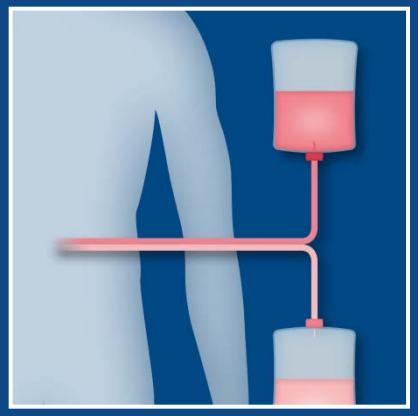
Nephro Update Europe 2017

6-7 October, Vienna

Peritoneal Dialysis



An De Vriese, Belgium

Infection Control

- Prevention of peritonitis
- Management of peritonitis

EXIT-SITE CARE: STATE OF THE ART

- We suggest screening for nasal *S. aureus* carriage prior to PD catheter insertion **(2D)**.
- If nasal carriage of *S. aureus* is found in PD patients, we suggest treating by topical nasal application of mupirocin **(1B)**.

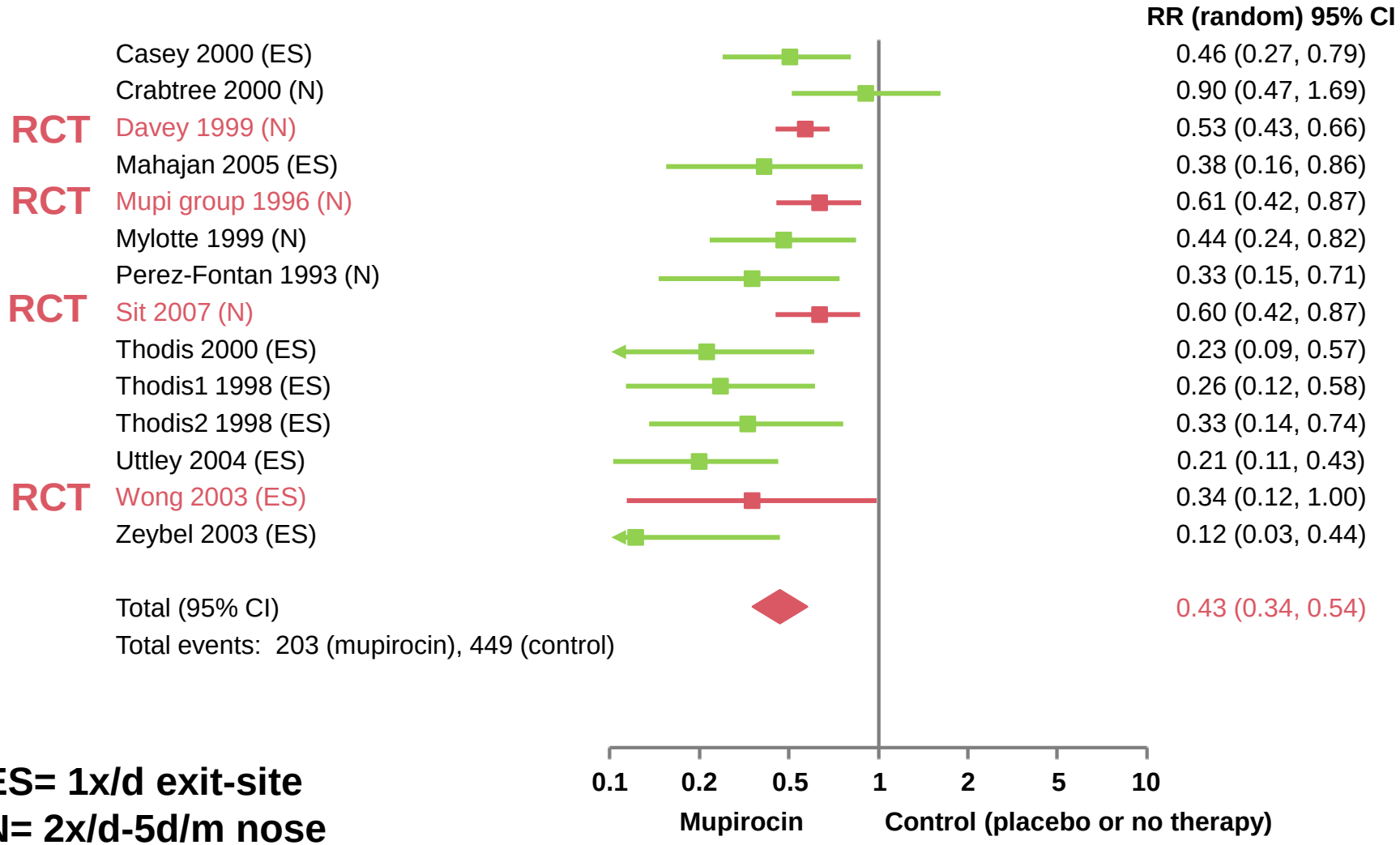
- We recommend daily topical application of antibiotic cream or ointment to the catheter exit site **(1A)**.
- We suggest that no cleansing agent has been shown to be superior with respect to preventing catheter-related infections **(2B)**.

Szeto et al. Perit Dial Int 2017, 37: 141

Topical Antibacterials, Antiseptics and Cleansing Agents for Prevention of Catheter-Related Infections

- Povidone-iodine
- Chlorhexidine 0.05% to 2% aqueous solution ± isopropyl alcohol
- Mupirocin cream or ointment
- Gentamicin cream or ointment
- Ciprofloxacin otologic solution
- Antibacterial honey
- Amuchina solution 3% to 10% (an electrolytic chloroxidizing solution containing sodium hypochlorite)
- Polysporin triple ointment
- Polyhexanide
- Hypertonic saline 3%

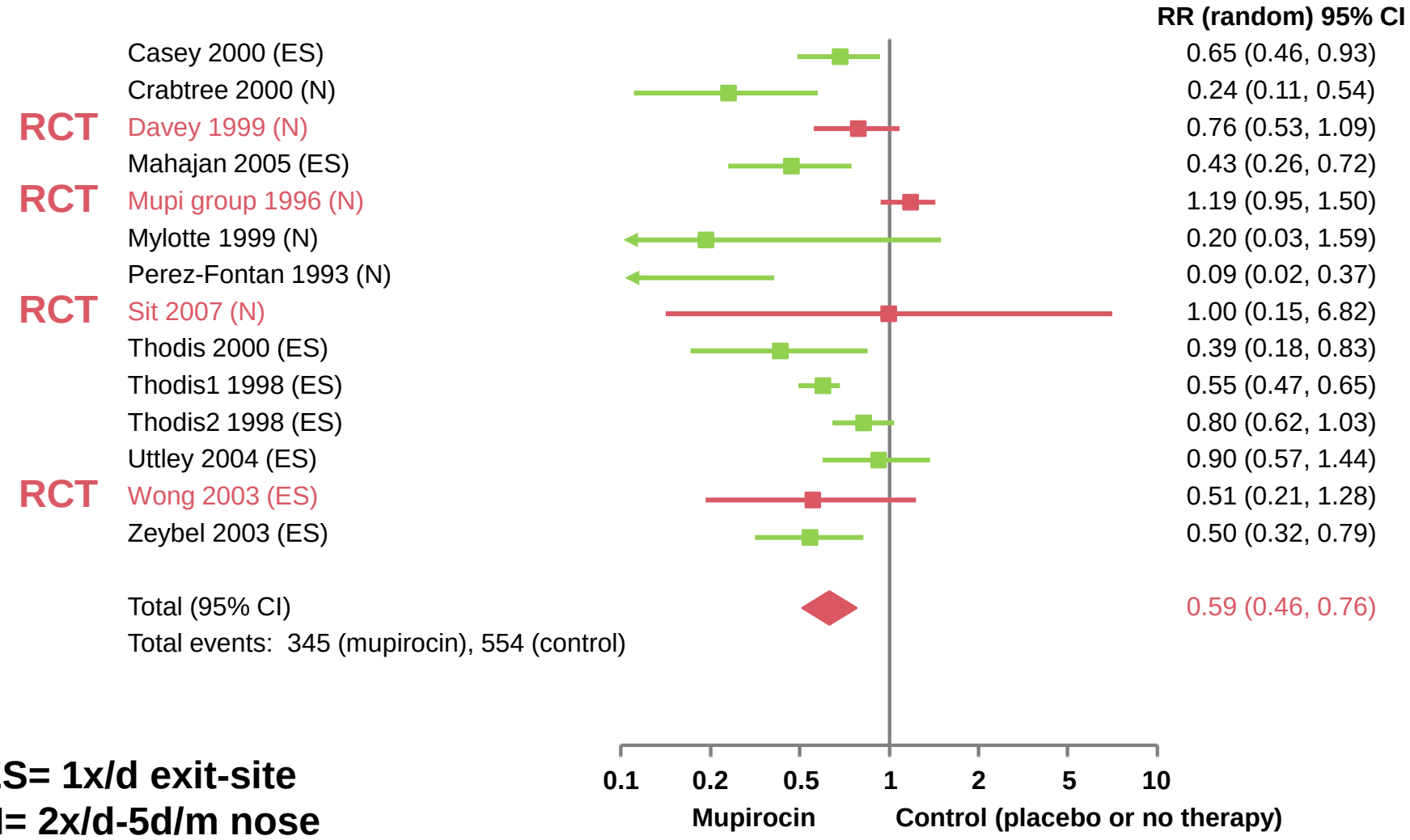
Mupirocin vs No Prophylaxis in Prevention of Exit-Site Infections



ES= 1x/d exit-site
N= 2x/d-5d/m nose

Xu et al. Nephrol Dial Transplant 2010, 25:587

Mupirocin vs No Prophylaxis in Prevention of Peritonitis



ES= 1x/d exit-site
N= 2x/d-5d/m nose

Xu et al. Nephrol Dial Transplant 2010, 25:587

CONCLUSION MUPIROCIN PROPHYLAXIS

- Reduced risk of ESI due to all organisms with 57%
- Reduced risk of peritonitis due to all organisms with 41%

- Shift from gram-positive to gram-negative, fungi, mycobacterium and other organisms?
- Mupirocin resistance?

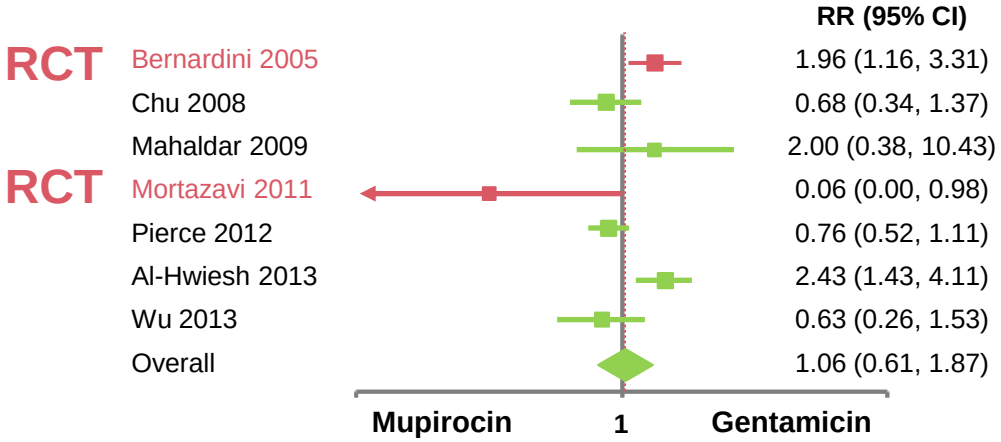
Mupirocin Resistance after Years of Mupirocin Prophylactic Practice

	1 year's use	4 years' use	7 years' use
Patients on peritoneal dialysis	–	150	174
Patients swabbed	167	149	147
SA carriers/patients swabbed	27/167 (16.2%)	26/149 (14.7%)	16/147 (10.9%)
MRSA carriers/patients swabbed	2/167 (1.2%)	0/149 (0%)	2/147 (1.4%)
MuRSA carriers/patients swabbed	0/167 (0%)	4/149 (2.7%)	4/147 (2.7%)
MuRSA carriers/mupirocin users	0	4/139 (2.9%)	4/137 (2.9%)
MuRSA carriers/SA carriers	0	4/26 (15%)	4/16 (25%)
MuRSA and MRSA strain	0	0	1

