Berkeley Public Health

THE FORUM For Collaborative Research℠

PSC Forum 6
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Session IV:

Definition of Acute Cholangitis

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Faculty Disclosure

Advisor

Abbvie, Albireo, BiomX, Boehringer Ingelheim, Cymabay, Falk, Gilead, Genfit, Hightide, Intercept, Jannsen, MSD, Novartis, Phenex, Pliant, Regulus, Siemens, Shire

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Property rights

The Medical Universities of Graz and Vienna have filed patents on medical use of *nor*UDCA and I am listed as co-inventor

Need for defining acute cholangitis

- Lack of a universally accepted definition
- Frequent clinical endpoint / event of special interest in studies
- Important exclusion criterium in clinical studies
- Definition will impact on study design and outcomes

Why does acute cholangitis / superimposed bacterial cholangitis matter in PSC

- Frequent
  - 30-40% of people with PSC experience this complication during the disease course
  - 6% at diagnosis of PSC
  - Most common PSC-related clinical event in recent SIM trial observed in 13% of patients over a median follow-up of 23 months
- Negative impact on quality of life
- Risk of biliary sepsis
  - Mortality rates for episodes of bacterial cholangitis (general lit.) range from 5% to 15%
- Recurrent cholangitis may play a role in progression of PSC
- Recurrent cholangitis can be primary indication for liver transplant

EASL CPG, *J Hepatol* 2022
AASLD PG, *Hepatology* 2023

Pathophysiological considerations – risk factors

- Bacterial cholangitis usually occurs in patients with a relevant / high-grade **biliary stricture**
  - Stagnation of bile may facilitate bacterial colonization
  - Stones / sludge neglected? (secondary to strictures?)
- **Portal bacteraemia**, reported in patients with **active colitis**, may be another important contributing factor
- **ERCP** (especially with stenting) is a major risk factor for bacterial cholangitis in PSC and prophylactic antibiotics should be routinely used
- Generally, biliary **sphincterotomy** is not recommended as a routine procedure, but can be considered if cannulation is difficult
  - Small sphincterotomy in PSC in order to avoid ascending cholangitis

EASL CPG, *J Hepatol* 2022

Need for defining acute cholangitis

COMMENTARIES

Defining Primary Sclerosing Cholangitis: Results From an International Primary Sclerosing Cholangitis Study Group Consensus Process

- Panel was unable to reach consensus through the Delphi processon the definition of acute bacterial cholangitis in the context of PSC
- This highlights an urgent, unmet need for dedicated studies comparing Tokyo, Wannhoff, and other potential criteria
- Uniform approach can be used as a clinical endpoint in therapeutic trials

Ponsioen et al., *Gastroenterology* 2021

Challenges in defining acute cholangitis in PSC

- More accurate term: superimposed bacterial cholangitis
- Wide spectrum
  - Oligosymptomatic ↔ suppurative cholangitis ↔ biliary sepsis
- Bile may not be sterile – bile microbiome
  - Enterococcus spp. in ductal bile was strongly correlated with concentration of the noxious secondary bile acid taurolithocholic acid
- Fungal cholangitis
  - Candida spp. – poor prognosis

EASL CPG, *J Hepatol* 2022
Liwinski et al., *Gut* 2022
Zigmond et al., *Clin Gastroenterol Hepatol* 2023

Challenges in defining acute cholangitis in PSC *Ctd.*

- Standard definitions (Tokyo guidelines) may not be universally applicable
- Symptoms may include a wide spectrum of severity and can be atypical
- Signs of bacterial cholangitis can be mild and nonspecific
  - Patients may present even without significant change in liver biochemistry, as infections can be limited to smaller (parts of) liver segments
  - In milder cases, it is often only the response to antibiotics that confirms the clinically suspected diagnosis
- Recently, new criteria for acute cholangitis in people with PSC have been proposed (Wannhoff citeria)

EASL CPG, *J Hepatol* 2022

J Hepatobiliary Pancreat Sci (2018) 25:17–30
DOI: 10.1002/jhbp.512

GUIDELINE

Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute cholangitis (with videos)

Table 2 TG18/TG13 diagnostic criteria for acute cholangitis [4]

A. Systemic inflammation
  A-1. Fever and/or shaking chills
  A-2. Laboratory data: evidence of inflammatory response
B. Cholestasis
  B-1. Jaundice
  B-2. Laboratory data: abnormal liver function tests
C. Imaging
  C-1. Biliary dilatation
  C-2. Evidence of the etiology on imaging (stricture, stone, stent etc.)

