IPNA

european society for paediatric nephrology

3rd IPNA - ESPN MASTER FOR JUNIOR CLASSES

LEUVEN – BELGIUM, OCTOBER 28-30, 2016

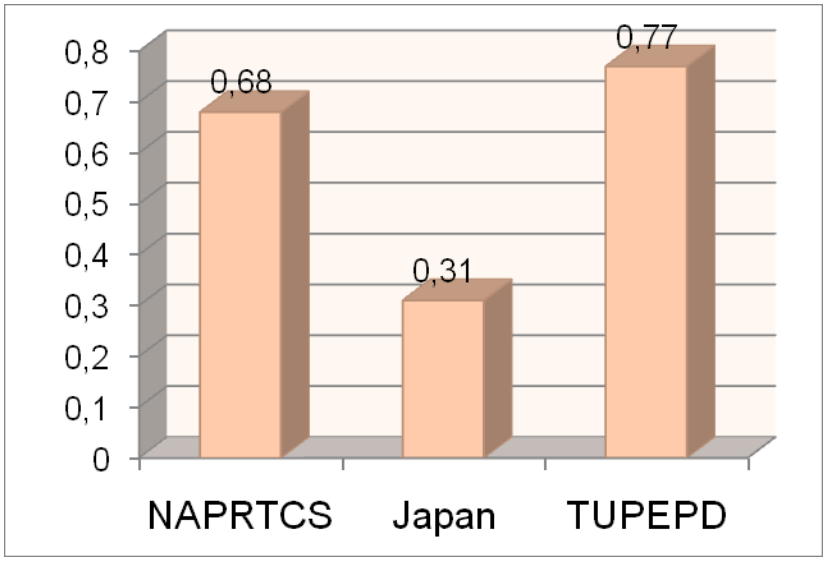
J. Vande Walle,

With special thanks to
S. Bakkaloğlu, C Aufricht, A. Edefonti,
R.Shroff,W. Van Biesen

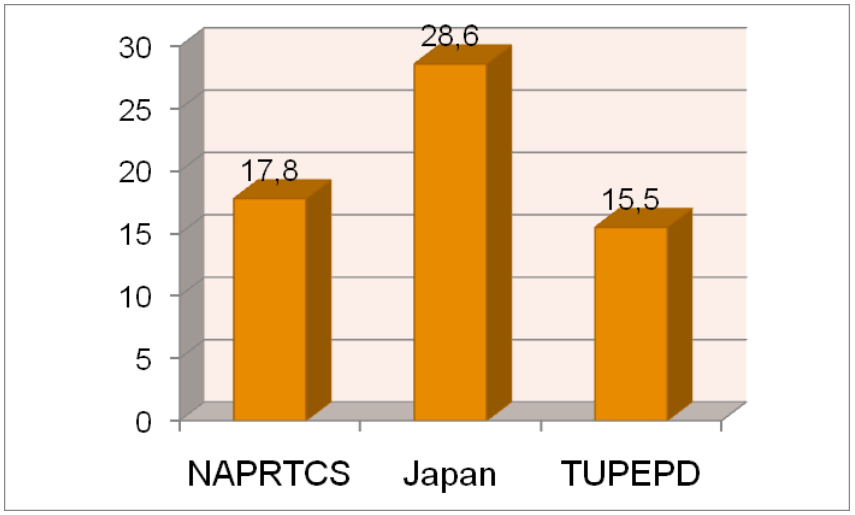
- PD Peritonitis prevention - diagnosis - management

- Exit-site infections
- tunnel infections

Peritonitis rate is decreasing!



Peritonitis rate
Episode/year



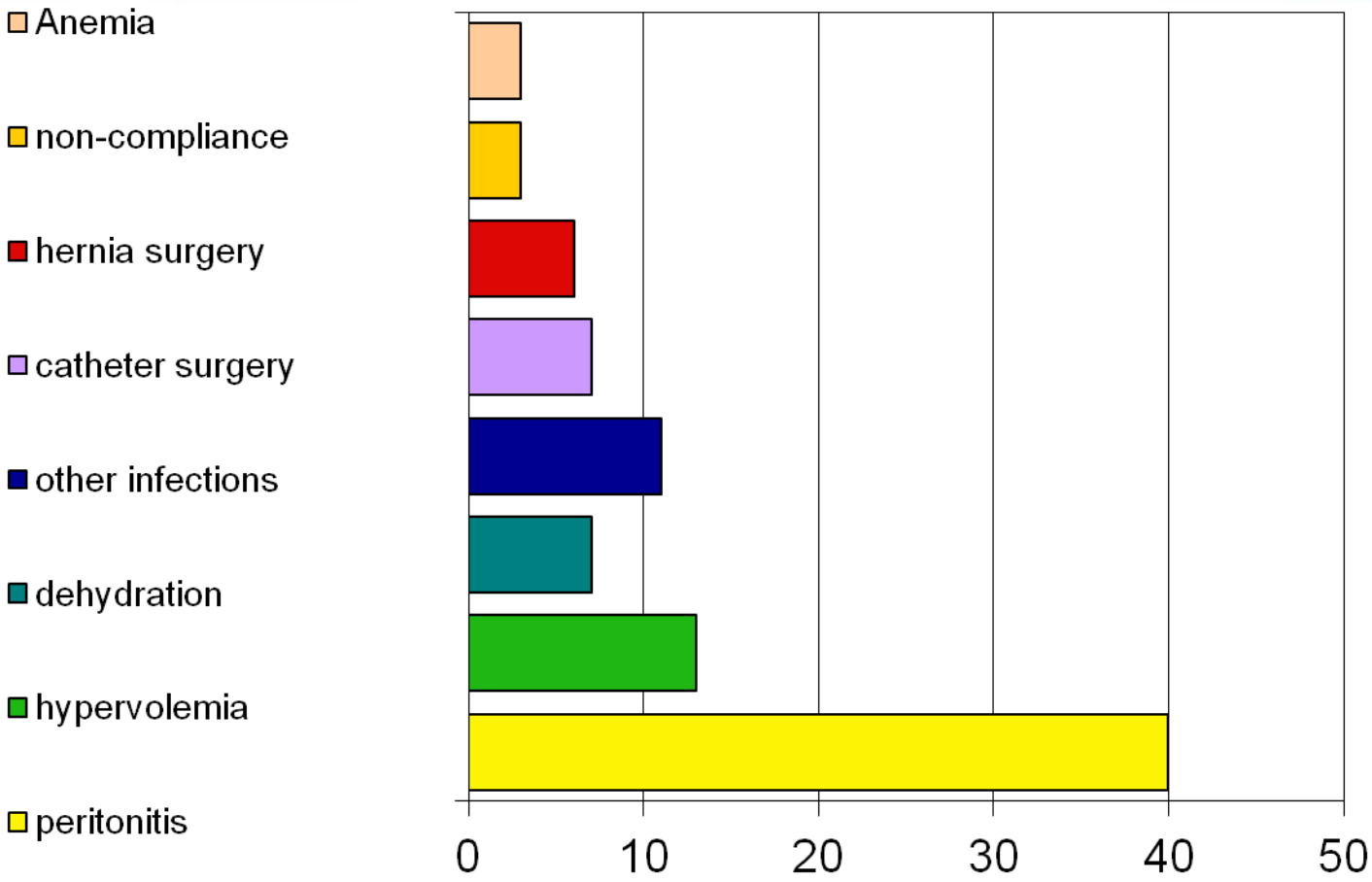
Peritonitis rate
Interval months

NAPRTCS 2007, Honda M, Proc Pediatr PD Conf 2002, Akman S, Pediatr Int 2009

NAPRTCS 2011 - Significant improvement is seen since 2002 with the annualized rate of infection **decreasing from 0.79 in 1992-1996 to 0.44 in recent years**

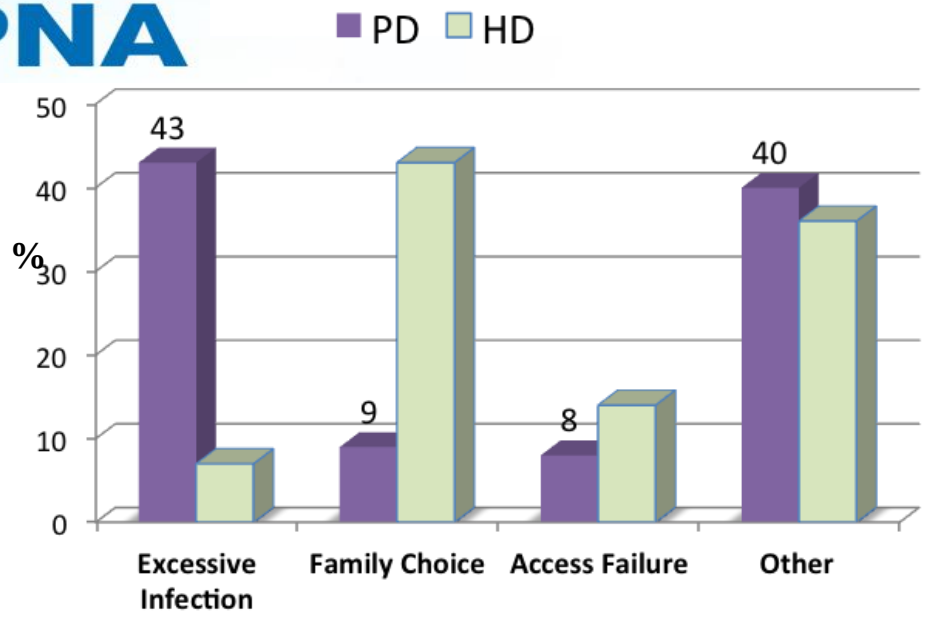
Higher than an annualized rate of 0.5 is not acceptable

Reasons for Hospitalizations



Scahefer F, Orlando 2008

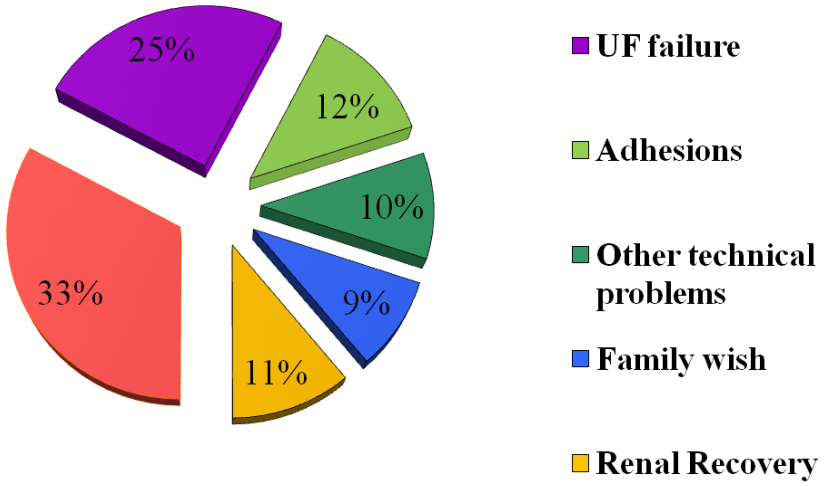
Reasons for dialysis termination



* Other than transplantation

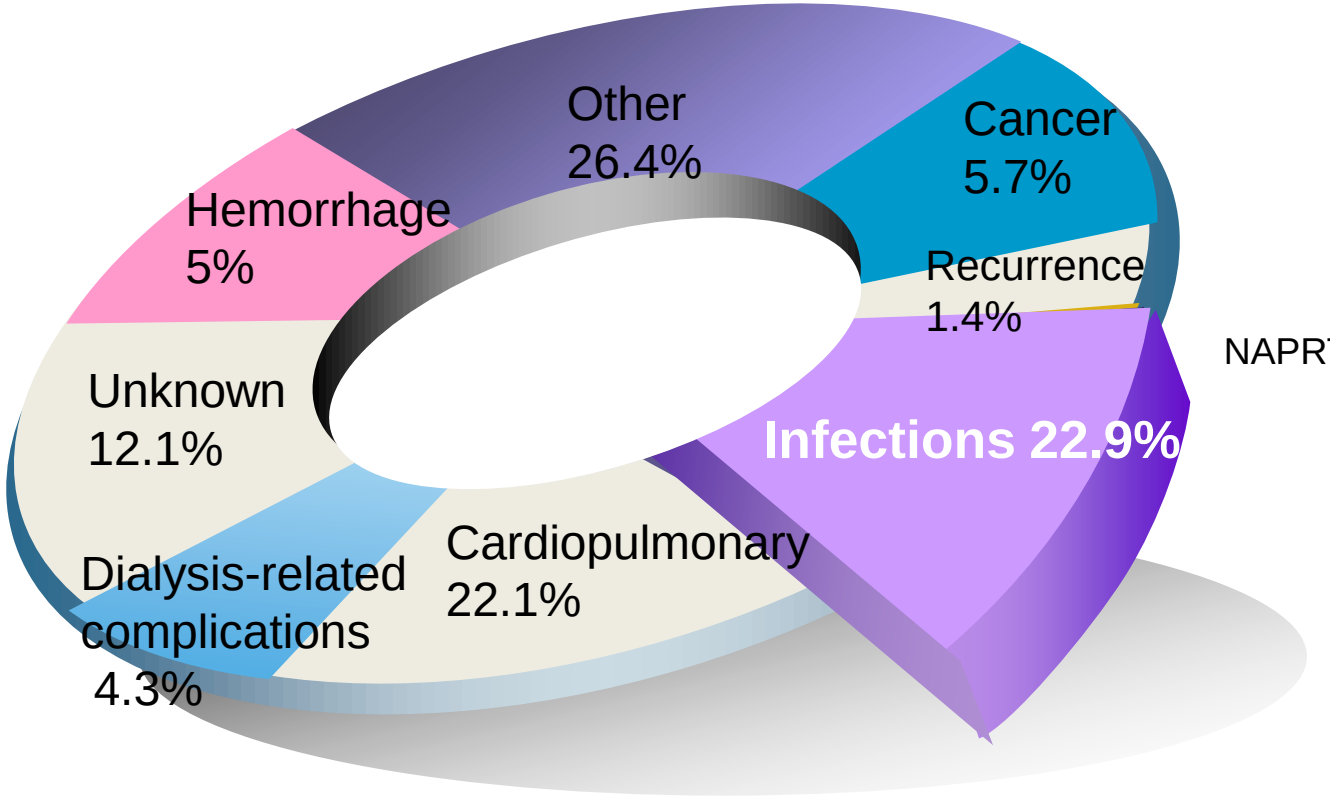
NAPRTCS 2007

n=1356, Tx: 370; death: 37, disc'd for other reasons: 146



Excessive infections accounted for more than 30 % of PD terminations – NAPRTCS 2011 Report

Causes of death in PD and HD patients(%)



NAPRTCS 2011

USRDS 2013 - infection is the leading cause for hospitalization and the second-most common cause of death in children receiving PD

Peritonitis

- Hospitalisation
  - Socio-economic cost
- Catheter loss
  - “ruining” life-time access-reservoir
  - Integrated care
- Loss “of dialysis capacity
  - Technique survival
- Burden (child /family)
- Risk of death

Need for guidelines

Do we need guidelines ?

