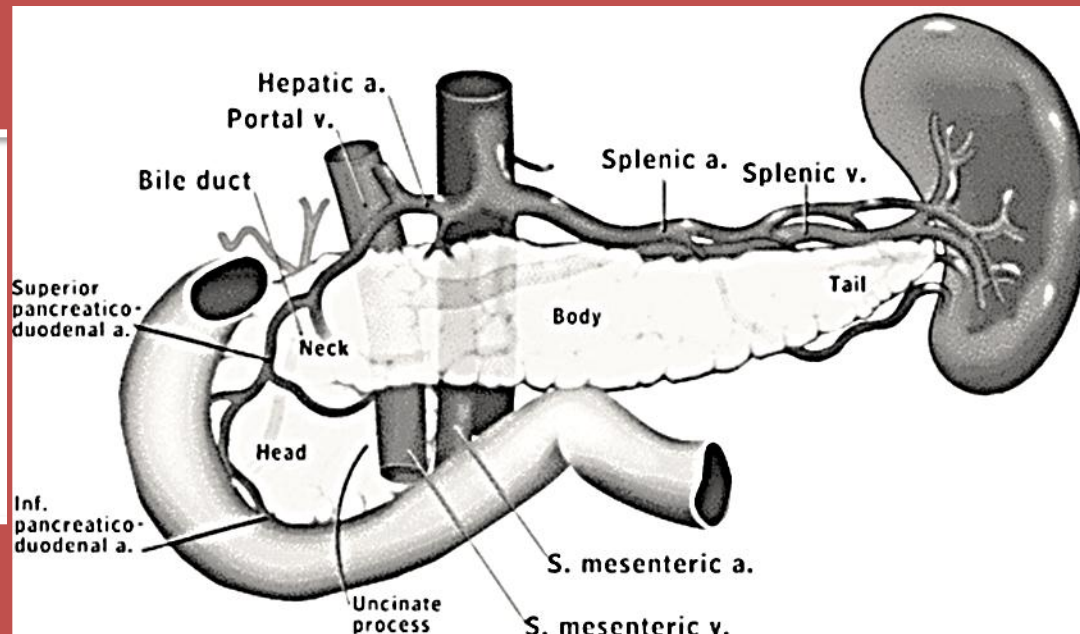


Get with the Program: The PROS and CONS of Procalcitonin




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Acute Pancreatitis: Presentation

- Hallmark Symptom:
 - acute upper abdominal pain + nausea and vomiting
 - Often epigastric or periumbilical with radiation

Review of Systems	Vitals	Fever, hypotension, tachycardia
	CNS	Decreased LOC (in shock)
	RESP	Respiratory distress
	CARDIO	Unremarkable
	GI/GU	Abdominal distension, guarding, nausea, vomiting
	MSK/DERM	Unremarkable



Acute Pancreatitis: Diagnosis

- Lipase- initial assessment
 - sensitivity 67%, specificity 97%
- Amylase- initial assessment
 - sensitivity 45%, specificity 97%
- CT scan- confirmation of diagnosis
- **CT scan with contrast- assess necrosis**

ANZ J Surg. 2001 Oct;71(10):577-82.

Am Fam Physician. 2007 May 15;75(10):1513-1520.

Case

ID	61 year old female with pancreatitis
HPI	Chest pain X 1 month Epigastric pain X 2 days with nausea and vomiting CT scan showed pancreatitis secondary to gallstones Underwent ERCP Post op day 3: Admitted to ICU post intubation with decreased LOC and signs of shock

Diagnosed with worsening acute, necrotizing pancreatitis

Case

- Received meropenem for 10 days total for empiric treatment of necrotizing pancreatitis
- Patient slowly improved

Meta-analysis of prophylactic parenteral antibiotic use in acute necrotizing pancreatitis

Žilvinas Dambrauskas^{1,2}, Antanas Gulbinas^{1,2}, Juozas Pundzius¹, Giedrius Barauskas¹

¹Department of Surgery, ²Institute for Biomedical Research, Kaunas University of Medicine, Lithuania

Key words: acute necrotizing pancreatitis; infected necrosis; antibiotic prophylaxis; meta-analysis.

- Use of antibiotics in necrotizing pancreatitis is controversial
- Meta-analysis suggest benefit from treatment
 - Recommend treatment with broad spectrum antibiotics (carbapenems)

Antibiotics in Necrotizing Pancreatitis

- Sanford recommends:
 - Antimicrobial prophylaxis in necrotizing pancreatitis if > 30% necrotic
- Bugs and Drugs recommends:
 - Against prophylactic antibiotics in acute necrotizing pancreatitis
 - Broad spectrum antibiotics for infected necrotizing pancreatitis:
 - Piperacillin-tazobactam
 - Imipenem

Infected? Not infected?

