SCOTTISH MICROBIOLOGY ASSOCIATION

NHS Greater Glasgow and Clyde

Antibiotic Management of Prosthetic Joint Infections

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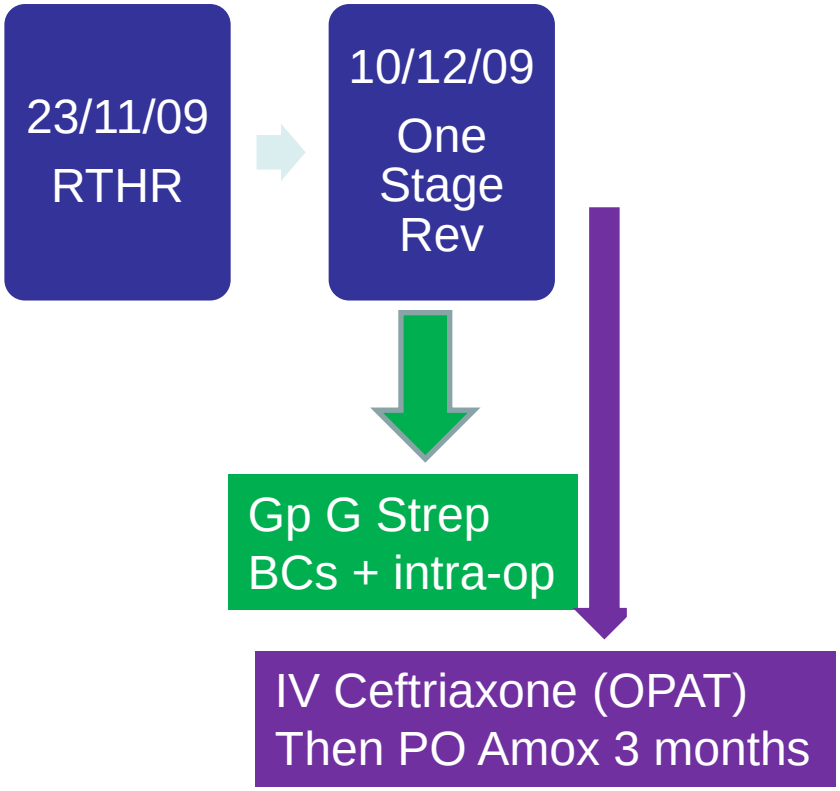
Declarations of interest

- Consultancy
  - Novartis
  - Pfizer
  - Astrazeneca
  - Astellas
  - Cubist
- Research funding
  - Novartis

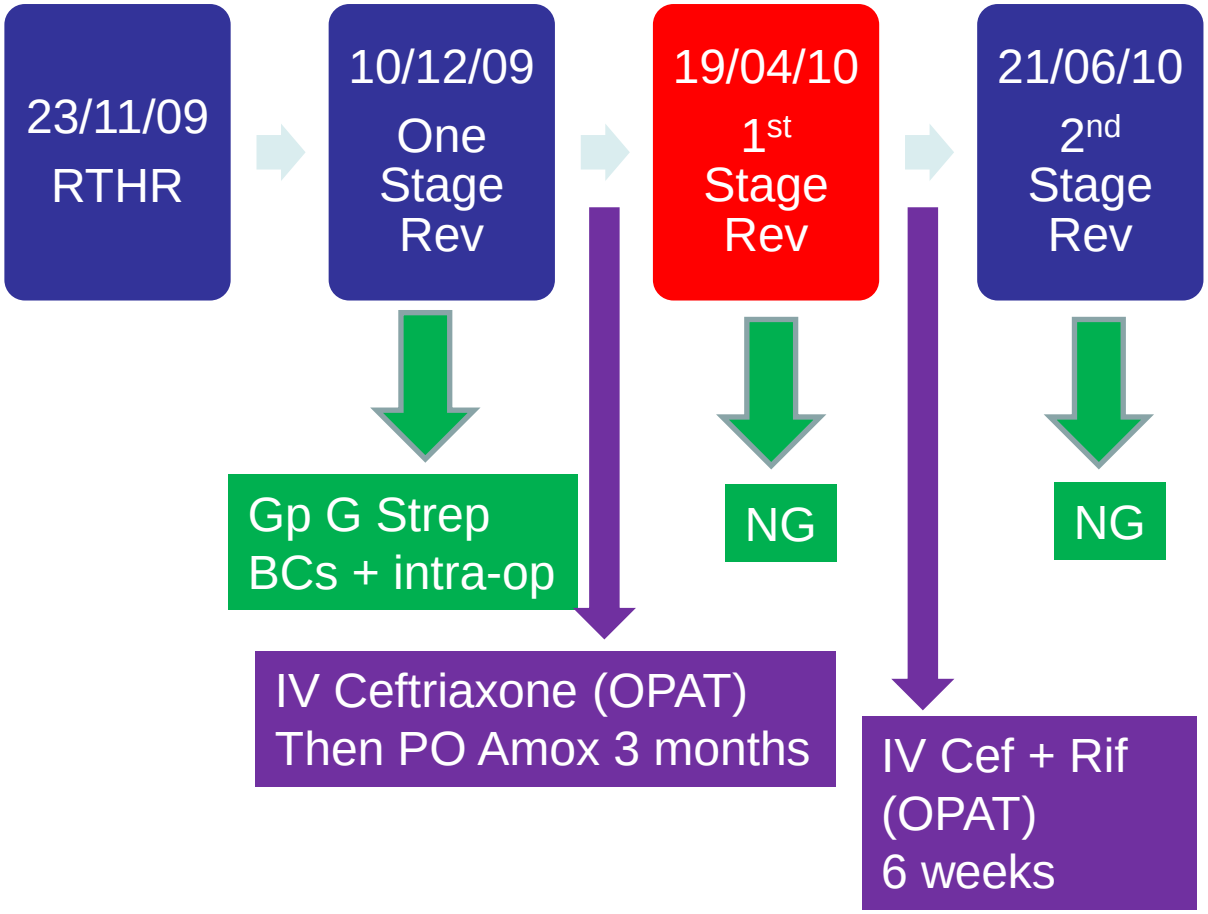
55 year old male, December 2014

- Sepsis + R Hip pain
- Background
  - COPD
  - Depression
  - Recent nasal polypectomy
  - LTHR 2004, RTHR 2009 (complicated)
- Medication
  - Oxycodone, Fluoxetine, Amitriptyline, Diazepam

