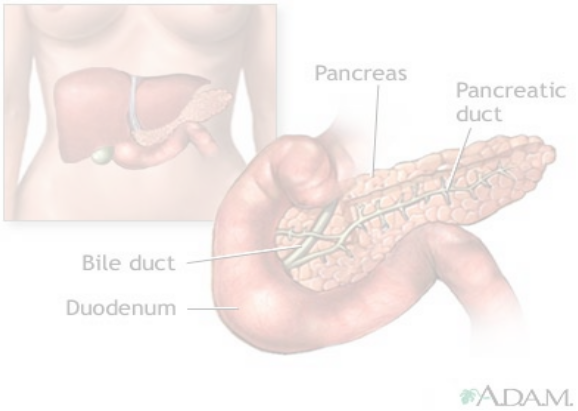
Akut pankreatit – översikt

- Hur vanligt är akut pankreatit hos barn?
- Hur ser mekanismerna bakom sjukdomen?
- Vilka är orsakerna?
- Akut pankreatit hos barn med cancer
- Fallbeskrivningar
- Medicinsk handläggning - riktlinjer
- Asparaginas-orsakad pankreatit
- Sammanfattning



Akut pankreatit

Hyperkalcemi
Hypertriglyceridemi
Läkemedel – valproat, steroid
Trauma
Systemsjukdom
Virus
Okänd