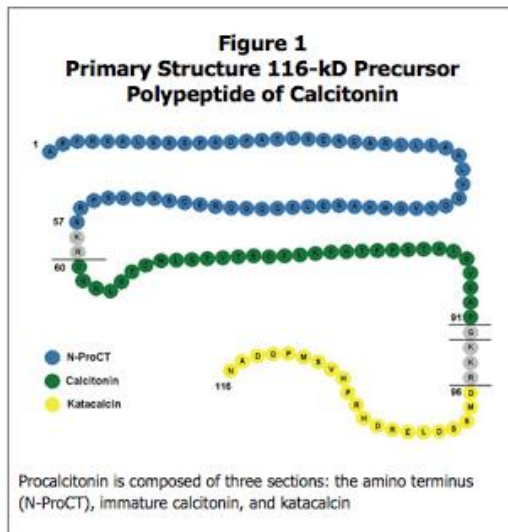


Usual Biomarkers in Infectious Diseases

Biomarker	Produced by	Infection related increases	Non-infectious related increases
WBC count	Bone marrow cells	Any infection	Many
Neutrophil Count	Bone marrow cells	Bacterial	Glucocorticoids
Lymphocytes count	Bone marrow cells	Viruses	Leukemia
CRP	Liver cells	Any infection	Any inflammation
PCT	Thyroid C cells	Bacterial	Trauma, gut wall dysfunction, ischemia

Procalcitonin

- Increased in pro-inflammatory state
 - Specific for bacterial infection
 - No increase with viral infections and non-infectious inflammation



T1/2	Normal level in healthy individuals
25-30 hours	< 10 pg/mL

Procalcitonin (PCT)?

- Peptide precursor of calcitonin
- FDA approved for assessment of progression to severe sepsis and shock

	Sensitivity	Specificity
Differentiating SIRS from sepsis	85%	91%
Diagnosis of bacteremia	76%	70%

[Ann Emerg Med.](#) 2007 Jul;50(1):34-41.

[Crit Care.](#) 2003 Feb;7(1):85-90. Epub 2002 Oct 30.

Clinical Question

Patient	In a patient with severe necrotizing, acute pancreatitis
Intervention	Does PCT
Comparator	Compared to traditional markers/assessment
Outcome	Predict necrotizing infection?
Search Strategy	PubMed, Medline, IPA, Google, Google Scholar, Cochrane Review
Keywords	Procalcitonin, necrotizing, pancreatitis, infection
Limits	Adults English
Results	10 studies 1 Systematic reviews - 1 with 7 prospective studies (2009) 2 Additional prospective studies

The value of procalcitonin at predicting the severity of acute pancreatitis and development of infected pancreatic necrosis: Systematic review

Reza Mofidi, MB, MCh,^a Stuart A. Suttie, MB, BCh,^b Pradeep V. Patil, MB, BS,^b Simon Ogston, BA, MSc,^c and Rowan W. Parks, MD,^a *Edinburgh, United Kingdom*

(Surgery 2009;146:72-81.)

Systematic Review

Design	Meta Analysis <ul style="list-style-type: none">• 17 prospective studies included• 7 prospective studies reviewed infected necrotic pancreatitis
Patients	Patients with confirmed diagnosis of acute pancreatitis N= 329 for assessment of pancreatic necrosis
Intervention	- Measured PCT
Outcome	Sensitivity, specificity and positive and negative predictive values for predicting infected necrotic pancreatitis Defined by: <ul style="list-style-type: none">• Fine-needle aspiration culture• Intraoperative finding

Systematic Review:

Characteristics of Included Studies

Study	N	Country of Origin	Etiology of Pancreatitis
Muller 2000	64	Switzerland	Alcohol 59%, biliary 27%, other 15%
Rau 1997	50	Germany	Alcohol 44%, biliary 38%, other 18%
Riche 2003	48	France	Biliary 81%, other 19%
Rau 2007	104	Europe	Alcohol 59%, biliary 27%, other 15%
Olah 2005	24	Unknown	Unknown
Pinkola 2003	24	Hungary	Unknown
Bertsch 1997	15	Germany	Unknown

Systematic Review:

Characteristics of Included Studies

Study	Timing of Samples	Method of PCT Measurements	Cut off Values for PCT (ng/mL)
Muller 2000	Daily for 14 days	BRAHMS-IA	0.48
Rau 1997	Daily for 14 days	BRAHMS-IA	1.8
Riche 2003	Daily for 5 days	BRAHMS-IA	2.0
Rau 2007	Daily for 14 days	BRAHMS-IA	3.5
Olah 2005	Daily for 3 days	PCT-Q	0.5
Pinkola 2003	Unknown	RIA	Unknown
Bertsch 1997	Daily for 3 days	RIA	0.5

Systematic Review:

Sensitivity and Specificity of PCT as a Predictor of Development of Infected Pancreatic Necrosis