Lobbedez et al. Nephrol Dial Transplant 2004; 19: 3140

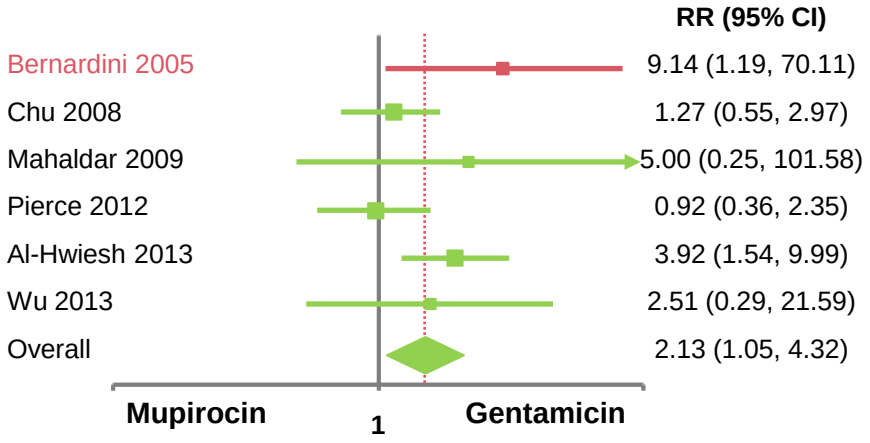
Mupirocin vs Gentamicin

All ESI



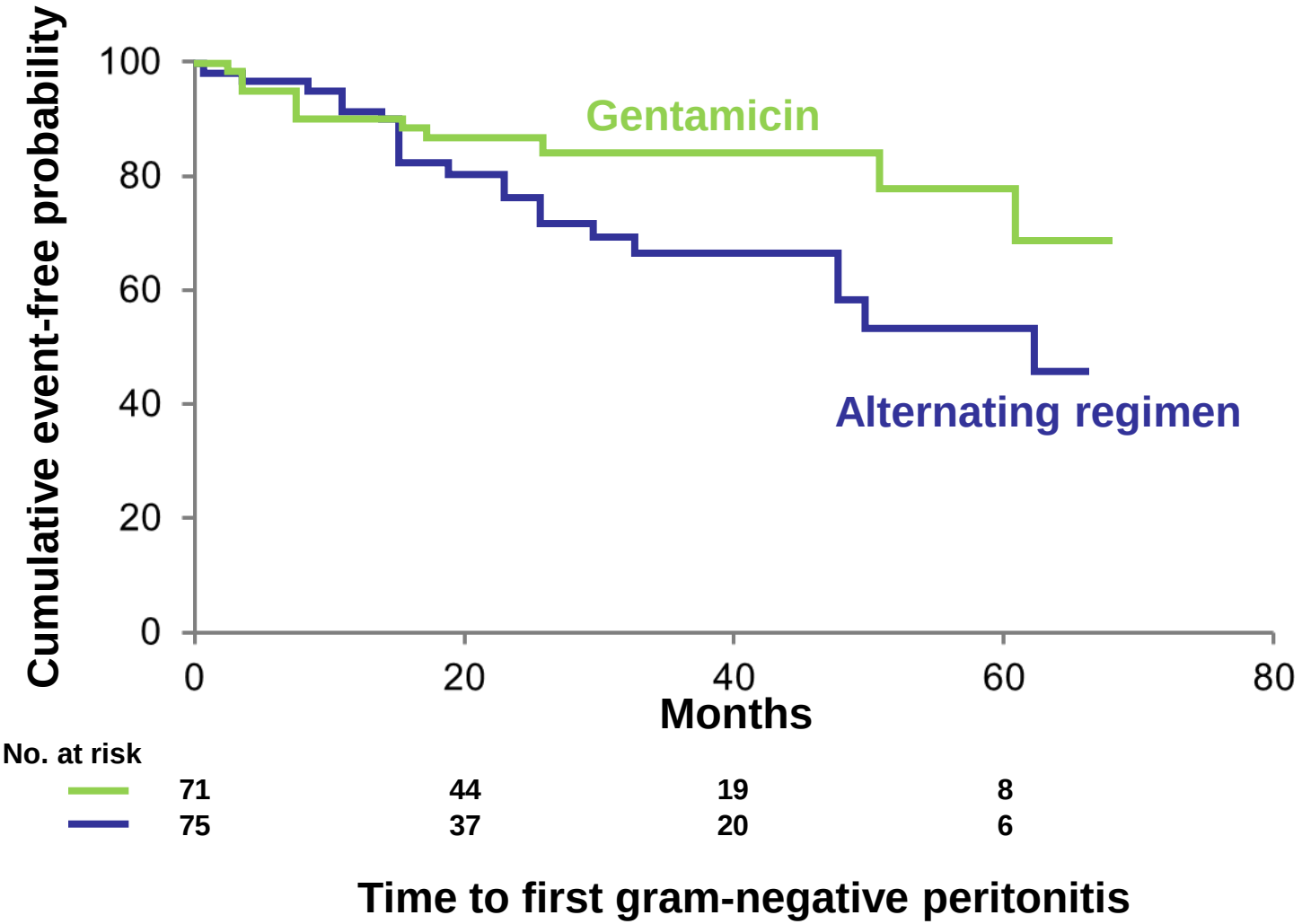
Staph aureus ESI

Gram-negative ESI



Tsai et al. Am J Surg 2017, in press

Monthly Alternating Mupirocin and Gentamicin versus Gentamicin



Wong et al. Perit Dial Int 2016; 36:340

Alternating Mupirocin and Gentamicin versus Gentamicin: Peritonitis Rate

Organism	Gentamicin		Alternating regimen		P
	n	Rate	n	Rate	
Total	39	0.22	58	0.32	<0.001
Gram-positive	19	0.11	20	0.11	0.99
Staphylococcus aureus	5	0.03	2	0.01	0.20
Other gram-positive	14	0.08	18	0.10	0.68
Gram-negative	14	0.08	25	0.14	<0.001
Pseudomonas aeruginsoa	0	0.00	2	0.01	0.97
Gram-negative other than Pseudomonas aeruginsoa	14	0.08	23	0.13	<0.001
Klebsiella species	3	0.02	8	0.04	0.02
Mixed gram-positive and gram-negative	1	0.006	0	0.00	0.31
Sterile	3	0.02	6	0.03	0.14
Fungal (yeast)	1	0.006	5	0.03	<0.001
Mycobaterium tuberculosis	1	0.006	2	0.01	0.14

Wong et al. Perit Dial Int 2016; 36:340

Mupirocin versus Chlorhexidine 1% after Standard Care with Povidone Iodine 10%

	Chlorhexidine	Mupirocin	IRR (95% CI)	P
Exit site infection				
Total ESI	0.22	0.12	1.82 (1.01, 3.31)	0.048
Total Gram-positive	0.10	0.08	1.21 (0.56, 2.61)	0.67
S. aureus	0.08	0.04	1.89 (0.70, 5.12)	0.21
Other Gram-positive	0.02	0.04	0.52 (0.13, 2.07)	0.35
Total Gram-negative	0.09	0.04	2.48 (0.87, 7.03)	0.09
P. aeruginosa	0.08	0.03	2.84 (0.90, 8.92)	0.07
Other Gram-negative	0.01	0.01	1.03 (0.06, 16.5)	0.98
Peritonitis				
Total peritonitis	0.31	0.32	0.99 (0.65, 1.50)	0.95
Total Gram-positive	0.12	0.12	0.97 (0.49, 1.92)	0.94
S. Aureus	0.02	0.01	1.03 (0.14, 7.34)	0.97
Other Gram-positive	0.10	0.11	0.96 (0.47, 2.00)	0.92
Total Gram-negative	0.13	0.12	1.09 (0.56, 2.12)	0.79
P. Aeruginosa	0.02	0.01	1.03 (0.15, 7.34)	0.97
Other Gram-negative	0.12	0.11	1.10 (0.55, 2.23)	0.79

Htay et al. Perit Dial Int 2017; 37:266

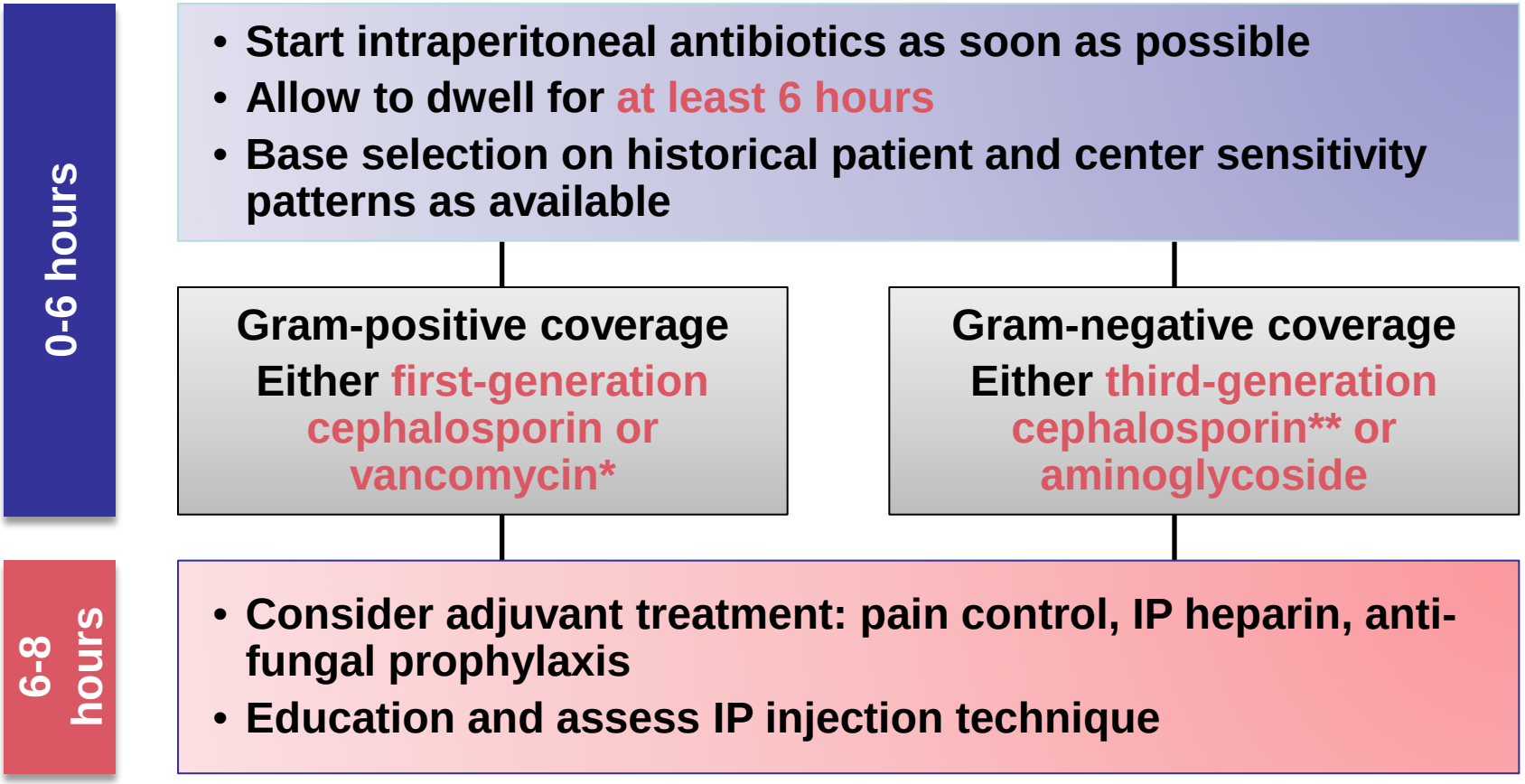
EXIT-SITE CARE: TAKE-HOME MESSAGE

- No strong evidence favors one topical regimen over another
- Mupirocin and gentamicin: concern about resistance
- Chlorhexidine: 2% aqueous solution
- Hypertonic saline 3% ?

Infection Control

- Prevention of peritonitis
- Management of peritonitis

INITIAL MANAGEMENT OF PERITONITIS: STATE OF THE ART



*Vancomycin: if patient has history of MRSA colonization/infection, is seriously unwell, or has severe allergy to penicillins and cephalosporins, if the center has increased rate of methicillin resistance.

**If the patient is cephalosporin allergic, aztreonam is an alternative.

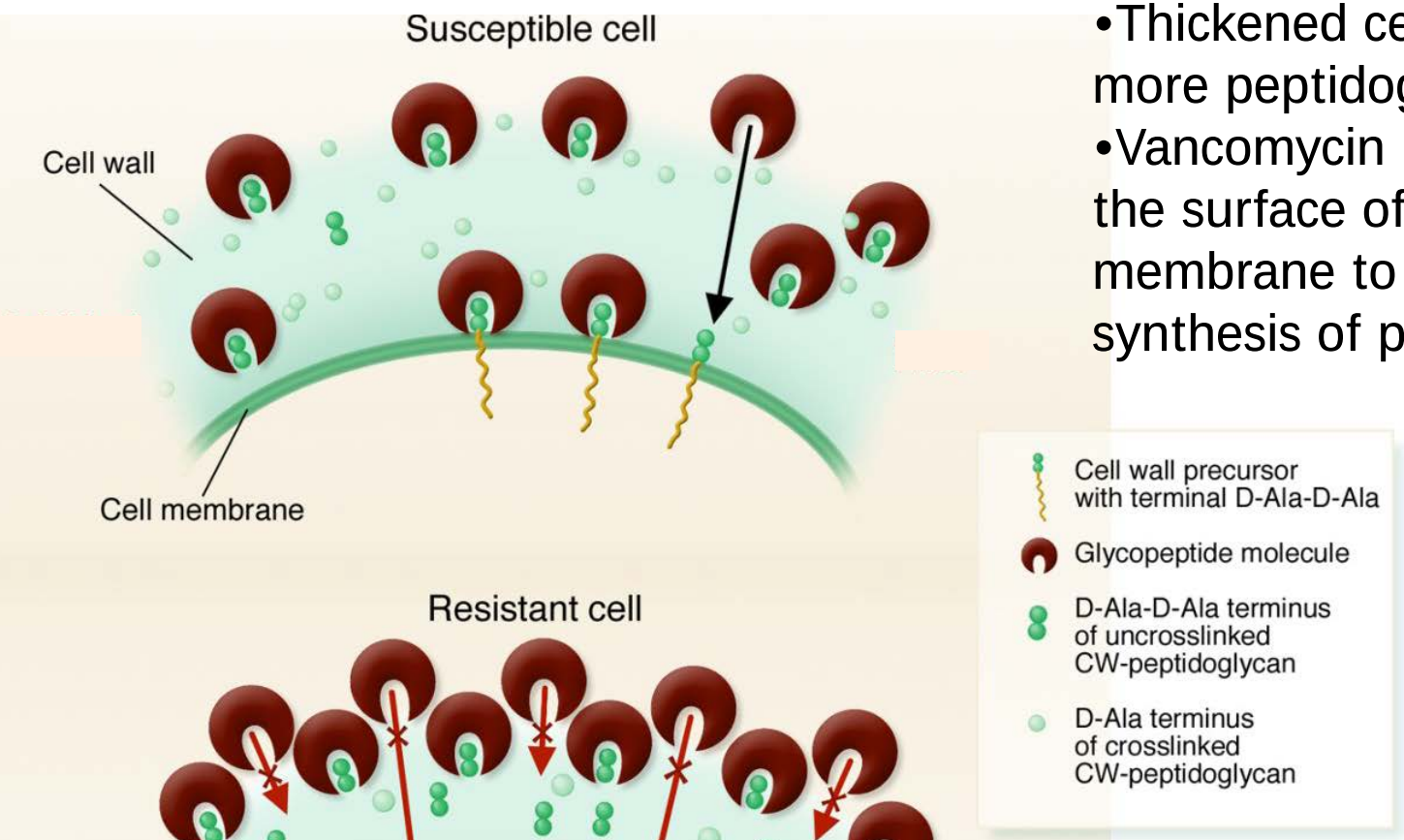
Li et al. Perit Dial Int 2016, 36: 481

ISPD PERITONITIS RECOMMENDATIONS: 2016 UPDATE

- We suggest that IP aminoglycoside be administered as daily intermittent dosing **(2B)**.
- We recommend that prolonged courses of IP aminoglycoside be avoided **(1C)**.
- We suggest that IP vancomycin be administered intermittently and the serum vancomycin level be kept above 15 µg/mL **(2C)**.
- We suggest that IP cephalosporin be administered either continuously (in each exchange) or on a daily intermittent basis **(2C)**.

