Updates in the management of acute and chronic pancreatitis

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Acute pancreatitis

- Guidelines
  - IAP/APA
    - GUIDELINES, APA Acute Pancreatitis, Pancreatology, 2013
      * IAP; International Association of Pancreatology
      * APA; American Pancreatic Association
  - American College of Gastroenterology
    - Tenner S, et al. Am J Gastroenterol. 2013
  - Japan guidelines 2010
    - Hirota M et al., J Hepatobiliary Pancreat Sci 2010
  - KPBA
    - Kim TH et al., Korean J Pancreas Biliary Tract 2014

Acute pancreatitis

- The assessment of the severity
- Initial resuscitation and management
- Management of local complications

Acute pancreatitis

- The assessment of the severity
- Initial resuscitation and management
- Management of local complications

AP - The assessment of the severity

- Clinical symptoms, signs, and lab tests
  - Presence of SIRS
  - BUN, Cr
- Diagnostic imaging
  - CT severity index
- Scoring systems
  - Ranson's score, Imrie-Glasgow score
    - require 48 hrs for the complete assessment
  - BISAP
  - The Harmless Acute Pancreatitis Score
  - APACHE II

Wu BU, et al, Gastroenterology. 2013

AP - The assessment of the severity

Definitions of severity in acute pancreatitis: comparison of Atlanta and recent revision

Atlanta criteria (1993)	Atlanta Revision (2013)
Mild acute pancreatitis	**Mild acute pancreatitis**
Absence of organ failure	Absence of organ failure
Absence of local complications	Absence of local complications
Severe acute pancreatitis	Moderately severe acute pancreatitis
1. Local complications **AND/OR**	1. Local complications **AND/OR**
2. Organ failure	2. Transient organ failure (<48 h)
GI bleeding (>500 cc/24 hr)	**Severe acute pancreatitis**
Shock – SBP ≤90 mm Hg	Persistent organ failure >48 h[a]
PaO 2 ≤60 %	
Creatinine ≥2 mg/dl	

Tenner S, et al., Am J Gastroenterol. 2013

AP - The assessment of the severity

Modified Marshall scoring system for organ dysfunction

	Score				
Organ system	**0**	**1**	**2**	**3**	**4**
Respiratory (PaO_2/FiO_2)	>400	301–400	201–300	101–200	≤101
Renal*					
(serum creatinine, μmol/l)	≤134	134–169	170–310	311–439	>439
(serum creatinine, mg/dl)	<1.4	1.4–1.8	1.9–3.6	3.6–4.9	>4.9
Cardiovascular (systolic blood pressure, mm Hg)†	>90	<90, fluid responsive	<90, not fluid responsive	<90, pH<7.3	<90, pH<7.2

For non-ventilated patients, the FiO_2 can be estimated from below:

Supplemental oxygen (l/min)	**FiO_2 (%)**
Room air	21
2	25
4	30
6–8	40
9–10	50

A score of 2 or more in any system defines the presence of organ failure.

*A score for patients with pre-existing chronic renal failure depends on the extent of further deterioration of baseline renal function. No formal correction exists for a baseline serum creatinine ≥134 μmol/l or ≥1.4 mg/dl.

†Off inotropic support.

Banks PA, et al., Gut 2013

Acute pancreatitis

- The assessment of the severity
- Initial resuscitation and management
- Management of local complications

AP - Initial resuscitation and management

- Optimal fluid infusion rate and response measurement?
  - IAP/APA
    - Goal-directed IV fluid therapy 5-10 mL/kg/h
      - MAP 65-85 mmHg
      - HR <120/min
      - Urine output 0.5-1 mL/kg/h
  - American College of Gastroenterology
    - IV isotonic crystalloid 250-500 mL/h
    - Goal of aggressive hydration

      : to decrease BUN level

AP - Initial resuscitation and management

- Optimal fluid infusion rate and response measurement?
  - Japan guidelines
    - Goal-directed IV fluid 60-160 mL/kg/day within 24h
    - During first 6h: about 1/2-1/3 of the amount required for the first 24h
  - KPBA
    - Goal-directed IV fluid 60-160 mL/kg/day
      - MAP ≥65 mmHg
      - Urine output 0.5-1 mL/kg/h

Chinese Medical Journal 2010;123(13):1639-1644

Original article

Rapid hemodilution is associated with increased sepsis and mortality among patients with severe acute pancreatitis

MAO En-qiang, FEI Jian, PENG Yi-bing, HUANG Jie, TANG Yao-qing and ZHANG Sheng-dao

Effect of extreme hemodilution on prognosis

Parameters	Rapid hemodilution (HCT <35%)	Slow hemodilution (HCT ≥35%)	*P* values
Balthazar CT Scores			
Admission	6.1±1.7	5.7±2.1	0.26
1 week	7.1±2.2	6.8±1.4	0.39
2 weeks	7.3±2.5	7.2±2.2	0.997
Time interval for sepsis presented (d)	7.4±1.9	10.2±2.3	0.000
Incidence of sepsis (%)	78.6 (44/56)	57.6 (34/59)	0.016
In-hospital Survival rate (%)	66.1 (37/56)	84.7 (50/59)	0.02

nature publishing group ORIGINAL CONTRIBUTIONS

Am J Gastroenterol 2011; 106:1843–1850; doi:10.1038/ajg.2011.236

see related editorial on page 1851

Influence of Fluid Therapy on the Prognosis of Acute Pancreatitis: A Prospective Cohort Study

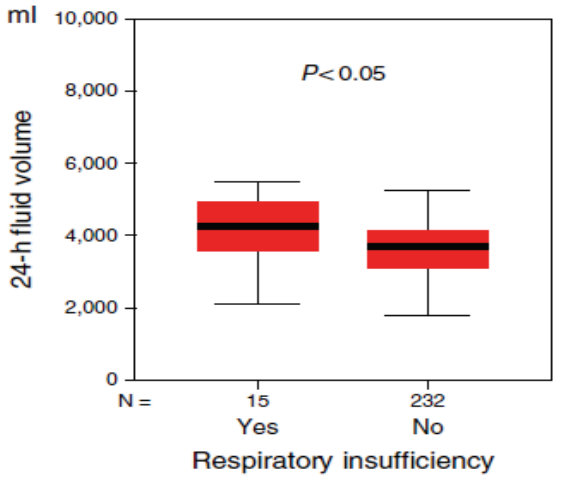
Enrique de-Madaria, MD[1], Gema Soler-Sala, MD[1], José Sánchez-Payá, MD[2], Inmaculada Lopez-Font, PhD[1], Juan Martínez, MD[1], Laura Gómez-Escolar, MD[1], Laura Sempere, MD[1], Cristina Sánchez-Fortún, MD[1] and Miguel Pérez-Mateo, MD[1]

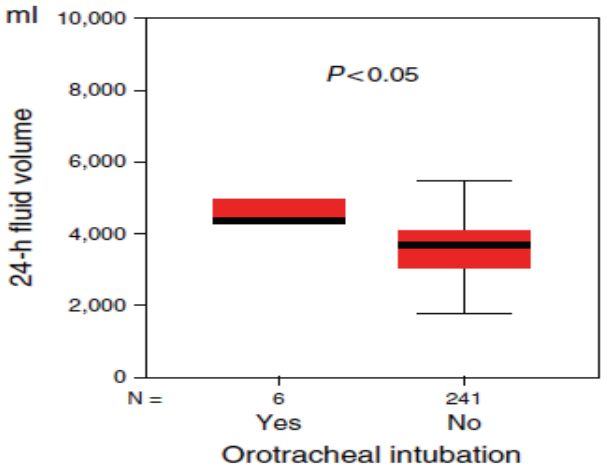
Initial 24 hr FLUID Therapy.

A. > 4.1 L, persistent organ failure, acute collections, respiratory & renal insufficiency

B. < 3.1 L, not associated with OF, local complications, or mortality

C. 3.1 ~ 4.1 L, excellent outcome





AP - Initial resuscitation and management

- What is the best fluid to use for initial fluid resuscitation in acute pancreatitis?