Study	Sensitivity (95% CI)	Specificity (95% CI)
Muller 2000	0.92 (0.62-1.00)	0.97 (0.85-1.00)
Rau 1997	0.83 (0.59-0.96)	0.94 (0.79-0.99)
Riche 2003	0.73 (0.45-0.92)	Unknown
Rau 2007	0.88 (0.64-0.99)	0.93 (0.86-0.97)
Olah 2005	0.75 (0.43-0.95)	0.85 (0.52-0.98)
Pinkola 2003	0.80 (0.44-0.97)	0.71 (0.42-0.92)
Bertsch 1997	0.63 (0.39-0.96)	0.71 (0.29-0.96)

Pooled Sensitivity= 0.80 (0.71 to 0.88)

Pooled Specificity= 0.91 (0.87 to 0.94)

Systematic Review:

Diagnostic Odds Ratio (DOR)

$$\text{DOR} = \frac{\text{Sensitivity} \times \text{Specificity}}{(1 - \text{Sensitivity}) \times (1 - \text{Specificity})}$$

- Definition:

The ratio of the

– odds of the test being positive if the subject has the disease

relative to

– odds of the test being positive if the subject does not have the disease

Example

- Lipase- initial assessment
 - sensitivity 67%, specificity 97%
- Amylase- initial assessment
 - sensitivity 45%, specificity 97%

DOR for Lipase= Sensitivity X Specificity

$$\begin{aligned} & (1- \text{Sensitivity}) \times (1- \text{Specificity}) \\ & = (0.67) \times (0.97) / (1-0.67) \times (1- 0.97) \\ & = 65.65 \end{aligned}$$

Systematic Review: DOR

Study	N	DOR (95% CI)
Muller 2000	64	20.78 (2.48-174.03)
Rau 1997	50	75 (11.29- 498.20)
Riche 2003	48	15.40 (3.48- 68.22)
Rau 2007	104	101.25 (18.65- 550.09)
Olah 2005	24	15.00 (2.02- 111.17)
Pinkola 2003	24	22.00 (2.53- 191.00)
Bertsch 1997	15	10 (0.78- 128.78)

Pooled DOR 28.33 (13.76 to 58.34)

Systematic Review: Summary

- PCT can potentially identify those with infected pancreatic necrosis
 - Guide initiation of treatment with antibiotics

Systematic Review: Critique

Strengths	Limitations
Prospective studies	Clinical application <ul style="list-style-type: none">• Multiple methods used to measure PCT
Multiple reviewers	<ul style="list-style-type: none">• Different cut-off values
Heterogeneity Assessed - No significant heterogeneity was found	<ul style="list-style-type: none">• Different timing of samples
	Search strategy incomplete
	Unclear how DOR were calculated

International Journal of Pancreatology, vol. 28, no. 1, 43–51, August 2000

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0169-4197/00/28:41–49 /\$12.25

Diagnostic Relevance of Procalcitonin, IL-6, and sICAM-1 in the Prediction of Infected Necrosis in Acute Pancreatitis

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and János Lonovics³*

*Departments of ¹Medical Microbiology, ²Surgery, ³Internal Medicine, and ⁴Medical Informatics,
Albert Szent-Györgyi Medical University, Szeged, Hungary*

Mandi et al: Prospective Study

Design	Prospective
Patients	N=20 with CT confirmed necrotizing pancreatitis <ul style="list-style-type: none">• 10 patients with aspiration confirmed sterile necrosis• 10 patients with aspiration & culture confirmed infected necrosis
Intervention	PCT concentration (immunoluminometric assay BRAHMS) every 24 hours X 14 days
Comparator	IL-6 concentration (bioassay) sICAM-1 (ELISA) Every 24 hours X 14 days
Outcome	Sensitivity, specificity and positive predictive values

