



**PSC Forum 7**

**Tuesday, June 4, 2024**

Starhotels Business Palace

Via Privata Pietro Gaggia, 3, 20139, Milan, Italy

# **PSC Forum Acute Cholangitis Working Group Update**

**Michael Trauner**

Div. of Gastroenterology & Hepatology

Dept. of Internal Medicine III



# Faculty Disclosure

I herewith declare the following paid or unpaid consultancies, business interests or sources of honoraria payments, and anything else which could potentially be viewed as a conflict of interest:

## **Advisor**

Abbvie, Albireo, Boehringer Ingelheim, Chemomab, Falk, Gilead, Genfit, Hightide, Intercept, Ipsen, Janssen, Novartis, Pliant

## **Grants / research support**

Alnylam, Cymabay, Falk, Genentech, Gilead, Intercept, UltraGenyx

## **Speakers bureau**

Albireo, Falk Foundation, Gilead, Intercept, Ipsen, Madrigal

## **Travel grants**

AbbVie, Falk Foundation, Gilead, Intercept, Janssen

## **Property rights**

Co-inventor for patents on medical use of *norUDCA* (filed by the Medical Universities of Graz and Vienna)

# Why does Acute 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 (13% over 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**



# Aims of the Acute Cholangitis working group

- Clear definition and grading system for acute cholangitis in PSC
- Establish acute cholangitis as a recognized endpoint in clinical trials
- Understand the impact of acute cholangitis on patient outcomes



Co-Leads	
Michael Trauner MD; Professor	Medical U of Vienna
Stephen Rossi PharmD; Chief Scientific Officer	PSC Partners Seeking a Cure
Academia-10	
Arun Sanyal MB, MBBS; Director	VCU
Kris Kowdley AGAF FAASLD FACP FACG; Director	Liver Institute Northwest
Sayed Aseem MD, PhD; Assistant Professor	VCU
John Eaton, MD; Gastroenterologist, Internist	Mayo Clinic
David Assis MD; Professor	Yale
Melissa Palmer MD; CEO	Liver Consulting LLC
Douglas Thorburn MD PhD; Prof.	Royal Free Hospital/U. College London
Dimitar Tonev, MD; Medical Director	HCV Research UK
Donna Evon, PhD; Professor of Medicine	U of North Carolina at Chapel Hill
Christopher (Chris) Bowlus MD; Chief Division	UC Davis
Industry-8	
Jennifer Schranz MD; SVP	Ipsen Pharmaceuticals
Richard Lirio MD; Executive Director	GSK
Matthew Frankel MD; Chief Med Officer	Chemomab
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Adrian Di Bisceglie MD; Lead,	Hightide Therapeutics
Patient Advocacy Groups -3	
José Willemse MSc; Director/Board Member LPI	Dutch Liver Pt Assoc. / Liver Pt. Inter.
Martine Walmsley BSc; Head of Research Strategy	PSC Support
Joanne Hatchett RN, MS; Med. Science Liaison	PSC Partners Seeking a Cure
Regulatory Agencies-2	
	Regulatory Agencies EMA
	Regulatory Agencies FDA

Potentials	
Cynthia Levy MD; Chair, Prof. Director	U of Miami
Theo Heller, MD; Section Chief	NIDDK, NIH
Sujal Shah, MS, MBA; President	CymaBay Therapeutics
Eric Lefebvre, MD; Chief Med Officer	Pliant Therapeutics
Kyoungsub Song, PhD; Director	LISCure Biosciences

Hopefully more to join – welcome!