Trigger
Enzymaktivering
Lokal skada
Systemisk reaktion

Diagnos
3x amylas/lipas
Buksmärtor
Radiologi

Endokrin 2%

Alfa - glukagon
Beta - insulin
Delta - somatostatin

Funktion

Exokrin 98%
Trypsinogen - trypsin
Chymotrypsin
Amylas
Lipas

Symtom

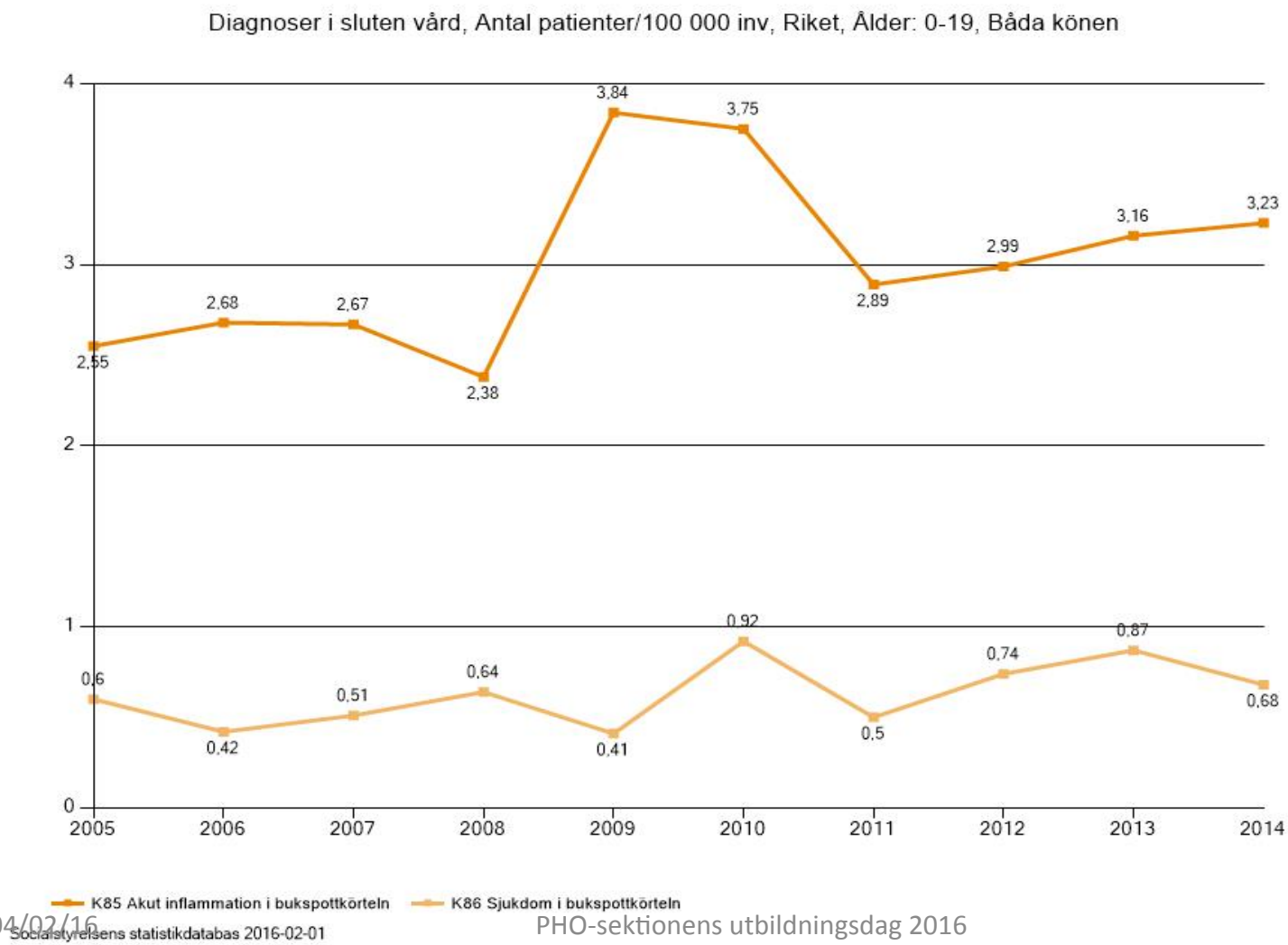
Diabetes mellitus

Pankreatit
Steatorré
Malabsorption

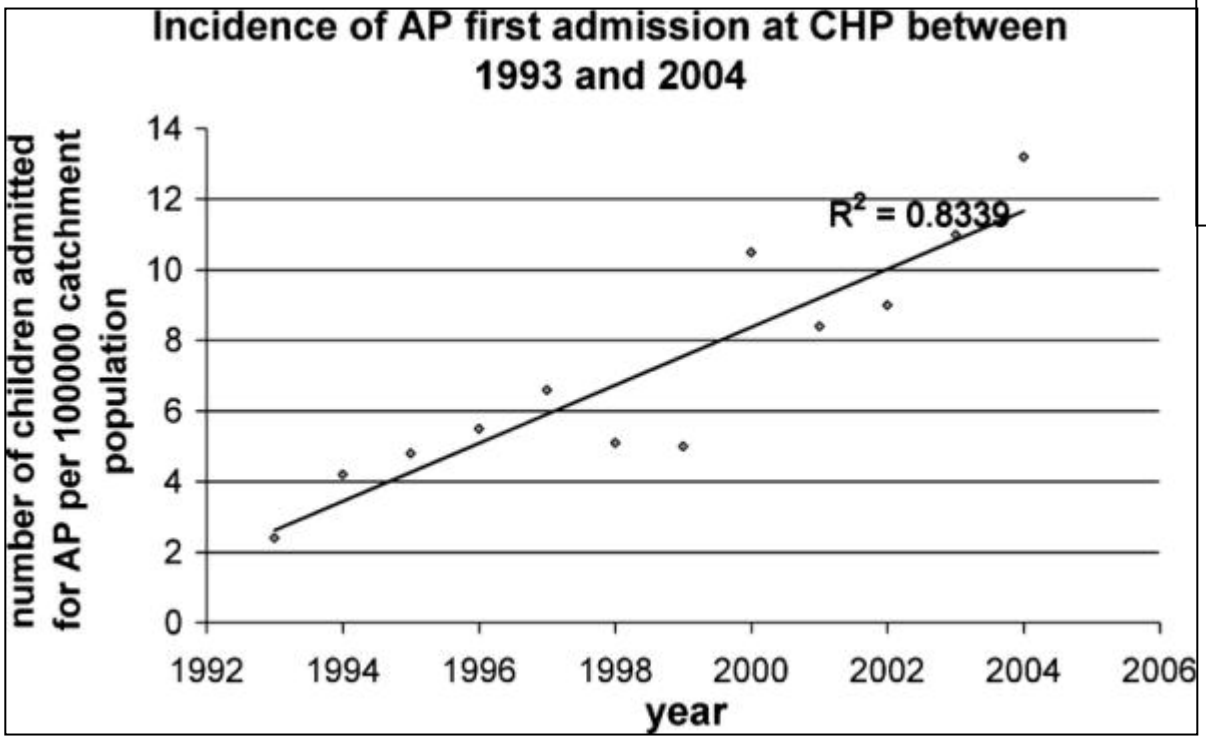
Incidensutveckling

PANKREATIT HOS BARN OCH UNGDOMAR

Incidensutveckling akut pankreatit hos barn i Sverige



Hur ser incidensutvecklingen ut i USA?



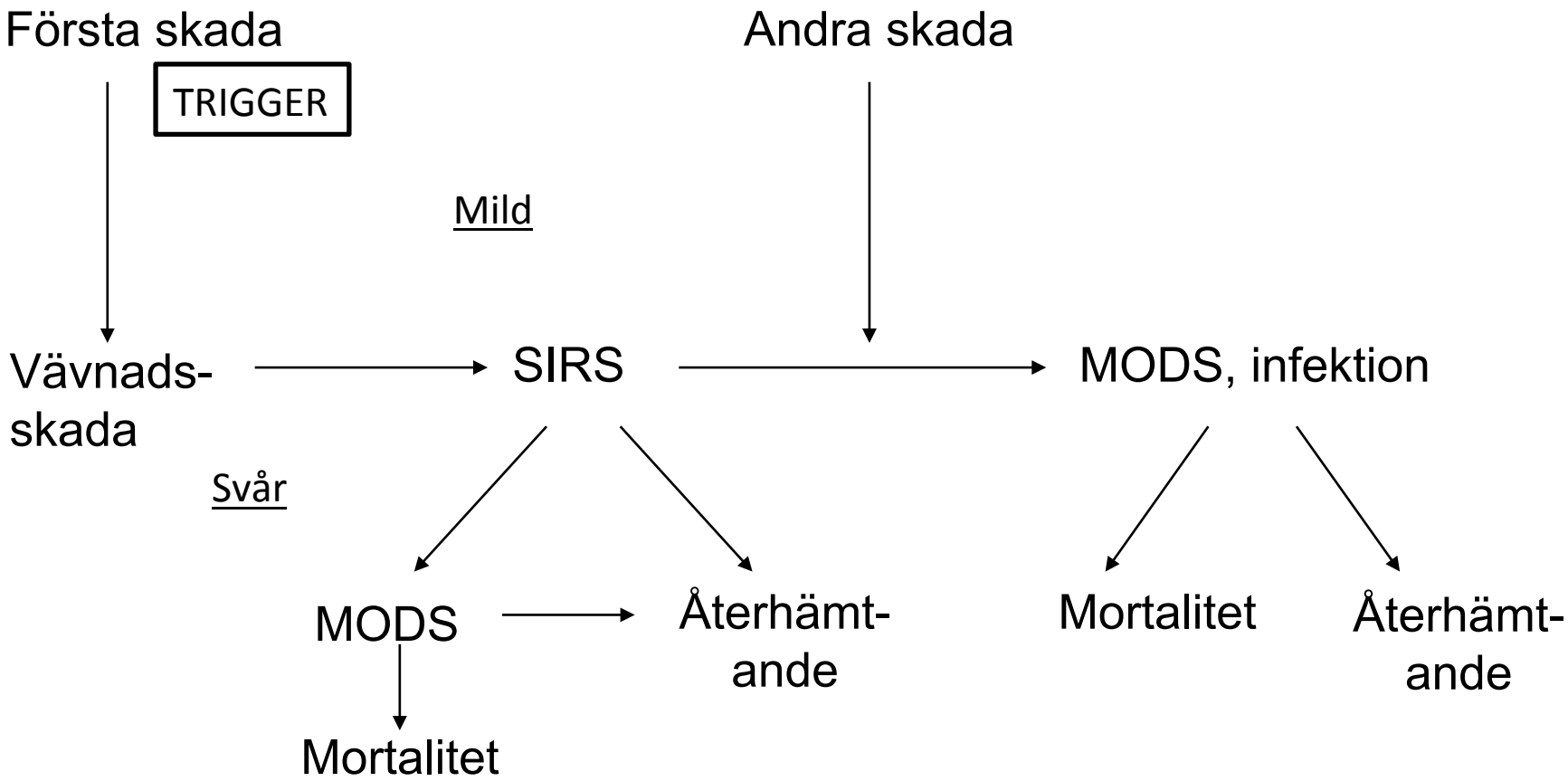
Increasing Incidence of Acute Pancreatitis at an American Pediatric Tertiary Care Center: Is Greater Awareness Among Physicians Responsible?
Morinville, Veronique; Barmada, M; Lowe, Mark; MD, PhD

Pancreas. 39(1):5-8, January 2010.
DOI: 10.1097/MPA.0b013e3181baac47

FIGURE 2 . Calculated incidence of first episode of AP at the CHP between 1993 and 2004. A strongly positive trend was demonstrated, with a regression coefficient r = 0.9132 and correlation coefficient r2 = 0.8339.

