

# ISPD Peritonitis Guidelines

## 2022 Update on Prevention and Treatment

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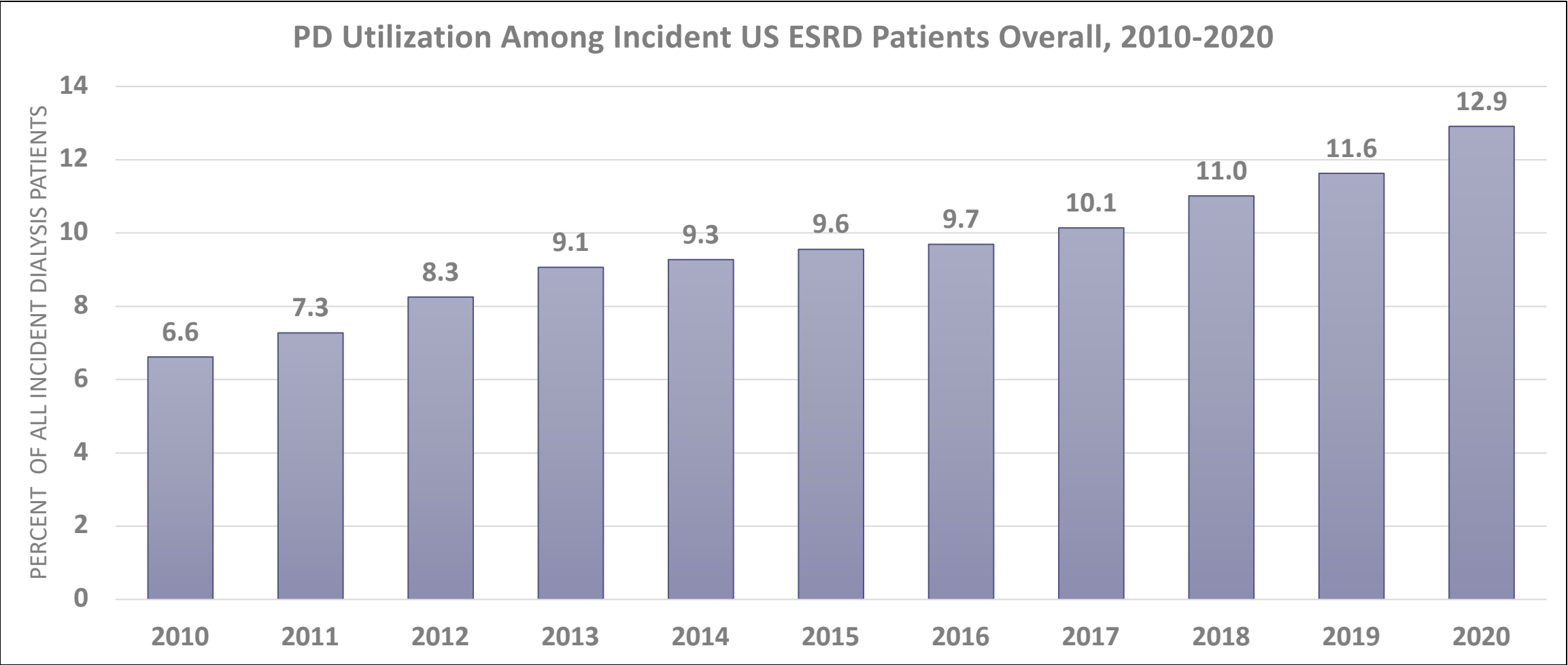
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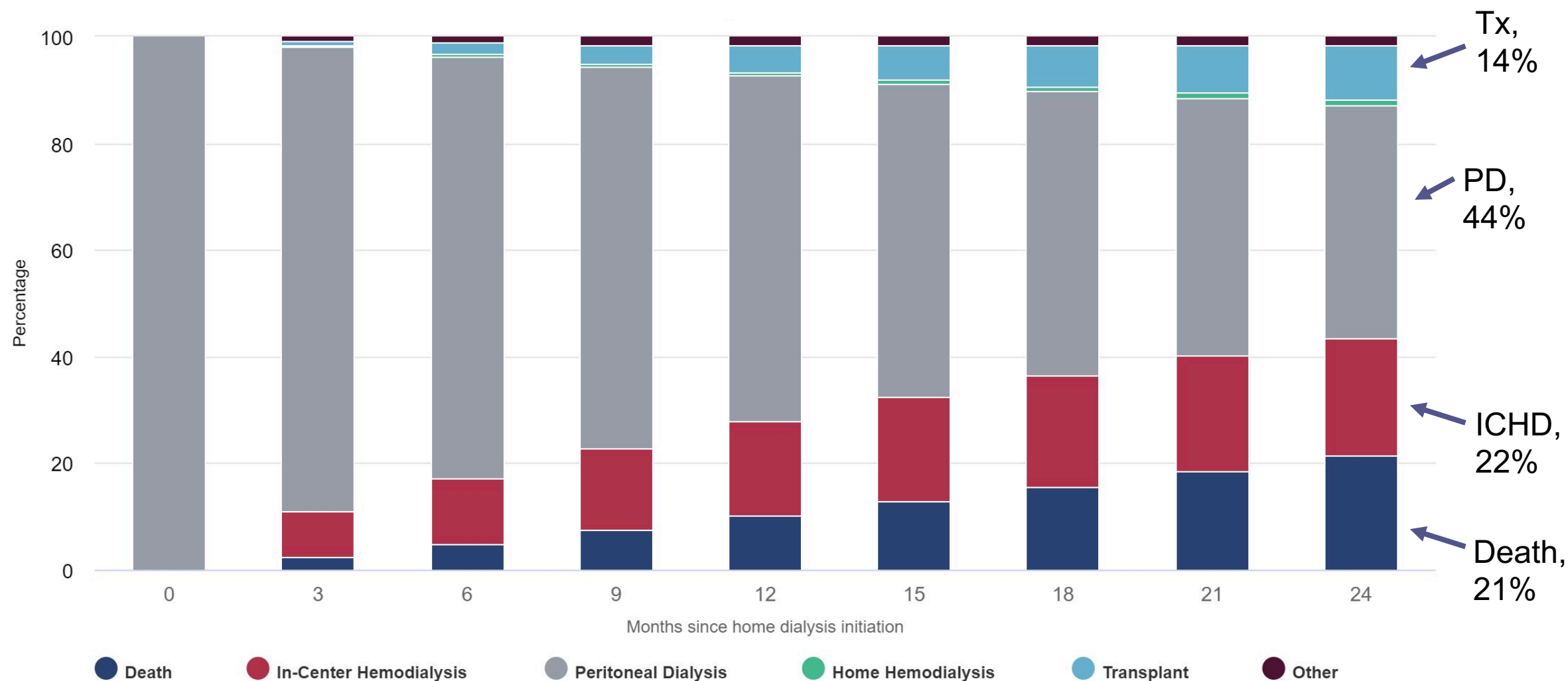
# Objectives

1. Summarize (many) recommendations from the 2022 update to the ISPD guidelines for prevention and treatment of PD peritonitis
2. Describe key changes and updates from the 2016 ISPD guidelines
3. Review data/literature supporting key updates