Do we need guidelines ?

Do we need guidelines ?

The spy who loved me
Licence to kill

Peritoneal Dialysis International, Vol. 32, pp. 532–586
doi: 10.3747/pdi.2011.00091

0896-8608/12 $3.00 + .00

ISPD GUIDELINES/RECOMMENDATIONS

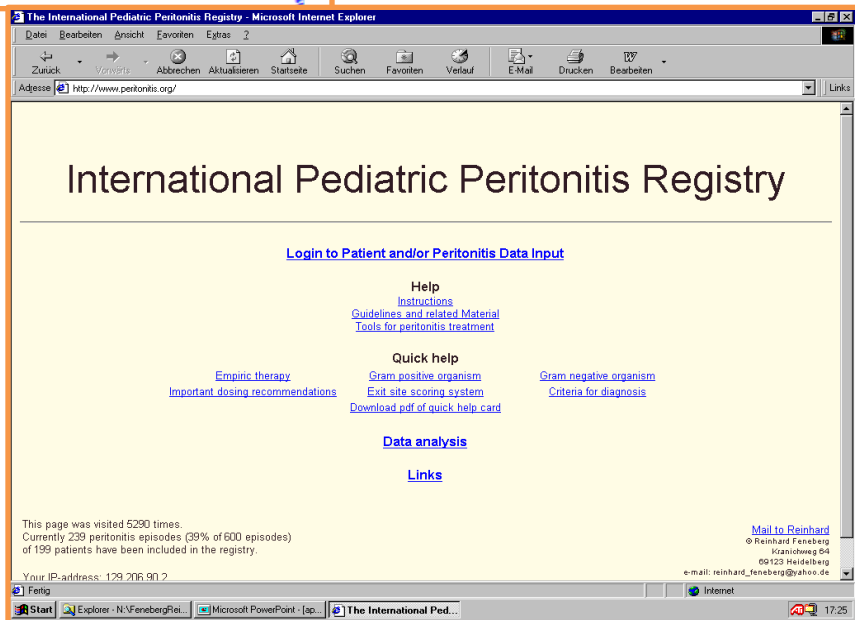
CONSENSUS GUIDELINES FOR THE PREVENTION AND TREATMENT OF CATHETER-RELATED INFECTIONS AND PERITONITIS IN PEDIATRIC PATIENTS RECEIVING PERITONEAL DIALYSIS: 2012 UPDATE

Bradley A. Warady,[1] Sevcan Bakkaloglu,[2] Jason Newland,[1] Michelle Cantwell,[3] Enrico Verrina,[4] Alicia Neu,[5] Vimal Chadha,[1] Hui-Kim Yap,[6] and Franz Schaefer[7]

Division of Pediatric Nephrology,[1] Children's Mercy Hospital and Clinics, Kansas City, Missouri, USA; Gazi University,[2] Ankara, Turkey; Great Ormond Street Hospital,[3] London, England; G. Gaslini Children's Hospital,[4] Genoa, Italy; Johns Hopkins University School of Medicine,[5] Baltimore, Maryland, USA; National University of Singapore,[6] Singapore; and University Children's Hospital,[7] Heidelberg, Germany

Peritoneal Dialysis International

european society for paediatric nephrology



GUIDELINE 1 – TRAINING

- 1.1 We suggest that PD training be performed by an experienced PD nurse with pediatric training, using a formalized teaching program that has clear objectives and criteria, and that incorporates adult-learning principles (2C).
- 1.2 We suggest that retraining be provided to all caregivers periodically. We also suggest that re-evaluation of the PD technique be conducted after development of a peritonitis episode (2C).

Consensus guidelines for the prevention and treatment of catheter-related infections and peritonitis in pediatric patients receiving peritoneal dialysis: 2012 update.Perit Dial Int. 2012 Jun;32 Suppl 2:S32-86..Warady B et al

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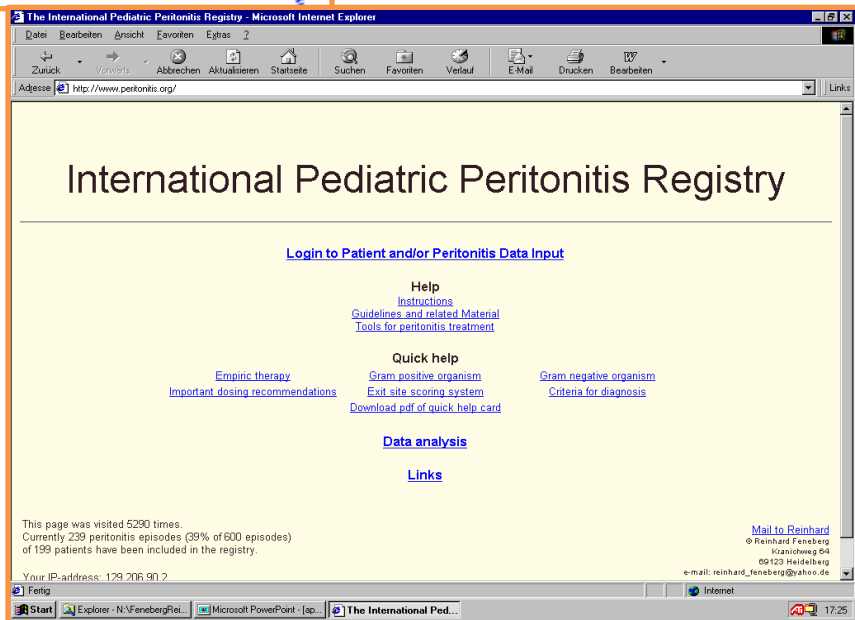


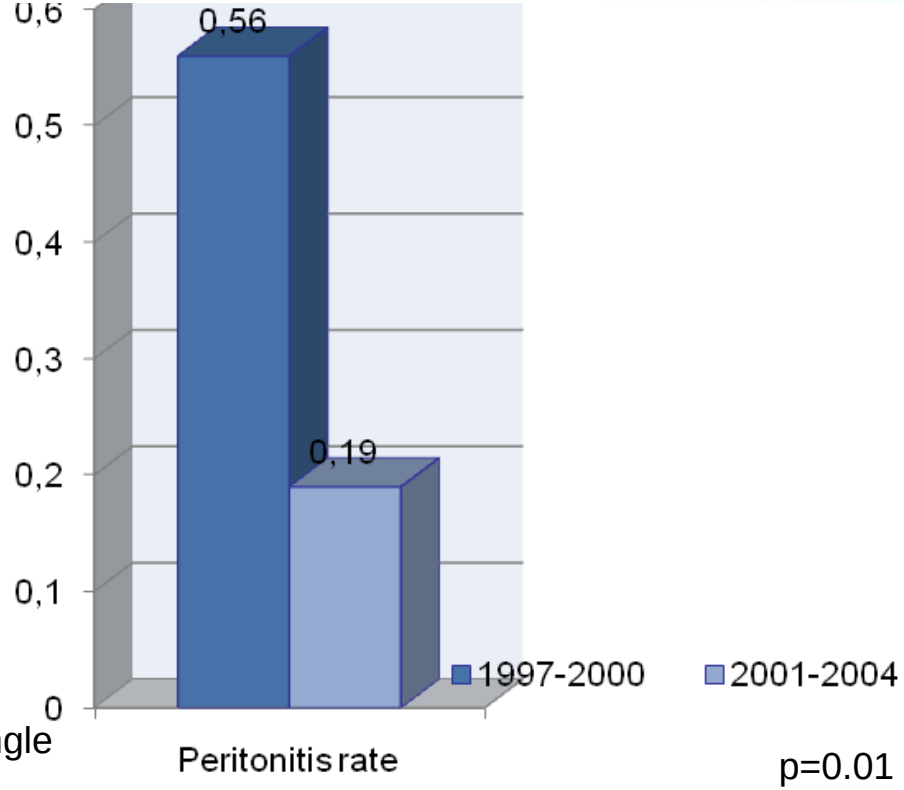
PD Catheter Related Interventions:!

- **Implantation/Care Best Practices and Preventive Strategies(Mostly Opinion based)**

  - **Pre-op prophylaxis with iv. antibiotics**
  - **Double cuffs, downward or lateral directed exit-site**
  - **Locate superficial cuff 2 cm from the exit site**
  - **No incision, no sutures at the exit site**
  - **Catheter anchoring and immobilization**
  - **Dressing changes should be avoided in the first week**
  - **If possible, do not use the catheter at least for two weeks**

- 54 patients
- Mean age: 6.9±6.7 yrs
- 1099 pt-months
- 36 patients received dx 1997-2000
- 18 patients: 2001-2004
- 14 patients: Both periods

- Prophylactic measures
  - Double cuff, swan neck Tenckhoff
  - Cefazolin at the cath insertion
  - Fibrin glue for immediate use
  - Weekly ES care until healed
  - Intranasal mupirocin to the carriers
  - Open surgical implantation mostly by a single surgeon
  - No sutures at the exit-site
  - Immediate ES care with poloxamer
  - Chronic ES care with clorhexidine/ daily
  - Fungal prophylaxis

