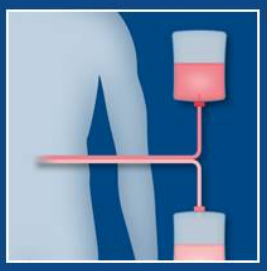
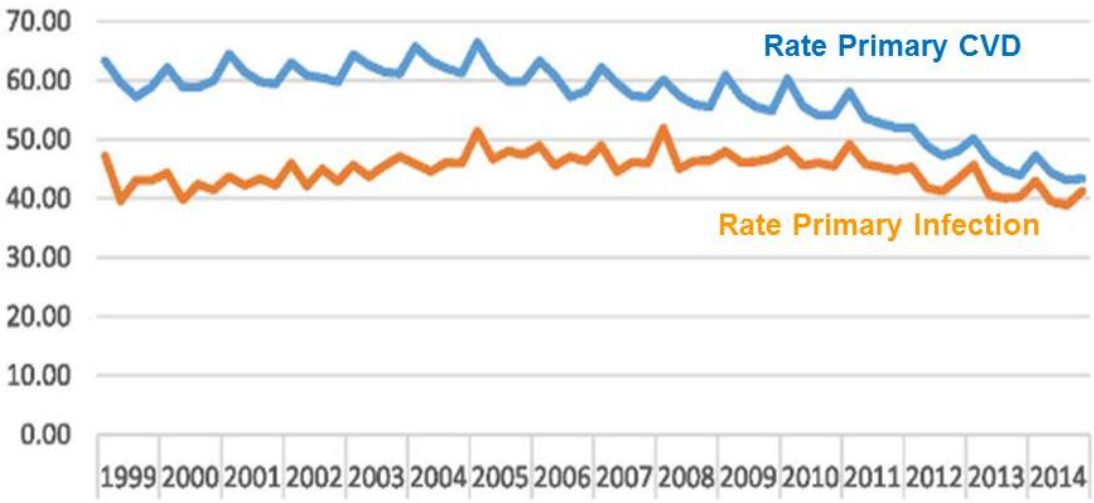
Nephro Update Europe 2019
20 – 21 September, Prague

Infectious Complications in Dialysis



An De Vriese, Belgium

Infection-related vs. Cardiovascular-related Hospitalization in Prevalent Dialysis Patients



Collins AJ *et al.* CJASN 2018; 13: 663

- Catheter-Related Bloodstream Infections
  - Desinfection of the catheter hub
  - Catheter lock
- Multidrug resistant gramnegatives
- Influenza

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CRBSI: STATE-OF-THE-ART

Prior to accessing the catheter hub it should be disinfected with an appropriate antiseptic (>0.5% chlorhexidine with alcohol, 70% alcohol, or 10% povidone-iodine). There is not enough evidence to recommend one antiseptic over the others.

Guidelines for the Prevention of Intravascular Catheter-Related Infections, 2011 Updated July 2017

https://www.cdc.gov/dialysis/prevention-tools/catheter-compatibility-information.html

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https://www.cdc.gov/infectioncontrol/guidelines/bsi/index.html
https://www.cdc.gov/dialysis/prevention-tools/scrub-protocols.html

Antimicrobial Catheter Hub Devices

Tego® neutral valve connector + Curos disinfecting cap (70% isopropyl alcohol)

ClearGuard® Antimicrobial barrier cap (chlorhexidine rod)

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RCT comparing 2 types of antimicrobial hub devices with respect to BSI rates

40 DaVita Dialysis Facilities
1671 patients
>183.000 CVC-days

	Tego® + Curos®	ClearGuard®	
3-month run-in	1.08/1000 days	1.02/1000 days	P=0.8
13-month intervention	0.75/1000 days	0.28/1000 days	P=0.001

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Brunelli *et al.* J Am Soc Nephrol 2018; 29: 1336

- Catheter-Related Bloodstream Infections
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CRBSI: STATE-OF-THE-ART

KDOQI CLINICAL PRACTICE GUIDELINE FOR VASCULAR ACCESS: 2018

Intraluminal agents to prevent CVC dysfunction

21.4 KDOQI considers it reasonable that the choice to use citrate or heparin as a CVC locking solution be based on the clinician's discretion and best clinical judgment as there is inadequate evidence to demonstrate a difference in CVC survival or complications between these locking solutions (Expert Opinion)

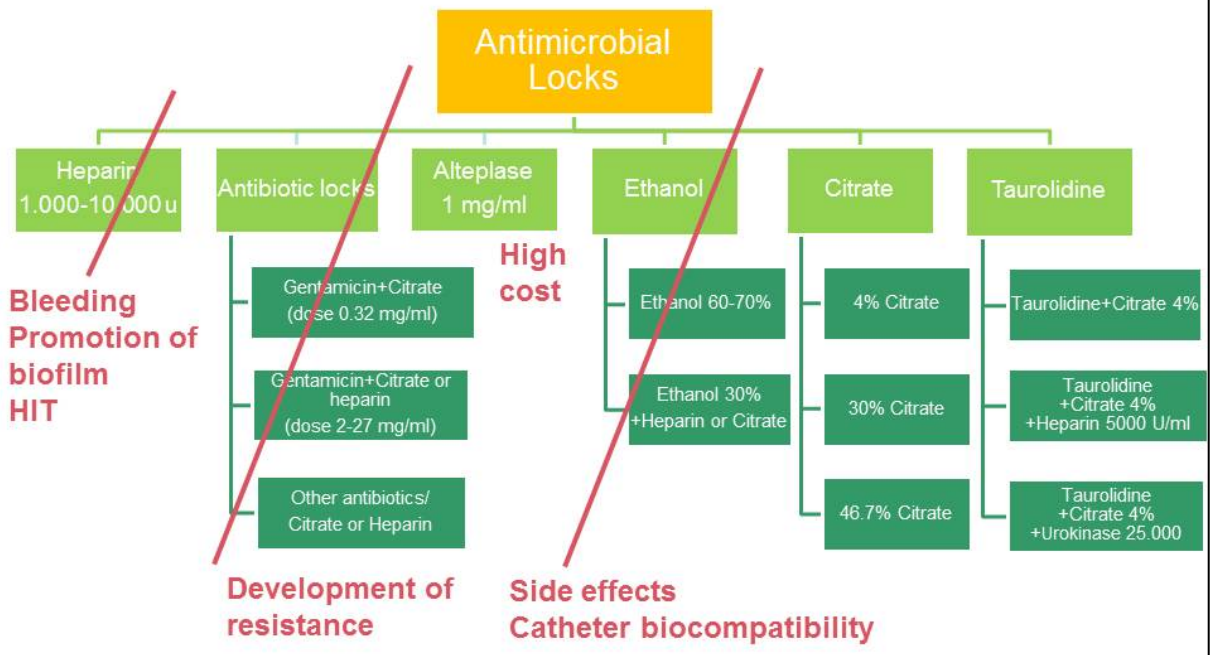
21.5 KDOQI suggests the use of low concentration citrate (<5%) CVC locking solution, if feasible, to help prevent CRBSI and CVC dysfunction (Conditional recommendation, Low quality of evidence)