MEKANISMER OCH PATOFYSIOLOGI

Förloppet vid akut pankreatit



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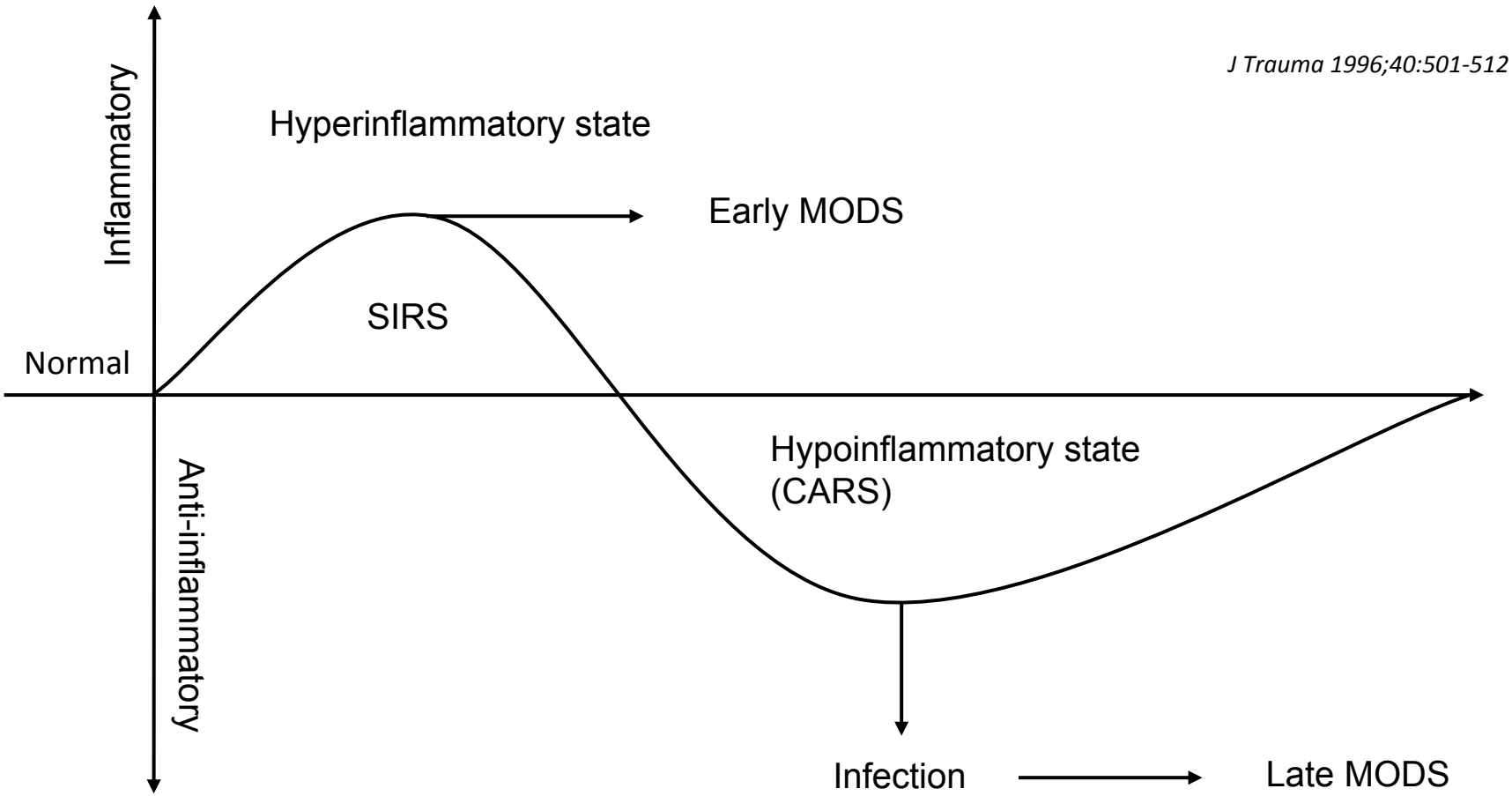
Akut inflammatoriskt svar efter kirurgiskt trauma och kritisk sjukdom



PANKREATIT INOM BARNONKOLOGI

Aspariginase-associerad pankreatit i ALL-2008-protokoll

bjh research paper

Asparaginase-associated pancreatitis in children with acute lymphoblastic leukaemia in the NOPHO ALL2008 protocol

Raheel A. Raja,[1] Kjeld Schmiegelow,[1, 9] Birgitte K. Albertsen,[2] Kaie Prunsild,[3] Bernward Zeller,[4] Goda Vaitkeviciene,[5] Jonas Abrahamsson,[6] Mats Heyman,[7] Mervi Taskinen,[8] Arja Harila-Saari,[7] Jukka Kanerva,[8] and Thomas L. Frandsen[1] on behalf of the Nordic Society of Paediatric Haematology and Oncology (NOPHO) group

[1]*Department of Paediatric and Adolescent Medicine, University Hospital Rigshospitalet, Copenhagen, Denmark,* [2]*Department of Paediatrics, Aarhus University Hospital Skejby, Aarhus, Denmark,* [3]*Department of Oncohaematology, Tallinn Children's Hospital, Tallinn, Estonia,* [4]*Department of Paediatrics, Oslo University Hospital, Oslo, Norway,* [5]*Clinic of Children's Diseases, Faculty of Medicine, Vilnius University, Vilnius, Lithuania,* [6]*Department of Clinical Sciences, Queen Silvia's Children's Hospital, Gothenburg, Sweden,* [7]*Department of Woman and Child Health, Karolinska Institutet, Stockholm, Sweden,* [8]*Children's Hospital, Helsinki University Central Hospital, University of Helsinki, Helsinki, Finland and* [9]*Faculty of Medicine, Institute of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark*

Summary

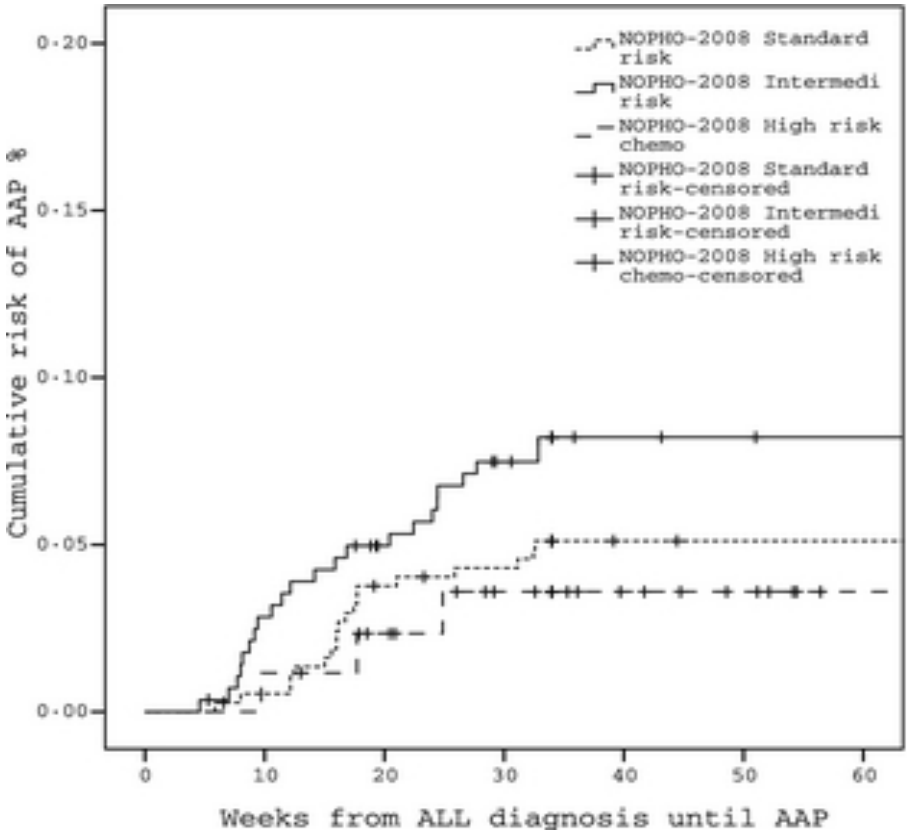
L-asparaginase is an important drug in the treatment of childhood acute lymphoblastic leukaemia (ALL). Treatment is associated with several toxicities, including acute pancreatitis. Clinical course, presentation, re-exposure to L-asparginase after pancreatitis and risk of recurrent pancreatitis within an asparaginase-intensive protocol has been poorly reported. Children (1–17 years) on the ongoing Nordic Society of Paediatric Haematology and Oncology (NOPHO) ALL2008 protocol with asparaginase-associated pancreatitis (AAP) diagnosed between 2008 and 2012 were identified through the online NOPHO ALL toxicity registry. NOPHO ALL2008 includes eight or 15 doses of intramuscular pegylated L-asparginase (PEG-asparaginase) 1000 iu/m^2/dose at 2–6 weeks intervals, with a total of 30 weeks of exposure to PEG-asparaginase (clinicaltrials.gov no: NCT00819351). Of 786 children, 45 were diagnosed with AAP with a cumulative risk of AAP of 5·9%. AAP occurred after a median of five doses (range 1–13), and 11 d (median) from the latest administration of PEG-Asparaginase. Thirteen patients developed pseudocysts (30%) and 11 patients developed necrosis (25%). One patient died from pancreatitis. Twelve AAP patients were re-exposed to L-asparginase, two of whom developed mild AAP once more, after four and six doses respectively. In conclusion, re-exposure to PEG-asparaginase in ALL patients with mild AAP seems safe.