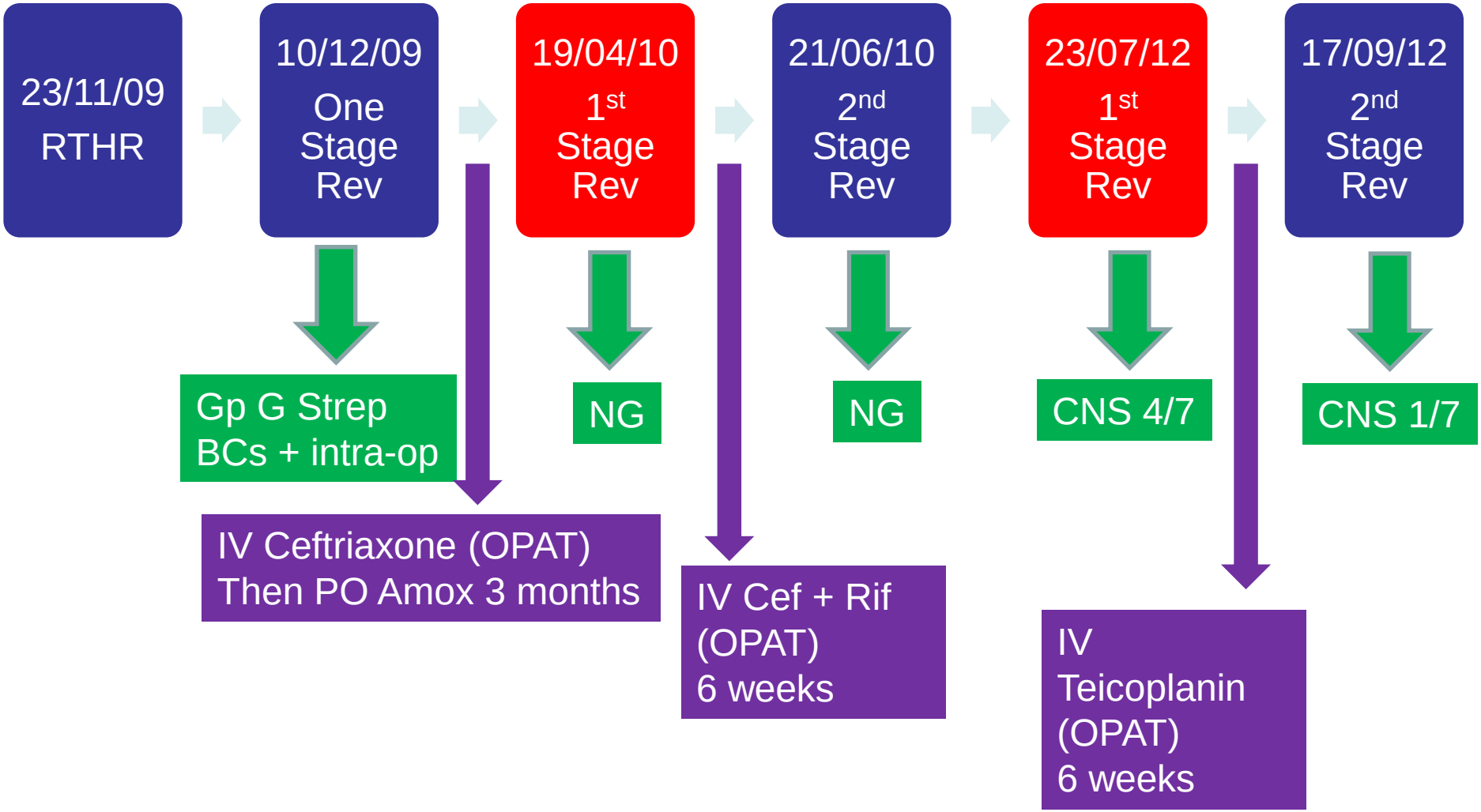
Orthopaedic History (1)



Orthopaedic History (2)



Orthopaedic History (3)



1st Stage Rev 26/01/15 (5th THR)

- GBS (7 samples)
  - **Sensitive:** Penicillin, Vancomycin, Ceftriaxone, Linezolid
  - **Resistant:** Doxycycline, Clindamycin, Levofloxacin

- Antibiotic Rx?

Antibiotic considerations

- Activity vs organism
- Penetration to site of infection
- (Activity in biofilm)
- Drug-Drug-Host interactions
- Side effects
- IV or oral
- Length of Rx
- Synergy

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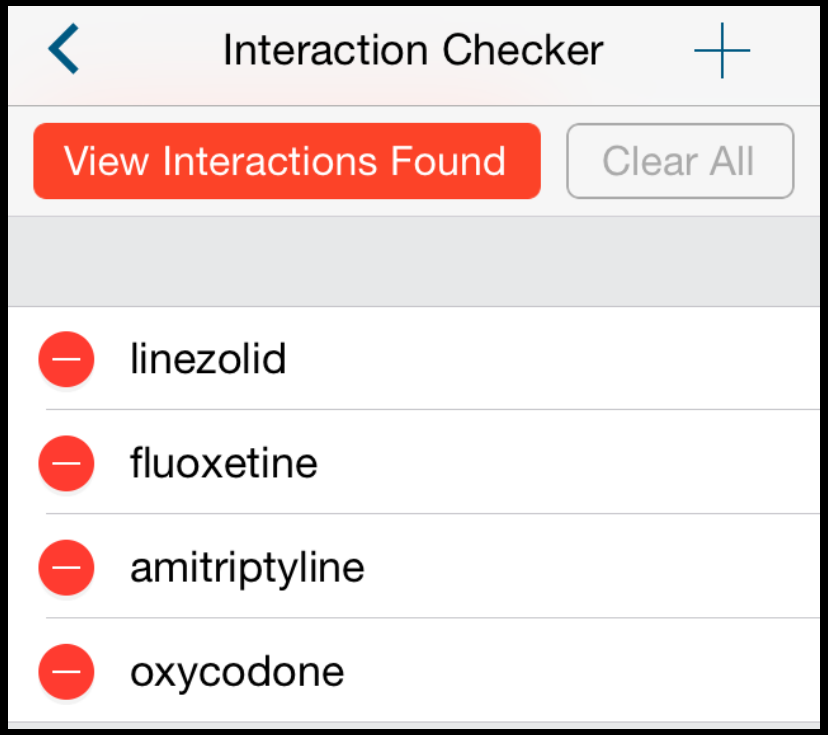
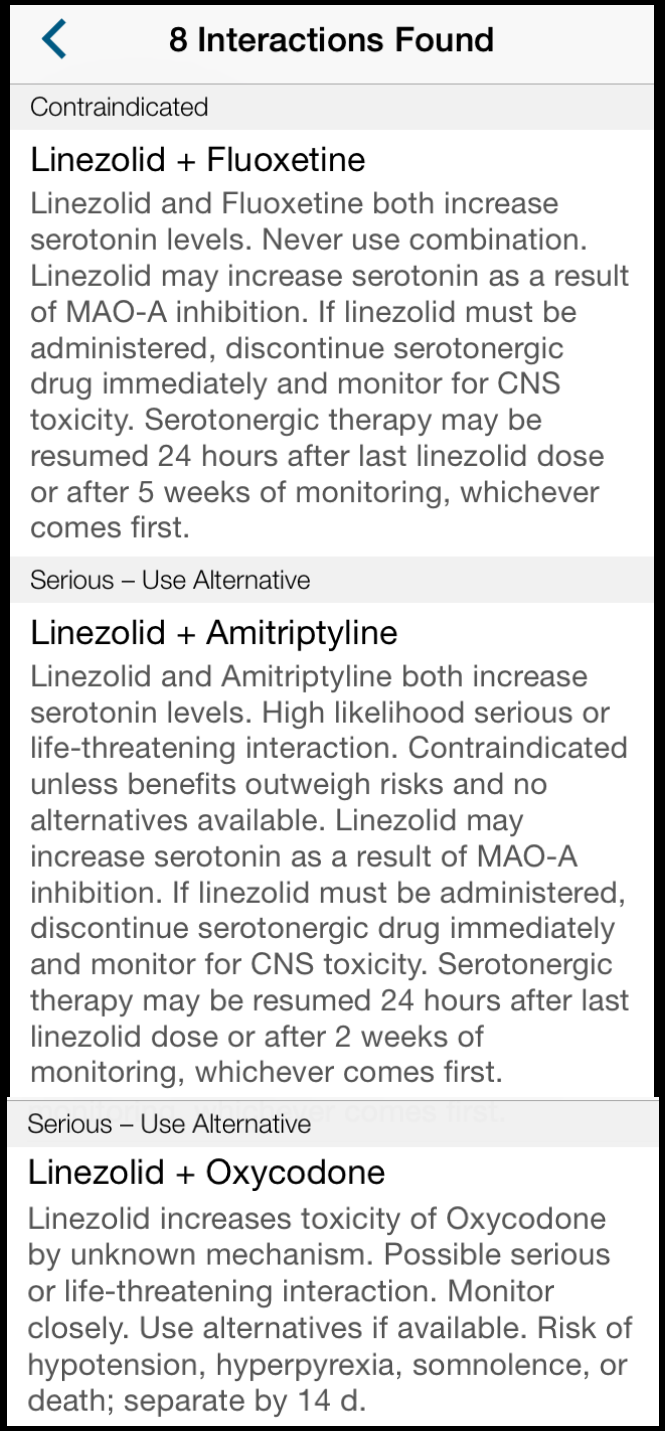
- Antibiotic Rx?