Li et al. Perit Dial Int 2016, 36: 481

VISA



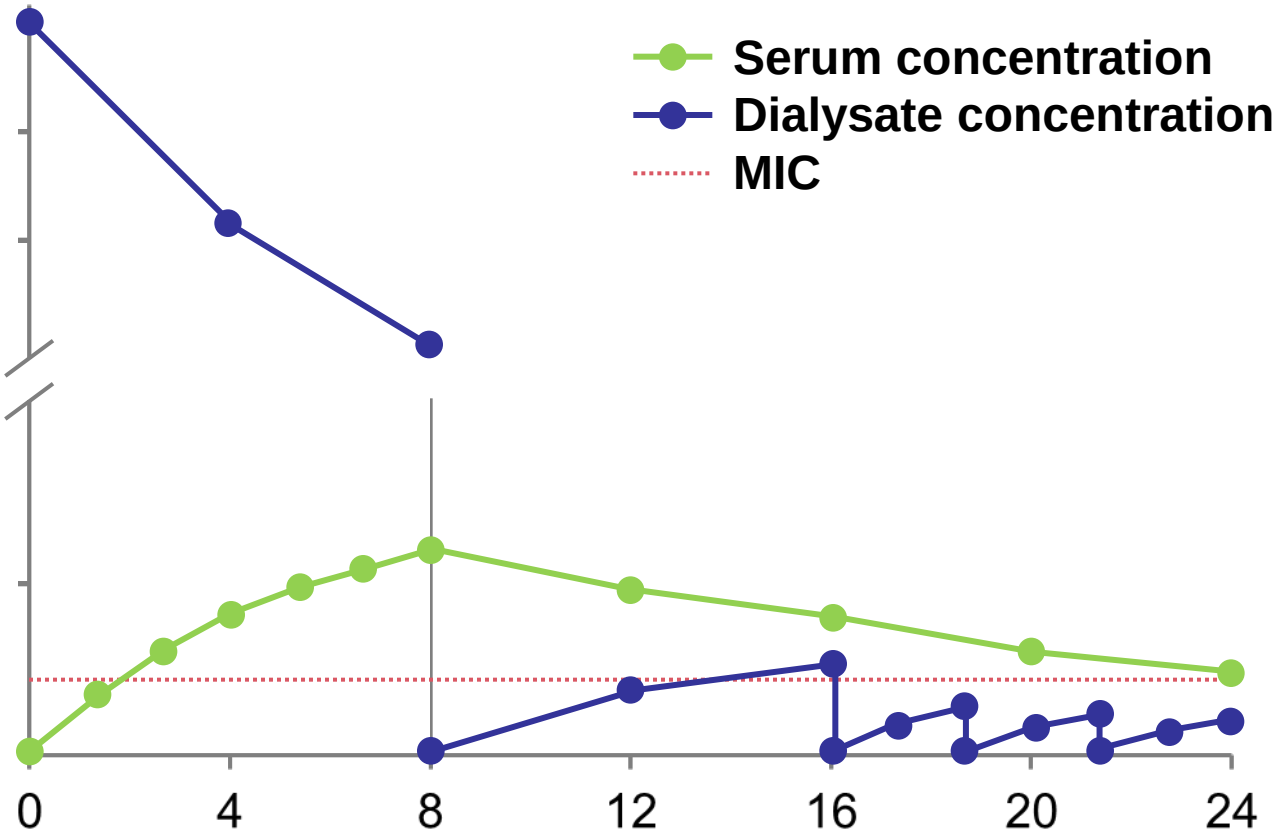
- Thickened cell wall with more peptidoglycan layers.
- Vancomycin never reaches the surface of the cytoplasmic membrane to affect the synthesis of peptidoglycan.

VRSA

- *Van*A gene=high-level vancomycin resistance
- D-ala-D-ala ➔ D-ala-D-lac

De Vriese et al. Perit Dial Int 2014; 34:154

HYPOTHETICAL SERUM AND DIALYSATE ANTIBIOTIC LEVELS IN CCPD



De Vriese et al. Perit Dial Int 2014; 34:154

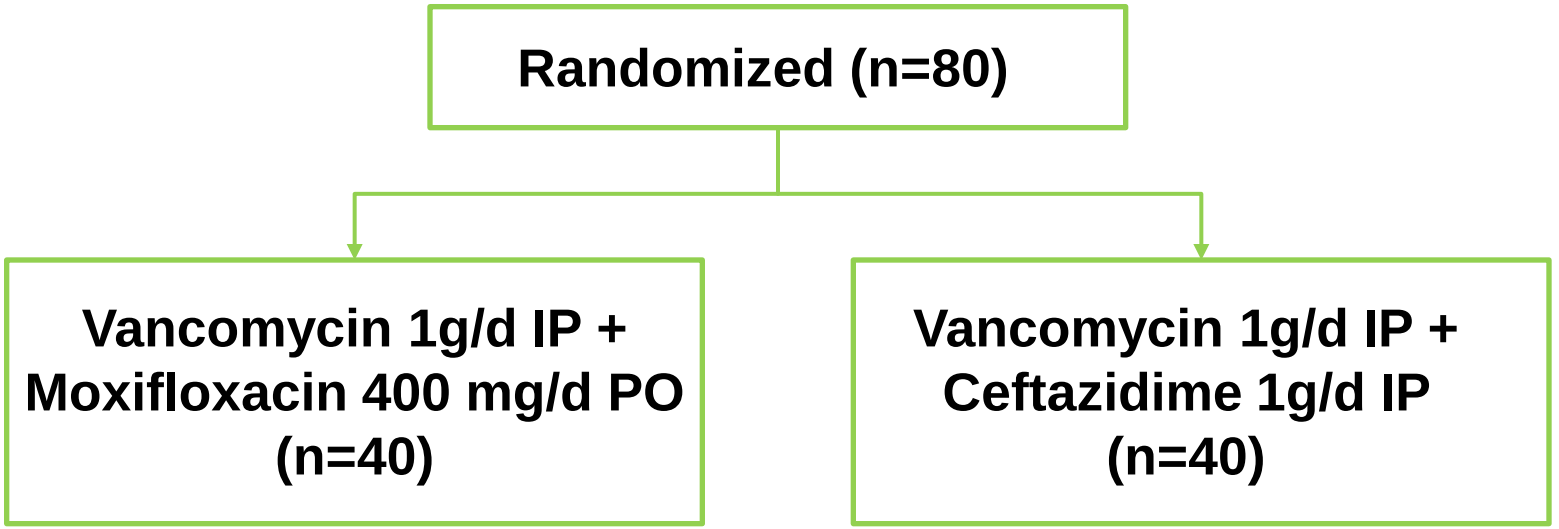
Current Guidelines and Suggested Vancomycin Dosing Schedule

	Dose type	
Applicability	**Loading**	**Maintenance**
ISPD guideline		
CAPD intermittent		15-30 mg/kg every 5-7 days
CAPD continuous	1000 mg/L	25 mg/L
CCPD intermittent	30 mg/kg	15 mg/kg every 3-5 days
Our proposal		
CAPD or CCPD continuous	20-25 mg/kg	25 mg/L

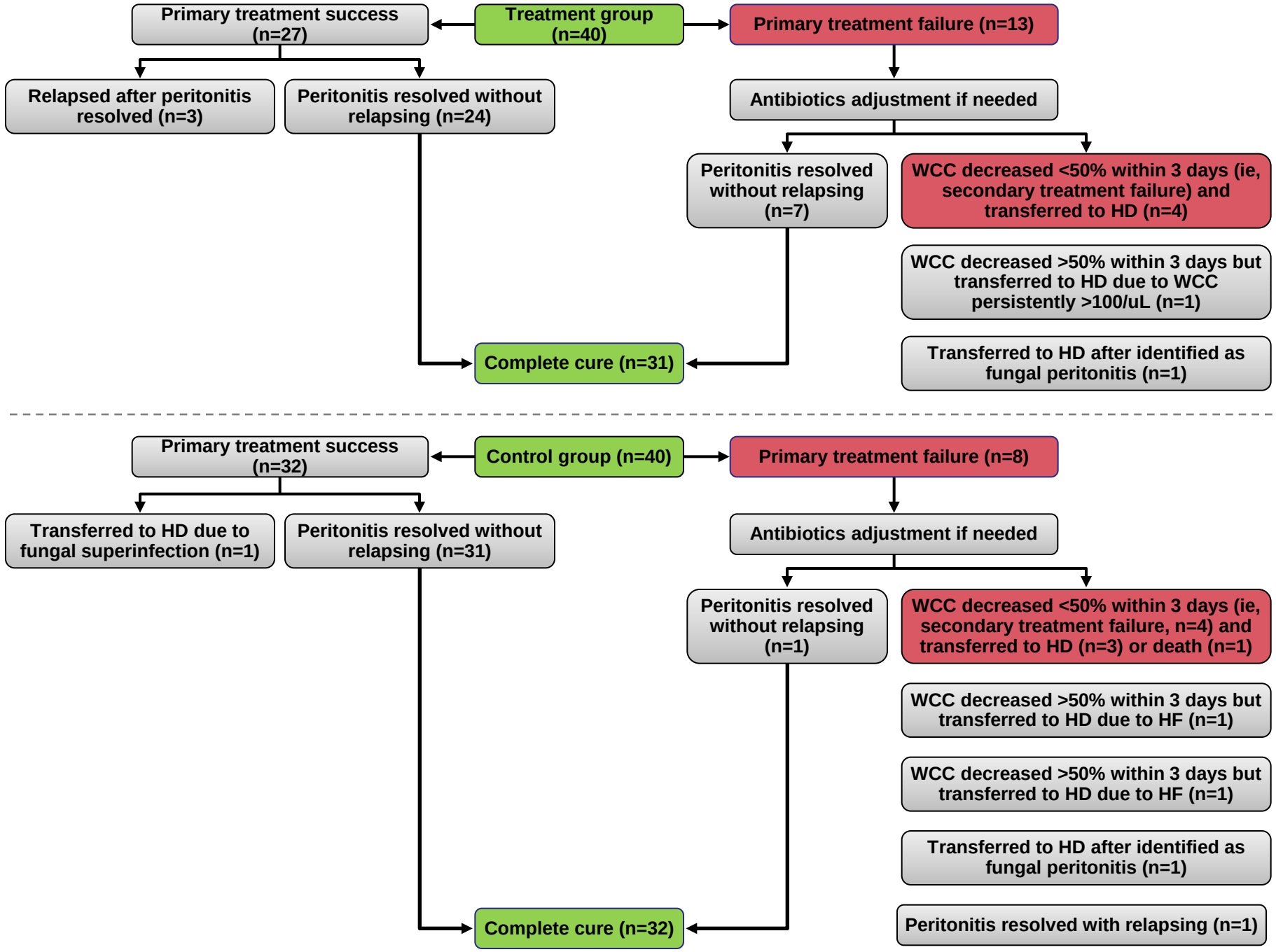
=higher local concentrations ➔ less failure / VISA
=lower systemic exposure ➔ less side effects