Keywords: L-asparaginase, leukaemia, pancreatitis, toxicity, risk factors.

Omfattning AP i ALL-protokoll

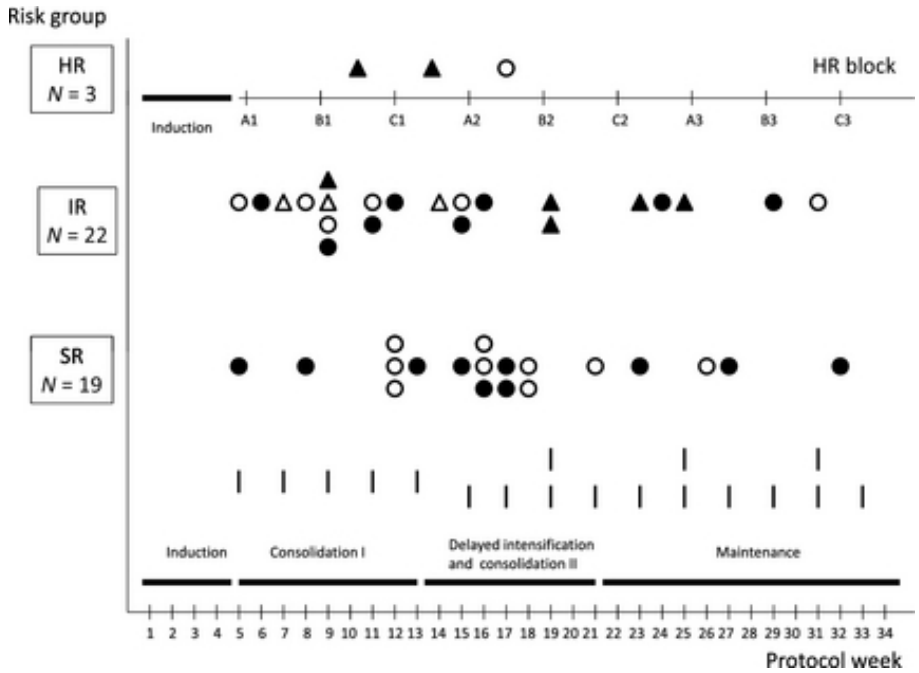
- Metoder
  - 2008-2012; n 789 patienter
  - Incidens AP **5,9%**
  - Insjuknande **11** d efter given inf.
  - RCT 8 jmf med **14** st aspariganase inj, 30 st veckors exponering
  - Ingen annan tydlig riskfaktor, prednisolon?

Asparaginase-associated pancreatitis in children with acute lymphoblastic leukaemia in the NOPHO ALL2008 protocol



British Journal of Haematology
Volume 165, Issue 1, pages 126-133, 15 JAN 2014 DOI: 10.1111/bjh.12733
http://onlinelibrary.wiley.com/doi/10.1111/bjh.12733/full#bjh12733-fig-0001

Asparaginase-associated pancreatitis in children with acute lymphoblastic leukaemia in the NOPHO ALL2008 protocol



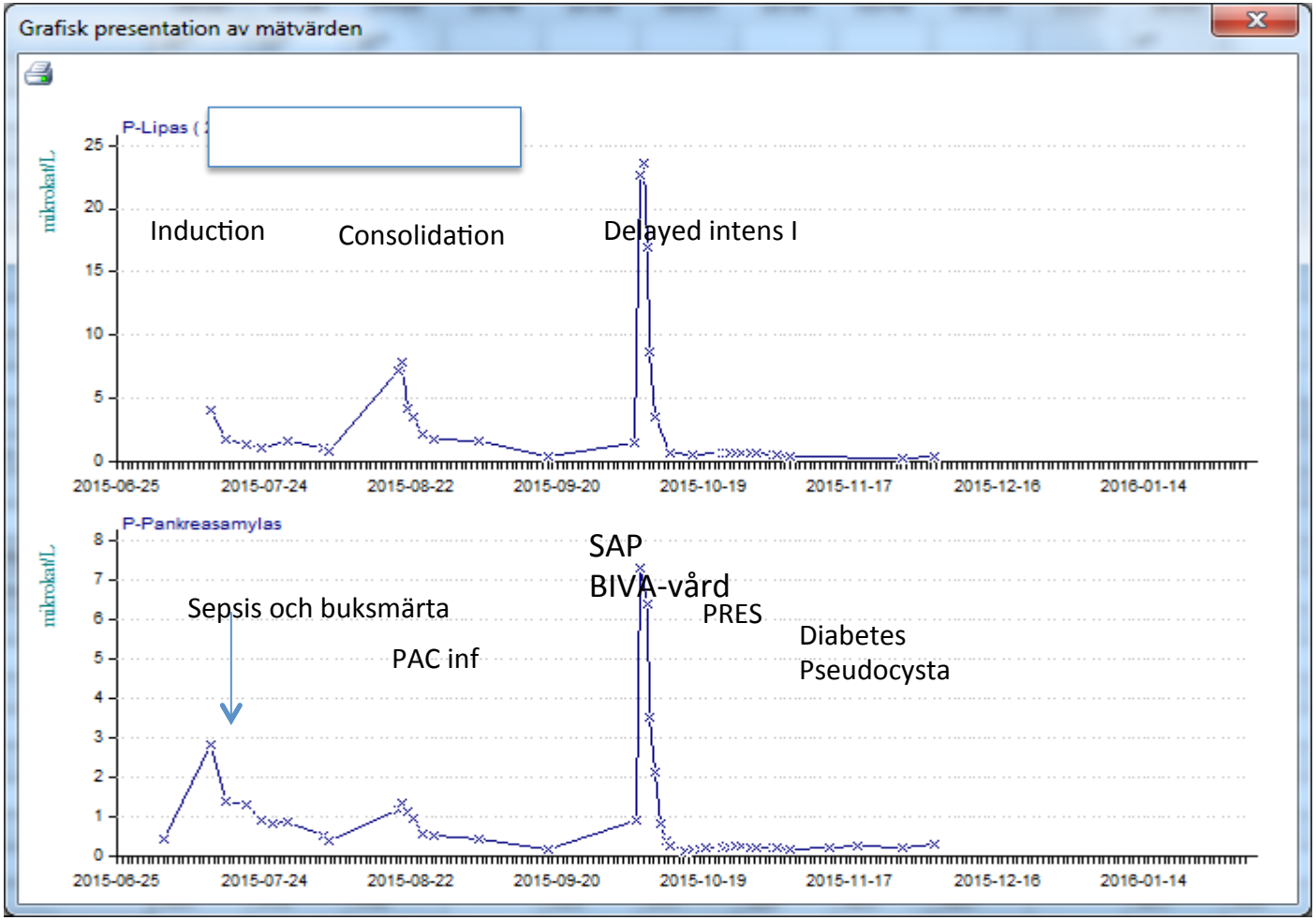
British Journal of Haematology
Volume 165, Issue 1, pages 126-133, 15 JAN 2014 DOI: 10.1111/bjh.12733
http://onlinelibrary.wiley.com/doi/10.1111/bjh.12733/full#bjh12733-fig-0002

