Resurgence of older oral therapies in OPAT: options for OPAT sparing

Dr Carolyn Hemsley

Consultant in Infectious Disease and Microbiology, Guy's and St Thomas', London

KING'S HEALTH PARTNERS

Pioneering better health for all

Guy's and St Thomas' NHS

NHS Foundation Trust

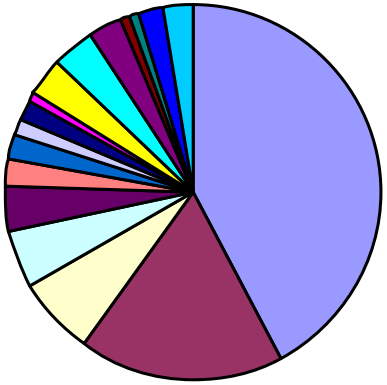
Why do we intravenous therapy?

- Evidence that IV better than oral or belief that it is superior
  - Endocarditis
  - *Staph aureus* bacteraemia
  - CNS infection
  - Bone and joint
- No oral option because of resistance profile dictates IV (or allergy issues)
- Problems with enteral route and absorbance
- Ensure patient compliance or choice

Why do we give oral therapy or IV oral switch?

- Evidence that oral is equivalent to IV
- Evidence or experience that oral works
- Ease
- Patient choice
- IV not possible
- and many more reasons …….

GSTT OPAT patient episodes (2014 - 2016) n = 411

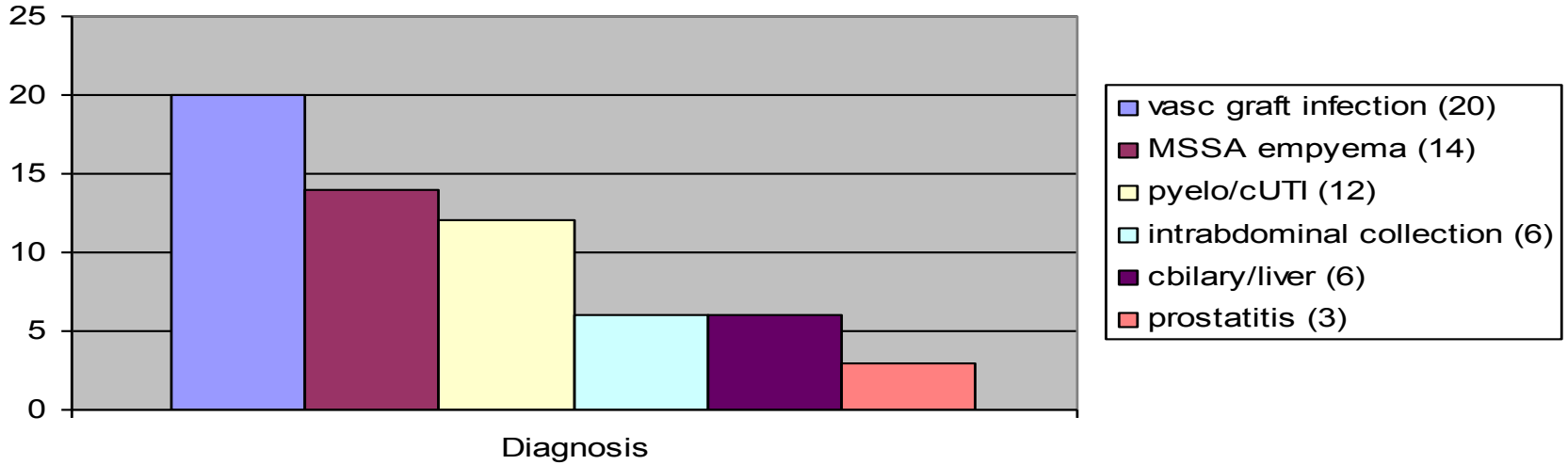


BJI (173)	DFI (74)	discitis (27)
vasc graft infection (20)	IE (17)	MSSA Bacteraemia (9)
Mycotic aneurysm (9)	cbilary/liver (6)	intrabdominal collection (6)
CNS (4)	MSSA empyema (14)	NecOE (14)
pyelo/cUTI (12)	prostatitis (3)	CMV (4)
cSSI (9)	other (10)	

Could I have used orals instead ?