Suspected diagnosis: one item in A + one item in either B or C
Definite diagnosis: one item in A, one item in B and one item in C

Thresholds:			
A-1	Fever		BT >38°C
A-2	Evidence of inflammatory response	WBC count (×1,000/μL)	<4 or >10
		CRP (mg/dL)	≥1
B-1	Jaundice		T-Bil ≥2 (mg/dL)
B-2	Abnormal liver function tests	ALP (IU)	>1.5 × STD[a]
		γGTP (IU)	>1.5 × STD[a]
		AST (IU)	>1.5 × STD[a]
		ALT (IU)	>1.5 × STD[a]

Kiriyama et al., *J Hepatobiliary Pancreat Sci* 2018

Wannhoff criteria of superimposed bacterial cholangitis

Clinical Gastroenterology and Hepatology 2015;13:2372–2379

Inflammation But Not Biliary Obstruction Is Associated With Carbohydrate Antigen 19-9 Levels in Patients With Primary Sclerosing Cholangitis

Andreas Wannhoff,[*] Christian Rupp,[*] Kilian Friedrich,[*] Maik Brune,[‡] Johannes Knierim,[*] Christa Flechtenmacher,[§,‖] Peter Sauer,[*] Wolfgang Stremmel,[*,‖] Johannes R. Hov,[¶,#] Peter Schirmacher,[§,‖] Karl Heinz Weiss,[*,‖] and Daniel N. Gotthardt[*,‖]

Wannhoff et al., *Clin Gastro Hepatol* 2015

Wannhoff criteria of superimposed bacterial cholangitis

Single criterion:	Suppurative cholangitis on ERC
Main criteria (≥ 1):	Body temperature > 38.0°C
	Leukocyte count > 12/nL or CRP > 75.0 mg/L
Minor criteria (≥ 2):	Clinical signs of acute cholangitis (e.g., right upper abdominal pain)
	Positive bile culture
	Increase in the level of ALP or total bilirubin above two times the upper limit of normal
	No other focus of infection

Wannhoff et al., *Clin Gastro Hepatol* 2015

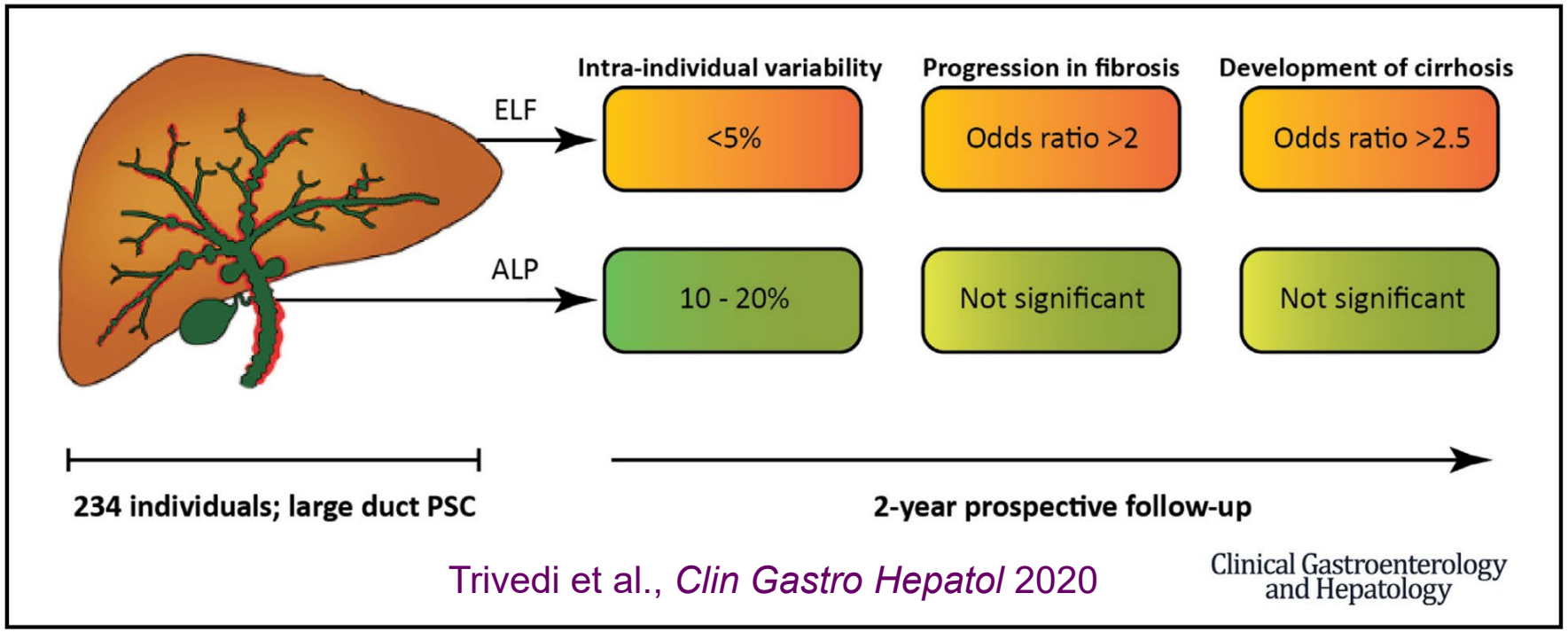
Wannhoff criteria of superimposed bacterial cholangitis