Oxycodone
Fluoxetine
Amitriptyline
Diazepam


Interaction Checker
View Interactions Found
Clear All
linezolid
fluoxetine
amitriptyline
oxycodone


8 Interactions Found
Contraindicated
Linezolid + Fluoxetine
Linezolid and Fluoxetine both increase serotonin levels. Never use combination. Linezolid may increase serotonin as a result of MAO-A inhibition. If linezolid must be administered, discontinue serotonergic drug immediately and monitor for CNS toxicity. Serotonergic therapy may be resumed 24 hours after last linezolid dose or after 5 weeks of monitoring, whichever comes first.
Serious – Use Alternative
Linezolid + Amitriptyline
Linezolid and Amitriptyline both increase serotonin levels. High likelihood serious or life-threatening interaction. Contraindicated unless benefits outweigh risks and no alternatives available. Linezolid may increase serotonin as a result of MAO-A inhibition. If linezolid must be administered, discontinue serotonergic drug immediately and monitor for CNS toxicity. Serotonergic therapy may be resumed 24 hours after last linezolid dose or after 2 weeks of monitoring, whichever comes first.
Serious – Use Alternative
Linezolid + Oxycodone
Linezolid increases toxicity of Oxycodone by unknown mechanism. Possible serious or life-threatening interaction. Monitor closely. Use alternatives if available. Risk of hypotension, hyperpyrexia, somnolence, or death; separate by 14 d.

Before Treatment: Prevention

- Patient factors: age, obesity, co-morbidity (DM)
- Asepsis, theatre airflow, maintain “normothermia”
- MSSA decolonisation
- Antibiotic prophylaxis: up to 24 hours (Norwegian arthroplasty study)
  - UK favours single dose
  - Choice: Fluclox + Gent associated with increase in risk of AKI (reversible), Cefuroxime: CDI risk
- Antibiotic-impregnated cement: Gent, Clinda, Vanc
- Negative pressure: “Jubilee dressing”
- Hand hygiene, ward environment, Pt education

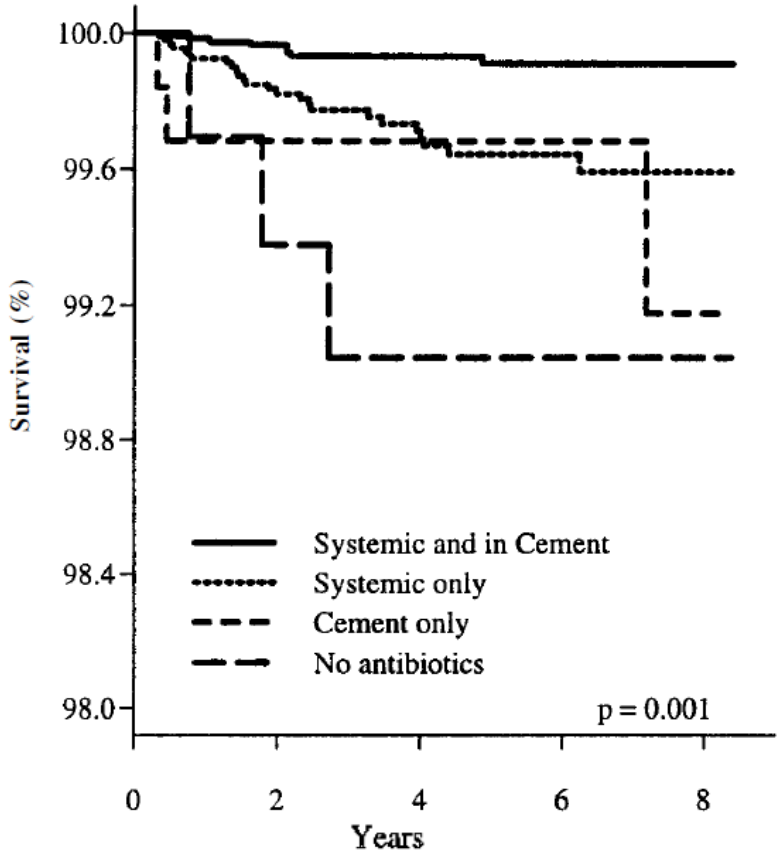


Fig. 1

Cox regression-adjusted survival curves of THRs performed in Norway from 1987 to 1995. The probabilities of survival were calculated with revisions due to infection as the endpoint for patients receiving different antibiotic regimes for prophylaxis. The p value refers to a test of homogeneity showing a statistically significant difference in survival among the regimes.

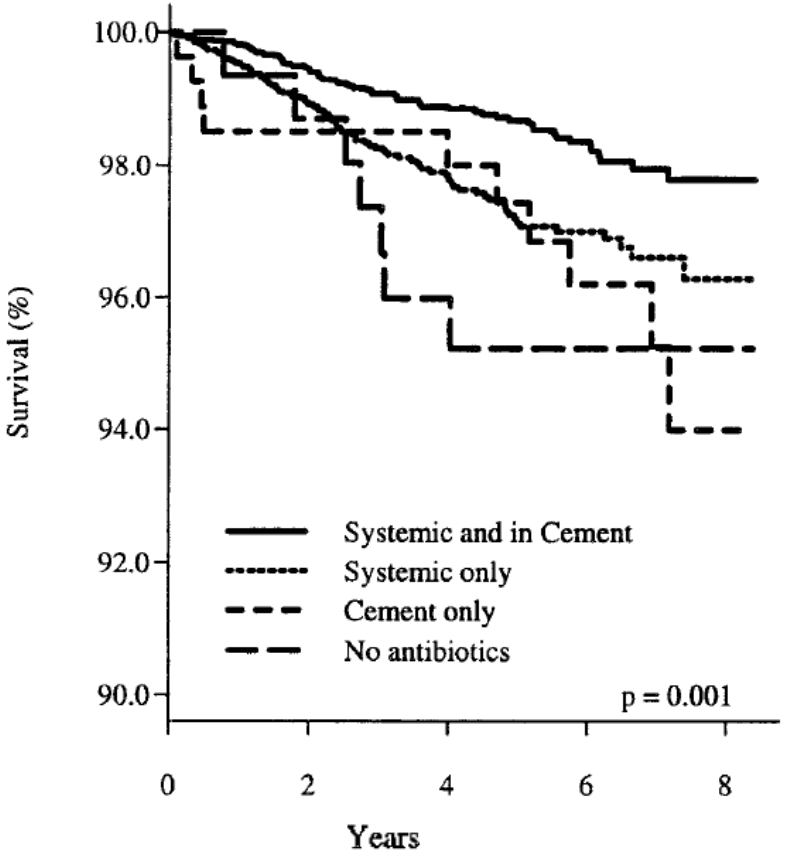


Fig. 2

Cox regression-adjusted survival curves of THRs performed in Norway from 1987 to 1995. The probabilities of survival were calculated with revisions due to any cause as the endpoint for patients receiving different antibiotic regimes for prophylaxis. The p value refers to a test of homogeneity showing a statistically significant difference in survival among the regimes.