Mandi et al: **Infected Results**

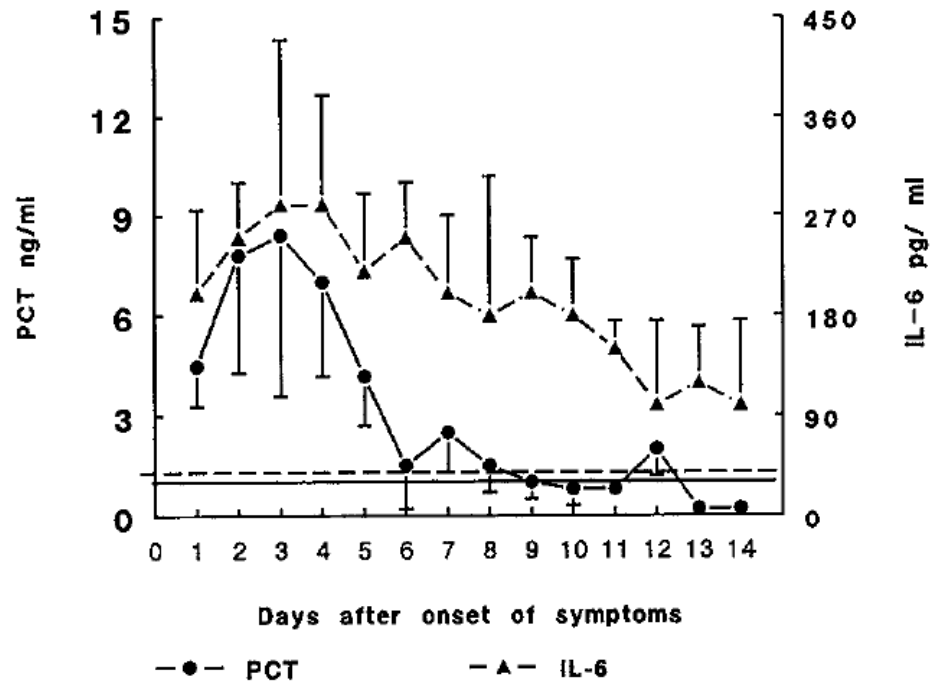


Fig. 1. Serum PCT and IL-6 levels in IPN. PCT and IL-6 determinations were started from the onset of the septic symptoms. Horizontal lines, PCT cut-off; horizontal dashes, IL-6 cutoff. Data are means \pm SD.

Mandi et al: Sterile Results

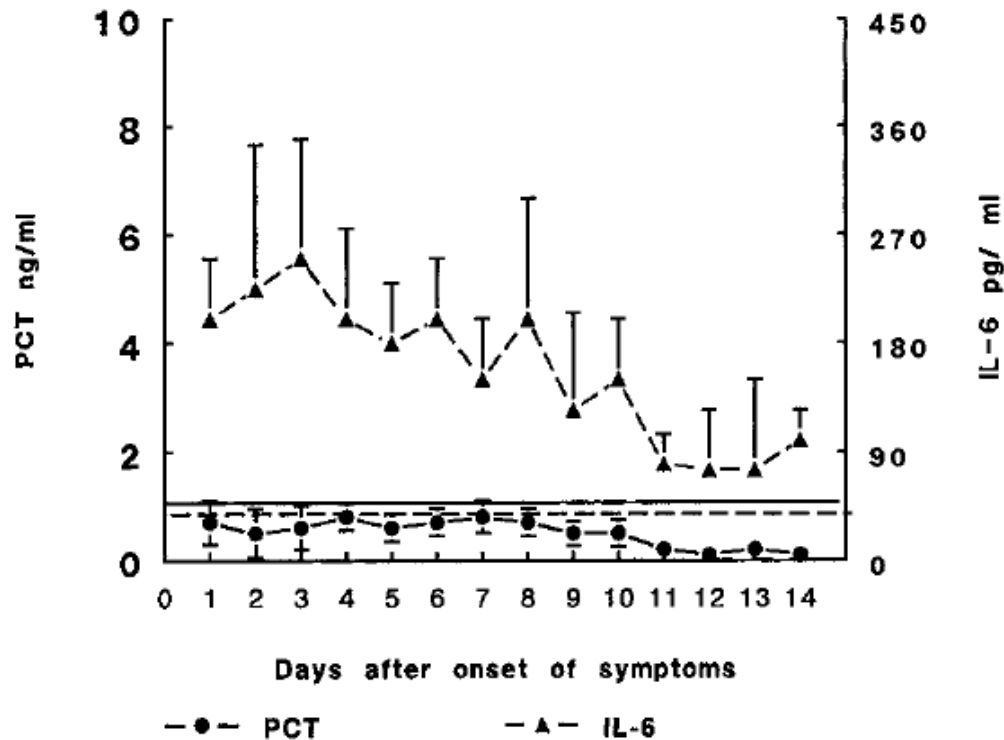


Fig. 3. Serum IL-6 and PCT levels in patients with SPN. Horizontal lines, PCT cut-off; horizontal dashes, IL-6 cut-off. Data are means \pm SD.

Mandi et al: Results

Table 2

Sensitivity, Specificity, Predictive Values, and *p* Values of PCT, IL-6, and sICAM-1 for Discriminating IPN and SPN

	Sensitivity (%)	Specificity (%)	PPV ^a (%)	NPV ^a (%)	<i>p</i> value ^b
PCT >1.2 ng/mL	90	100	100	99	<0.0001
IL-6 >50pg/mL	100	20	55	100	0.474 ^c
sICAM-1 >250 ng/mL	90	10	50	50	1.000 ^c

^aPPV, positive predictive value; NPV, negative predictive value.

^b*p* values calculated according to Fischer's exact test.

^cNot significant.