The image downloaded from www.nejm.org

AP - Initial resuscitation and management

- What is the best fluid to use for initial fluid resuscitation in acute pancreatitis?
  - IAP/APA
    - Ringer's lactate is recommended for initial fluid resuscitation in acute pancreatitis
  - American College of Gastroenterology
    - Lactated Ringer's solution may be the preferred isotonic crystalloid replacement fluid

- Lactated Ringer's solution
  - reduced the incidence of SIRS by > 80% compared with saline

Working Group IAPAPAAPG,Pancreatology 2013
Tenner S, et al., Am J Gastroenterol. 2013
Wu BU, et al., Clin Gastroenterol Hepatol 2011

AP - Initial resuscitation and management

- What are the indications for admission to an intensive care unit in acute pancreatitis?
  - IAP/APA
    - one or more of the parameters identified at admission as defined by the guidelines of the Society of Critical Care Medicine (SCCM).
    - patients with severe acute pancreatitis as defined by the revised Atlanta Classification (i.e. persistent organ failure)
  - American College of Gastroenterology
    - patients with organ failure

AP - Initial resuscitation and management

- What are the indications for referral to a specialist center?
  - IAP/APA
    - Management in, or referral to, a specialist center is necessary for patients with severe acute pancreatitis and for those who may need interventional radiologic, endoscopic, or surgical intervention.
  - Japan guidelines
    - Patients with severe acute pancreatitis (prognostic factor ≥3) assessed by the new Japanese criteria should be transferred promptly to a specialist medical institution.
  - KPBA
    - 중증 급성 췌장염으로 평가된 환자는 집중치료실이 있고, 내시경 중재 시술, 영상 중재 시술 및 수술 처치가 가능한 병원으로 전원 해야 한다.

AP - Initial resuscitation and management

- Why should be the patients with severe acute pancreatitis refered to a specialist center?
  - High volume center
    - ≥ 118 admissions/y
  - 25% lower relative risk of death

Singla A, et al.,Gastroenterology 2009

AP - Initial resuscitation and management

- When should oral feeding be restarted in patients with predicted mild pancreatitis?

  - IAP/APA
    - Oral feeding in predicted mild pancreatitis can be restarted once abdominal pain is decreasing and inflammatory markers are improving.
  - American College of Gastroenterology
    - In mild AP, oral feedings can be started immediately if there is no nausea and vomiting, and abdominal pain has resolved
  - KPBA
    - 경증의 급성 췌장염에서 자연적인 식이진행은 대부분 3~7일내 가능하므로 비경구 영양법이나 경장관 영양법이 모든 환자에서 필요하지는 않다.

AP - Initial resuscitation and management

- What type of enteral nutrition should be used?
  - IAP/APA
    - Either elemental or polymeric enteral nutrition formulations can be used in acute pancreatitis.

  - American College of Gastroenterology
    - In mild AP, initiation of feeding with a low-fat solid diet appears as safe as a clear liquid diet
  - KPBA
    - 경구식이는 탄수화물과 단백질이 충분하고 지방이 전체 에너지 섭취의 30% 미만의 저지방 식이를 추천한다

AP - Initial resuscitation and management

- Is enteral nutrition initiated in the early phase of severe acute pancreatitis more useful than intravenous hyperalimentation?
  - IAP/APA
    - Enteral tube feeding should be the primary therapy in patients with predicted severe acute pancreatitis who require nutritional support
  - American College of Gastroenterology
    - In severe AP, enteral nutrition is recommended to prevent infectious complications. Parenteral nutrition should be avoided unless the enteral route is not available, not tolerated, or not meeting caloric requirements
  - Japan
    - If there is no ileus, enteral nutrition initiated in the early phase of severe acute pancreatitis is superior to intravenous hyperalimentation.

AP - Initial resuscitation and management

- Is enteral nutrition initiated in the early phase of severe acute pancreatitis more useful than intravenous hyperalimentation?
  - KPBA
    - 중증의 급성 췌장염 초기에 경장관 영양법은 장마비가 없다면 조기에 시작하는 것이 경정맥 영양법 보다 우수하다.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early versus On-Demand Nasoenteric Tube Feeding in Acute Pancreatitis

O.J. Bakker, S. van Brunschot, H.C. van Santvoort, M.G. Besselink, T.L. Bollen, M.A. Boermeester, C.H. Dejong, H. van Goor, K. Bosscha, U. Ahmed Ali, S. Bouwense, W.M. van Grevenstein, J. Heisterkamp, A.P. Houdijk, J.M. Jansen, T.M. Karsten, E.R. Manusama, V.B. Nieuwenhuijs, A.F. Schaapherder, G.P. van der Schelling, M.P. Schwartz, B.W.M. Spanier, A. Tan, J. Vecht, B.L. Weusten, B.J. Witteman, L.M. Akkermans, M.J. Bruno, M.G. Dijkgraaf, B. van Ramshorst, and H.G. Gooszen, for the Dutch Pancreatitis Study Group

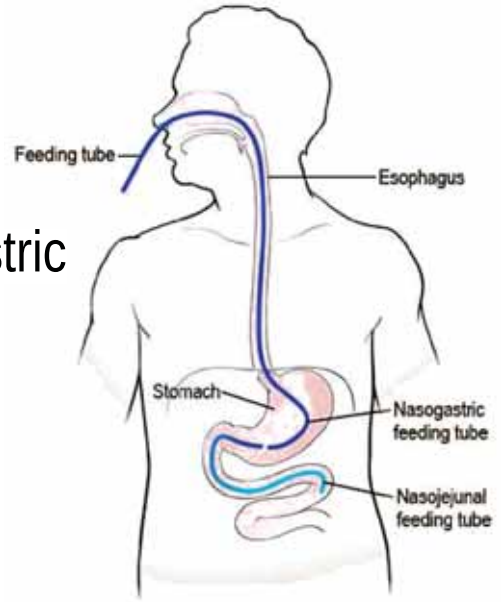
ABSTRACT

BACKGROUND

Early enteral feeding through a nasoenteric feeding tube is often used in patients with severe acute pancreatitis to prevent gut-derived infections, but evidence to support this strategy is limited. We conducted a multicenter, randomized trial comparing early nasoenteric tube feeding with an oral diet at 72 hours after presentation

AP - Initial resuscitation and management

- Should enteral nutrition be administered via a nasojejunal or nasogastric route?
  - IAP/APA
    - Enteral nutrition in acute pancreatitis can be administered via either the nasojejunal or nasogastric route



  - American College of Gastroenterology
    - Nasogastric delivery and nasojejunal delivery of enteral feeding appear comparable in efficacy and safety
  - KPBA
    - 경로는 일반적으로 경비공장 배액관을 추천한다.

AP - Initial resuscitation and management

- Nasojejunal vs. Nasogastric
  - A randomized study of early nasogastric versus nasojejunal feeding in severe acute pancreatitis

    - 27 to NG feeding and 23 to NJ.
    - No Clinical differences and mortality

    →The simpler, cheaper, and more easily used NG feeding is as good as NJ feeding

Eatock FC. Am J Gastroenterol 2005

AP - Initial resuscitation and management

- Is the prophylactic administration of antibiotics in severe acute pancreatitis effective in preventing bacterial infections?
  - IAP/APA
    - Intravenous antibiotic prophylaxis is not recommended for the prevention of infectious complications in acute pancreatitis
  - American College of Gastroenterology
    - Routine use of prophylactic antibiotics in patients with severe acute pancreatitis is not recommended

AP - Initial resuscitation and management

- Is the prophylactic administration of antibiotics in severe acute pancreatitis effective in preventing bacterial infections?
  - Japan
    - Prophylactic administration of broad-spectrum antibiotics with good tissue penetration in severe acute pancreatitis is effective in reducing the frequency of complications related to infections.
  - KPBA
    - 중증의 췌장염에서 감염과 연관된 합병증 빈도 감소를 목적으로 조직침투가 좋은 광범위 항생제를 예방적으로 투여해 볼 수 있다