Excluded – IE, mycotic AA, MSSA BSI, BJI, DFI, discitis, cSSI, CNS, CMV, few others

Remaining – 61/411 (~14%)



Could we have IV to oral switched sooner?

Could/should we have consider any older less commonly used agents?

In which areas might oral therapy be an option?

- cUTI – ESBLs (12)
- Prostatitis – ESBL/cipro resistance (3)
- Biliary infection/liver abscess – polymicrobial or ESBL harbouring organisms (12)

Should we have considered any of the following?

- Fosfomycin
- Pivemecillinam
- Chloramphenicol

Fofosfomycin

Licensed indications: treatment of acute lower uncomplicated urinary tract infections in adult and adolescent females.

AND

prophylaxis in diagnostic and surgical transurethral procedures.

- Phosponic acid derivative available Iv and oral preparations.
- Bactericidal inhibits bacterial cell wall synthesis

- Single 3g dose orally (~£5 per sachet). NICE 2015 suggest 2 doses in men

  - CMax >4000 mg/L (urine) 26- 32mg/L (serum)
  - Mean half life 5.6 hours
  - Maintain urinary conc >128 mg/L for 24-36 hours

- (compare to non-licensed suggested Rx dose 2-4g qds IV for systemic infections)

Fofosfomycin

Clinical breakpoints

BSAC : uncomplicated UTI

E coli and Proteus only S≤ 32 R ≥ 32 mg/L

EUCAST : uncomplicated UTI

Enterobacteriacae uncomplicated UTI S≤ 32 R ≥ 32

CLSI :uncomplicated UTI

Enterobacteriacae and Enterococcus faecalis S≤ 64 R ≥ 256

Wider spectrum of activity *in vitro*

– Consider MCI data for multiple organisms

2. MIC distributions and epidemiological cut-off (ECOFF) values

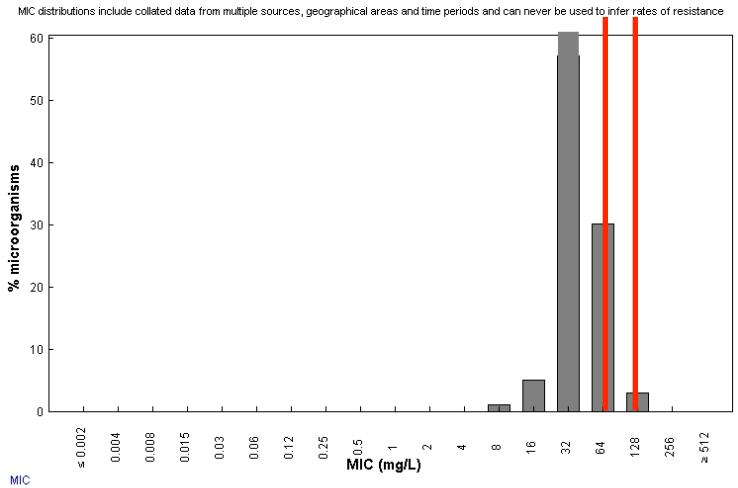
	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF
Acinetobacter spp	0	0	0	0	0	0	0	1	0	1	1	0	0	7	6	21	31	18	0	ND
Citrobacter spp	0	0	0	0	0	6	38	2	2	2	1	0	0	0	0	0	0	0	0	ND
Enterobacter aerogenes	0	0	0	0	0	0	0	0	0	0	1	2	7	19	32	13	6	0	0	ND
Enterobacter cloacae	0	0	0	0	0	0	0	0	0	0	3	23	13	18	24	75	105	0	0	ND
Enterobacter spp	0	0	0	0	0	0	0	0	8	14	6	11	29	69	35	16	18	21	5	ND
Enterococcus faecalis	0	0	0	0	0	0	0	0	2	2	0	1	17	98	959	502	64	9	12	ND
Enterococcus faecium	0	0	0	0	0	0	0	0	1	0	0	0	0	3	54	373	52	0	0	ND
Enterococcus spp	0	0	0	0	0	0	0	1	0	0	0	0	8	46	31	6	3	1	0	ND
Escherichia coli	0	0	0	0	1	1	54	74	513	890	922	1013	801	483	243	89	33	0	0	8
Haemophilus influenzae	0	0	0	0	0	0	0	0	0	37	5	5	0	0	1	1	1	0	0	ND
Klebsiella spp	0	0	0	0	0	0	6	3	27	50	47	73	138	147	127	64	25	16	35	ND
Proteus mirabilis	0	0	0	0	0	0	6	15	89	188	200	199	242	100	78	88	89	34	0	8
Proteus spp	0	0	0	0	0	0	0	0	17	23	30	20	37	37	36	29	14	16	23	ND
Providencia spp	0	0	0	0	0	0	1	2	2	2	24	15	5	1	2	0	0	0	0	ND
Pseudomonas aeruginosa	0	0	0	0	0	0	0	0	8	4	32	46	58	100	174	350	216	14	22	ND
Serratia marcescens	0	0	0	0	0	0	0	0	3	7	20	51	30	36	7	6	4	0	0	ND
Shigella spp	0	0	0	0	0	0	0	0	4	63	101	8	6	0	0	3	0	0	0	ND
Staphylococcus aureus	0	0	0	0	0	0	2	2	91	226	389	366	465	309	121	50	25	2	3	32
Staphylococcus epidermidis	0	0	0	0	0	0	0	0	49	116	135	95	141	100	30	47	182	1	0	ND
Staphylococcus saprophyticus	0	0	0	0	0	0	0	0	0	0	0	2	0	2	7	23	5	10	0	ND
Streptococcus pneumoniae	0	0	0	0	0	0	0	0	0	0	0	16	32	6	3	0	0	0	0	ND
Streptococcus pyogenes	0	0	0	0	0	0	0	0	0	0	1	0	1	3	25	20	0	0	0	ND

