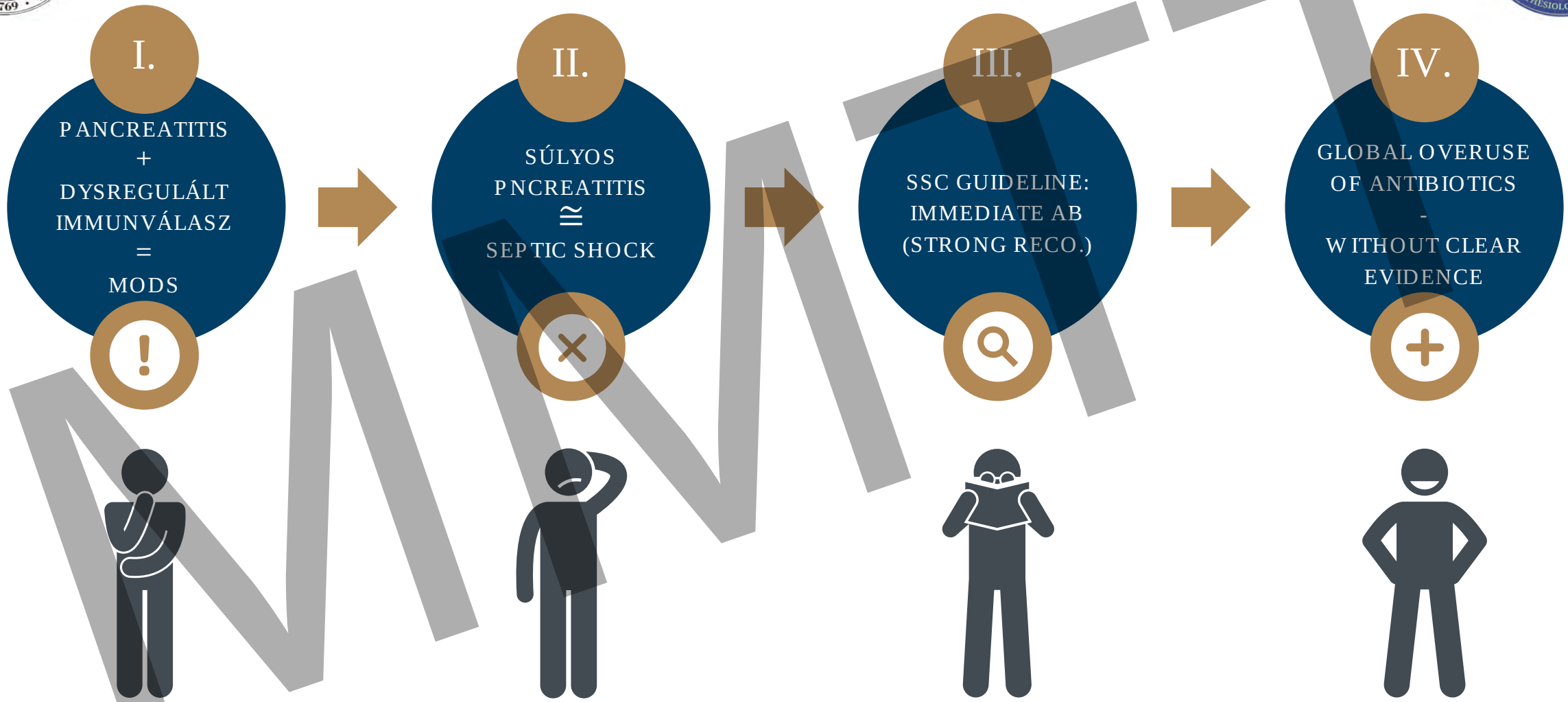
NEM BETEGSÉGET – BETEGET KEZELÜNK



Az akut pancreatitis intenzív terápiás kihívásai

Prof. Zsolt Molnár

Department of Anesthesiology and Intensive Therapy, Semmelweis University, Budapest, Hungary
Centre for Translational Medicine, Semmelweis University, Budapest, Hungary
Department of Anaesthesiology and Intensive Therapy, Poznan University of Medical Sciences, Poznan, Poland

Mikor, milyen indikációval?