<i>Palak Trivedi, University of Birmingham</i>
<i>Joannes Taminiau, European Medicines Agency</i>



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**PSC Forum Acute Cholangitis Working Group Update**  
**Clinical Definition Considerations**

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# Recent efforts in defining acute cholangitis

DOI: 10.1002/hep.32771

**PRACTICE GUIDANCE**

*AASLD, Hepatology 2022*



## **AASLD practice guidance on primary sclerosing cholangitis and cholangiocarcinoma**

Christopher L. Bowlus<sup>1</sup> | Lionel Arrivé<sup>2</sup> | Annika Bergquist<sup>3</sup> |  
Mark Deneau<sup>4</sup> | Lisa Forman<sup>5</sup> | Sumera I. Ilyas<sup>6</sup> | Keri E. Lunsford<sup>7</sup> |  
Mercedes Martinez<sup>8</sup> | Gonzalo Sapisochin<sup>9</sup> | Rachna Shroff<sup>10</sup> |  
James H. Tabibian<sup>11</sup> | David N. Assis<sup>12</sup>

Clinical Practice Guidelines

*EASL, J Hepatol 2022*

**JOURNAL  
OF HEPATOLOGY**

## **EASL Clinical Practice Guidelines on sclerosing cholangitis<sup>☆</sup>**

European Association for the Study of the Liver<sup>\*</sup>

## **COMMENTARIES**

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



*IPSCSG, Gastro 2021*

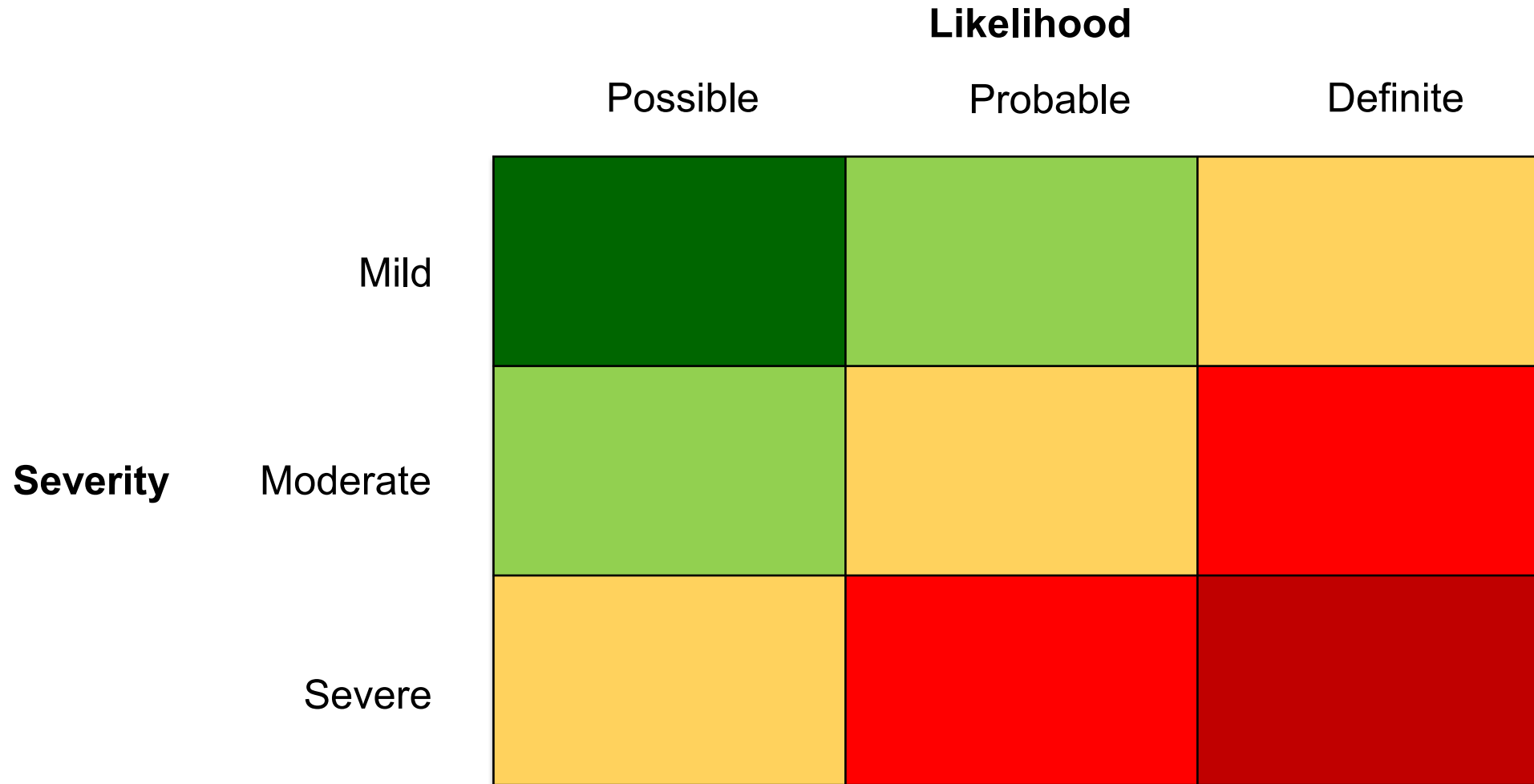


# Classifying and grading acute cholangitis

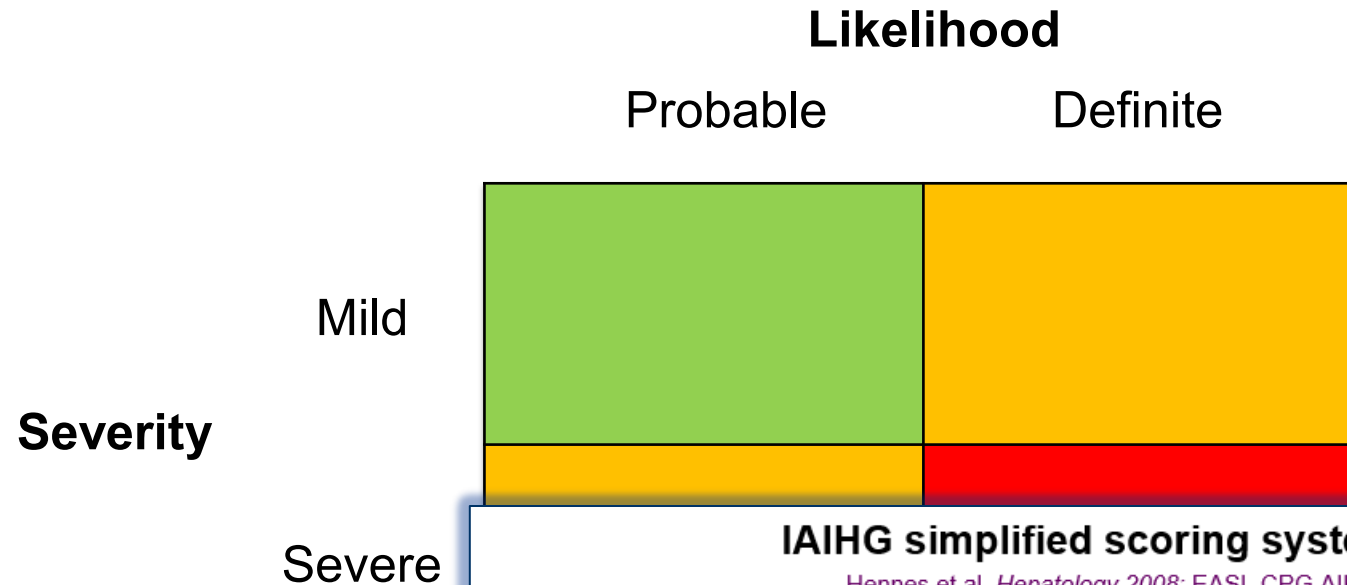
		Likelihood		
		Possible	Probable	Definite
Severity	Mild			
	Moderate			
	Severe			