De Vriese et al. Perit Dial Int 2014; 34:154

Oral quinolones as empirical therapy for PD peritonitis

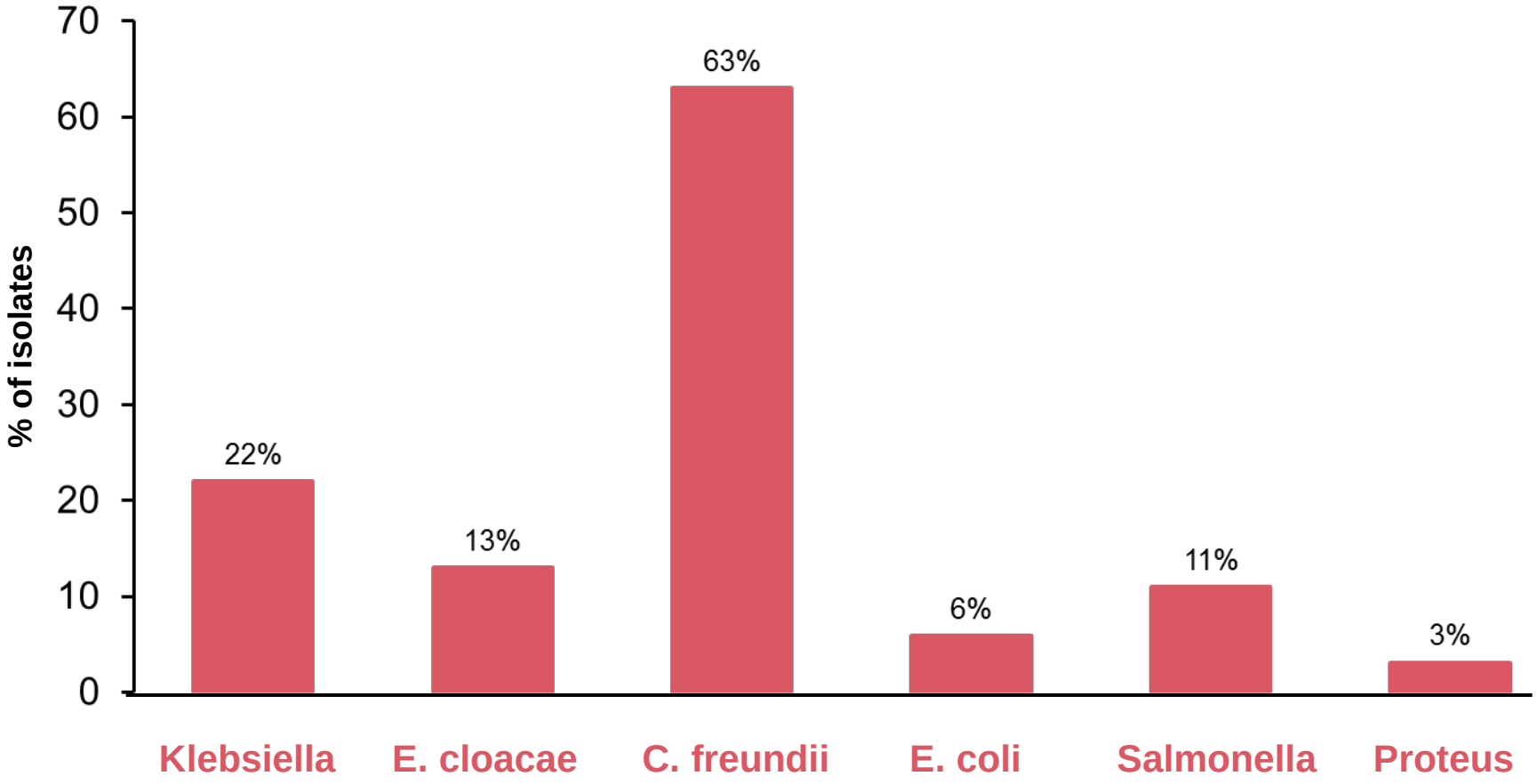


Xu et al. Am J Kidney Dis 2016; 70:30



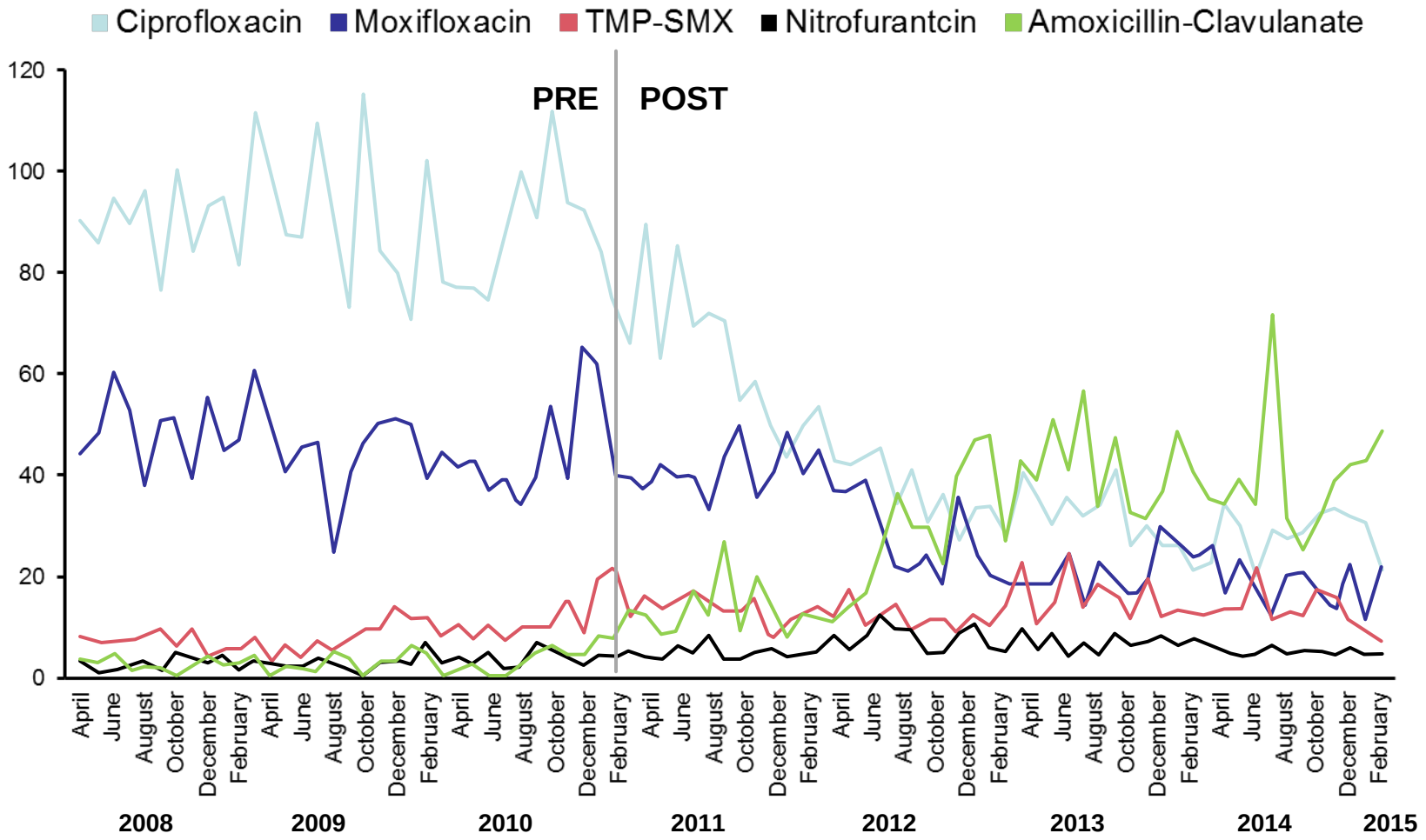
Xu et al. Am J Kidney Dis 2016; 70:30

Prevalence of Quinolone Resistance in Enterobacteria



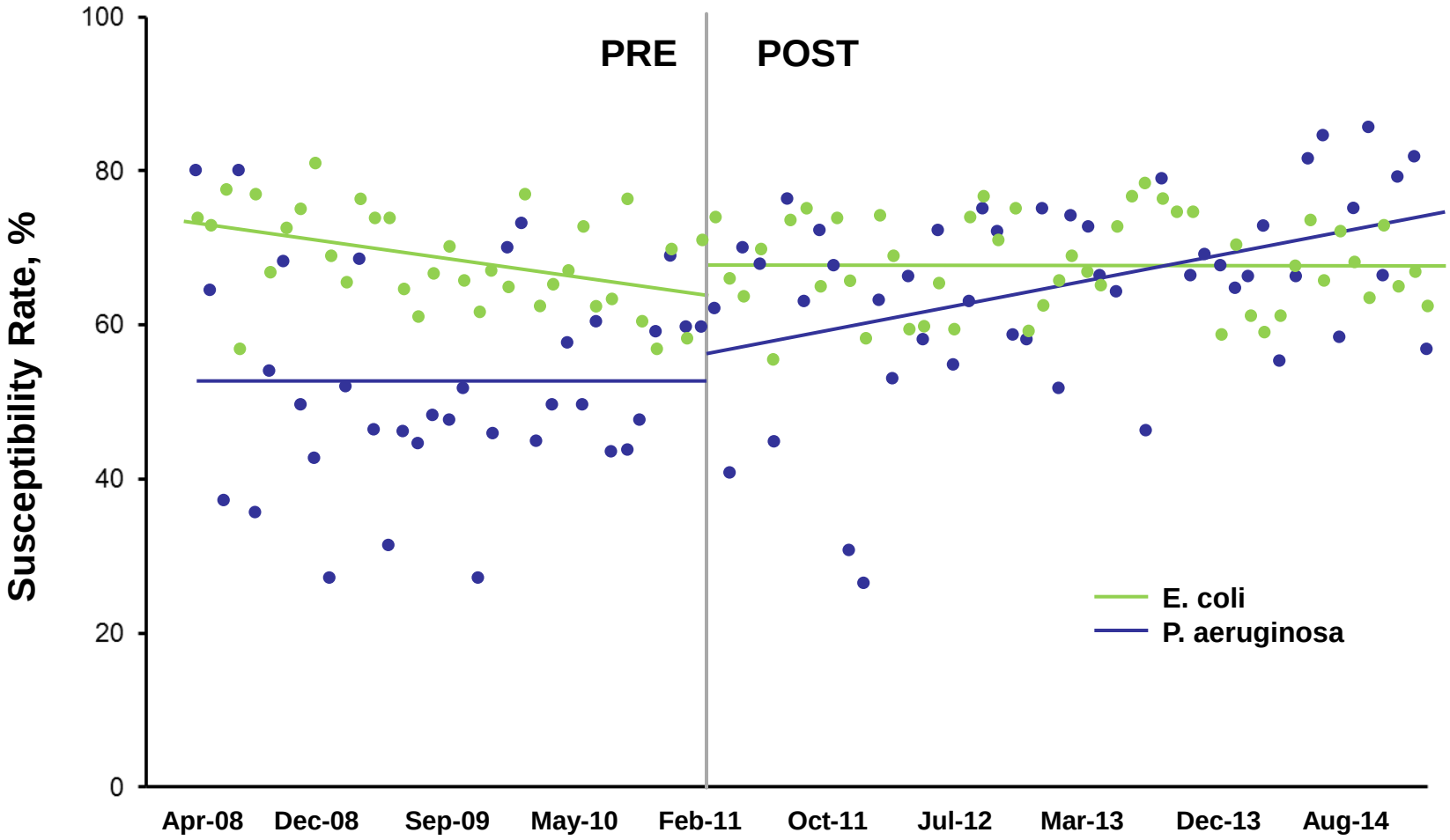
Albornoz et al. Microb Drug Resist 2017;23:177

Antimicrobial Utilization Before and After Ciprofloxacin Selective Reporting



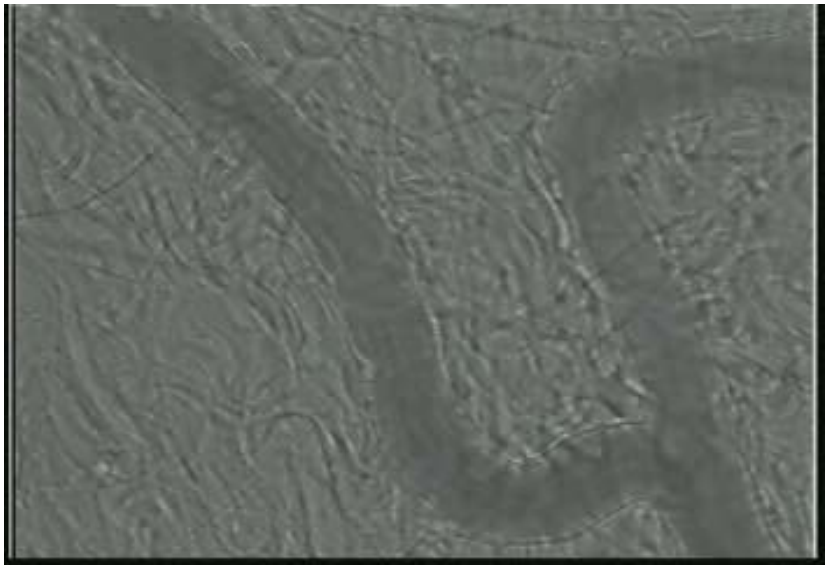
Langford et al. J Clin Microbiol 2016; 54:2343