- Antibiotikum terápia
- Intervenció („góctalanítás”)
- Hemoadszorpció

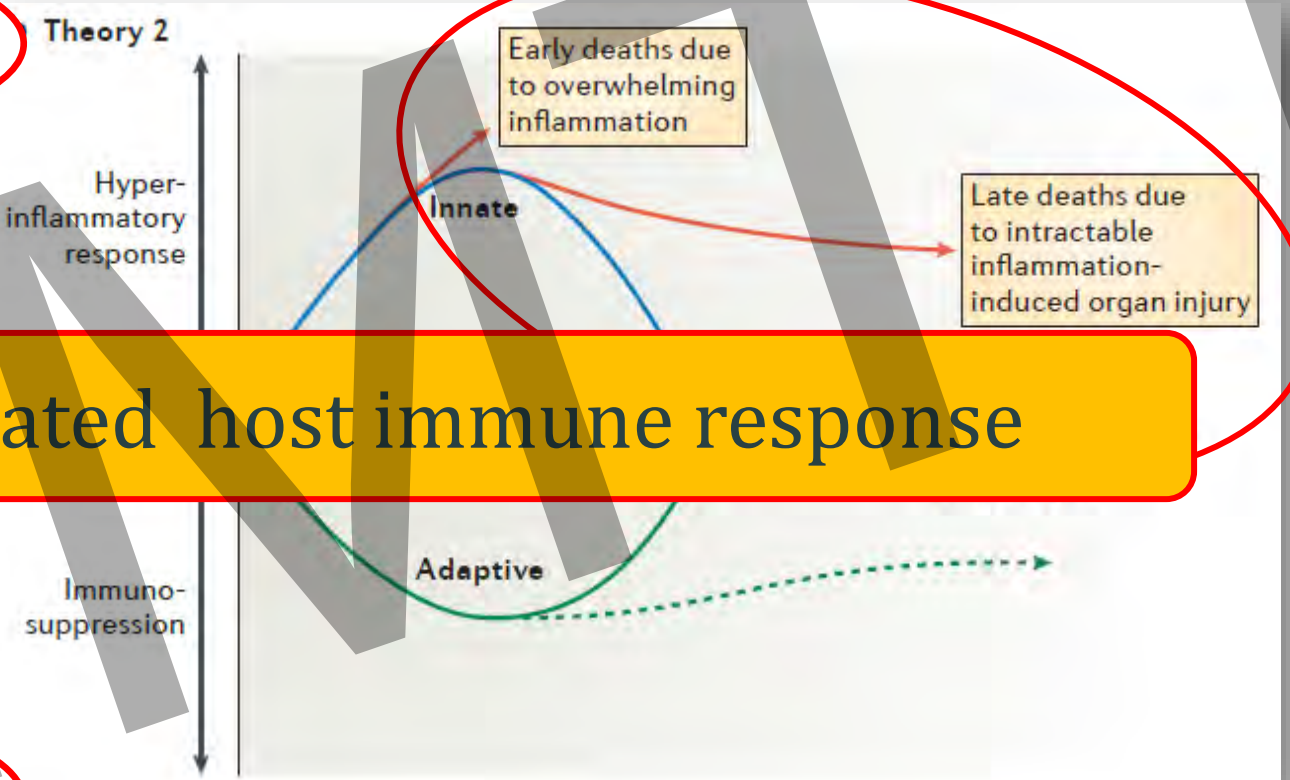
Fogalmak

Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy

Richard S. Hotchkiss[1], Guillaume Monneret[2] and Didier Payen[3]

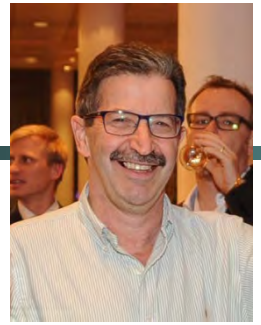
Nature Reviews | Immunology Volume 13 | December 2013 | 862-874

Pro-inflammation



Dysregulated host immune response

Anti-inflammation



Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH

JAMA. 2016;315(8):801-810.

Table 2. Terminology and *International Classification of Diseases* Coding

Current Guidelines and Terminology	Sepsis	Septic Shock
1991 and 2001 consensus terminology[9,10]	Severe sepsis Sepsis-induced hypoperfusion	Septic shock[13]
2015 Definition	Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection	Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality
nical ia	Suspected or documented infection and an acute increase of ≥2 SOFA points (a proxy for organ dysfunction)	Sepsis[a] and vasopressor therapy needed to elevate MAP ≥65 mm Hg and lactate >2 mmol/L (18 mg/dL) despite adequate fluid resuscitation[13]
mended y ICD		
-9	995.92	785.52
D-10[a]	R65.20	R65.21
ramework for implementation for coding and research	Identify suspected infection by using concomitant orders for blood cultures and antibiotics (oral or parenteral) in a specified period[b] Within specified period around suspected infection[c]: 1. Identify sepsis by using a clinical criterion for life-threatening organ dysfunction 2. Assess for shock criteria, using administration of vasopressors, MAP <65 mm Hg, and lactate >2 mmol/L (18 mg/dL)[d]	

Organ dysfunction
+
dysregulated host response
+
Infection

Vasopressor
+
>2 mmol/L lactate

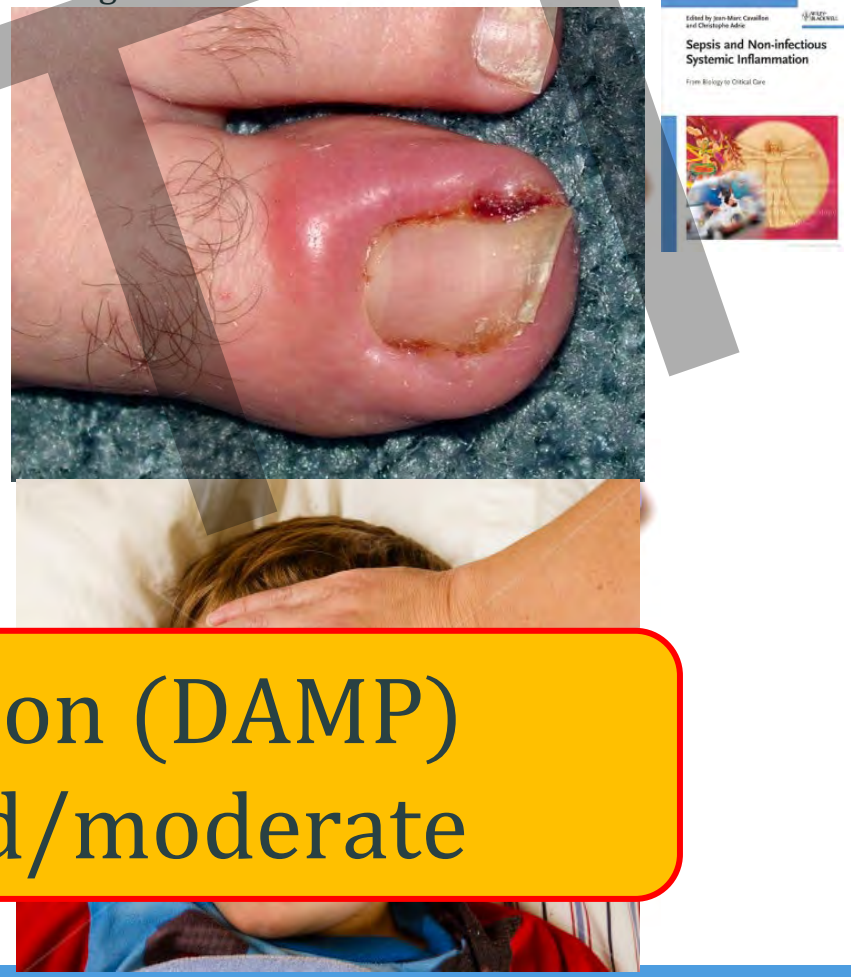
Injury: DAMP or PAMP

DAMP

Damage Associated Molecular Pattern

PAMP

Pathogen Associated Molecular Pattern



ANP: sterile inflammation (DAMP)
>95% of cases it is mild/moderate

Three-tiered critical care management of acute pancreatitis

Piroska Pázmány [a, b, c], Anna Kanjo [a, b, c], Zsanett Macht-Szalai [a], Noémi Gede [a], Nelli Farkas [a], Bálint Erőss [a, c, d], Andrea Szentesi [a], Áron Vincze [a, c, d], Roland Hagendorn [a, c, d], Zsolt Márton [a, c, d], Andrea Párniczky [a, b, c, d, 1], Péter Hegyi Zsolt Molnár [a, f, g, h, 1, *]

Pancreatology 25 (2025) 39–47

N=1540, ICU: 60 (~4%)

Table 2
Clinical Outcomes of Critical Care population.