# Heatmap of acute cholangitis



# Simplified heatmap of acute cholangitis



## IAIHG simplified scoring system (2008)

*Hennes et al. Hepatology 2008; EASL CPG AIH. J Hepatol 2015*

Score  $\geq 7$  = Definite AIH  
Score  $\geq 6$  = Probable AIH

Feature/parameter	Discriminator	Score
<b>Antibodies (max 2 points)</b>		(0–2 points total)
ANA or SMA+	$\geq 1:40$	+1
ANA or SMA+ or LKM+ or SLA/LP+	$\geq 1:80$ $\geq 1:40$ Any titre	+2 +2 +2
<b>IgG or <math>\gamma</math>-globulins level</b>	$>ULN$ $>1.1x ULN$	+1 +2
<b>Liver histology</b> (evidence of hepatitis is required)	Compatible with AIH Typical of AIH Atypical	+1 +2 0
<b>Absence of viral hepatitis</b>	No Yes	0 +2



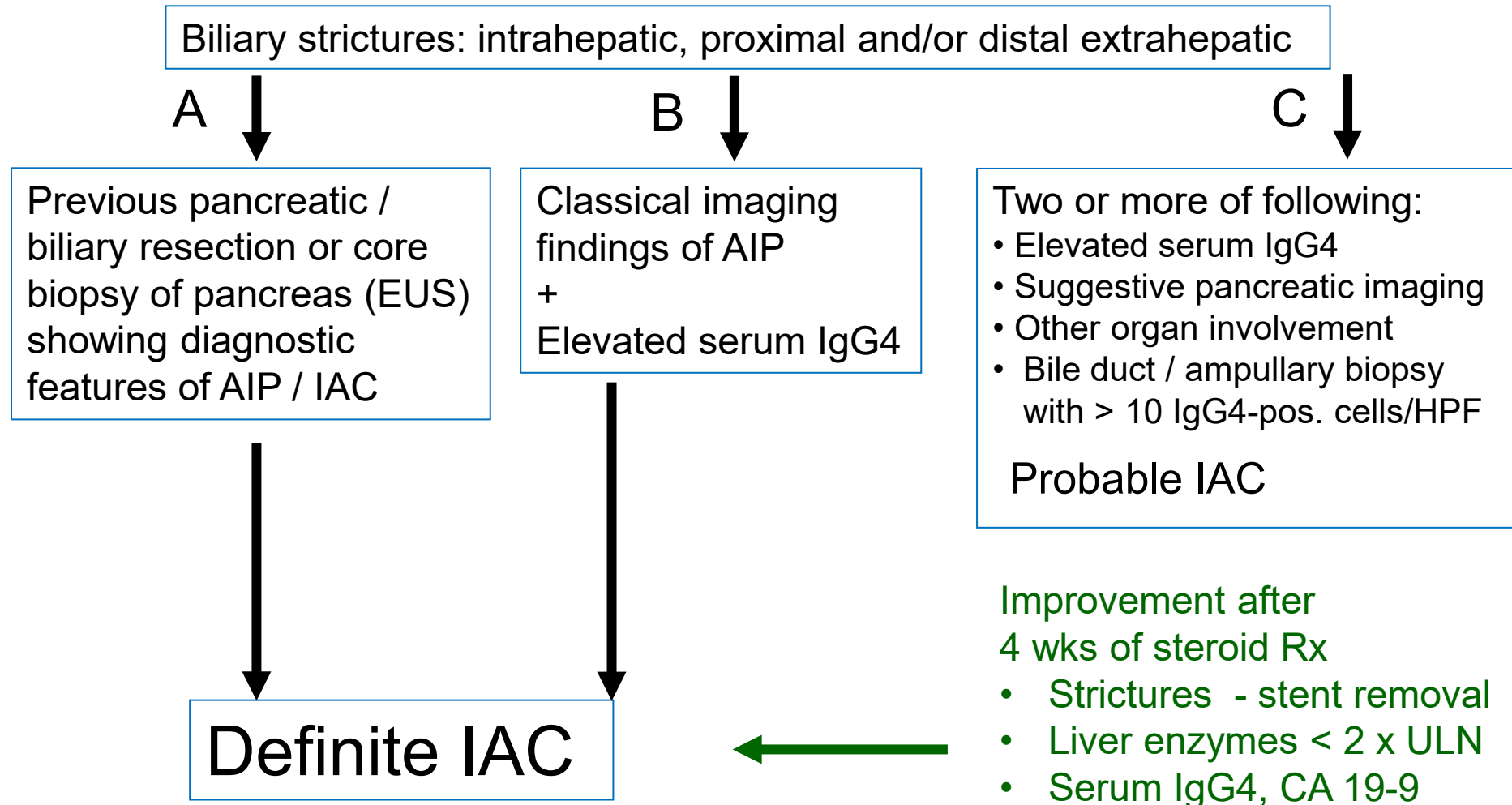
# Symptoms/Labs/Imaging/Treatment (SPLIT)

