patients approaching transplantation with prior history of recurrent cholangitis may be highly antibiotic-exposed and with known prior history of MDROs.
- **Bloodstream infections:** Patients with BA who receive parenteral nutrition via central venous catheters are at risk for bloodstream infections (BSI), predominantly due to enteric gram-negative bacteria, *Staphylococcus* species, and *Candida* species [14].
- **Spontaneous bacterial peritonitis:** This is a consideration in children with BA or chronic liver disease who have ascites, *E. coli* and *Klebsiella* are the most commonly identified pathogens [15,16].

Infectious complications in pediatric liver transplant recipients

- **Infection frequency and risk factors:** Approximately half of pediatric LT recipients develop bacterial infection during the early postoperative phase (first 1 month following transplantation) [17]. Identified risk factors include pre-existing biliary atresia, young age (< 1 year), small body size (<10kg), and surgical complexity (intraoperative transfusion requirement, cold ischemia time, abdominal wall closure with prosthetic mesh) [18–22]. Increased infection risk has also been associated with duration of invasive devices such as central venous catheters, and need for re-operation [21,23]. Microbiology differs by center, but frequently identified organisms include *Enterococcus* species, *Staphylococcus* species, *E. coli*, *Klebsiella*, *Pseudomonas*, and *Candida* species [18,20–22,24–27].
- **Intra-abdominal infection:** The most frequently identified focal source following pediatric LT is intra-abdominal infection (IAI) [18–20,28]. American Society of Transplantation Infectious Diseases Community of Practice guidelines for management of IAI recommend that empiric treatment consist of gram-positive and broad-spectrum aerobic and anaerobic gram-negative coverage, with exact selection depending on scenario and severity of illness [29]. Empiric regimens are recommended to be tailored to the pathogens with which the patient is known to be colonized, potential side effect profile, drug-drug interactions, and hospital and/or unit-specific antibiogram. The guidelines recommend consideration of empiric therapy for MDR gram-negative organisms in patients with

known colonization, those with septic shock who are hospitalized at institutions with high rates of these organisms, or in the setting of an active outbreak. Administration of an empiric anti-VRE agent may be considered in patients with VRE colonization and hemodynamic instability. Empiric antifungal therapy with an echinocandin can be considered on a case-by-case basis, especially in patients with bowel leaks, perforations, and septic shock of unclear origin.

- **Multidrug resistant organisms:** Pediatric LT recipients are at risk for infection due to MDROs and this risk has been associated with being colonized with such organisms before LT, prior exposure to broad spectrum antimicrobials, and duration of intensive care preceding LT. Infection with MDROs (vs. more susceptible organisms) have been associated with a higher likelihood of developing severe sepsis or septic shock, and increased need for support such as mechanical ventilation [21,22,28,30]. Thus, it is important to minimize selective pressure on the patient's microbial flora to the extent possible prior to LT. The frequency of infections due to MDROs and the specific MDROs involved vary by center with approximate proportions of MDRO among all infectious episodes ranging from 7-62% [17,28,30]. Because of the variability in MDRO epidemiology by center, it is important to consider both individual patient and local population antimicrobial isolates when selecting antimicrobial therapy.
- **Invasive fungal diseases:** Risk factors specific to invasive fungal disease (predominantly *Candida* spp) post-LT include higher intraoperative transfusion needs, prolonged use of CVC, prolonged IV antibiotic treatment, surgical complications (abdominal hemorrhage, vascular thrombosis or bile leak), pulse steroid treatment and living donor liver transplantation [31].

