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Rare Kidney Disease
Reference Network

Non-infectious complications of PD in children

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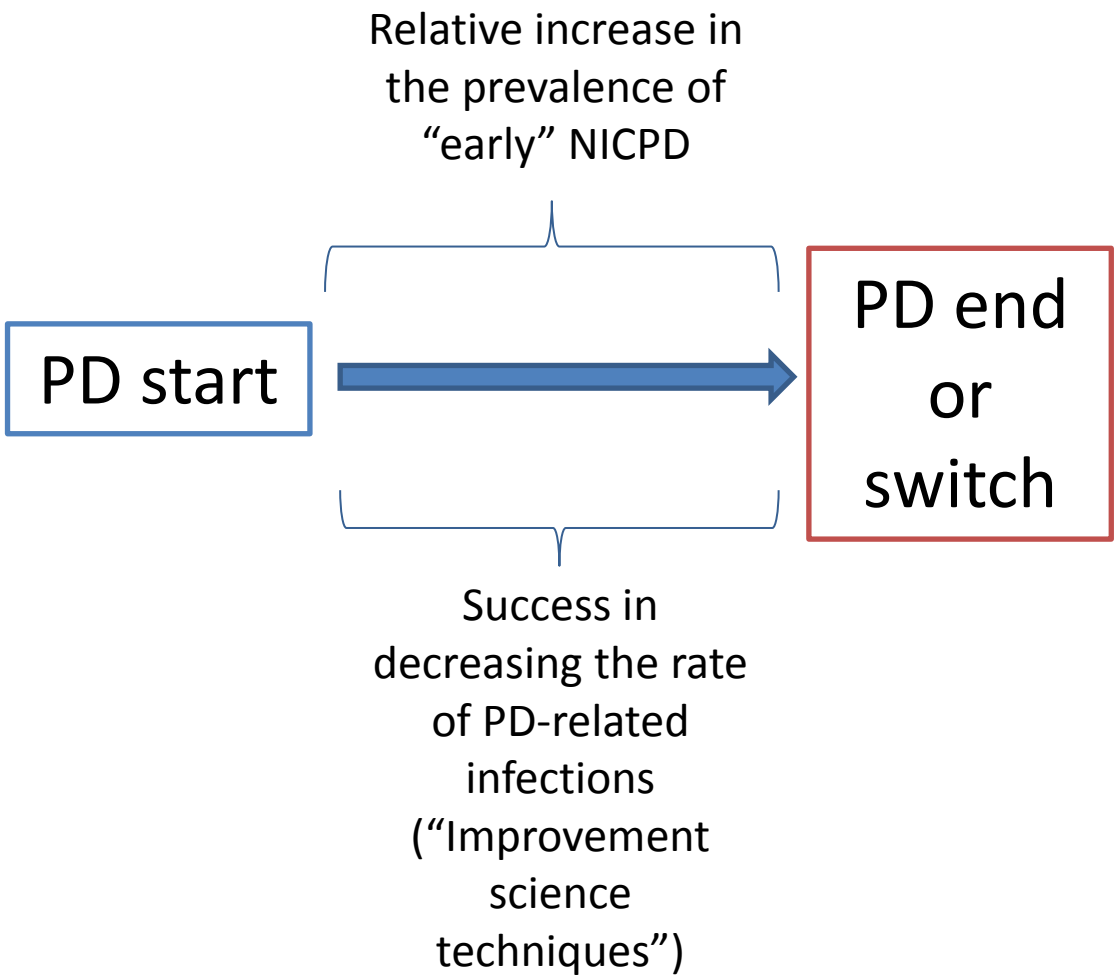
Frequency of Peritonitis Episodes by Era

	N° of Episodes	Years of FU	Annualized Rates		Expected months between infections	
			Rates	95% CI	Months	95% CI
Total	4487	7596	0.59	(0.57-0.61)	20.3	(19.7-20.9)
Year of Dialysis Initiation						
• 1992-1997	2555	3282	0.78	(0.75-0.81)	15.4	(14.8-16.0)
• 1998-2003	1215	2200	0.55	(0.52-0.58)	21.7	(20.6-23.0)
• 2004-2009	534	1471	0.36	(0.33-0.39)	33.1	(30.5-36.1)
• 2010-2016	183	644	0.28	(0.24-0.33)	42.2	(36.9-49.4)

NAPRTCS

Non-Infectious Complications of PD (NICPD)



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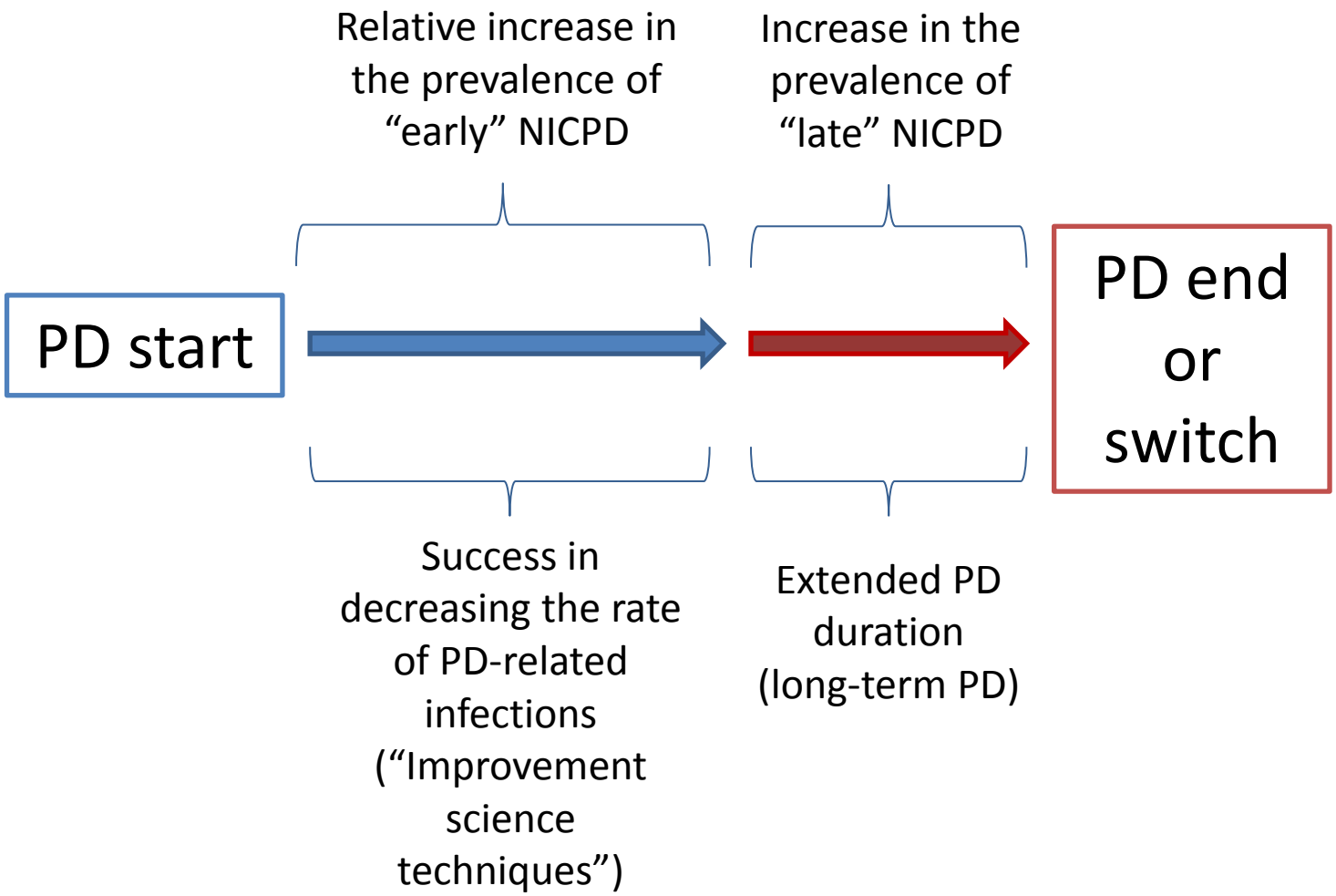

NICPD

1. **Mechanical:**
   - Catheter-related
   - Related to the increase in intraabdominal pressure due to dialysate:
     - Hernia
     - Pleural leak
     - Back pain
     - Gastroesophageal reflux and delayed gastric emptying

2. **Technique-related:**
   - Membrane/UFF failure:
     - Encapsulated Peritoneal Sclerosis
   - Metabolic effects of the absorption of glucose and its degradation products:
     - Hyperglicemia / hyperinsulinemia
     - Hypertriglyceridemia
   - “Other complications”:
     - Pancreatitis
     - Hemoperitoneum
     - Ischemic colitis and necrotizing enterocolitis

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Access for paediatric dialysis

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NICPD

1. **Mechanical:**
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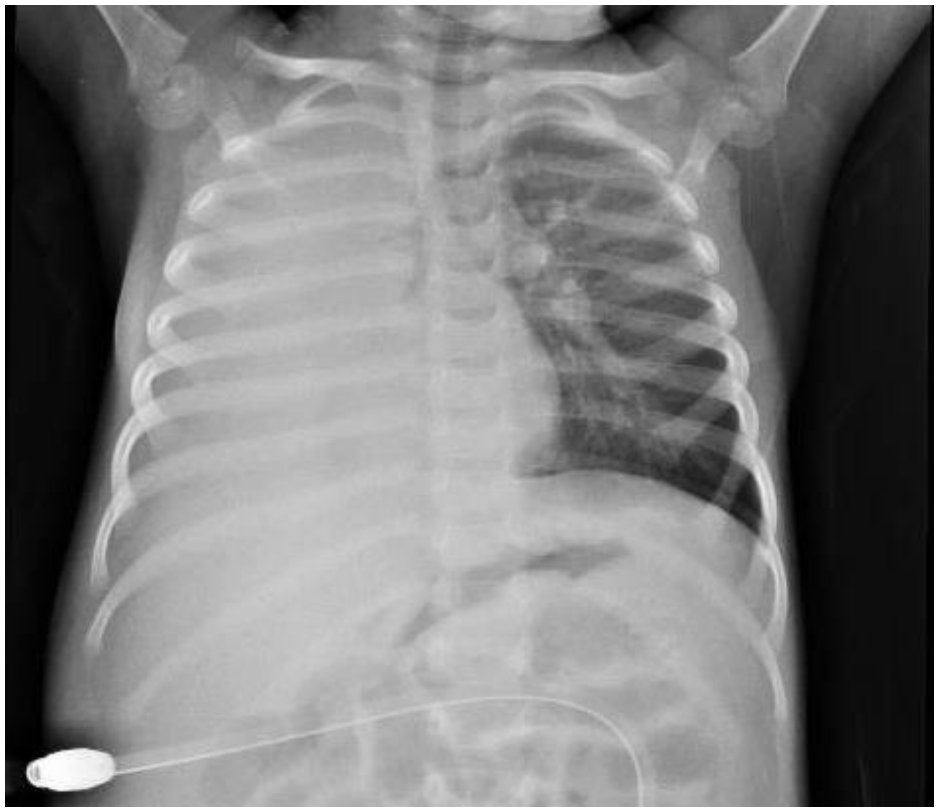
Hydrothorax