## Cholangitis Score © Chris Bowlus

Domain	Item	Criteria
<b>Symptom/Sign</b>		
	RUQ Pain	New or worsening
	Pruritus	New or worsening
	Fatigue	New or worsening
	Fever	T > 38C or <36C
	Tachycardia	HR > 90 beats/min
	Respiration	> 20 breaths/min or CO2 < 32 mmHg
	Hypotension	
	...	
<b>Labs</b>		
	WBC	
	ALP	
	T Bili	
	...	
<b>Imaging</b>		
	New biliary dilation	
	Liver abscess	
	DWI, gadoxate...	
<b>Treatment</b>		
	ERCP Findings	Pus on ERCP
	ERCP Response	Improvement in liver tests with 48 hours after ERCP
	Antibiotic Response	Improvement in liver tests with 48 hours after starting



# Diagnosis of IgG4-related Cholangitis - HISORt Criteria -



Ghazale et al., *Gastroenterology* 2008;134:706

EASL Clinical Practice Guidelines *J Hepatol* 2009; 51: 237-67

UEG Guidelines - Loehr et al., *United European Gastroenterology Journal* 2020; 8: 637-666



# Heatmap of acute cholangitis - hypothetical trial

14 cases PBO vs 9 cases XYZ

PBO

	Probable	Definite
Mild	4	2
Severe	2	6

XYZ

	Probable	Definite
Mild	5	1
Severe	1	2



# Acute Cholangitis working group – next steps

- Move forward with clinical definition subgroup over summer
  - European and US experts (3-4 x 2)
  - More granular definition (beyond Tokyo and Wannhoff), discussion of case examples
  - Integrate experience from adjudication committees (clinical trials) – industry input
- Integrate data form patient experience subgroup