The table includes MIC distributions available at the time breakpoints were set. They represent combined distributions from multiple sources and time periods. The distributions are used to define the epidemiological cut-offs (ECOFF) and give an indication of the MICs for organisms with acquired or mutational resistance mechanisms. They should not be used to infer resistance rates. When there is insufficient evidence no epidemiological cut-off has been determined (ND).

KING'S HEALTH PARTNERS
Pioneering better health for all

Guy's and St Thomas' NHS
NHS Foundation Trust

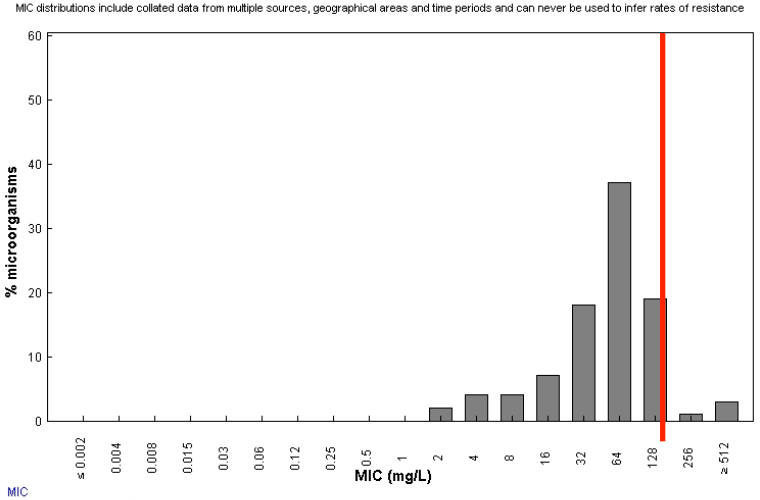
Fosfomycin / Enterococcus faecalis
International MIC Distribution - Reference Database 2016-11-21



MIC
Epidemiological cut-off (ECOFF): -
Wildtype (WT) organisms:

1666 observations (6 data sources)