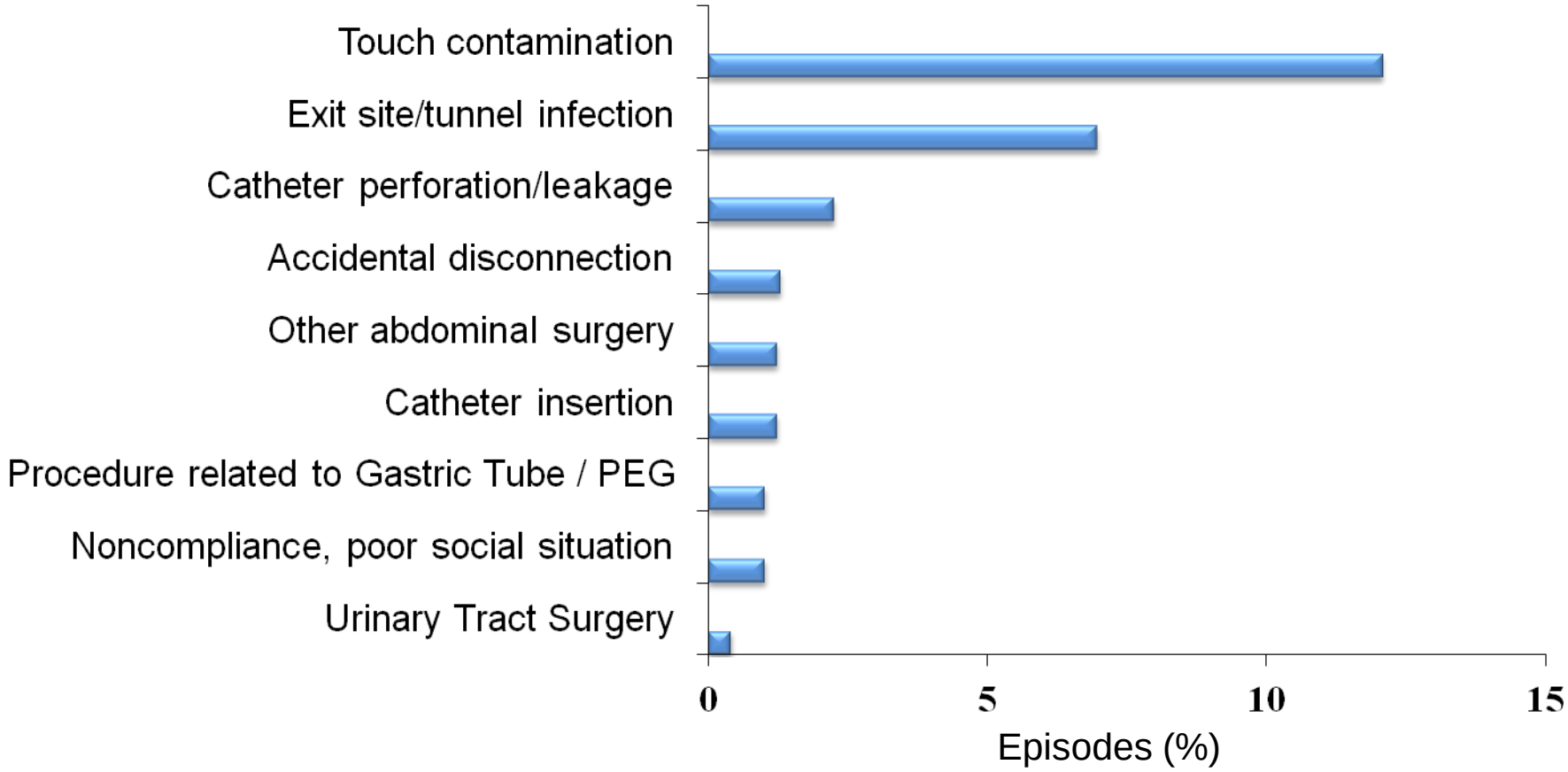


p=0.01

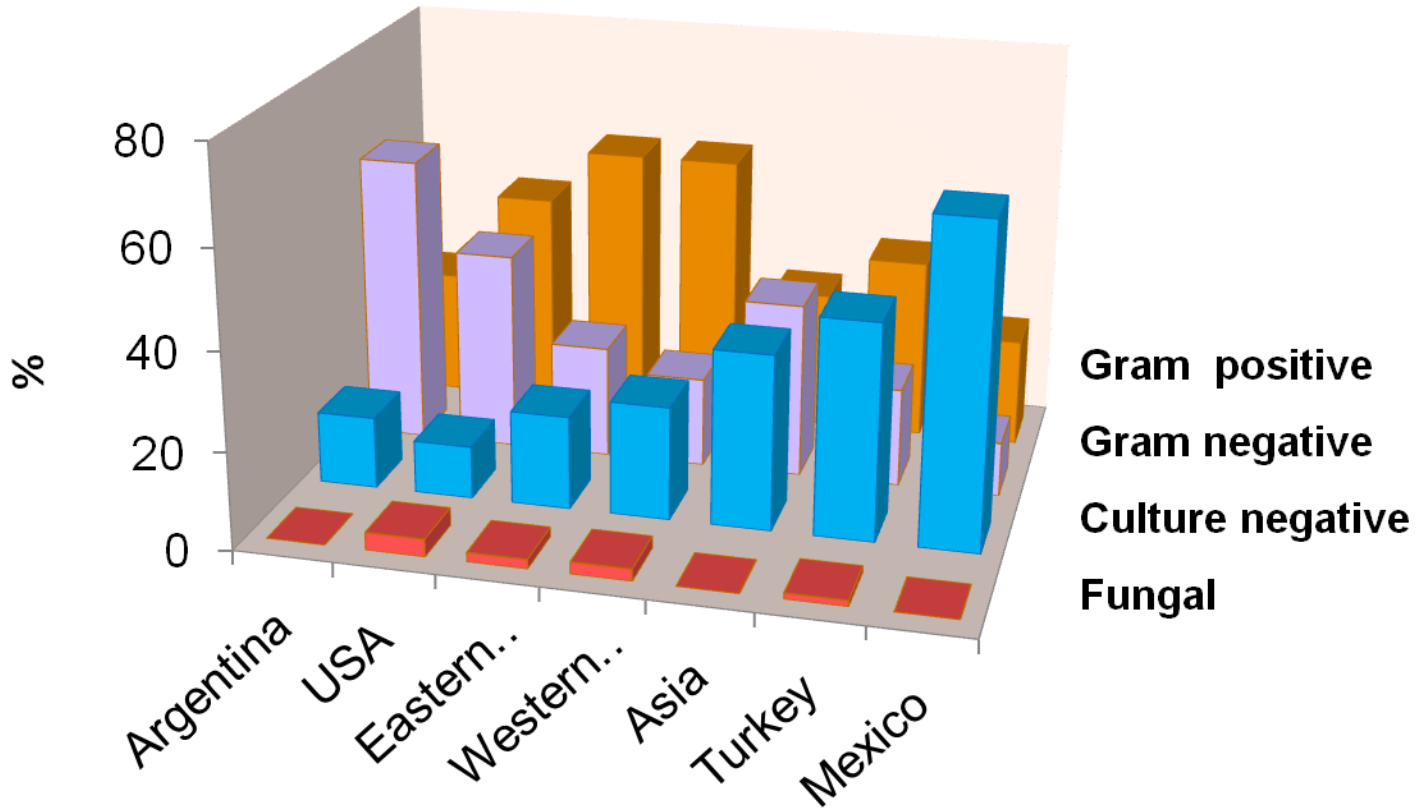
Auron et al. Pediatr Nephrol 2007;22:578-585

Peritonitis: Source of Infection - IPPR

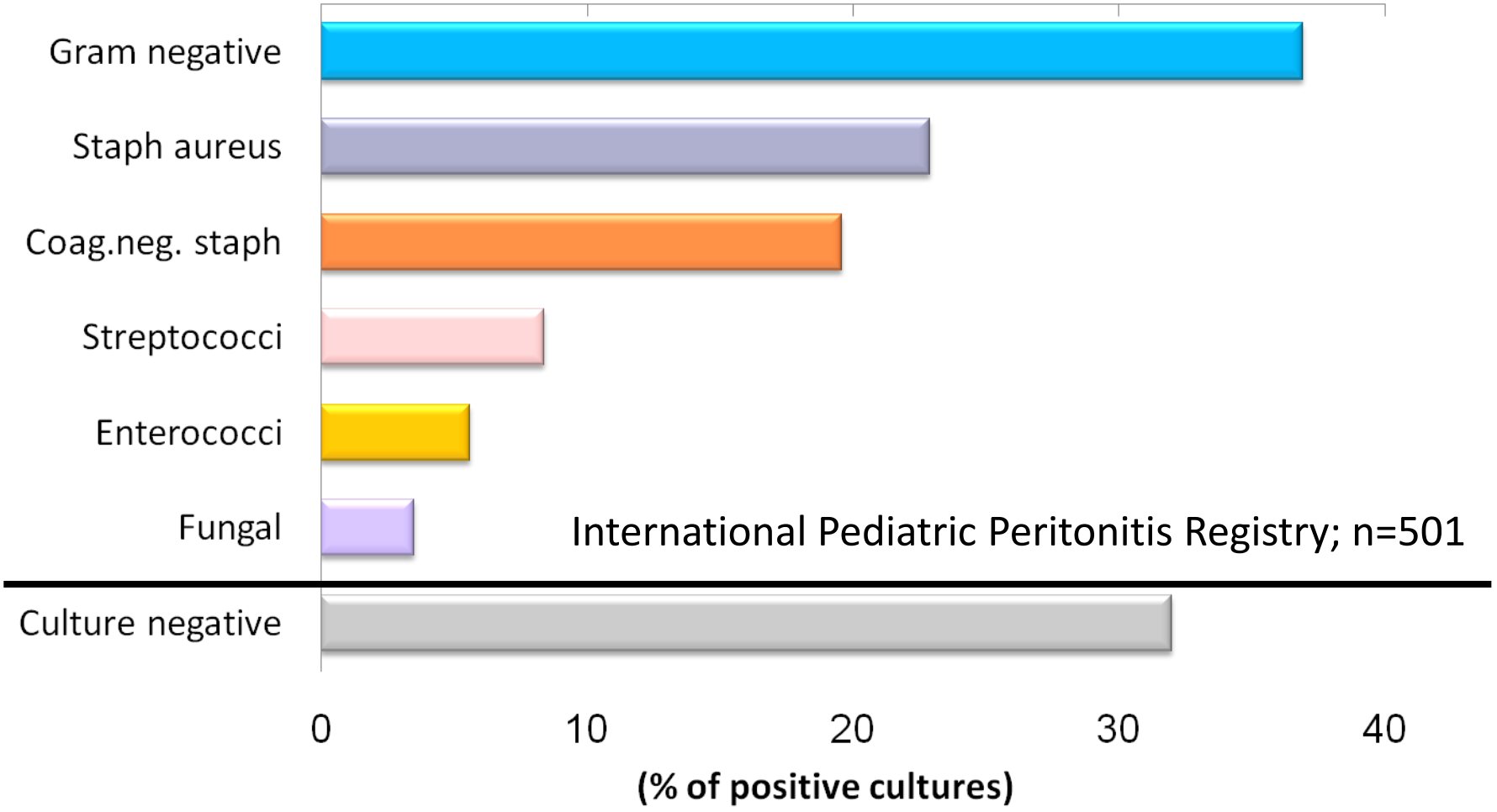
Unknown: 70 %



Regional Variation of Culture Results - IPPR



Spectrum of Causative Organisms - IPPR



Clinical presentation

Cloudy Fluid	98-100%
Abdominal pain	67-97%
Abdominal tenderness	62-79%
Fever	34-36%
Nausea	30-35%
Vomiting	25-30%
Diarrhoea	7-15%

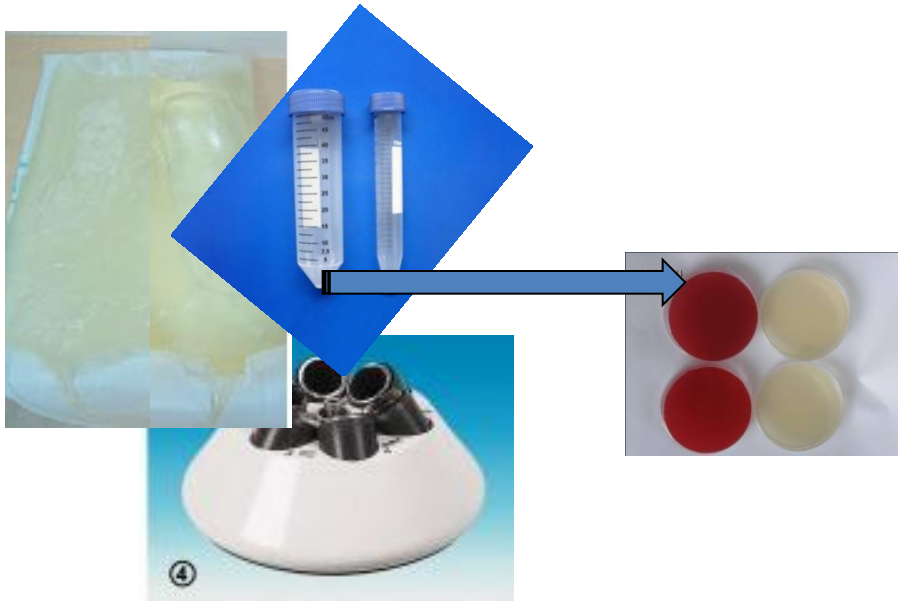
Piraino B In Peritoneal Dialysis 2000

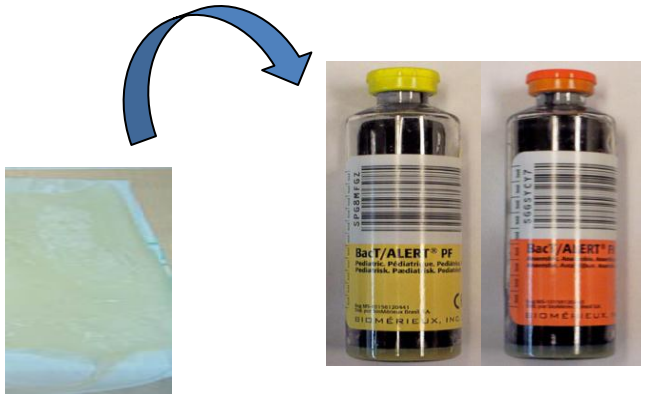
Diagnosis

- cell count,
- differential count
- culture to confirm the diagnosis of peritonitis

- WBC> 100/mm^3, and at least 50% of the WBCs are PMNL

- centrifugation of effluent
- culture of sediment
- blood-culture bottles as the standard culture technique