	Possible	Probable	Definite
Mild			
Moderate			
Severe			

	Probable	Definite
Mild		
Severe		

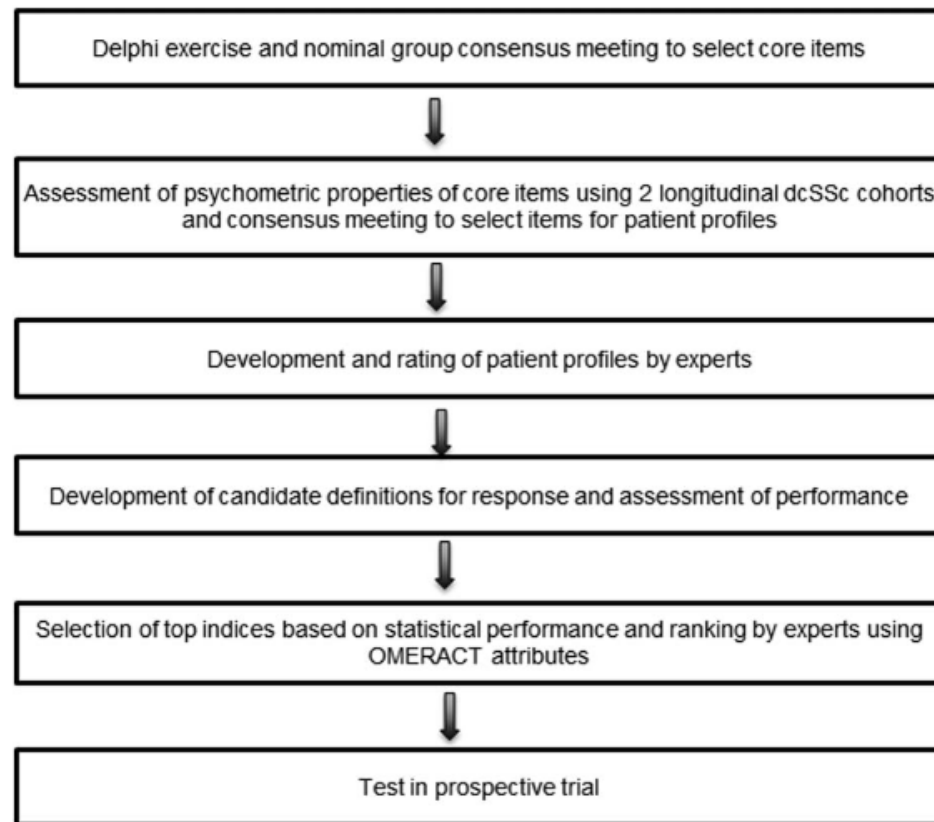


# CRISS hailed as transforming systemic sclerosis drug development

**Publish date:** July 10, 2018

By [Mitchel L. Zoler](#); Rheumatology News

## The American College of Rheumatology Provisional Composite Response Index for Clinical Trials in Early Diffuse Cutaneous Systemic Sclerosis



**Figure 1.** Expert consensus and data-driven approaches used to develop the composite response index in systemic sclerosis. dcSSc = diffuse cutaneous systemic sclerosis; OMERACT = Outcome Measures in Rheumatology.

**Table 2.** Predictive characteristics of the final CRISS model consisting of the 5 core items with the highest face validity\*

Overall area under the curve	0.9861
Overall sensitivity (95% CI)	0.9821 (0.9816–0.9827)
Overall specificity (95% CI)	0.9310 (0.9300–0.9321)
Unadjusted beta coefficient (by core item)	
MRSS	−0.81
MRSS	0.21
FVC % predicted	−0.44
HAQ DI	−3.41
HAQ DI	0.21
Patient global assessment	0.08
Patient global assessment	0.24
Physician global assessment	0.26
Physician global assessment	1.75

\* CRISS = composite response index in diffuse cutaneous systemic sclerosis; 95% CI = 95% confidence interval; MRSS = modified Rodnan skin thickness score; FVC = forced vital capacity; HAQ DI = Health Assessment Questionnaire disability index.





**Thank you for  
your attention!**  
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**Backup slides**

## 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) CRP (mg/dL)	<4 or >10 ≥1
B-1	Jaundice		T-Bil ≥2 (mg/dL)
B-2	Abnormal liver function tests	ALP (IU) γGTP (IU) AST (IU) ALT (IU)	>1.5 × STD <sup>a</sup> >1.5 × STD <sup>a</sup> >1.5 × STD <sup>a</sup> >1.5 × STD <sup>a</sup>



# Wannhoff criteria of superimposed bacterial cholangitis

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**Single criterion:** Suppurative cholangitis on ERC

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**Main criteria ( $\geq 1$ ):** Body temperature  $> 38.0^{\circ}\text{C}$

Leukocyte count  $> 12/\text{nL}$  or CRP  $> 75.0 \text{ mg/L}$

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**Minor criteria ( $\geq 2$ ):** 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 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 least 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