E. Coli and P. aeruginosa Susceptibility to Ciprofloxacin Before and After Selective Reporting

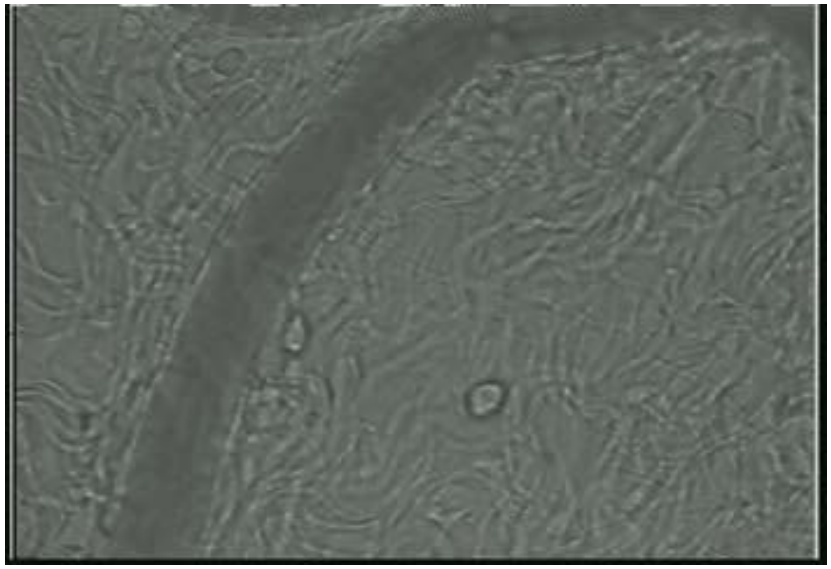


Langford et al. J Clin Microbiol 2016; 54:2343

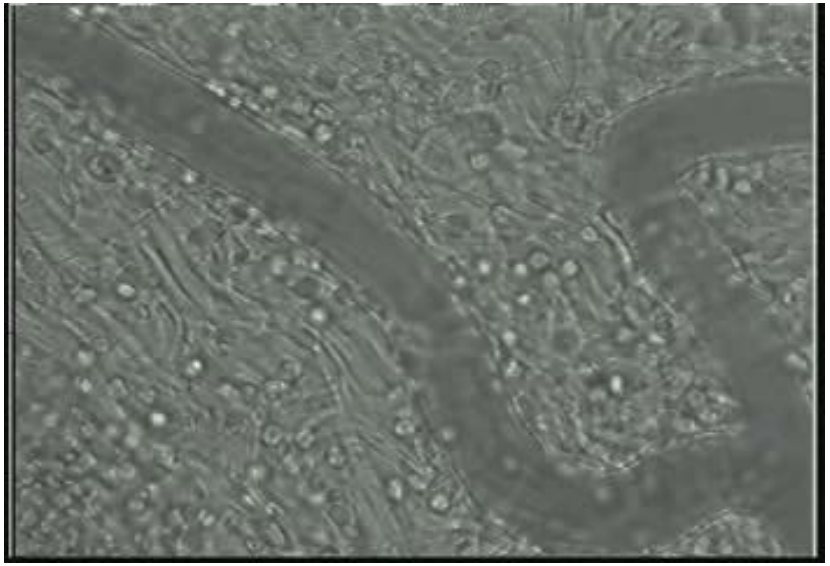
Control t=0 min



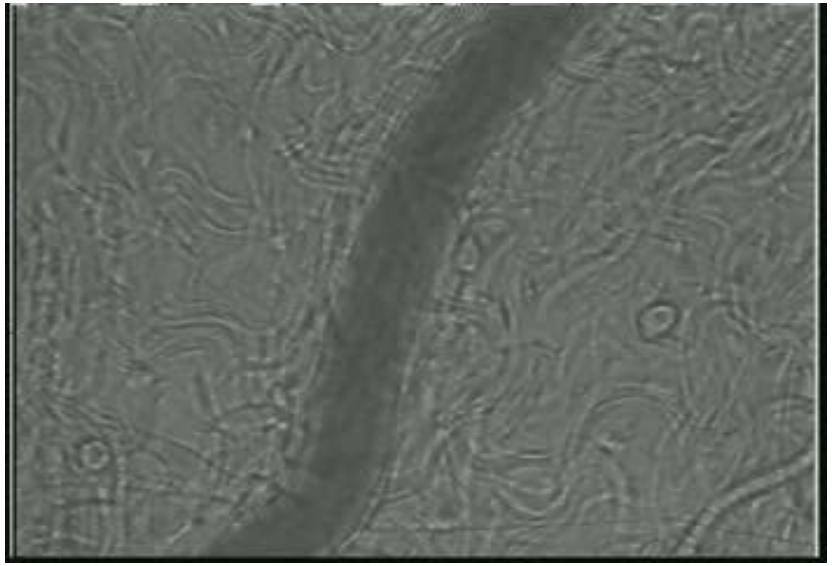
Dialysate t=0 min



Control t=150 min after LPS



Dialysate t=150 min after LPS



Mortier, De Vriese et al. JASN 2003; 14:1296

Enteric Microorganism Peritonitis

VUmc

Standard PD peritonitis treatment

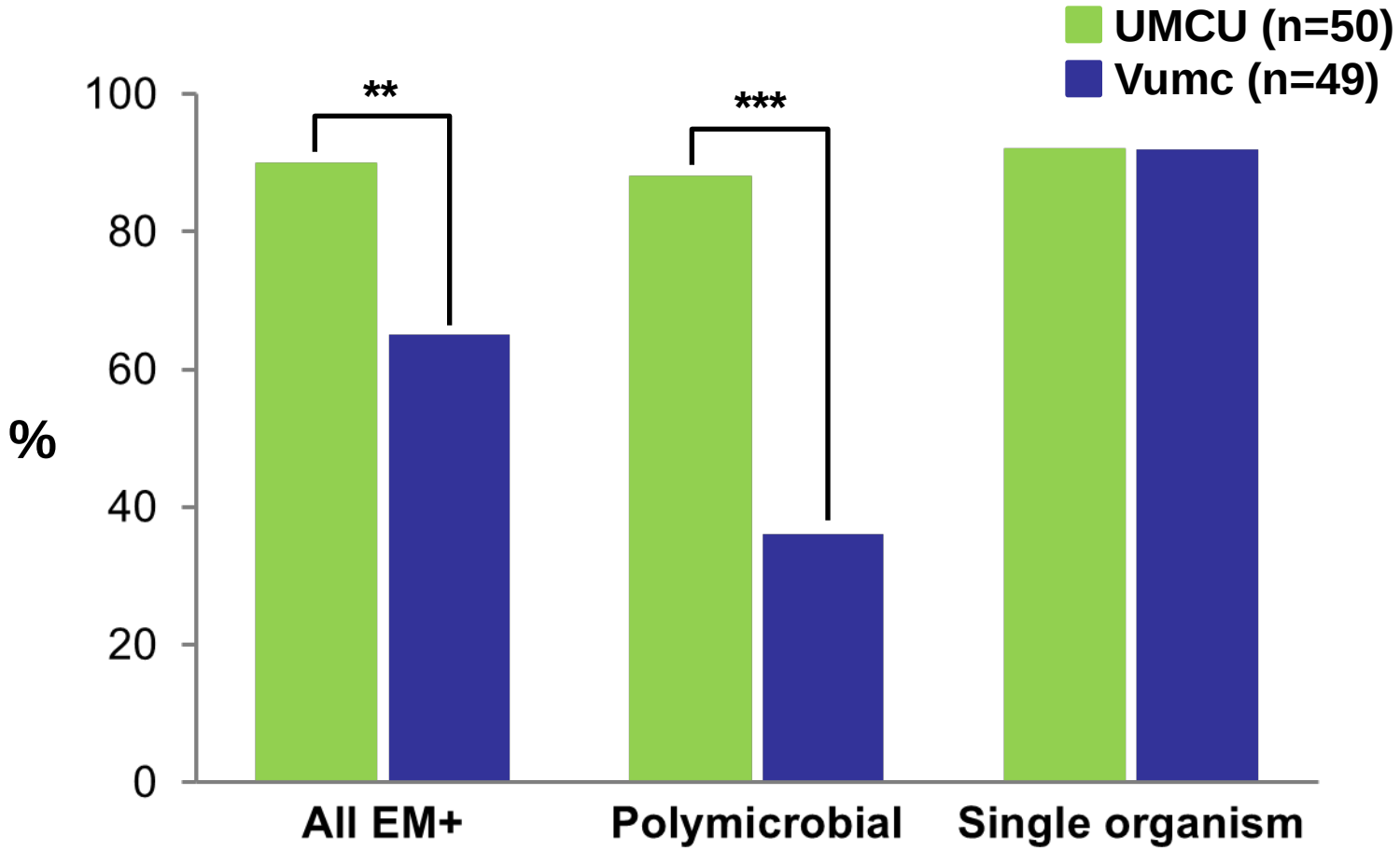
UMCU

MeroRest=
-stop PD without removal PD katheter
-Meropenem IV 500 mg/d
-Meropenem katheter lock 125 mg in 25 ml saline/d

NB: Enteric microorganisms were defined as pathogens commonly found in the gut, including *Enterobacteriaceae*, enterococci, and anaerobic bacteria.

Abahams et al. Perit Dial Int 2017; 37:298

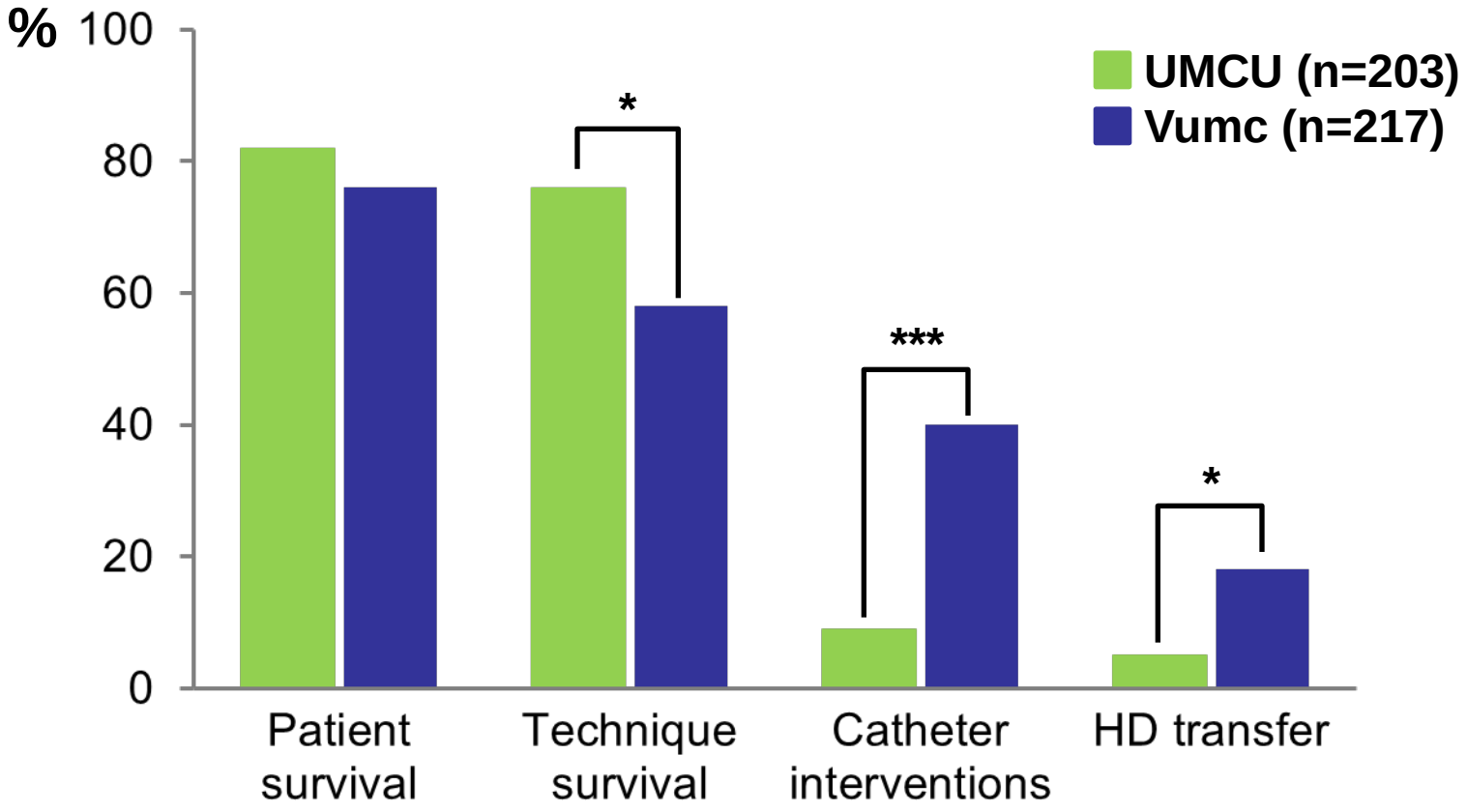
Primary Cure Rate of Enteric Microorganism Peritonitis



**P<0.01; ***P<0.001

Abahams et al. Perit Dial Int 2017; 37:298

Outcome in all episodes of PD peritonitis



**P<0.01; ***P<0.001

Abahams et al. Perit Dial Int 2017; 37:298

MANAGEMENT OF PERITONITIS: TAKE-HOME MESSAGE

- Vancomycin: continuous regimen is preferable
- IP vancomycin + PO moxifloxacin as empirical regimen? Quinolone resistance!
- Improved outcome of polymicrobial EM peritonitis by discontinuation of PD without catheter removal + IV and intracatheter meropenem

Technical Issues

- Urgent start peritoneal dialysis
- Intraperitoneal pressure

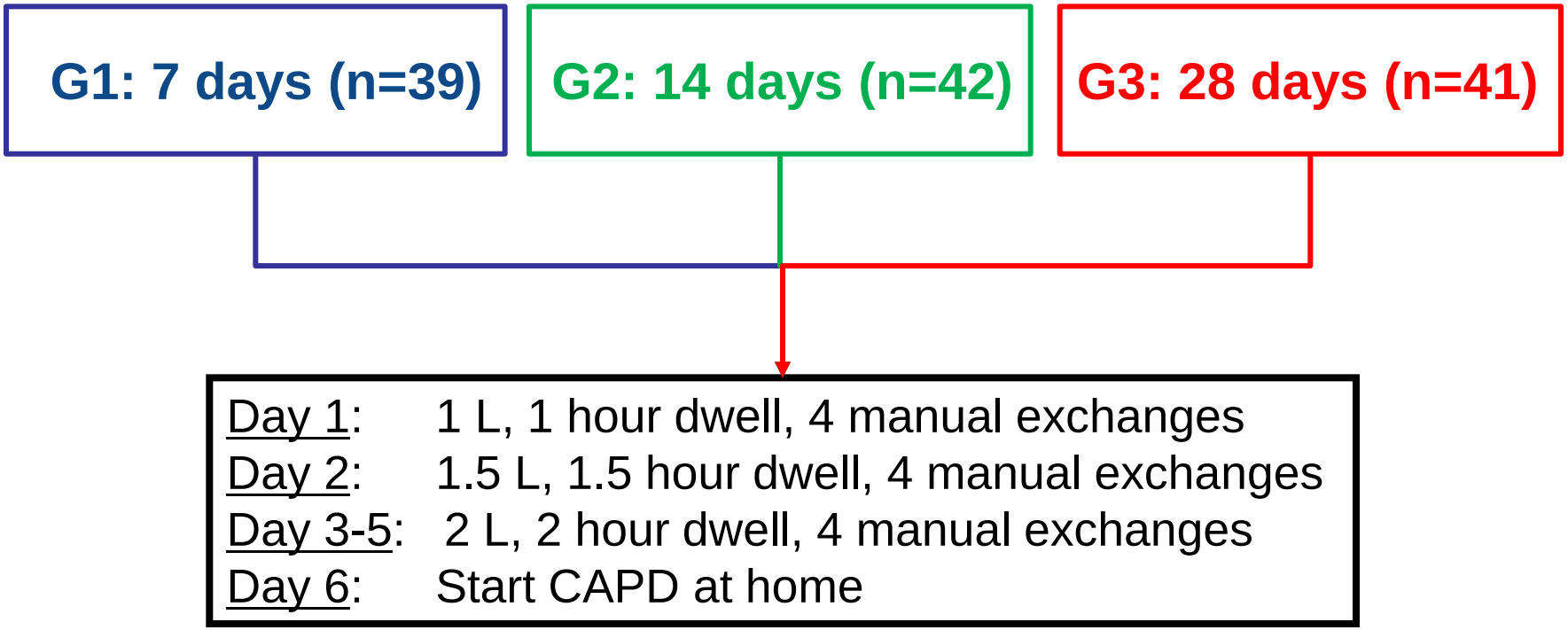
PERITONEAL ACCESS: STATE OF THE ART

Guideline 2.1: Timing and Coordination of Referral and Surgery (2B): We suggest that, whenever possible, catheter insertion should be performed at least 2 weeks before starting PD. Small dialysate volumes in the supine position can be used if dialysis is required earlier.