	HDU	HDU-ICU	ICU	Total critical care population
Number of patients	32	26	34	92
Mortality n (%)	7 (22)	17 (65)	18 (53)	42 (47)
Mortality in first 28 days n (% of mortality)	7 (100)	15 (88)	12 (67)	35 (81)
Length of critical care unit stay (days)	6 (3-9)	12 (5-22)	12 (3-30)	8 (3-16)
Organ support free days[a]	6 (2-8)	0 (0–10)	3 (0–9)	

Semmelweis University 2023-5 *(unpublished data)*:
N= 1934, ICU: 75(+14), M: 38%

Challenge – extrapolating AP study results for the ICU

Current Concepts in Severe Acute and Necrotizing Pancreatitis: An Evidence-Based Approach

Guru Trikudanathan[1,*] Daniel R. J. Wolbrink Hjalmar C. van Santvoort[2] Shawn Mallery[1] Martin Freeman[1,§] Marc G. Besselink[4,§]

Gastroenterology 2019;156:1994–2007

Table 2. Summary of Randomized Controlled Trials Comparing Endoscopic and Minimally Invasive Surgical Step-Up Approach

	PENGUIN trial[77]		TENSION trial[96]		MISER trial[78]	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
Modality	Endoscopic	Surgical	Endoscopic	Surgical	Endoscopic	Surgical
No. of patients	10	10	51	47	34	32
Infected necrosis, n (%)	10 (100)	9 (90)	23 (45)	27 (57)	31 (91)	30 (94)
New-onset organ failure, n (%)						
Single	NR	NR	7 (14)	13 (28)	NR	NR
Multiple	0 (0)	5 (50)	2 (4)	6 (13)	2 (6)	3 (9)
Death, n (%)	1 (10)	4 (40)	9 (18)	6 (13)	3 (9)	2 (6)
Composite endpoint, n (%)	2 (20)	8 (80)	22 (43)	21 (45)	4 (12)	13 (41)
Complications, n (%)						
Bleeding					0	3 (9)
Perforation					0	0
Fistula (pancreat					0	9 (28)

Very low case numbers
„Not sick enough”

A procalcitonin-based algorithm to guide antibiotic use in patients with acute pancreatitis (PROCAP): a single-centre, patient-blinded, randomised controlled trial

*Ajith K Siriwardena, Santhalingam Jegatheeswaran, James M Mason, on behalf of the PROCAP investigators**

Lancet Gastroenterol Hepatol
2022; 7: 913–21

Patient population

Admission organ function			
APACHE II	6·1 (4·6)	6·9 (4·4)	6·5 (4·5)
MODS	0 (0–1)	0 (0–1)	0 (0–1)

80% mild/moderate AP
Not an ICU population

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Immediate versus Postponed Intervention for Infected Necrotizing Pancreatitis

N Engl J Med 2021;385:1372-81.
DOI: 10.1056/NEJMoa2100826

Dutch Pancreatitis Study Group*

N=932

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Immediate Catheter Drainage (N=55)	Postponed Catheter Drainage (N=49)
Organ failure	13 (24)	8 (16)
Multiple organ failure	8 (15)	6 (12)

MOF in our population: ~100%

Antibiotics: should we give or not?

A typical case of ours

NE: 0.5γ
Lac: 4.6 mmol/L

FiO_2: 0.6
PEEP: 12 cmH_2O

Would you give AB?