Mandi et al: Conclusions

- IL-6 and sICAM-1 levels were elevated in infectious and SIRS states
 - Not specific for infectious conditions
- PCT may be a helpful parameter that can discriminate between infectious and sterile pancreatitis

Mandi et al: Critique

Strengths	Limitations
Prospective	Small sample size
Gold-standard of guided aspiration used to assess for infectious necrotic pancreatitis	

B. Rau
G. Steinbach
K. Baumgart
F. Gansauge
A. Grünert
H. G. Beger

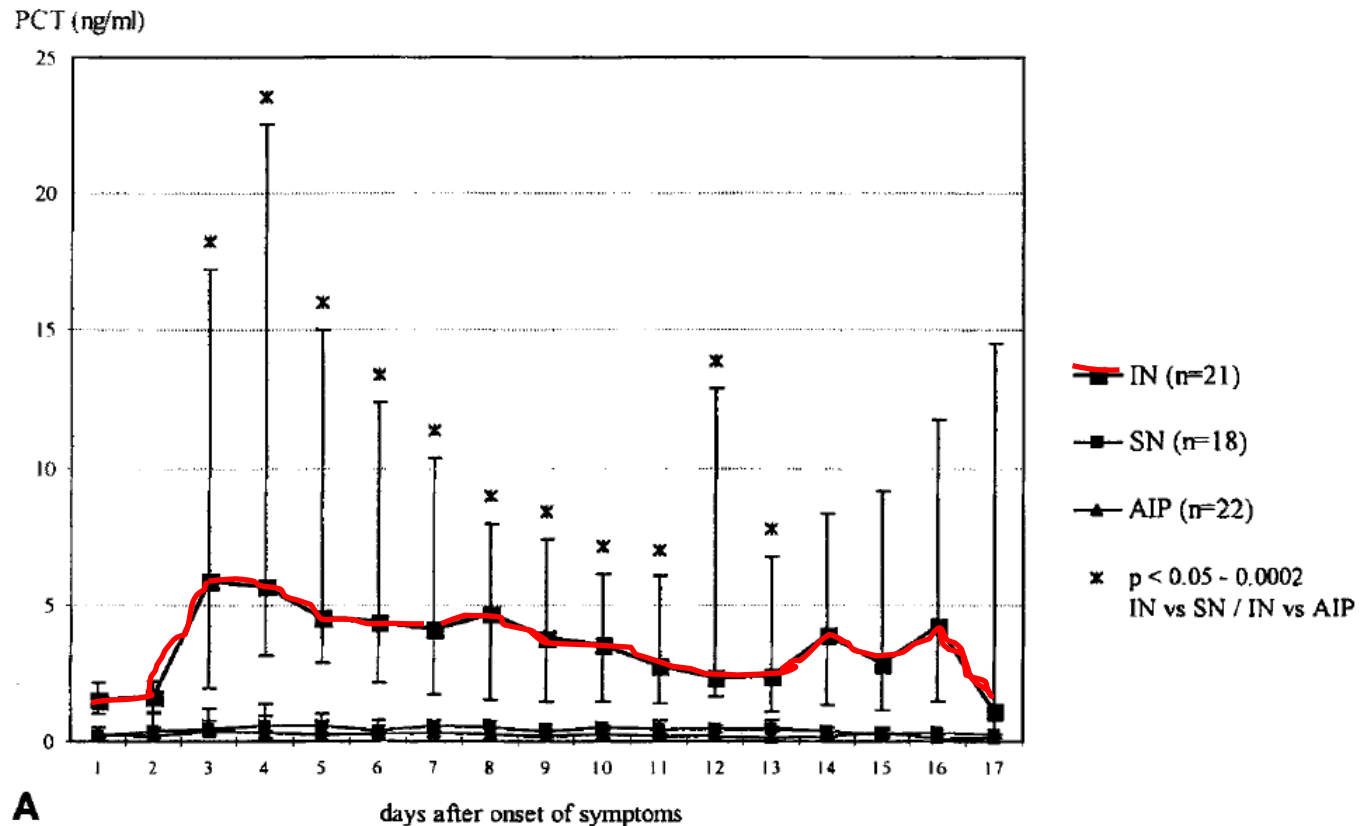
The Clinical Value of Procalcitonin in the Prediction of Infected Necrosis in Acute Pancreatitis

Rau et al.

Design	Prospective
Patient	N=61 confirmed by CT with contrast <ul style="list-style-type: none">• 22 with edematous pancreatitis• 18 with sterile necrosis confirmed by aspiration & culture• 21 with infected necrosis confirmed by aspiration & culture
Intervention	PCT concentration measured by immunoluminometry every 24 hours X 14 days
Comparator	CRP level every 24 hours X 14 days
Outcome	Sensitivity, specificity and accuracy