21.6 KDOQI suggests that r-TPA may be prophylactically used as a CVC locking solution once per week to help reduce CVC dysfunction (Conditional recommendation, Low quality of evidence)

21.7 There is inadequate evidence for KDOQI to make a recommendation on the comparative use of the following CVC locking agents for CVC dysfunction or infection prophylaxis: tinzaparin vs. unfractionated heparin; taurolidine/citrate vs. heparin with or without gentamicin; neutral valve connector (Tego®) vs. citrate (46.7%) locking solution

American Society of Diagnostic and Interventional Nephrology 2008
European Renal Best Practice 2010
UK Renal Association 2015
CDC 2017

Nephro Update Europe 2019 https://www.kidney.org



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Citrate

- Calcium chelation: local anticoagulant effect – no systemic effects
- Fe/Ca/Mg chelation: prevention of biofilm – antibacterial effect

4% citrate: anticoagulant
≥30% citrate: also antibacterial

46.7% citrate:
Side effects➔ underfill ➔ more thrombosis
Fatal hypocalcemia: FDA recall in 2000

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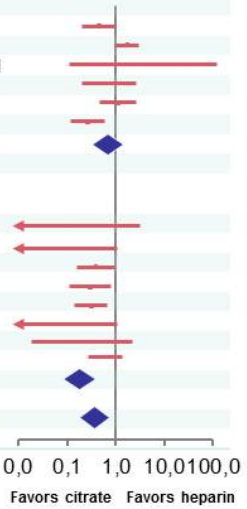
Catheter-related Bloodstream Infection

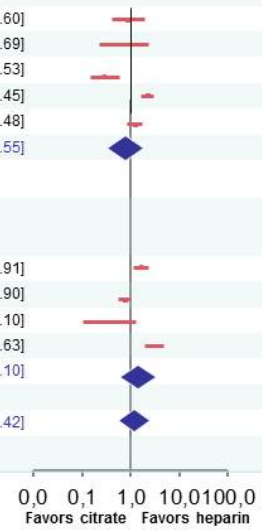
		Citrate		Heparin			
		Events	Total	Events	Total	Wt (%)	Risk Ratio M-H, Random 95% CI
	Citrate alone vs heparin						
4%	Abdel et al, 2018	11	3628	23	3288	10.4	0.43 [0.21, 0.89]
30%	Barcellos et al, 2017	31	6052	24	6927	11.9	1.48 [0.87, 2.52]
30%	Luiz et al, 2017	1	2000	0	1957	1.7	2.94 [0.12, 72.02]
4%	MacRae et al, 2008	5	2273	6	1818	7.1	0.67 [0.20, 2.18]
46,7%	Power et al, 2009	13	19008	12	17100	9.9	0.97 [0.44, 2.14]
30%	Weijmer et al, 2005	9	8431	33	8116	10.3	0.26 [0.13, 0.56]
	Subtotal (95% CI)	70	41392	98	39206	51.2	0.69 [0.35, 1.35]
	Antimicrobial-containing citrate vs heparin						
	Betjes et al, 2004	0	1519	4	1885	2.0	0.14 [0.01, 2.56]
	Dogra et al, 2002	0	3280	7	2643	2.0	0.05 [0.00, 0.94]
	Filiopoulos et al, 2011	8	2179	20	2016	9.6	0.37 [0.16, 0.84]
	Maki et al, 2011	6	25274	20	24395	8.9	0.29 [0.12, 0.72]
	Moran et al, 2012	11	39827	30	32933	10.6	0.30 [0.15, 0.60]
	Nori et al, 2006	0	2002	7	1734	2.0	0.06 [0.00, 1.01]
	Pervez et al, 2002	1	1613	4	1311	3.2	0.20 [0.02, 1..82]
	Solomon et al, 2010	11	8129	23	9642	10.4	0.57 [0.28, 1.16]
	Subtotal (95% CI)	37	83823	115	76559	48.8	0.34 [0.24, 0.49]
	Total (95% CI)	107	125,215	213	115,765	100.0	0.45 [0.29, 0.71]



Nephro Update Europe 2019 Mai *et al.* Int Urol Nephrol 2019; 51: 1019

Thrombolytic Treatment

	Experimental		Control			
	Events	Total	Events	Total	Wt (%)	Risk Ratio M-H, Random 95% CI
Citrate alone vs heparin						
Abdel et al, 2018	15	3628	17	3288	10.1	0.80 [0.40, 1.60]
Hendrickx et al, 2001	6	1703	8	1493	7.4	0.66 [0.23, 1.69]
MacRae et al, 2008	13	2273	37	1818	10.7	0.28 [0.15, 0.53]
Power et al, 2009	153	19008	74	17100	13.3	1.86 [1.41, 2.45]
Weijmer et al, 2005	69	8431	63	8116	12.9	1.05 [0.75, 1.48]
Subtotal (95% CI)	256	35043	199	31815	54.3	0.82 [0.43, 1.55]
Antimicrobial-containing citrate vs heparin						
Maki et al, 2011	97	25274	67	24395	13.1	1.40 [1.02, 1.91]
Moran et al, 2012	94	39827	113	32933	13.3	0.69 [0.52, 0.90]
Nori et al, 2006	4	2002	10	1734	6.7	0.35 [0.11, 1.10]
Solomon et al, 2010	79	8129	38	9642	12.6	2.47 [1.68, 3.63]
Subtotal (95% CI)	274	75232	228	68704	45.7	1.07 [0.54, 2.10]
Total (95% CI)	530	110,275	427	100,519	100.0	0.94 [0.62, 1.42]