PCT: 11 ng/mL

UO: 30 mL/h

A typical case of ours

NE: 0.5γ
Lac: 4.6 mmol/L

FiO_2: 0.6
PEEP: 12 cmH_2O

Sepsis-3: it is [almost] septic shock

PCT: 11 ng/mL

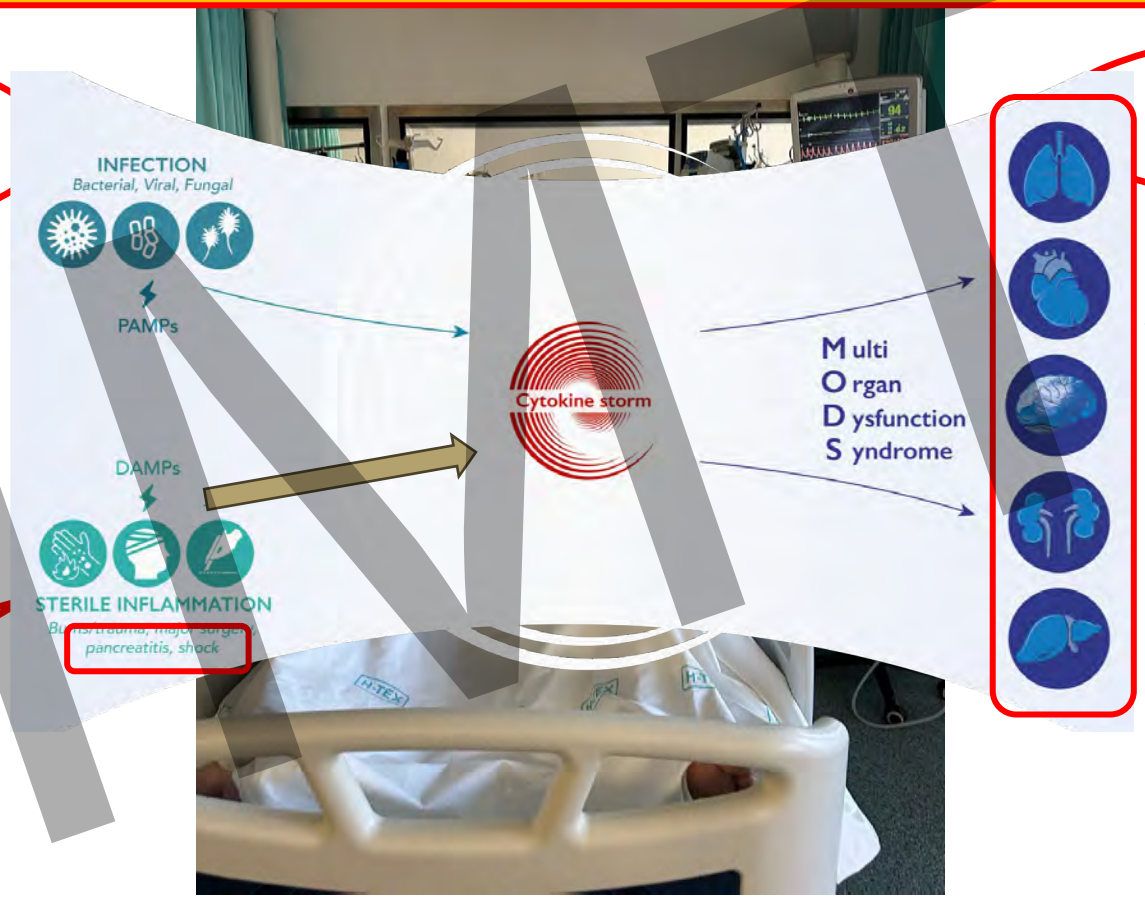
UO: 30 mL/h

A typical case of ours

The phenotype is identical with Septic Shock

NE: 0.5γ
Lac: 4.6 mmol/L

FiO_2: 0.6
PEEP: 12 cmH_2O



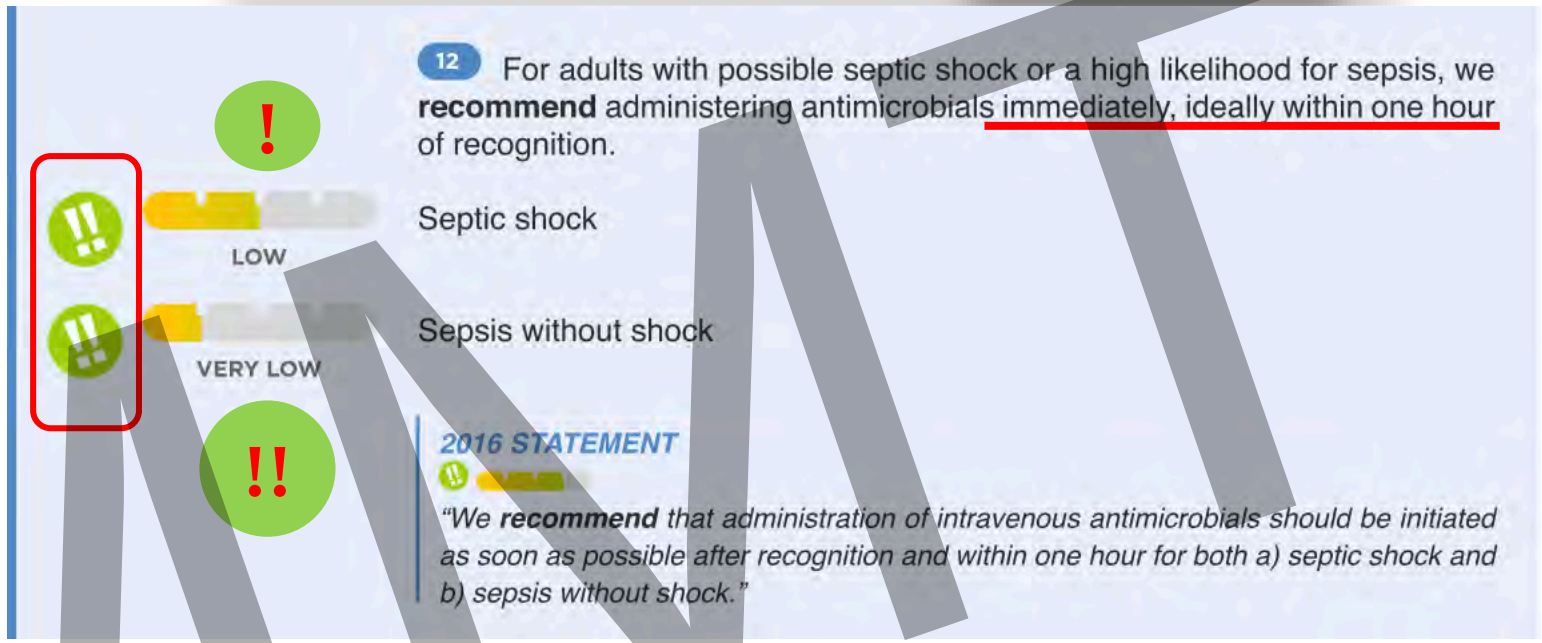
PCT: 11 ng/mL

UO: 30 mL/h

GUIDELINES

Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021

Intensive Care Med (2021) 47:1181–1247
https://doi.org/10.1007/s00134-021-06506-y



