

# **Randomized Controlled Trial on Adjunctive Lavage for Severe Peritoneal Dialysis- Related Peritonitis**

Steve SM Wong

Alice Ho Miu Ling Nethersole Hospital

# Background

- PD peritonitis is a major cause of PD technique failure, associated with significant morbidity and even mortality
- Appropriate IP antibiotic is the standard treatment of PD peritonitis
  - No adjunctive treatment has been proven to improve the efficacy of IP antibiotic
- Gold standard for refractory cases – Tenckhoff catheter removal

# Background

- Problems after TK removal
    - Recurrent intra-abdominal collections
      - 14% patients developed collection required drainage

*Szeto CC, et al. PDI 2011*
    - “2nd hit” of encapsulating peritoneal sclerosis
      - 63% patients showed CT evidence of peritoneal inflammation/ collection
      - 31% of these patients developed full-blown EPS afterwards

*Wong YY, et al. PDI 2013*
- It will be desirable to have adjunctive measures that can improve antibiotic response, without delaying TK removal if necessary

# Background

## Potential role of lavage as an adjunctive treatment?

- Lavage may enhance the removal of bacteria and inflammatory cells

*O'Brien PE, et al. Aust N Z J Surg 1987*

- 6/9 (66.7%) refractory bacterial peritonitis cases, PD effluent cleared up after adjunctive lavage for 2-3 days while pending TK removal
  - Apparently had a beneficial effect in severe cases
  - Limitations
    - Uncontrolled
    - Antibiotics switch shortly before lavage could be a confounding factor

*Wong SS, et al. PDI 2014*

# Background

## **Adjunctive lavage is not recommended**

- Peritoneal defence impaired during early phase of each PD cycle

*Alobaidi HM, et al. NDT 1986*

*Topley N, et al. KI 1988*

- RCT (n=36) showed similar outcome between initial 24hr lavage vs. standard treatment
  - Success rate 72% vs. 89%, p=ns
  - Limitation – non-selective, i.e. including non-severe cases

*Ejlersen E, et al. PDI 1991*

# Background

- Postulations on adjunctive lavage
  - unlikely to have detrimental effect on the peritoneal defence
  - its benefits can be demonstrated only among severe cases (IP antibiotic alone is always very effective in non-severe cases)

# Methods

- Recruitment of patients with severe PD peritonitis
  - Lack of significant clinical response to empirical antibiotics (cefazolin & ceftazidime), AND
  - Dialysate leukocyte count  $>1090/\text{mm}^3$  on day 3
- Exclusion criteria
  - Concomitant exit site/ tunnel infection
  - Relapsing peritonitis
  - Fungal/ mycobacterial peritonitis
  - Suspected surgical cause of peritonitis
  - Allergic to penicillin/ cephalosporins (thus cefazolin/ ceftazidime could not be used as initial empirical treatment)
  - Unable/ refusal to give informed consent

# Methods

- Randomization (1:1)
  - Lavage group
    - APD (2L per exchange, Q2H for 2-3 days), resume usual CAPD regimen after APD lavage completed
    - Antibiotics switched to IV route during lavage
  - Control group
    - Usual CAPD regimen continued
    - Antibiotics kept on IP route
- Standardized antibiotics in both groups
  - Cefazolin/ ceftazidime empirically escalated to vancomycin/ gentamicin on day 3
  - Antibiotics to be adjusted when microbiology report available
  - Dosages followed ISPD Peritonitis Guidelines 2010



# Methods

- **Monitoring** (*every 2 days*)
  - PD effluent from overnight dwell (\*omitted if patients were on APD lavage)
    - Leukocyte count, Gram-stain & culture
  - Blood
    - CBC, electrolytes, urea, creatinine, albumin, C-reactive protein
  - Pain score (1-10)
- **Primary outcome**
  - Treatment success – PDE leukocyte count  $<100/\text{mm}^3$  without the need of TK removal
  - Treatment failure – persistent symptoms with TK removed/ death
- **Secondary outcome**
  - Duration of hospitalization
  - Serial changes in PDE leukocyte count, serum CRP, pain score
  - Relapsing peritonitis
  - Early re-hospitalization within 12 weeks of completion of antibiotics

# Methods

- Sample size

- Treatment failure rate ~60%, when PDE leukocyte count  $>1090/\text{mm}^3$  on day 3 in a validation set of peritonitis cases

*Chow KM, et al. CJASN 2006*

- Postulated a reduction in failure rate to 20% by adjunctive lavage

*Wong SS, et al. PDI 2014*

- $\geq 20$  subjects in each arm required, with 80% power at significance level of 5% (2-tailed)

# Results

- Subject recruitment started in Mar 2014
  - Recruitment ended in Aug 2017
  - A total of 431 peritonitis in AHNH, peritonitis rate 0.3 episodes/ year (i.e. one episode every 40.2 patient-months)
  - A majority of peritonitis episodes (385) not recruited
    - 288 significant early clinical response
    - 40 hospitalized in other centers
    - 8 concomitant exit site/ tunnel infection
    - 5 fungal/ mycobacterial growth from PD effluent
    - 8 allergic to cephalosporin/ penicillin
    - 14 refusal/ unable to give informed consent
    - 4 TK catheter drainage dysfunction
    - 4 suspected surgical peritonitis
    - 14 missed recruitment