FALL: SVÅR AKUT PANKREATIT

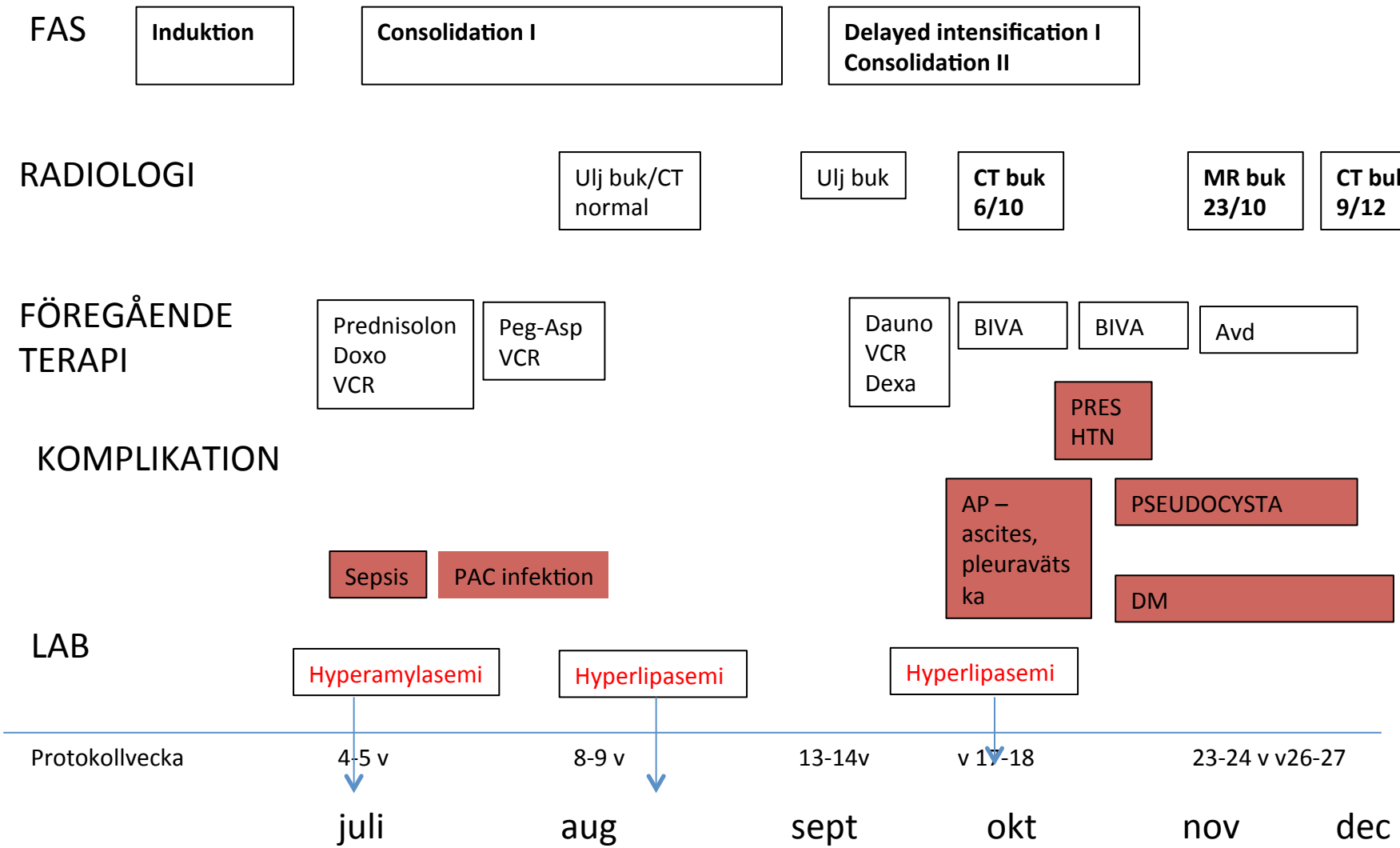
13-årig flicka

- Debuterar med anemi och svimning
- Tid väs frisk
- Diagnos sommar 2015 och start induktion 25 juni
- Behandlas enligt ALL-2008 IR (hyperdiploid)
- Randomiseras till standardbehandling av Peg-ASP

Amylas- och lipasvärden i relation till symtom och behandlingsfas



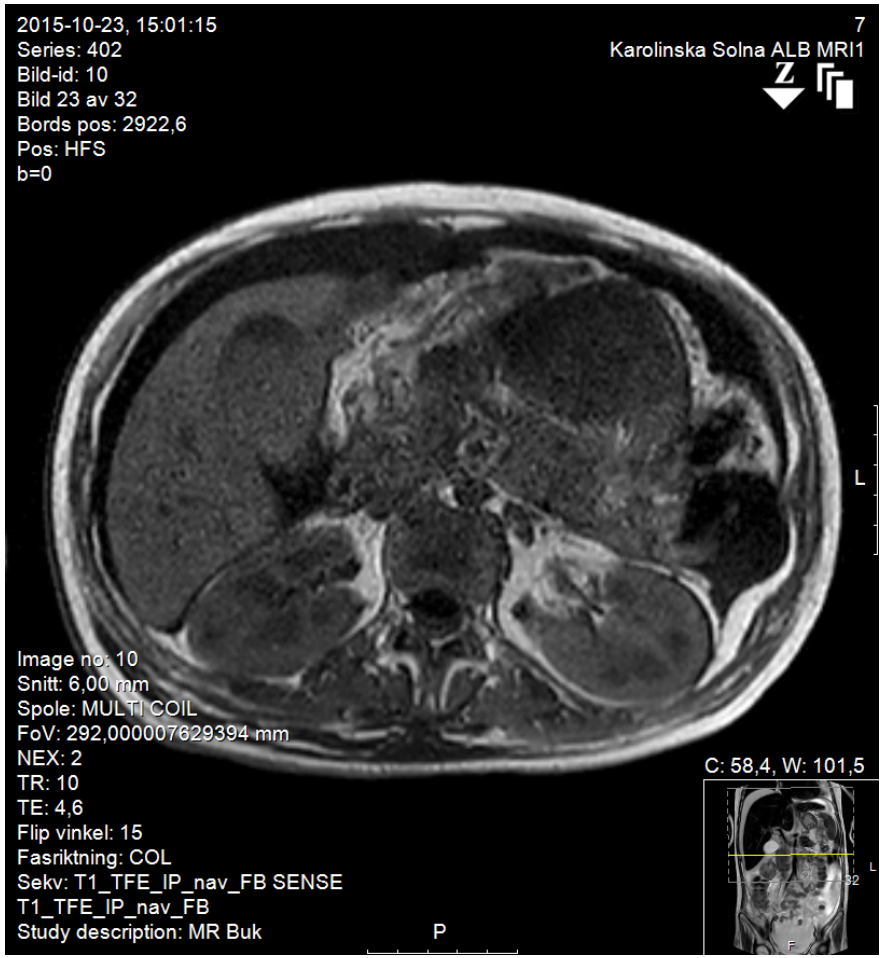
13-årig flicka med ALL, diagnos juni 2015