- If the SINGLE criterion was met, no further requirements had to be fulfilled for the diagnosis of cholangitis
- In all other cases:
  - presence of at least ONE of the MAIN criteria, indicating inflammation
  - AND at east TWO MINOR criteria were mandatory for the diagnosis of cholangitis
- Minor criteria were chosen to differentiate between cholangitis-induced increase in inflammation markers and increase due to other causes

Wannhoff et al., *Clin Gastro Hepatol* 2015

Potential confounders

- Gallbladder distension (RUQ pain without signs of cholecystitis)
- Pain in ‘right-side domininant‘ PSC-IBD not always clearly RLQ
- Variability of ALP (intra-individual, intestinal…)

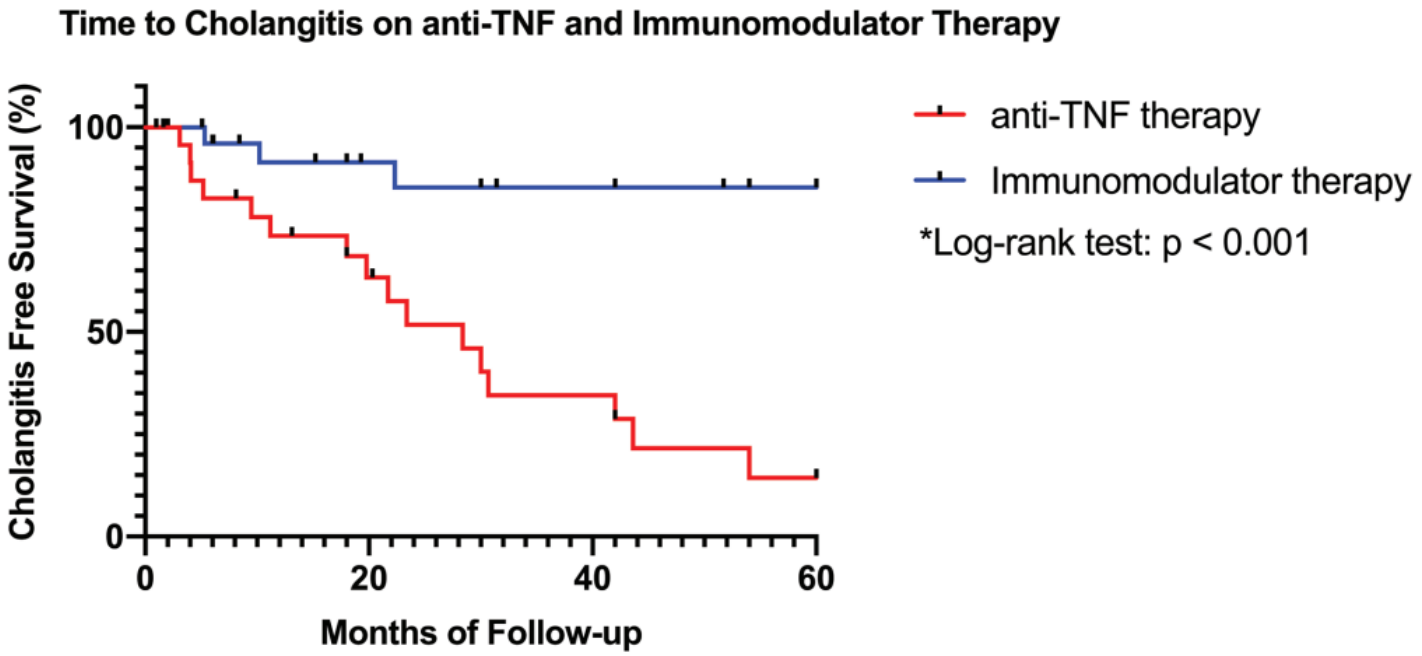


IBD and cholangitis

- Does IBD activity / flares drive cholangitis?
  - Theoretically yes (gut permeability…), no hard data
- Does immunosuppression for IBD trigger cholangitis?
  - Anti-TNF signal?
  - Vedo appears to be safe(r)
  - Newer therapies??
  - PSC patients usually excluded from classic IBD study designs

Association of Anti-TNF Therapy With Increased Risk of Acute Cholangitis in Patients With Primary Sclerosing Cholangitis

Chiraag Kulkarni, MD,[*] Soumya Murag, MD,[†] George Cholankeril, MD,[,‡] Touran Fardeen,[*] Ajitha Mannalithara, PhD,[*] Robert Lerrigo, MD,[†] Ahmad Kamal, MD,[†] Aijaz Ahmed, MD,[*] Aparna Goel, MD,[*] and Sidhartha R. Sinha, MD[*]*



- Incidence of cholangitis in patients prescribed anti-TNF therapy was 23% by 12 months, 38% by 24 months, and 50% by 36 months **(OR 7.3)**
- In contrast, in patients prescribed immunomodulatory therapy the incidence was 7% by 12 months, 11% by 24 months, and 11% by 36 months **(OR 0,23)**

Kulkarni et al., *Inflamm Bowel Dis* 2021

Clinical Gastroenterology and Hepatology 2020;18:2295–2304

PANCREAS, BILIARY TRACT, AND LIVER