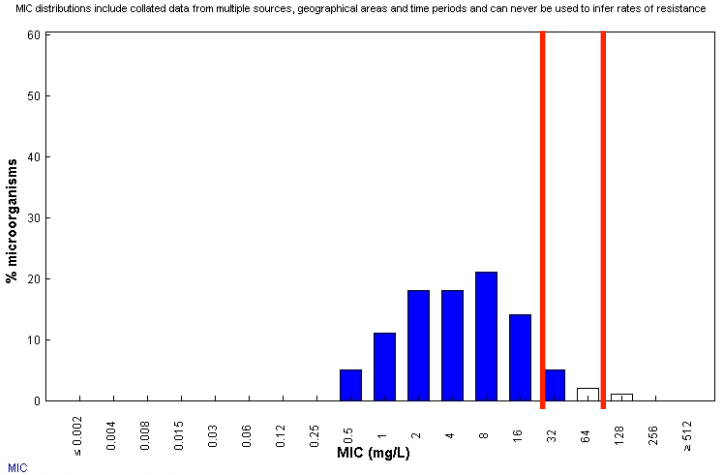
Fosfomycin / Pseudomonas aeruginosa
International MIC Distribution - Reference Database 2016-11-21



MIC
Epidemiological cut-off (ECOFF): -
Wildtype (WT) organisms:

1250 observations (5 data sources)

Fosfomycin / Staphylococcus aureus
International MIC Distribution - Reference Database 2016-11-21



MIC
Epidemiological cut-off (ECOFF): 32 mg/L
Wildtype (WT) organisms: ≤ 32 mg/L

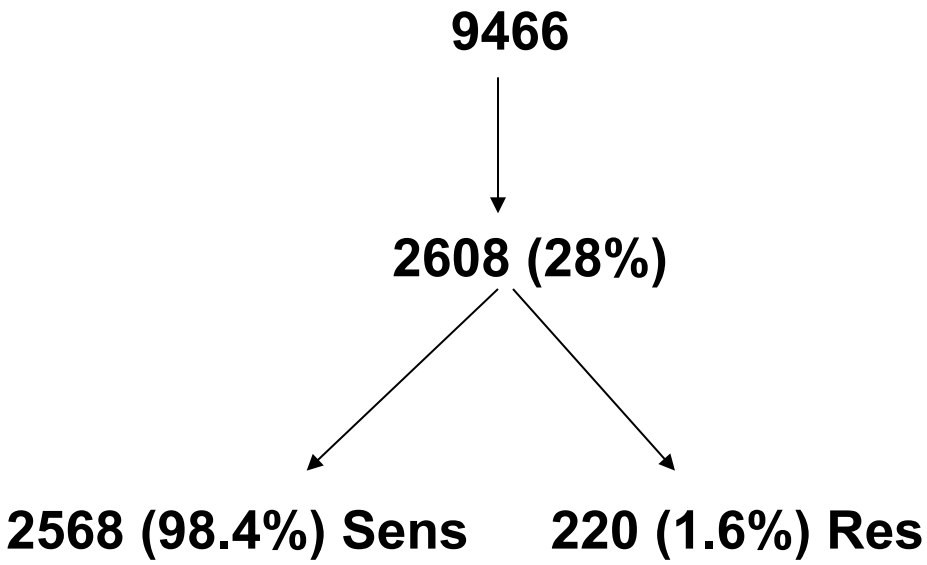
2213 observations (8 data sources)

KING'S HEALTH PARTNERS
Pioneering better health for all

Guy's and St Thomas' NHS
NHS Foundation Trust

Resistance rates to fosfomycin

- All urine *E coli* isolates at GSTT 2015 (S ≤ 32mg/L)



Oxford 2016 18, 474 *E coli* and *Kleb* 3% resistance

German study 2014 n=499 *E coli* 98% susceptible

Chinese study 2012 *E coli* ESBL 6.2% resistance

German study CREs 2014 n=107 enterobacteriacae 72% susceptible

GSTT – using fosfomycin routinely for uncomplicated MDR UTI for ~ 5 years and as step down oral therapy for bacteraemic UTI in not transplant population

Could we use Fosfo in place of OPAT erta/temocillin for lower urinary tract infection?