# Growing proportional use of PD in the US

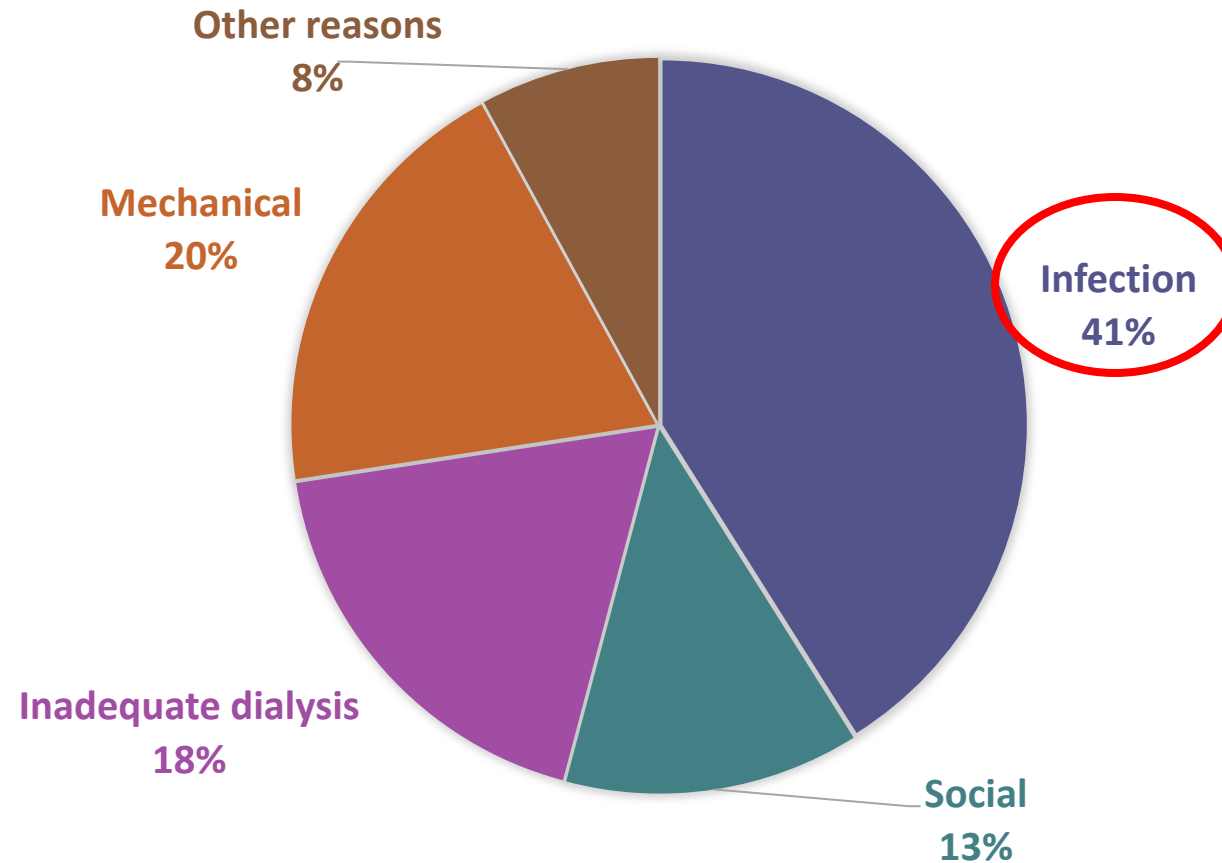


# Outcomes over the 24 months following PD initiation, 2017-2018





# Reasons for transfer from PD to HD among incident PD patients



# Peritonitis remains Achilles heel for PD

- The most common infection in PD patients
- Major cause of morbidity and mortality in PD
  - Increased incidence of temporary and permanent transfer to in-center HD
  - Increased risk for hospitalization and death
  - Patient pain & enhanced burden of treatment
  - Injury to peritoneal membrane leading to higher rates of small solute transport
    - Problems with subsequent volume control and overload



# ISPD peritonitis guideline recommendations: 2022 update on prevention and treatment

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## Abstract

Peritoneal dialysis (PD)-associated peritonitis is a serious complication of PD and prevention and treatment of such is important in reducing patient morbidity and mortality. The ISPD 2022 updated recommendations have revised and clarified definitions for

# Grading quality of evidence and strength of recommendations

- GRADE (Grading of Recommendations, Assessment, Development, and Evaluations)

Certainty	What it means
Very low	The true effect is probably markedly different from the estimated effect
Low	The true effect might be markedly different from the estimated effect
Moderate	The authors believe that the true effect is probably close to the estimated effect
High	The authors have a lot of confidence that the true effect is similar to the estimated effect

**Grade has inherent subjectivity – 2 individuals evaluating the same body of evidence might reasonably come to different conclusions about its certainty!**

# Recommendations in ISPD 2022 peritonitis guidelines

Grade	Meaning	# of recommendations
1A	We recommend (high quality evidence)	1
1B	We recommend (moderate quality evidence)	5
1C	We recommend (low quality evidence)	16
1D	We recommend (very low quality evidence)	1
2A	We suggest (high quality evidence)	1
2B	We suggest (moderate quality evidence)	4
2C	We suggest (low quality evidence)	17
2D	We suggest (very low quality evidence)	11
Not graded	N/A	13
<b>Total</b>	<b>N/A</b>	<b>69</b>

**More research needed in PD peritonitis to enhance level of evidence!**

# What is NOT new...

1. General definition of peritonitis in a patient on PD
2. Definitions of recurrent, relapsing, repeat, and refractory peritonitis
3. Systemic prophylactic antibiotics at time of PD catheter placement
4. Antibiotic prophylaxis prior to colonoscopy and invasive GYN procedures
5. Anti-fungal prophylaxis whenever PD patients receive an antibiotic course
6. Empiric antibiotics should generally include gram positive (vanc or 1<sup>st</sup> gen cephalosporin) and gram negative (3<sup>rd</sup> gen cephalosporin or AG) coverage
7. IP route of antibiotics preferred unless patient has signs of sepsis
8. Recommendations for organism-specific treatment regimens and durations are generally unchanged (with a few exceptions)
9. Still insufficient evidence to support novel diagnostic techniques for peritonitis

# PD Peritonitis - diagnosis

We recommend that peritonitis should be diagnosed when at least two of the following are present (1C):

1. Clinical features consistent with peritonitis (abdominal pain and/or cloudy effluent)
2. Dialysis effluent WBC  $> 100/\mu\text{L}$  or  $> 0.1 \times 10^9/\text{L}$  (after dwell time of at least 2 hours)
  - $> 50\%$  are neutrophils
3. Positive dialysis effluent culture

# ISPD peritonitis definition NOT consistently used in the literature

Table 2. Peritonitis definitions across the included studies.

Study no.	Publication year	Criteria						Number of criteria required for diagnosis	As per ISPD guidelines (no further details)			No definition provided
		1. Dialysis effluent		2. Positive culture	3. Clinical features							
		WBC >100 cells/ $\mu$ L	Neutrophils >50%		Cloudy effluent	Abdomen pain	Fever					
1	2017						2/3					
2	2007											
3	2009						2/2					
4	2010											
5	2009						3/3					
6	2017											
7	2016											
8	2010						1/1					
9	2011						1/1					
10	2011						2/2					
11	2010						2/3					
12	2013											
13	2012						2/2					
14	2013						2/2					
15	2012						2/2					
16	2009						1/1					
17	2011											
18	2016											
19	2010						3/3					
20	2016											
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24	2015											
25	2008						2/2					
26	2010											
27	2010						2/3					
28	2007						2/2					
29	2010						1/1					
30	2018											
31	2013											
32	2014						2/2					
33	2012											
34	2011						2/3					
35	2010						3/3					
36	2013						2/3					
37	2014											
38	2016											
39	2017						2/2					
40	2011											
41	2011											
42	2013											

43	2011										
44	2015										
45	2012										
46	2009										
47	2018										
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66	2010										
67	2015										
68	2012										
69	2017										
70	2007										
71	2008										
72	2016										
73	2012										
74	2018										
75	2008										
76	2008										
77	2013										

Black shade indicates factor was present in study.

**77 studies (including 3 RCTs)**  
**29% did not state criteria for peritonitis diagnosis**  
**42% used a criteria different/modified from ISPD**



# Outcome-specific definitions following PD peritonitis



## Refractory peritonitis

Peritonitis persistently after 5 days of appropriate antibiotic therapy



## Recurrent peritonitis

Peritonitis - within 4 weeks of completion of therapy of a prior episode, **different organism**



## Relapsing peritonitis

Peritonitis within 4 weeks of therapy of a prior episode with the **same organism** or **one culture negative episode followed by culture negative** (or specific organism)

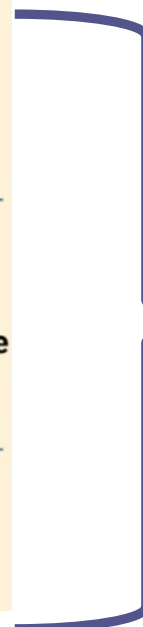


## Repeating peritonitis

Peritonitis > 4 weeks of therapy of a prior episode with the **same organism**



“We recommend that PD catheter be removed.” (1D)