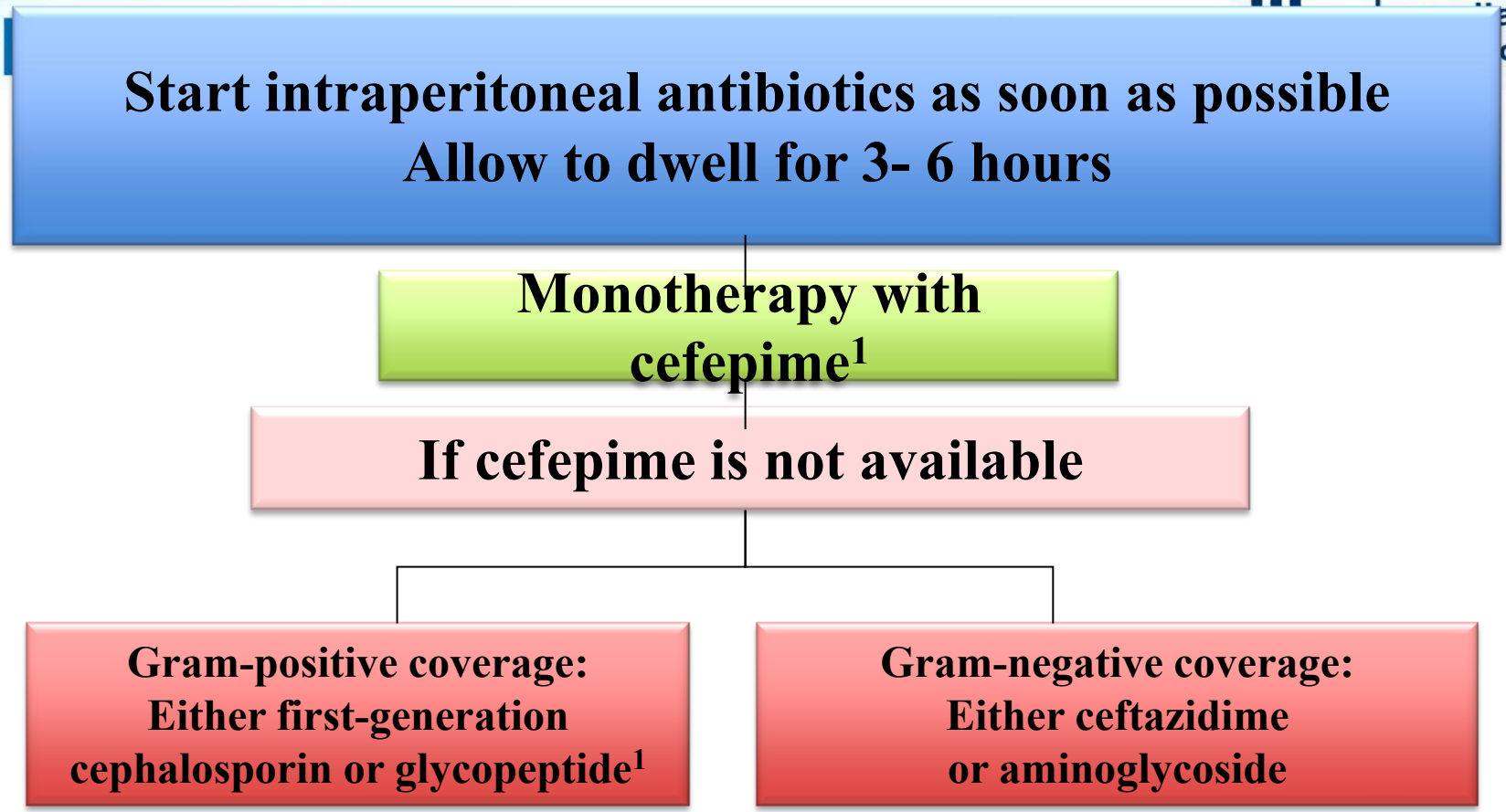




Other causes of cloudy dialysate

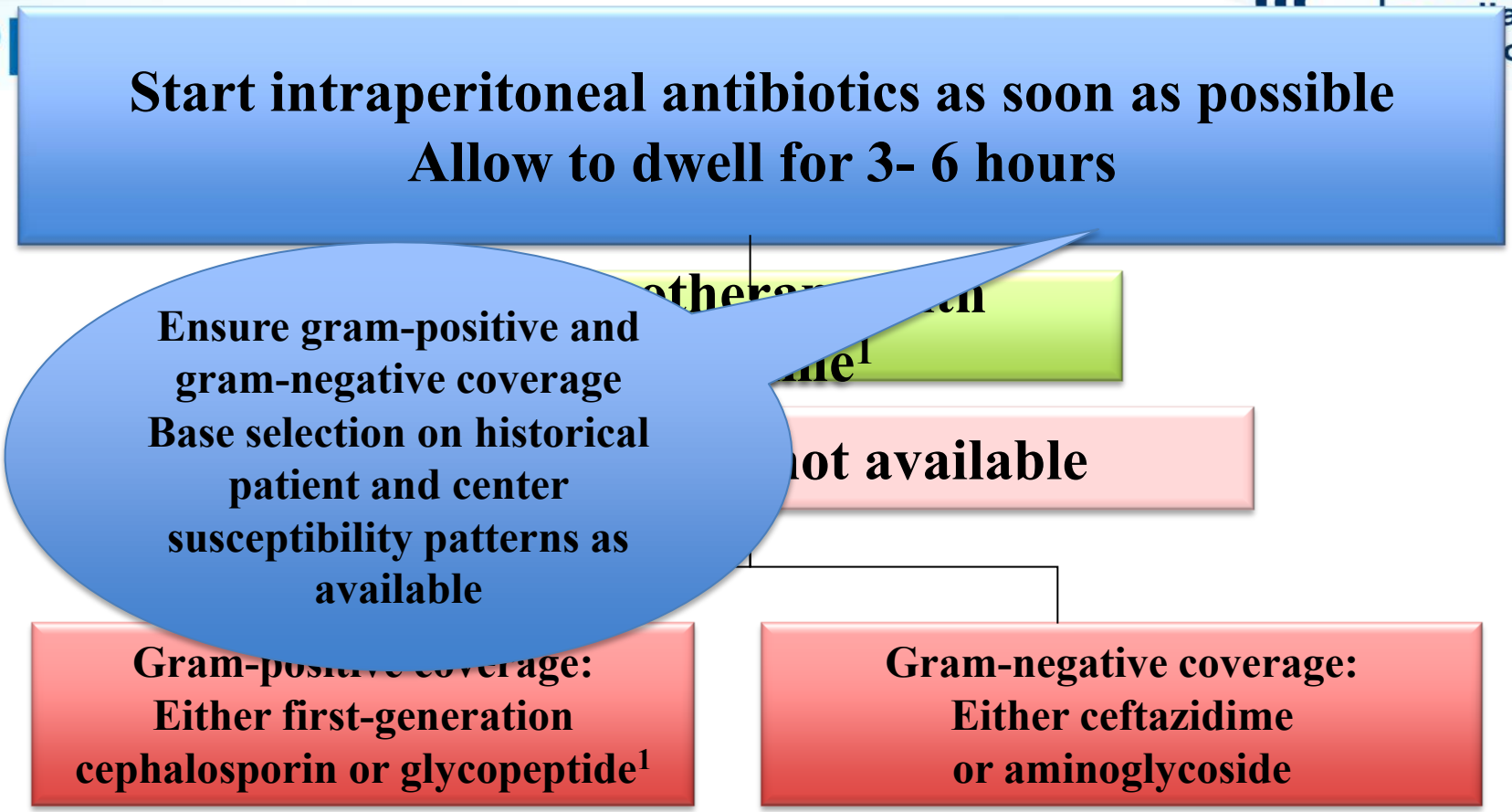
- Non-infectious inflammation
  - Sterile peritonitis
    - Peptidoglycans
    - Excess GDP
    - Chemical peritonitis e.g. some brands of vancomycine (additives)
    - Eosinophilic peritonitis on air exposure
    - pancreatitis
  - Non- inflammatory
    - Chylous leakage: lymphatic obstruction
    - Triglycerides
    - menstruation

Empiric antibiotic therapy



If the center's MRSA rate exceeds 10% or patient has history of MRSA colonization, glycopeptide should be added to cefepime or should replace the first generation cephalosporin for gram-positive coverage. Glycopeptide usage can also be considered if patient has a history of severe allergy to penicillins and cephalosporins.

Empiric antibiotic therapy



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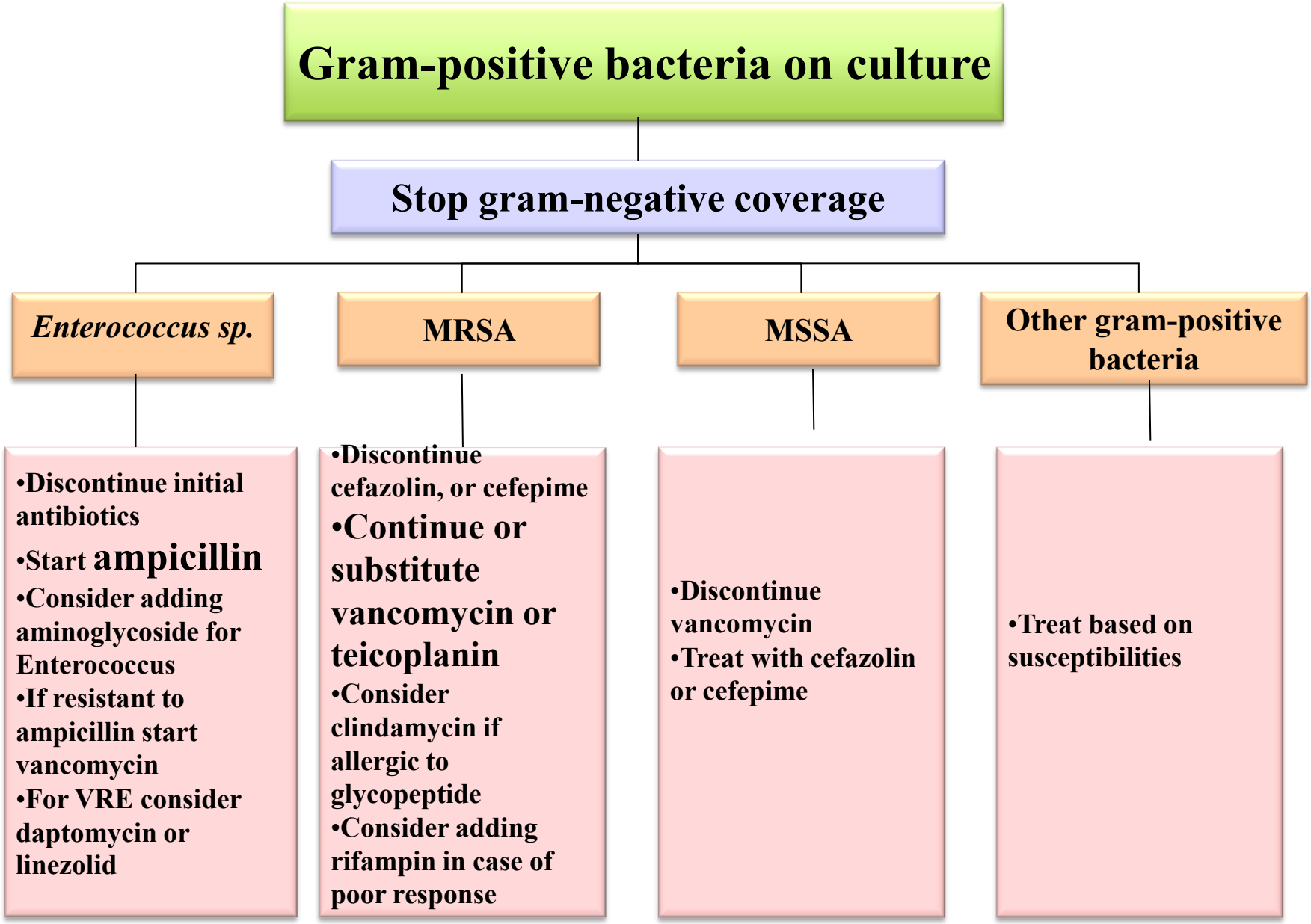
Cefepime

- 4th generation cephalosporine
- Coverage of methicillin-sensitive Gram positive and Gram negative spectrum
- Superior coverage of Enterobacteriaceae, comparable Pseudomonas coverage as ceftazidime (80%); 50% ESBL sensitivity
- Mainly renal elimination, half-life 12 hours
- Excellent systemic absorption upon ip administration, good penetration from circulation into peritoneal cavity
- Dose: 15 mg/kg i.p. once daily during ≥ 6-hour dwell