Acute pancreatitis

- The assessment of the severity
- Initial resuscitation and management
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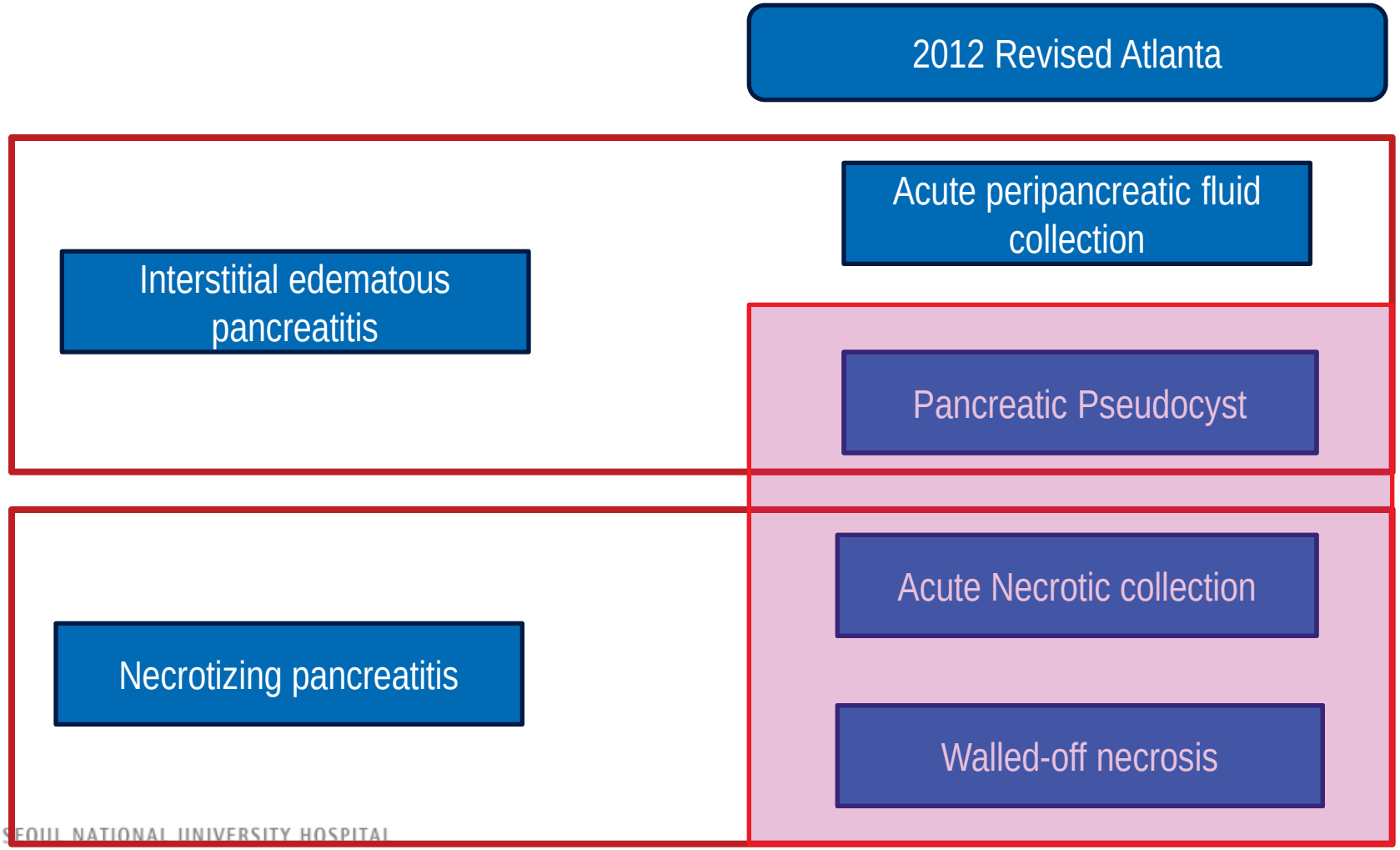
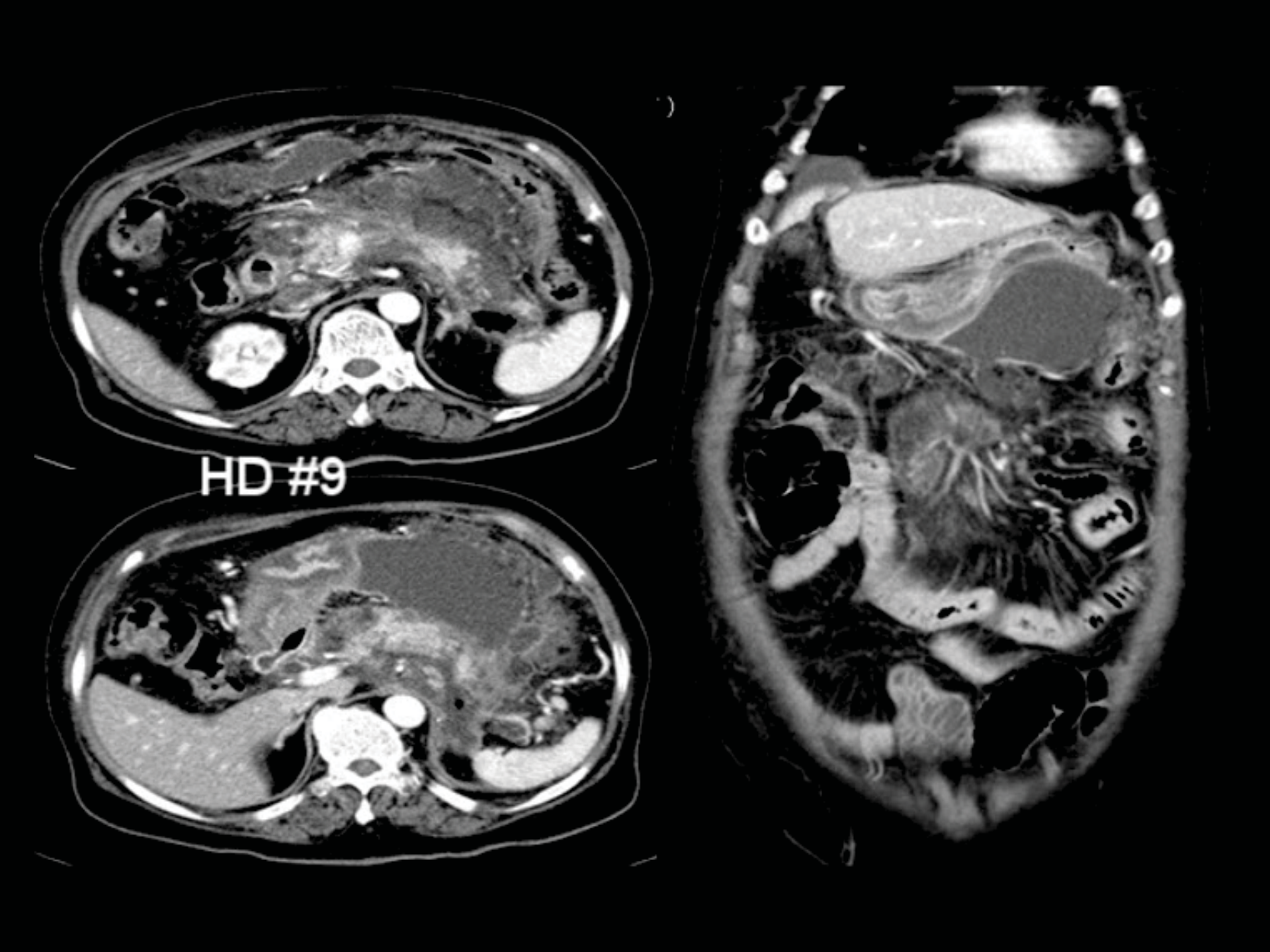
AP - Management of local complications

- Local complications




HD #9

AP - Management of local complications

Issues in interventional treatment of necrotizing pancreatitis

1. *What is the indication for surgical intervention in necrotizing pancreatitis?*
2. *What is the optimal timing for surgical intervention?*
3. *What is the optimal surgical procedure for infected pancreatic necrosis?*
4. *What is the optimal minimal invasive intervention for infected pancreatic necrosis?*

AP - Management of local complications

1. What is the indication for surgical intervention in necrotizing pancreatitis?

- Infected pancreatic necrosis accompanied by signs of sepsis despite medical treatment
- Selected sterile pancreatic necrosis with persistent organ complications or severe clinical deterioration despite maximum intensive care

Ranson JHC. Adv Surg 1995
Fernandez-del Castillo C, et al. Ann Surg 1998
Beger HG, et al. Br J Surg 1988

AP - Management of local complications

2. What is the optimal timing for surgical intervention?

Urgent intervention

예방적 항생제의 효과가 완전히 입증되지 않았다.

감염 조직이 그대로 있으면 사망률이 100%에 이른다.

Delayed intervention

감염에 의한 합병증은 대개 2주 이후에 발생한다.

조기 수술 후 사망률이 높게는 65%에 이른다.

괴사 조직과 정상 췌실질 사이의 구분이 모호하다.

Am J Surg. 1997 Feb;173(2):71-5.

Early versus late necrosectomy in severe necrotizing pancreatitis.

Mier J, León EL, Castillo A, Robledo F, Blanco R.

Department of General and Gastrointestinal Surgery, Hospital de Especialidades, Centro Médico Nacional Siglo XXI (IMSS), Mexico City, Mexico.

Abstract

BACKGROUND: Debate as to whether surgery in severe necrotizing pancreatitis (SNP) should be done early or late has been present ever since the disease was described. There are no prospective, randomized studies addressing this specific issue.

METHODS: Patients with SNP, documented clinically, with Ranson's criteria, and dynamic pancreatography (DP) findings were randomly allocated in two groups for treatment. Group A included early necrosectomy (within 48 to 72 hours of onset) and group B, late necrosectomy (at least 12 days after onset). Both groups continued with open packing and staged necrosectomies. Cultures were obtained at each laparotomy and necrosis was verified histologically in all instances.