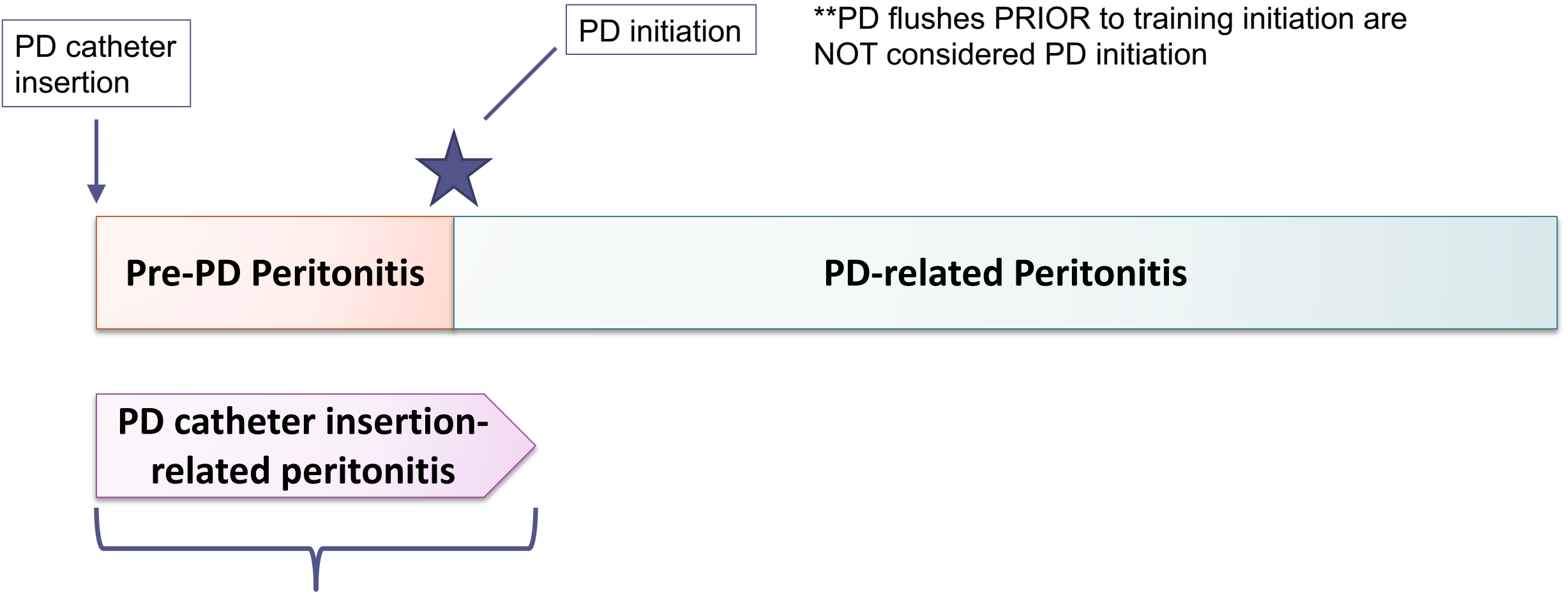
We recommend timely PD catheter removal be considered (1C)

We suggest that simultaneous PD catheter removal and reinsertion be considered when PD effluent WBC count <100/uL in absence of ESI or tunnel infection (2C)

# What IS new...

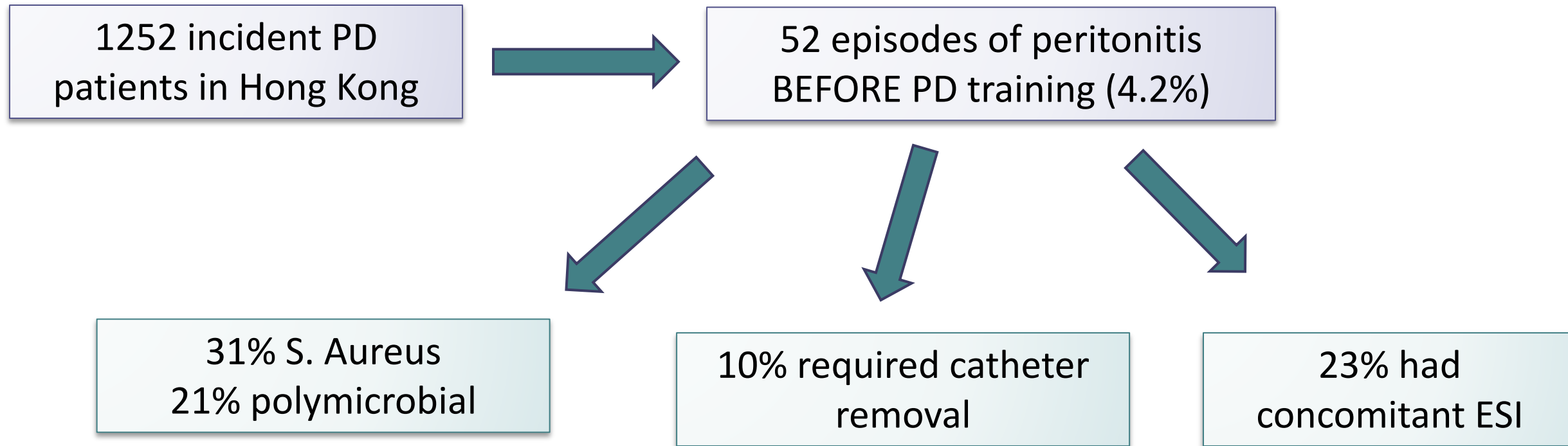
1. New definitions for time-specific and cause-specific peritonitis in PD patients
2. Decrease in goal peritonitis rate to  $<0.4$  episodes per patient-year
3. Updated recommendations on “wet” contamination of the PD system
4. Enhanced focus on prompt empirical antibiotics (IV or IP, though IP preferred)
5. A new recommendation to consider NAC in patients treated with aminoglycosides
6. Hypokalemia treatment prevent peritonitis in PD patients
7. Suggestion to avoid H2 antagonists to prevent enteric peritonitis
8. Suggestion to consider icodextrin for volume overload during acute peritonitis
9. Revised recommendations about removing PD catheter in patients with peritonitis with improving WBC count