Espehaug et al *J Bone Joint Surg [Br]* 1997;79-B:590-5.

Accepted wisdom?

"Osteomyelitis is rarely controlled without the combination of careful, complete surgical debridement and **prolonged parenteral antibiotic therapy at high dosage**"

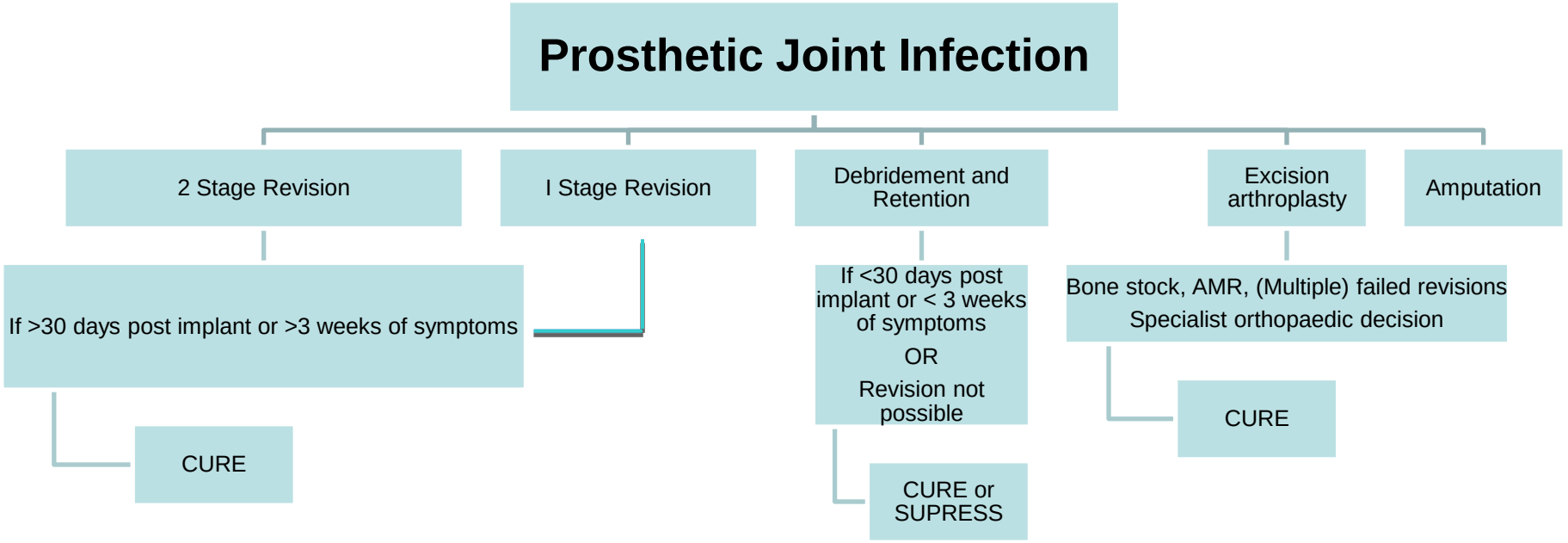
Waldvogel et al

N Engl J Med. **1970**;282:316-22

Surgical approach

- Debridement of bone, Removal of polyethylene and metal work
- Antibiotic-impregnated spacers: Gentamicin, Vancomycin
- Retention of metal work only if
  - Acute infection
  - very recent implant i.e. before formation of biofilm
  - Inoperable

Aim of Surgery: cure or suppress infection and maintain function



Osman et al CID 2013; 56: 1

Aim of antibiotic therapy

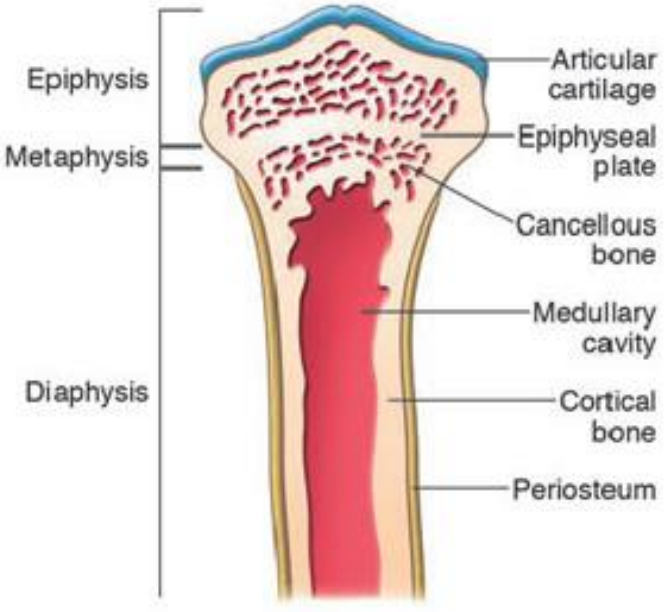
- To deliver an optimum concentration of antibiotic to which the organism is sensitive, direct to the site of infection to effect a cure
- To augment/ support (but not replace) the surgical approach
- For agents with time dependent characteristics, concentration must remain above the MIC of the organism for the maximum duration of the dosing interval

Route of administration in PJI

- Topical: Beads/ cement (primary or adjunct Rx)
- Intra-articular: infusion
- Oral
- **Intravenous (+/- Oral, +/- Topical)**
- Intramuscular

Factors affecting antibiotic bone penetration

- Reduced penetration if:
  - Low concentration of drug at site of infection
  - Cortical bone (c.f. cancellous)
  - Poor vascularity
  - Uninfected/ uninflammed
  - Presence of biofilm



Free drug concentration correlates with concentration in bone (in β-lactams)