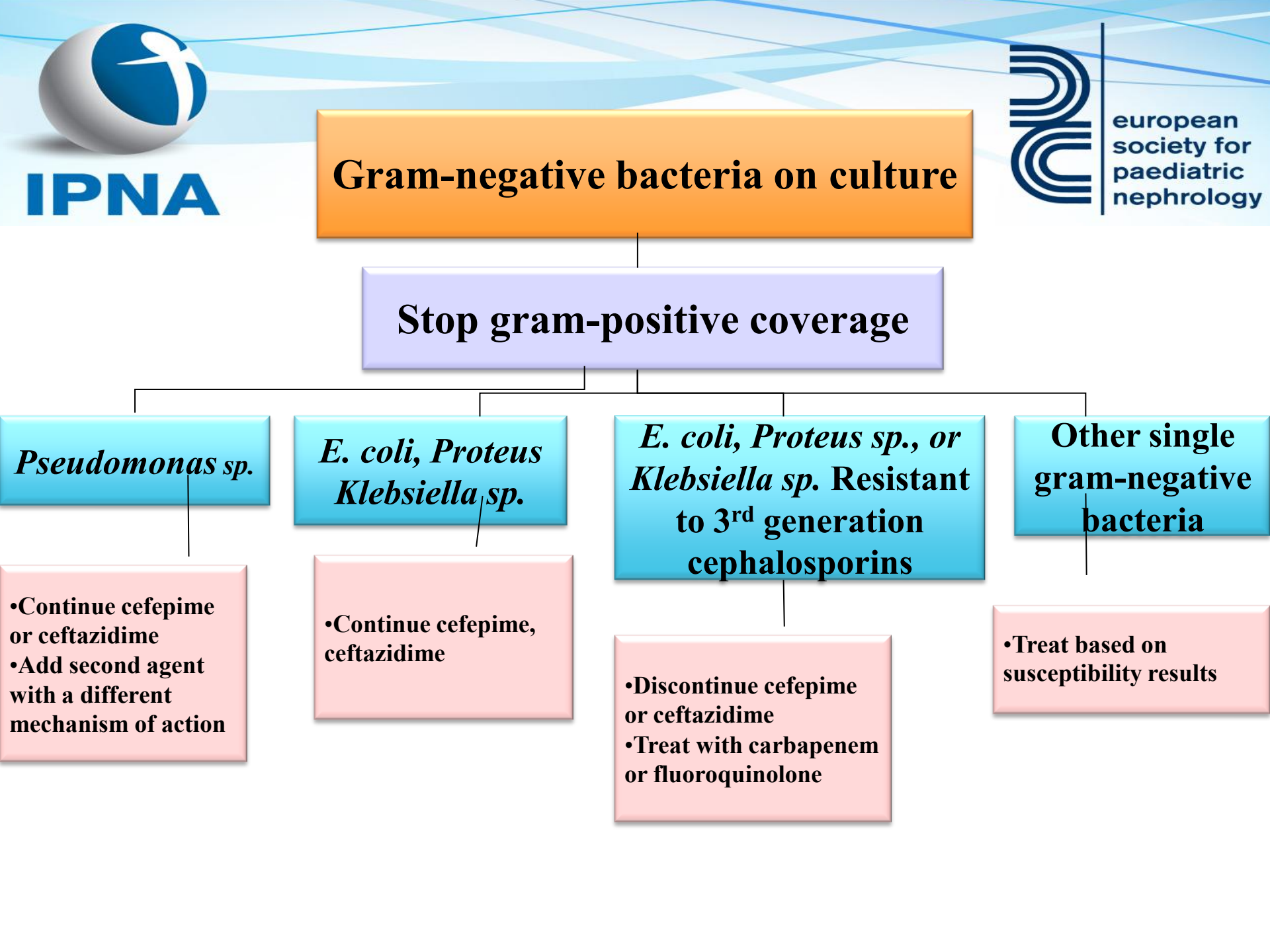
	Continuous therapy		Intermittent therapy
	Loading dose	Maintenance dose	
Aminoglycosides[a]			
Gentamicin	8 mg/L	4 mg/L	anuric: 0.6 mg/kg non-anuric: 0.75 mg/kg.
Netilmycin	8 mg/L	4 mg/L	
Tobramycin	8 mg/L	4 mg/L	
Cephalosporins			
Cefazolin	500 mg/L	125 mg/L	20 mg/kg
Cefepime	500 mg/L	125 mg/L	15 mg/kg
Cefotaxime	500 mg/L	250 mg/L	30 mg/kg
Ceftazidime	500 mg/L	125 mg/L	20 mg/kg
Glycopeptides[b]			
Vancomycin	1000 mg/L	25 mg/L	30 mg/kg; repeat dosing 15 mg/kg every 3-5 days
Teicoplanin[c]	400 mg/L	20 mg/L	15 mg/kg q 5 – 7 days
Penicillins[a]			
Ampicillin	----------	125 mg/L	----------
Quinolones			
Ciprofloxacin	50 mg/L	25 mg/L	----------
Others			
Aztreonam	1000 mg/L	250 mg/L	----------
Clindamycin	300 mg/L	150 mg/L	----------
Imipenem/Cilastin	250 mg/L	50 mg/L	----------
Oral			
Linezolid	< 5 yrs: 30 mg/kg/day divided TID; 5-11 yrs: 20 mg/kg/day divided BID; ≥ 12 yrs 600 mg/dose BID		
Metronidazole	30 mg/kg/day divided TID		
Rifampin	10-20 mg/kg/day divided BID		
Antifungals			
Fluconazole	6 – 12 mg/kg IP, IV or PO every 24-48 hrs (max dose 400 mg)[#]		
Caspofungin	IV only: initial dose 70 mg/m^2 on day 1 (max dose 70 mg); Subsequent dosing 50 mg/m^2 daily (max dose 50 mg)		



MRSA-methicillin resistant *S. aureus*; methicillin sensitive *S. aureus*; VRE-vancomycin resistant enterococci.

Gram-positive bacteria + recommended AB and length of therapy

	Recommended Antibiotic(s)*	Length of Therapy
Methicillin-resistant S. aureus	Vancomycin/ Teicoplanin , Clindamycin	3 weeks
Methicillin-susceptible S. aureus	Cefazolin, Cefepime	3 weeks
Coagulase negative staphylococci	Vancomycin/ Teicoplanin , Clindamycin if MR	2 weeks
Enterococcus sp.	Ampicillin, vancomycin/ teicoplanin	3 weeks
Vancomycin resistant enterococcus	Ampicillin, linezolid	3 weeks
Streptococcus species	Ampicillin, cefazoline, cefepime	2 weeks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Gram-negative bacteria on culture
Stop gram-positive coverage
Pseudomonas sp.
E. coli, Proteus Klebsiella sp.
E. coli, Proteus sp., or Klebsiella sp. Resistant to 3rd generation cephalosporins
Other single gram-negative bacteria
•Continue cefepime or ceftazidime
•Add second agent with a different mechanism of action
•Continue cefepime, ceftazidime
•Discontinue cefepime or ceftazidime
•Treat with carbapenem or fluoroquinolone
•Treat based on susceptibility results

Gram-negative bacteria and the recommended antibiotics and length of therapy.

Bacteria	Recommended Antibiotic(s)*	Length of Therapy
E. coli, Klebsiella sp.	Cefazolin, cefepime, ceftazidime, ceftriaxone/ cefotaxime	2 weeks
E. coli, Klebsiella sp. resistant to 3rd generation cephalosporins	Carbapenem** or fluoroquinolone	3 weeks
Enterobacter sp., Citrobacter sp., Serratia sp., Proteus sp.	Cefepime, ceftazidime or carbapenem**	2-3 weeks
Acinetobacter sp.	Cefepime, ceftazidime or carbapenem	2-3 weeks
Pseudomonas species	Cefepime, ceftazidime, piperacillin or ticarcillin, plus aminoglycoside or fluoroquinolone	3 weeks – 4 weeks
Stenotrophomonas maltophila	Trimethoprim/sulfamethoxazole, Ticarcillin/clavulanic acid, tigecycline, colistin	3 weeks – 4 weeks

Culture

- If the initial cultures remain sterile at 72 hours and signs and symptoms of peritonitis are improved
  - empiric antibiotic therapy consisting of cefepime, cefazolin, a glycopeptide and/or ceftazidime be continued for 2 weeks
  - the administration of an aminoglycoside be discontinued
  - If no improvement,
    - repeat culture studies
    - After 5 days, remove the catheter

Fungal peritonitis

- <2% of all peritonitis episodes in children
- Risk factors
  - Prior antibiotic use
  - Gastrostomy ?
  - Antifungal prophylaxis during antibiotic usage in programs with high rates of fungal peritonitis
- If fungi are identified by Gram stain or culture of peritoneal effluent, therapy should consist of treatment with an antifungal agent and early catheter removal
- Following catheter removal, antimycotic therapy be administered for 2 weeks or longer after catheter removal and complete resolution of the clinical symptoms of infection

Treatment

- Fluconasole for Candida species
- Caspofungin for non responding non-albicans Candida
- Voriconasole for Asergillus

- Treatment duration following catheter removal should be 2 weeks or longer following complete resolution of the clinical symptoms of infection

  - Amphotericin B
    - Poor peritoneal penetration
    - Intraperitoneal irritation and abdominal pain

Indications for catheter removal and replacement

Catheter removal		Reinsertion
	Refractory bacterial peritonitis	After 2-3 weeks
	Fungal peritonitis	After >2 weeks
	ESI/TI in conjunction with peritonitis with the same organism (mainly, S. aureus and P. aeruginosa; except CNS)	After 2-3 weeks
Simultaneous removal and replacement of the catheter	Relapsing or refractory ESI/TI (including P. aeruginosa) Relapsing peritonitis	
Relative indications for removal	Repeat peritonitis	After 2-3 weeks
	Peritonitis with multiple enteric organisms due to an intra-abdominal pathology/ abscess; so-called surgical peritonitis	Dependent upon the clinical course of the patient; at least 2-3 weeks

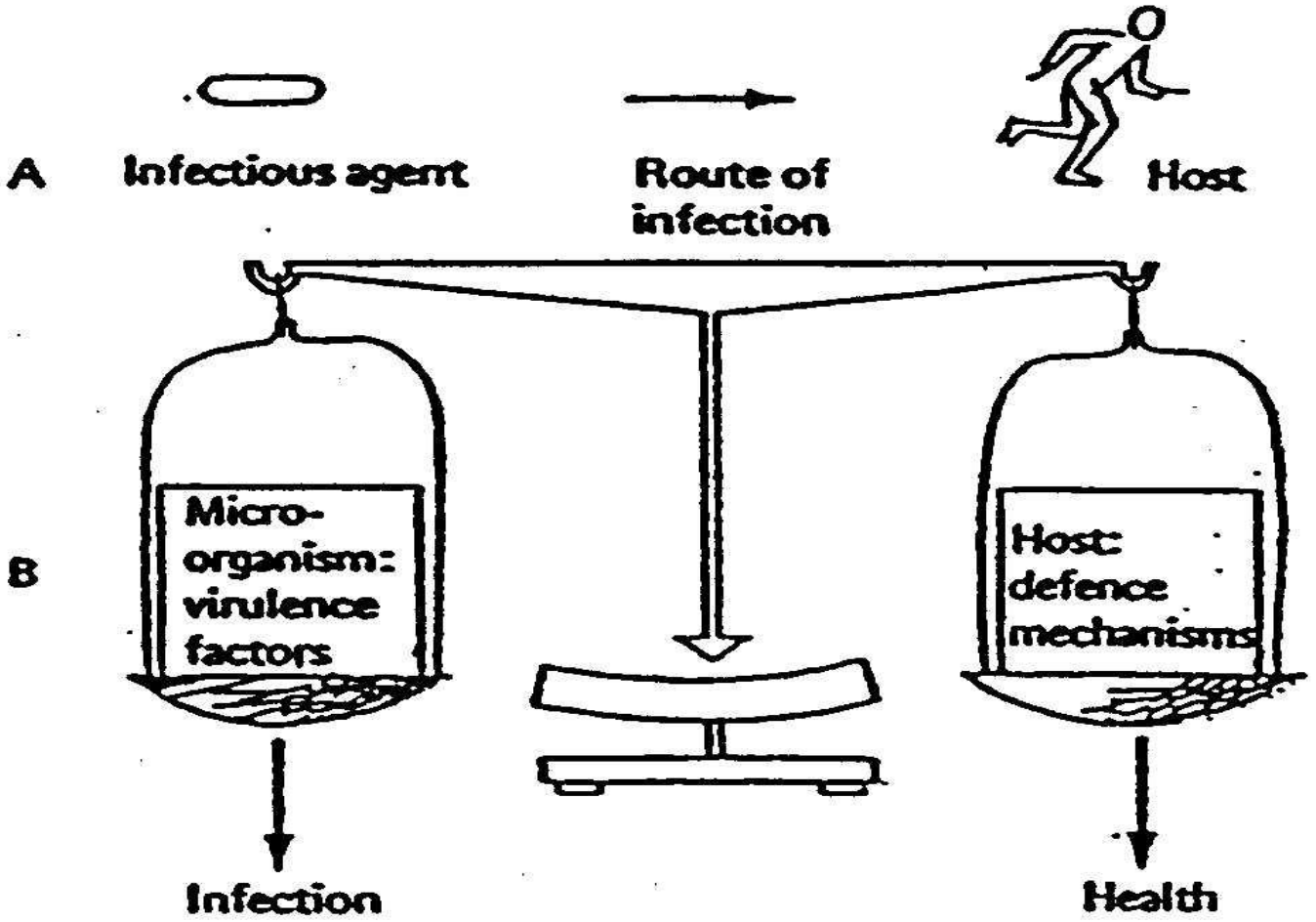
Indications for removal of the catheter

- Fungal peritonitis
- Severe intrabdominal sepsis or shock
- Exit site infection due to the same organism
- Relapse with same organism after 4 weeks
- WCC>100 after 3-4 days if infection severe, 7 days if mild
- Symptomatic after 3-4 days

After catheter removal

- Continue antibiotics for 5-7 days
- Do not reinsert catheter until
  - Peritonitis gone
  - Staph aureus eliminated
  - Catheter tunnel clear of infection