- Observational prospective - Fos vs carbapenem (27 vs 20). Clinical failure equivalent (21/27 vs 19/20) J Chem 2010 22;355)
- Retrospective cohort study - 89 each arm. 30 day revisit rate same 14.6% (FT) vs 13.% (erta).Erta longer course 10 vs 6 days. J Int Antimicrob Agents . 2016;47:269

Other evidence for clinical efficacy for oral Fosfomycin + MDR pathogens/cUTI

- Retrospective study Follow up on 58. (JAC 2016;71:2563)
  - 30% had stents of structural abnormalities
  - 33% CKD sage 3 or greater
  - Clinical cure in fosfo susc orgs 63%
  - CKD only predictor of failure
- Retrospective ≥ 1 dose for culture pos UTI with symptoms n=57 only 28 evaluated (Chemotherapy 2016;62;100)
  - 77.2% complicated UTI and 63% MDR
  - 96% cure
- Retrospective study ≥ I dose with MDR pathogen. N=44. VRE, Pseud, CPEs, ESBL (AAC 2012;56:5744)
  - Microbiological cure rate 60%
  - Solid organ transplant associated with failure
  - Urethral stents associated with failure

When should you IV to oral switch in cUTI or pyelonephritis?

- Licensing trials for Ertapenem 89% clinical cure rate average 4 days IV before oral switch
- Trial of Erta vs Ceftriaxone for Pyelo average was 5.6 days before IV to oral switch
- Effectiveness of oral antibiotics for definitive therapy of Gram-Neg bloodstream infections (JAA 2016;48:498)

  Retrospective cohort study over 4 years 362 episodes.

  Mean of 4.7 days of IV therapy and 9.1 oral.

  Univariate cox proportional hazards regression model – liver cirrhosis, immunocompromised host and bioavailability of definitive oral antibiotic was associated with treatment failure. (failure rate 2% vs 12% vs 14% in high, med, low bioavailability)

Prostatitis

1. FOS gets in to prostate

•26 participants prostatic levels from Bx post oral 3g dose 6.5 ± 4.9 mg/L detectable up to 17 hours post dose (non inflammed prostate) (CID 2014;58:e101)

2. SUCCESSFUL in salvage therapy

•2 cases successfully treated with pos fosfo post failure with IV erta. Showed plasma concentrations of 5.3 mg/L ±1.3 in chronic prostatitis 3g po od (CID 2015;61:114). Daily 3g dose

•15 cases with Chronic bacterial prostatitis failed alternative therapy. 3g alternate days. 47% cure rate (AAC 2016;60;1854)

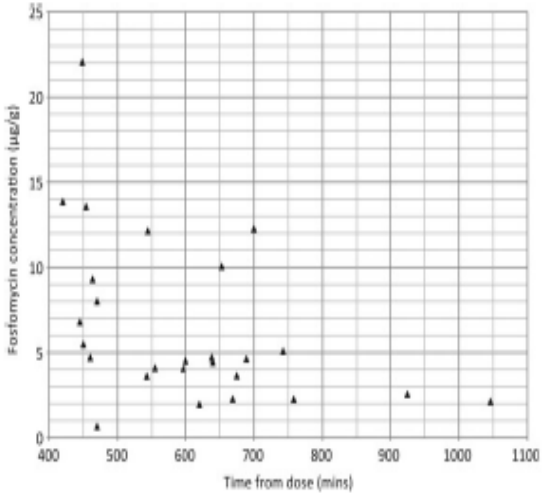


Figure 1. Mean fosfomycin prostate concentrations by time after single oral 3-g dose.

Probably need 3g od dose. Dose escalation limited by GI Side effects

KING'S HEALTH PARTNERS
Pioneering better health for all

Guy's and St Thomas' NHS
NHS Foundation Trust

Summary for Genitourinary infection

Excreted in urine in active form in high doses

Evidence for use to Rx cUTI – but no comparative trial data for pyelo

It's distributed to the kidneys, bladder wall, prostate, and seminal vesicles BUT significantly lower doses to urine.

Concentrated in prostate, seminal vesicles and testes – serum level not representative of tissue concentrations BUT every 72 hours may be incorrect dose schedule.

Questions raised

What is correct dose for conditions other than uncomplicated UTI?

Alternative to po cipro for pseudomonal UTI?