Effects of Tumor Necrosis Factor Antagonists in Patients With Primary Sclerosing Cholangitis

Charlotte Rose Hawkey Hedin,[*****,‡‡‡‡‡,§§§§§] Gina Sado,[*,§§§§§] Nelson Ndegwa,[‡] Ellina Lytvyak,[§] Andrew Mason,[§] Aldo Montano-Loza,[§] Alessio Gerussi,[||,¶,§§§§§] Francesca Saffioti,[||,#,§§§§§] Douglas Thorburn,[||,§§§§§] Emma Nilsson,[**] Geir Larsson,[‡‡,§§§§§] Bjørn A. Moum,[‡‡,§§§§§] Kim N. van Munster,[§§,§§§§§] Cyriel Y. Ponsioen,[§§,§§§§§] Cynthia Levy,[||||] Nicholas F. Nogueira,[¶¶] Christopher L. Bowlus,[##] Neta Gotlieb,[***] Oren Shibolet,[***] Kate D. Lynch,[‡‡‡] Roger W. Chapman,[‡‡‡] Christian Rupp,[§§§] Mette Vesterhus,[||||||] Kristin K. Jørgensen,[¶¶¶] Fredrik Rorsman,[###] Christoph Schramm,[****,§§§§§] João Sabino,[‡‡‡‡,§§§§§] Severine Vermeire,[‡‡‡‡,§§§§§] Alessandra Zago,[§§§§,§§§§§] Nora Cazzagon,[§§§§,§§§§§] Hanns-Ulrich Marschall,[||||||||,§§§§§] Henriette Ytting,[¶¶¶¶,§§§§§] Karima Ben Belkacem,[####,§§§§§] Olivier Chazouilleres,[####,§§§§§] Sven Almer,[*,§§§§§] and International PSC Study Group, Annika Bergquist[*,§§§§§]

What You Need to Know

Background

The authors assessed the effects of tumor necrosis factor (TNF) antagonists (adalimumab or infliximab) in patients with primary sclerosing cholangitis (PSC) and inflammatory bowel diseases (IBD).

Findings

In a retrospective analysis of 141 patients with PSC and IBD, the authors observed response of IBD to treatment in 48% and remission of IBD to treatment in 23%, with no specific safety signals. Serum levels of alkaline phosphatase decreased with adalimumab, but not infliximab.

Implications for patient care

Anti-TNF agents are effective in the treatment of IBD in patients with PSC, although not as effective as in patients with non-PSC IBD. PSC should not be a contraindication to treatment with anti-TNF agents.