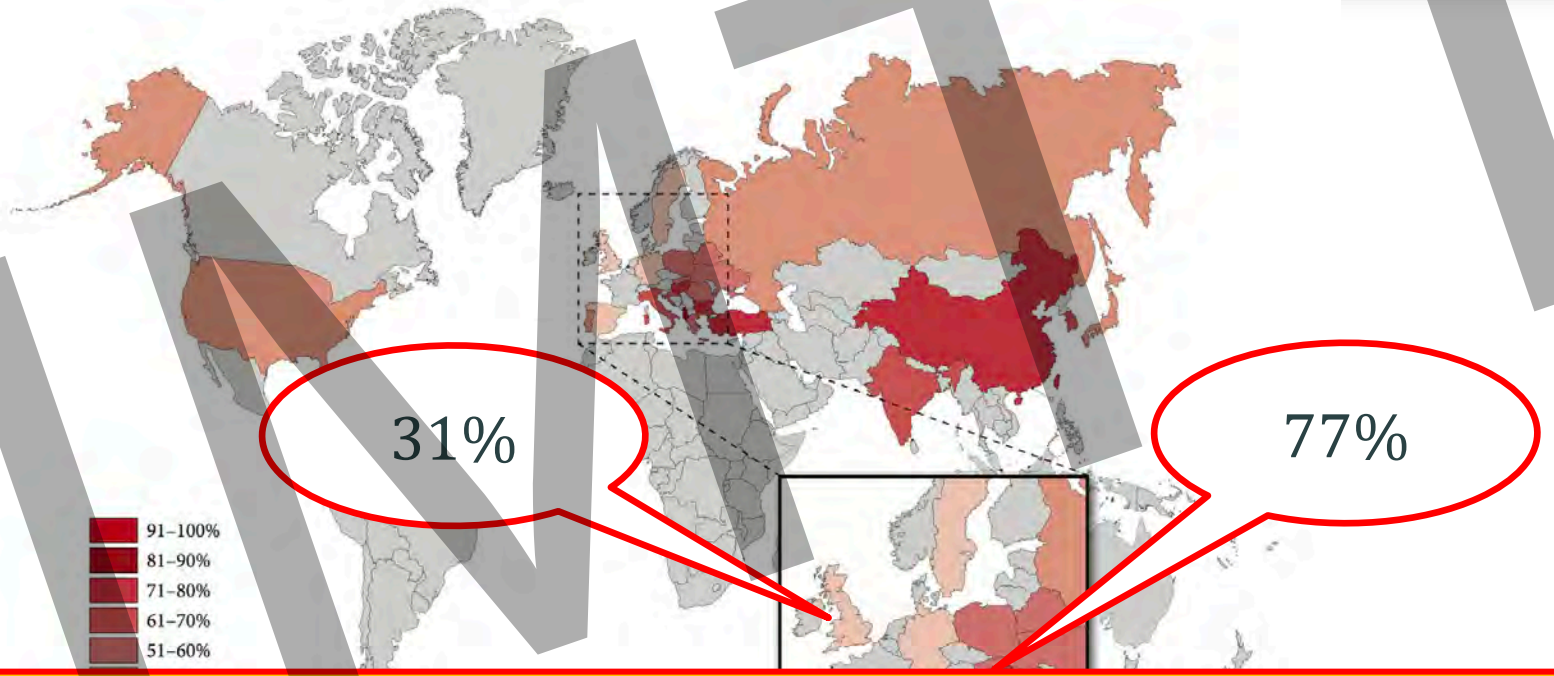
High risk of overuse of AB therapy

Antibiotic therapy in acute pancreatitis: From global overuse to evidence based recommendations

Andrea Párniczky [a, b, 1], Tamás Lantos [c, 1], Eszter Margit Tóth [d, e, 1], Zsolt Szakács [a], Péter Hegyi [a, e, h, bk, *], on behalf of the Hungarian Pancreatic Study Group

Pancreatology 19 (2019) 488–499

N=9869



31%

77%

No data from the ANP-ICU population (100%?)

Europe (Albania 78.6%, Bulgaria 78%), whereas the lowest rates are observed in Western Europe (Spain 31.8%, United Kingdom 31.2%).

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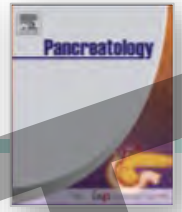

Pancreatology 19 (2019) 488–499

Table 1
Summary of the consensus statements.

	Statements	Grade of evidence	Level of agreement
1	There is a general overuse of antibiotics in AP, therefore, centres should make a strong effort to reduce it to a justifiable level.	1C	full (99%)
2	CRP and WBC values are not associated with infection in the early phase of AP, therefore CRP and WBC should not be used as biomarkers for decision making concerning AB therapy in the early phase of AP.	1C	full (97%)
3	Progressive elevation of CRP is part of the inflammatory response in AP, therefore, an upward trend of CRP levels should not be an indicator for AB treatment in the early phase of AP.	1C	full (97%)
4	Elevation of PCT levels during the early phase of AP is associated with infection, therefore, it can guide the choice to start antibiotic treatment in the absence of proven infection.	2C	full (96%)

Why „almost” septic shock?

NE: 0.5γ
Lac: 4.6 mmol/L

FiO_2: 0.6
PEEP: 12 cmH_2O

Is there infection?

PCT: 11 ng/mL

UO: 30 mL/h

Antibiotic therapy in acute pancreatitis: From global overuse to evidence based recommendations

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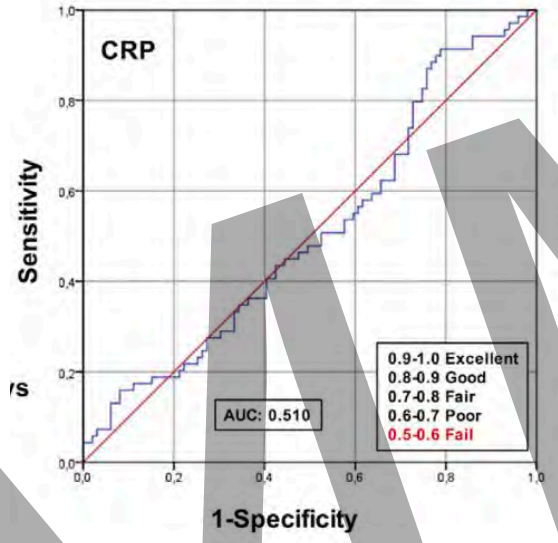
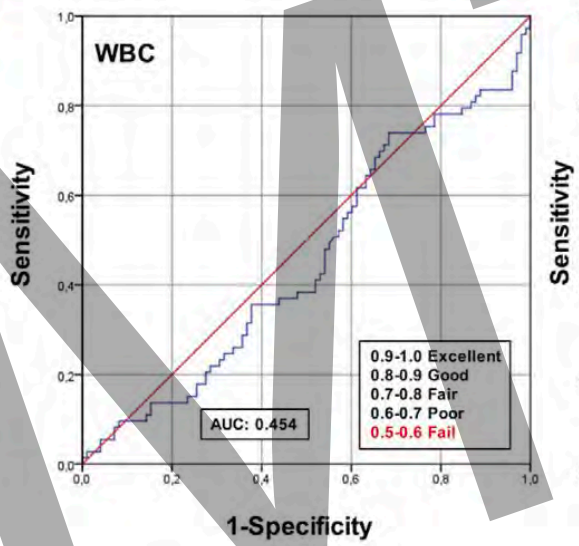
Pancreatology 19 (2019) 488–499