# Time-specific peritonitis



Up to 30 days after PD catheter insertion

# Pre-PD peritonitis under-recognized

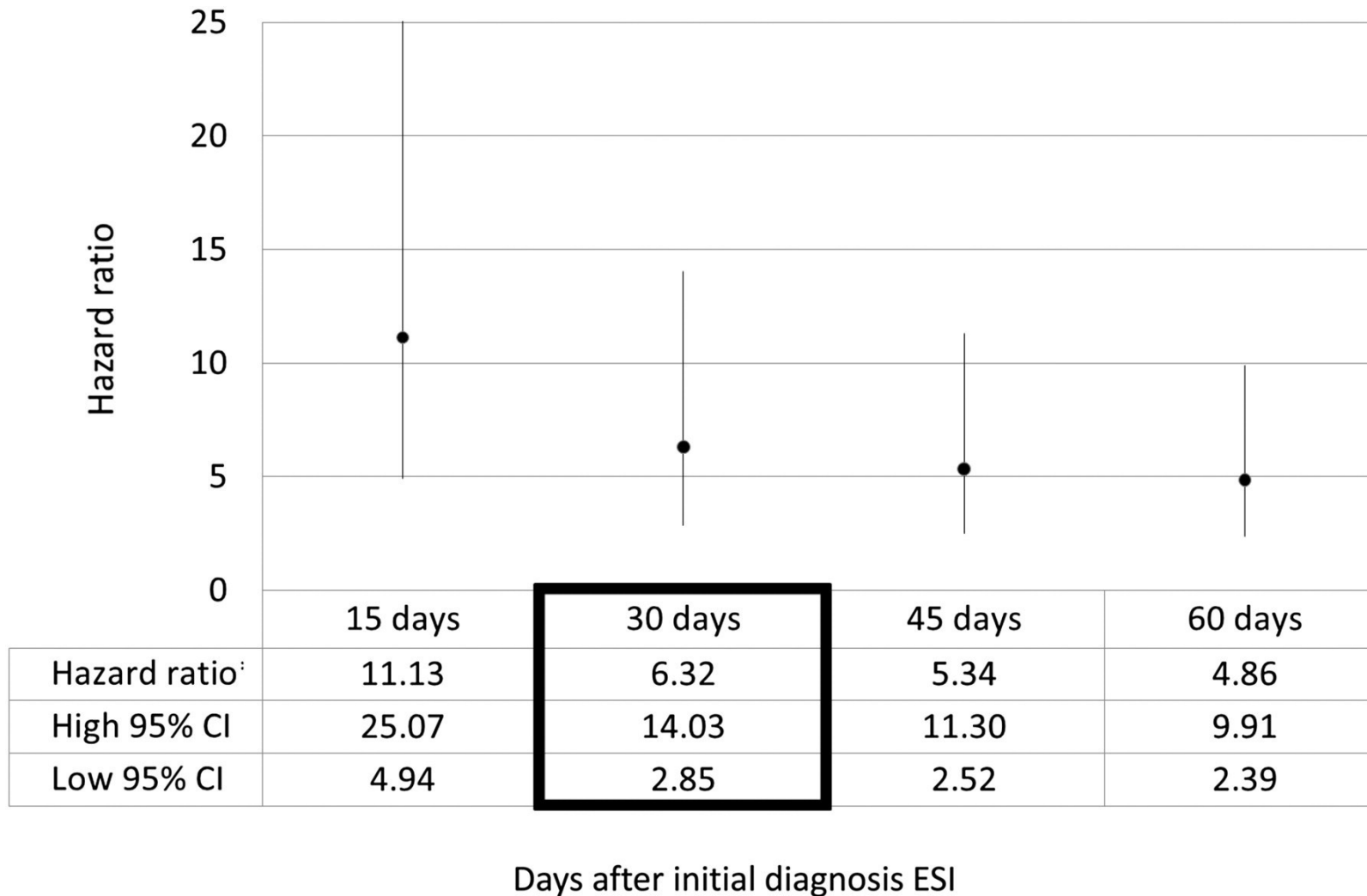


Low serum albumin only significant predictor of Pre-PD peritonitis compared to matched controls

## 2 new cause-specific peritonitis definitions

- Catheter-related peritonitis (not graded)
  - Peritonitis that occurs within 3 months of a catheter infection (exit-site infection or tunnel infection) with the same organism (or with one site sterile in the context of antibiotic exposure)
- Enteric peritonitis (not graded)
  - Peritonitis arising from an intestinal source involving processes such as inflammation, perforation or ischemia of abdominal organs. If a peritonitis episode in this context is culture negative, “we suggest that it be classified/recorded as enteric peritonitis”

# Risk of peritonitis greatly increased after ESI

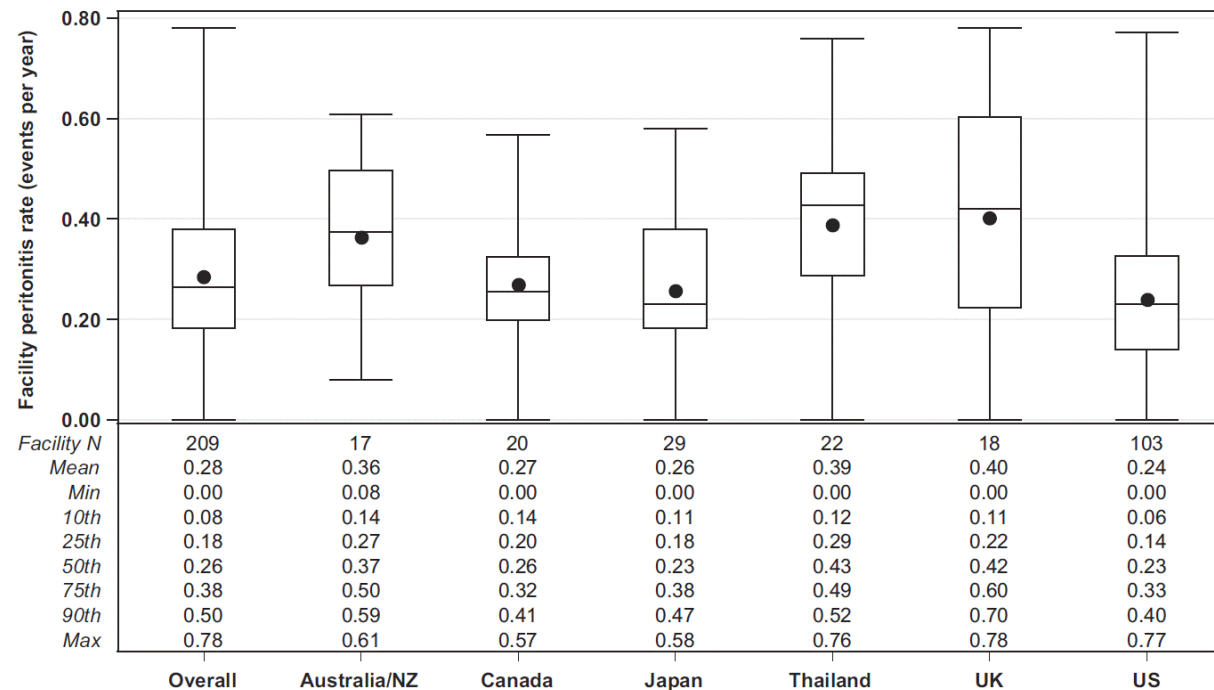


- Post-hoc analysis of RCT comparing antibiotic ointments for prevention of ESI
- 203 adult PD patients followed for 18 months
- 40% of patients had DM2
- 44 ESIs in 34 patients
- 87 peritonitis episodes in 57 patients

**Strong association between ESI and subsequent risk of peritonitis in PD patients at least out to 60 days**

# Decrease in overall goal peritonitis rate in PD patients

- “We recommend that the overall peritonitis rate should be no more than 0.40 episodes per year at risk.” **(1C)**

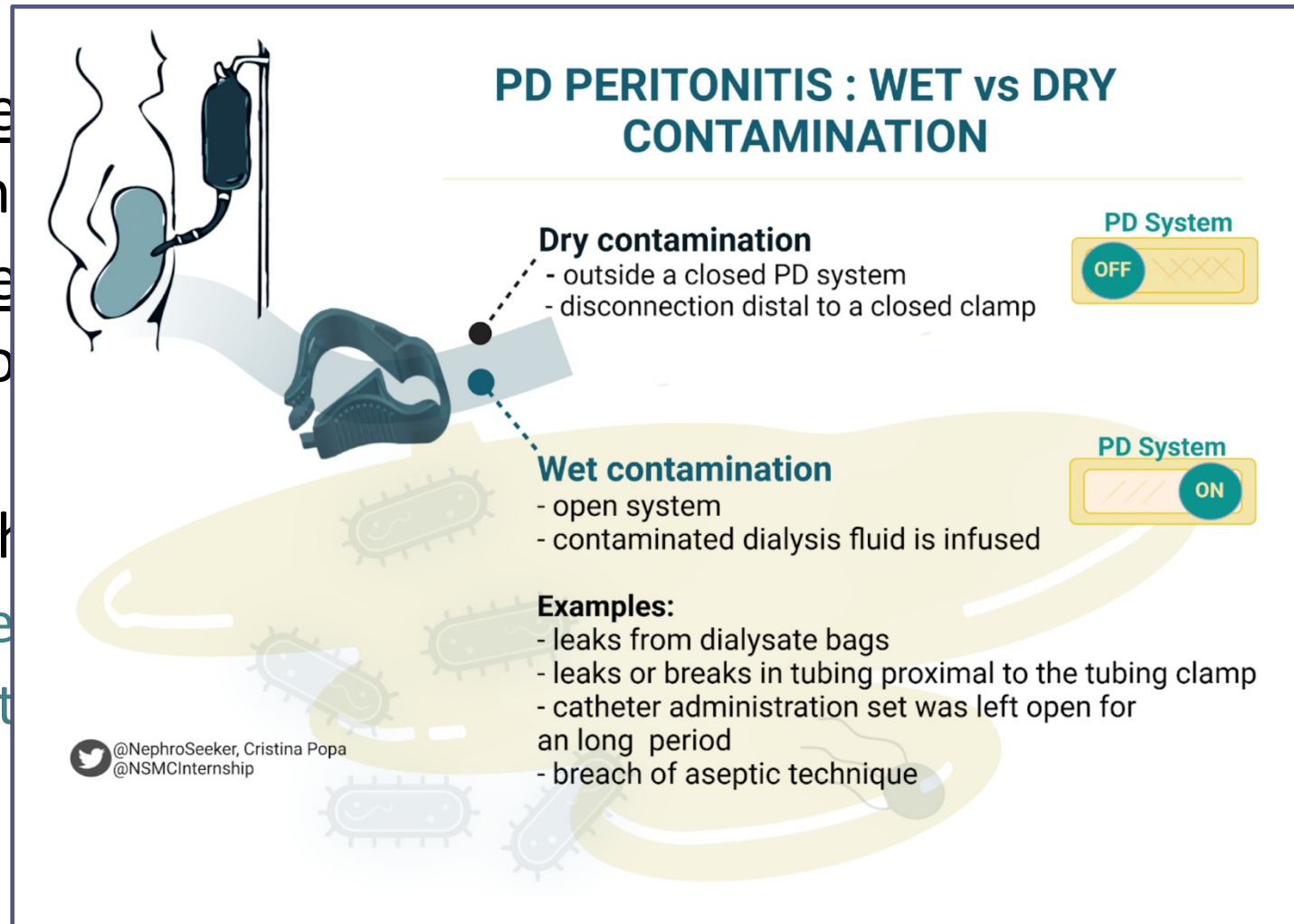


**US Mean:  
0.24 episodes per patient-  
year**

# Contamination of the PD system

- We suggest contamin
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# Wet contamination is associated with incident peritonitis