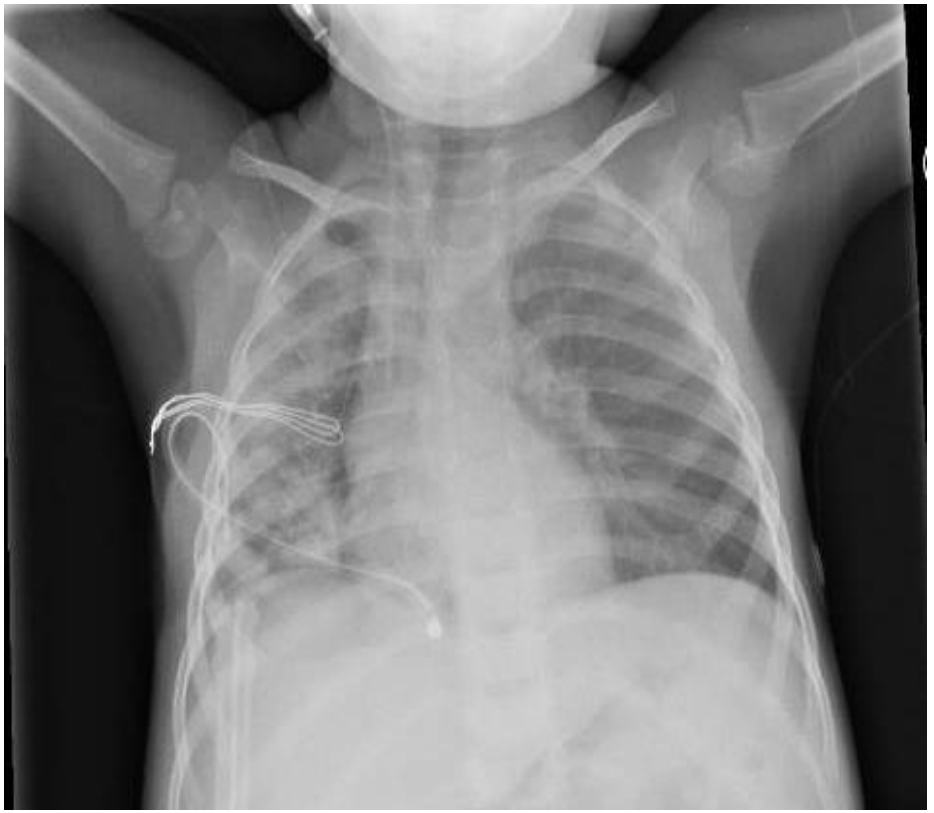
- Pleuro-peritoneal and pericardio-peritoneal fistula.
- The pleural to peritoneal connection is almost always on the **right side**:
  - More common tendinous defects on the right
  - Ascending peristalsis of the right colon sweeping pelvic fluids into the right upper quadrant
  - Piston-like action of the liver during diaphragm contraction, driving fluid through the diaphragm pores

Pathophysiology

- Pleuro-peritoneal pressure gradient: negative intrathoracic pressure combined with an increased intra-abdominal pressure caused by PD fluid may open small defects in the diaphragm (i.e. ARPKD)
- Congenital diaphragmatic defects (i.e. WT1)

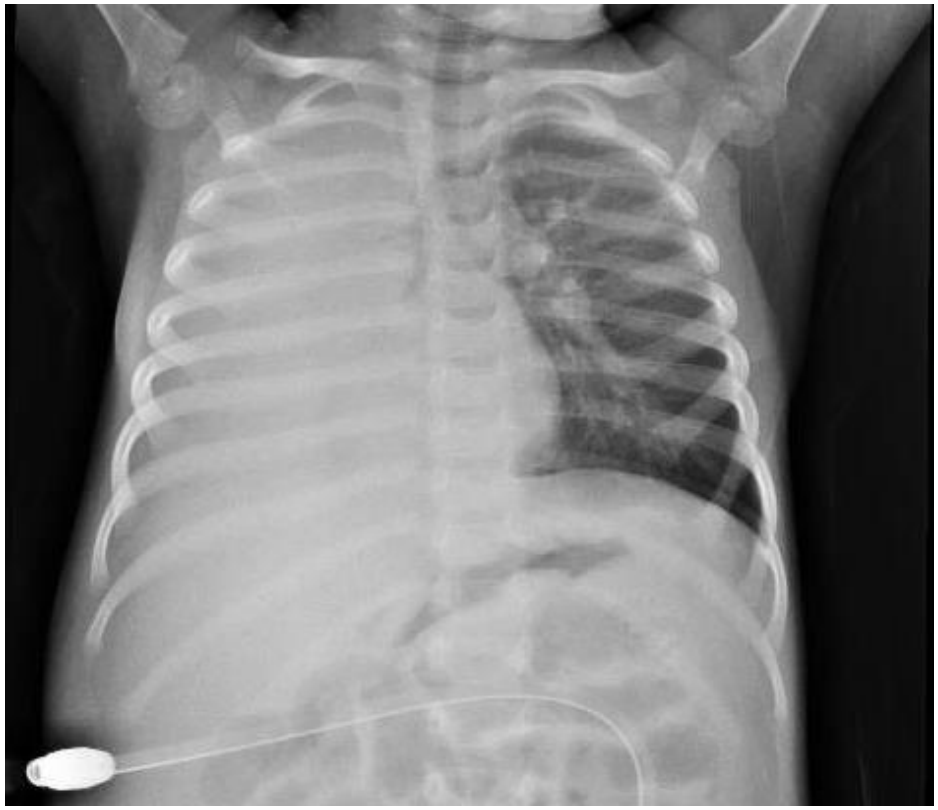
Pleuro-peritoneal fistula





X-ray courtesy of Andrea Pasini, MD

Pleuro-peritoneal fistula

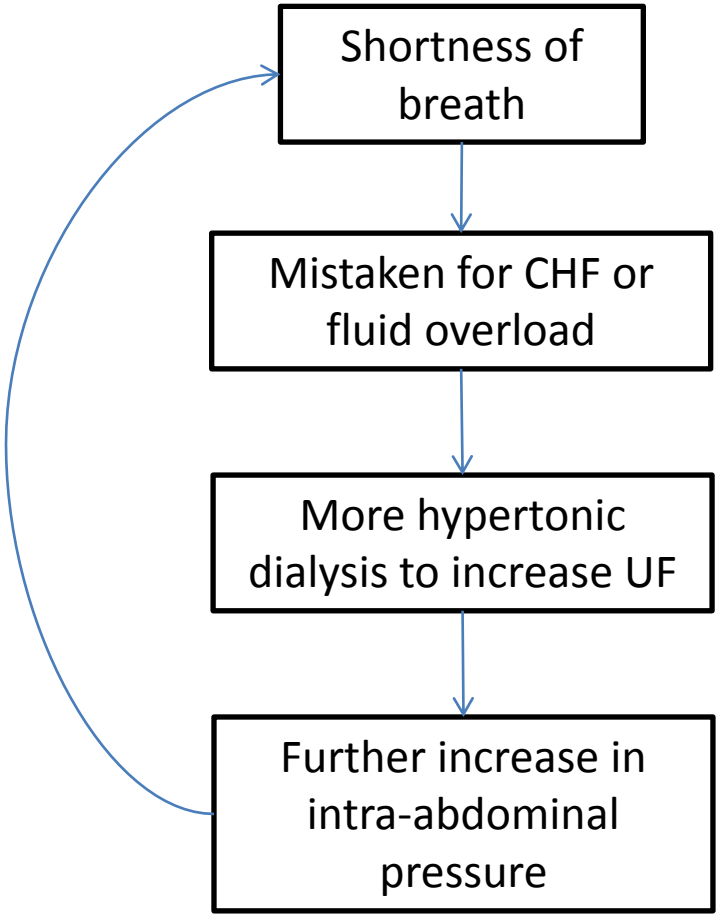


Diagnosis

Demonstration of PD fluid in the pleural space:

- Thoracentesis (“sweet hydrothorax”)
- Thoracentesis with peritoneal methylene blue instillation
- Peritoneal contrast radiography*
- Peritoneal contrast scintigraphy*
- Peritoneal contrast MRI*

Clinical features



Pediatr Nephrol (2015) 30:2021–2027
DOI 10.1007/s00467-015-3137-z

ORIGINAL ARTICLE

Pleuro-peritoneal or pericardio-peritoneal leak in children on chronic peritoneal dialysis—A survey from the European Paediatric Dialysis Working Group

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Abstract

Background Pleural or pericardial effusions secondary to pleuro-peritoneal fistula (PPF) and pericardio-peritoneal fistula (PcPF) are rare but serious complications of peritoneal dialysis (PD).

Methods We conducted a 10-year survey across all participating centres in the European Paediatric Dialysis Working Group to review the incidence, diagnostic techniques, therapeutic options and outcome of children on chronic PD with PPF and/or PcPF.

Results Of 1506 children on PD there were ten cases (8 of PPF, 1 each of PcPF and PPF+PcPF), with a prevalence of 0.66 %. The median age at presentation was 1.5 [inter-quartile range (IQR) 0.4–2.4] years, and nine children were <3 years. The time on PD before onset of symptoms was 4.3 (IQR 1.3–19.8) months. Eight children had herniae and seven had abdominal surgery in the preceding 4 weeks. Symptoms at presentation were respiratory distress, reduced ultrafiltration and tachycardia. PD was stopped in all children; three were managed conservatively and thoracocentesis was performed in

Prevalence

- 15/15 centre responded
- **1506 children received chronic PD**
  (2580 patient-years on chronic PD)
- **10 children** developed PPF and/or PcPF
  - 8 PPF
  - 1 PcPF
  - 1 PPF and PcPF
- **Prevalence 0.66%**
  - PPF: 0.6%
  - PcPF: 0.13%
- 3.9 cases per 1000 patient-years on PD

Courtesy of Stephanie Dufek, MD

Patients demographics

Patient	Gender	Underlying diagnosis	Age at start of PD (months)	Age at presentation (months)	Time on PD at presentation (months)	Type of peritoneal leak	Side of PPF
1	M	CAKUT	123.6	129.3	5.7	PPF	Bilateral
2	M	Congenital nephrotic syndrome	28	28.2	0.2	PPF	R
3	M	CAKUT	0.4	5.3	4.9	PPF	R
4	M	Haemolytic uraemic syndrome	0.6	4.2	3.6	PPF	L
5	M	Congenital nephrotic syndrome	8.4	11.5	3.1	PPF	R
6	M	CAKUT, trisomy 21	0.2	33.8	33.6	PPF	R
7	F	ARPKD	3.3	4.2	0.9	PPF+PcPF	Bilateral
8	M	Congenital nephrotic syndrome	10.1	11.5	1.4	PPF	R
9	M	Prematurity, sepsis	7	24.3	17.3	PcPF	PcPF
10	M	Neonatal asphyxia	0.2	27.7	27.5	PPF	R

- 90% male
- Age at start of PD: Median 5.2 (0.3–14.6) months
- Age at presentation: Median 1.5 (0.4 – 2.4) years
  - **9/10 (90%) were < 3 years** and 5 (50%) < 1 year at presentation
- Time on PD at presentation: Median 4.3 (1.3 – 19.8) months
  - **7/10 (70%) on PD for ≤ 12 months**
- Predominantly right sided: 80%