Nephro Update Europe 2019 Mai *et al.* Int Urol Nephrol 2019; 51: 1019

Taurolidine

- **Direct effect on bacterial and fungal cell walls**
- **Broad-spectrum antimicrobial activity – decreases biofilm**
- **No resistance reported**
- **No adverse effects**

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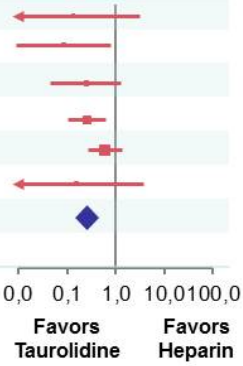
CRBSI for Taurolidine vs. Heparin

	Taurolidine		Heparin			Risk Ratio
	Events	Total	Events	Total	Wt (%)	M-H, Random 95% CI
Betjes, 2004	0	1519	4	1885	2.7	0.14 [0.01, 2.56]
Bisseling, 2010	1	5370	10	4939	5.5	0.09 [0.01, 0.72]
Dumichen, 2012	2	6576	9	7233	10.0	0.24 [0.05, 1.13]
Handrup, 2013	7	19955	26	19172	33.6	0.26 [0.11, 0.60]
Solomon, 2010	11	8129	23	9642	45.4	0.57 [0.28, 1.16]
Zwiech, 2013	0	785	3	873	2.7	0.16 [0.01, 3.07]
Total (95% CI)	21	42334	75	43744	100.0	0.34 [0.21, 0.55]

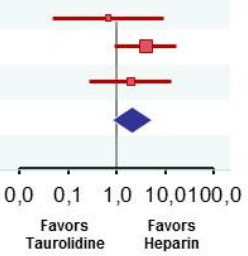


Equally effective as antibiotic containing catheter locks

Nephro Update Europe 2019 Liu *et al.* PLOS One 2013; 8: e79417

Thrombosis for Taurolidine vs. Heparin

Study or Subgroup, year	Taurolidine Events	Taurolidine Total	Heparin Events	Heparin Total	Wt (%)	Risk Ratio M-H, Random 95% CI
Betjes, 2004	1	1519	2	1885	16.5	0.62 [0.06, 6.84]
Solomon, 2010	8	8129	3	9642	53.9	3.16 [0.84, 11.92]
Dumichen, 2012	3	6576	2	7233	29.6	1.65 [0.28, 9.87]
Total (95% CI)	12	16224	7	18760	100.0	1.99 [0.75, 5.28]



Nephro Update Europe 2019 Liu *et al.* PLoS One. 2013; 8(11): e79417

RCT: Citrate 4% vs. Taurolidine lock

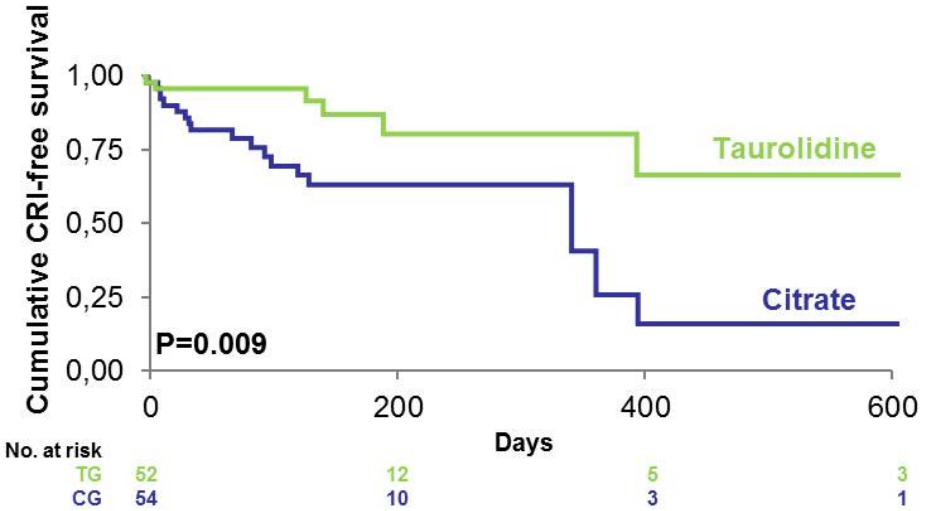
106 incident hemodialysis patients
3 Austrian dialysis units
15.690 catheter days

4% Citrate 3x/wk
(n = 54)

TauroLock - Hep500 2x/wk
TauroLock - U25.000 1x/wk
(n = 52)