Note: Many patients are treated with bridging HD

Figueiredo A et al. Perit Dial Int 2010, 30:424

Appropriate time to start PD: a RCT

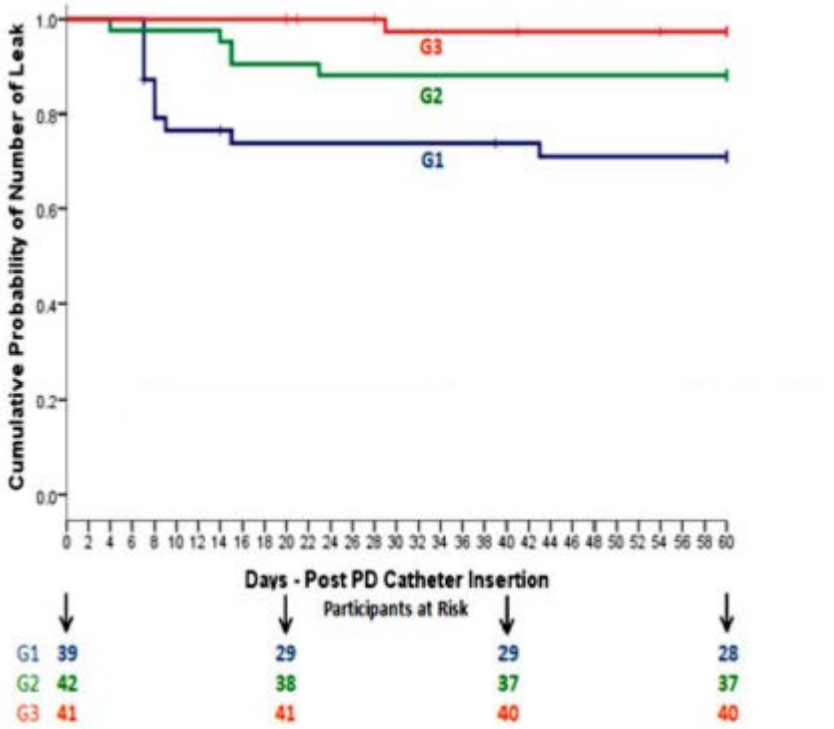


Ranganathan et al. Perit Dial Int 2017; 37:420

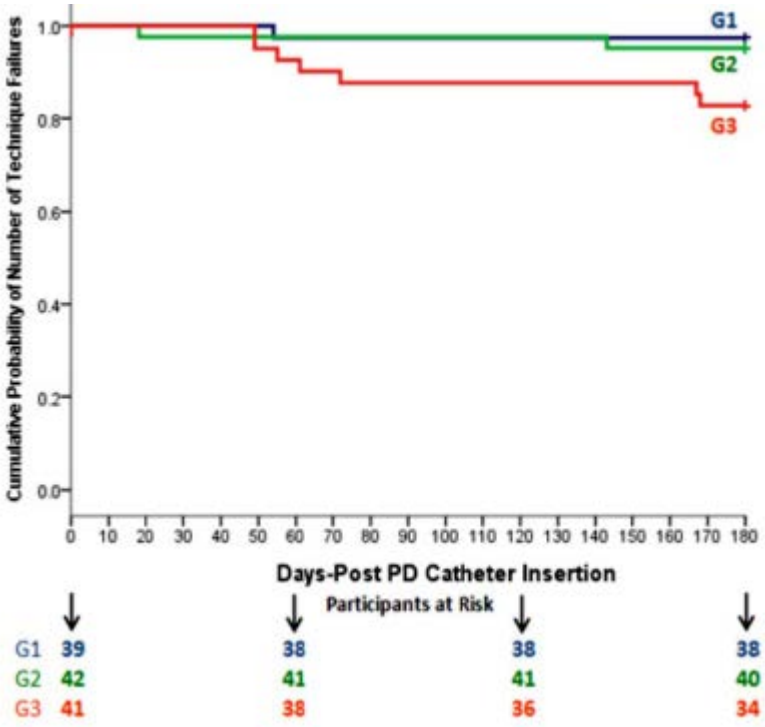
Appropriate time to start PD: a RCT

G1: 7 days – G2: 14 days – G3: 28 days

Leaks – 60 days



Technique Failure – 180 days



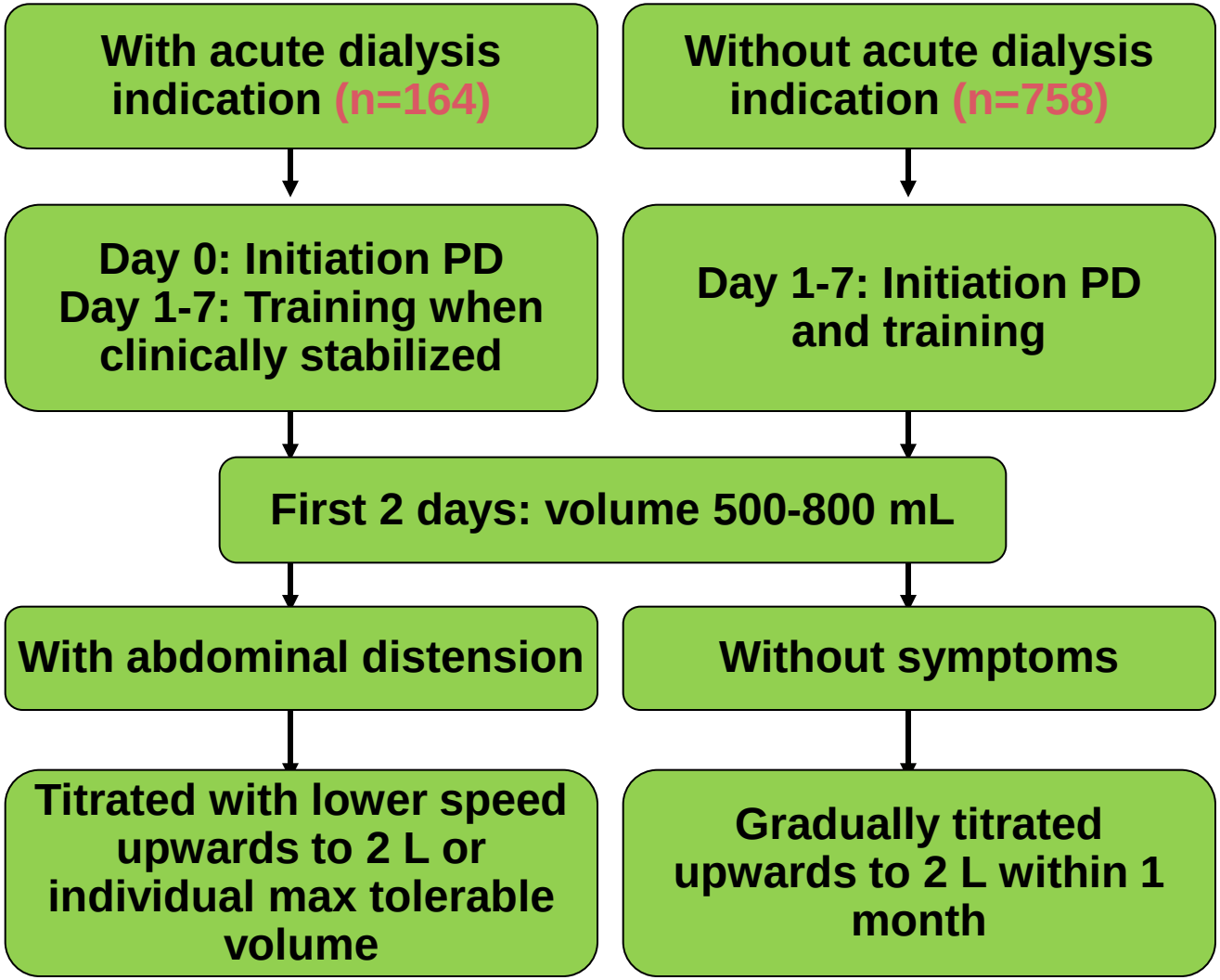
Ranganathan et al. Perit Dial Int 2017; 37:420

URGENT START PD: BREAK-IN <2w

- Abdominal wall complications: inguinal hernia, umbilical hernia, hydrothorax, hydrocoele, subcutaneous leak, pericatheter leak
- Catheter complications: obstruction, migration, omental wrap

- Small patient numbers, short follow-up, absent conventional-start PD control groups