ROLE OF HOST DEFENSE IN INFECTIOUS COMPLICATIONS

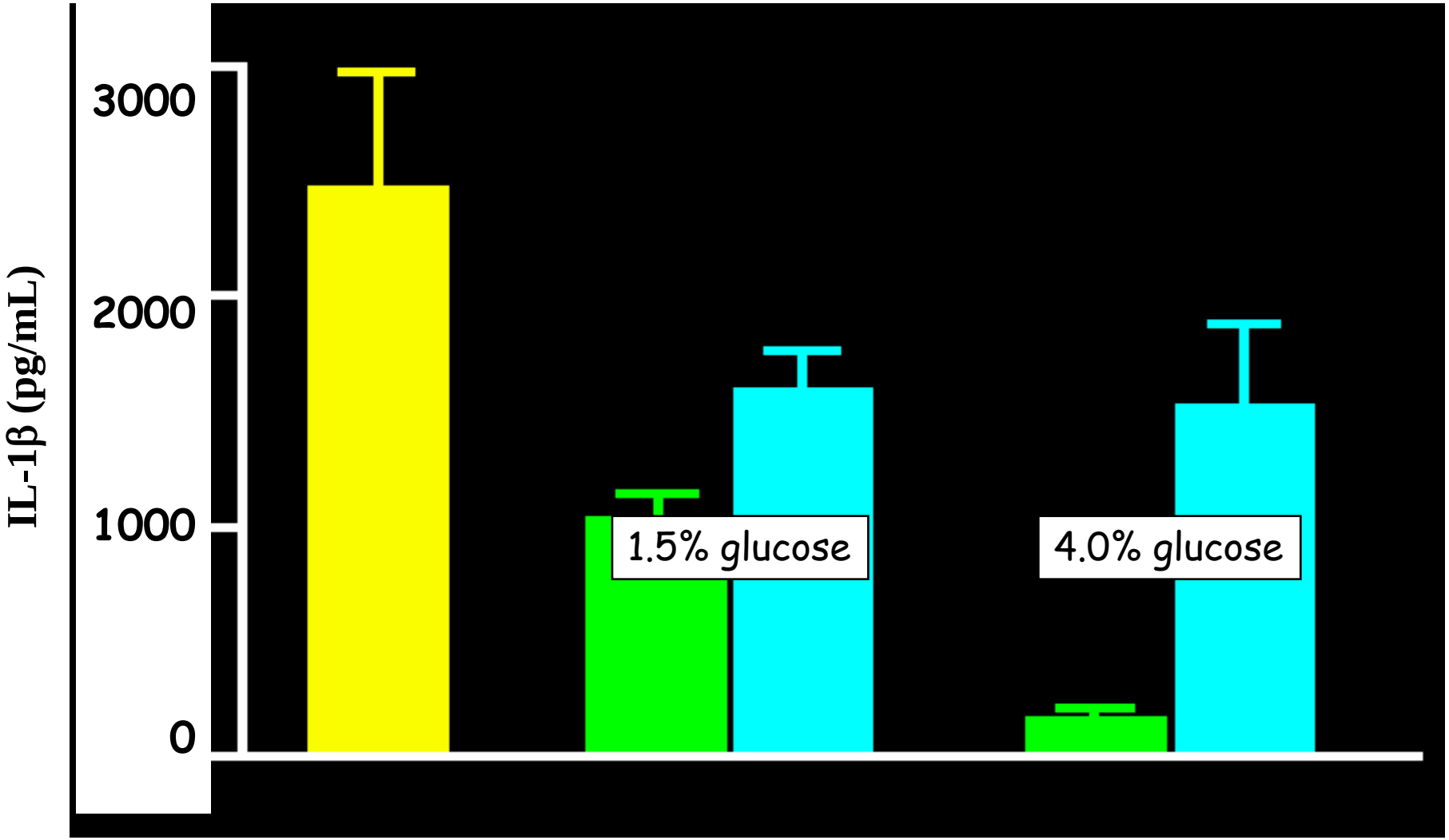


Peritoneal defense mechanisms

- Cellular defense :
  - Peritoneal PMN in PD-patients are in a “chronically elicited” state, with a decreased response upon stimulation, possibly due to low pH, glucose, GDP’s, osmolarity and the presence of uremic toxins in the dialysate

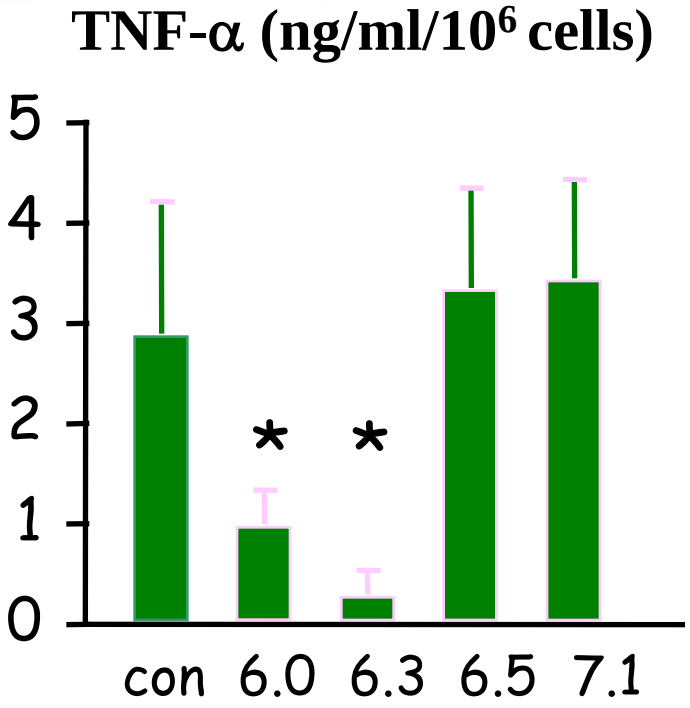
Topley et al, oa Kidney Int, 34, 404-411, 1988
Jörres et al, Perit Dial Int, 13, suppl 2, S291-S294
Vanholder et al, Kidney Int, 50, 643-652, 1996

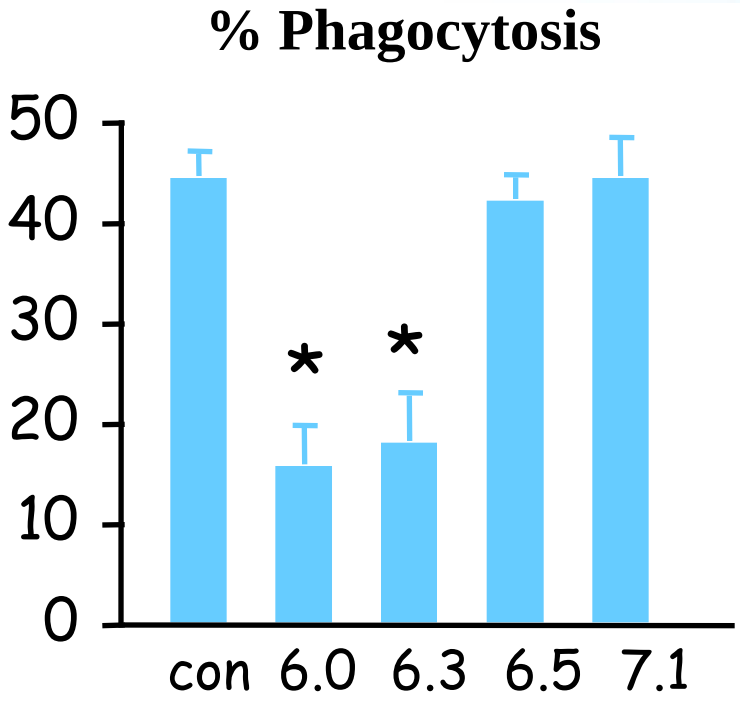
GDP : Effects on Host Defense



Wieslander et al, PDI, 15, S52-59, 1995.

Phagocytosis and TNF-α release in monocytes are dependent on intracellular pH



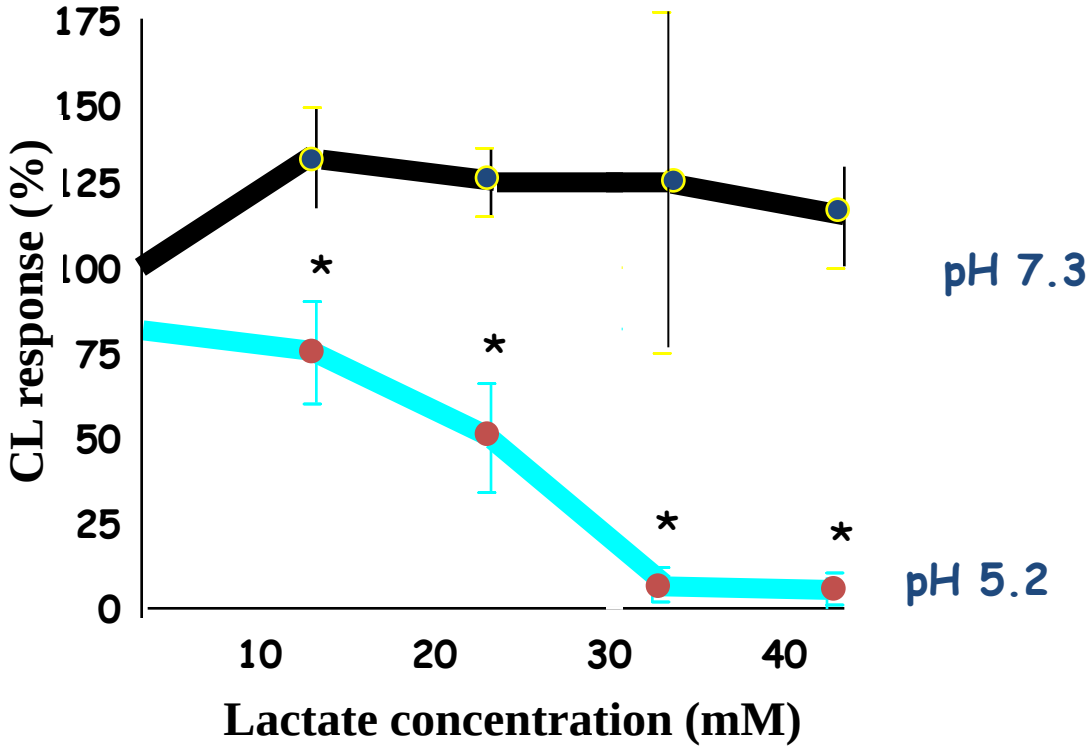


* p < 0.05 vs. control

Douvdevani et al, J Am Soc Nephrol 1995, 6: 207-213

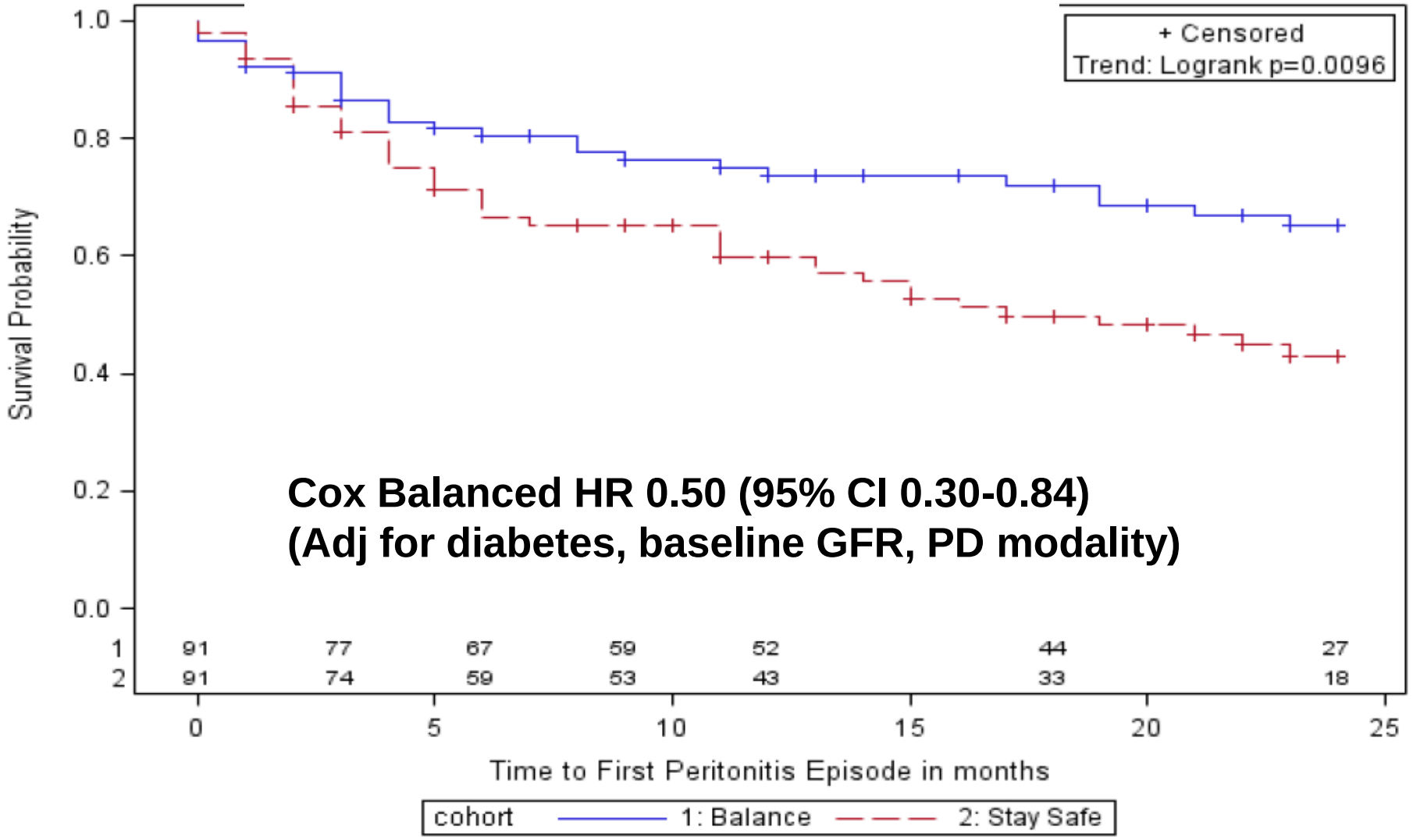
Effect of pH on respiratory burst activation of PMN