RESULTS: During a 36-month study period, 150 patients with unequivocal acute pancreatitis were admitted for treatment. Forty-one with SNP initially entered the study; there were 5 drop outs. Patients in group A (25) and group B (11) had no difference in distribution by gender or mean age, etiology, mean Ranson's signs (4 versus 3.8), DP findings, rate of infected necrosis, or necrosectomies required per patient. Although the mortality rate (58% versus 27%) did not reach statistical significance, the odds ratio for mortality was 3.4 times higher in group A, which made us finish the study.

CONCLUSION: This prospective, randomized study from a single institution clearly demonstrates that early intensive conservative treatment with late necrosectomy for selected cases is the current rationale approach for SNP.

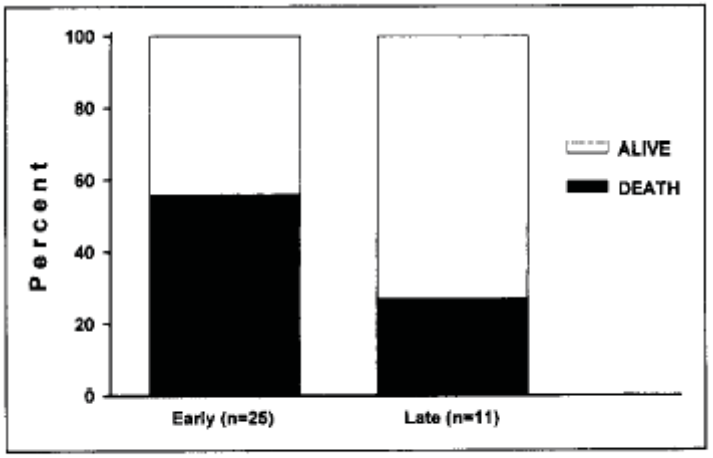


Figure 1. Mortality rate, early versus late surgery (chi-square $P > 0.05$, odds ratio 3.39).

Causes of Death

	Group A (N = 14)	Group B (N = 3)
Multiple organ failure	4	1
Hemodynamic/cardiovascular collapse	4	—
Acute respiratory distress syndrome	1	1
Sepsis	1	—
Renal insufficiency	1	1*
Pulmonary thromboembolism	1*	—
Bronchial obstruction (foreign body)	1*	—
Postoperative bleeding	1*	—

* *Patients with sterile pancreatic necrosis.*

Mier J, et al. Am J Surg 1997

AP - Management of local complications

2. What is the optimal timing for surgical intervention?

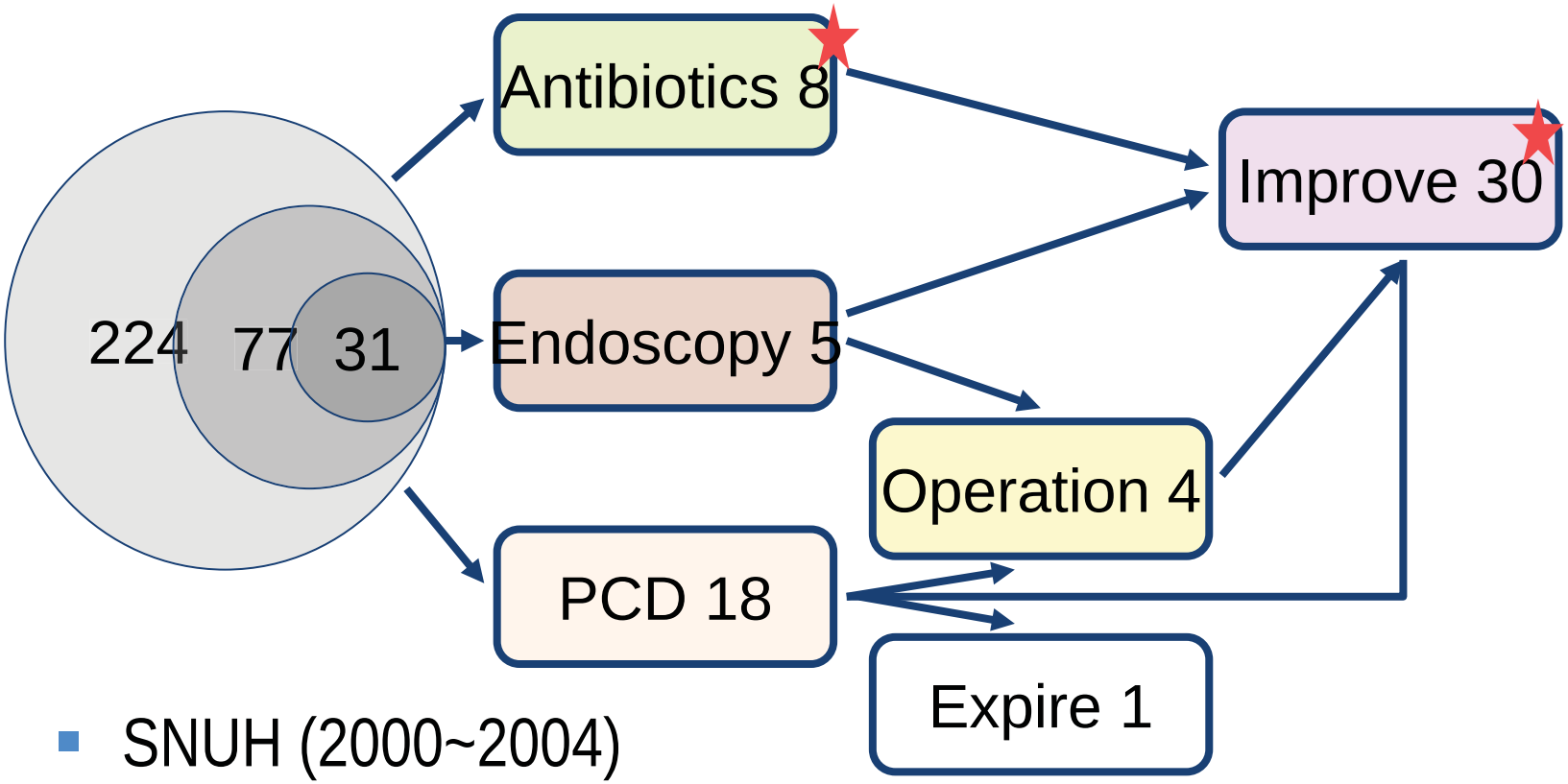
- Early surgery is not recommended for necrotizing pancreatitis
- Specific indication for early intervention
  - Abdominal compartment syndrome (ACS)
  - Non-occlusive mesenteric ischemia

Mier J, et al. Am J Surg 1997
Hartwig W, et al. J Gastrointest Surg 2002

AP - Management of local complications

3.What is the optimal surgical procedure for infected pancreatic necrosis?

(step-up approach vs. primary open necrosectomy)



- SNUH (2000~2004)

Lee JK, et al. Pancreas 2007

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Step-up Approach or Open Necrosectomy for Necrotizing Pancreatitis

Hjalmar C. van Santvoort, M.D., Marc G. Besselink, M.D., Ph.D., Olaf J. Bakker, M.D., H. Sijbrand Hofker, M.D., Marja A. Boermeester, M.D., Ph.D., Cornelis H. Dejong, M.D., Ph.D., Harry van Goor, M.D., Ph.D., Alexander F. Schaapherder, M.D., Ph.D., Casper H. van Eijck, M.D., Ph.D., Thomas L. Bollen, M.D., Bert van Ramshorst, M.D., Ph.D., Vincent B. Nieuwenhuijs, M.D., Ph.D., Robin Timmer, M.D., Ph.D., Johan S. Laméris, M.D., Ph.D., Philip M. Kruyt, M.D., Eric R. Manusama, M.D., Ph.D., Erwin van der Harst, M.D., Ph.D., George P. van der Schelling, M.D., Ph.D., Tom Karsten, M.D., Ph.D., Eric J. Hesselink, M.D., Ph.D., Cornelis J. van Laarhoven, M.D., Ph.D., Camiel Rosman, M.D., Ph.D., Koop Bosscha, M.D., Ph.D., Ralph J. de Wit, M.D., Ph.D., Alexander P. Houdijk, M.D., Ph.D., Maarten S. van Leeuwen, M.D., Ph.D., Erik Buskens, M.D., Ph.D., and Hein G. Gooszen, M.D., Ph.D., for the Dutch Pancreatitis Study Group*

AP - Management of local complications

4.What is the optimal minimal invasive intervention for infected pancreatic necrosis? (retroperitoneal surgical necrosectomy vs endoscopic transluminal necrosectomy)

Endoscopic Transgastric vs Surgical Necrosectomy for Infected Necrotizing Pancreatitis

A Randomized Trial

Olaf J. Bakker, MD
Hjalmar C. van Santvoort, MD, PhD
Sandra van Brunschot, MD
Ronald B. Geskus, PhD
Marc G. Besselink, MD, PhD
Thomas L. Bollen, MD
Casper H. van Eijck, MD, PhD
Paul Fockens, MD, PhD
Eric J. Hazebroek, MD, PhD
Rian M. Nijmeijer, MD
Jan-Werner Poley, MD
Bert van Ramshorst, MD, PhD
Frank P. Vleggaar, MD, PhD
Marja A. Boermeester, MD, PhD
Hein G. Gooszen, MD, PhD
Bas L. Weusten, MD, PhD
Robin Timmer, MD, PhD
for the Dutch Pancreatitis Study Group

Context Most patients with infected necrotizing pancreatitis require necrosectomy. Surgical necrosectomy induces a proinflammatory response and is associated with a high complication rate. Endoscopic transgastric necrosectomy, a form of natural orifice transluminal endoscopic surgery, may reduce the proinflammatory response and reduce complications.

