Are We Dosing or Administering Antibiotics Accurately in Peritoneal Dialysis Patients?

Sim Mui Hian

SENIOR CLINICAL PHARMACIST

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Objectives

- Appropriate administration?
- Accurate dosing?

Intraperitoneal Administration

- Advantages
  - Maximal concentration at the site of infection
  - Can be done by patients, outpatient setting
- “Disadvantage”
  - Absorbed systemically

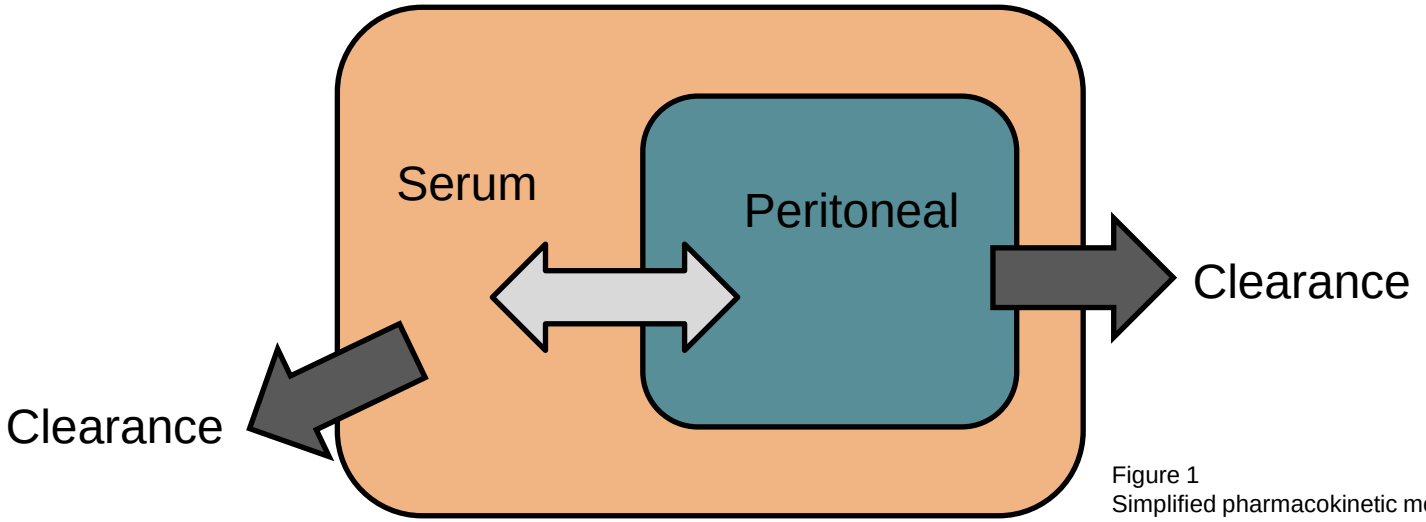

Figure 1
Simplified pharmacokinetic model

Singapore General Hospital

What to Use Empirically and How much?