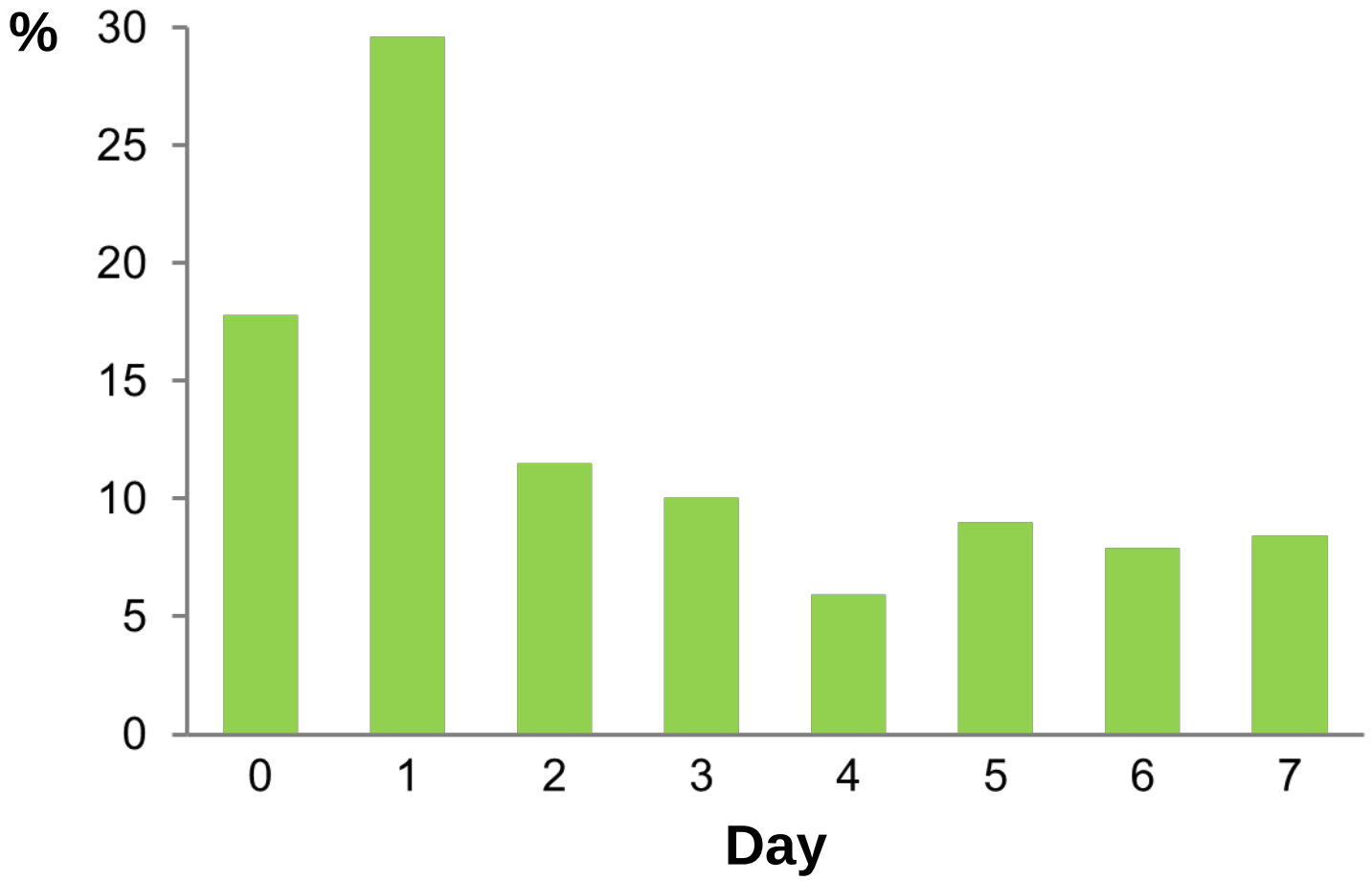
Large cohort urgent start PD



Note: dialysate volume of most patients (80.5%) at 1 mo was <2 L

Xu et al. Am J Kidney Dis 2017;70:102

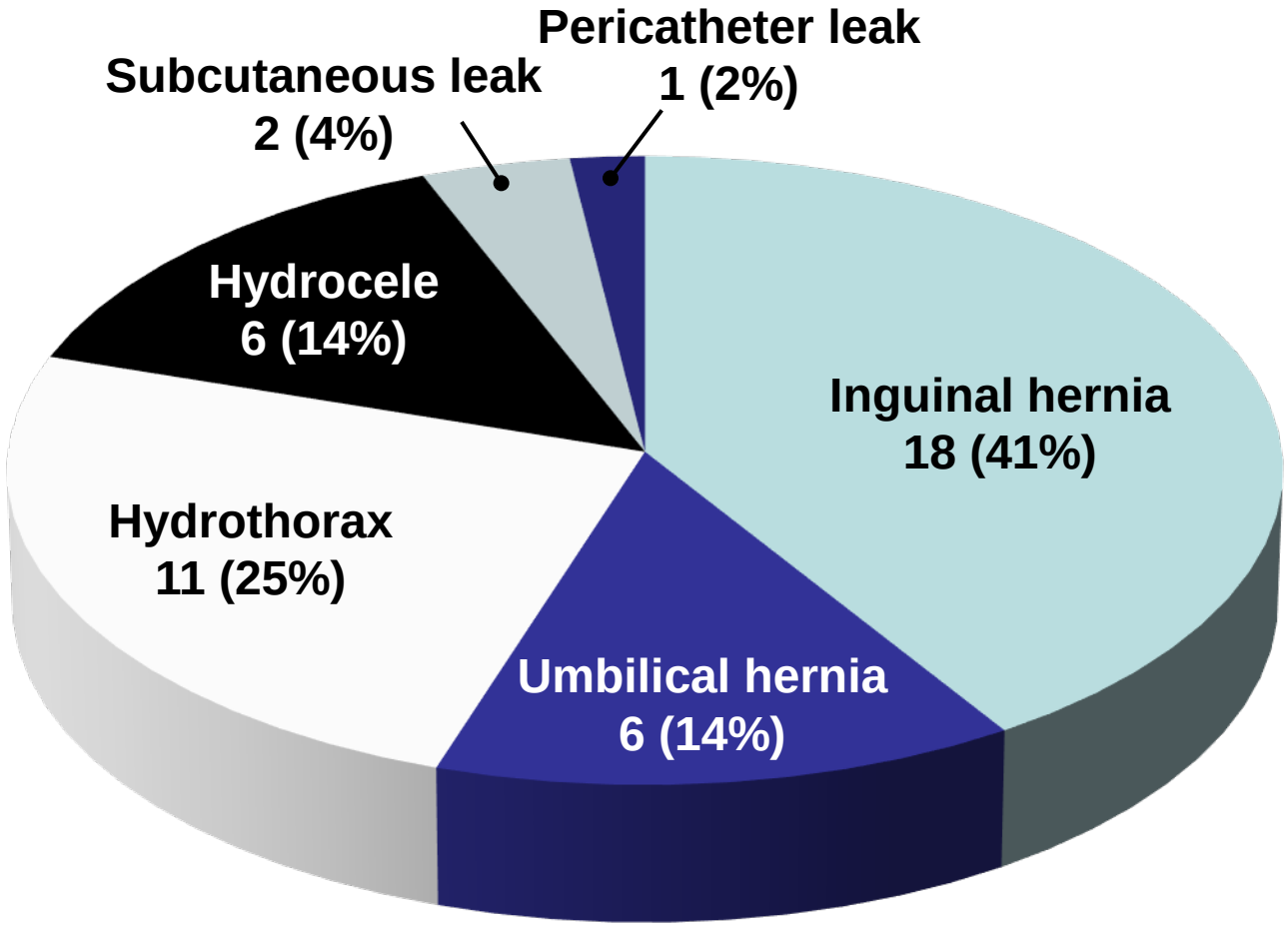
Distribution of Break-In Periods



Xu et al. Am J Kidney Dis 2017;70:102

Abdominal Wall Complications

44 patients (4.8%) at 5.2m follow-up
= 1.5/100 patient years



Xu et al. Am J Kidney Dis 2017;70:102

Characteristics of Mechanical Complications

	Total	Early (<1m) Complications	Surgical repair	Transfer to HD
Abdominal wall complications	44	9	18	21
Hernia	24	2	18	4
Inguinal hernia	18	2	14	2
Umbilical hernia	6	0	4	2
Hydrothorax	11	3	0	10
Hydrocele	6	2	0	6
Pericatheter leak	1	1	0	0
Subcutaneous leak	2	1	0	1
Catheter complications	18	18	3	1
Catheter obstruction	13	13	0	0
Catheter shift	4	4	3	0
Omental wrap	1	1	0	1

Xu et al. Am J Kidney Dis 2017;70:102

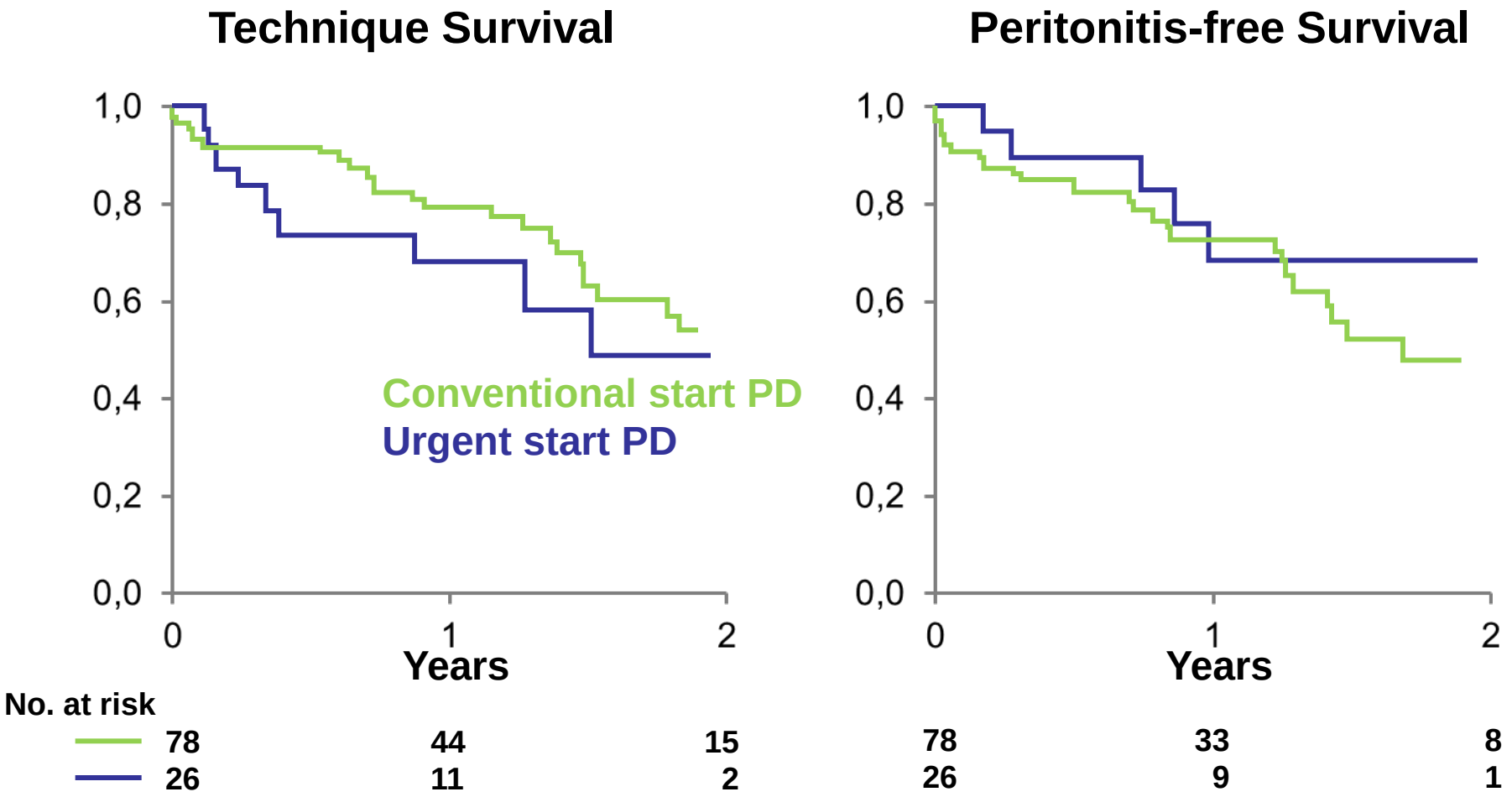
Matched cohorts urgent and conventional start PD

Urgent start: supine, intermittent PD, initial exchange volumes 0.5 – 1.5 L

	Complications within 4 weeks of catheter insertion			Complications within 4 weeks of PD commencement		
	USPD n=26	CSPD n=78	P	USPD n=26	CSPD n=78	P
Leak	3 (12%)	1 (1%)	0.047	3 (12%)	2 (3%)	0.10
Catheter blockage	1 (4%)	0 (0%)	0.25	1 (4%)	0 (0%)	0.25
Catheter migration	3 (12%)	3 (4%)	0.16	3 (12%)	1 (1%)	0.047
Exit-site infection	4 (15%)	10 (13%)	0.92	4 (15%)	5 (6%)	0.38
Peritonitis	0 (0%)	3 (4%)	0.57	0 (0%)	7 (9%)	0.19

See et al. Perit Dial Int 2017; 37:414

Matched Cohorts Urgent and Conventional start PD



See et al. Perit Dial Int 2017; 37:414

URGENT START PD: PRACTICAL ISSUES

- Contraindications: DBP >120 mmHg, pulmonary edema, K>6.5 mmol/L), uremic pericarditis
- Prescription APD:

Body weight	≤60 kg	>60 kg	
Time overnight	12 hours	12 hours	supine
Total volume	9.5 L	12 L	
Max dwell volume	1.2 L	1.5 L	
Tidal volume	50 %	50 %	gradually ↑75–85% during first week
No. of cycles	14	14	
Dwell time (min)	43	41	

Povlsen et al. Perit Dial Int 2015; 35:622

URGENT-START DIALYSIS

178 patients:

- 82 HD: start immediately after catheter placement
- 96 PD: 0.75–1.2 L supine, increased to 2L within 2w

Dialysis-related complications: bleeding, thrombosis, malposition, leakage, infection

Predictors of Short-Term Dialysis-Related Complications

Factor	OR	95% CI	P
Urgent-start HD vs PD	5.024	1.760-14.341	0.003
Heart failure (NYHA III-IV)	2.261	0.915-5.585	0.077

Jin et al. PloS ONE 2016, 11: e0166181

START OF PD: TAKE-HOME MESSAGE

- Optimal time to start PD: 2w after catheter insertion
- Early break-in: small increased risk of mechanical complications but no detrimental effect on mortality, peritonitis-free survival, or PD technique survival
- PD could be an alternative for urgent-start dialysis
- Incremental PD regimen

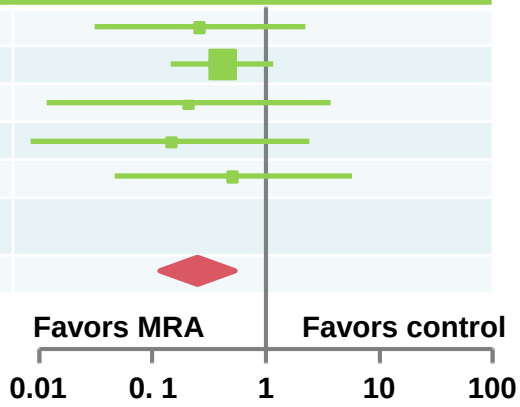
Cardiovascular Disease

MINERALOCORTICOID RECEPTOR ANTAGONISTS (MRAs)

- Less focus on atherosclerotic heart disease, more focus on LVH and cardiac fibrosis
- In the non-dialysis population, MRAs reduce mortality in heart failure and reduce LV mass
- Benefits in dialysis patients unclear
- Is hyperkalemia a problem?

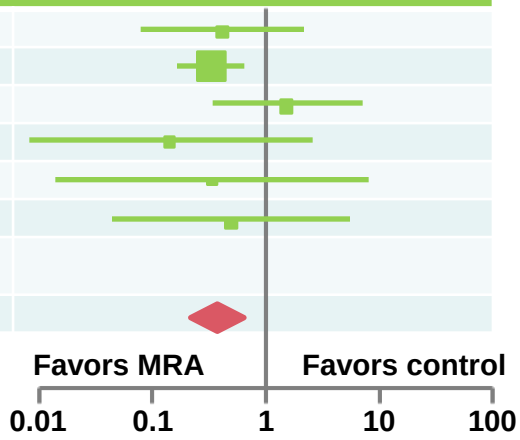
Effects of MRAs on Cardiovascular Mortality in Dialysis

	MRA		Control				
	Events	Total	Events	Total	Weight (%)	Risk ratio 95 % CI	Risk ratio 95 % CI
Ito 2013	1	78	4	80	13.3	0.26 [0.03, 2.24]	
Matsumoto 2014	5	157	12	152	60.3	0.40 [0.15, 1.12]	
Taheri 2009	0	8	2	8	7.5	0.20 [0.01, 3.61]	
Taheri 2012	0	9	3	9	7.8	0.14 [0.01, 2.42]	
Walsh 2015	1	77	2	77	11.1	0.50 [0.05, 5.40]	
Total (95% CI)		329		326	100.0	0.34 [0.15, 0,75]	



Effect of MRAs on All-Cause Mortality in Dialysis

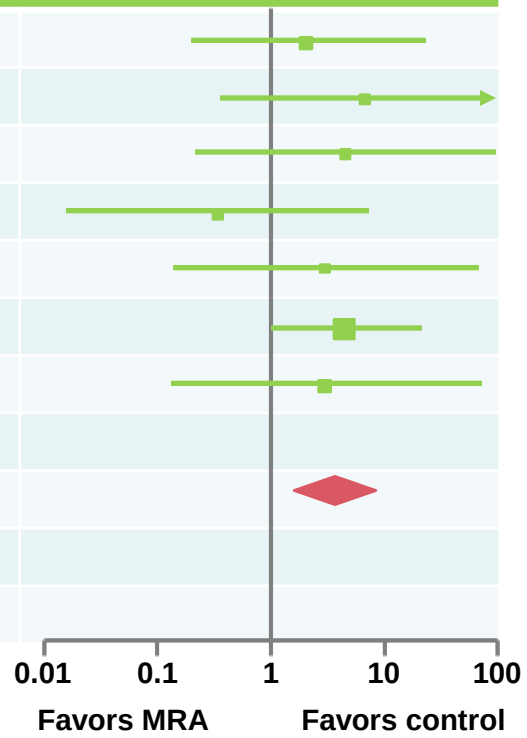
	MRA		Control				
	Events	Total	Events	Total	Weight (%)	Risk ratio 95 % CI	Risk ratio 95 % CI
Ito 2013	2	78	5	80	11.4	0.41 [0.08, 2.05]	
Matsumoto 2014	10	157	30	152	63.7	0.32 [0.16, 0.64]	
Taheri 2009	3	8	2	8	13.1	1.50 [0.34, 6.70]	
Taheri 2012	0	9	3	9	3.7	0.14 [0.01, 2.42]	
Vukusich 2010	0	33	1	33	2.9	0.33 [0.01, 7.90]	
Walsh 2015	1	77	2	77	5.2	0.50 [0.05, 5.40]	
Total (95% CI)		362		359	100.0	0.40 [0.23, 0.69]	