Objective To compare the proinflammatory response and clinical outcome of endoscopic transgastric and surgical necrosectomy.

Design, Setting, and Patients Randomized controlled assessor-blinded clinical trial in 3 academic hospitals and 1 regional teaching hospital in the Netherlands between August 20, 2008, and March 3, 2010. Patients had signs of infected necrotizing pancreatitis and an indication for intervention.

Interventions Random allocation to endoscopic transgastric or surgical necrosectomy. Endoscopic necrosectomy consisted of transgastric puncture, balloon dilatation, retroperitoneal drainage, and necrosectomy. Surgical necrosectomy consisted of video-assisted retroperitoneal debridement or, if not feasible, laparotomy.

Main Outcome Measures The primary end point was the postprocedural proinflammatory response as measured by serum interleukin 6 (IL-6) levels. Secondary clinical end points included a predefined composite end point of major complications (new-onset multiple organ failure, intra-abdominal bleeding, enterocutaneous fistula, or pancreatic fistula) or death.

Results We randomized 22 patients, 2 of whom did not undergo necrosectomy following percutaneous catheter drainage and could not be analyzed for the primary end point. Endoscopic transgastric necrosectomy reduced the postprocedural IL-6 levels compared with surgical necrosectomy ($P=.004$). The composite clinical end point occurred less often after endoscopic necrosectomy (20% vs 80%; risk difference [RD], 0.60; 95% CI, 0.16-0.80; $P=.03$). Endoscopic necrosectomy did not cause new-onset multiple organ failure (0% vs 50%, RD, 0.50; 95% CI, 0.12-0.76; $P=.03$) and reduced the number of pancreatic fistulas (10% vs 70%; RD, 0.60; 95% CI, 0.17-0.81; $P=.02$).

Conclusion In patients with infected necrotizing pancreatitis, endoscopic necrosectomy reduced the proinflammatory response as well as the composite clinical end point compared with surgical necrosectomy.

Trial Registration isrctn.org Identifier: ISRCTN07091918

JAMA. 2012;307(10):1053-1061 www.jama.com

ACUTE PANCREATITIS IS A COMmon and potentially lethal disorder.[1] In the United States alone, more than 50 000 patients are admitted with acute pancreatitis each year.[2] One of the most dreaded complications in these patients is infected necrotizing pancre-

Transluminal endoscopic necrosectomy for pancreatic necrosis: in all hands and for all patients, or with selected endoscopists in selected patients?

Marc Barthet, Salah Ezzedine

In this issue of *Gut*, Seifert *et al*[1] ***(see page 1260)***, in a multicentre study from Germany, have investigated the results of endoscopic treatment of pancreatic necrosis. The paper highlights the long-term results of this endoscopic management, considered from an endoscopic point of view as an aggressive treatment but from a surgical point of view as a minimally invasive treatment. The endoscopic management of pancreatic necrosis is moving to the frontier between surgery and endoscopy. Transluminal endoscopic

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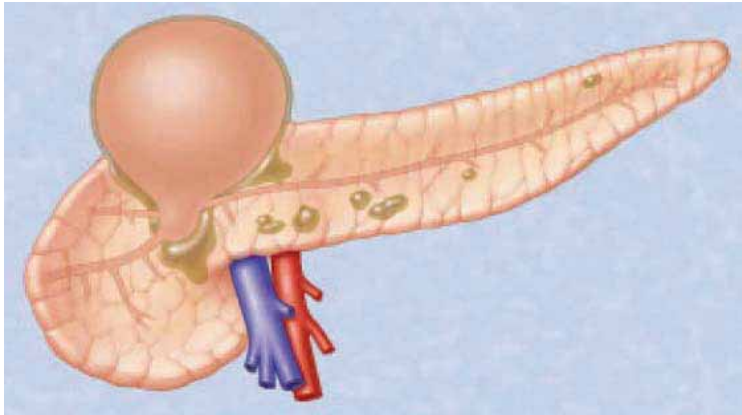
necrosectomy is probabl
NOTES (natural orifice
surgery) procedures in h

The first limitation
endoscopic necrosectomy
creatitis (TENAP) series i
pancreatic necrosis. Trans
drainage of pancreatic
abscesses has been perf
1980s and is becoming
procedure.[2] Recently, e
sound (EUS) guidance c
tions of acute pancreati
the field of the endosco
pancreatic pseudocysts a
More than half of the ps
bulge through the diges
not amenable to conven
drainage.[2] In addition, pc
due to thrombosis or co
splenic vein by the pseu
the risk of bleeding. It
strated that EUS guidar
about half of the pat
drainage of pancreatic

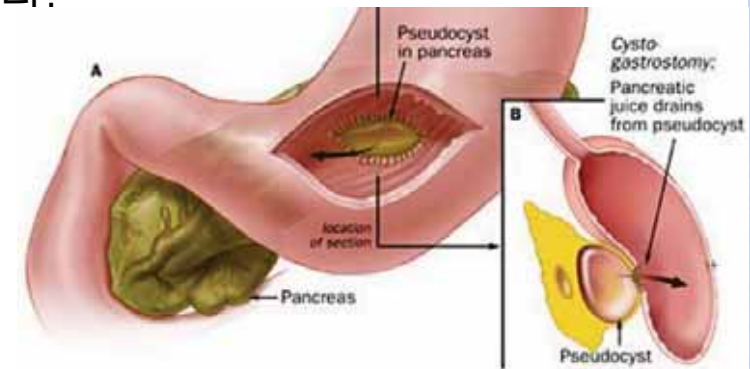
AP - Management of local complications

- What are the indications for intervention in pancreatic pseudocysts?
  - Japan
    - Interventional treatment should be performed for pancreatic pseudocysts that give rise to symptoms, accompany complications or increase the diameter of cyst
  - KPBA
    - 가성낭종의 치료 적응증은 임상적 증상을 유발하는 낭종, 크기가 커지는 낭종, 합병증이 발생한 낭종이다.



AP - Management of local complications

- How is interventional treatment selected for pancreatic pseudocysts?
  - Japan
    - Percutaneous drainage, endoscopic drainage or surgical procedures are selected in accordance with the conditions of individual cases including the communication with the pancreatic duct and the positional relationship between the digestive tract walls.
  - KPBA
    - 췌장 가성낭종의 치료는 내시경적 배액술, 경피적 배액술, 수술적 배액술이 이용될 수 있다. 각 치료법의 선택은 낭종의 위치, 낭종과 췌관의 연결 유무, 낭종과 위장관과 해부학적 위치 관계, 병원의 시설에 따라서 결정될 수 있다.



AP - Management of local complications

- What is the treatment policy for sterile pancreatic necrosis?
  - Japan
    - Conservative treatment should be performed as a rule in sterile pancreatic necrosis.
  - KPBA
    - 무균성 췌장 괴사는 첫 2-3주 동안에는 보존적(내과적) 치료가 최우선이다.

AP - Management of local complications

- What are the indications for intervention in sterile necrotizing pancreatitis?
  - IAP/APA
    - Ongoing gastric outlet, intestinal, or biliary obstruction due to mass effect of walled-off necrosis
    - Persistent symptoms in patients with walled-off necrosis without signs of infection
    - Disconnected duct syndrome (i.e. full transection of the pancreatic duct in the presence of pancreatic necrosis) with persisting symptomatic collection(s) with necrosis without signs of infections

AP - Management of local complications

- What are the indications for intervention in sterile necrotizing pancreatitis?
  - KPBA
    - 무균성 췌장 괴사 환자에서 보존적 치료에도 불구하고 그 이후 복통이 지속되거나 다장기 부전이 발생하면 괴사 제거술이 필요하다

AP - Management of local complications

- What is the optimal timing of surgery for suspected or confirmed infected necrosis?
  - IAP/APA
    - For patients with proven or suspected infected necrotizing pancreatitis, invasive intervention should be delayed where possible until at least 4 weeks after initial presentation to allow the collection to become 'walled-off'
  - American College of Gastroenterology
    - In stable patients with infected necrosis, surgical, radiologic, and/or endoscopic drainage should be delayed preferably for more than 4 weeks to allow liquefication of the contents and the development of a fibrous wall around the necrosis (walled-off necrosis)

AP - Management of local complications

- What is the optimal timing of surgery for suspected or confirmed infected necrosis?
  - Japan
    - Early surgery for necrotizing pancreatitis is not recommended.
      If surgery (necrosectomy) is performed, it should be delayed as long as possible
  - KPBA
    - 괴사성 췌장염에서 수술적 치료는 췌장염 발생 4주 후로 최대한 연기하여야 한다

AP - Management of local complications

- What is the optimal interventional strategy for suspected or confirmed infected necrotizing pancreatitis?