Courtesy of Stephanie Dufek, MD

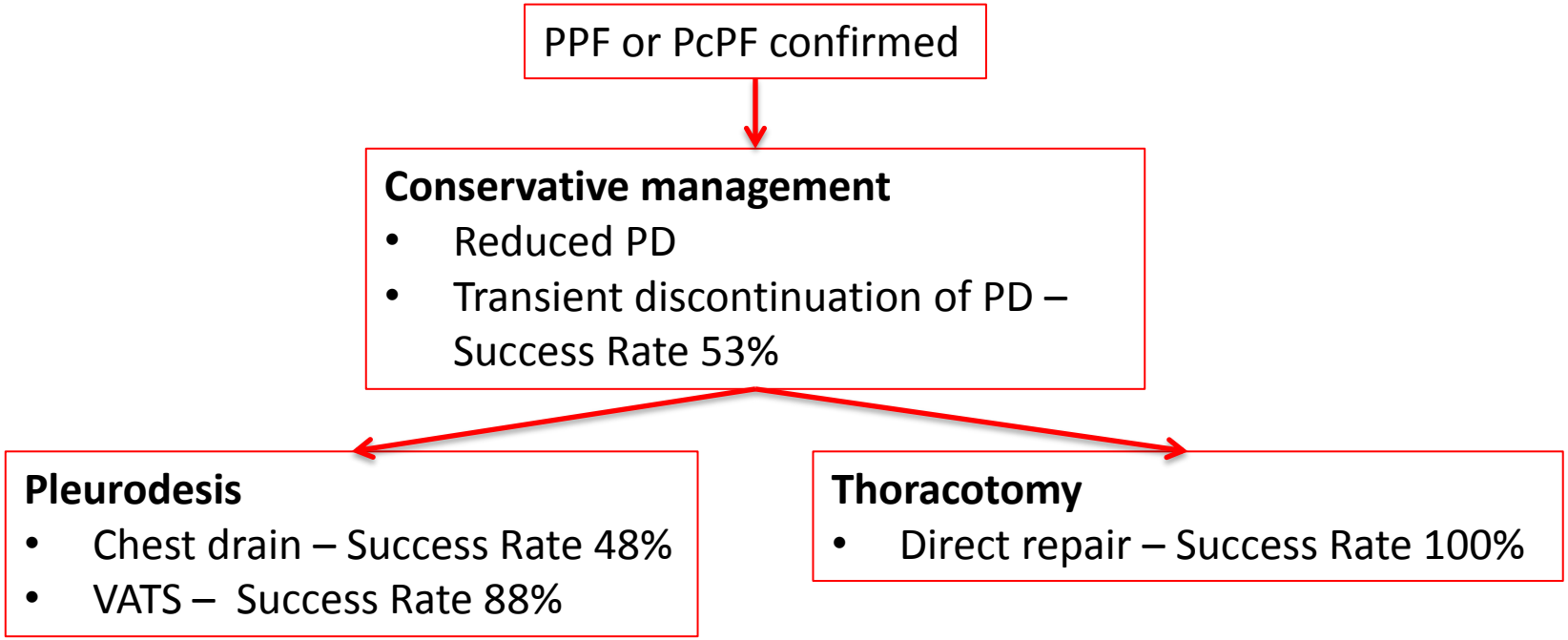
PD specifications

Patient	PD type	Type – dry day	Fill volume (ml/m^2 BSA)	Type of dialysate	Glucose concentration (%)	Total therapy time (hours)	Peritonitis episodes	Hernia
1	Tidal	No	1207	Balance	1.5	10	0	No
2	CCPD	No	368	Physioneal 35	2.3	22	0	Yes
3	CAPD	No	308	Physioneal 40	3.1 (mix)	24	3	Yes
4	CCPD	Yes	484	BicaVera	1.5	11.5	0	Yes-multiple
5	CCPD	No	714	BicaVera	1.5	24	0	Yes
6	CAPD	No	364	Balance	1.5	12	7	Yes
7	CAPD	No	714	BicaVera	2.3	24	0	Yes
8	CCPD	No	810	Physioneal 40	1.5	13	0	Yes
9	CCPD	Yes	587	Balance	1.5	6	3	Yes-multiple
10	CCPD	Yes	349	BicaVera	1.5	10	0	No

- 6 children (60%) were on CCPD and 7 (70%) had a day-time dwell
- Fill volume: median 535 (360 – 738) ml/m^2 BSA
- Hernia: 8/10 (80%)
  - Inguinal n = 5
  - Umbilical n = 2
  - Ventral abdominal hernia n = 2
- Previous “abdominal surgery”: 7/10 (70%)
  - median of 27 (18 – 41) days before onset

Courtesy of Stephanie Dufek, MD

Management



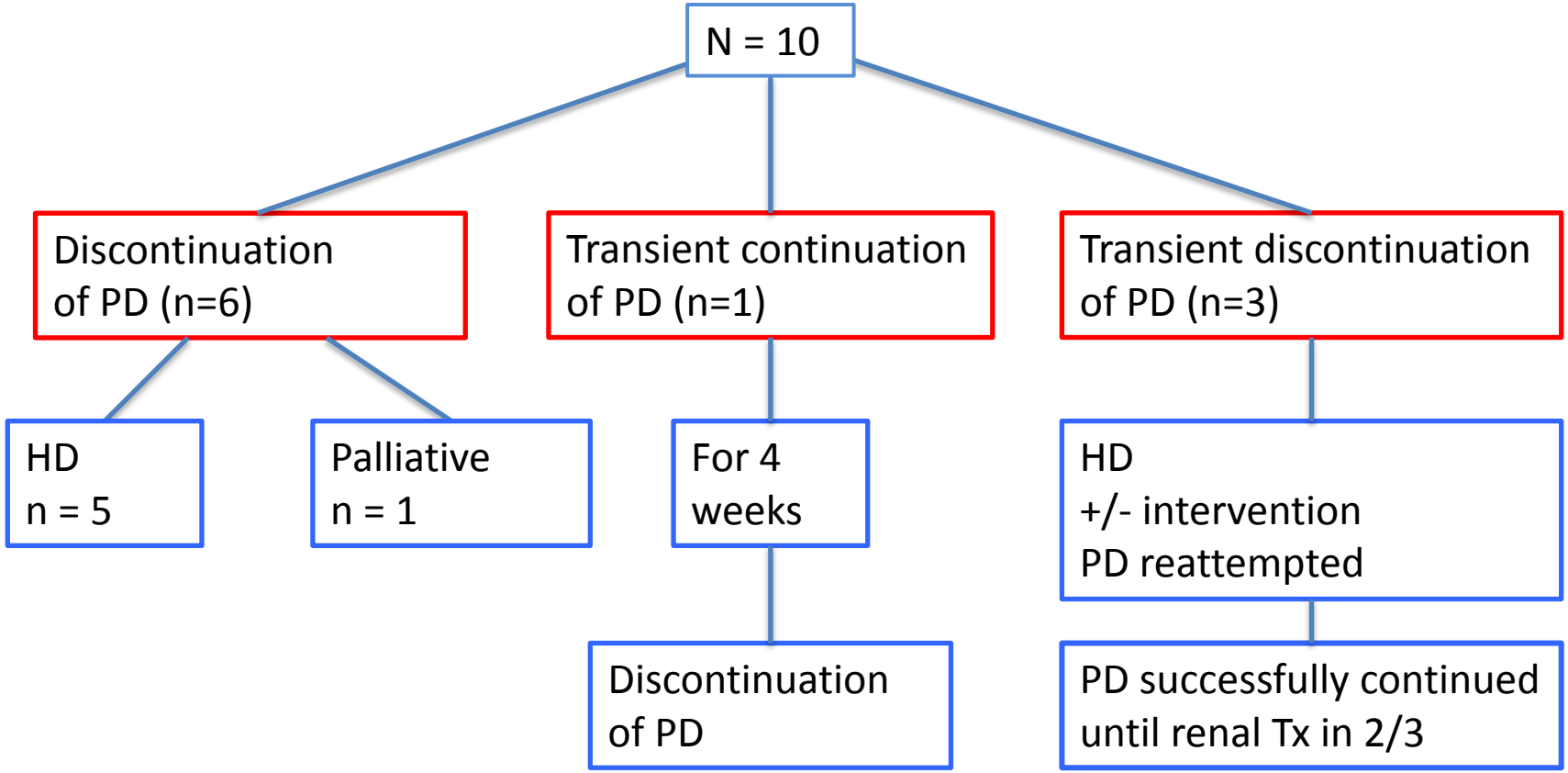
Chow KM et al. Perit Dial Int 2002;22:525-528.

Management

- PD interruption: 10/10
- Conservative management: 3/10
- Thoracentesis: 7/10
  - Pleurodesis: 3/10
    - Chest drain: 1/10
    - Video assisted thoracoscopic surgery (VATS): 2/10
    - Agents used: betadine, talc powder and fibrin glue

Courtesy of Stephanie Dufek, MD

Management and Outcome

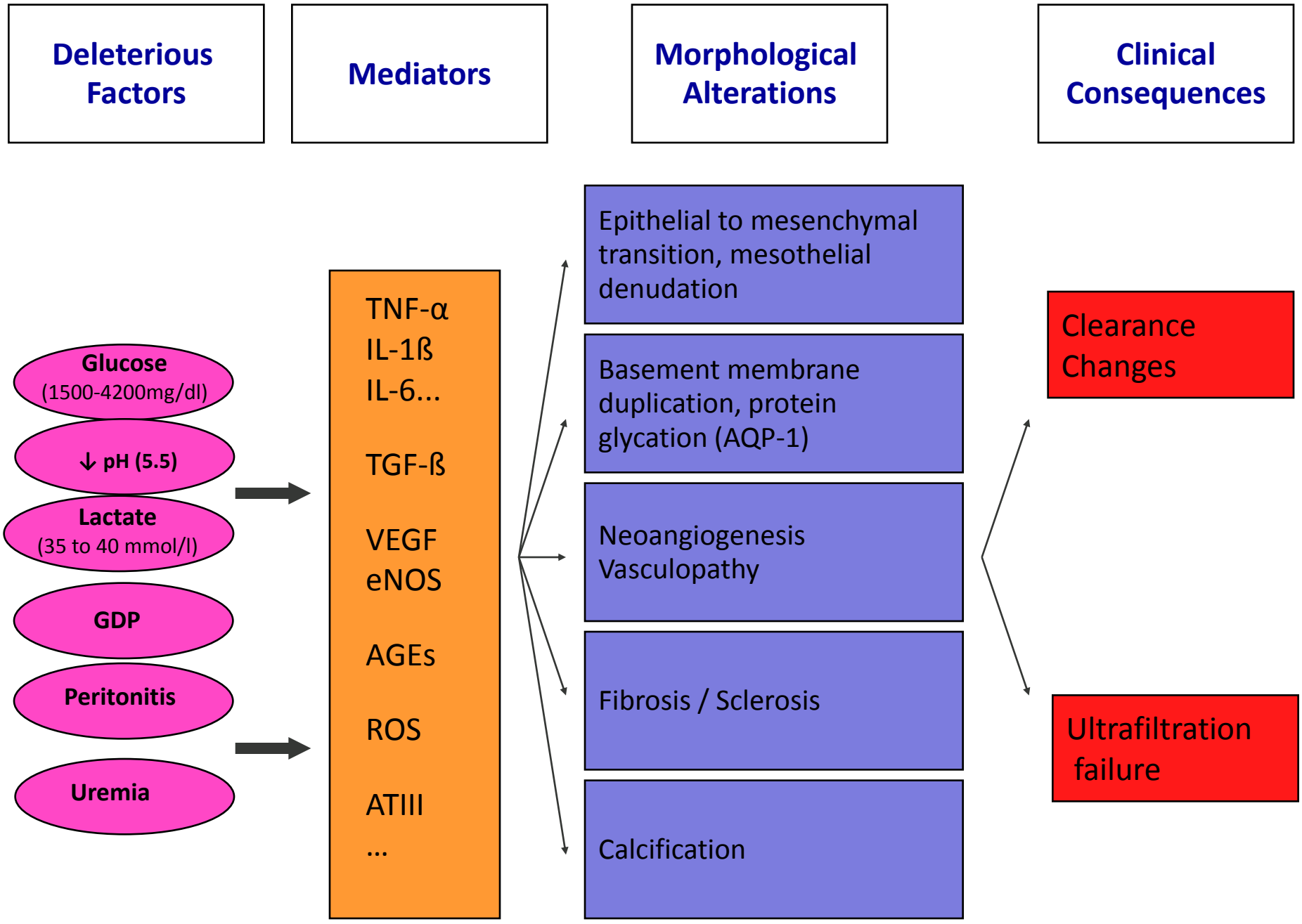


Courtesy of Stephanie Dufek, MD

Conclusion

- PPF and PcPF are rare in children on chronic PD
- Risk factors for PPF and PcPF development include age <3 years, preceding hernia and recent abdominal surgery
- All children required a change of dialysis modality to achieve complete resolution of the peritoneal leak