Rau et al: PCT Results

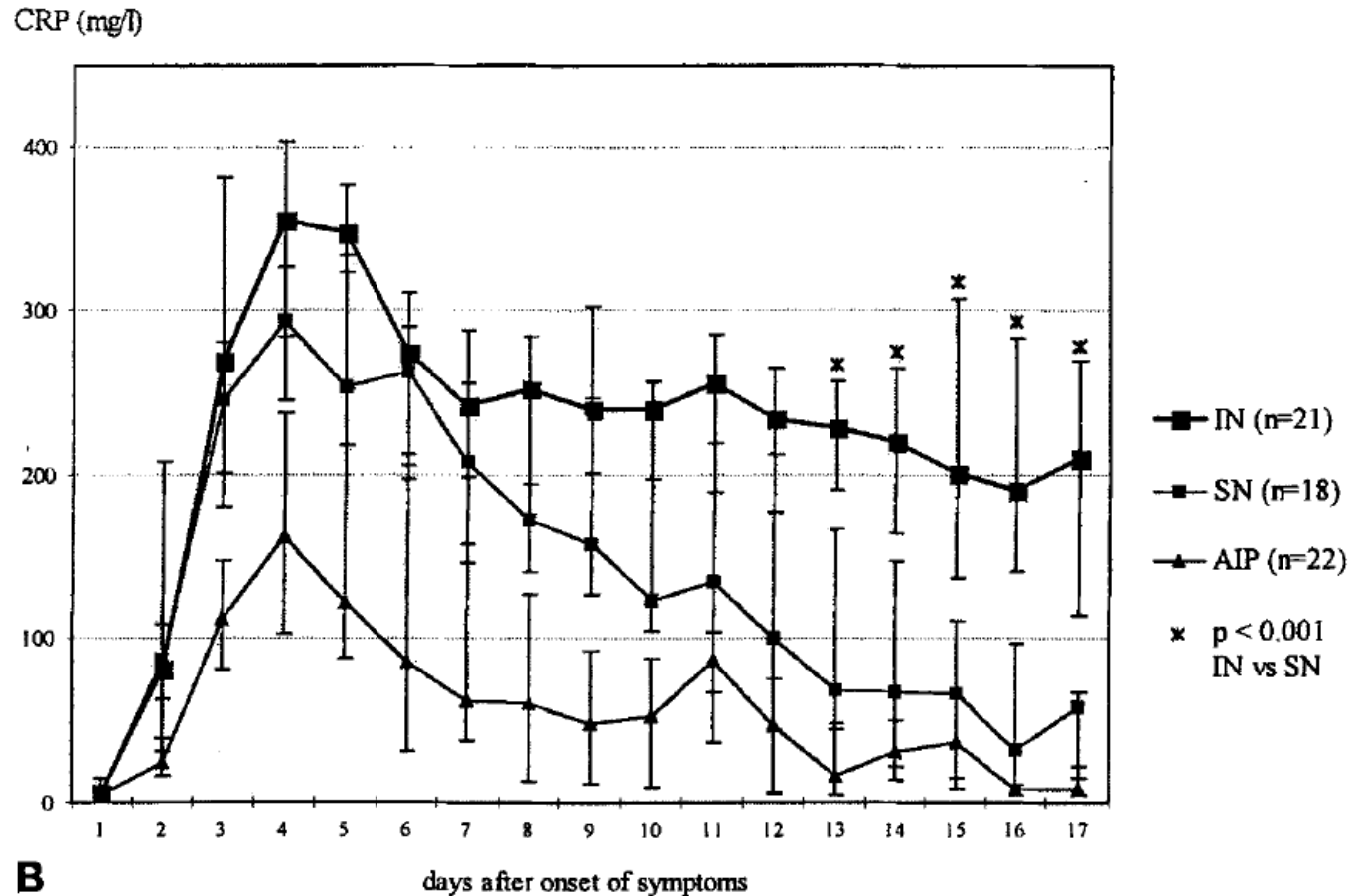
Fig. 1 Course of PCT (A) and CRP (B) in patients with infected necrosis (IN), sterile necrosis (SN), and interstitial edematous pancreatitis (AIP). PCT concentrations were significantly higher from day 3–13 after onset of symptoms in patients with IN, whereas CRP revealed no difference between IN and SN during the same time period



A

Rau et al: CRP Results

Fig.1 Course of PCT (A) and CRP (B) in patients with infected necrosis (IN), sterile necrosis (SN), and interstitial edematous pancreatitis (AIP). PCT concentrations were significantly higher from day 3–13 after onset of symptoms in patients with IN, whereas CRP revealed no difference between IN and SN during the same time period



Rau et al: Sensitivity and specificity of PCT and CRP in predicting infected necrosis

	Cut- Cuff	Sensitivity	Specificity
PCT (ng/mL)	≥ 1.8	95%	88%
CRP (mg/L)	≥ 300	86%	75%

Analysis was based on a least two peaks levels reached during the total observation period

Rau et al: Conclusions

- PCT showed high sensitivity and specificity for diagnosis of infectious necrotizing pancreatitis
 - Potential new parameter for identifying patients at risk of developing infectious complications

Rau et al: Critique

Strengths	Limitations
Prospective	Small sample size
Gold-standard of guided aspiration used to assess for infectious necrotic pancreatitis	Replication of previously studied patients (Rau 1997)
	Inconsistent methods: Duration of PCT sampling