Pivmecillinam

Licensed indications: treatment of acute lower uncomplicated urinary tract infections in adult

Active agent is mecillinam. Bactericidal inhibition PBP2

- DOSE - UTIs in adults is 400mg single dose followed by 200mg tds (3/7 total course length)
  - CMax 176-1324 mg/L (urine) after 400mg dose
  - 2.38 +/- 0.65mg/L Serum

- EUCAST/BSAC/CLSI clinical breakpoints
  - BSAC : uncomplicated UTI E coli, Klebsiella and Proteus only S≤ 8 R ≥ 8 mg/L
  - EUCAST : Enterobacteriacae uncomplicated UTI S≤ 8 R ≥ 8 mg/L
  - CLSI : Enterobacteriacae S≤ 8 R ≥ 16 mg/L

Resistance rates

- >20 years of clinical experience in Nordic countries
- 20-30% prescriptions for cystitis in Nordic countries are pivmecillinam
- UK study ESBL E coli 6.2% resistance to mecillinam (JAC 2010;65:79)
- >20,000 E coli isolates Sweden 4% resistance in E coli
- We've only just started testing GSTT (not routinely) in context of NEW PHE guidance as empirical therapy for UTI

URINARY TRACT INFECTIONS – refer to PHE UTI guidance for diagnosis information

As *E. coli* bacteraemia in the community is increasing ALWAYS safety net and consider risks for resistance [1C]

UTI in adults (no fever or flank pain) PHE URINE SIGN CKS women, CKS men RCGP UTI clinical module SAPG UTI	**Treat women** with severe/or ≥ 3 symptoms;[1, 2A, 3C] **women** mild/or ≤ 2 symptoms AND Urine NOT cloudy 97% negative predictive value, do not treat unless other risk factors for infection. If cloudy urine use dipstick to guide treatment. Nitrite plus blood or leucocytes has 92% positive predictive value; nitrite, leucocytes, blood all negative 76% NPV.[4A-] Consider a back-up / delayed antibiotic option.[20A] **Men**: Consider prostatitis and send pre-treatment MSU[1,5C] OR if symptoms mild/non-specific, use negative dipstick to exclude UTI.[6C] **Always safety net.** **First line**: nitrofurantoin if GFR over 45ml/min.[24-5] GFR 30-45: only use if resistance & no alternative. *In treatment failure:* always perform culture.[1B]	Nitrofurantoin[8B+ 9C 10B+] Trimethoprim[7B+] Pivmecillinam[13,21,22,29,30A] *(400mg if resistance risk)* *If organism susceptible:* amoxicillin[14B+]	100mg m/r BD[11C] 200mg BD 200mg TDS[13,29,30A] *400mgTDS[13]* 500mg TDS	Women all ages 3 days[2,12,13A+] Men 7 days[1,5C]
	Use nitrofurantoin first line as general resistance and community multi-resistant. Extended-spectrum Beta-lactamase *E. coli* are increasing. Trimethoprim (if low risk of resistance) and pivmecillinam are alternative first line agents. **Risk factors for increased resistance include:** care home resident, recurrent UTI, hospitalisation >7d in the last 6 months, unresolving urinary symptoms, recent travel to a country with increased antimicrobial resistance (outside Northern Europe and Australasia) especially health related, previous known UTI resistant to trimethoprim, cephalosporins or quinolones.[19] **If increased resistance risk**, send culture for susceptibility testing & give safety net advice. If GFR<45 ml/min or elderly consider pivmecillinam 400mg TDS[2,13,21,3] or fosfomycin (3g stat in women[15,16B,17A] plus 2nd 3g dose in men 3 days later).[18]			
People > 65 years: do not treat asymptomatic bacteriuria; it is common but is not associated with increased morbidity.[1B+]				
Catheter in situ: antibiotics will not eradicate asymptomatic bacteriuria; only treat if systemically unwell or pyelonephritis likely.[2B+] Do not use prophylactic antibiotics for catheter changes unless history of catheter-change-associated UTI or trauma (NICE, SIGN).[3B]				
Acute:	Send MSU for culture and start antibiotics[1C]	Ciprofloxacin[1C]	500mg BD	28 days[1C]

Clinical efficacy for pivmecillinam - MDR pathogens/cUTI

- Pubmed search – 'Pivmecillinam' 291 hits
- 'Pivmecillinam' and 'ESBL' OR' MDR' : 14 hits only 2 were clinical treatment studies as opposed to MIC data
- Swedish study prospective follow up of patients with ESBL E coli treated with pivmec n=39 84% clinical cure rate, 80% bacteriological cure rate (JAC 2014;69:769)
- N=8 clinical response 8/8 (Microb Drug Resist 2012;18:189)
- Case report – use as salvage therapy in ESBL E coli pyelo post carbapenem failure (2 year of abx) (Scand J Infect Dis 2016)
- NO publications in pyelo

Summary for pivmecillinam

Excreted in urine in active form in high doses

Evidence for use to Rx uncomplicated UTI

Questions raised wrt OPAT sparing–

Oral step down in complicated UTI?