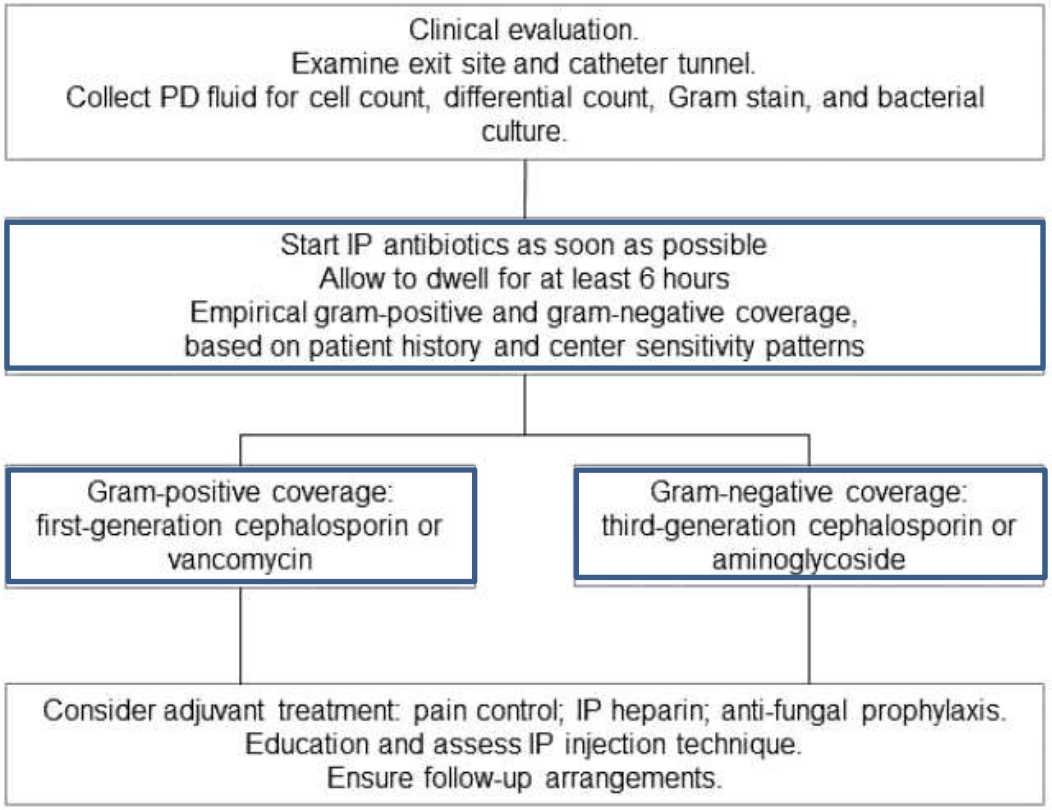

Figure 1 — Initial management of peritonitis. IP = intra-peritoneal.

Reference
Li PK, et al. Perit Dial Int. 2016; 36(5):481-508

Singapore General Hospital

What to Use Empirically and How much?

TABLE 5
Intraperitoneal Antibiotic Dosing Recommendations for Treatment of Peritonitis

	Intermittent (1 exchange daily)	Continuous (all exchanges)
Aminoglycosides		
Amikacin	2 mg/kg daily (252)	LD 25 mg/L, MD 12 mg/L (253)
Gentamicin	0.6 mg/kg daily (254)	LD 8 mg/L, MD 4 mg/L (255,256)
Netilmicin	0.6 mg/kg daily (233)	MD 10 mg/L (257)
Tobramycin	0.6 mg/kg daily (253)	LD 3 mg/kg, MD 0.3 mg/kg (258,259)
Cephalosporins		
Cefazolin	15–20 mg/kg daily (260,261)	LD 500 mg/L, MD 125 mg/L (254)
Cefepime	1,000 mg daily (262,263)	LD 250–500 mg/L, MD 100–125 mg/L (262,263)
Cefoperazone	no data	LD 500 mg/L, MD 62.5–125 mg/L (264,265)
Cefotaxime	500–1,000 mg daily (266)	no data
Ceftazidime	1,000–1,500 mg daily (267,268)	LD 500 mg/L, MD 125 mg/L (236)
Ceftriaxone	1,000 mg daily (269)	no data
Penicillins		
Penicillin G	no data	LD 50,000 unit/L, MD 25,000 unit/L (270)
Amoxicillin	no data	MD 150 mg/L (271)
Ampicillin	no data	MD 125 mg/L (272,273)
Ampicillin/Sulbactam	2 gm/1 gm every 12 hours (274)	LD 750–100 mg/L, MD 100 mg/L (253)
Piperacillin/Tazobactam	no data	LD 4 gm/0.5 gm, MD 1 gm/0.125 gm (275)
Others		
Aztreonam	2 gm daily (242)	LD 1,000 mg/L, MD 250 mg/L (243,244)
Ciprofloxacin	no data	MD 50 mg/L (276)
Clindamycin	no data	MD 600 mg/bag (277)
Daptomycin	no data	LD 100 mg/L, MD 20 mg/L (278)
Imipenem/Cilastatin	500 mg in alternate exchange (244)	LD 250 mg/L, MD 50 mg/L (236)
Ofloxacin	no data	LD 200 mg, MD 25 mg/L (279)
Polymyxin B	no data	MD 300,000 unit (30 mg)/bag (280)
Quinupristin/Dalfopristin	25 mg/L in alternate exchange[a] (281)	no data
Meropenem	1 gm daily (282)	no data
Teicoplanin	15 mg/kg every 5 days (283)	LD 400 mg/bag, MD 20 mg/bag (229)
Vancomycin	15–30 mg/kg every 5–7 days[b] (284)	LD 30 mg/kg, MD 1.5 mg/kg/bag (285)
Antifungals		
Fluconazole	IP 200 mg every 24 to 48 hours (286)	no data
Voriconazole	IP 2.5 mg/kg daily (287)	no data

LD = loading dose in mg; MD = maintenance dose in mg; IP = intraperitoneal; APD = automated peritoneal dialysis.
[a] Given in conjunction with 500 mg intravenous twice daily (281).
[b] Supplemental doses may be needed for APD patients.