Table 3. Table of All Adverse Events

Adverse event	Infliximab, n = 147	Adalimumab, n = 39	Total, n = 186
Allergy, n (%)	11 (7)	3 (8)	14 (8)
Infection, n (%)	10 (7)	2 (5)	12 (6)
Skin disease, n (%)	7 (5)	2 (5)	9 (5)
Malignancy, n (%)	3 (2)	0 (0)	3 (2)
SLE, n (%)	1 (1)	0 (0)	1 (1)
Recurrent cholangitis, n (%)	7 (5)	1 (3)	8 (4)
Unknown, n (%)	8 (5)	3 (38)	11 (6)

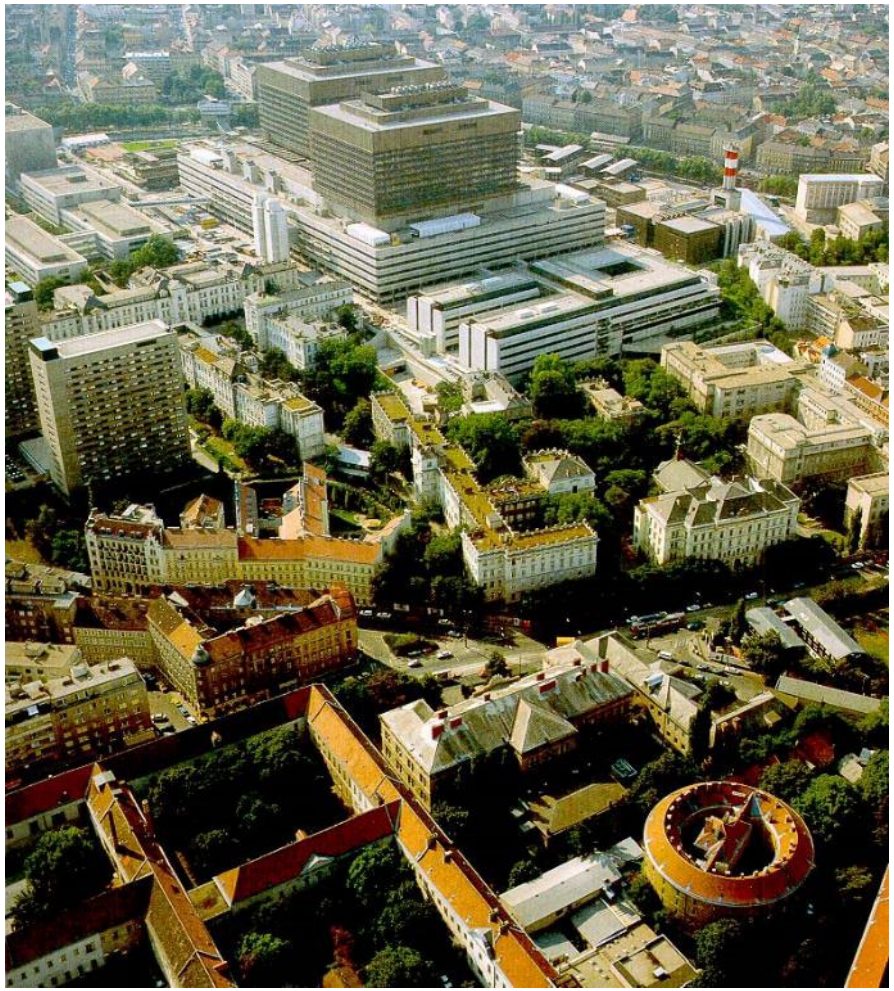
Hawkey Hedin et al., *Clin Gastro Hepatol* 2020

Key exclusion citeria (examples)

- Ascending cholangitis within 30 days of screening
- History of cholangiosepsis with hospitalization within 3 months
- Current episode of suppurative cholangitis
- Endoscopic treatment for bile duct stenosis needed or planned within 5 months post randomization

Summary - Definition of acute cholangitis

- Lack of a universally accepted definition
- Definition will impact on study design and outcomes
- Important exclusion criterium and clinical endpoint / event
- Broad range of clinical presentations
  - Wannhoff criteria may be a step in the right direction
- Broad range of predisposing risk factors
  - Biliary system (strictures, interventions, papilla…), IBD (activity, drugs…)
- Uniform definition critical for comparability of study results
- Urgent need for establishing a study group for definition



Thank you for your attention!

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