Courtesy of Stephanie Dufek, MD


Deleterious Factors
Mediators
Morphological Alterations
Clinical Consequences
Glucose (1500-4200mg/dl)
↓ pH (5.5)
Lactate (35 to 40 mmol/l)
GDP
Peritonitis
Uremia
TNF-α
IL-1ß
IL-6...
TGF-ß
VEGF
eNOS
AGEs
ROS
ATIII
...
Epithelial to mesenchymal transition, mesothelial denudation
Basement membrane duplication, protein glycation (AQP-1)
Neoangiogenesis Vasculopathy
Fibrosis / Sclerosis
Calcification
Clearance Changes
Ultrafiltration failure

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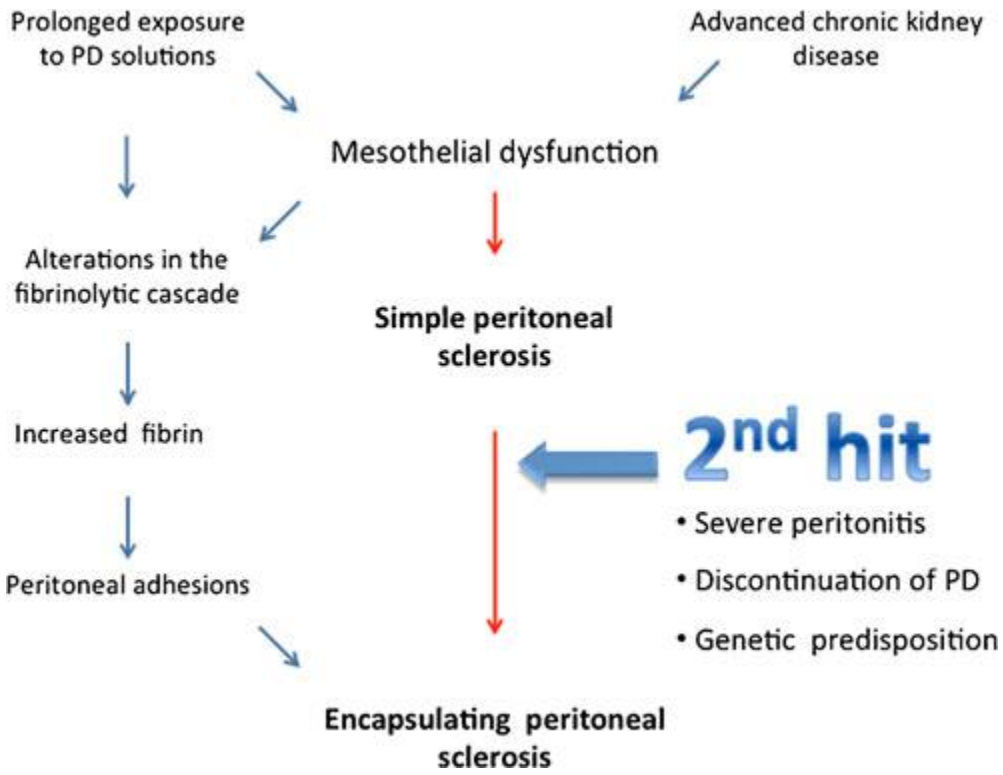
Optimizing PD in Children

Claus Schmitt

Centre for Pediatric and Adolescent Medicine
Heidelberg, Germany

Encapsulating Peritoneal Sclerosis



Stefanidis CJ & Shroff R. Pediatr Nephrol 2014;29(11):2093-103.

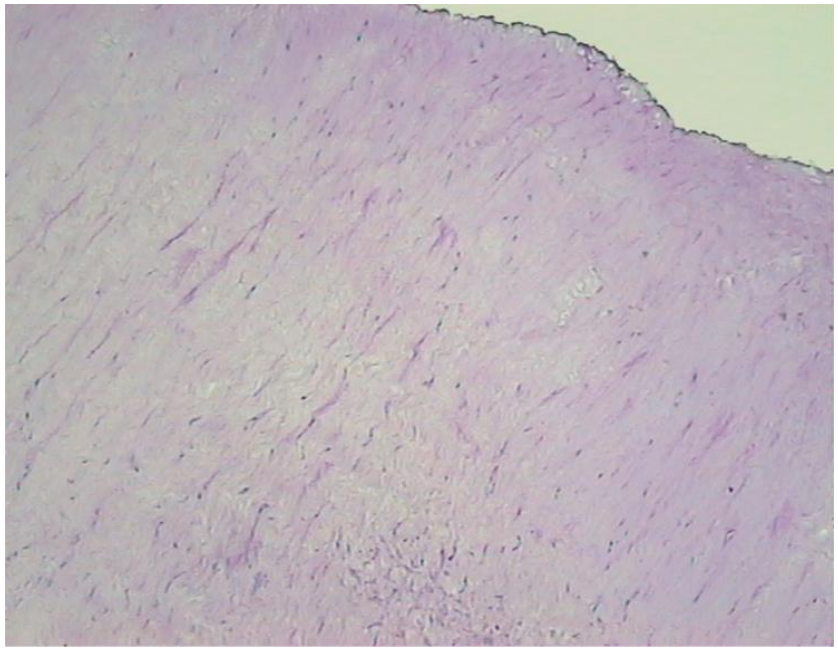
Encapsulating Peritoneal Sclerosis

- Clinical syndrome, characterized by symptoms/signs of obstructive ileus, with or without a systemic inflammatory reaction

- Presence of peritoneal thickening and encapsulation, intestinal obstruction, cocooning and peritoneal calcification, confirmed by radiological investigations or at laparotomy ± typical biopsy

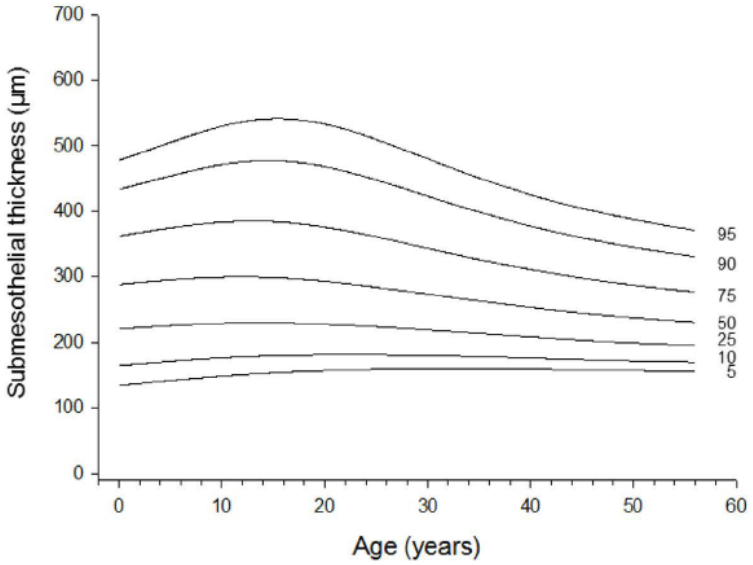
Japanese SEP Study Group, Am J Kidney Dis 1996;28:420-427
ISPD Ad Hoc Commitee on UF management in PD, PDI 2000;20(4):S43-S55

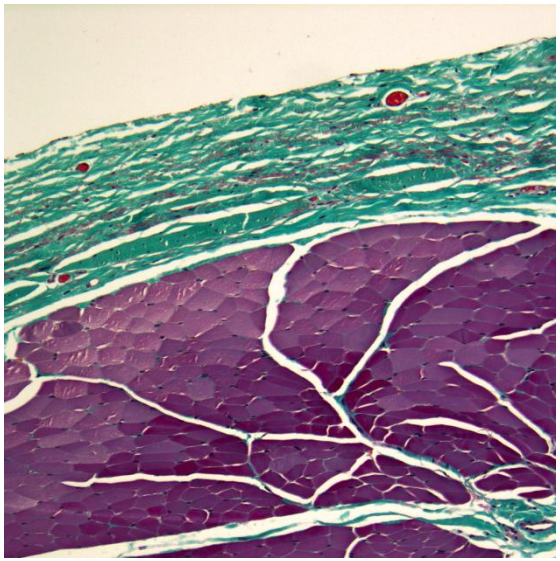
Encapsulating Peritoneal Sclerosis



PAS, 20x

Encapsulating Peritoneal Sclerosis

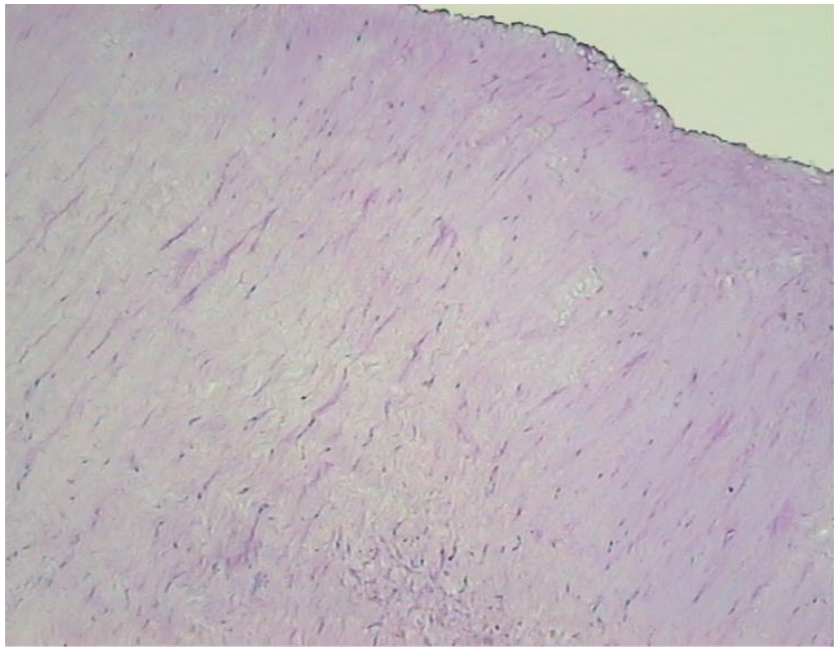




TRI, 10x

Schaefer B et al. Sci Rep 2016;6, 21344

Encapsulating Peritoneal Sclerosis



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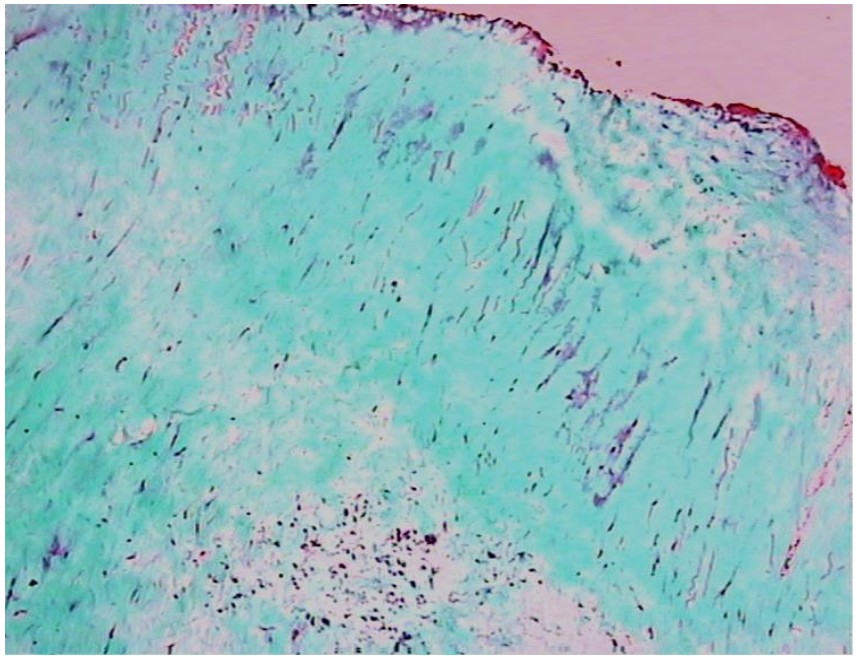