  - IAP/APA
    - The optimal interventional strategy for patients with suspected or confirmed infected necrotizing pancreatitis is initial image-guided percutaneous (retroperitoneal) catheter drainage or endoscopic transluminal drainage, followed, if necessary, by endoscopic or surgical necrosectomy
  - American College of Gastroenterology
    - In symptomatic patients with infected necrosis, minimally invasive methods of necrosectomy are preferred to open necrosectomy
  - KPBA
    - 수술적 괴사 제거술 전 경피적 또는 내시경적 배액술을 시행하여 가능한 수술적 괴사 제거술을 피하거나 연기할 수 있다.

Chronic pancreatitis

- Recent updates in the management

  - *Forsmark CE, Gastroenterology. 2013*
    - Management of chronic pancreatitis.

  - *Issa Y, et al., Nat Rev Gastroenterol Hepatol. 2014*
    - Treatment options for chronic pancreatitis.

  - *Talukdar R, et al., Curr Opin Gastroenterol. 2014*
    - Endoscopic therapy for chronic pancreatitis

Chronic pancreatitis

- Treatment of pain
  - Medical treatment
  - Endoscopic therapy
  - Surgical therapy
- Management of exocrine insufficiency

Chronic pancreatitis

- Treatment of pain
  - Medical treatment
  - Endoscopic therapy
  - Surgical therapy
- Management of exocrine insufficiency

CP - Treatment of pain: Medical treatment

- Abdominal pain
  - 80-90% of chronic pancreatitis patients
  - pathophysiology?
    - ductal and mechanical
    - Neuropathic
- alcohol abstinence, smoking cessation
  - reduces pain, slows disease progression
  - reduces complications such as carcinomas
  - prolongs life

Thuluvath PJ, et al., J Clin Gastroenterol. 2003
Gachago C, et al., World J Gastroenterol. 2008
Braganza JM, et al., Lancet. 2011
Mullady DK, et al.,Gut. 2011
Lieb JG, et al., Aliment Pharmacol Ther. 2009

CP - Treatment of pain: Medical treatment

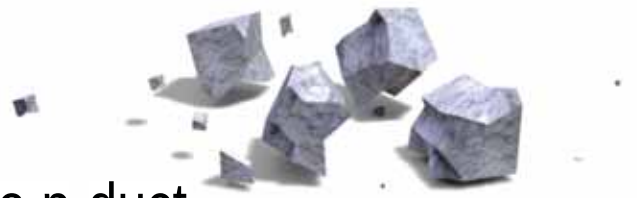
- Analgesics
  - acetaminophen, NSAID →less-potent opioids (ex; tramadol) → more-potent opioids
- adjuvant agents with opioids
  - TCA, SSRI, SNRI
  - α2δ inhibitor: pregabalin, gabapentin
- Others
  - Pancreatic enzymes
    - mixed results
  - Octreotide
    - rarely used
  - Antioxidants
    - controversial

Trikudanathan G, et al., Gastroenterol Clin North Am. 2012
Olesen SS, et al., Gastroenterology. 2011
Winstead NS, et al., Pancreatology 2009
Siriwardena AK, et al., Gastroenterology. 2012
Bhardwaj P, et al., Gastroenterology. 2009
Uhl W, et al., Digestion. 1999

Chronic pancreatitis

- Treatment of pain
  - Medical treatment
  - Endoscopic therapy
  - Surgical therapy
- Management of exocrine insufficiency

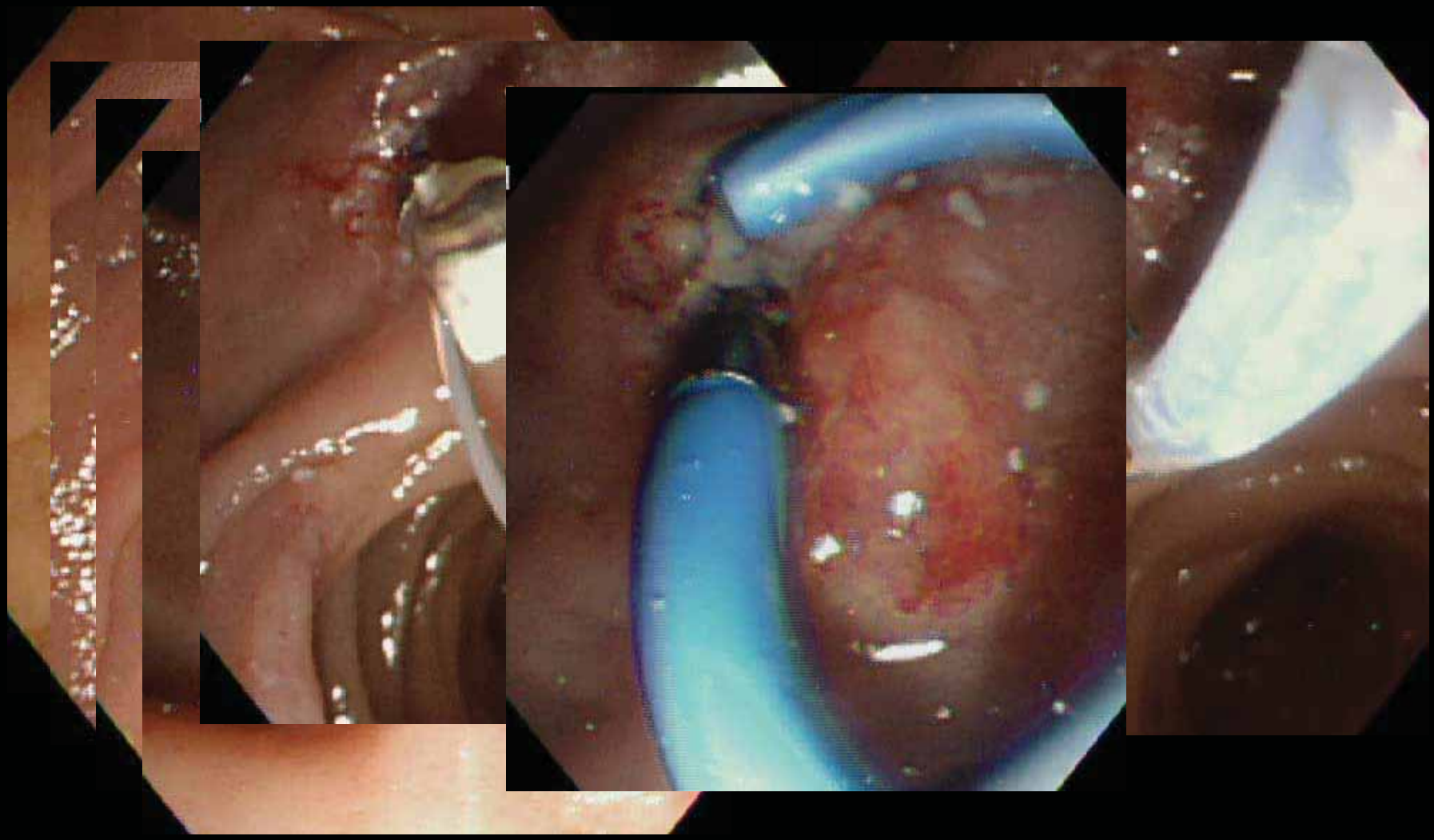
CP - Treatment of pain: Endoscopic therapy