CT buk 2015-10-06

Pleuravätska

Acidos och hypotension

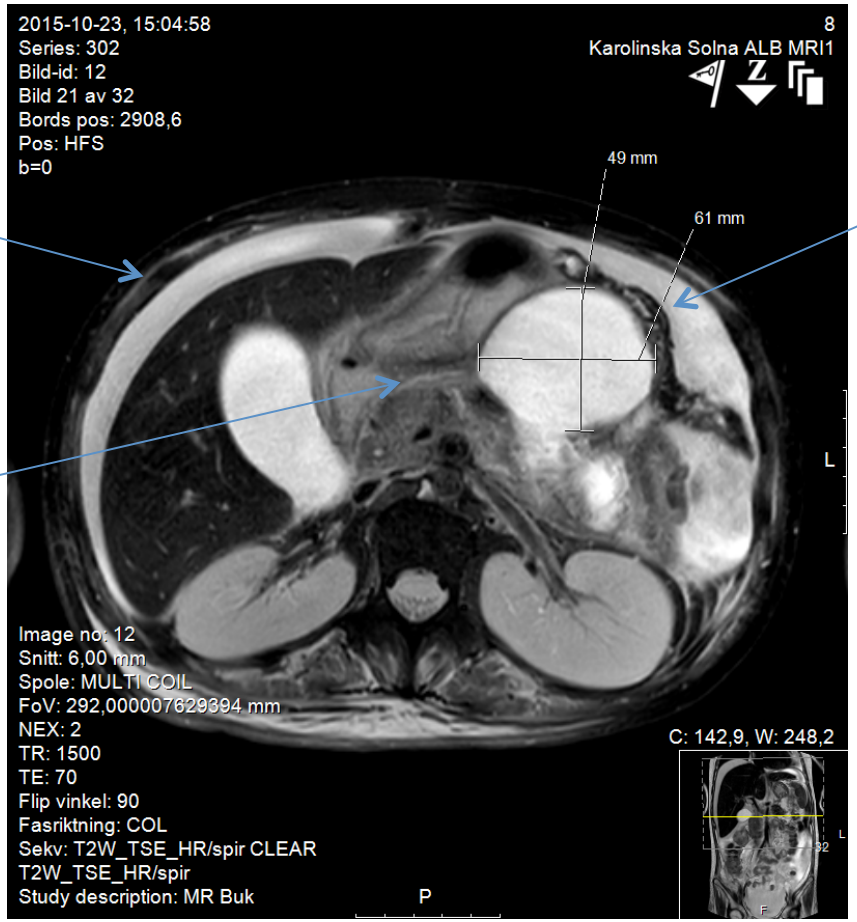


Inflammation och ödem

MR buk 2015-10-23

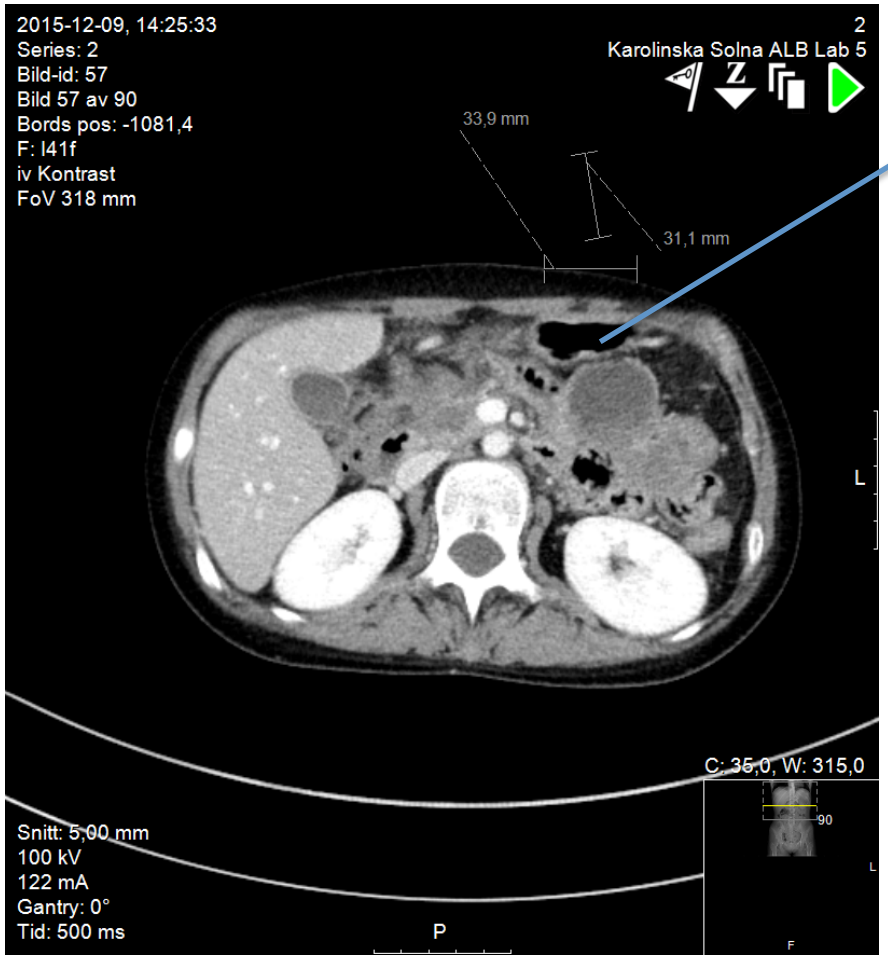
Pleuravätska

Ödem och inflammation



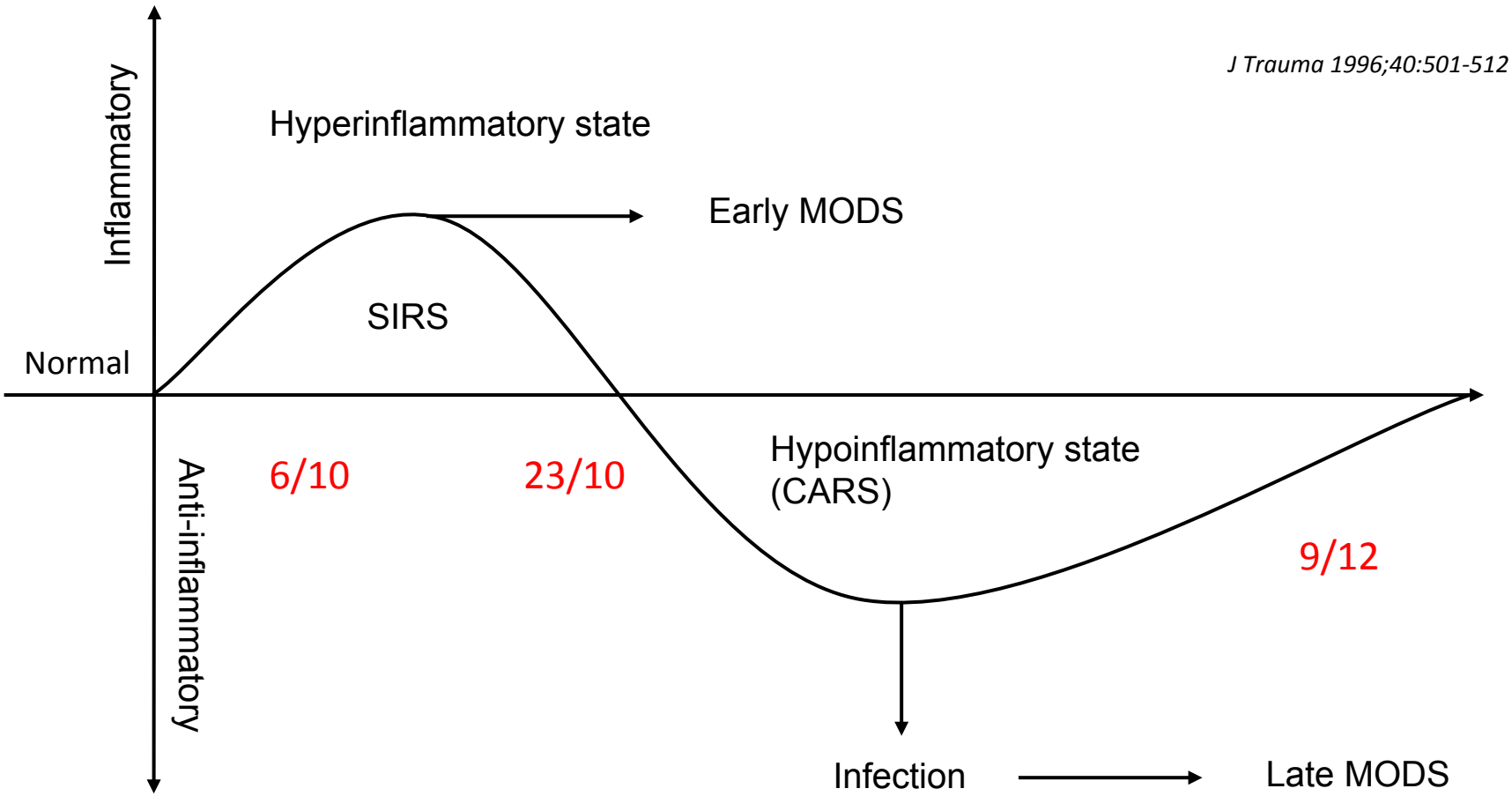
Pseudocysta

DT buk 2015-12-09



Pseudocysta

Akut inflammatoriskt svar efter kirurgiskt trauma och kritisk sjukdom



Frågor kring detta fall

- V-sond?
- TPN?
- Vad orsakade pankreatiten?
- När var den första episoden?
- När dränera absess/cysta?
- När sätta ut PEG-asp?

HANDLÄGGNING OCH RIKTLINJER

Guidelines enligt IAP/APA

- Ventrikel- alt jejunalsond?
- Pseudocysta?
- Radiologi?
- När sätta ut PEG-asp efter re-challenge eller direkt?

- Rekommenderas tidigt och även vid svår akut pankreatit
  - Förkortar vårdtid
- Konservativ, men dränage om infekterad eller kliniskt försämrad
  - Ultraljud, upprepas
  - CT efter 72h om diagnostisk osäker eller bedöma svårighetsgrad
  - MR förlopp och kontroll av cysta

Handläggning enligt Scandinavian Guidelines for acute pancreatitis

- Ingen specifik medicinsk intervention
  - Proteasinhibitorer, somatostatinanaloger, allopurinol

- Mild akut pankreatit
  - Ingen specifik medicinsk behandling
  - Adekvat vätskeersättning
  - Smärtstillande
  - Oral/enteral feeding förkortar sjukhusvistelse – när buksmärta och inflammatoriska markörer avtar

Handläggning av svår akut pankreatit

- Persisterande tecken på organsvikt efter 48 h
- Minimera ischemi/reperfusion genom vätsketerapi kan påverka sjukdomsförloppet
- Profylaktisk antibiotika kan inte rekommenderas akut(svår/ nekrotiserande) pankreatit

HUR ORSAKAR PEG-ASP PANKREATIT OCH HUR AVGÖRA ETIOLOGI?

L-Asparaginase-Induced Pancreatic Injury is Associated with an Imbalance in Plasma Amino Acid Levels