- Retrospective cohort study of 296 patients at 1 high-volume Hong Kong PD unit
- 548 episodes of PD system contamination
  - 246 dry contamination
  - 302 wet contamination
- 17 total peritonitis episodes after contamination
  - All in wet contamination group
  - None in dry contamination group
- Only 1 patient who received prophylactic antibiotics developed peritonitis

Incidence of Peritonitis in Patients Receiving or Not Receiving Prophylactic Antibiotics after Wet Contamination			
Patient group	Antibiotic prophylaxis		TOTAL
	Yes	No	
No peritonitis	181	104	285
Peritonitis	1	16	17
TOTAL	182	120	302
<sup>a</sup> Statistically significant difference at $p < 0.001$ .			

# New enhanced focus on empiric antibiotics ASAP

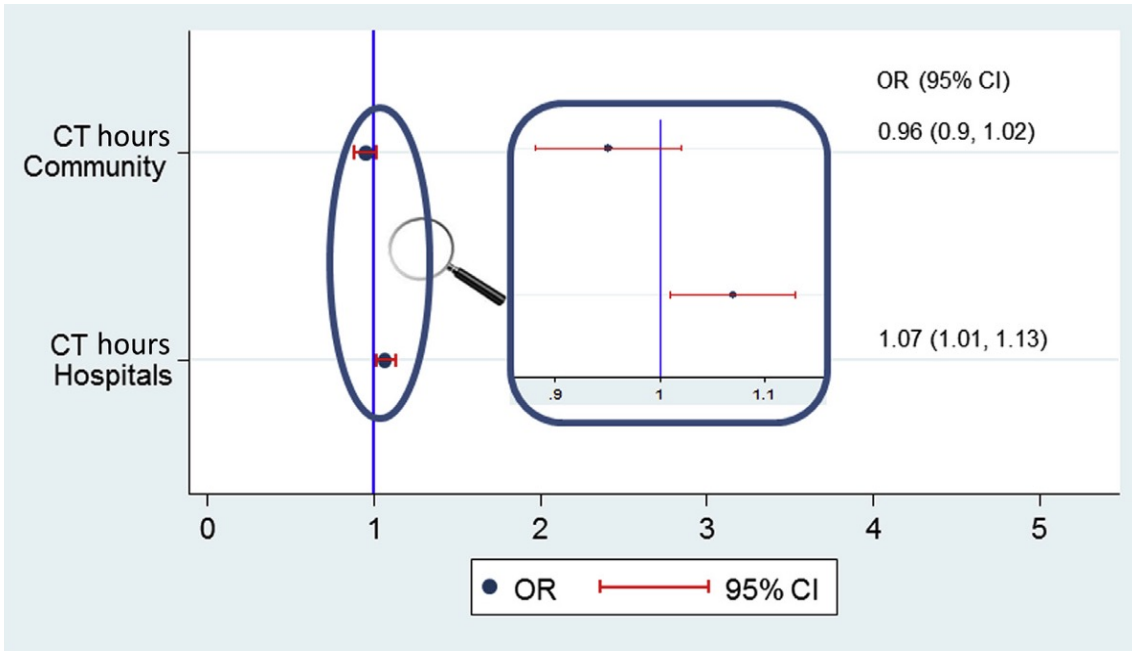
- “We recommend that IP antibiotics be the preferred route of administration...unless the patient has features of systemic sepsis (**1B**).

**But...**

- “We recommend that empirical antibiotic therapy be initiated as soon as possible, using either IP or systemic route, after appropriate microbiological specimens have been obtained (**1B**).

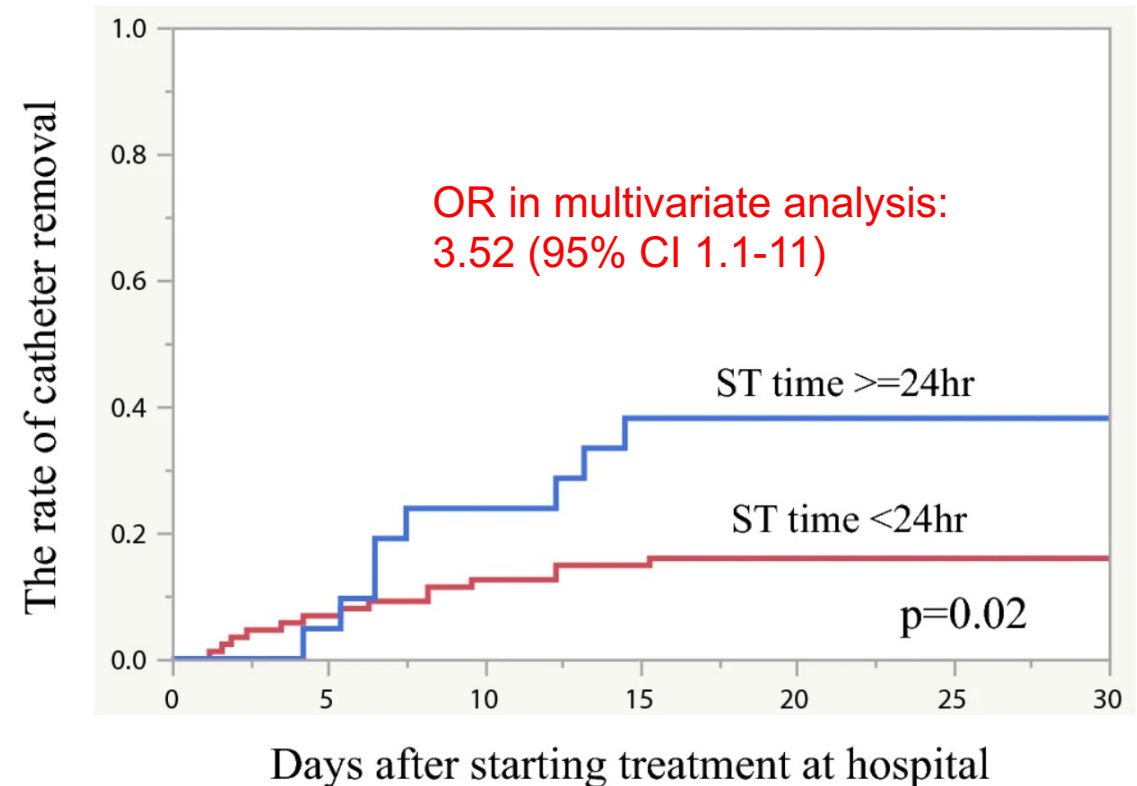
# Delay in antibiotics in peritonitis leads to higher risk of death and HD transfer

- Prospective study, 116 Australian PD patients, 159 peritonitis episodes
- Median contact—treatment time (CT) was 2.3 hours
- Primary outcome: catheter removal or death at 30 days



Each hour of delay in administering antibiotics associated with 7% higher odds of catheter removal or death

- 66 peritonitis episodes among 159 incident Japanese PD patients
- Assessed association of time from symptoms/signs to abx with subsequent need for PD catheter removal



# NAC for patients treated with aminoglycosides

- “We suggest that adjunctive oral N-acetylcysteine therapy may help to prevent aminoglycoside ototoxicity.” (2B)

	NAC group (n=23)		Control group (n=17)		P values	
	From baseline to 1 month	From baseline to 12 months	From baseline to 1 month	From baseline to 12 months	p1	p2
Right ear parameters						
2,000 Hertz	-20 (-40±110)	+25 (0±67)	+41 (11±100)	+88 (39±150)	<0.001	<0.001
4,000 Hertz	-14±21	14±30	31±14	60±20	<0.001	<0.001
6,000 Hertz	-14±16	21±14	21±10	37±14	<0.001	0.001
Left ear parameters						
2,000 Hertz	-20 (-47±110)	+25 (-11±257)	47 (10±67)	+88 (50±200)	<0.001	<0.001
4,000 Hertz	-20 (-44±25)	20±33	35 (0±67)	63±23	<0.001	<0.001
6,000 Hertz	-21±13	18±13	15±7	32±9	<0.001	0.001

NAC = N-acetylcysteine.