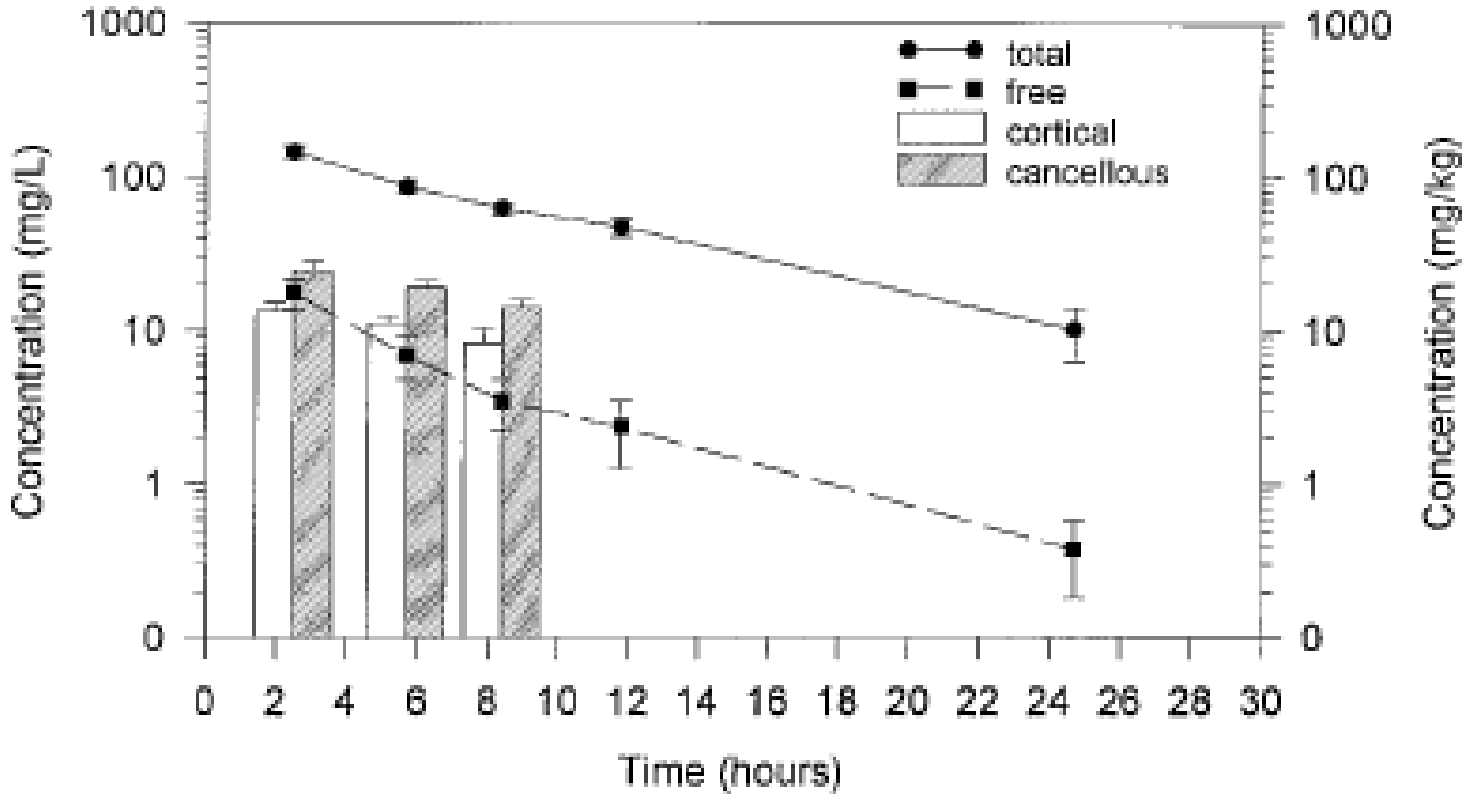
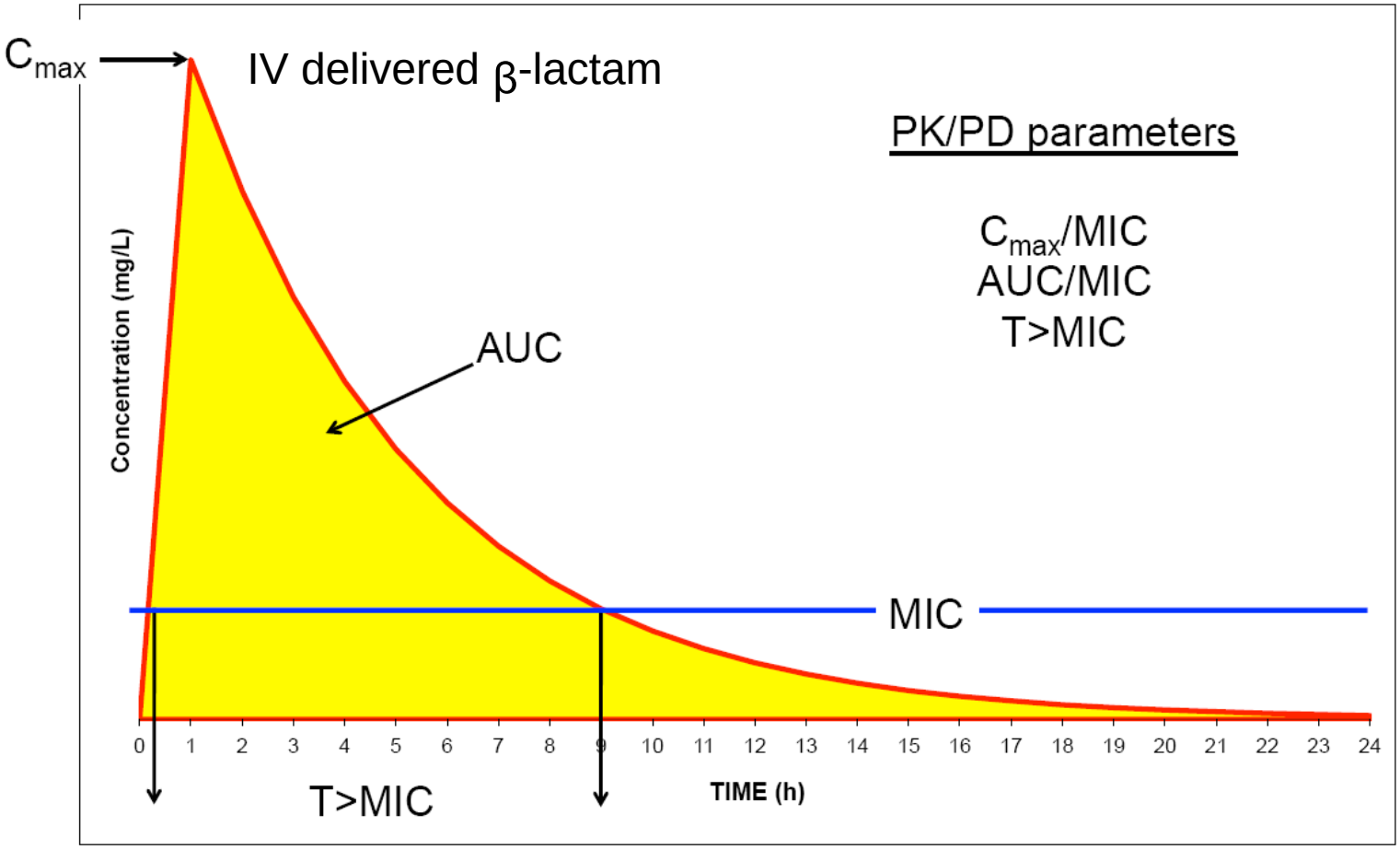