APPENDIX

Appendix 1: Empiric Treatment of Suspected Infection in a Previously Healthy Neonatal/Pediatric Patient with Acute Liver Failure

Appendix 2: Empiric Treatment of Suspected Infection in Pediatric Patients with End-Stage Liver Disease/Biliary Atresia

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

Appendix 4: List of collaborators providing content review of guidelines

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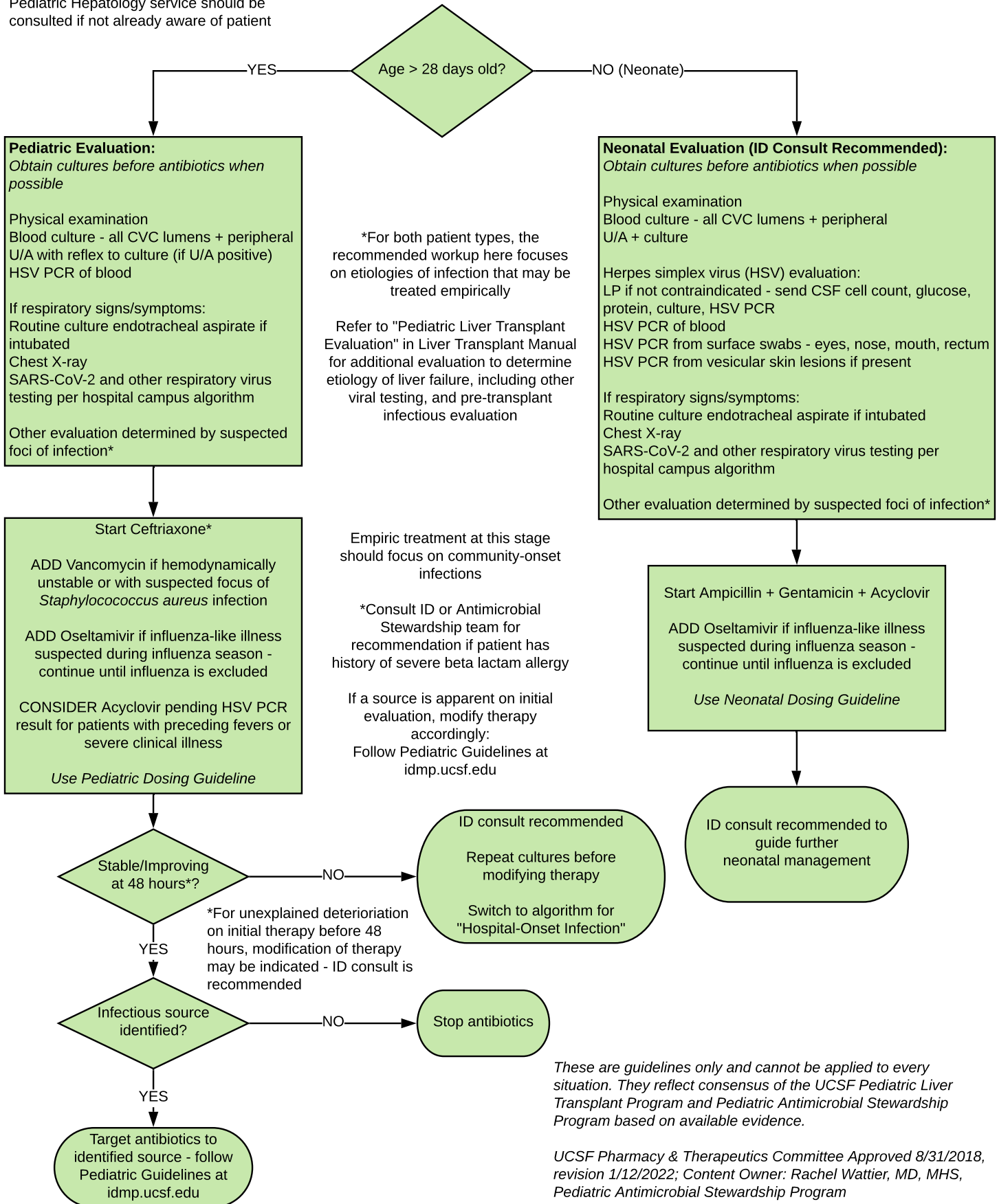
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Revision History	
Revision Date	Update(s)
January 12, 2022	<ul style="list-style-type: none"> ● Revised with stakeholder input to apply to both BCH campuses ● Testing considerations incorporated for SARS-CoV-2/COVID-19 ● Updated literature review including intra-abdominal infection guidelines for solid organ transplantation with incorporation into treatment algorithms (e.g. to review patient prior microbiology) ● Updated review of population-specific antimicrobial isolates and susceptibility (available separately upon request) ● Specific guidance for de-escalation of antimicrobial therapy included ● Including guidance addressing risk for nephrotoxicity with concurrent vancomycin and piperacillin-tazobactam therapy ● Cefotaxime replaced with gentamicin for neonatal empiric therapy due to cefotaxime no longer being available ● Removing advice to dose adjust caspofungin - some experts recommend giving full dose, though Lexi-comp advises to dose adjust for hepatic dysfunction in adults, there is no specific recommendation for pediatrics ● Adding micafungin option to account for BCH OAK formulary and anticipated West Bay formulary change

