Cholangitis Clinical Pathway

Background

Cholangitis is a clinical diagnosis classically defined in adults as the Charcot triad of fever, jaundice, and right upper quadrant abdominal pain. Diagnosis in adults has been standardized to also include possible variables such as systemic inflammation and evidence of abnormal bile ducts.(1) This adult definition is ill suited to our pediatric population, particularly those with Biliary Atresia who have undergone Kasai hepatoportoenterostomy. This patient population is particularly at risk for adverse outcomes related to episodes of cholangitis, with repeated episodes of cholangitis and development of bile lakes indications for liver transplantation evaluation.

Pathogens

Based on published literature, the most commonly isolated organisms are as follows:

- *Klebsiella* species
- *Escherichia coli*
- *Enterococcus faecalis*
- *Enterobacter* species
- *Pseudomonas aeruginosa*

Antibiotic prophylaxis for the prevention of cholangitis:

- **Medication choice:**
  - 1st line
    - Standard BA: TMP/SMX 2.5 mg TMP/kg/dose BID (maximum dose = 160 mg as TMP per day)
    - BA-splenic malformation syndrome – includes asplenia prophylaxis: amoxicillin/clavulanate 10 mg/kg/dose BID (maximum dose = 250 mg amoxicillin per day)
  - 2nd line (cholangitis despite prophylaxis with TMP/SMX or culture driven): amoxicillin/clavulanate 10 mg/kg/dose BID (maximum dose = 250 mg amoxicillin per day)
  - 3rd line / alternate:
    - Age <5: Levofloxacin 10 mg/kg/dose BID (maximum dose = 500 mg per dose)
    - Age 5+: Levofloxacin 10 mg/kg/dose q24h (maximum dose = 500 mg)
    - All ages: Ciprofloxacin 15 mg/kg/dose q12h (maximum dose = 500 mg per dose)
- **Duration**: continue for at least 6 months post-Kasai HPE. If no episodes of cholangitis, consider discontinuing. If antibiotics were stopped and there are subsequent episodes of cholangitis after 6 months, restart with new 6 month duration

Definitions:

	Required Criteria	Additional Criteria	Alternate Criteria	Management**
Cholangitis	Fever >38ºC in absence of other convincing source	2 of the following: 1. RUQ abdominal pain or acholic stools 2. Direct/conjugated bilirubin >25% above baseline* 3. >25% above baseline* increase in two of: GGT, ALT, and/or alkaline phosphatase AND evidence of inflammation (as defined by: leukocytosis, elevated ANC, elevated CRP, elevated procalcitonin) 4. Bile lakes on imaging	Required criteria + positive blood culture not felt to be from CLABSI or other source	1st line management per protocol
Possible Cholangitis	Meets criteria for *Cholangitis*	Insufficient improvement in previously met criteria for *Cholangitis* within 72 hours of appropriate antibiotic therapy		Stop antibiotics and consider other source OR Consider Refractory Cholangitis
Refractory Cholangitis	Meets criteria for *Cholangitis*	Previously met criteria for *Cholangitis* show insufficient improvement within 72 hours of appropriate antibiotic therapy		Escalate antibiotic therapy to 2nd line and ID consult

Relapsed Cholangitis may be defined as an episode occurring<4weeks from previous while Recurrent Cholangitis occurs > 4 weeks from previous episode with improvement of clinical and lab parameters to baseline or near baseline.

**Baseline value defined as the average over 3 prior measurements*
***Antibiotic choice should be driven by culture speciation and sensitivities when available*

Antibiotics for the treatment of cholangitis (2):

Medication choice:

1st line: Ceftriaxone 50-75 mg/kg/dose q24h; max 2000 mg/dose (75 mg/kg for hard to treat/penetrate infections, such as in the presence of bile lakes)

2nd line/ escalation in therapy clinically indicated: Piperacillin/tazobactam 75 mg/kg/dose piperacillin q6h; max 3000 mg/dose piperacillin

Duration: The patient should receive antibiotics until afebrile with improvement in clinical markers of cholangitis. The minimum durations are defined below, but may be extended in the presence of bile lakes or abscesses.

- Cholangitis: 14 days

Special considerations:

- If past episodes of cholangitis required escalation in antibiotic therapy beyond ceftriaxone or growth on prior culture that would not be covered with ceftriaxone, move to 2nd line / consider ID consult for more guided therapy. Refer to antibiotic tables for assistance with antibiotic choices.
- For *Refractory Cholangitis*:
    - Consider broadened coverage to include organisms not covered by empiric regimen. Refer to antibiotic tables for assistance with antibiotic choices
        - Metronidazole for anaerobes.
            - Note: avoid concurrent treatment with metronidazole and piperacillin-tazobactam given impact of double anaerobic coverage on microbiome.
        - Additional anti-pseudomonal or other gram negative coverage
        - Vancomycin for *Enterococcus*
    - Consider coverage for yeast
        - Use empiric fluconazole as first line
    - Consider ID consult for review and consideration of alternative treatment strategies
- For *Relapsed* or *Recurrent Cholangitis*
    - If there was a good response to initial treatment and you feel that the relapse is due to inadequate duration of therapy, then resume initial treatment and extend duration of therapy.
    - If relapse is felt to be due to inadequate coverage, consider broadening antimicrobial therapy.
    - Consider imaging to ensure there is not a focus that would dictate a longer course of antibiotics (i.e. bile lake).
    - Recommend ID consult for review and consideration of alternative treatment strategies.