Nephro Update Europe 2019 Winnicki *et al.* Kidney Int 2018; 93: 753

Catheter-Related Infection-Free Survival for Taurolidine and Citrate



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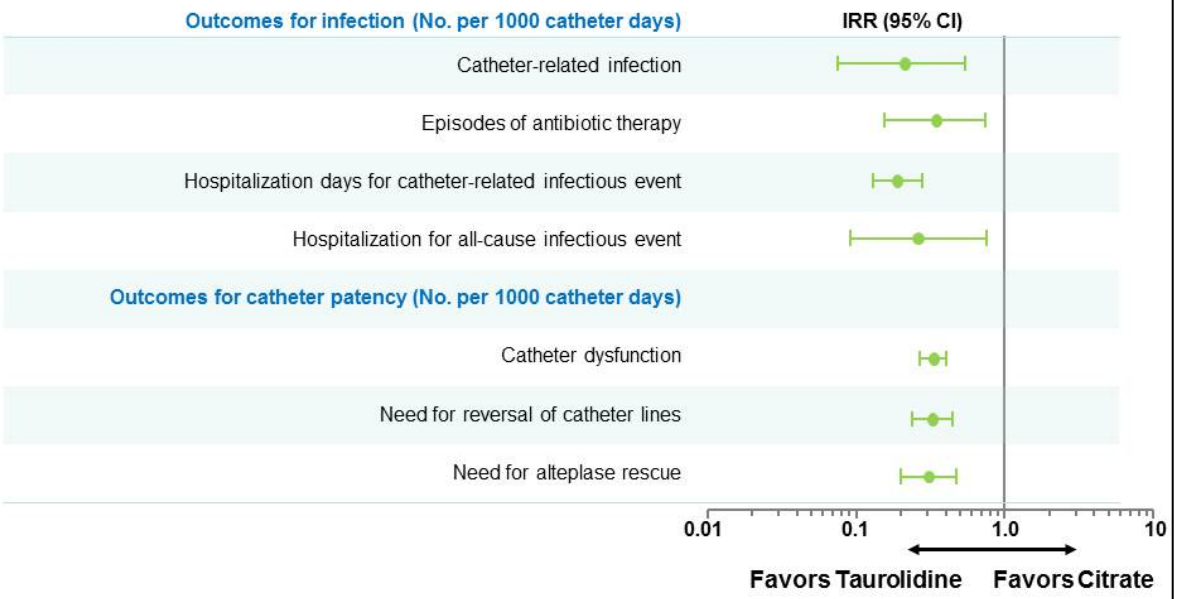
Winnicki *et al.* Kidney Int 2018; 93: 753

Taurolidine versus Citrate 4%

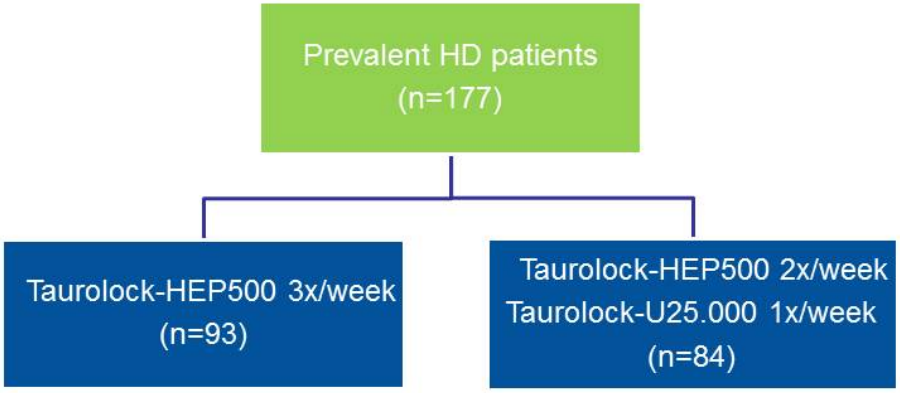


Overall costs per patient year were 43% lower

Nephro Update Europe 2019

Winnicki *et al.* Kidney Int 2018; 93: 753

Taurolidine/urokinase vs Taurolidine/heparin lock



CRBSI	0.3/1000 catheter-days	0.08/1000 catheter-days	P=NS
Catheter exchanges	7/93	1/84	P=0.028
Repeated use rtPA	4.37±3.58	2.17±1.30	P=0.006

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Al-Ali *et al.* Nephrol Dial Transplant 2018; 33: 619

CRBSI: TAKE-HOME MESSAGE

Antiseptic:

- **>0.5% chlorhexidine with alcohol (70% alcohol, or 10% povidone-iodine)**
- **ClearGuard HD Antimicrobial Barrier Cap**

Catheter lock:

- **Citrate 4% - 30%**
- **Taurolock-HEP500 2x/week + Taurolock-U25.000 1x/week**

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- **Catheter-Related Bloodstream Infections**
- **Multidrug resistant gramnegatives**
- **Influenza**

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PRIORITY PATHOGENS FOR R&D OF NEW ANTIBIOTICS

Priority 1: Critical

- *Acinetobacter baumanii*, carbapenem-resistant
- *Pseudomonas aeruginosa*, carbapenem-resistant
- *Enterobacteriaceae*, carbapenem-resistant, 3rd generation cephalosporin-resistant

Priority 2: High

- *Enterococcus faecium*, vancomycin-resistant
- *Staphylococcus aureus*, methicillin-resistant, vancomycin intermediate and resistant
- *Helicobacter pylori*, clarithromycin-resistant
- *Campylobacter*, fluoroquinolone-resistant
- *Salmonella spp.*, fluoroquinolone-resistant
- *Neisseria gonorrhoea*, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: Medium

- *Streptococcus pneumoniae*, penicillin-non-susceptible
- *Haemophilus influenzae*, ampicillin-resistant
- *Shigella spp.*, fluoroquinolone-resistant

World Health Organization
https://www.who.int/news-room/detail/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed

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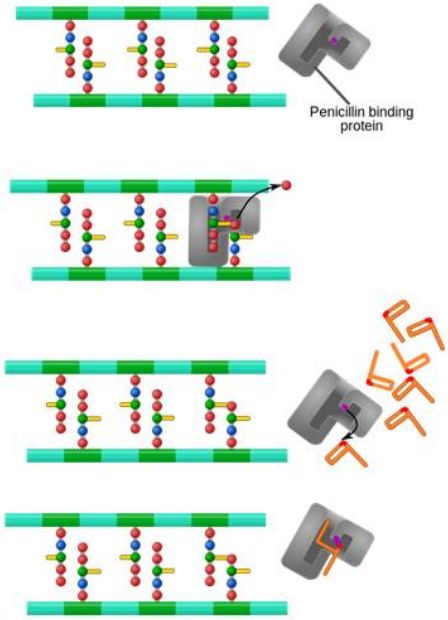
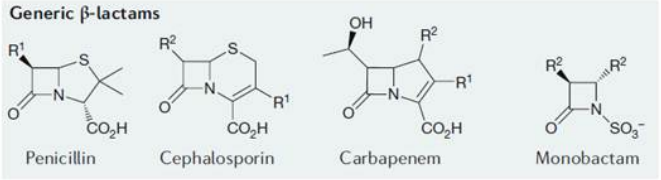