δ hearing function: [baseline hearing function – hearing function at 1 month (or at 12 months)/baseline hearing function] × 100.

p1: Comparison of δ hearing function from baseline to 1 month between N-acetyl cysteine and control groups.

p2: Comparison of δ hearing function from baseline to 12 months between N-acetyl cysteine and control groups.

- RCT of 40 PD patients in Turkey presenting with first peritonitis
- All patients treated with empiric IP cefazolin + amikacin (2mg/kg daily)
- Patients randomized to NAC 600mg BID x 1 month vs no treatment
- Blinded audiologist assessment at baseline, 1 month, 12 months

# PD catheter removal for refractory peritonitis

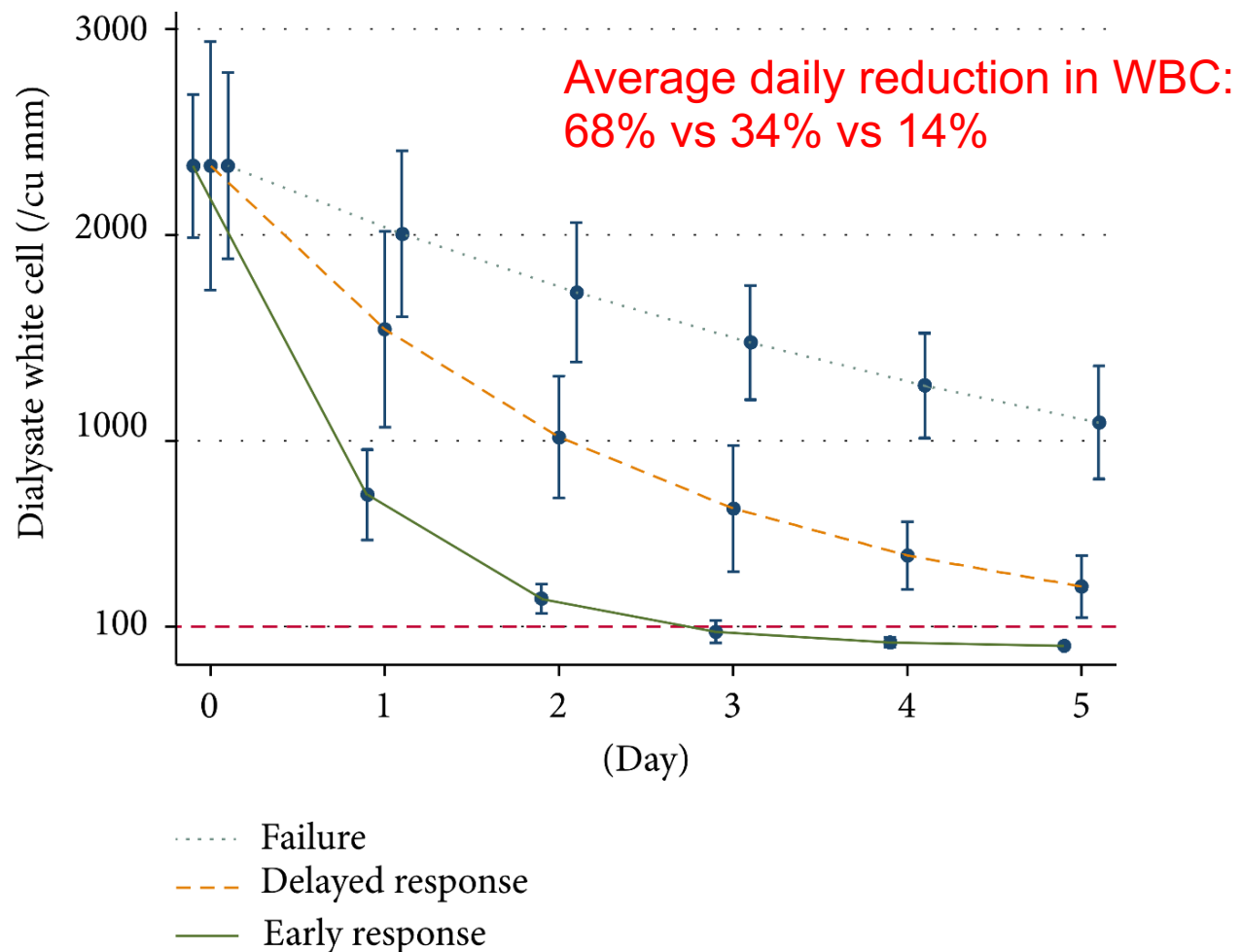
- We recommend that PD catheter be removed in refractory peritonitis episodes, defined as failure of the PD effluent to clear after 5 days of appropriate antibiotics (**1D**).

**But...**

- We suggest that observation for antibiotic effect longer than 5 days is appropriate if PD effluent white cell count is decreasing towards normal, instead of mandatory PD catheter removal if effluent does not clear by day 5 (**2C**).

# Trajectory of effluent WBC count related to treatment outcome

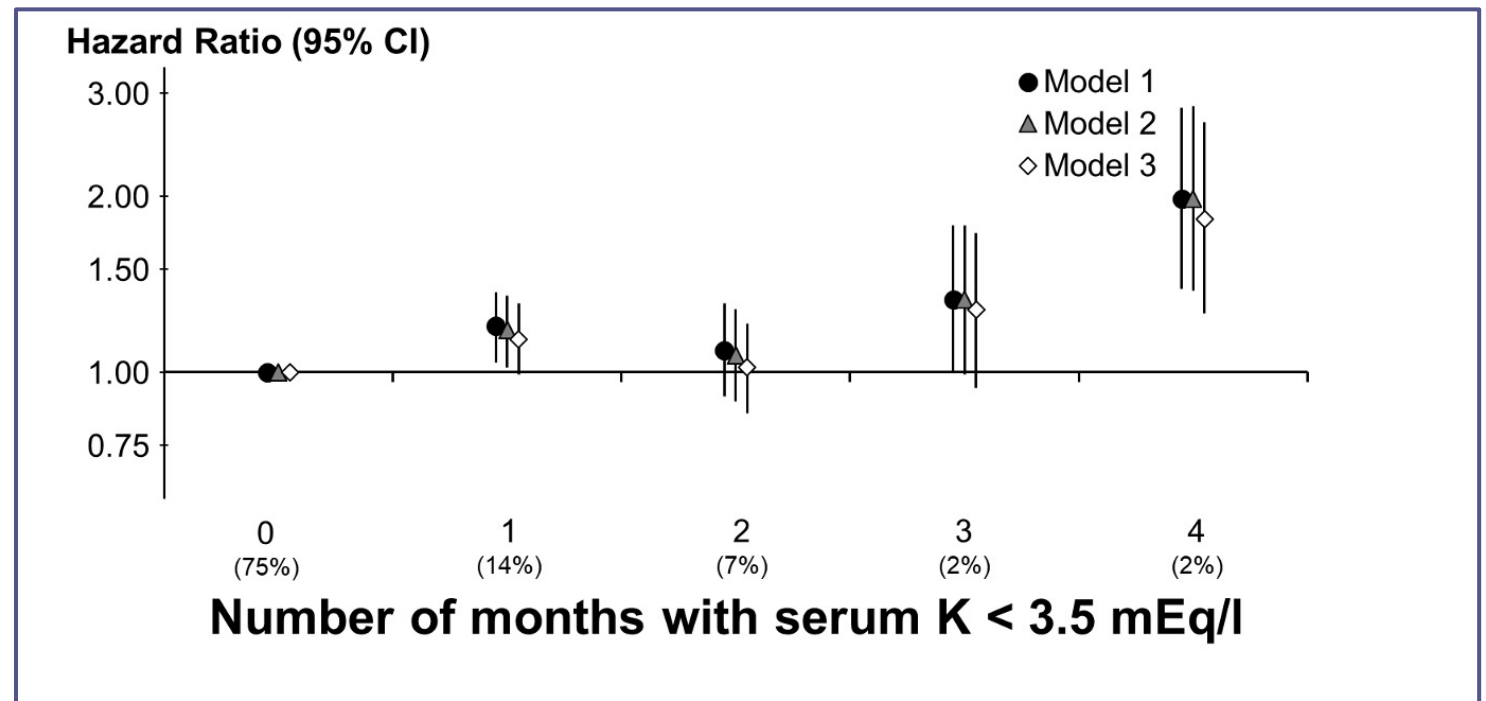
- 644 peritonitis episodes among 455 CAPD patients at a high-volume PD center in Thailand
- Standard empiric antibiotics (cefazolin + ceftazidime) followed by narrowing based on culture
- Treatment failure (n = 144, **22%**) – failure of antibiotics with death or transfer to HD
- Early response (n=378, **59%**) – decrease in effluent WBC count to  $<100$  cells/ $\text{m}^3$  at day 5
- Delayed response (n = 122, **19%**) – decrease in WBC count by day 5 but  $>100$  cells/ $\text{m}^3$  AND eventual treatment success