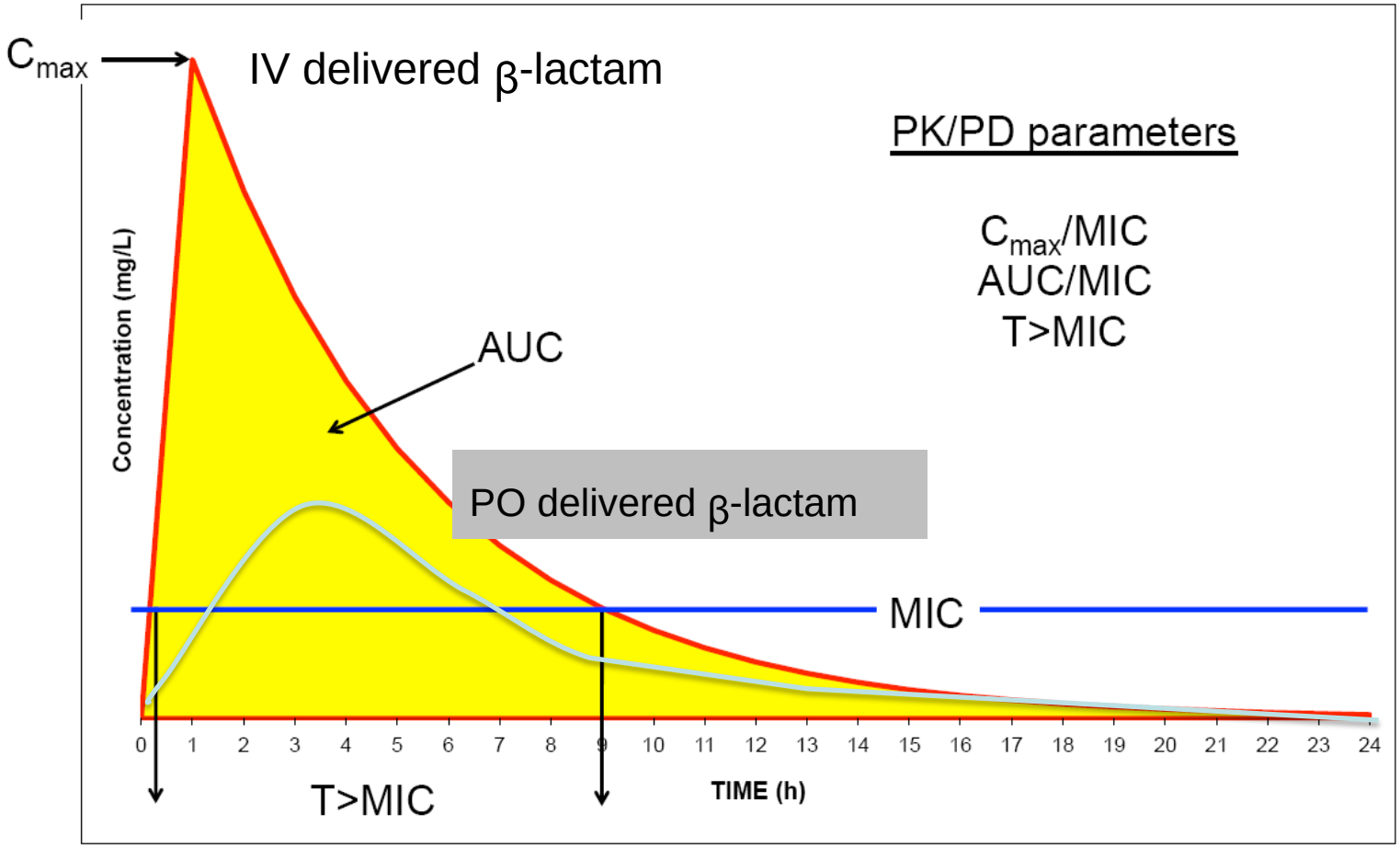
FIG. 2. Mean concentrations of ceftriaxone in serum (total and free levels) and in cancellous and cortical bone.