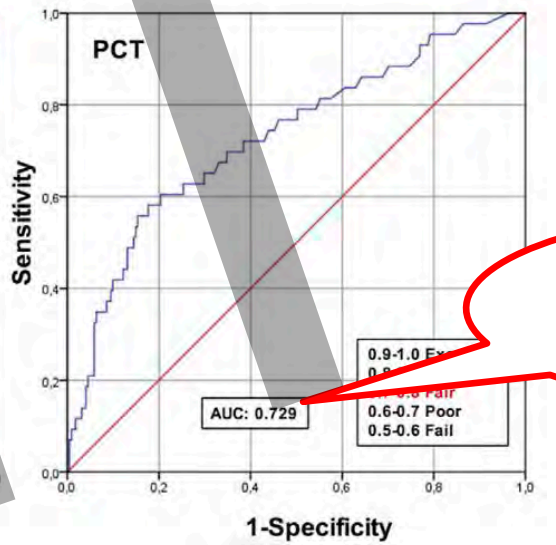
L



M



N

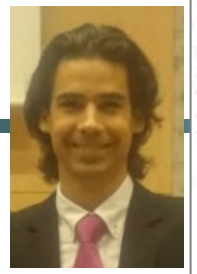


AUC: 0.729

Groups/n

4b	18	18	15	16	12	11
5	19	17	23	18	18	16

Group	cAVE	p
4b	4.43±1.72	0.026
5	37.51±18.67	

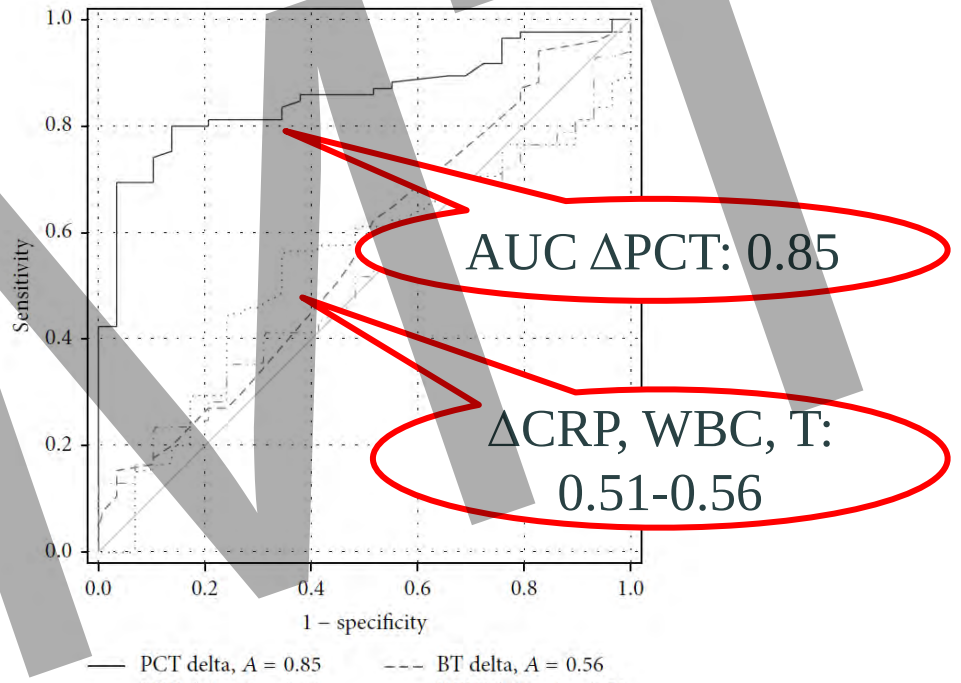


Research Article

Delta Procalcitonin Is a Better Indicator of Infection Than Absolute Procalcitonin Values in Critically Ill Patients: A Prospective Observational Study

Domonkos Trásy,[1] Krisztián Tánczos,[1] Márton Németh,[1] Péter Hankovszky,[1] András Lovas,[1] András Mikor,[1] Edit Hajdú,[2] Angelika Osztroluczki,[1] János Fazakas,[3] and Zsolt Molnár[1]

Journal of Immunology Research
Volume 2016, Article ID 3530752, 9 pages
http://dx.doi.org/10.1155/2016/3530752



AUC ΔPCT: 0.85

ΔCRP, WBC, T: 0.51-0.56

Kinetics are better than absolute values

Antibiotic therapy in acute pancreatitis: From global overuse to evidence based recommendations

Andrea Párniczky [a, b, 1], Tamás Lantos [c, 1], Eszter Margit Tóth [d, e, 1], Zsolt Szakács [a], Péter Hegyi [a, e, h, bk, *], on behalf of the Hungarian Pancreatic Study Group

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A procalcitonin-based algorithm to guide antibiotic use in patients with acute pancreatitis (PROCAP): a single-centre, patient-blinded, randomised controlled trial

Lancet Gastroenterol Hepatol 2022; 7: 913–21

*Ajith K Siriwardena, Santhalingam Jegatheeswaran, James M Mason, on behalf of the PROCAP investigators**

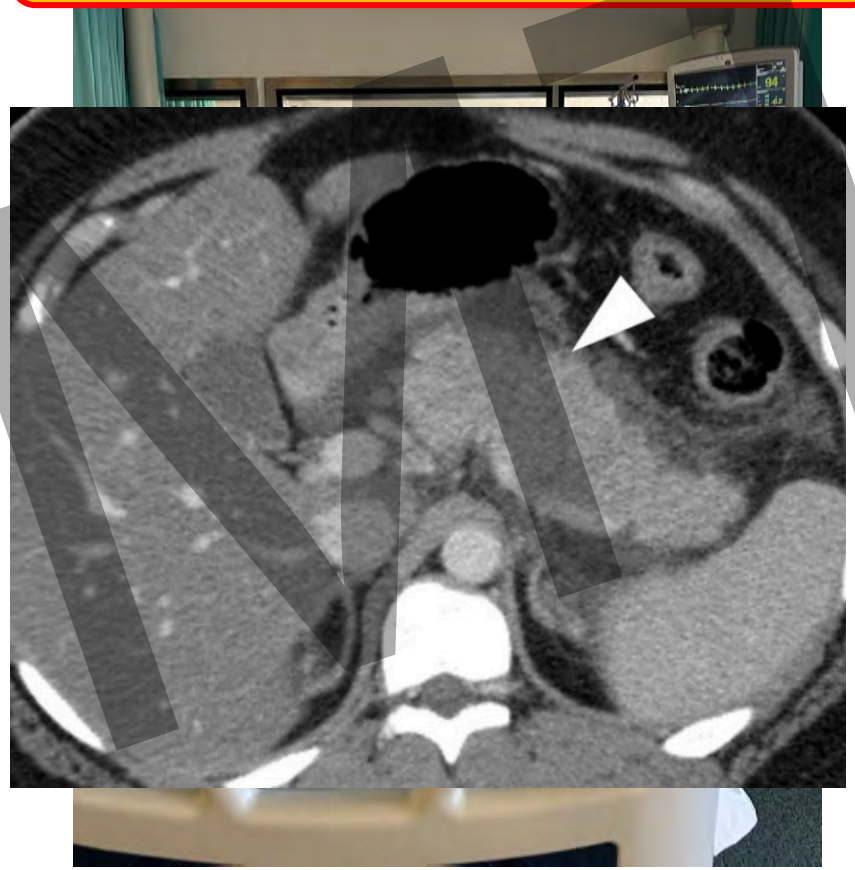
Trigger PCT 1.0 ng/mL

	Procalcitonin-guided ca (n=132)	Usual care (n=128)	Adjusted difference (95% CI); p value*
Antibiotic use	59 (45		–15·6% (–27·0 to –4·2); 0·0071
Prophylactic use excluded	41 (31		–14·2% (–24·4 to –4·1); 0·0061
All-cause mortality	4 (3%		0·69% (–3·24 to 4·62); 0·73
Days			

11 ng/mL is high enough to start AB!