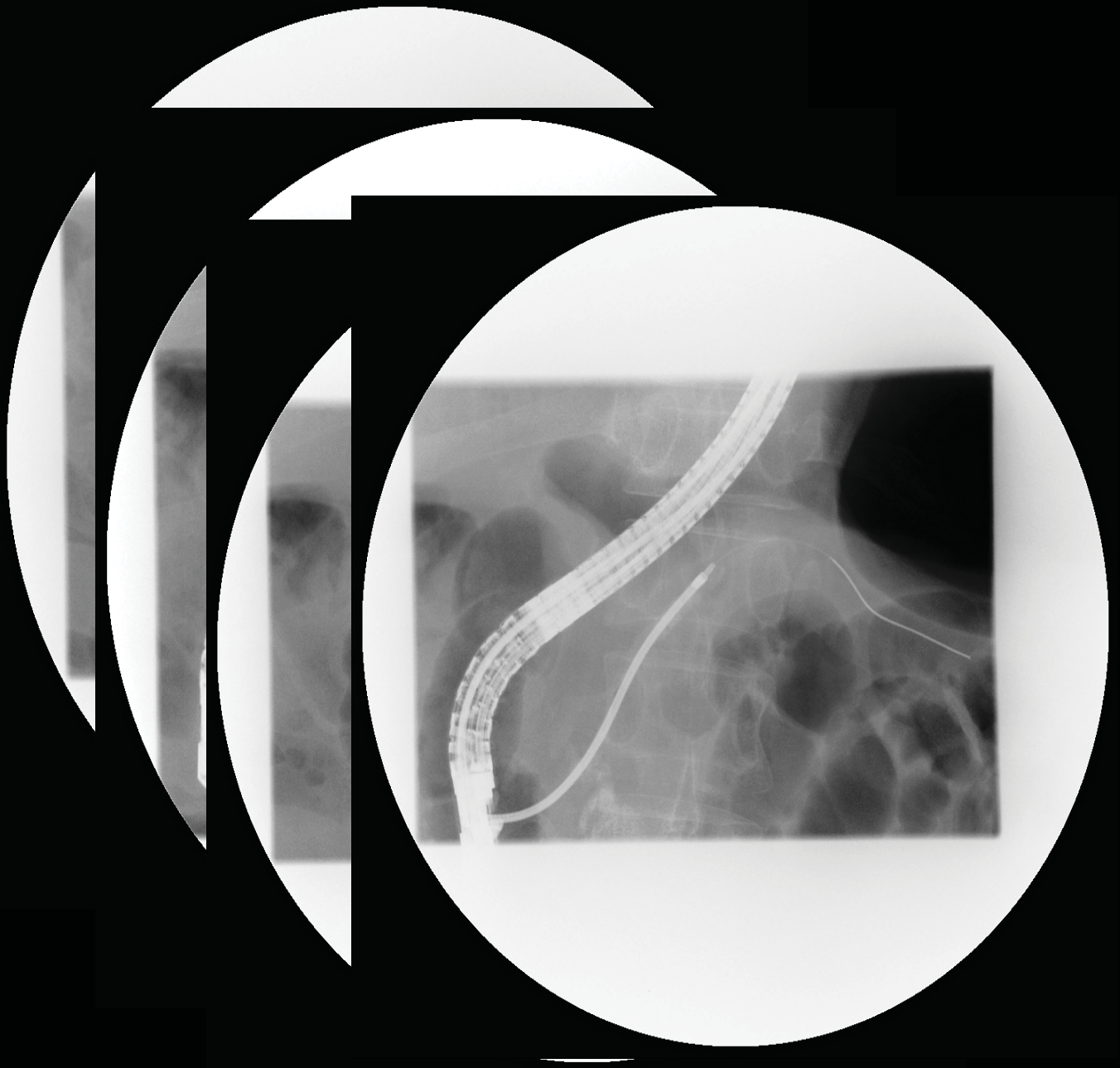


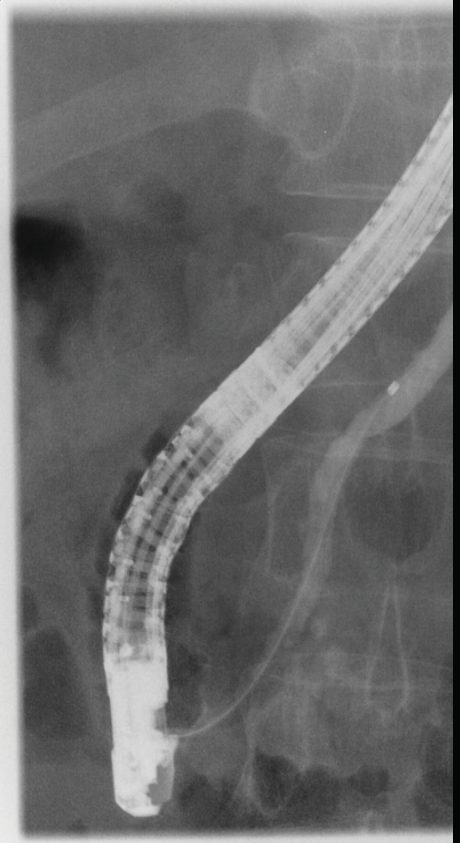
- Pancreatic calculi
  - 32-90% of chronic pancreatitis patients
  - cause outflow obstruction and dilatation of the p-duct
  - ESWL as a first-line therapy for lithotrypsy of large pancreatic stone
- Pancreatic duct stricture
  - up to 18% of chronic pancreatitis patients
  - p-duct stent
    - technical success rate 85-98%
    - sustained pain relief 52-90% (14-69 mo f/u)
    - planned stent exchange: within 3 months / 1 year
  - type of stents
    - plastic - multiple stents(2-4):
      - 84% asymptomatic
      - 10.5% stricture recurrence
    - metal - SEMS: unsatisfactory results

Maydeo A, et al., Endoscopy. 2007
Dumonceau JM, et al., Endoscopy. 2012
Issa Y, et al., Nat Rev Gastroenterol Hepatol. 2014
Dumonceau JM, et al., Gut. 2007
Tandan M, et al., World J Gastroenterol. 2013
Costamagna G, et al., Endoscopy. 2006
Moon SH, et al., Gastrointest Endosc. 2010

- 58/M, Hx. of acute pancreatitis (2009, 2013)
- Severe LUQ pain (1DA)
- O/S hospital CT: Acute exacerbation of the chronic pancreatitis.
- - with pancreaticoliths in the downstream p duct.
- - mild peripancreatic infiltration & pancreatic swelling
- - no definite parenchymal necrosis
-







CP - Treatment of pain: Endoscopic therapy

- EUS-guided celiac plexus block
  - rationale: peripancreatic and celiac neuronal inflammation
  - overall technical success rate 95%
  - short-term pain improvement 50-55%
  - long-term pain relief at 12wks(26%), 24wks(10%)
  - temporizing measure reserved for those where oral analgesia is ineffective or who are intolerant to medication side-effects pending a more definitive intervention

Avula H, et al., Therap Adv Gastroenterol 2010

Chronic pancreatitis

- Treatment of pain
  - Medical treatment
  - Endoscopic therapy
  - Surgical therapy
- Management of exocrine insufficiency
- Management of endocrine insufficiency

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

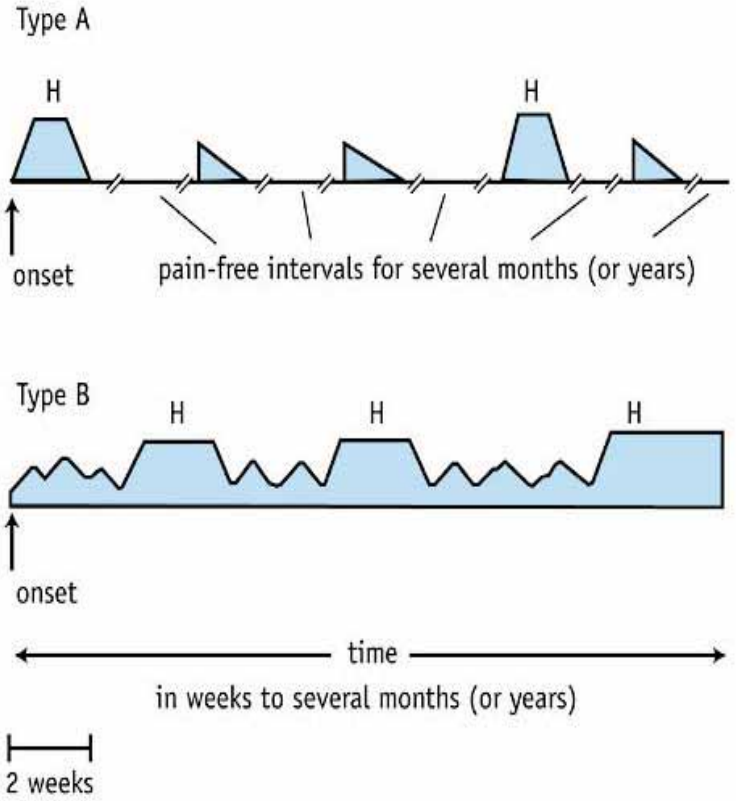
Endoscopic versus Surgical Drainage of the Pancreatic Duct in Chronic Pancreatitis

Djuna L. Cahen, M.D., Dirk J. Gouma, M.D., Ph.D., Yung Nio, M.D., Erik A. J. Rauws, M.D., Ph.D., Marja A. Boermeester, M.D., Ph.D., Olivier R. Busch, M.D., Ph.D., Jaap Stoker, M.D., Ph.D., Johan S. Laméris, M.D., Ph.D., Marcel G.W. Dijkgraaf, Ph.D., Kees Huibregtse, M.D., Ph.D., and Marco J. Bruno, M.D., Ph.D.