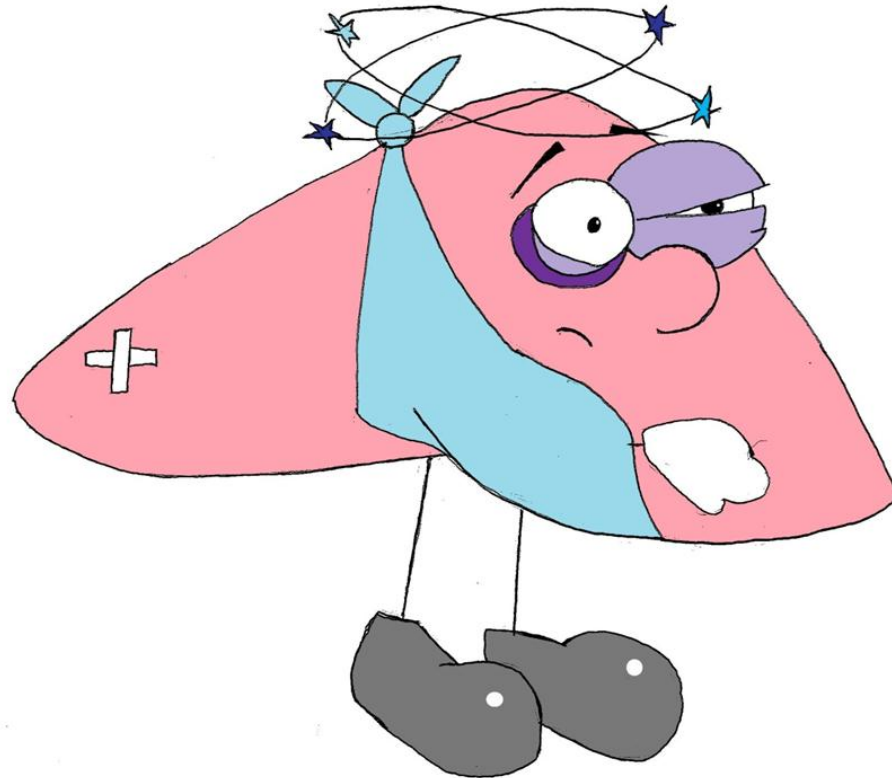
Summary

- Studies showed potential benefit of PCT for diagnosis of infectious necrotizing pancreatitis
 - Less invasive than other methods
 - Cut-off point for diagnosis unclear
- Studies were inconsistent in:
 - When they monitored PCT level
 - For how long they monitored PCT
 - Their method for measuring PCT

What would I recommend?

- In patients with CT confirmed pancreatic necrosis who are severally ill
 - Daily procalcitonin level at onset of SIRS
 - Obtain a level for a few days as peak is delayed

Questions?



Acute Pancreatitis: Etiology

- Rapid onset
- Inflammation of the pancreas

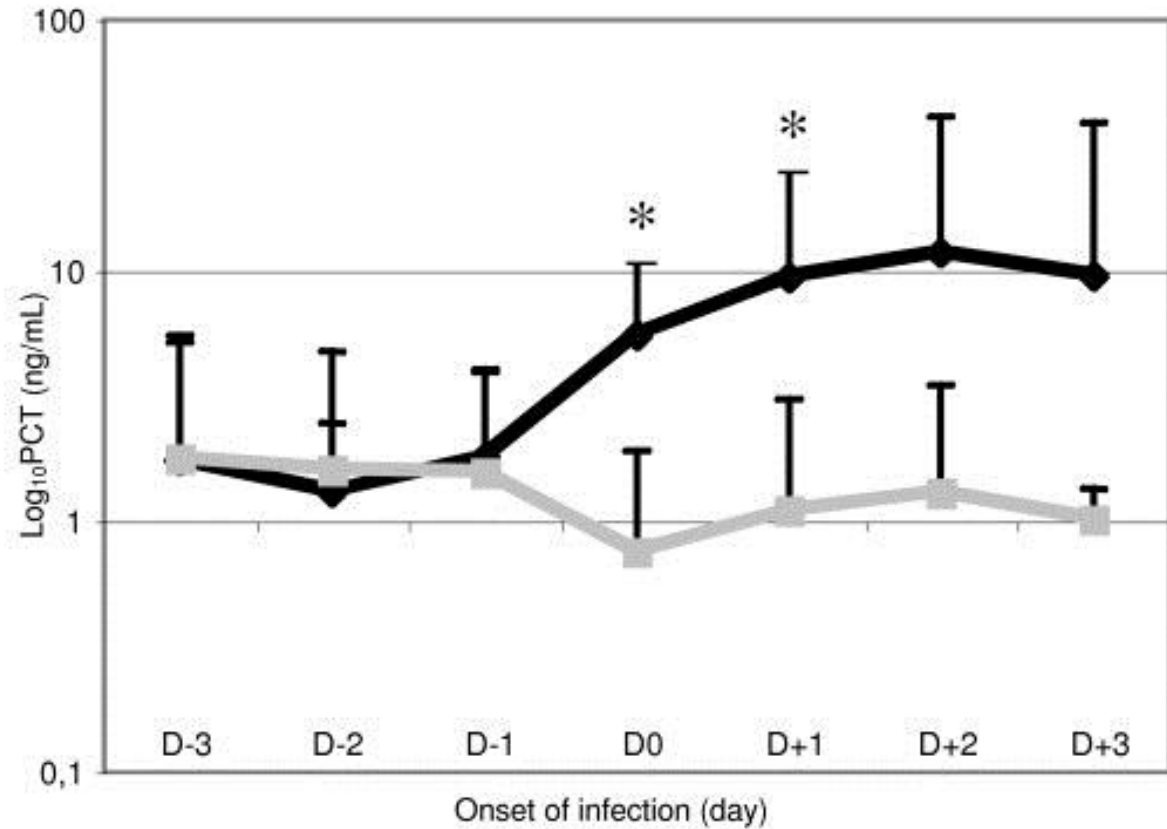
- Causes/Risk Factors:
 - **Alcohol**
 - **Gallstones**
 - **ERCP**
 - Hypertriglyceridemia
 - Trauma
 - Cystic Fibrosis
 - Hyperparathyroidism