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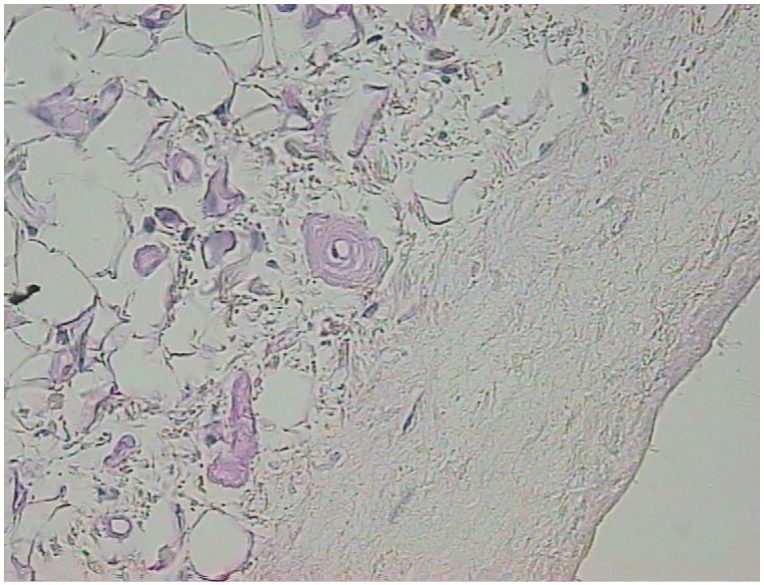
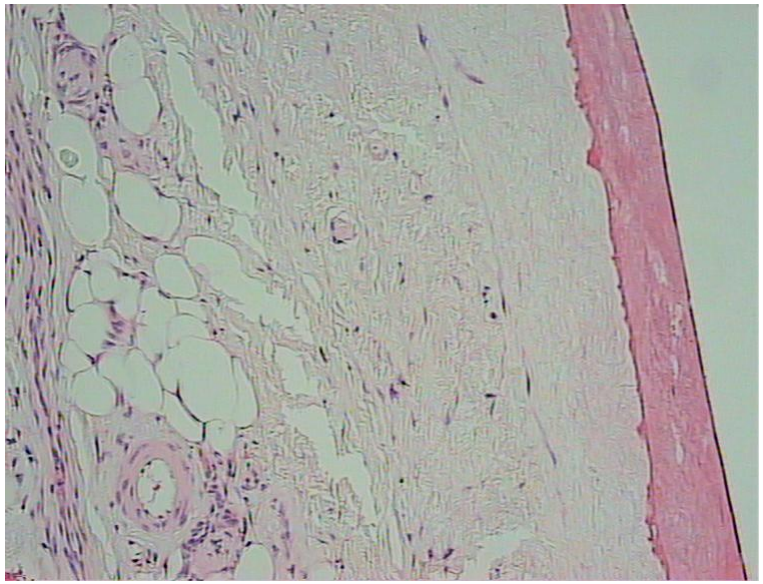
Encapsulating Peritoneal Sclerosis



PAS, 200x



PAS, 100x

Nephrol Dial Transplant (2013) 28: 1603–1609
doi: 10.1093/ndt/gft061
Advance Access publication 12 April 2013

Encapsulating peritoneal sclerosis in paediatric peritoneal dialysis patients: the experience of the Italian Registry of Pediatric Chronic Dialysis

ABSTRACT

Background. Paediatric literature about encapsulating peritoneal sclerosis (EPS) is limited and comes primarily from anecdotic experiences. In this study, we described the incidence and characteristics of EPS in a large paediatric chronic peritoneal dialysis (CPD) patient population.

Methods. We reviewed files of patients starting CPD at <16 years of age, recorded from January 1986 to December 2011 by the Italian Registry of Pediatric Chronic Dialysis ($n = 712$). Moreover, in December 2011, a survey was performed involving all the Italian Pediatric Nephrology Units to report such EPS cases that occurred after CPD withdrawal.

Results. Fourteen EPS cases were reported, resulting in a prevalence of 1.9%. The median age of EPS cases was 4.8 years (range 0.6–14.4) at the start of CPD and 14.3 years (6.5–26.8) at EPS diagnosis. Eleven EPS cases received CPD for longer than 5 years. At diagnosis, nine patients were still on CPD, two were on haemodialysis and three were transplanted. In eight patients, the primary renal disease was represented by glomerulopathy, mainly focal segmental glomerulosclerosis ($n = 5$). In the last 6 months prior to CPD discontinuation, 10 patients were treated with solutions containing more than

EPS: the experience of the Italian Registry of Pediatric Chronic Dialysis

Table 3: Clinical features of the 14 patients with EPS

Pt	Primary disease	CPD duration (months)	No. of peritonitis	Transport status	Age (years) at EPS diagnosis	Status at EPS diagnosis	Diagnostic imaging	Biopsy-proven EPS	Treatment	Status at last available follow-up
1	FSGS	116.7	3		12.6	Transplanted	+	+	Steroids/ CsA surgery	Deceased
2	FSGS	60.5	2	High	8.6	PD		+	Steroids	Transplanted
3	CNS	57.8	0	High	12	PD		+	Steroids	HD
4	CAKUT	102.3	3		8.5	HD	+			Deceased
5	FSGS	62.1	9		18.4	HD			Steroids	HD
6	CAKUT	71.4	0	High	6.5	PD	+		Steroids/ AZA surgery	HD
7	Lymphoma	51.7	7		19.5	PD	+	+	Surgery	Deceased
8	Cystinosis	84.8	2	High	26.8	PD	+		Steroids/ tamoxifen	Deceased
9	FSGS	117.4	5		19.5	PD			Surgery	HD
10	FSGS	55.5	3		20.4	PD	+	+		HD
11	IgAN	86.1	2		18.5	PD	+	+		HD
12	CNS	138.8	7		16.1	PD	+	+	Steroids	Deceased
13	CAKUT	106.2	3		7.3	Transplanted	+	+	Steroids/ TAC/MPA surgery	Deceased
14	CAKUT	75.1	2		11.1	Transplanted	+	+	Steroids/ Sirolimus surgery	Still functioning graft

8/14 chronic glomerulopathies

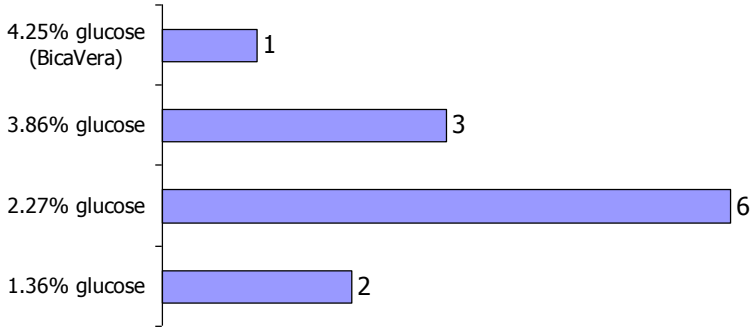
Median CPD duration 85 months

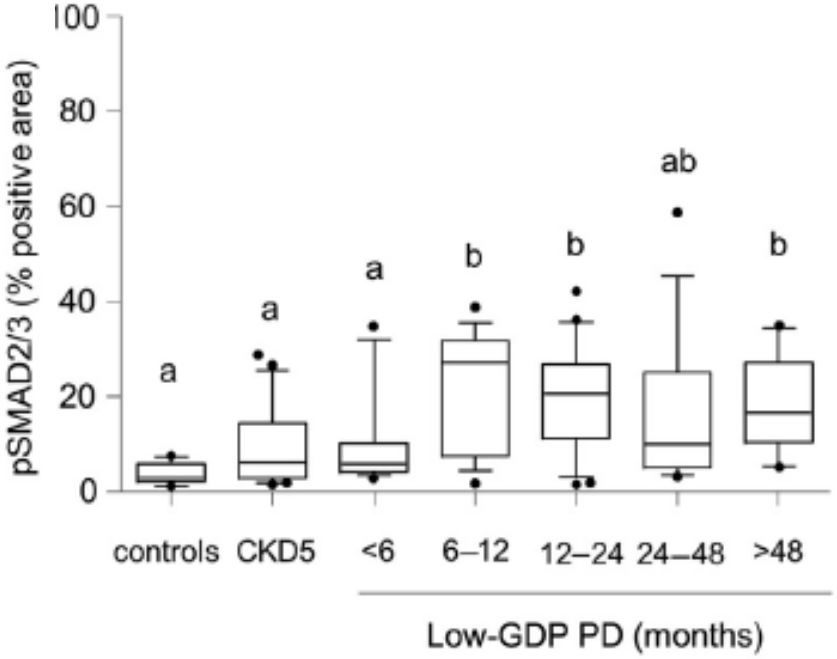
1:26.8 CPD-months
vs.
1:21.9 CPD-months total registry population

Mortality rate = 43%

EPS: the experience of the Italian Registry of Pediatric Chronic Dialysis

Hyperosmolar solutions

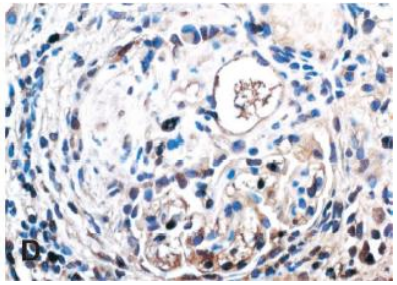




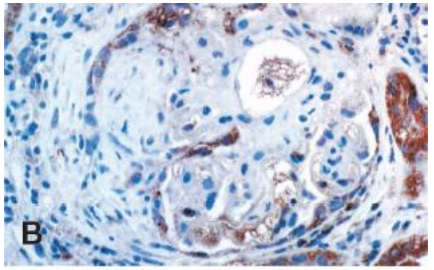
Schaefer B et al. KI 2018;94:419-429.