Where is the source?!

Pancreas?



NE: 0.5γ
Lac: 4.6 mmol/L

FiO_2: 0.6
PEEP: 12 cmH_2O

PCT: 11 ng/mL

UO: 30 mL/h

The NEW ENGLAND JOURNAL of MEDICINE

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Dutch Pancreatitis Study Group*

N=932

Table 1. Characteristics of the Patients at Baseline.*

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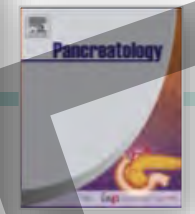
No. of days from onset of symptoms to diagnosis of necrotizing pancreatitis	8±8	9±7
No. of days from onset of symptoms to diagnosis of infected necrosis	21±6	19±7

International Association of Pancreatology Revised Guidelines on Acute Pancreatitis 2025: Supported and Endorsed by the American Pancreatic Association, European Pancreatic Club, Indian Pancreas Club, and Japan Pancreas Society

https://doi.org/10.1016/j.pan.2025.04.020

IAP/APA/EPC/IPC/JPS Working Group[1,*]



VII. Use of Antibiotics to prevent and control infectious complications

17. Recommendation: Antibiotics should be used if there is proven extrapancreatic infection or strong suspicion of infected necr
recommendation; moderate quality evidence)

18. Recommendation: i. Positive microbiologic cultures from body fluids, e.g. blood, sputum, bile, urine, and drain fluid, are defi
ii.The presence of gas bubbles within the pancreatic/peri-pancreatic necrotic collection on a CT scan suggests infected necrotizi
antibiotic therapy.
iii. Elevated levels of C-reactive protein (CRP), white blood cell (WBC) count, or procalcitonin (PCT) alone should not be used as
(Strong recommendation; moderate quality evidence)

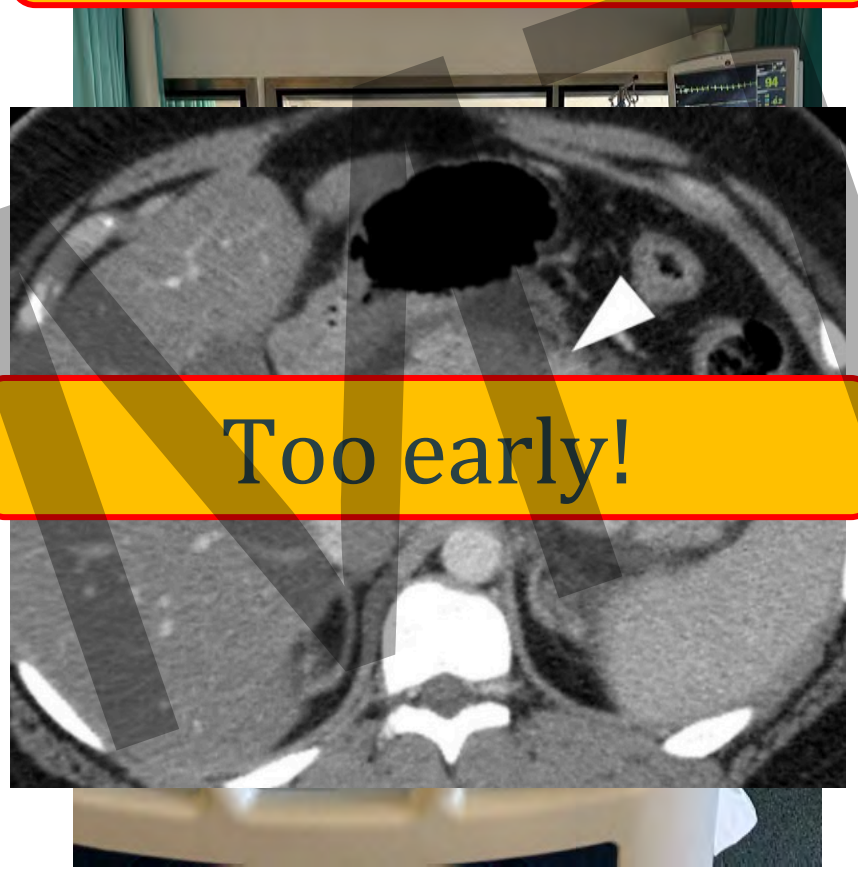
31. Recommendation: A diagnosis of infected necrotizing pancreatitis should be established based on a comb
Routine use of fine needle aspiration (FNA) to confirm infected necrotizing pancreatitis is not recommended. (

Where is the source?

Pancreas?

NE: 0.5γ
Lac: 4.6 mmol/L

FiO_2: 0.6
PEEP: 12 cmH_2O



Too early!

PCT: 11 ng/mL

UO: 30 mL/h

Where is the source?

Lungs?

Unlikely

NE: 0.5γ
Lac: 4.6 mmol/L

FiO_2: 0.6
PEEP: 12 cmH_2O

PCT: 24 ng/mL

UO: 30 mL/h

Other sources?

UTI, BSI, else?

NE: 0.5γ
Lac: 4.6 mmol/L

FiO_2: 0.6
PEEP: 12 cmH_2O

In 1 day? Unlikely

Are we risking anything by giving AB?

PCT: 24 ng/mL

UO: 30 mL/h

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*Ajith K Siriwardena, Santhalingam Jegatheeswaran, James M Mason, on behalf of the PROCAP investigators**

Lancet Gastroenterol Hepatol
2022; 7: 913–21

	Procalcitonin-guided care (n=132)	Usual care (n=128)	Total (n=260)
(Continued from previous page)			
Admission microbiology			
Positive blood culture	10 (8%)	3 (2%)	13 (5%)
Positive urine culture	3 (2%)	2 (2%)	5 (2%)
Positive sputum culture	2 (2%)	0	2 (1%)
Skin MRSA	116; 1 (1%)	120; 2 (2%)	236; 3 (1%)
Positive drain culture	1 (1%)	2 (2%)	3 (1%)
Positive faecal culture	3 (2%)	1 (1%)	4 (2%)

260/30 pts!

ABs are potentially harmful

Organ injury

Wright J, Paauw DS. Complications of antibiotic therapy. *Med Clin North Am* 20

Mito tion

Singh R, cterial infectio rion 2014;1

Microbio nfections

Alverdy J of the pathob ed 2017;4

Clostr ctions

Kalghatg JR, Slomovic S, Molina A, Shirihai OS, Collins JJ. Bactericidal antibiotics induce mitochondrial dysfunction and oxidative damage in mammalian cells. *Sci Transl Med* 2013;5:192ra85.