Chemiluminescence response



Liberek, Topley, Jörres et al, Nephron 1993; 65: 260-265

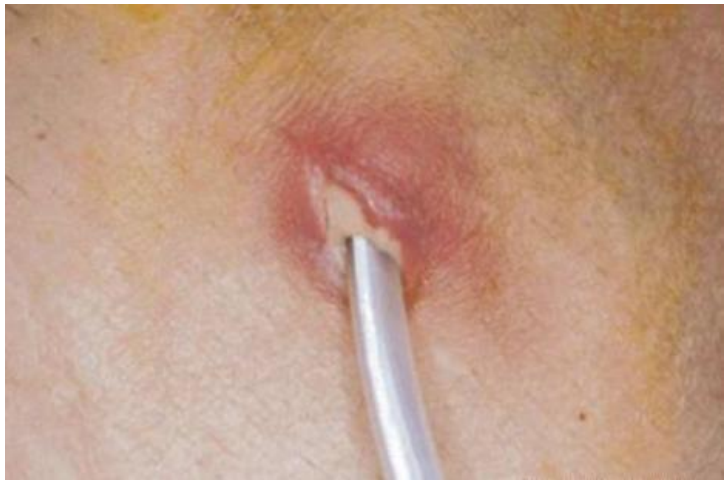
Peritonitis: BalANZ

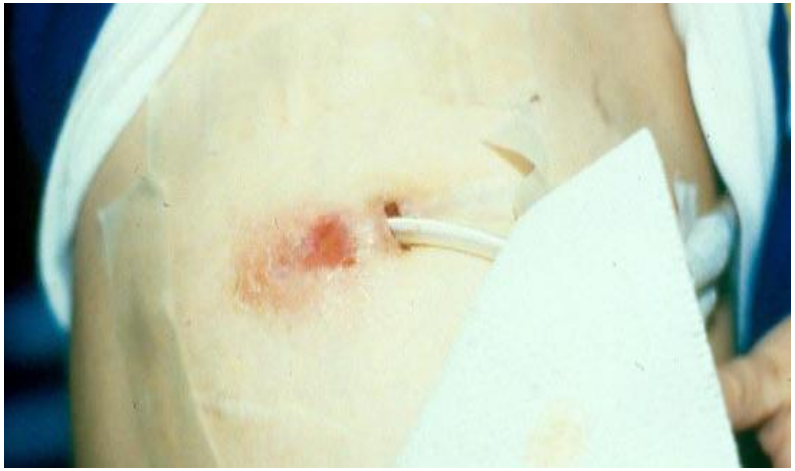


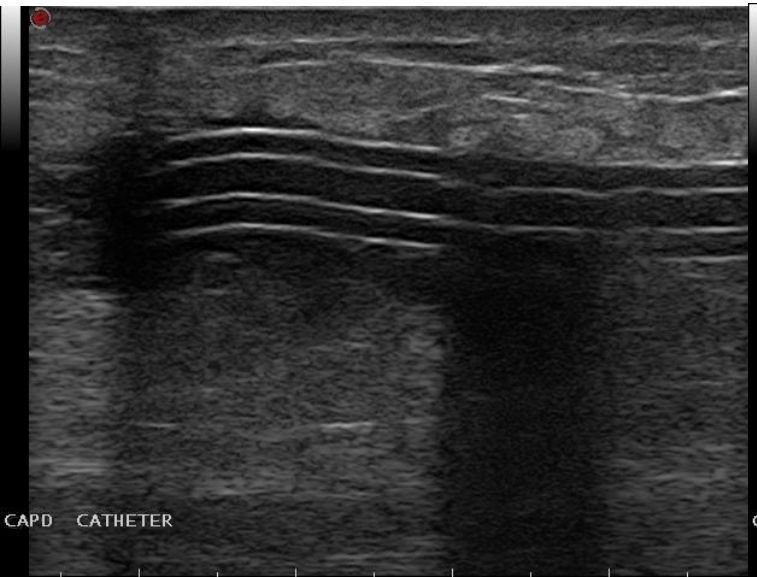
Cox Balanced HR 0.50 (95% CI 0.30-0.84)
(Adj for diabetes, baseline GFR, PD modality)

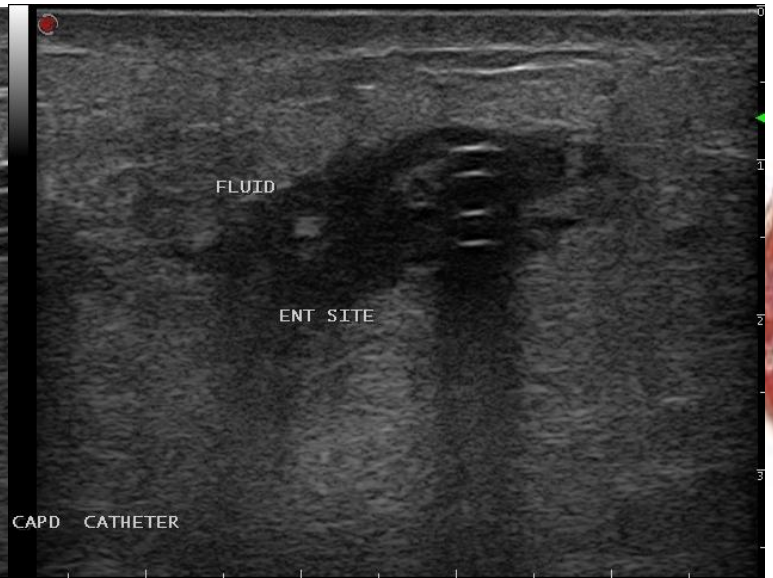
Johnson D PDI 2012

Exit-site / Tunnel infections







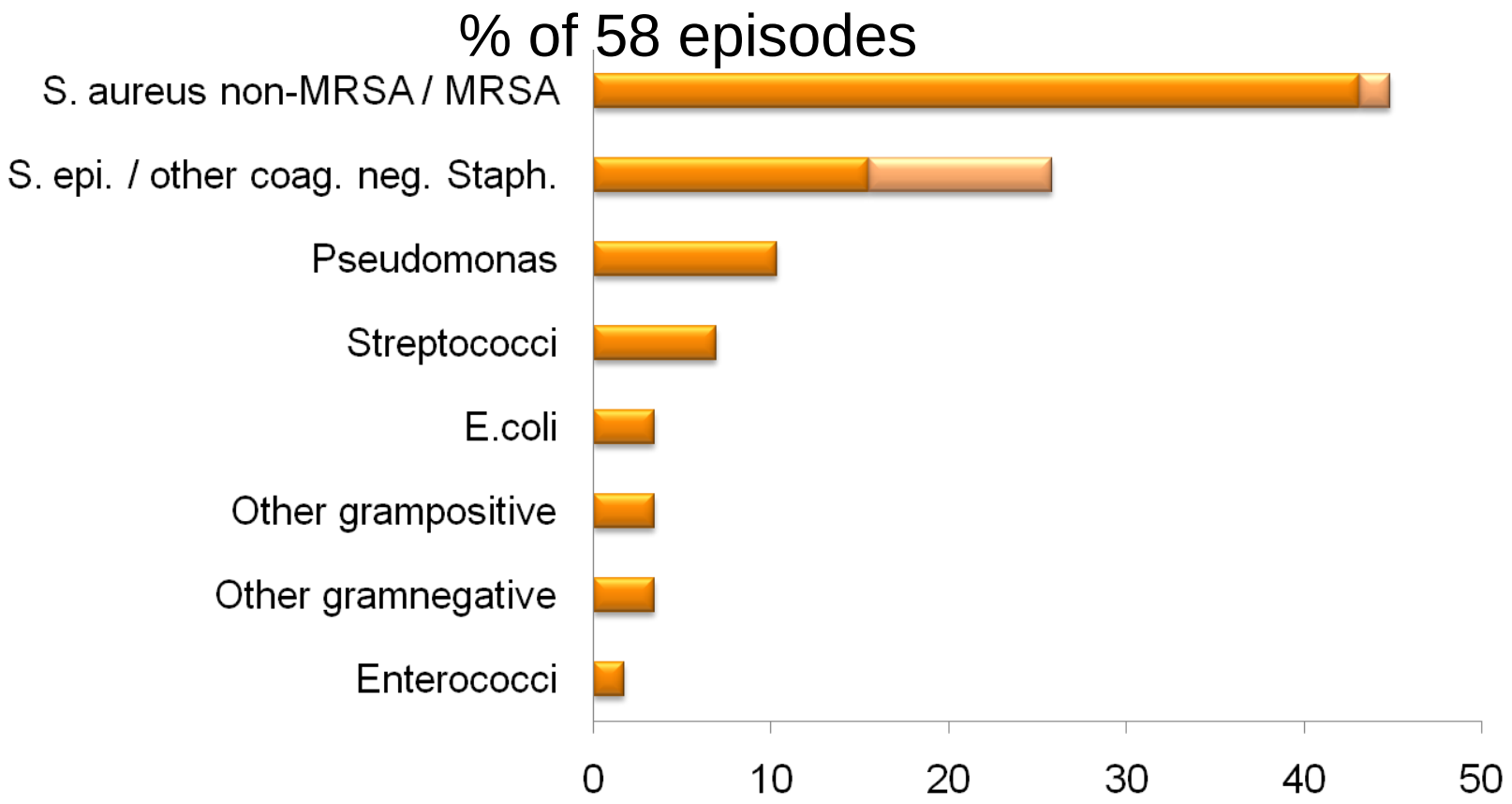


Exit-site scoring system

	0 Points	1 Point	2 Points
Swelling	No	Exit only (< 0.5cm)	Including part of or entire tunnel
Crust	No	< 0.5cm	> 0.5cm
Redness	No	< 0.5cm	> 0.5cm
Pain on pressure	No	Slight	Severe
Secretion	No	Serous	Purulent

Schaefer et al., J Am Soc Nephrol 1999

Causative Organisms at Exit Site



Scahefer F, Orlando 2008

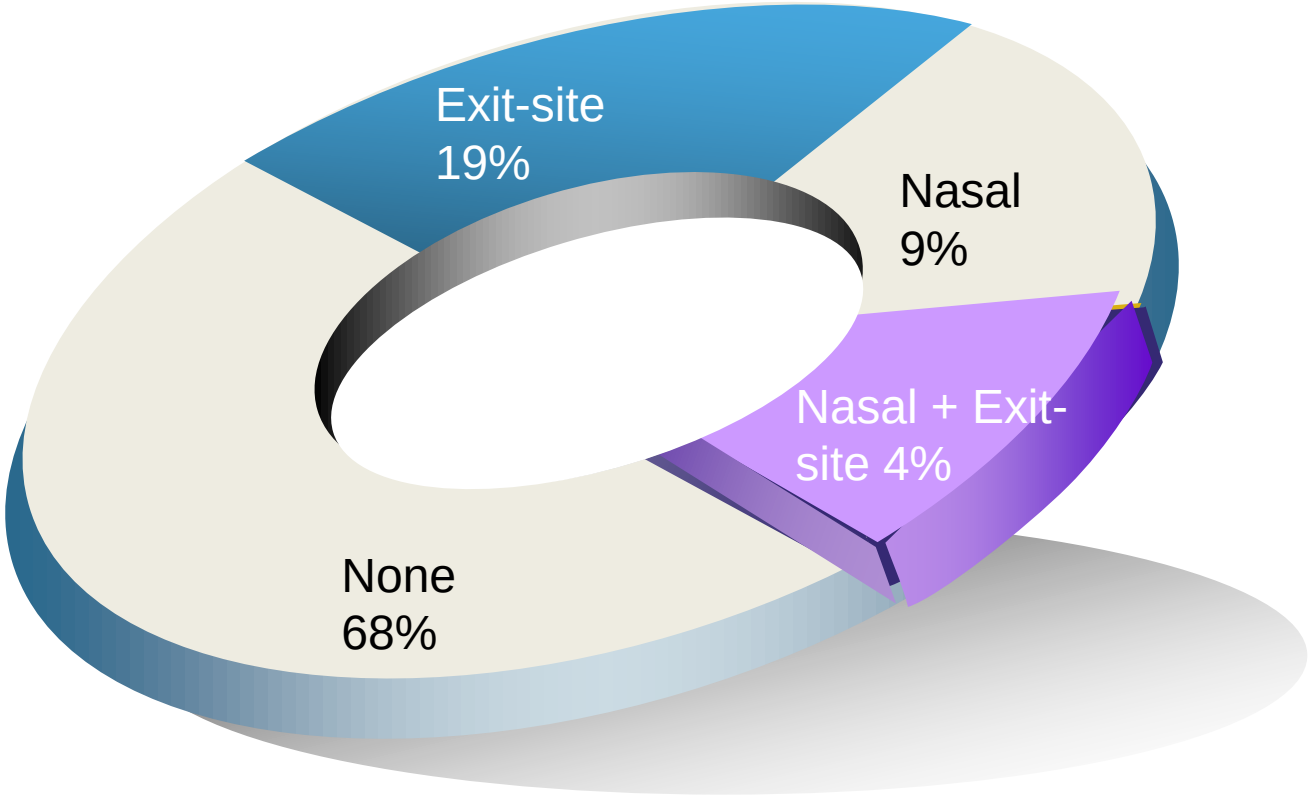
Treatment of Exit-site / Tunnel Infections