What is the bilary excretion and could it be of use in bilary infection? – rabbit study showing good levels in bile after enteral administration

Chloramphenicol

Discovered in 1947 – use in typhoid, meningitis

80% bioavailability and excellent tissue penetration (CNS, pleura, lung, ascites, synovial fluid, bile)
Not excreted in active form into urinary tract so not good for UTI

WHO list of Essential Medicines – meningitis, neonatal sepsis

Wide spectrum activity

- EUCAST/BSAC/CLSI clinical breakpoints
  - Enterobacteriacae
  - Staphylococci
  - Streptococci (beta haem, pneumo, viridans)
  - Neisseria
  - Anaerobes (gram po and neg)
  - Haemophilus

Chloramphenicol

1980s - ‘Do not use chloramphenicol if safer effective medicines can be used’

Why?

Aplastic anaemia – idiosynchratic and dose independent ~1 in 20,000 – 40,000 cases

AND Only ~10% case reversible.

Typically 3-12 weeks after initiation of therapy (can present as early as 5 days)

Separate from chloramphenicol bone marrow suppression which is reversible

Safety data

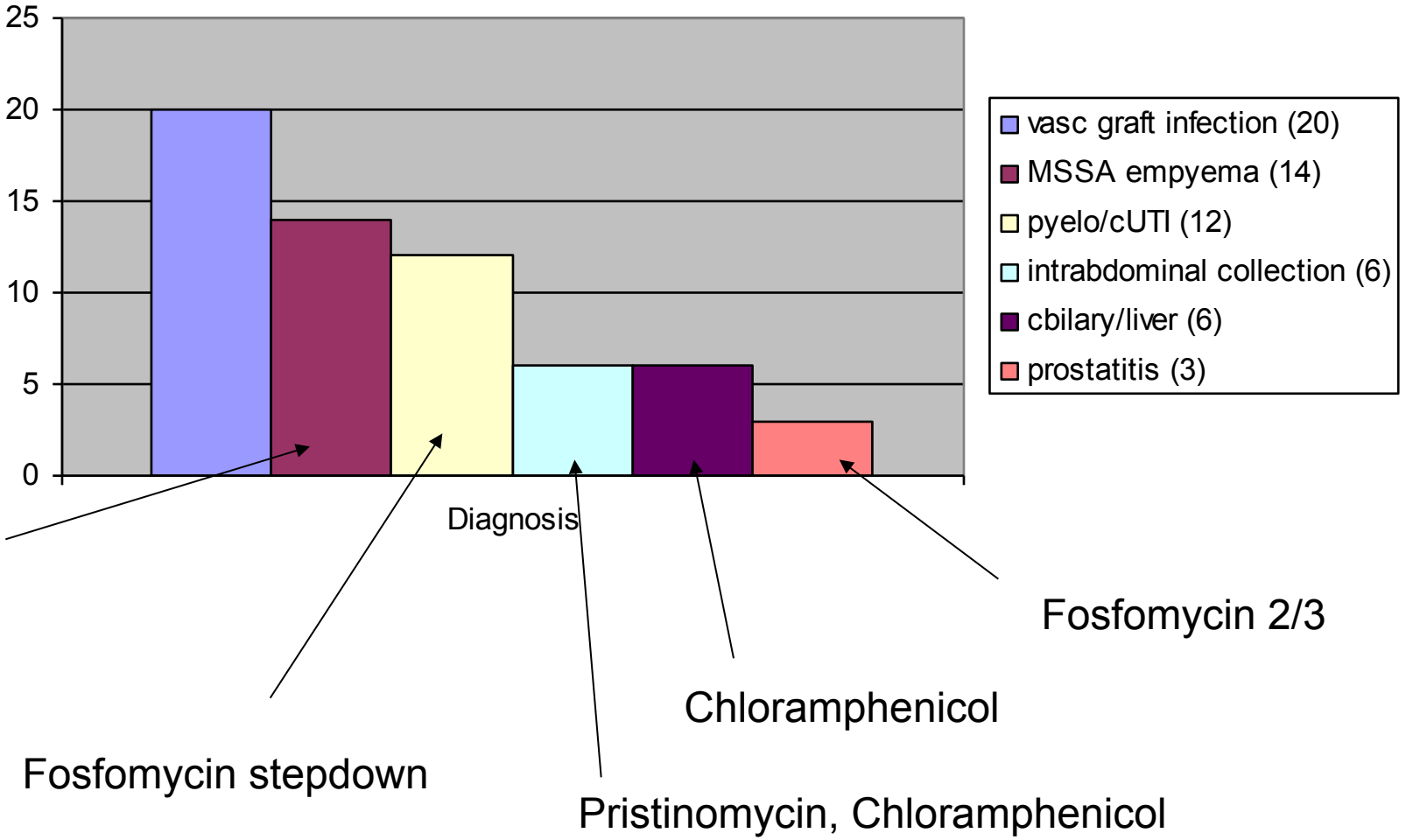
Efficacy and safety of chloramphenicol: systematic review and meta-analysis of randomised controlled trials (JAC 2015;70:979)