Abdominal pain in chronic pancreatitis

- Type A (recurrent):
  - 지속기간 10일 미만
  - 간헐적 동통
  - 환자의 44%
  - 수술적 치료가 필요 없음,
  - 발병 후 6년 이내 50% 복통 소멸

- Type B (continous):
  - 일주일에 2일 이상 지속되는 복통
  - 최소한 2개월 이상 지속
  - 내시경 또는 수술적 치료가 필요
  - 환자의 56%
  - 발병 후 8년 후에 80% 이상에서 복통 소멸



Ammann RW, et al, Gastroenterology, 1999

Natural History of abdominal pain in chronic pancreatitis

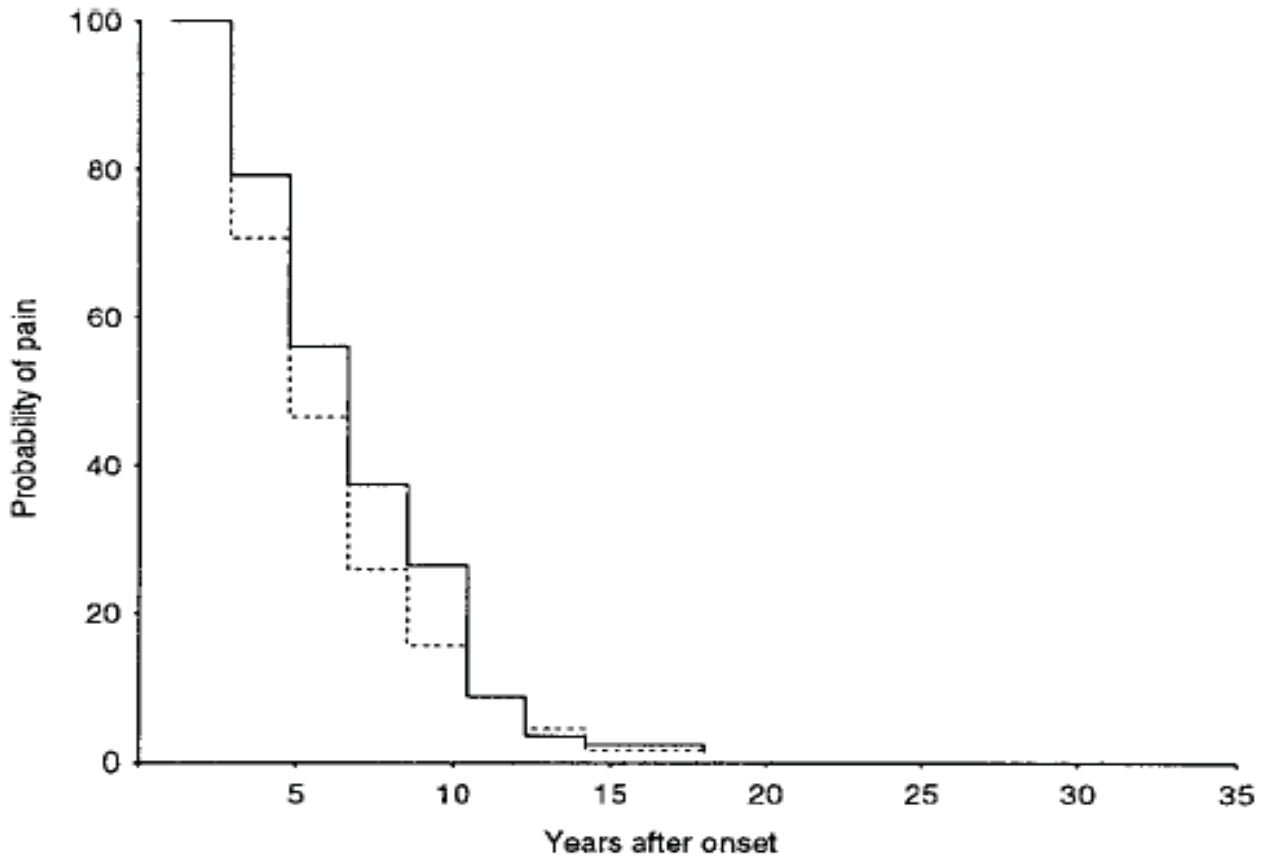


Figure 3. Probability of remaining free from pain recurrence for nonsurgical (––––) and surgical (. . . .) patients.

Ammann RW, et al. Gastroenterology 1999

CP - Treatment of pain: Surgical therapy

- Indications for surgical treatment
  - not responded to medical or endoscopic therapy
  - local complications such as duodenal or biliary obstruction
  - suspected malignancy

Bachmann K, et al., Best Pract Res Clin Gastroenterol. 2010
Nealon WH, et al., Ann Surg. 1993
van der Gaag NA, et al.,Ann Surg. 2012

Chronic pancreatitis

- Treatment of pain
  - Medical treatment
  - Endoscopic therapy
  - Surgical therapy
- Management of exocrine insufficiency

CP - Management of exocrine insufficiency

- Exocrine pancreatic insufficiency
  - 40-50% of chronic pancreatitis patients
  - Symptoms related with fat malabsorption
    - Steatorrhea
    - Cachexia
    - Deficiencies of fat-soluble vitamins
    - Decreased bone mass, osteoporosis
    - Atherogenesis and cardiovascular events
  - Enzyme replacement therapy

Trikudanathan G, et al., Gastroenterol Clin North Am. 2012
Dominguez-Munoz JE, et al., Aliment Pharmacol Ther. 2005

Pathogenesis of Exocrine pancreatic insufficiency

Mechanism	Explanation
Decreased pancreatic production	Lack of functional tissue or decreased endogenous neurohormonal stimulation
Decrease in delivery	Pancreatic duct obstruction
Decreased activation	Low duodenal pH
Premature enzymatic degradation	Decreased contact time due to increased motility, impaired interaction with chyme and biliary salts, and intestinal bacterial overgrowth

Secretion of pancreatic enzyme < 10% / Lost of function > 90%

R Pezzilli, et al., World J Gastroenterol 2013

Pancreatic Digestive Enzyme

- **탄수화물 분해 효소**: Amylase
- **단백 분해 효소**: Trypsin, chymotrypsin, elastase, carboxypeptidase, endopeptidase
- **지방 분해 효소**: Lipase, colipase, phospholipase A2, carboxylesterase
- **핵산 분해 효소**: deoxyribonuclease, ribonuclease
- 기타: collagenase

Amylase & Trypsin

- Amylase
  - Digest of carbohydrate
  - Compensatory release of salivary gland
  - Compensatory release of intestinal mucosal enzyme
  - Activity in terminal ileum : 74%
- Trypsin
  - Resist to gastric acid
  - Compensatory gastric & intestinal proteinase
  - Bioability : 22%
  - Activity in terminal ileum : 20~30%

Lipase

- Digestion of highest dietary source of calories
- Between the pylorus and the ligament of Treitz
- PH > 4.0 in duodenum by bicarbonate
- Easy destruction by gastric acid & activated chemotrypsin
- No compensatory lipase on intestine
- Bioability : 8%
- Activity in terminal ileum : 1%

Pancreatic Enzyme Secretion

Duodenal enzyme outputs

	interdigestive	early / maximal postprandial	late / mean postprandial
Lipase (U/min)	1000	3000 - 6000	2000-4000
Amylase (U/min)	50 -250	500 - 1000	500
Trypsin (U/min)	50 - 100	200 - 1000	150 - 500

Data are derived from studies using test meals with 300 – 600 kcal.

Per Meal:
2000 lipase units per minute X 120 min = 240, 000 lipase units
6000 lipase units per minute X 120 min = 720, 000 lipase units

10% are the minimal necessary amount
➔24,000 – 72,000 lipase units on site/in time
which need to be doubled or tripled in order to be made available by exogenous source

Keller J et Layer P. Gut 2005

Enteric-coated mini-microspheres

- Pellets or micro-tablets of less than 2mm in size
- Adequate intra-gastric mixture of exogenous enzymes with chyme
- pH-sensitive microspheres coat

  : acid resistant polymers, enzyme release at pH 5.0-5.5
- Simultaneous gastric emptying with nutrients
- Higher compliance
- Efficacy better than enteric-coated enzyme tablets or pancreatin preparations

Norzyme cap® (Lipase 25,000U)
Creon cap® (Lipase 25,000U)

Summary

- Recent advances in the treatment of acute and chronic pancreatitis
- Recent clinical practice guidelines
  - new evidences
  - new therapeutic modalities such as endoscopic therapy
- Still needs more researches

Thank you for your kind attention !

SNUH 서울대학교병원
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