Quach et al. Am J Kidney Dis 2016, 68:591

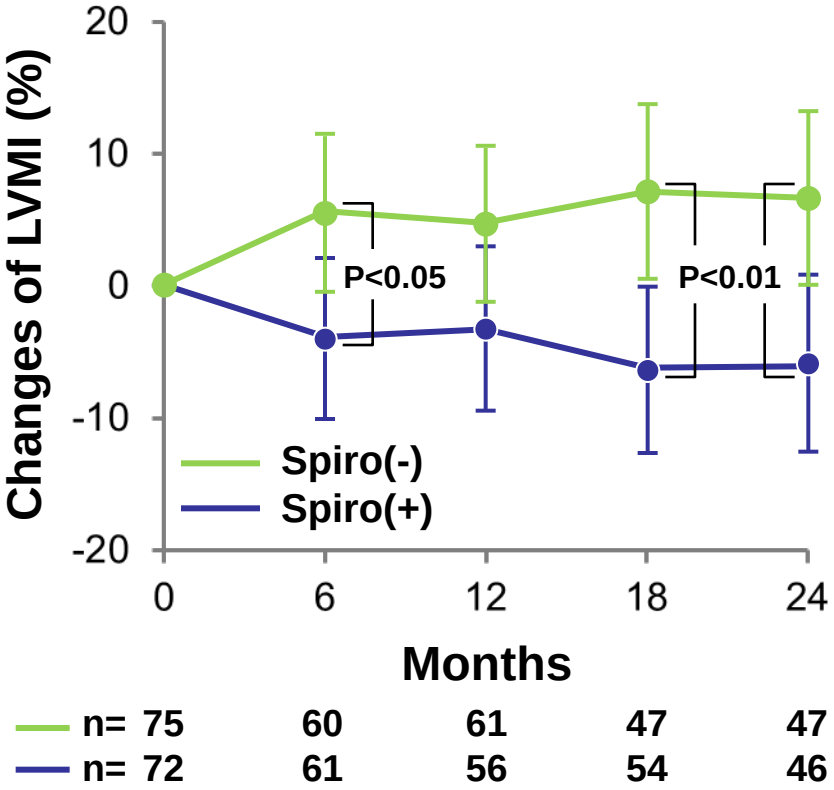
Effects of MRAs on Hyperkalemia in Dialysis Patients

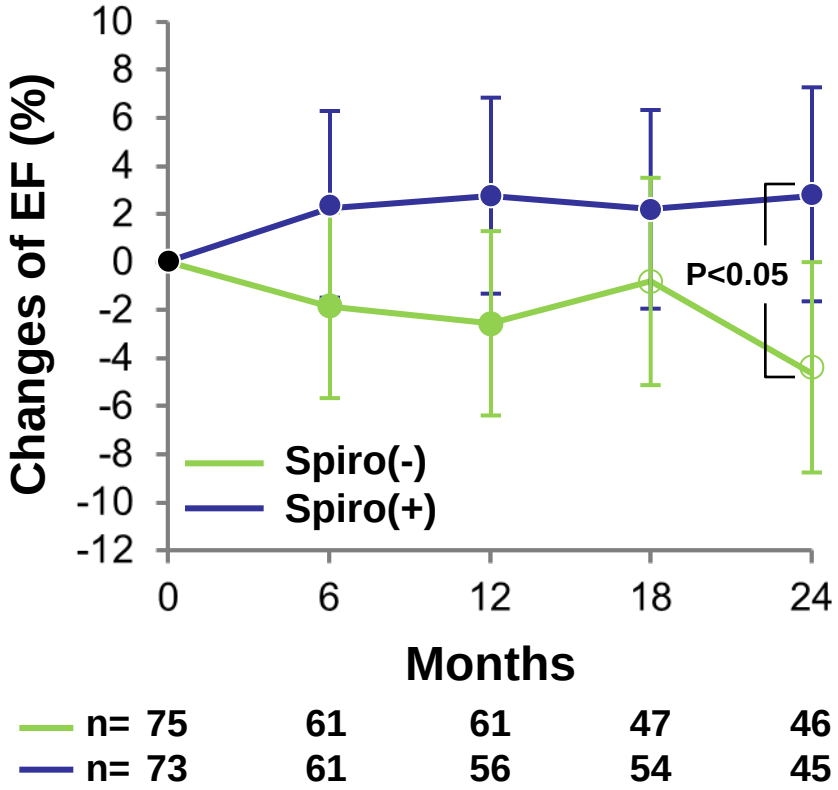
	MRA		Control				
	Events	Total	Events	Total	Weight (%)	Risk ratio 95 % CI	Risk ratio 95 % CI
Ito 2013	2	78	1	80	15.2	2.05 [0.19, 22.17]	
Matsumoto 2014	3	157	0	152	9.9	6.78 [0.35, 130.14]	
Ni 2014	2	40	0	36	9.5	4.51 [0.22, 90.96]	
Taheri 2009	0	8	1	8	9.2	4.51 [0.22, 90.96]	
Taheri 2012	1	9	0	9	9.1	3.00 [0.14, 65.16]	
Walsh 2015	9	77	2	77	38.3	4.50 [1.00, 20.15]	
Yongsiri 2015	1	12	0	12	8.9	3.00 [0.13, 67.06]	
Total (95% CI)		381		374	100.0	3.05 [1.21, 7.70]	



Quach et al. Am J Kidney Dis 2016, 68:591

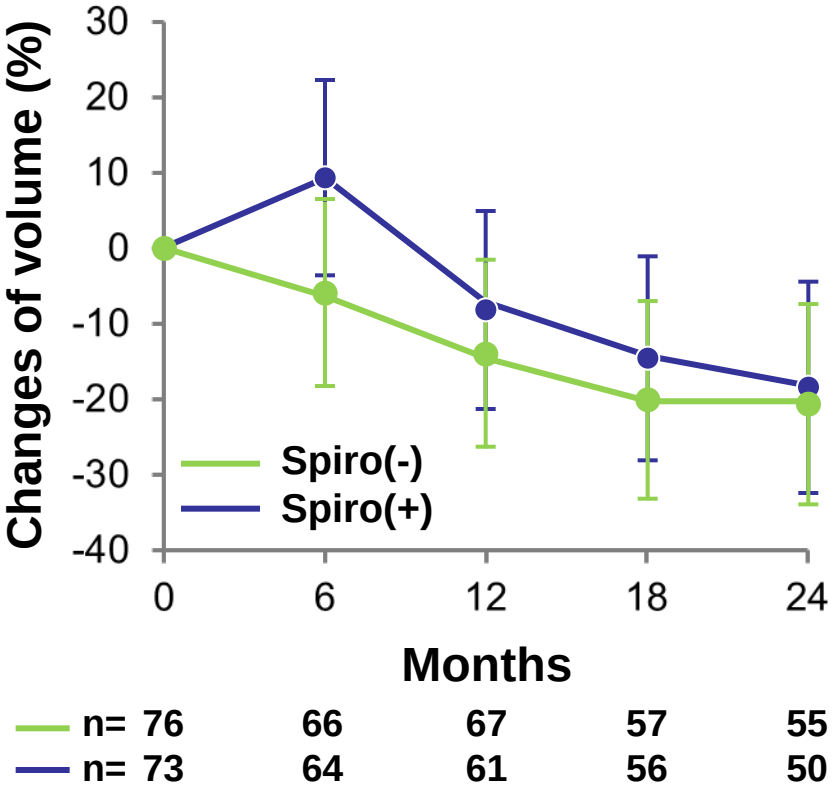
MRA vs Control in PD: Changes of LVMI and EF

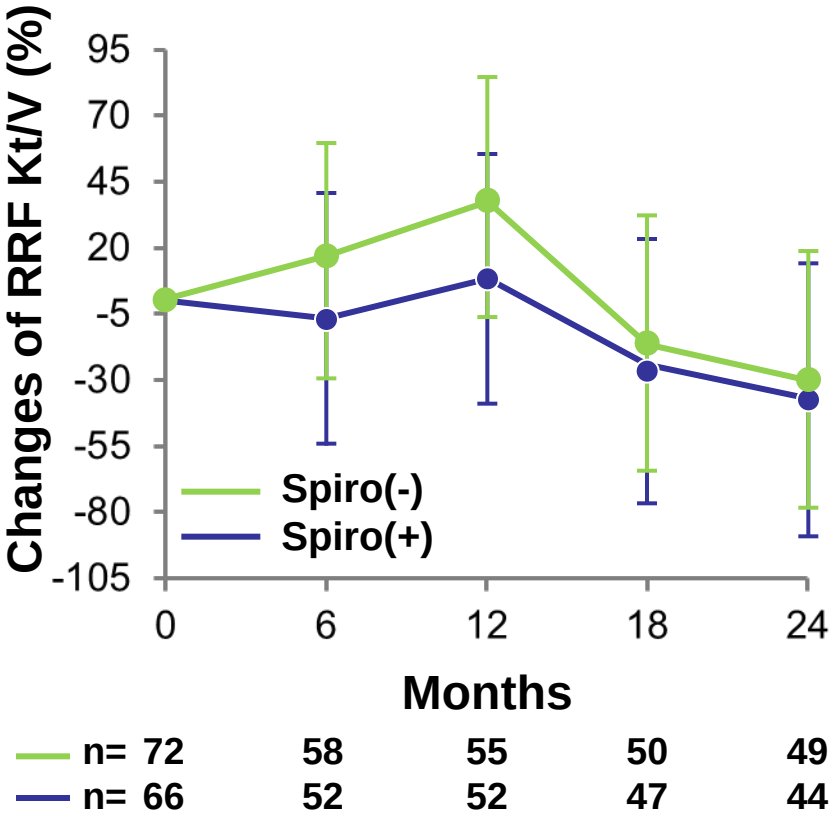




Ito et al. J Am Soc Nephrol 2014, 25:1094

MRA vs Control in PD: Changes of Urine Volume and Renal Kt/V





Ito et al. J Am Soc Nephrol 2014, 25: 1094

Adverse Events

Adverse event	Spironolactone (n=78)	Control (n=80)	P
Cerebral bleeding	1	2	>0.99
Cerebral infarction	4	4	>0.99
Acute MI	2	8	0.10
Hypotension (BP<100 mm Hg)	6	5	0.76
Hyperkalemia (K>6.0 mEq/L)	2	1	0.62
Hypokalemia (K<3.0 mEq/L)	12	20	0.17
Gynecomastia	11	2	0.01
Peritonitis	16	17	>0.99

Ito et al. J Am Soc Nephrol 2014, 25: 1094

MINERALOCORTICOID RECEPTOR ATG: TAKE-HOME MESSAGE

- MRAs may improve all-cause and CV mortality in dialysis
- Adding 25 mg spironolactone to ACEI/ARB in PD decreases LVH an improves LVEF
- No potassium problems in PD

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List of Abbreviations

- APD= automated peritoneal dialysis
- BMI= body mass index
- CI= confidence interval
- CSPD= conventional start peritoneal dialysis
- DBP= diastolic blood pressure
- EF= ejection fraction
- EM= enteric microorganism
- ESI= exit-site infection
- IPP= intraperitoneal pressure
- ISPD= International Society Peritoneal Dialysis
- LVH= left ventricular hypertrophy
- LVMI= left ventricular mass index

List of Abbreviations

- MIC= minimal inhibitory concentration
- MRA= mineralocorticoid receptor antagonist
- OR= odds ratio
- UF-PET= ultrafiltration peritoneal equilibration test
- USPD= urgent start peritoneal dialysis
- UMCU= University Medical Center Utrecht
- VISA= vancomycin intermediary Staphylococcus aureus
- VUmc= Vrije Universiteit Medical Center Amsterdam
- VRSA= vancomycin resistant Staphylococcus aureus

Oral Antibiotics Used in Catheter-Related Infections

Amoxicillin	250–500 mg BD (182)
Amoxicillin/clavulanate	875 mg/125 mg BD (183)
Cephalexin	500 mg BD to TID (86)
Ciprofloxacin	250 mg BD (164) or 500 mg daily (184)
Clarithromycin	500 mg loading, then 250 mg BD (165)
Clindamycin	300–450 mg TID (185)
Cloxacillin/flucloxacillin	500 mg QID (186)
Erythromycin	250 mg QID (187)
Fluconazole	oral 200 mg loading, then 50–100 mg daily (188)
Levofloxacin	300 mg daily (189)
Linezolid	300–450 mg BD (190–192)
Metronidazole	400 mg TID (193)
Moxifloxacin	400 mg daily (194)
Rifampicin	450 mg daily for BW <50 kg; 600 mg daily for BW ≥50 kg (144,145)
Trimethoprim/ sulfamethoxazole	80 mg/400 mg daily (8) to 160 mg/800 mg BD (195)

Szeto et al., PDI 2017, 37: 141

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

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Systemic Antibiotic Dosing Recommendations for Treatment of Peritonitis

Drug	Dosing
Anti-bacterials	
Ciprofloxacin (237)	oral 250 mg BD[a]
Colistin (288)	IV 300 mg loading, then 150–200 mg daily[b]
Ertapenem (289)	IV 500 mg daily
Levofloxacin (239)	oral 250 mg daily
Linezolid (290–292)	IV or oral 600 mg BD
Moxifloxacin (293)	oral 400 mg daily
Rifampicin (294,295)	450 mg daily for BW <50 kg; 600 mg daily for BW ≥50 kg
Trimethoprim/ Sulfamethoxazole (252)	oral 160 mg / 800 mg BD
Anti-fungals	
Amphotericin (296)	IV test dose 1 mg; starting dose 0.1 mg/kg/day over 6 hours; increased to target dose 0.75–1.0 mg/kg/day over 4 days
Caspofungin (297,298)	IV 70 mg loading, then 50 mg daily
Fluconazole (299)	oral 200 mg loading, then 50–100 mg daily
Flucytosine (296)	oral 1 gm/day
Posaconazole (300)	IV 400 mg every 12 hours
Voriconazole (301–303)	oral 200 mg every 12 hours

Li et al., PDI 2016, 36: 481