Dwell ≥ 6 hours to allow adequate absorption

Reference
Li PK, et al. Perit Dial Int. 2016; 36(5):481-508

What to Use and How much?

- Substantial knowledge gap for dosing in patients on automated peritoneal dialysis (APD)
- Extrapolation of intermittent IP dosing in continuous ambulatory peritoneal dialysis (CAPD) to day dwell of APD
  - May lead to under-dosing
  - Rapid exchanges lead to inadequate time to achieve therapeutic levels
  - Higher peritoneal clearance of antibiotics than CAPD

Reference
Li PK, et al. Perit Dial Int. 2016; 36(5):481-508

What Affects the Dose?

- Patient-related factors
  - Residual renal function
  - Membrane transport characteristics
  - Blood flow rate
- Dialysis-related factors
  - Type of dialysis
  - Dwell time
  - Number of exchanges
- Drug-related factors
  - Molecular size
  - Volume of distribution
  - Type of clearance
  - Protein binding

Reference
O'Brien MA, et al. Clin Pharm. 1992; 11(3):246-54

What We Know from Studies

- Higher systemic absorption in peritonitis

Study	Sample Size	Design	Results
Peritoneal Absorption of Vancomycin During and After Resolution of Peritonitis in Continuous Ambulatory Peritoneal Dialysis Patients [1]	5	• Absorption of loading dose of IP vancomycin 30mg/kg at peritonitis and after resolution (7 days after free of S/Sx) • 6 hour dwell	Absorption of 74% in peritonitis vs 51% after resolution
Pharmacokinetics of Intraperitoneal Gentamicin in Peritoneal Dialysis Patients with Peritonitis [2]	24	• IP gentamicin 0.6mg/kg • Serial blood samples at 1, 3, 6, 7, 24 hours • Serial dialysate samples at 3, 6 hours and end of 3 subsequent dialysis exchanges • 6 hour dwell	• Median percentage of absorption=76% (interquartile range=69-82%) • Significant difference between low average, high average and high peritoneal membrane transporter status (P=0.03)

References
1. Bastani B, et al. Perit Dial Int. 1988; 8(2):135-6
2. Varghese JM, et al. Clin J Am Soc Nephrol. 2012; 7:1249-56

The Unknowns in Reality...

- How permeable is the membrane?
- How to quantify the clearance by peritoneal dialysis?
- How to quantify renal clearance?

Therapeutic Drug Monitoring (TDM)

- Not all drugs have established TDM
- Blood drug levels ≠ peritoneal drug levels
- Vancomycin and aminoglycosides do not follow one-compartment model
- Timing of the levels matter!
  - Peak and trough levels inform us differently
- Taking multiple levels in a day is impractical and costly

Therapeutic Drug Monitoring (TDM)

- 2016 ISPD guidelines
  - Vancomycin: role is ‘controversial’ though substantial inter-individual variability in dosing interval
  - Aminoglycosides: ‘small role’ as relationship between level and risk of ototoxicity is ‘conflicting’ and often ‘negative result’; ‘no firm evidence that monitoring aminoglycoside levels mitigates toxicity risk or enhances efficacy’

Reference
Li PK, et al. Perit Dial Int. 2016; 36(5):481-508

Do Studies Suggest we do Vancomycin TDM?

Study	Sample Size	Design	Results		
The role of monitoring vancomycin levels in patients with peritoneal dialysis-associated peritonitis [1]	150 patients, 256 episodes (gram-positive or culture-negative)	• Single centre, observational, cohort • Unit protocol: D2 level, every 2-3 days for 1st week • Load and re-dose IP vancomycin 30mg/kg (max 2g) when level <15mg/L		Cure	Not Cured
			D2 level	18.0±5.9	16.6±3.2
			1st week average	18.6±5.1	18.6±4.3
			Nadir	14.5±4.1	13.6±4.2