Mechanism of Action of β-lactams



(aztreonam)

β-lactamases

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Bush K *et al.* Nat Rev Microbiol 2019; 17: 295

β-lactamases

- Primary resistance determinants in gram-negative bacteria
- Penicillins, 1st generation cephalosporins
- Extended spectrum β-lactamases (ESBLs): penicillins, 1st 2nd/3rd generation cephalosporins, monobactams
- Carbapenemases: all β-lactams
- >2800 unique variants characterized to date
- Classified into four molecular classes (A–D)

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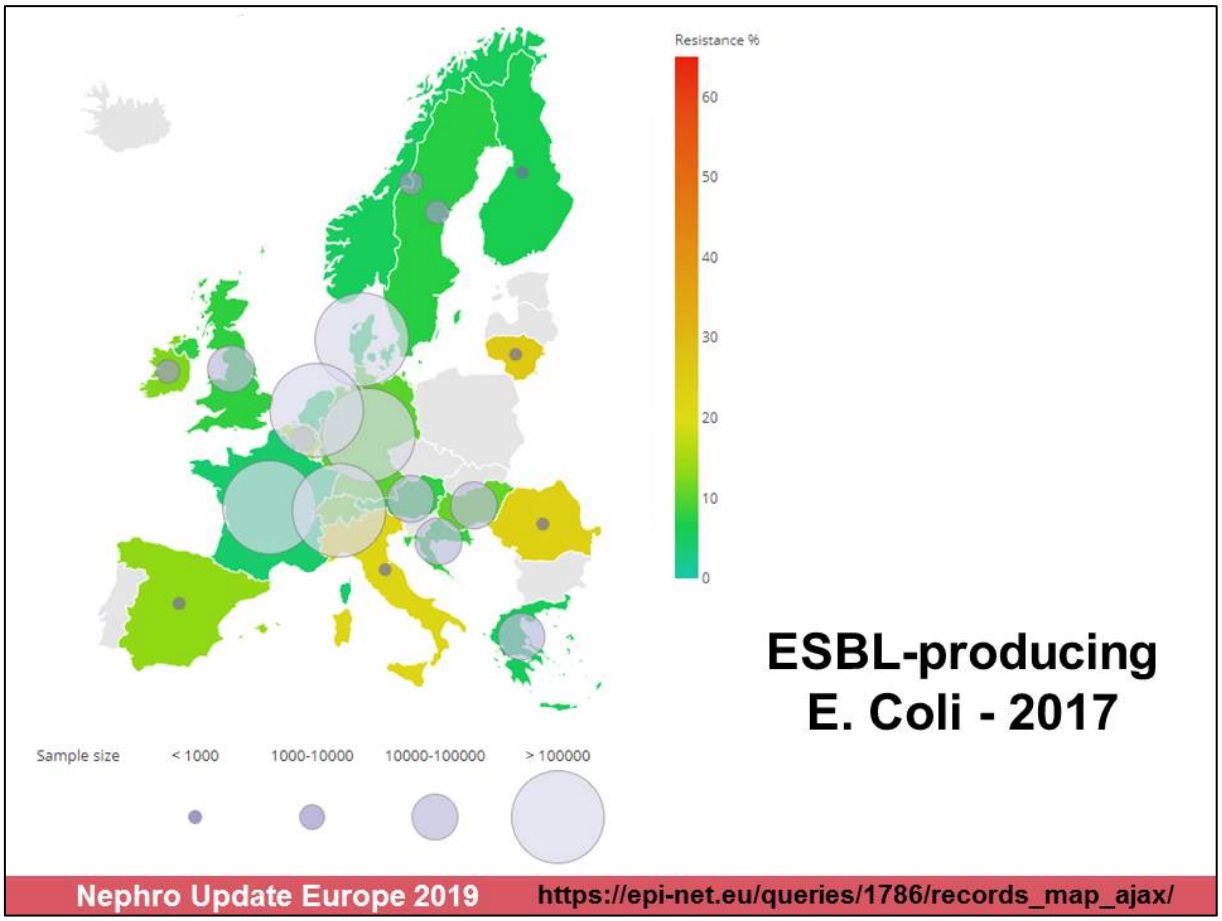
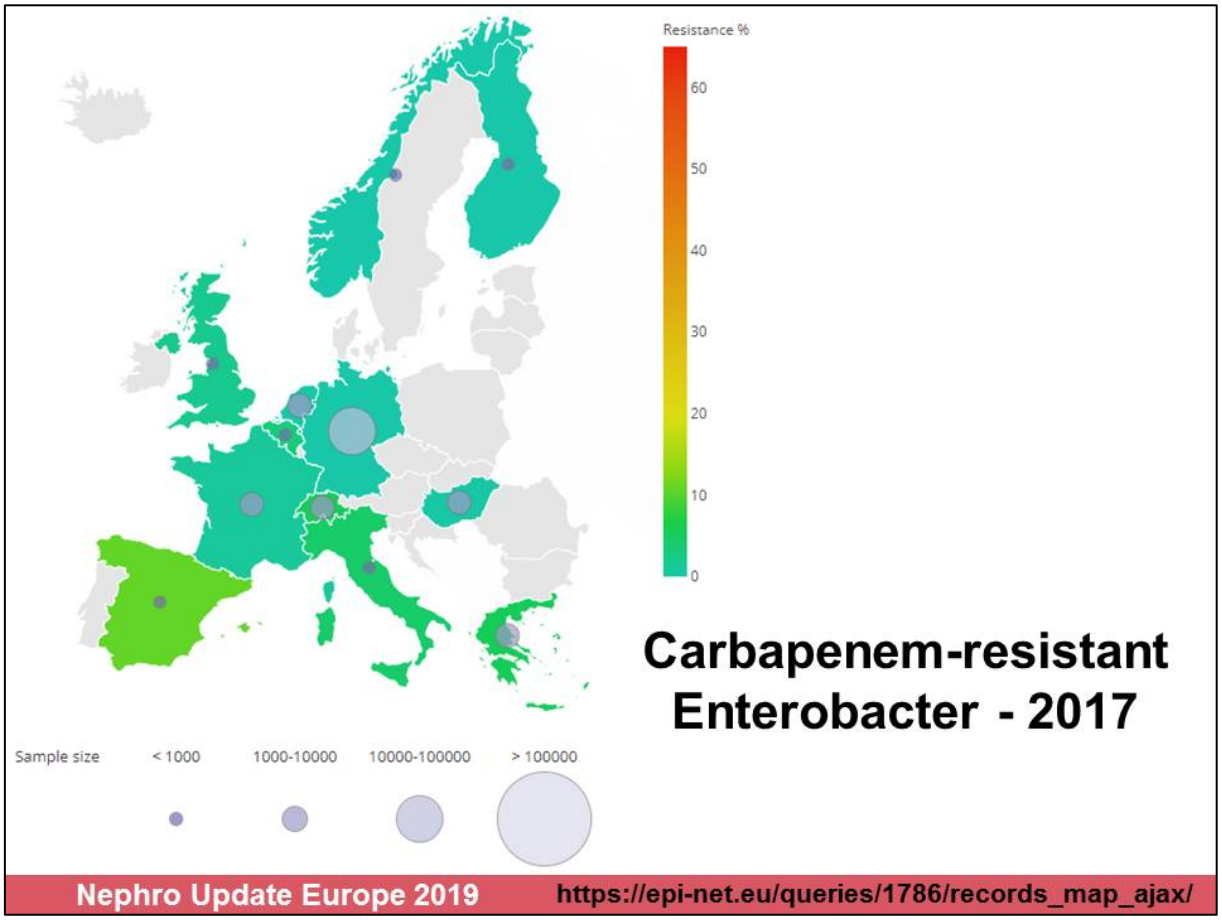