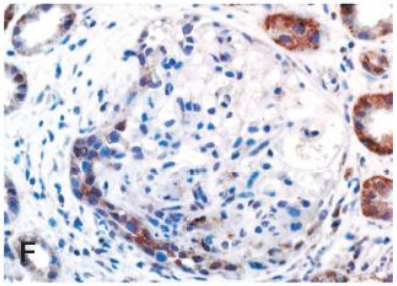
FSGS

TGF-β/Smad signaling pathway

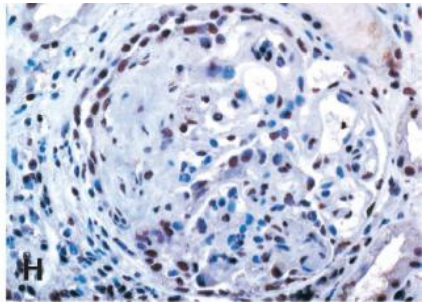


TSP-1 → TGFβ-1





TGFβII-R → Smad2/Smad3



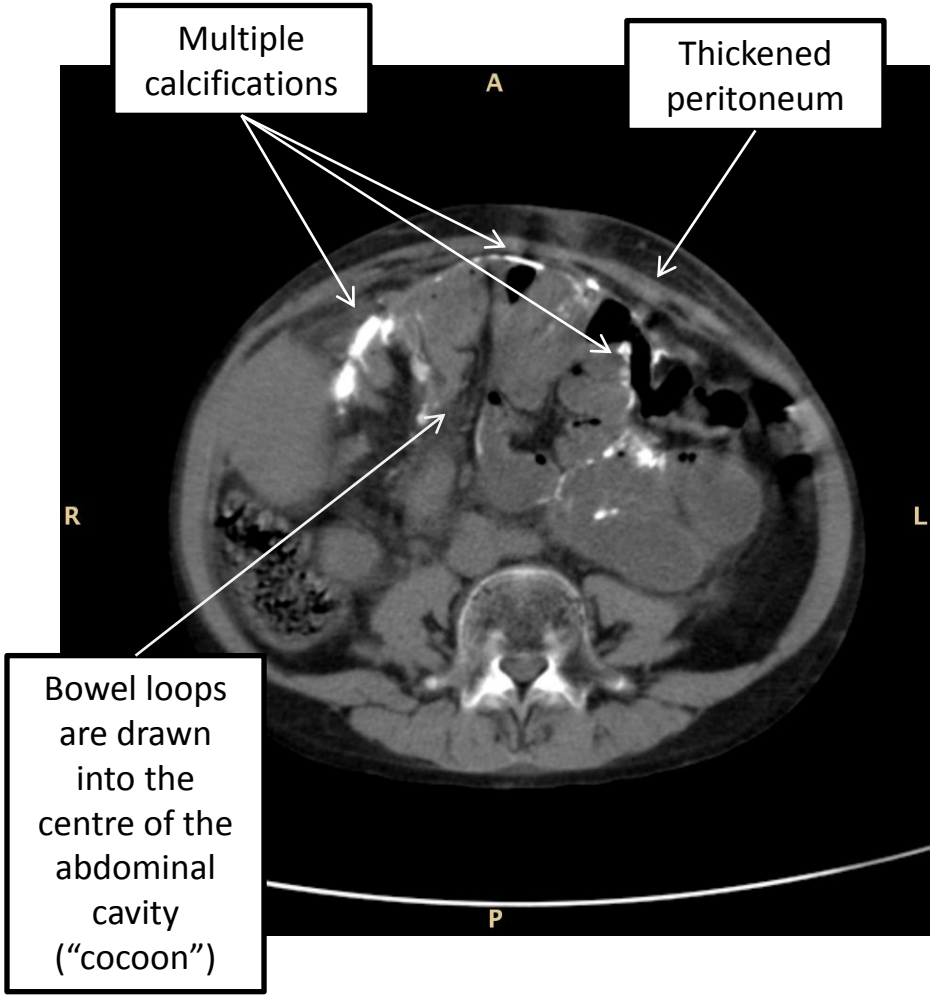
KI 2003;64:1715-1721

EPS: the experience of the Italian Registry of Pediatric Chronic Dialysis

Table 1: Main symptoms and radiological abnormalities found in the 14 cases of EPS

Symptoms	*n*	Imaging findings (US or CT scan)	*n*
Abdominal pain	14	Peritoneal membrane thickening	6
Vomiting	12	Bowel adhesion or aggregation	6
Weight loss	9	Peritoneal calcification	5
Ascites	5	Loculated ascites	3
Fever	3	Gas-fluid levels	3
Diarrhoea	3	Stenotic small bowel loops	3
ESA resistance	3	Dilated small bowel loops	2
		Bowel wall thickening	2

US, ultrasound; CT, computerized tomography; ESA, erythropoiesis-stimulating agents.



Post-transplantation EPS cases

- Diagnosis of EPS was made at 3, 17 and 88 months from PD discontinuation.
- **All** patients had an **acute onset**
  (intestinal occlusion 1 case; intestinal perforation 2 cases)
- **All** patients were on **CNI-based IS regimens**:
  - 1 case: prednisone + CycA
  - 1 case: prednisone + CycA + MMF
  - 1 case: prednisone + Tac + MMF
- **Mortality**: 2/3 (sepsis)
- 1 patient with still functioning renal graft
  (eGFR is 80 ml/min/1.73 m^2 at 4.5 yrs after kidney transplantation and at 3 yrs after EPS diagnosis)

Conclusions

- The incidence of EPS is associated with the duration of CPD.

- In children on long-term PD, dialysis termination should be considered according to individual risk factors, early signs and symptoms of EPS:
  - Children on CPD for longer than 5 years + UFF (<300 ml/mq/day): STOP (Araki *et al*. PDI 2000:20)
  - Further studies are required to analyse the clinical correlation between FSGS and EPS occurrence

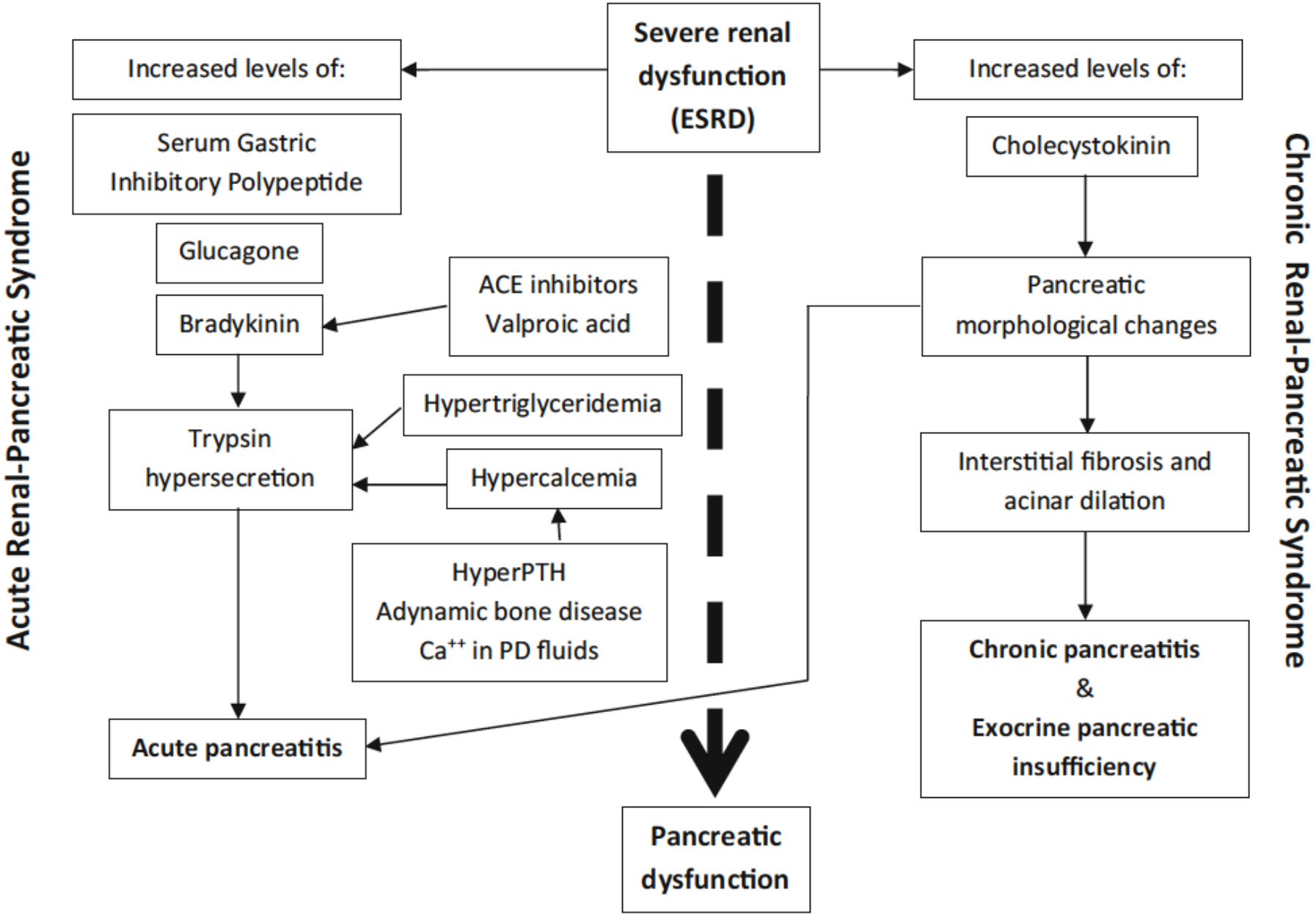
- Children on long-term PD who get transplanted: CNI minimization immunosuppressive regimens.

Acute Pancreatitis in PD Patients

Specific population risk factors

Risk factors related to renal insufficiency

Risk factors related to type of dialysis



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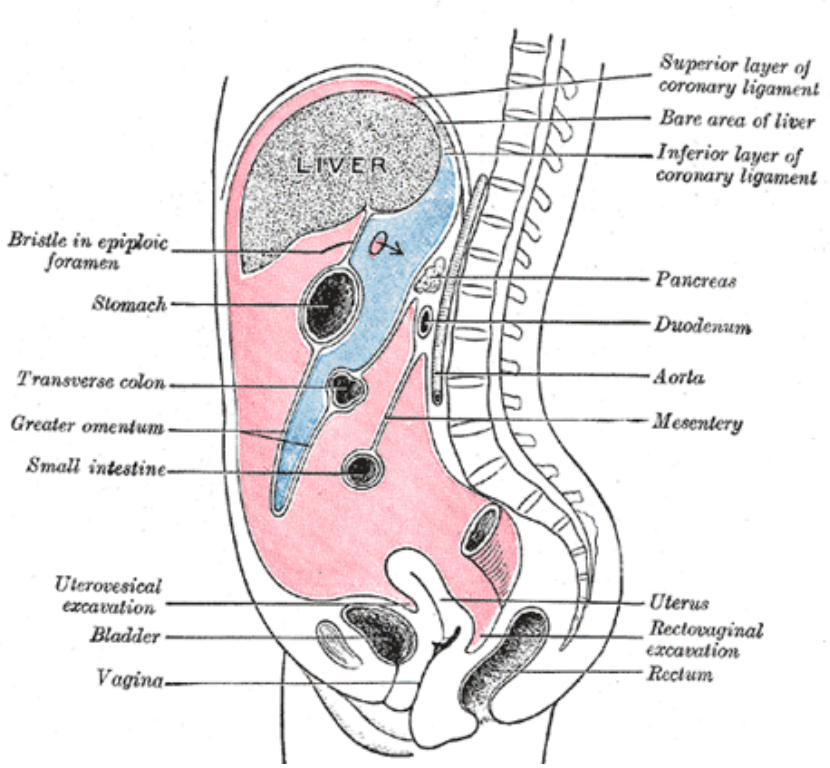
Pathophysiology of Acute Pancreatitis in PD patients

- Anatomical reason.
- Repeated bouts of peritonitis , with subsequent administration of “irritants” (i.e. antibiotics and heparine).
- Supraphysiologic concentration of glucose in the dialysate solutions, leading to hyperglicemia and hypertrigliceridemia.



Acute Pancreatitis in Children on Chronic Dialysis

- DM Ford, *Pediatr Nephrol 1990:*

  «Pancreatitis in children on chronic dialysis treated with valproic acid»

- S Fujinaga, *Clinical Nephrology 2011*:

  «Acute pancreatitis in a 2-year-old girl on peritoneal dialysis and using icodextrin solution»

Pediatric Nephrology (2019) 34:1501–1512
https://doi.org/10.1007/s00467-018-4043-y

EDUCATIONAL REVIEW

Acute pancreatitis in children on chronic maintenance dialysis

Enrico Vidal[1] · Irene Alberici[1] · Enrico Verrina[2] · on behalf of the Italian Registry of Pediatric Chronic Dialysis

- Retrospective study: first chronic dialysis cycle: 1 st January 2000 – 31th December 2014.
- To assess if the incidence of acute pancreatitis (AP) is increased in children with end-stage renal disease on dialysis.
- To evaluate the clinical course and outcome of AP in this pediatric cohort.