- 66 RCTs (1964-2011) included (involving 9711 patients).
- RCTs meningitis ,resp tract, enteric fever, mediterranean spotted fever
- NO statistically significant differences in adverse events between Chloramphenicol and other abx including all haematological events except for anaemia (RR 2.8, CI 1.65-4.75)

Should we use it more?

- Polymicrobial infection
- Anareobic infections
- MDR gram negatives
- Complicated Staphyloccocal/streptococcal infections as alternative agent
- VRE infections (linezolid alternative)
- Suppression/as alternative to palliative OPAT?

GSTT OPAT sparing



Clinical Prevalence, Antimicrobial Susceptibility, and Geographic Resistance Patterns of Enterococci: Results from the SENTRY Antimicrobial Surveillance Program, 1997–1999

Donald E. Low,[1] Nathan Keller,[2] Alfonso Barth,[3] and Ronald N. Jones[4]

Table 5. Potency and spectrum of 12 selected antimicrobial agents tested against 409 vancomycin-resistant enterococcal isolates in the SENTRY Antimicrobial Surveillance Program (1997–1999).

	MIC_{50}, μg/mL (% of tested isolates susceptible)				
Antimicrobial agent	Canada (n = 7)	United States (n = 354)	Latin America (n = 3)	Europe (n = 40)	Asia-Pacific (n = 5)
Ampicillin	>16 (29)	>16 (12)	1 (100)	>16 (35)	1 (60)
Penicillin	>32 (29)	>32 (10)	4 (100)	>32 (35)	2 (60)
Erythromycin	>8 (14)	>8 (3)	>8 (0)	>8 (3)	>8 (20)
Quinupristin-dalfopristin	1 (71)	0.5 (82)	>8 (0)	1 (50)	2 (20)
Chloramphenicol	8 (86)	8 (90)	>16 (33)	8 (68)	8 (80)
Doxycycline	>4 (43)	4 (53)	>4 (0)	0.5 (65)	>4 (40)
Ciprofloxacin	>2 (0)	>2 (3)	>2 (0)	>2 (10)	>2 (0)
Gatifloxacin	>4 (14)	>4 (6)	>4 (33)	>4 (23)	0.5 (60)
Gentamicin-HL[a]	≤500 (57)	>1000 (40)	>1000 (33)	≤500 (50)	≤500 (60)
Streptomycin-HL[a]	>2000 (14)	>2000 (21)	>2000 (33)	2000 (48)	>2000 (40)
Nitrofurantoin	64 (29)	64 (40)	≤32 (67)	≤32 (83)	≤32 (60)
TMP-SMZ	>1 (14)	>1 (28)	≤0.5 (67)	>1 (30)	≤0.5 (80)

NOTE. TMP-SMZ, trimethoprim-sulfamethoxazole.

[a] HL, high-level resistance to aminoglycosides (susceptibility rates are listed), indicating potential synergy.

Clinical Infectious Diseases 2001; 32(Suppl 2):S133–45

KING'S HEALTH PARTNERS
Pioneering better health for all
NHS
NHS Foundation Trust