Resistance %
60
50
40
30
20
10
0
ESBL-producing
E. Coli - 2017
Sample size
< 1000
1000-10000
10000-100000
> 100000
Nephro Update Europe 2019
https://epi-net.eu/queries/1786/records_map_ajax/


Resistance %
60
50
40
30
20
10
0
Carbapenem-resistant
Enterobacter - 2017
Sample size
< 1000
1000-10000
10000-100000
> 100000
Nephro Update Europe 2019
https://epi-net.eu/queries/1786/records_map_ajax/

Old β-lactam - β-lactamase Inhibitor Combinations

- Amoxicillin – Clavulanic acid
- Ticarcillin – Clavulanic acid
- Ampicillin – Sulbactam
- Piperacillin – Tazobactam

- Only active on serine-β-lactamases (Class A)
- Mutations leading to resistance
- New class A β-lactamases

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New β-lactam - β-lactamase Inhibitor Combinations

- Ceftolozane – Tazobactam
- Ceftazidime – Avibactam
- Meropenem – Vaborbactam

No single "magic bullet" β-lactam β-lactamase inhibitor combination

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Activity Against Problematic Gram-negative Pathogens

Organism	Resistance Present	Ceftazidime/ Avibactam	Meropenem/ Vaborbactam
Enterobacteriaceae	ESBL	+++	+++
	AmpC	+++	+++
	KPC	+++	+++
	MBL	-	*
	OXA-48-like	+++	*
Acinetobacter baumannii	Carbapenem-resistant	-	-
Pseudomonas aeroginosa	Carbapenem-resistant	++	-
	Pan-β-lactam resistant	+	-
Stenotrophomonas maltophilia	Ceftazidime-resistant	-	-

*might have activity, but driven by meropenem, and vaborbactam does not add anything in this setting

Nephro Update Europe 2019 Pogue *et al.* Clin Infect Dis 2019; 68: 519

Ceftazidime-Avibactam

- Approved EMA (FDA)
- Complicated intra-abdominal and urinary tract infections, hospital-acquired and ventilator-associated pneumonia
- Systematic review (12 studies, 4591 patients): as effective as carbapenems in the treatment of gram-negative bacteria
- Side effects mild (cfr. Ceftazidime)
- 318 €/day (Ceftazidime: 38 €/day)

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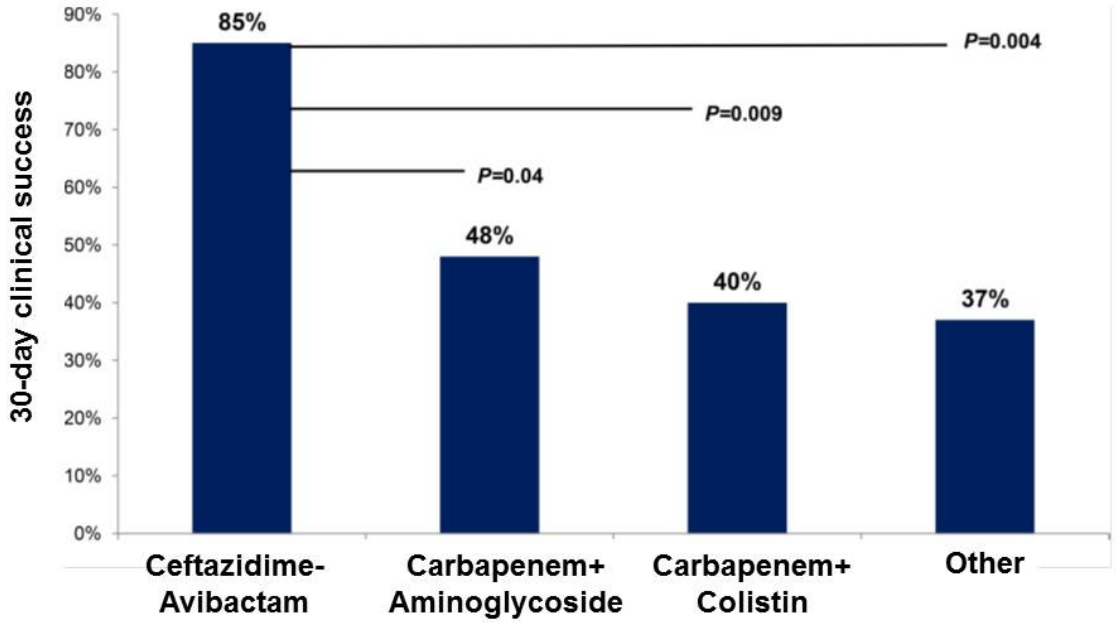
Ceftazidime-Avibactam Is Superior to Other Treatment Regimens against Carbapenem-Resistant *Klebsiella pneumoniae* Bacteremia