 - Medications
 - Azathioprine
 - Estrogens
 - Thiazide Diuretics
 - Corticosteroids
 - Viruses
 - Mumps
 - Coxsackies B
 - Mycoplasma Pneumonia
 - Campylobacter

Procalcitonin Levels

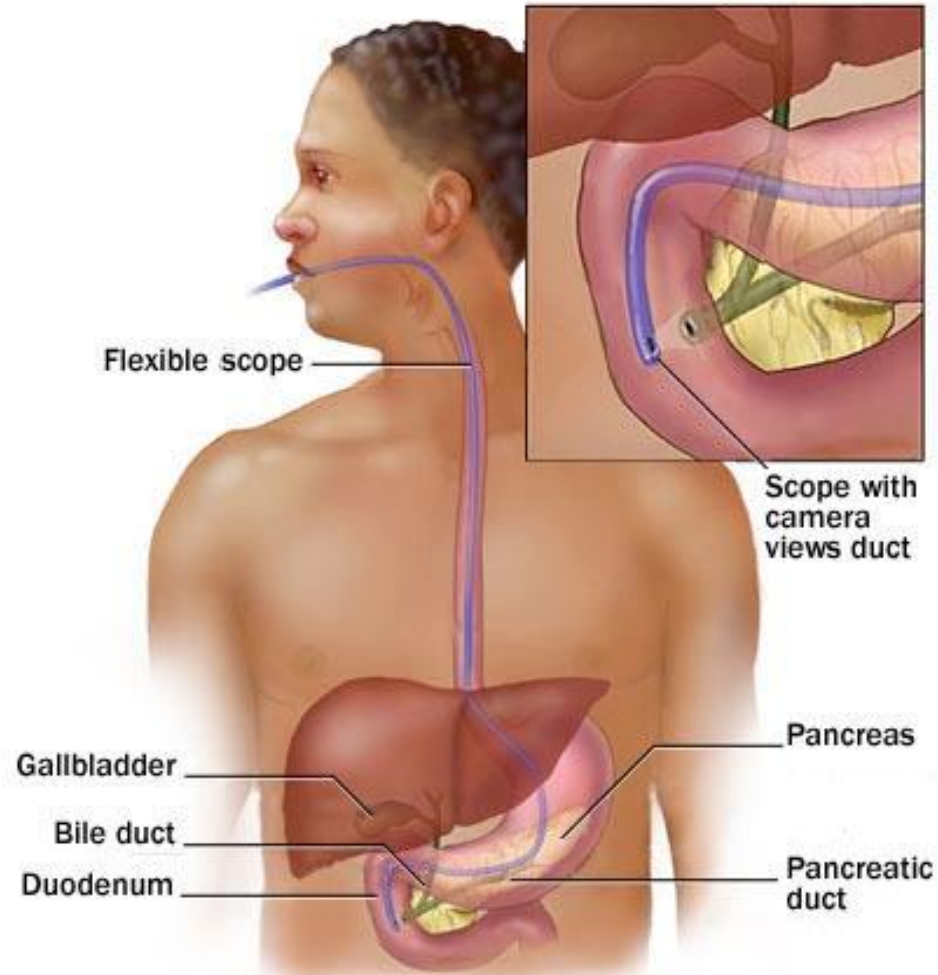
Nosocomial Infection

Unproven Infection



N. of patients with PCT	D-3	D-2	D-1	D0	D+1	D+2	D+3
Nosocomial infection	34	28	32	47	39	40	34
Unproven nosocomial infection	17	16	13	23	18	16	15

ERCP: Endoscopic retrograde cholangiopancreatography



ERCP

- Worsening pancreatitis most serious complication of ERCP
- Several proposed factors:
 - Mechanical injury
 - Hydrostatic injury from overinjection
 - Chemical or allergic injury from contrast medium
 - Enzymatic injury from intestinal content
 - Infection
 - Thermal injury

From VIHA

Algorithm for Procalcitonin Testing in ER/ICU