Kei Minowa,[1] *Mitsuyoshi Suzuki,*[1] *Junya Fujimura,*[1] *Masahiro Saito,*[1] *Katsuyoshi Koh,*[2] *Akira Kikuchi,*[3] *Ryoji Hanada*[2] and *Toshiaki Shimizu*[1]

1 Department of Pediatrics, Juntendo University School of Medicine, Tokyo, Japan
2 Division of Hematology and Oncology, Saitama Children's Medical Center, Saitama, Japan
3 Department of Pediatrics, Teikyo University, Tokyo, Japan

Förlopp av aminosyror i plasma veckor efter PEG-asp

Table I. Time course of plasma amino acid levels

Amino acid	Level before ASNase injection [days 13–15] (nmol/mL)	Level after ASNase injection (nmol/L)					
		Week 1 [day 22]	Week 2 [day 29]	Week 3 [day 36]	Week 4 [days 41–43]	Week 5 [days 48–50]	Week 7 [days 64–66]
Aspartic acid	2.7 ± 2.2	8.4 ± 4.7**	9.9 ± 6.4**	12.6 ± 9.5**	13.2 ± 8.4**	6.1 ± 5.9	3.2 ± 3
Asparagine	46.2 ± 13.9	2.3 ± 8.0**	0 ± 0**	2.6 ± 7.7**	7.5 ± 15.3**	36.7 ± 14.3**	37.1 ± 8.6**
Glutamic acid	58.4 ± 20.1	160.5 ± 123.7**	160.4 ± 109.1**	190.1 ± 148.5**	90.3 ± 46.0	69.0 ± 23.3	50.0 ± 14.0
Glutamine	453.8 ± 89.3	294.3 ± 124.7**	295.9 ± 145.6**	294.9 ± 162.8**	380.2 ± 103.2**	462.8 ± 107.9	464.6 ± 82.6
Threonine	124.6 ± 44.3	148.4 ± 96.8	216.9 ± 96.8**	221.4 ± 110.0**	136.4 ± 69.2	106.9 ± 46.6	103.8 ± 33.0
Cystine	37.2 ± 10.0	33.5 ± 8.0	32.9 ± 8.7	32.2 ± 10.5*	37.1 ± 9.5	42.3 ± 9.4	40.8 ± 8.1*
Methionine	22.4 ± 7.8	20.3 ± 6.7	22.9 ± 8.3	24.3 ± 9.2	18.1 ± 7.5	20.6 ± 6.9	19.0 ± 5.4
Lysine	189.1 ± 58.1	137.1 ± 42.3**	138.5 ± 39.1**	168.7 ± 76.5	156.7 ± 57.5*	160.7 ± 52.3*	154.3 ± 42.2*
Arginine	75.4 ± 34.7	48.8 ± 21.9**	51.4 ± 21.4**	63.3 ± 30.0*	57.1 ± 23.4**	60.7 ± 33.5*	56.2 ± 22.7**
Citrulline	17.6 ± 7.0	18.2 ± 6.8	19.9 ± 8.7	19.4 ± 9.0	17.8 ± 7.7	20.2 ± 4.8	16.5 ± 6.3