# Results

- A total of 46 episodes of peritonitis, involving 42 patients were recruited
  - 6 patients excluded
    - 1 – later development of ES infection
    - 1 – mycobacterial growth from PDE
    - 3 – fungal growth from PDE
    - 1 – secondary peritonitis due to appendicitis

# Baseline characteristics

	Lavage group (n=20)	Control group (n=20)	P value
Age, years	64.2 ± 9.6	59.4 ± 9.5	0.12
Male gender, n (%)	13 (65)	8 (40)	0.21
Etiology of ESRD, n (%)			
Hypertension	3 (15)	4 (20)	1.00
Diabetes mellitus	10 (50)	7 (35)	0.52
Glomerulonephritis	2 (10)	5 (25)	0.41
Others	5 (25)	4 (20)	1.00
Body mass index, kg/m <sup>2</sup>	23.3 (22.1-27.6)	24.5 (22.2-28.2)	0.64
PD vintage, years	3.5 (1.8-5.7)	4.5 (2.5-8)	0.45
Prior peritonitis episodes, n	1 (0-3)	1 (0-4)	0.72

# Presentation

	Lavage group (n=20)	Control group (n=20)	P value
Symptom and sign, in addition to abd pain & cloudy effluent, n (%)			
Fever (>38C over 24hrs)	13 (65)	10 (50)	0.52
Ileus*	10 (50)	3 (15)	0.04
Diarrhoea	9 (45)	8 (40)	1.00
PD effluent leukocyte count on Day 3, /mm <sup>3</sup>	4871 (2868-11114)	4143 (2609-7863)	0.46
Serum C-reactive protein, mg/L	225.3 ± 82.0	233.9 ± 114.7	0.79

\* Ileus defined as the inability to tolerate enteral feeding >24hrs due to repeated vomiting, reduced bowel sound or dilated bowels in XR

# Microbiology

	Lavage group (n=20)	Control group (n=20)	P value
Gram-positive peritonitis, n (%)	7 (35)	10 (50)	0.52
Gram-negative peritonitis, n (%)	10 (50)	7 (35)	0.52
Mixed gram-positive & gram-negative peritonitis, n (%)	3 (15)	2 (10)	1.00
Culture-negative peritonitis, n (%)	0 (0)	1 (5)	1.00
Polymicrobial peritonitis, n (%)	7 (35)	4 (20)	0.48

<i>Gram-positive organisms reported, n</i>			
<i>MRSA</i>	4	1	
<i>MSSA</i>	2	2	
<i>Enterococcus</i>	3	0	
<i>Coagulase-negative staphylococcus</i>	0	4	
<i>Streptococcus</i>	3	5	
<i>Other G+ve organisms</i>	2	2	
<i>Gram-negative organisms reported, n</i>			
<i>Escherichia coli</i>	7	6	
<i>Pseudomonas</i>	0	1	
<i>Klebsiella</i>	4	2	
<i>Bacteroides</i>	2	0	
<i>Other G-ve organisms</i>	3	1	

# Antibiotic treatment

	Lavage group (n=20)	Control group (n=20)	P value
Single antibiotic, n (%)	5 (25)	7 (35)	0.73
Dual antibiotics, n (%)	12 (60)	12 (60)	1.00
Triple antibiotics, n (%)	3 (15)	1 (5)	0.61
Duration of antibiotics among treatment success cases, days	21 (19-23)	17 (14-21)	0.12



# Outcome

	Lavage group (n=20)	Control group (n=20)	P value
Primary outcome – Treatment success, n (%)	15 (75)	14 (70)	1.00
Secondary outcome			
Hospitalization, days	11 (7-19)	7 (6-12)	0.16
Early re-hospitalization, n (%)	7 (41.2)	8 (44.4)	1.00
Relapsing peritonitis, n (%)	1 (6.7)	2 (14.3)	0.60
Parameter changes within 1st week			
% reduction in PDE leukocyte	86.9 (64.8-96.2)	96.9 (71.7-98.1)	0.23
% reduction in serum CRP	80 (62.7-86.9)	78.7 (63.1-89.7)	0.57
% improvement in pain score	70 (0-100)	100 (60-100)	0.07

# Primary outcome in G+ve & G-ve peritonitis

	Lavage group	Control group	P value
Gram-positive – total n=17 Treatment success, n (%)	4/7 (57.1)	8/10 (80)	0.59
Gram-negative – total n=17 Treatment success, n (%)	9/10 (90)	4/7 (57.1)	0.25

- More pronounced beneficial effect in G-ve peritonitis?

# Limitations

- Single-center
- Treatment failure rate lower than expected
- Small sample size

# Conclusions

- Adjunctive lavage does not bring additional merits
  - Unlikely to be harmful on peritoneal defence
  - Imbalanced randomization?
    - More severe patients in the lavage group?
      - More ileus
      - More virulent bacteria with higher intrinsic treatment failure rate
- Benefits in Gram-negative peritonitis?
  - Need larger clinical trial
- Respectable treatment outcome despite severe nature of peritonitis in both groups
  - Early antibiotic escalation, before microbiology report became available, could be beneficial

# Acknowledgement

- Special thanks
  - Dr. Alex Yu, Dr. YL Cheng & AHNH Renal team

AHNH Dialysis unit staff



AHNH Renal ward E5