Results

	Entire cohort
Incident patients	650
Median age at dialysis start (yrs)	8.5 (IQR 2.6-13.7)
Median dialysis duration (months)	18.8 (IQR 8.7-32.2)
N° of patients with AP	12
AP incidence proportion	1.8%
AP incidence rate (AP/1000 person-years)	9.5
Risk Ratio (general pediatric population*)	60.4 (95% CI 3.2-214)

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Results

	HD	PD	P
Incident patients	237	413	
Median age at dialysis start (yrs)	13 (IQR 9.4-15.6)	5.1 (IQR 1.1-11.4)	*<0.001*
Median dialysis duration (months)	16.7 (IQR 7-30)	20.2 (IQR 10.6-34)	0.19
N° of AP events	7	5	
AP incidence proportion	2.9%	1.2%	*0.04*
AP incidence rate (AP/1000 person-years)	15.4	6.2	*0.13*
Risk Ratio (general pediatric population*)	102.6 (95% CI 15-356)	41.3 (95% CI 1.35-60.5)	

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	AP cases	Non-AP cases	*p*
N	12	638	
PD/HD	5/7 (42%)	408/230 (63.5%)	0.002
Age at dialysis start (years)	7.9 (IQR 3.5–10.5)	8.5 (2.6–13.7)	0.36
Gender (male, %)	75%	55%	0.018
Primary renal disease			<0.001
CAKUT	8 (66.7%)	260 (41.3%)	
Glomerulonephritis	0 (0%)	176 (27%)	
Hereditary	2 (16.7%)	45 (7.2%)	
Ischemic	1 (8.3%)	11 (1.8%)	
Metabolic	1 (8.3%)	21 (3.4%)	
Other/unknown	0 (0%)	125 (19.3%)	
Comorbidities (at least 1)	6[a] (50%)	134 (20.6%)	0.012
Age at AP (years)	10.1 (IQR 4.3–15.3)	–	
Length of dialysis at AP (months)	15.3 (IQR 6.1–43.5)	–	
Length of hospital stay (days)	20 (IQR 12.5–25.5)	–	
Dialysis duration (months)	15.3 (IQR 6.1–43.3)	18.8 (IQR 8.7–32.2)	0.32
Mortality rate[b]	25%	4.3%	<0.001

CAKUT congenital anomalies of the kidney and urinary tract, *HD* hemodialysis, *PD* peritoneal dialysis, *AP* acute pancreatitis

[a] Cognitive impairment 6/6, motor impairment 3/6, cardiac abnormality 2/6, ocular abnormality 2/6

[b] Deaths were non-AP related; mortality rate was registered at last follow-up (December 2015)

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Presence of/exposure to known risk factors

Pt n°	Potential Risk Factors
1 HD	None
2 PD	Rotavirus gastroenteritis
3 HD	Gallbladder stones and abdominal surgery with exposure to Propofol before AP onset
4 HD	None
5 PD	Valproic Acid
6 HD	Enalapril, Valproic Acid
7 HD	Enalapril
8 HD	Valproic Acid
9 PD	None
10 HD	None
11 PD	None
12 HD	None

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Labs and Imaging

Pt n°	Amylase at admission (U/l)	Peak amylase (U/l)	Lipase at admission (U/l)	Peak lipase (U/l)	US	CT scan	Necrotising AP	Pancreatic pseudocyst
1 HD	234	1343	1064	1064	+	+	-	+
2 PD	650	650	6522	6521	+	+	-	-
3 HD	3431	3700	8140	8600	-	+	-	-
4 HD	1125	1125	3614	3614	+	N.P.	-	-
5 PD	2826	3005	4615	5738	+	+	-	+
6 HD	764	764	1757	1757	+	+	-	-
7 HD	1800	3080			N.P.	+	-	-
8 HD	1890	1896	2156	2243	+	N.P.	-	-
Median (IQR)	1125 (650-1890)	1343 (764-3005)	2885 (1583-5091)	2928 (1583-5933)				

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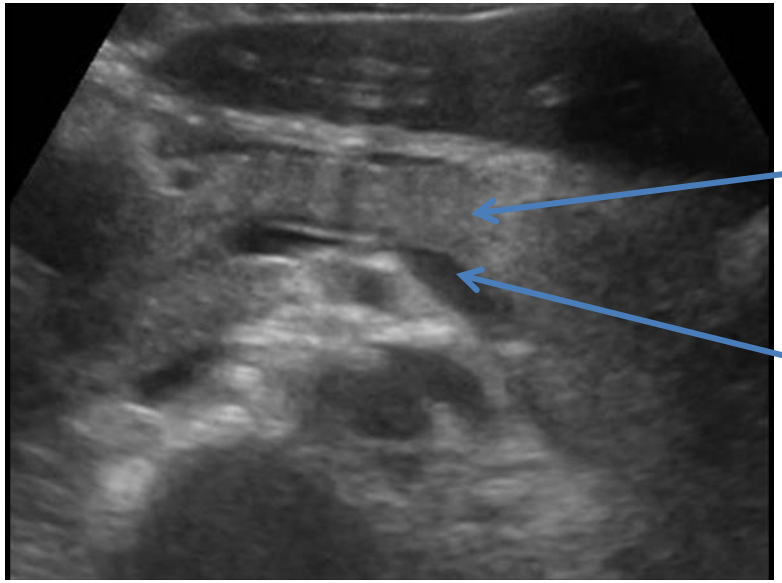
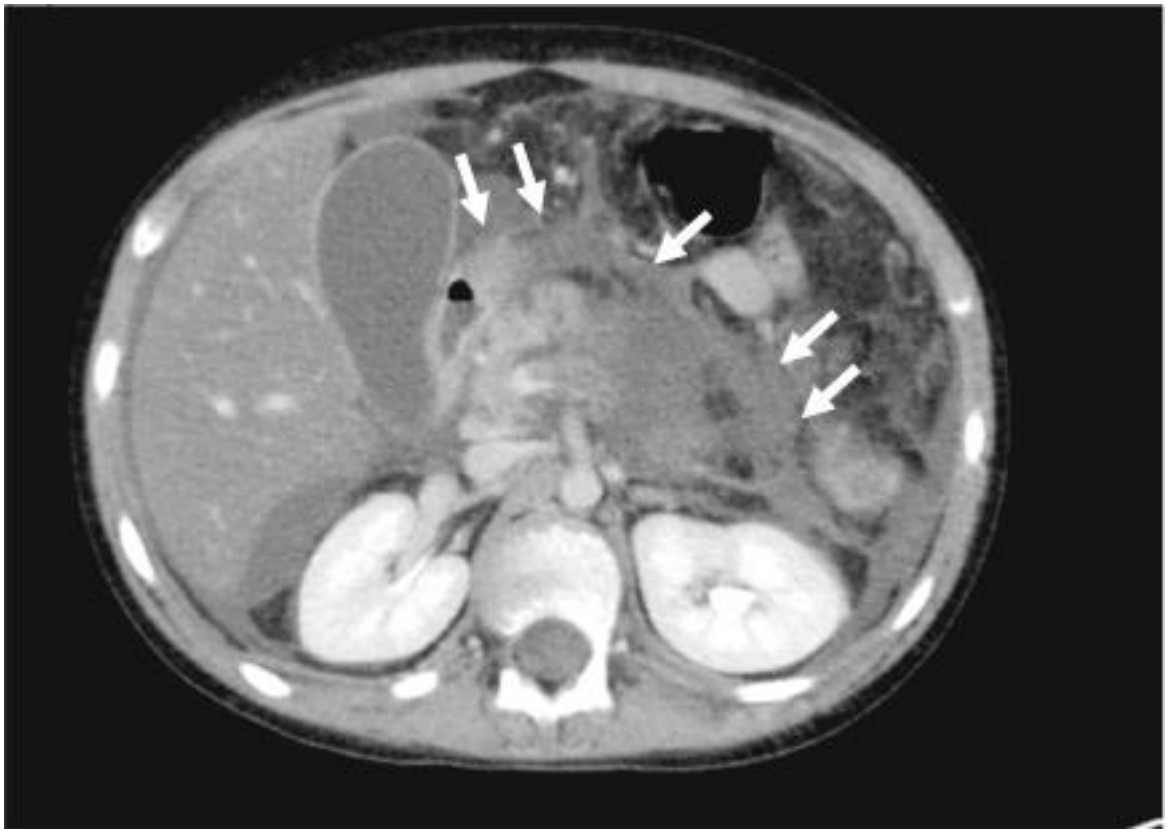
Ultrasonography