# Hypokalemia and peritonitis risk

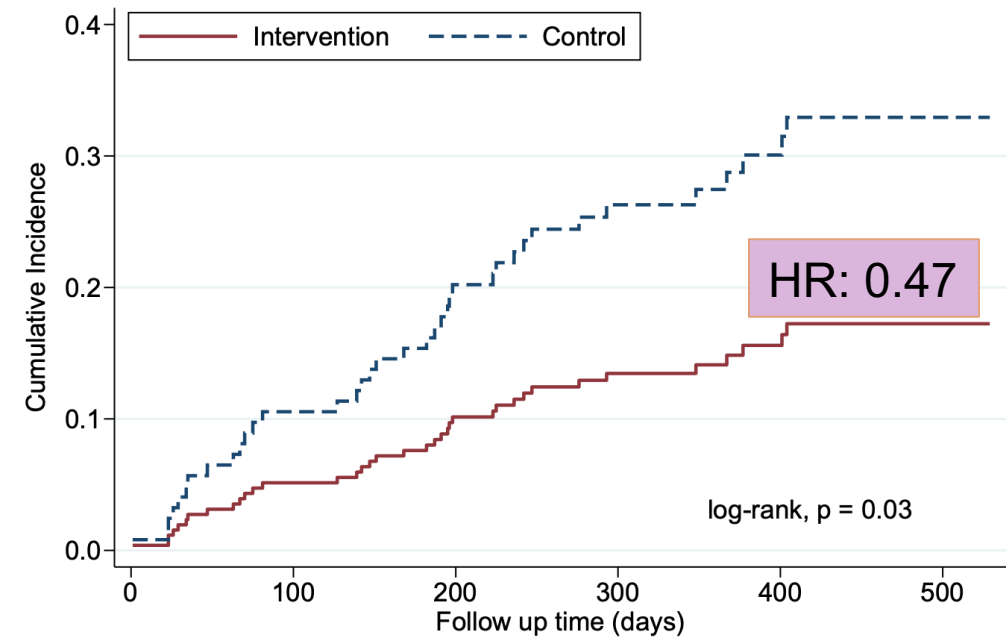
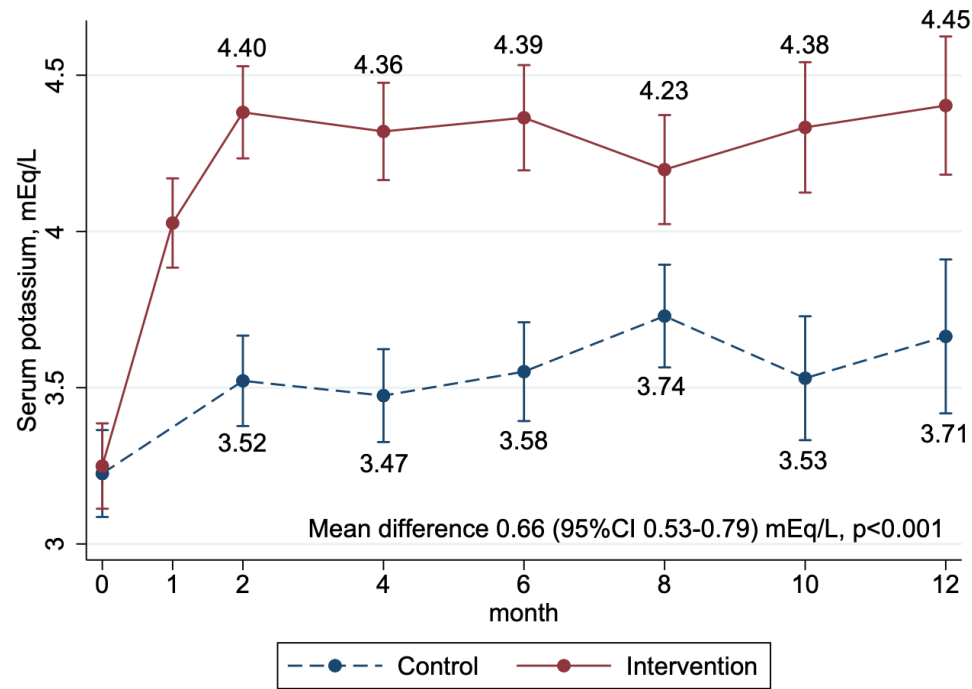
- “We suggest the avoidance and treatment of hypokalemia may reduce the risk of peritonitis.” **(2C)**

- 7421 patients from 7 countries in PDOPPS
  - Australia, NZ, Canada, Japan, Thailand, UK, US
- Primary exposures:
  - average serum potassium in 4 months prior
  - number of months with serum potassium <3.5 mEq/L in 4 months prior



**Number of months with K <3.5 associated with peritonitis risk**

# More aggressive potassium supplementation reduces peritonitis risk in PD patients



167 patients at 7 PD centers in Thailand  
Randomized to:

- 1) proactive potassium supplement (goal 4-5 mEq/L)
- 2) reactive (supplement when <3.5 mEq/L)

Primary outcome: time to first peritonitis



# Avoiding H2 blockers to prevent peritonitis

- “We suggest that avoiding or limiting the use of histamine-2 receptor antagonists may prevent enteric peritonitis (**2C**).

- Retrospective cohort study of 691 incident PD patients at single center in Spain
- Primary exposures:
  - H2 antagonist use
  - PPI use
- Primary outcomes:
  - Enteric peritonitis
  - Mortality

	HR	95% CI	P-value
<b>Enteric peritonitis</b>			
PPI	1.61	0.98, 2.51	0.06
H2A	1.67	1.02, 2.80	0.04
<b>Infectious mortality</b>			
PPI	0.68	0.65, 1.82	0.75
H2A	1.78	1.01, 3.21	0.049

# Icodextrin for volume overload in PD peritonitis

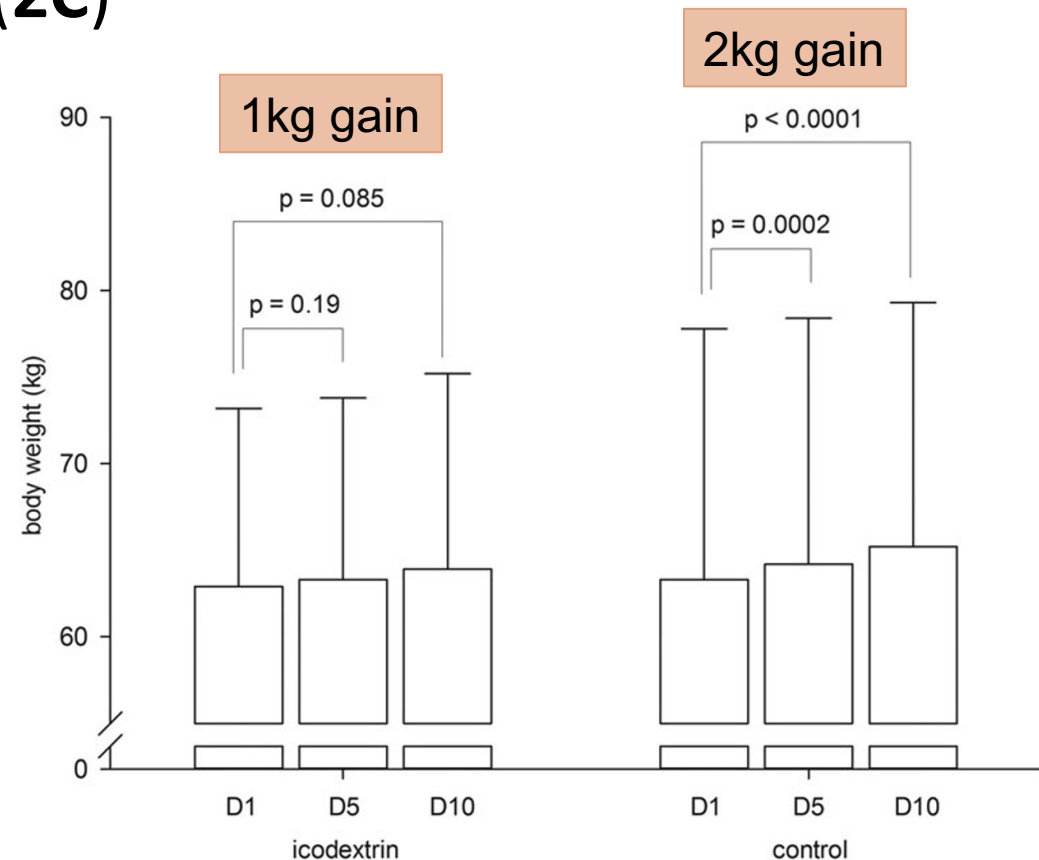
- “We suggest that icodextrin be considered for volume overload which occurs during acute PD peritonitis” (2C)