- **Exit-site infections:**
  - **Score 4-5**
  - **Oral antibiotic therapy when culture results and susceptibilities available**
  - **Gram positive usually penicillinase-resistant penicillin or cefalexin**
  - **Gram negative IP ceftazidime, combination therapy for Pseudomonas**
  - **a minimum of 2 weeks (3 weeks for *S. aureus* and *P. aeruginosa,* max 4 weeks)**
  - **at least 7 days following complete resolution of the infection**

Tunnnel infections:

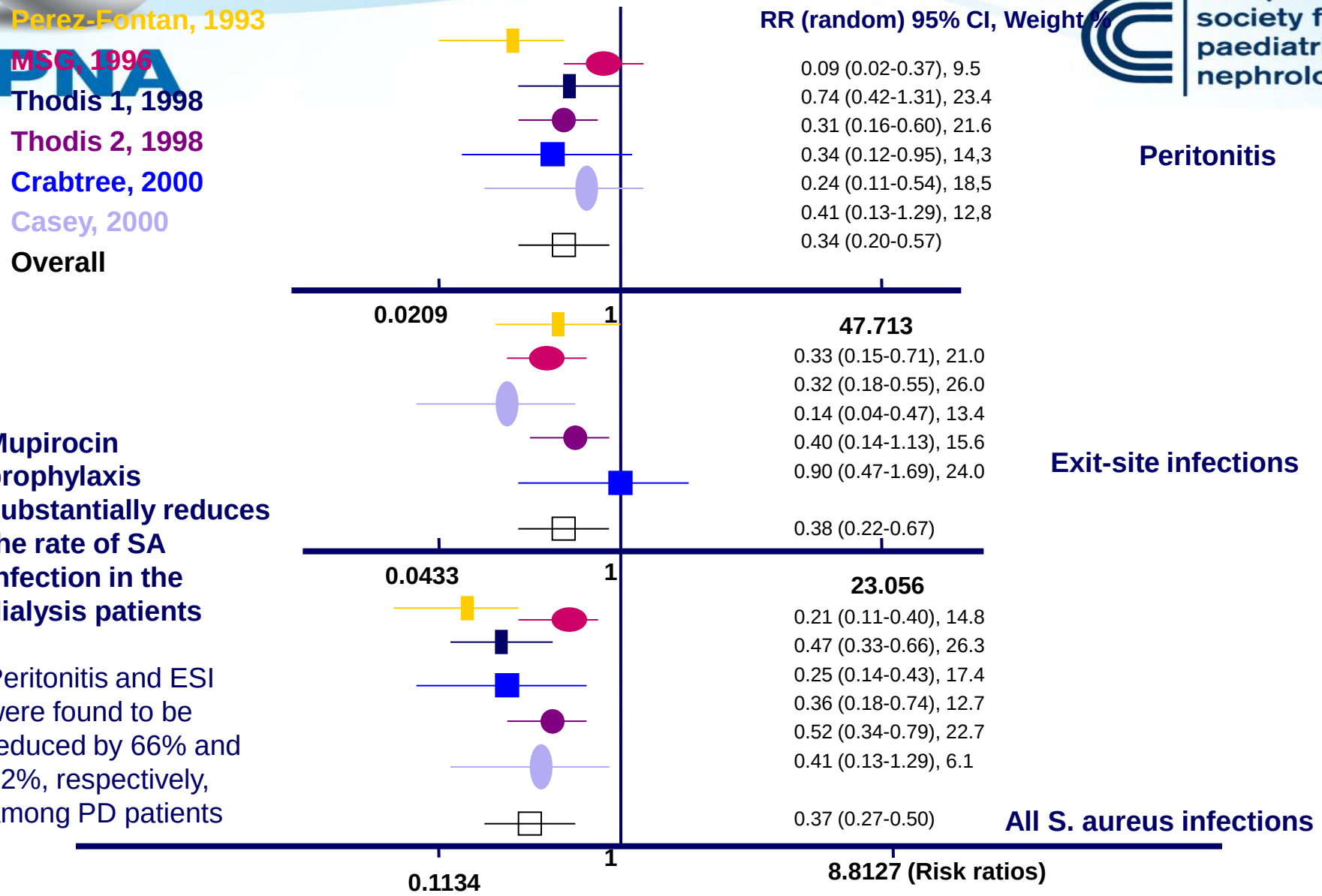
- **Score ≥6**
- **Antibiotic therapy after culture and susceptibility results have been obtained**
- **Signs of severe infection, and/or a history of S. aureus or P. aeruginosa initiation of empiric therapy should be considered.**
- **Oral, intraperitoneal or intravenous routes**
- **MRSA IV**
- **Treatment duration should be 2-4 weeks**

Topical S. aureus Prophylaxis



Scahefer F, Orlando 2008

Risk ratios and 95% CIs for mupirocin vs. plc or no prophylaxis in clinical trials on S. aureus-related infections



Mupirocin prophylaxis substantially reduces the rate of SA infection in the dialysis patients

Peritonitis and ESI were found to be reduced by 66% and 62%, respectively, among PD patients

Tacconelli et al, CID 2003

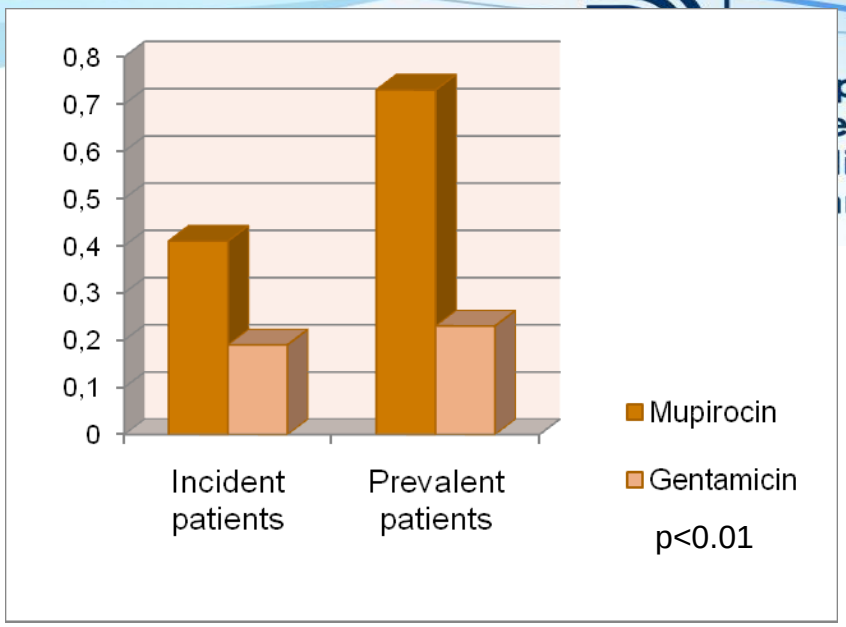
First RCT

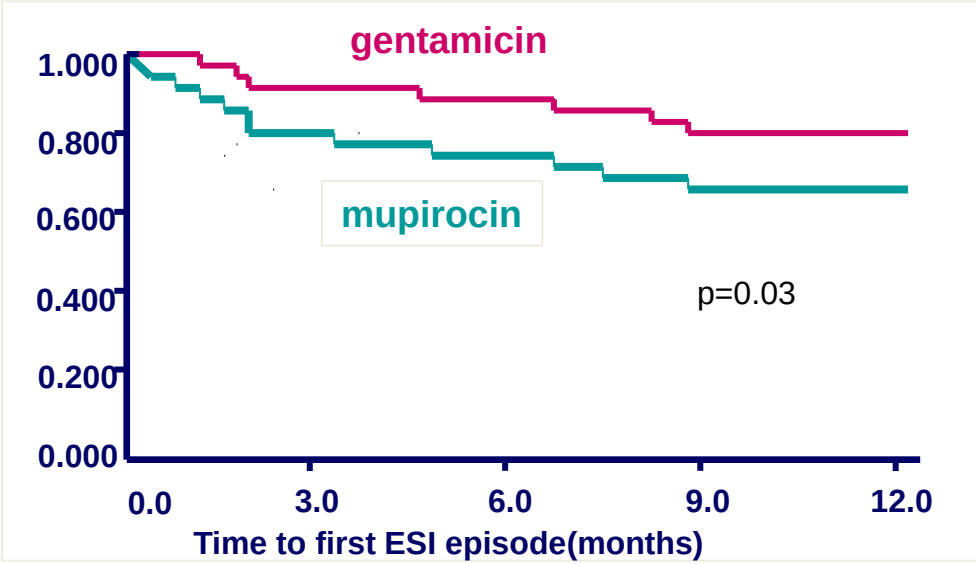
Gentamicin vs Mupirocin

- Gentamicin cream daily to the exit site was highly effective in reducing *P. aeruginosa ESI and* as effective as mupirocin cream in preventing *S. aureus ESI*

- 57% reduction in ESI
- 35% reduction in peritonitis

- Peritonitis with Gr (-) agents occurred less often using gentamicin (0.22/year vs 0.15/year, p=0.003).

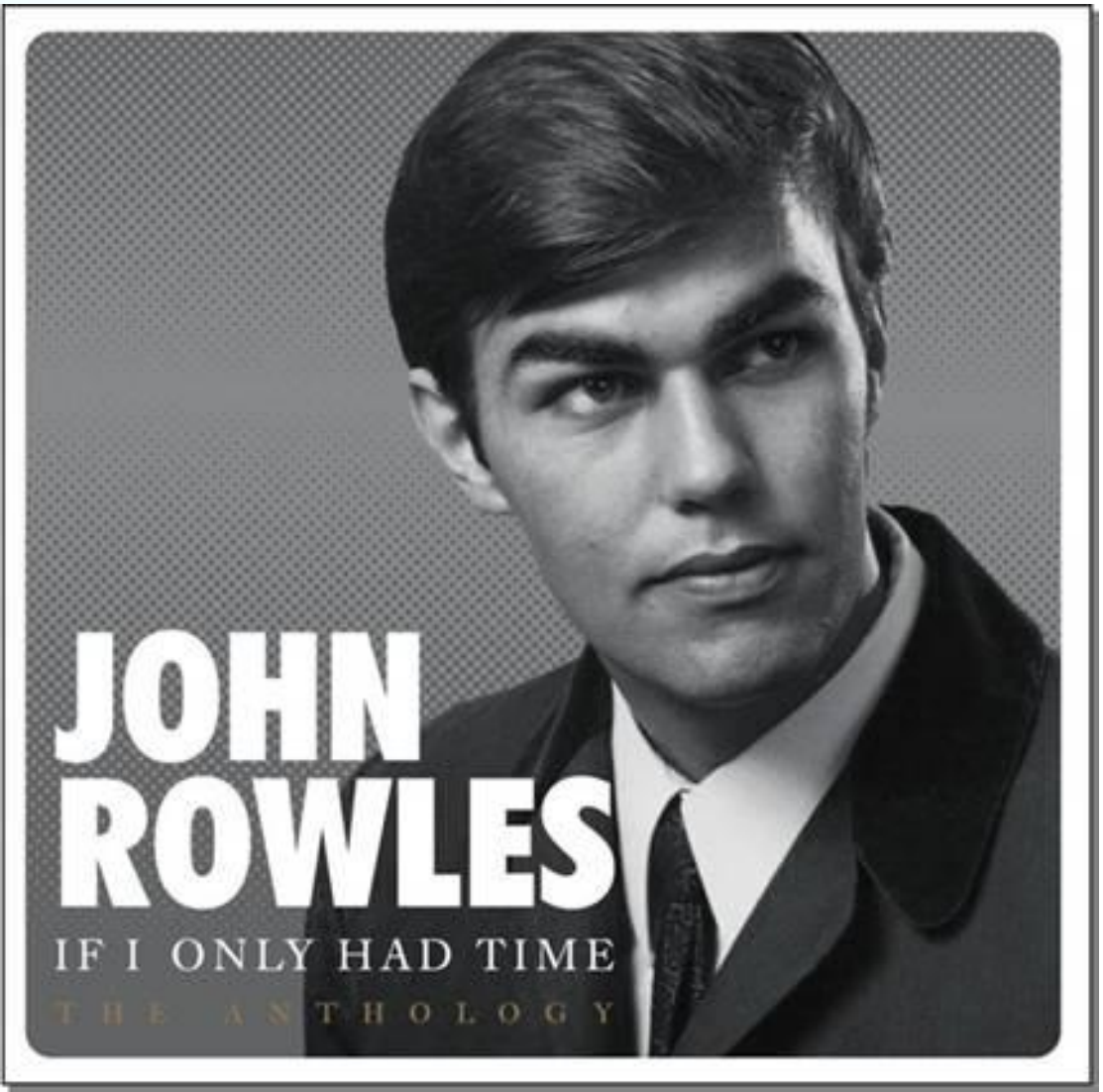




Bernardini J, JASN 2005;16:539-545

IPNA

european society for paediatric nephrology



- Annual dialysis conference USA
- Plan ESPN-WG: HD + PD-course