Other regimens: aminoglycoside (*n* =11), carbapenem (*n*=8), colistin (*n* =4), tigecycline (*n* =4), ciprofloxacin (*n* =2) monotherapy, and combination of colistin+tigecycline (*n* =3), aminoglycoside+tigecycline (*n* =2), and 1 each of aminoglycoside+cefepime, aminoglycoside+colistin+tigecycline, colistin+aztreonam, colistin+cefepime, colistin+ciprofloxacin, carbapenem+doxycycline, and carbapenem+tigecycline.

Nephro Update Europe 2019 Shields *et al.* Antimicrob Agents Chemother 2017; 61: 8

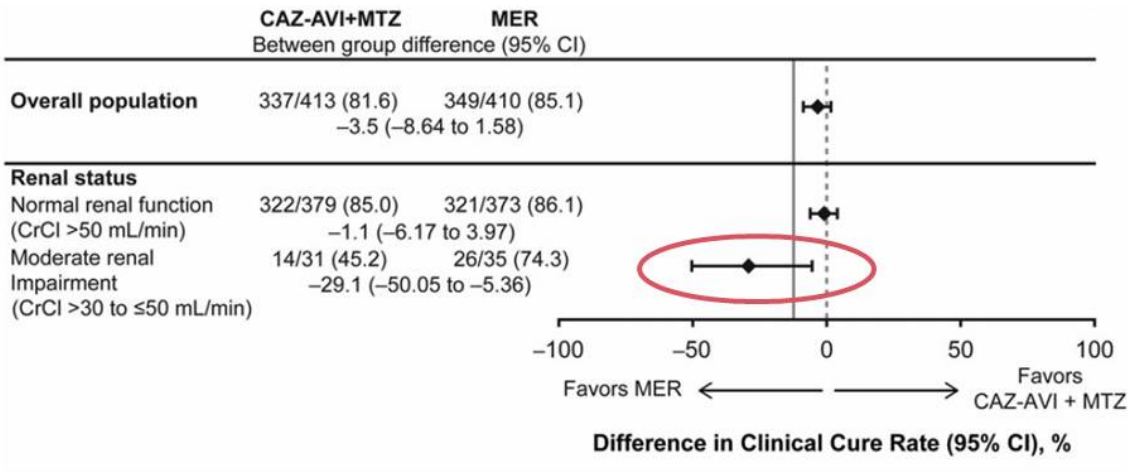
Ceftazidime - Avibactam

Dose	Adjustment to renal function	CRRT
2.5 g (2 g/0.5 g) q8h (infusion over 2 h)	CrCl > 50: 2.5 g q8h CrCl 31-50: 1.25 g q8h CrCl 10-30: 0.94 g q12h CrCl < 10: 0.94 g q48h Hemodialysis: 0.94 g q48h (administration after hemodialysis)	1.25 g q8h

- **Ceftazidime and Avibactam pharmacokinetics are similar**
- **Extensive removal by dialysis (±55% of the dose)**

Nephro Update Europe 2019 Karaiskos *et al.* Front Public Health 2019; 7 : 151

Ceftazidime-Avibactam + Metronidazole vs. Meropenem in Complicated Intra-abdominal Infections



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Mazuski *et al.* Clin Infect Dis 2016; 62: 1380

CEFTAZIDIME-AVIBACTAM: TAKE-HOME MESSAGE

- **Potential to improve outcomes in MDR gram-negative infections**
- **High cost**
- **Development of resistance**
- **<u>Strictly limit</u> to MDR *Pseudomonas aeruginosa* and *Enterobacteriaceae***
- **Dose adjustment in renal failure: official vs. real-life**

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- Catheter-Related Bloodstream Infections
- Multidrug resistant gramnegatives
- Influenza

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Response to Influenza Vaccination

Immunogenicity	Normal adult population (n=66)			Dialysis adult population (n=76)		
	H1N1	H3N2	B	H1N1	H3N2	B
Baseline seroprotection rate %	16.7%	31.8%	13.6%	22.4%	30.3%	9.2%
3 weeks seroprotection rate %	92.4%	84.9%	42.4%	67.1%	68.4%	23.7%

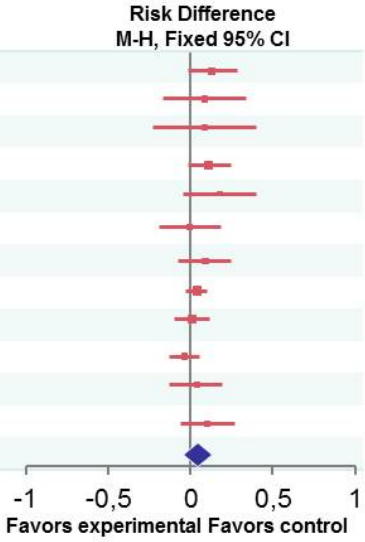
Immunogenicity	Normal elderly population (n=48)			Dialysis elderly population (n=74)		
	H1N1	H3N2	B	H1N1	H3N2	B
Baseline seroprotection rate %	25.0%	56.3%	14.6%	12.2%	31.1%	8.1%
3 weeks seroprotection rate %	81.3%	87.5%	29.2%	47.3%	58.1%	6.8%