56 PD patients in Hong Kong with peritonitis

Randomized to icodextrin or conventional glucose-based solution during peritonitis treatment

Primary outcome was WBC count day 3 (no difference)

Secondary outcome: fluid control



# Cefepime monotherapy for empiric antibiotic coverage

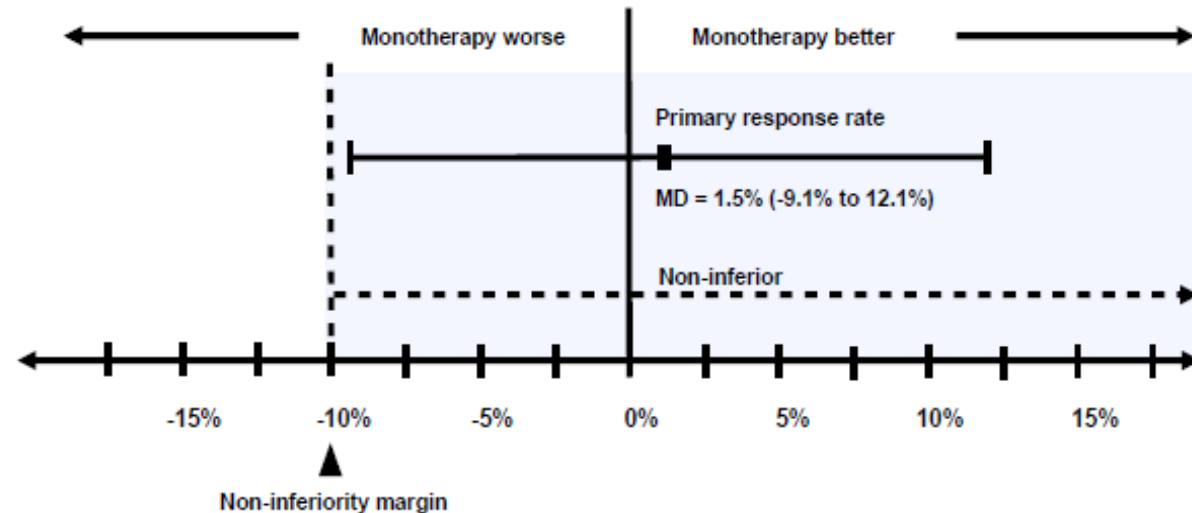
- “We recommend that gram-positive organisms be covered by a first-generation cephalosporin or vancomycin and gram-negative organisms by a third-generation cephalosporin or an aminoglycoside (**1B**).”

But...

- “We suggest that cefepime monotherapy may be an acceptable alternative for empirical antibiotic regimens (**2B**).”

# Cefepime empiric monotherapy

- Multicenter open-label RCT
- 144 patients with CAPD-associated peritonitis at 8 PD centers in Thailand
- Patients randomized to IP cefazolin/ceftazidime or IP cefepime monotherapy
- Primary outcome: resolution of peritonitis at 10 days
- Complete response was 80% in both groups



**Figure 2.** Effect of cefepime monotherapy versus combined cefazolin and ceftazidime therapy on the primary outcome (primary response) in a noninferiority analysis. Abbreviation: MD, mean difference.

IP Cefepime non-inferior to IP cefazolin/ceftazidime combination

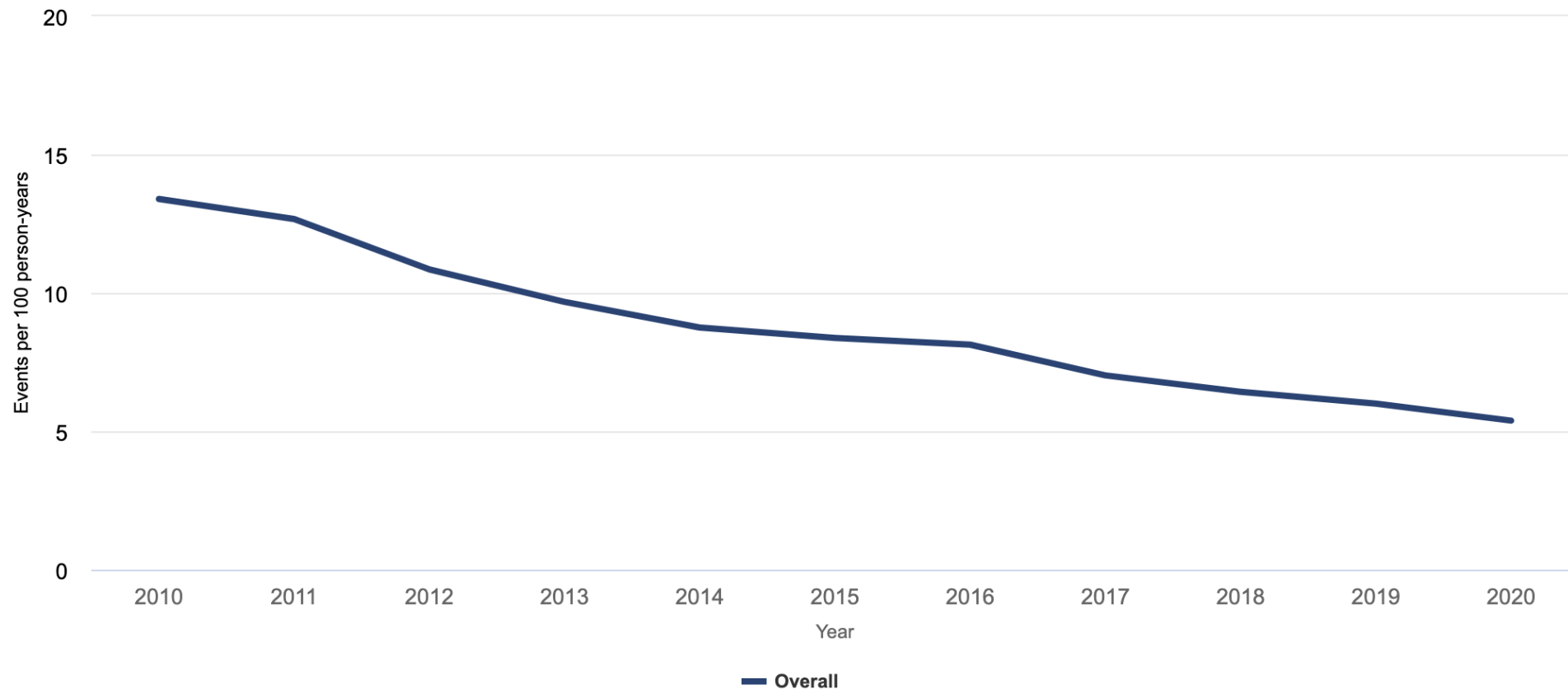
Secondary outcomes including relapse/recurrence and PD catheter removal also similar

# 2022 updates to ISPD peritonitis guidelines NOT reviewed today

- Specific suggestion to drain PD fluid prior to endoscopic or GYN procedures
- New recommendations to take “extra precautions” with domestic pets
- Updates to recommendations on specific antibiotic regimens for specific peritonitis causative organisms
  - Coagulase-negative staph, *Corynebacteria*, *enterococcus*, *Pseudomonas*, *Acinetobacter*, *Stenotrophomonas*, and non-TB mycobacteria
- Updated complete table of IP antibiotic dosing recommendations

# A closing bit of optimism...

Rate of peritonitis in adult PD patients, 2010-2020



# Questions?



A collaboration between  
Northwest Kidney Centers and UW Medicine