Enlarged pancreas
80%

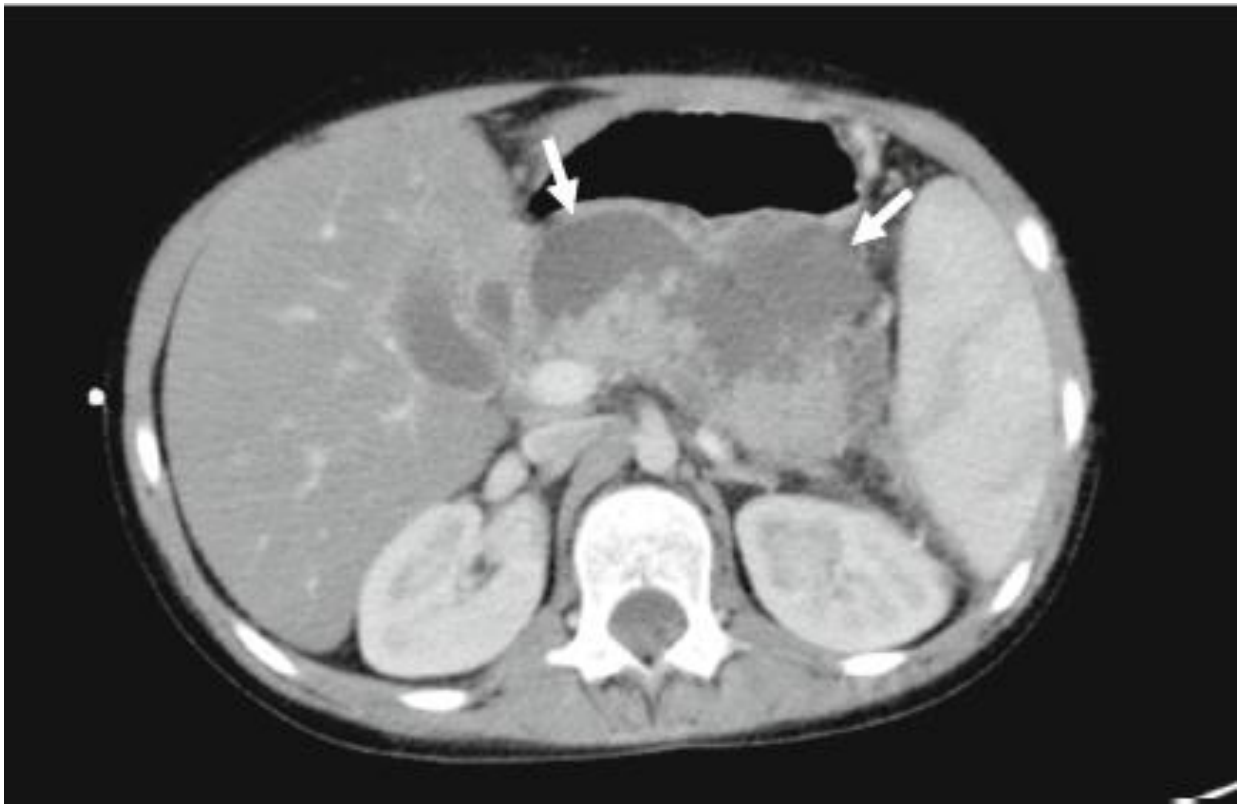
Peripancreatic fluid collections
33%

CT scan and (cholangio)MRI



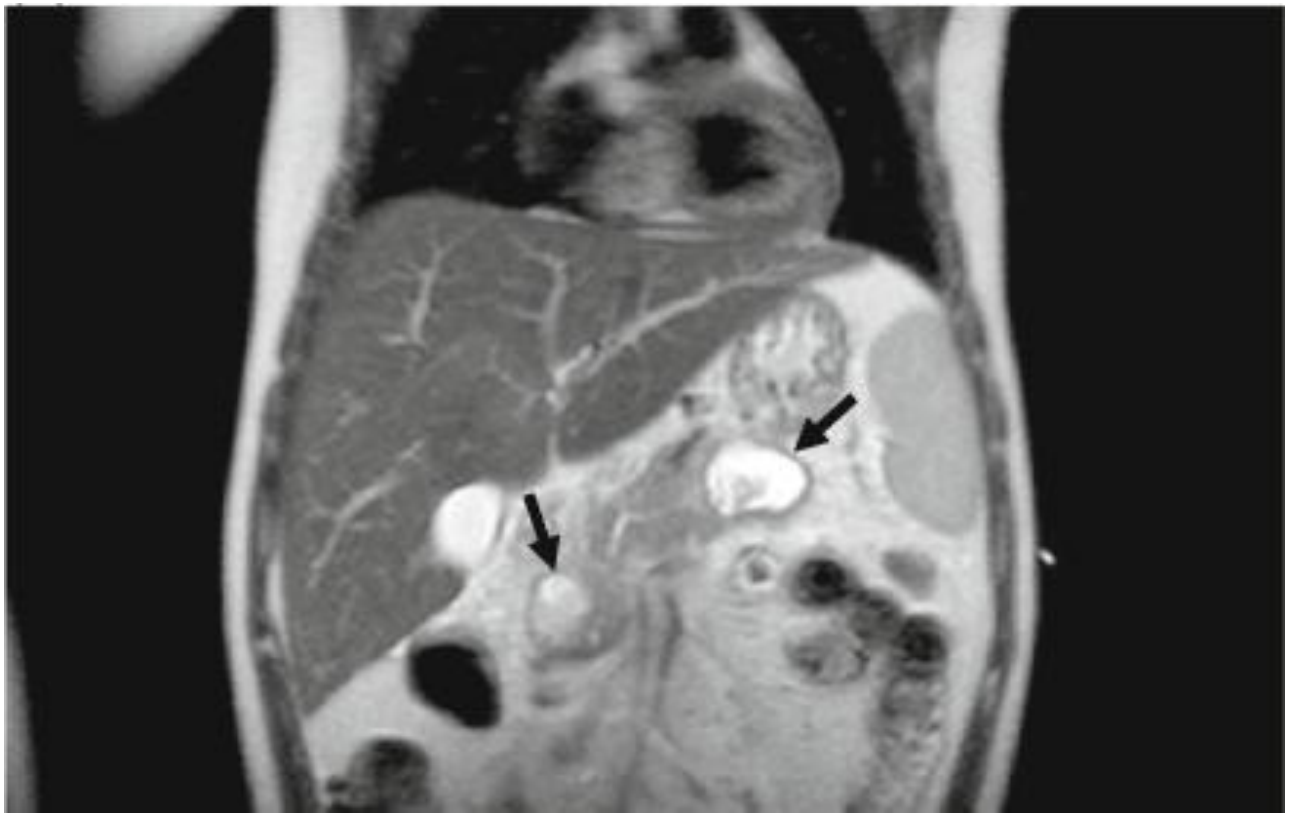
Axial **contrast material-enhanced computed tomography** (CT) image obtained **4 days after** the onset of acute abdominal pain showed a heterogenous appearance of pancreas and peripancreatic fluid

CT scan and (cholangio)MRI



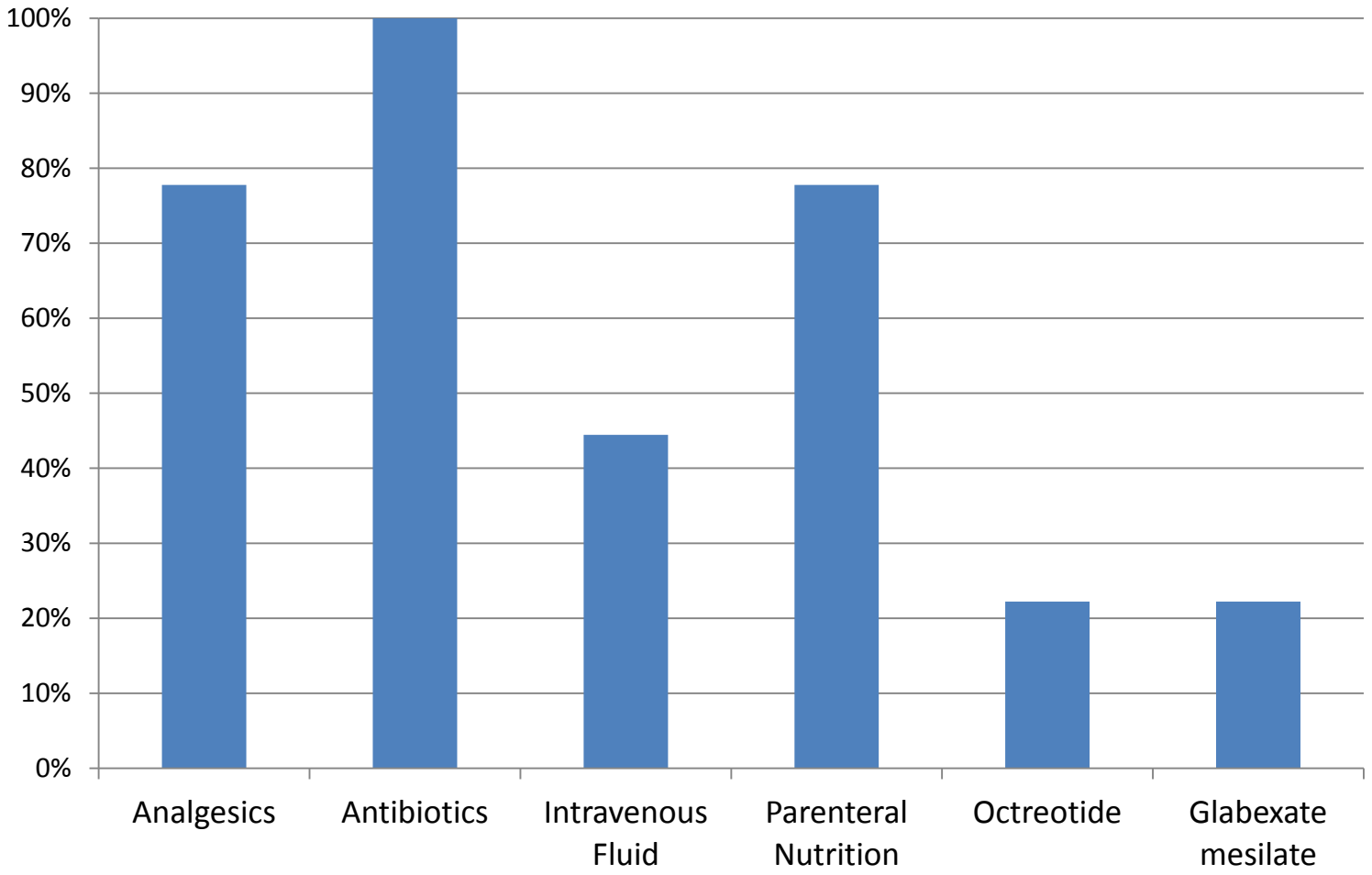
Axial **contrast-enhanced CT** image obtained **8 days later** reveals two well defined hypoattenuating regions in the body of the pancreas (arrows), suggesting pancreatic necrosis.

CT scan and (cholangio)MRI



T2-weighted cholangio-magnetic resonance (MR) acquired **30 days later** reveals evolution into two pancreatic pseudocysts (arrows). Pancreatic duct resulted normal without dilations or strictures.

Results: Treatment



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Results: Outcome

- Pancreatic pseudocysts: 2 pts
- AP-related deaths: 0
- Temporary shift from PD to HD: 1 pt
- AP relapse: 1 pt had 2 AP

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Conclusions

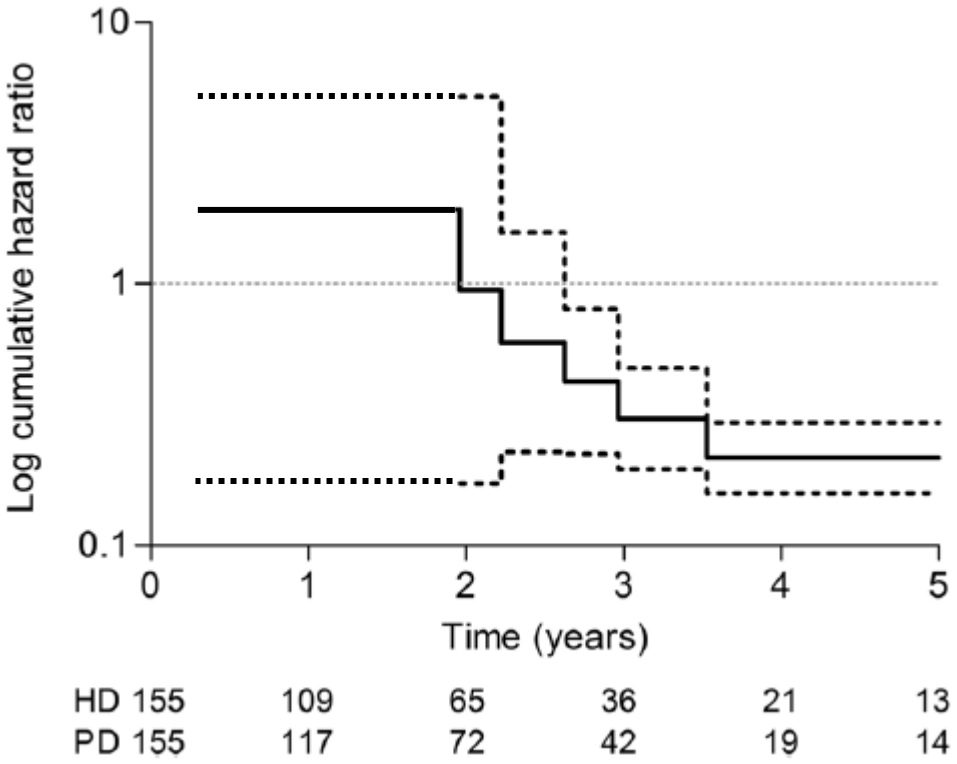
- Children on dialysis have a significantly increased risk for AP compared with the general pediatric population.
- Most children on dialysis are exposed to potential risk factors (medications) for AP.
- A higher incidence is observed in children with neurological co-morbidities
- Risk factors related to ESRD >> risk factors related to type of dialysis
- Outcome is good.

Take home messages

- PD represents the preferred dialysis modality for children with ESRD (!)
- A relative increase in the prevalence of NICPD has been observed in recent years, as consequence of the reduction in infectious complications.
- Prevention of **early** NICPD is mainly based on a **conservative approach**.
- Prevention of **late** NICPD might require an **integrative approach**.

A propensity-matched comparison of hard outcomes in children on chronic dialysis

Adjusted cumulative hazard ratios (HD:PD) for death



Italian Registry of Pediatric Dialysis. Pediatr Nephrol 2018;177(1):117-124.

Next Webinar

November,12

“Clinical Implications of Genetics in Nephrotic Syndrome in Children”

by Olivia Boyer, Paris (France)