- Booster dose
- High dose
- Pre-exposure prophylaxis

Nephro Update Europe 2019 Chang *et al.* Sci Rep 2016; 6: 20725

Booster Dose of Influenza Vaccine in RRT

	Weight (%)	Risk Difference M-H, Fixed 95% CI
Beyer, 1987 (HD)	11.0	0.09 [–0.05, 0.24]
Beyer, 1987 (PD)	2.3	0.05 [–0.19, 0.30]
Brakemeier, 2012	2.3	0.05 [–0.26, 0.36]
Le Corre, 2012	14.4	0.08 [–0.05, 0.20]
Quintana, 2013 (PD)	1.7	0.14 [–0.07, 0.35]
Quintana, 2013 (RT)	6.4	–0.04 [–0.22, 0.14]
Quintana, 2013 (HD)	7.1	0.05 [–0.10, 0.21]
Scharpe, 2008	20.3	0.00 [–0.06, 0.06]
Scharpe, 2009	16.6	–0.03 [–0.12, 0.07]
Song, 2006	5.2	–0.07 [–0.17, 0.02]
Tanzi, 2007	7.1	0.00 [–0.16, 0.16]
Vogtlander, 2004	5.4	0.07 [–0.10, 0.23]
Total (95% CI)	100.0	0.02 [–0.02, 0.06]



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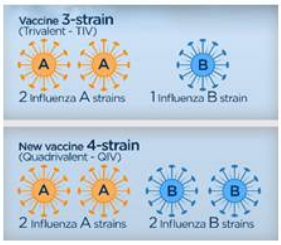
Liao *et al.* Hum Vaccin Immunother 2016; 12: 2909

High-Dose Influenza Vaccine in Dialysis



Prevalent Dialysis Patients
(n=9843) / (n=9314)

2015-2016
2016-2017

Standard Dose (15µg)
Trivalent Vaccine
H1N1, H3N2, B
(n=3057) / (NA)

Standard Dose (15 µg)
Quadrivalent Vaccine
H1N1, H3N2, 2xB
(n=5981) / (n=3614)

High Dose (60 µg)
Trivalent Vaccine
H1N1, H3N2, B
(n=805) / (n=5700)

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Miskulin *et al.* Clin J Am Soc Nephrol 2018; 13: 1703

Hospitalisation Rate after Influenza Vaccine

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Miskulin *et al.* Clin J Am Soc Nephrol 2018; 13: 1703

Oseltamivir

- Neuramidase inhibitor
- Generally safe and well tolerated
- Predominantly renal clearance
- Normal renal function:
  - Treatment: 75 mg bid
  - Prophylaxis: 75 mg od
- Hemodialysis (package insert, low-flux):
  - Treatment: 30 mg after each hemodialysis session
  - Prophylaxis: 30 mg after every other hemodialysis session

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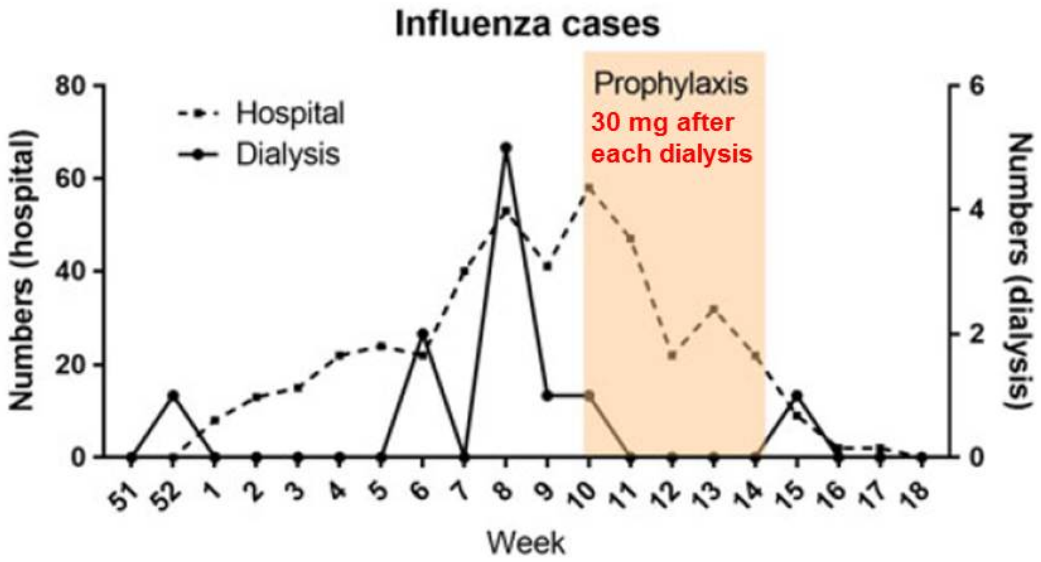
Pre-exposure Prophylaxis with Oseltamivir in Vaccinated Hemodialysis Patients



Nephro Update Europe 2019 Van Praet *et al.* Infect Control Hosp Epidemiol 2019; 40: 497

Influenza: TAKE-HOME MESSAGE

- Booster dose does not enhance immunogenicity
- High dose vaccination may reduce hospitalization in ≥65y
- Preliminary evidence for oseltamivir pre-exposure prophylaxis in vaccinated patients

Nephro Update Europe 2019

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List of Abbreviations

- CI=confidence interval
- CrCl=Creatinine Clearance
- CRBSI=Catheter-Related Bloodstream Infections
- CRRT=continuous renal replacement therapy
- CVC=Central Venous Catheter
- CVD=cardiovascular disease
- EMA=European Medicines Agency
- ESBL=Extended Spectrum Beta-Lactamase
- FDA=Food and Drug Organization
- MDR=multidrug-resistant
- MH=Mantel-Haenszel Test
- rtPTA=recombinant tissue plasminogen activator
- Wt=weight