Antibiotic choices: All antibiotics in the table below have gram negative coverage and would be considered treatment for GI pathogens. Differences in Enterococcal, Pseudomonal and Anaerobic coverage are noted.

Antibiotic	Dosing for cholangitis	Antimicrobial spectrum				Home IV regimen	Oral regimen (best)
		Enterococcus	*Pseudomonas*	Anaerobes	Enteric Gram Negative		
Ceftriaxone	50-75 mg/kg/day divided q24h Max dose: 2000 mg/day	No	No	No	Yes	Ceftriaxone	Amoxicillin/clavulanic acid
Piperacillin/ tazobactam	300 mg/kg/day as piperacillin divided q6h Max Dose: 12,000 mg piperacillin per day	Yes	Yes	Yes	Yes	Can be given as continuous or extended infusion	No direct alternative, ciprofloxacin/levofloxacin + metronidazole
Alternative therapies							
Ampicillin & sulbactam	200 mg/kg/day as ampicillin divided q6h Max dose: 2000 mg ampicillin	Yes	No	Yes	Yes	None (drug instability)	Amoxicillin/clavulanic acid
Amoxicillin & clavulanate	60 mg/kg/day as amoxicillin divided q8h Max dose: 875 mg amoxicillin	Yes	No	Yes	Yes	None	N/A
Ciprofloxacin	Ciprofloxacin 10mg/kg/dose IV q12h Max dose: 400 mg	No	Yes	No	Yes	Only need IV formulation if poor absorption or oral intolerance	Ciprofloxacin 15mg/kg/dose PO q12h Max dose: 750 mg
Levofloxacin	<5 years of age 10mg/kg/dose IV/PO q12h ≥ 5 years of age 10 mg/kg/dose q24h Max dose: 750 mg	+/-	Yes	No	Yes	Only need IV formulation if poor absorption or oral intolerance	PO is equivalent to IV if absorption is normal
Cefepime	50 mg/kg/dose q8h Max dose: 2000 mg	No	Yes		Yes	Cefepime	No direct alternative, cipro/levo

Cefotaxime **(alternative to ceftriaxone in neonates)**	150-200 mg/kg/day divided q8h Max dose: 2000 mg	No	No	No	Yes	Cefotaxime	Amoxicillin/ clavulanic acid or trimethoprim/sulfamethoxazole (treatment dosing)
Meropenem	20 mg/kg/dose q8h Max dose: 1000 mg	+/-	Yes	Yes	Yes	Meropenem	No direct alternative, cipro/levo + metro
Metronidazole (Add to increase anaerobic coverage)	Metronidazole 10mg/kg/dose IV or PO q8h Max dose: 500 mg	No	No	Yes	No	Does not have GNR coverage	PO is equivalent to IV if absorption is normal
Trimethoprim &Sulfamethoxazole	12 mg/kg/day trimethoprim divided q12h Max dose: 160 mg trimethoprim	No	No	No	Yes	Only need IV formulation if poor absorption or oral intolerance	PO is equivalent to IV if absorption is normal
Vancomycin (add for ampicillin resistant enterococcal coverage if indicated)	See age related guidelines and renal adjustment	Yes	No	No	No	Vancomycin	< 12 years: Linezolid 10 mg/kg/dose q8h >/= 12 years: Linezolid 10 mg/kg/dose q12h
Fluconazole (if concern for fungus)	12 mg/kg/ dose q24h	No	No	No	No	Only need IV formulation if poor absorption or oral intolerance	PO is equivalent to IV if absorption is normal

References

1. Miura F, Okamoto K, Takada T, Strasberg SM, Asbun HJ, Pitt HA, Gomi H, et al. Tokyo Guidelines 2018: initial management of acute biliary infection and flowchart for acute cholangitis. J Hepatobiliary Pancreat Sci 2018;25:31-40.

2. Calinescu, A.M.; Madadi-Sanjani, O.; Mack, C.; Schreiber, R.A.; Superina, R.; Kelly, D.; Petersen, C.; Wildhaber, B.E. Cholangitis Definition and Treatment after Kasai Hepatoportoenterostomy for Biliary Atresia: A Delphi Process and International Expert Panel. J. Clin. Med. 2022, 11, 494. https://doi.org/10.3390/jcm11030494