Let’s do a trial!

Multimodal, individualized approach in acute pancreatitis caused multiple organ dysfunction to reduce unnecessary antibiotic treatment

Background

PROBLEM

- **ANP in 5%** requires ICU admission due to **MOF:** mortality **35-65%** [1, 2]
- MOF is due to: **dysregulated host response**
- **SSC: immediate AB** administration is **strongly** recommended [3]

WHAT WE ALREADY KNOW?

- Global **overuse** of ABs in ANP **31-82%** [2]
- **Infective** AP accounts only for **5%** [4,5,6]
- **PCT-guided** AB therapy on ICU reduce [7]:
  - AB duration by 2 days
  - Mortality by 16%

[1] Pazmany et al. 2025, Pancreatol.
[2] Parniczky et al. 2019, Pancreatol
3] Evans et al. 2021, ICM
[4] Boxhooorn et al. 2021 NEJM

MISSING LINK

- What is the **real incidence** of **infective-ANP** on ICU admission due to **MOF**?
- Can **a holistic approach** [8] (Clinical+PCT+Micro) help to **individualize** AB therapy?

[5] Siriwardena et al. 2022, Lancet GastroHep
[6] Trikudanathan et al. 2019, Gastroenterol
[7] Papp et al. 2023, Crit Care
[8] Fazakas et al. 2016, Annual Update

AIMS

To investigate whether **a multimodal, individualized approach** can avoid unnecessary AB therapy in **ANP-MOF**

ANP *– Acute Necrotising Pancreatitis*
MOF *– Multiple Organ Failure*
ICU *– Intensive Care Unit*
SSC*: Surviving Campaign Guideline*
AB *- Antibiotics*
PCT *– Procalcitonin*

Research question

Can a multimodal, individualized approach reduce the overuse of antibiotics in patients with ANP induced MOF?

P: Patients with ANP+MOF admitted to ICU

I: Multimodal, individualized approach*

C: Conventional AB therapy

O1: TBD (Length of AB treatment, Complication rate?)

O2: Mortality, Length of ICU stay, recurrent infections

Hypothesis: This approach will result in shorter AB treatment without worsening clinical outcomes

*Organ function and PCT level changes + Microbiology on day 2-3

ANP *– Acute Necrotising Pancreatitis*
MOF *– Multiple Organ Failure*
ICU *– Intensive Care Unit*
AB *- Antibiotics*
PCT *– Procalcitonin*

The flow

1. All included patients AB on day 1
2. C-group: min of 7 days TBD with infectologists
3. T-group: re-evaluation on day 2 or 3

Interpreting Procalcitonin at the Bedside

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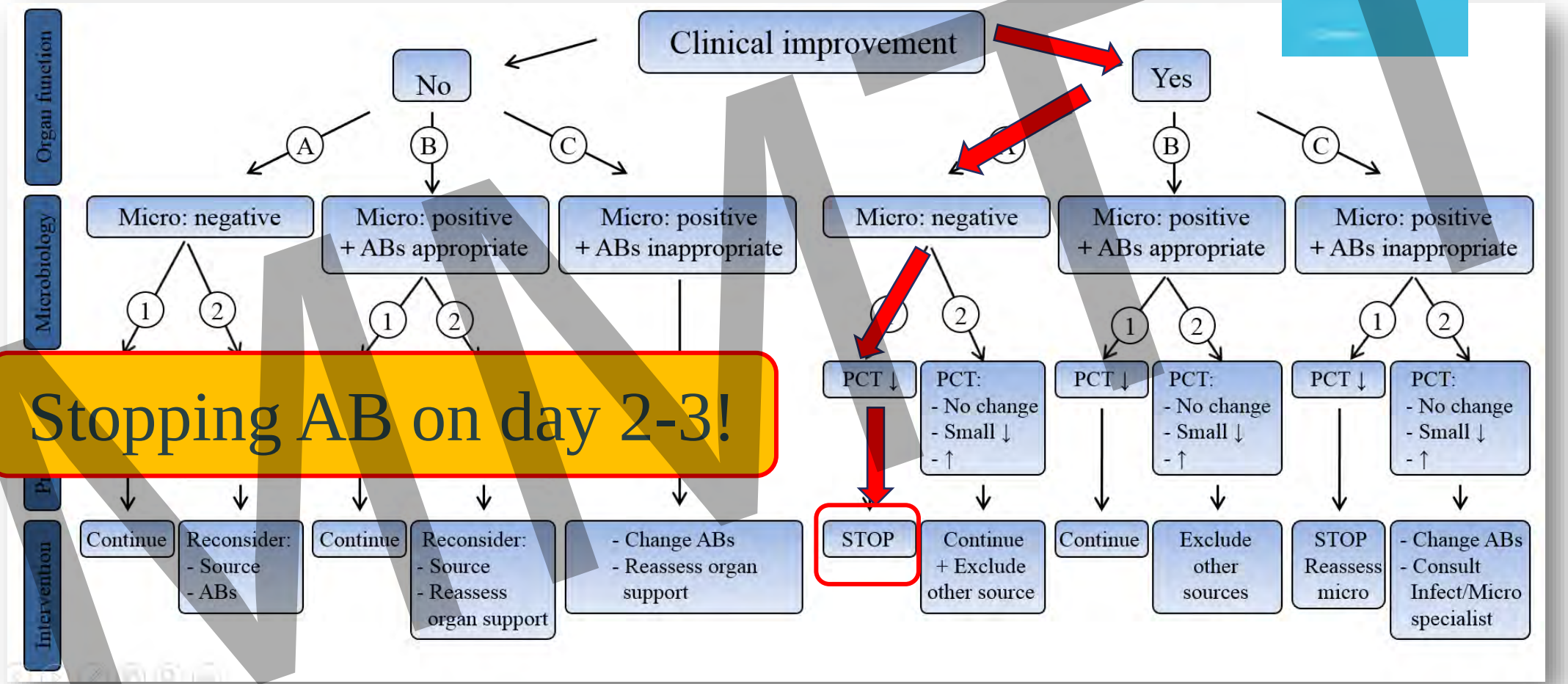

Stopping AB on day 2-3!

Take home message

- High risk of unnecessary AB admininstration
- There is no data on the incidence of infected ANP on ICU
- No reliable markers of infection in ANP-MOF
- Give AB for the time being!
- BUT, no way out: a ICU-RCT is not just a possibility, but a MUST!

Mark it in your calendar!