Single UK centre experience on the treatment of PD peritonitis– antibiotic levels and outcomes [2]	613 patients, 283 episodes of gram-positive, 166 episodes culture-negative	• Retrospective
		• IP 25mg/kg, ↑25% if not anuric
		• D5 dose titrated according to serum vancomycin levels
		  • <12mg/L: ↑500mg
		  • 12-25mg/L: same dose
		  • >25mg/L: ↓500mg
				D5 <12mg/L	D10 <12mg/L

			Anuric CAPD	9.2%	0%
			Non-anuric CAPD	16.0%	21%
			Anuric APD	16.1%	13%
			Non-anuric APD	21%	25%

References
1. Stevenson S, et al. Perit Dial Int. 2015; 35(2):222-8
2. Blunden M, et al. Nephrol Dial Transplant. 2007; 22:1714-9

Do Studies Suggest we do Vancomycin TDM?

Study	Sample Size	Design	Results

Trough serum vancomycin levels predict the relapse of gram-positive peritonitis in peritoneal dialysis patients [1]	31 episodes	• Retrospective
		• 4 weekly IP vancomycin
		  • Dose 1 & 2: 15mg/kg, ≥1g
		  • Dose 3 & 4: adjusted to maintain level >12mg/L
			• Relapse vs non-relapse: 7.8±0.6mg/L vs 13.7±0.9mg/L (P=0.0004)
			• 9/14 with 4-week mean trough level <12mg/L relapsed vs 0/17 with level>12mg/L (P<0.05)
			• 9/13 with initial 7-day trough <9mg/L: relapse

Intraperitoneal vancomycin concentrations during peritoneal dialysis-associated peritonitis: correlation with serum levels [2]	48	• Single dose IP vancomycin 30mg/kg • Peritoneal dialysate effluent (PDE) concentration measured on D5, 4 hour dwell	• 98% had serum vancomycin level>12mg/L but 11 patients (23%) had PDE <4mg/L • Poor correlation between concentration of vancomycin in serum and dialysate (R^2=0.18)

References
1. Mulhern JG, et al. Am J Kidney Dis.1995; 25:611-5
2. Fish R, et al. Perit Dial Int. 2012; 32(3):332-8

Do Studies Suggest we do Aminoglycoside TDM?

<table>
<tr><th>Study</th><th>Sample Size</th><th>Design</th><th colspan="2">Results</th></tr>
<tr><td>The role of monitoring gentamicin levels in patients with gram-negative peritoneal dialysis-associated peritonitis [1]</td><td>66 episodes</td><td>• Single centre, observation, retrospective, cohort
• D2 serum gentamicin trough levels</td><td colspan="2">• Levels taken in 51 (77%) episodes
• Average level was 1.83±0.84mg/L
• 22 (43%) cases had levels >2mg/L
• D2 levels significantly higher for polymicrobial episodes that were cured (2.06±0.41 vs 1.29±0.71, P=0.01)
• No ototoxicity</td></tr>
<tr><td rowspan="5">Single UK centre experience on the treatment of PD peritonitis—antibiotic levels and outcomes [2]</td><td rowspan="5">613 patients, 137 gram-negative episodes</td><td rowspan="5">• Retrospective
• IP 0.6mg/kg gentamicin, ↑25% if not anuric
• Dwell for ≥ 6-8 hours
• Serum trough level on D5
• Dose titration to ↓toxicity:
• <2mg/L: same dose
• >2mg/L: ↓10mg
• >3mg/L: omit D5 dose, ↓10mg
• Not designed to detect toxicity</td><td></td><td>D5 level>2mg/L</td></tr>
<tr><td>Anuric CAPD</td><td>52.6%</td></tr>
<tr><td>Non-anuric CAPD</td><td>55.7%</td></tr>
<tr><td>Anuric APD</td><td>31.4%</td></tr>
<tr><td>Non-anuric APD</td><td>54.5%</td></tr>
</table>

References
1. Tang W, et al. Perit Dial Int. 2014; 34(2):219-26
2. Blunden M, et al. Nephrol Dial Transplant. 2007; 22:1714-9

Singapore General Hospital

Singapore General Hospital's Experience

- Vancomycin
  - Re-dose to ensure therapeutic level of 15-20mg/L
- Amikacin
  - Ensure trough <5mg/L
  - Accumulation with repeated dosing
- Medical cure rates
  - 2015-2018: ~62-80%

Conclusion

- IP route is preferred
- Accurate dose?
  - We don’t know…
- It looks like we are on the right track?
- Much work needed

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