ASNase = L-asparaginase; * $p < 0.05$, ** $p < 0.01$ versus levels before the ASNase injection.

Förlopp av enzymnivåer efter PEG-asp

Table II. Time course of serum pancreatic enzyme, pancreatic protease inhibitor, and rapid turnover protein levels

Parameter	Level before ASNase injection [days 13–15]	Level after ASNase injection					
		Week 1 [day 22]	Week 2 [day 29]	Week 3 [day 36]	Week 4 [days 41–43]	Week 5 [days 48–50]	Week 7 [days 64–66]
Amylase (IU/L)	60.6±27.6	56.0±28.5	55.3±25.4	52.1±21.3	51.4±22.5	55.2±22.2	55.7±39.1
Lipase (IU/L)	18.7±8.2	16.2±4.6	19.1±8.9	20.7±9.0	21.3±6.4	23.8±8.1	29.2±35.7
Trypsin (ng/mL)	285.7±142.3	326.5±131.2	330±133.5**	371.3±157.5**	362.2±202.9**	306.4±170.2	324.1±470.4
Pancreatic protease inhibitors							
PSTI (ng/mL)	10.7±4.9	35.7±24.8	83.1±83.6**	74.9±47.8**	53.3±48.3**	12.2±7.0	13.2±10.0
α1-AT (mg/dL)	139.3±43.3	120±33.8	113.5±31.5	131.6±48.6	168.6±50.2**	145.6±54.8	148.7±40.5
α2-M (mg/dL)	271.1±45.4	263.0±51.8	250.3±42.7	265.5±55.8	302.1±69.8	354.0±60.4**	346.5±75.7**
Rapid turnover proteins							
PA (mg/dL)	33.8±7.8	23.0±7.0**	18.7±7.2**	25.3±11.4**	26.8±11.4**	22.3±7.0**	23.5±8.1**
RBP (mg/dL)	4.3±1.0	3.1±1.2**	2.6±1.0**	4.3±4.4**	4.2±2.0	3.2±0.9**	3.4±1.3**
Tf (mg/dL)	233.3±46.4	164.9±40.3**	120.7±34.5**	120.7±41.2**	154.2±50.0**	208.1±30.8**	172.6±24.1**

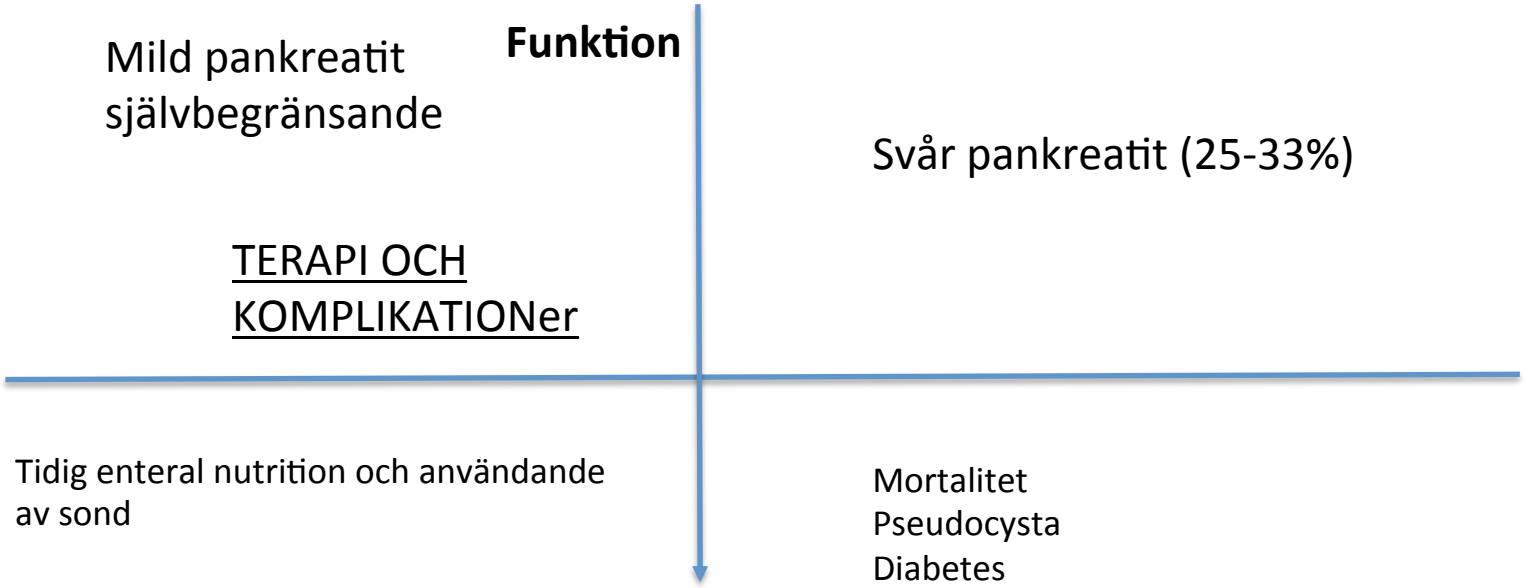
α1-AT = α1-antitrypsin; **α2-M** = α2-macroglobulin; **ASNase** = L-asparaginase; **PA** = prealbumin; **PSTI** = pancreatic secretory trypsin inhibitor; **RBP** = retinol-binding protein; **Tf** = transferrin; * $p < 0.05$, ** $p < 0.01$ versus levels before the ASNase injection.

SAMMANFATTNING

Akut pankreatit

Predisponerande faktorer
ger förhöjd baseline-risk
Subklinisk pankreatit med
peg-asp i kombination med
andra riskfaktor som
läkemedel och samsjuklighet

Trigger
Enzymaktivering
Lokal skada
Systemisk reaktion



Tack!

GREY TURNER[1] SIGN **CULLEN[2] SIGN** **FOX[3] SIGN**

1. Named after British surgeon George Grey Turner(1877-1951)

2. Named for Thomas Stephen Cullen (1869-1953), Canadian gynecologist who first described the sign in ruptured ectopic pregnancy in 1916

3.Named after George Henry Fox(1846-1937), American dermatologist