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

Applies to patients without pre-existing liver disease upon initial assessment/hospitalization

Pediatric Hepatology service should be consulted if not already aware of patient



These are guidelines only and cannot be applied to every situation. They reflect consensus of the UCSF Pediatric Liver Transplant Program and Pediatric Antimicrobial Stewardship Program based on available evidence.

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

Applies to pre-transplant pediatric patients with known liver disease primarily at risk for infection with enteric organisms

Pediatric Hepatology service should be consulted if not already aware of patient

See separate algorithm for neonatal and pediatric patients with suspected infection at initial evaluation for acute liver failure

See separate algorithm for suspected hospital-onset infection in patients with acute liver failure or early post-transplantation

Initial Evaluation:
Obtain cultures before antibiotics when possible

Physical examination
 Blood culture - all CVC lumens + peripheral U/A + urine culture
 AST, ALT, total & direct bilirubin, GGT, alkaline phosphatase

If respiratory signs/symptoms:
 Routine culture of endotracheal aspirate if intubated
 Chest X-ray
 SARS-CoV-2 and other respiratory virus testing per hospital site algorithm

If ascites present: Paracentesis if able

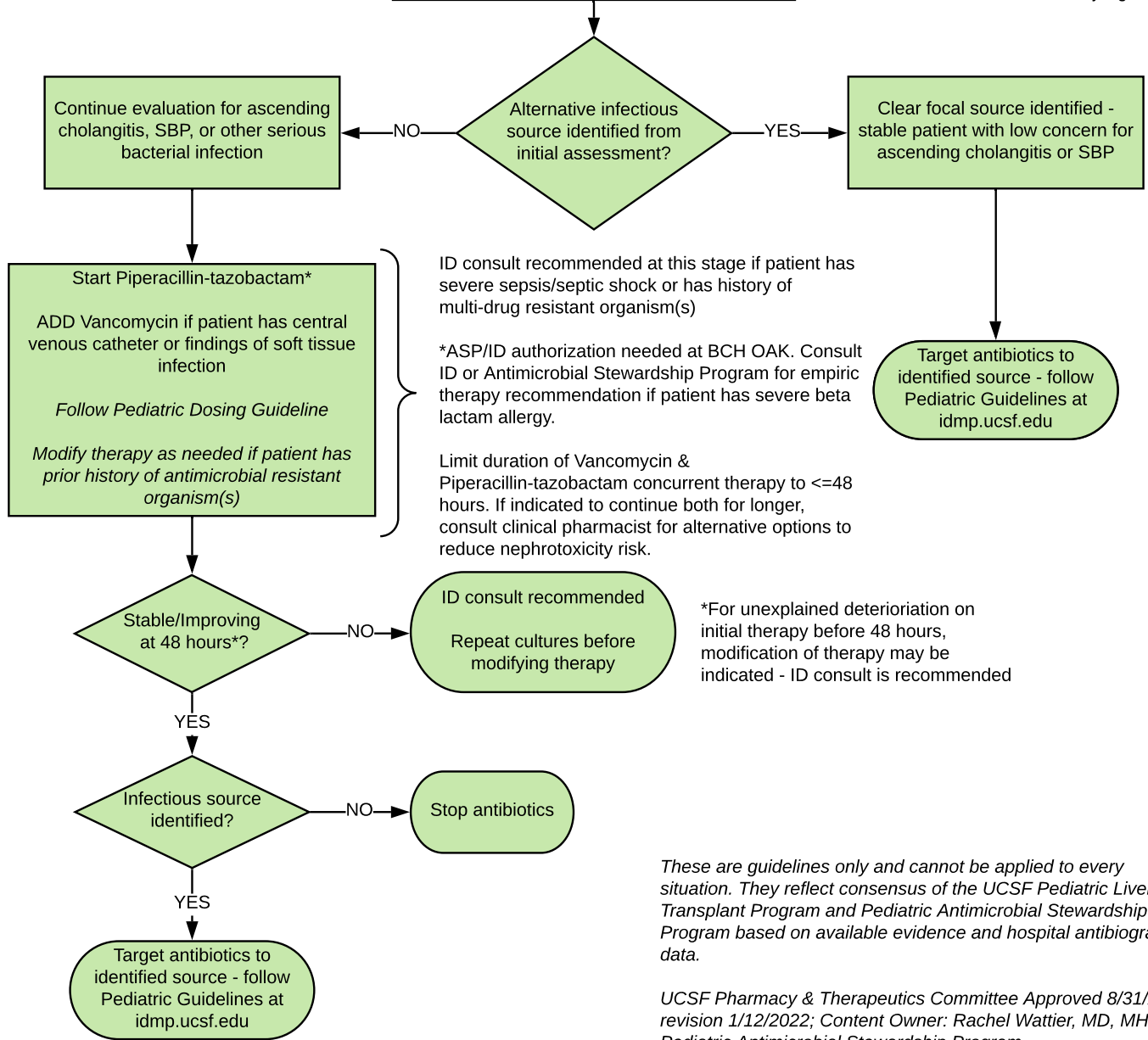
Avoid culturing long term biliary drains

Initial evaluation should determine likelihood of ascending cholangitis, vs. spontaneous bacterial peritonitis (SBP), vs. other community- or hospital-onset infectious source.

Ascending cholangitis should be suspected with fever and an increase in bilirubin from baseline

SBP should be suspected in a patient with ascites who has fever and abdominal pain/tenderness

If the patient is clinically stable and an obvious focal source is identified on exam (e.g. acute otitis media, URI), not all of the recommended evaluation may be needed. Use clinical judgement.



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

Applies to non-neonatal patients with acute liver failure > 48 hours into hospitalization and/or pediatric patients < 2 months s/p liver transplantation (for any indication)

Pediatric Hepatology service should be consulted if not already aware of patient

See separate algorithm for neonatal and pediatric patients with suspected infection at initial evaluation for acute liver failure

See separate algorithm for suspected infection in pre-transplant patients with biliary atresia

Initial Evaluation:
Obtain cultures before antibiotics when possible

Physical examination
 Blood culture - all CVC lumens + peripheral
 U/A with reflex to culture

If respiratory signs/symptoms:
 Routine culture of endotracheal aspirate if intubated
 Chest X-ray
 SARS-CoV-2 and other respiratory virus testing per hospital site algorithm