Scaglioni et al AAC 1997; 41: 2292

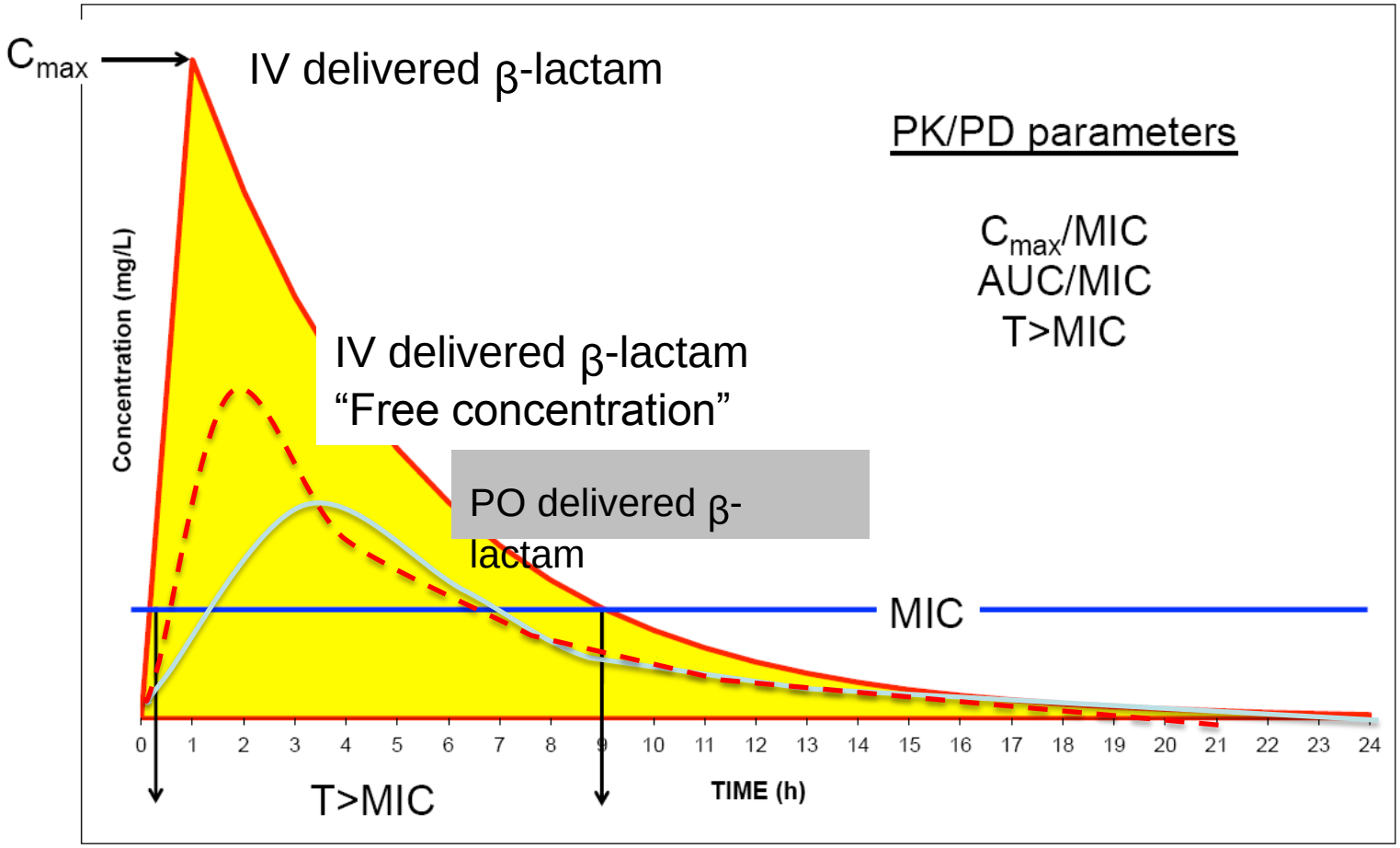
PK / PD Principles



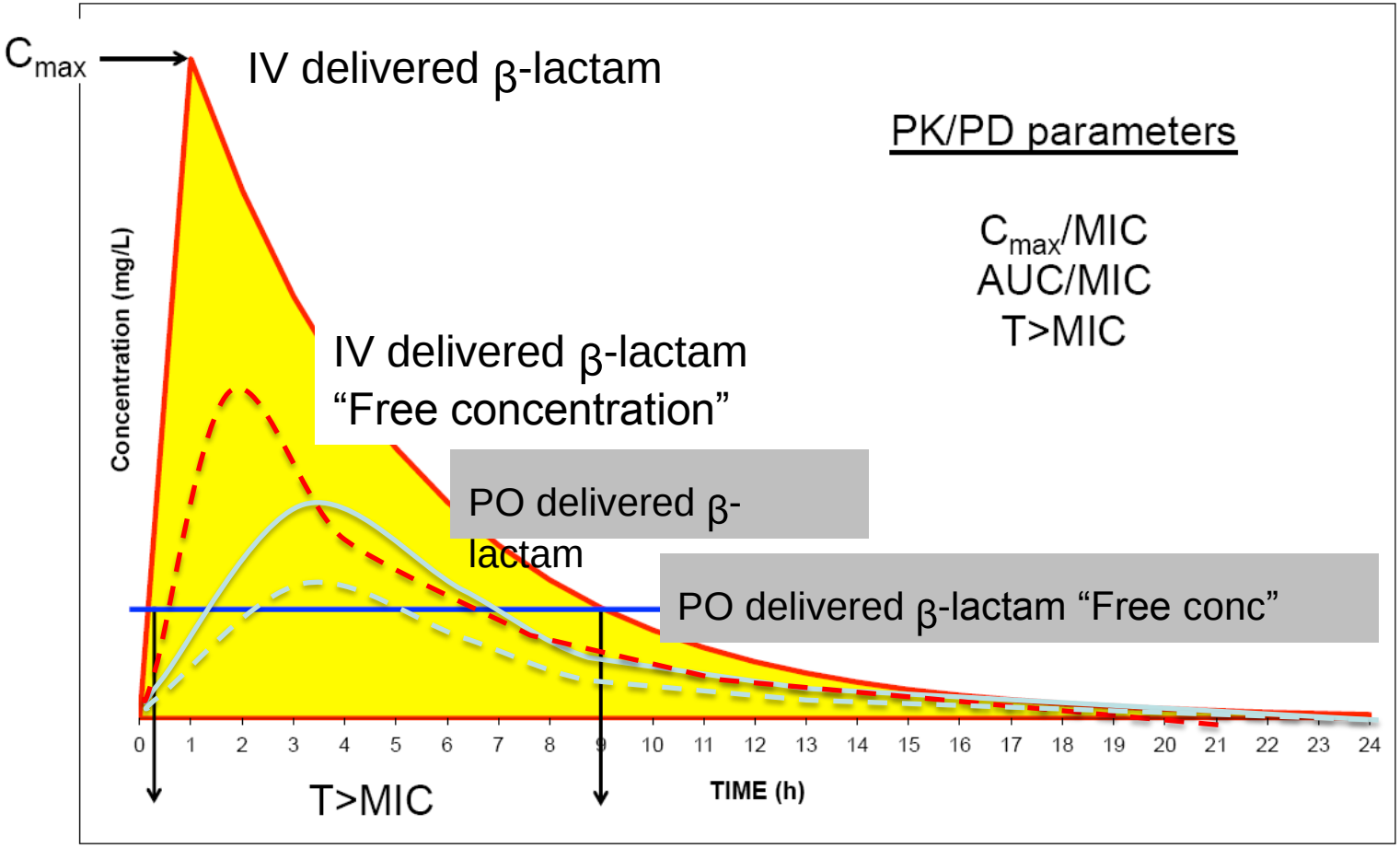
PK / PD Principles



PK / PD Principles



PK / PD Principles



β-lactams and bone penetration

- β-lactams penetrate bone at approximately 5-20% of serum concentrations

  (oxacillin, cefazolin, ceftriaxone, ceftazidime, piperacillin, meropenem, aztreonam all studied)

- IV delivered [β-lactam] far exceed the MICs of likely organisms in most cases (free concentration is adequate)

- Serum concentration of oral delivered β-lactams <10% of IV therefore unlikely to achieve adequate bone concentration

Spellberg, Lipsky CID 2012; 54: 393

β-lactams and bone penetration

Historical data support oral penicillins when used in combination with probenecid

- Reduction in renal excretion
- Higher peak serum concentration
- Limited data available

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Widely used in SSTI in Aus/NZ

SM Bell, Med J Aust 1976; 2: 592

Vancomycin: non infected bone

TABLE 1. Group 1 (total hip arthroplasty) data

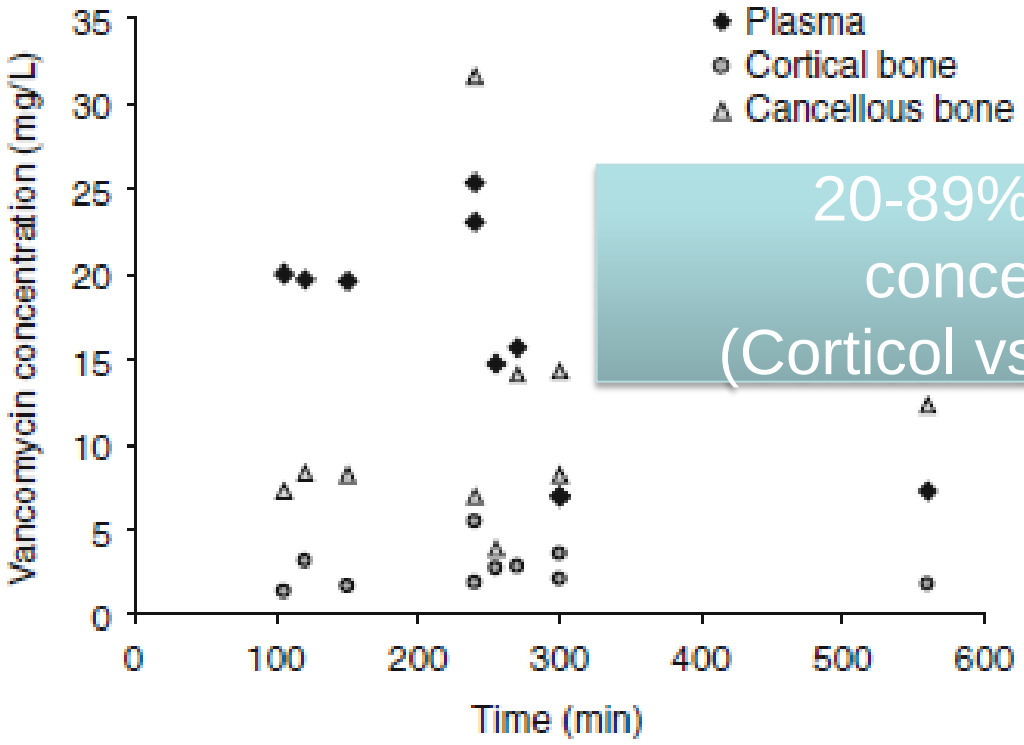
Patient no.	Concn (μg/g) in bone		Time (min) postdose	Concn (μg/ml) in serum		Bone/serum ratio	
	Cancellous	Cortical		Simultaneous	Peak	Cancellous	Cortical
1	1.49	0.83	0	38.6	35.6	0.04	0.02
2	1.32	ND[a]	0	52.9	37.9	0.03	NA[b]
3	0.81	2.26	185	10.5	24.2	0.08	0.21
4	1.53	0.59	95	10.5	21.1	0.15	0.06
5	2.2	1.75	11	37.0	—[c]	0.06	0.05
6	2.65	1.60	50	14.4	23.4	0.17	0.10
7	0.61	0.50	100	18.2	26.8	0.03	0.03
8	0.53	ND	90	17.1	25.4	0.03	NA
9	0.95	ND	106	10.9	24.0	0.09	NA
10	0.58	0.52	138	16.2	30.0	0.04	0.03
11	16.0	2.58	70	17.0	26.0	0.94	0.15
12	1.0	0.57	92	15.7	28.0	0.06	0.04
13	0.71	0.19	98	20.9	37.3	0.03	0.01
14	1.63	ND	45	16.7	28.0	0.10	NA
Mean	2.3	1.14	77.1	22.1	28.3	0.132	0.07
Range	0.5–16.0	ND–2.58	0–185	10.5–52.9	21.1–37.9	0.03–0.94	0.01–0.21
SD	4.0	0.84	52.6	12.6	5.45	0.24	0.066

[a] ND, Vancomycin not detectable in bone supernatant.