If ascites present: Paracentesis if able

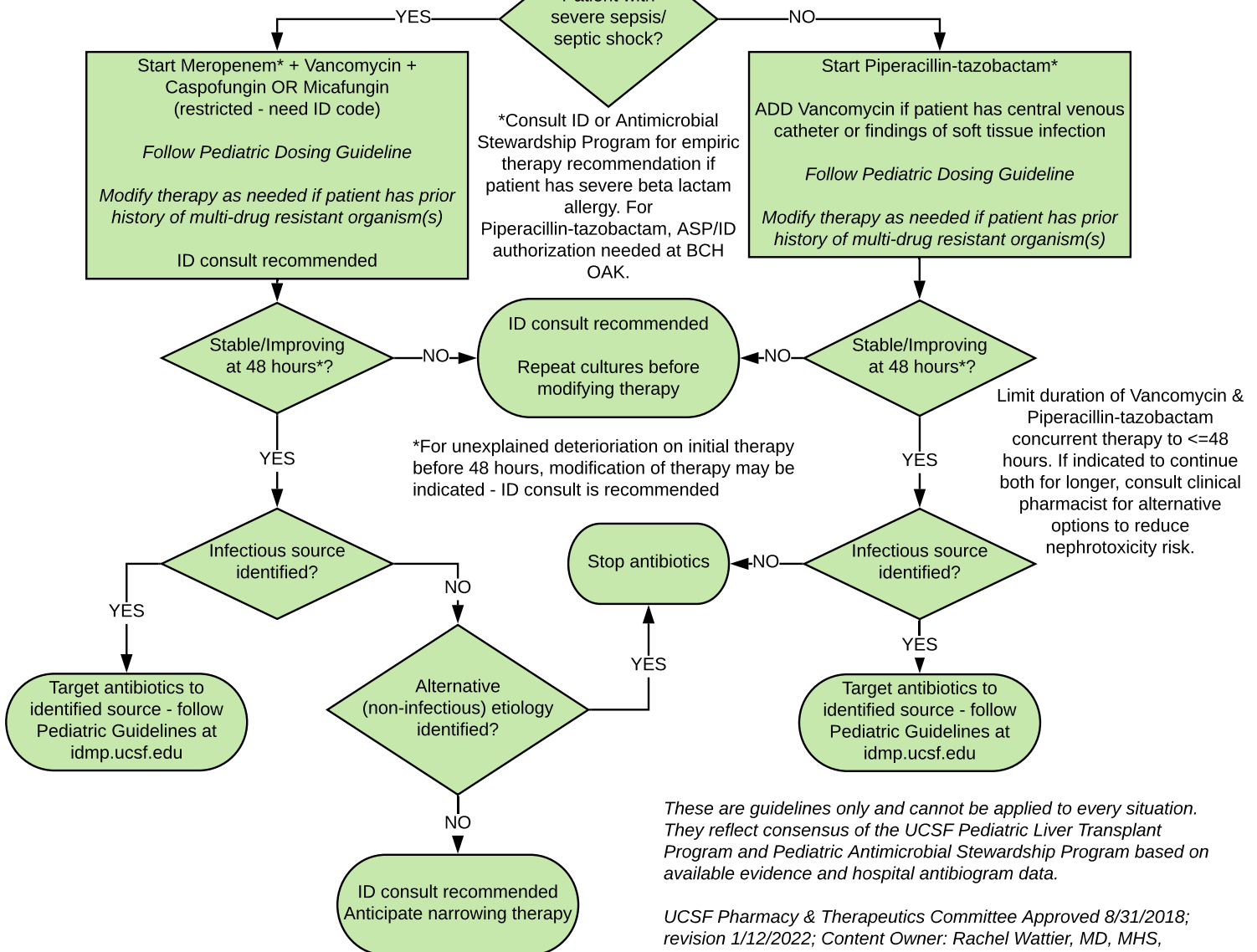
If > 1 month post-transplant, send blood for CMV PCR, EBV PCR; adenovirus PCR if febrile

Additional evaluation should be considered based on patient characteristics + focal signs/symptoms

ID consult recommended for:

- Severe/evolving presentation
- Evaluation for opportunistic infection if > 1 month post-transplant or with previous transplant
- Evaluation for donor-derived infection based on presentation + risk factors

Systemic inflammatory response criteria and specific evidence of hypo-perfusion or organ dysfunction not explained by an alternative process



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

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