7-13% of serum concentration (- free drug concentration)

Graziani et al AAC 1988; 32: 1320

Vancomycin: infected bone

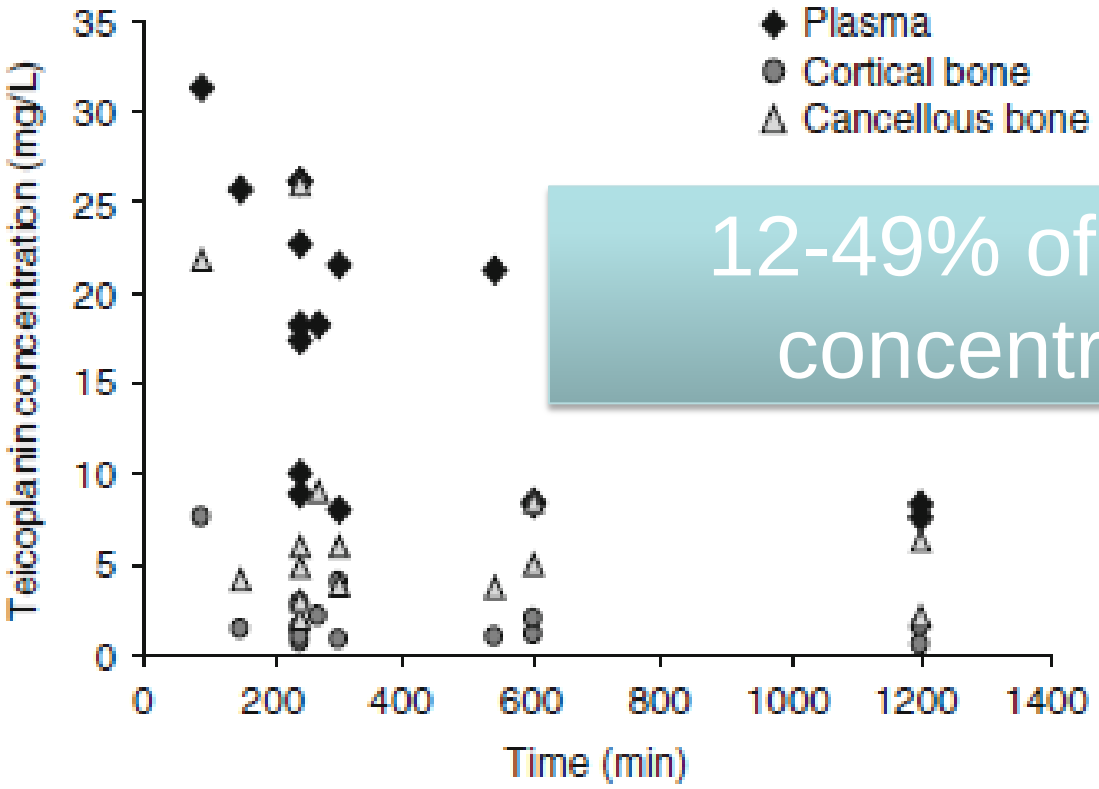


20-89% of serum concentration (Corticol vs Cancellous)

Fig. 1. Vancomycin concentrations in plasma and bone versus time.

Grazzino Clin Pharmakokinet 2008; 47: 793

Teicoplanin: infected bone



12-49% of serum concentration

Fig. 3. Teicoplanin concentrations in plasma and bone versus time.

Grazzino Clin Pharmakokinet 2008; 47: 793

Daptomycin 8mg/kg Penetration into Bone

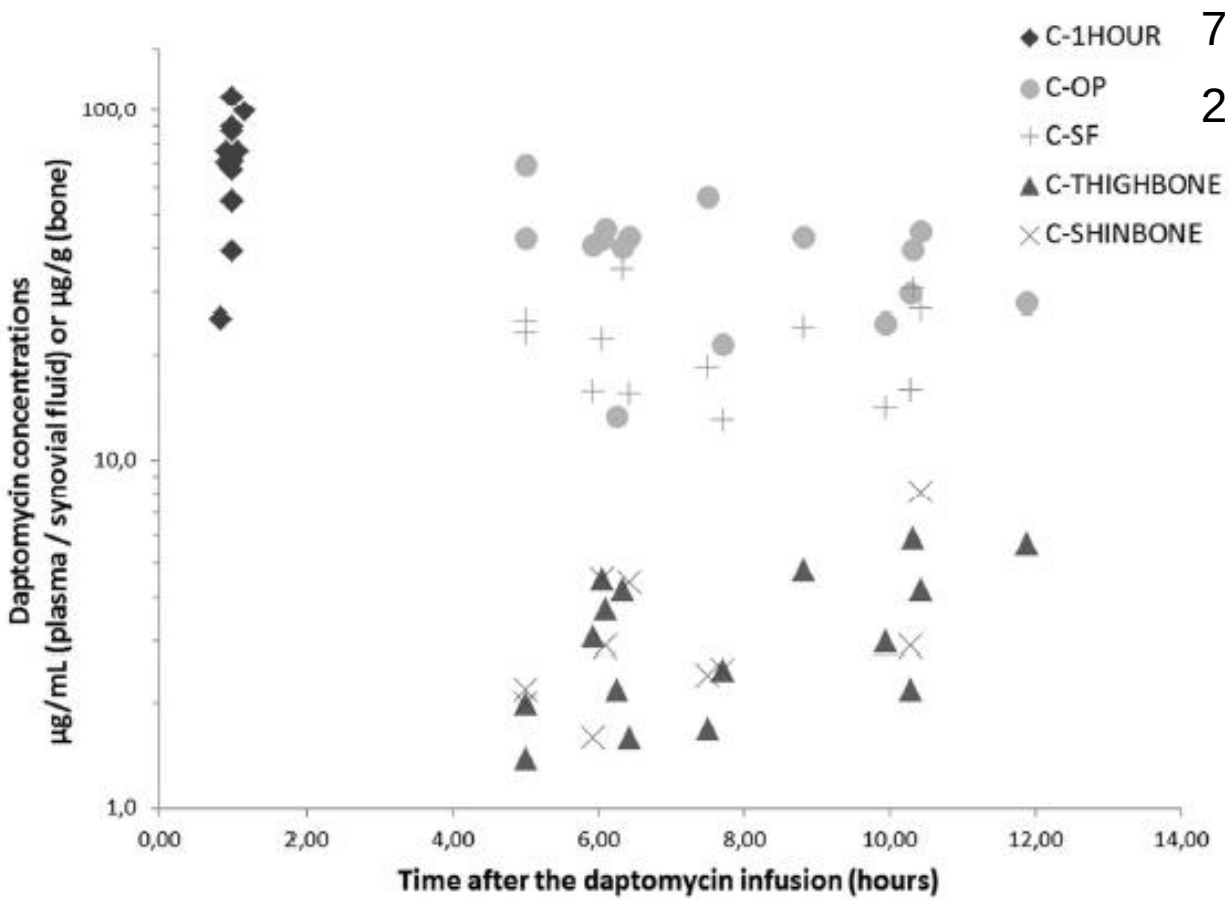
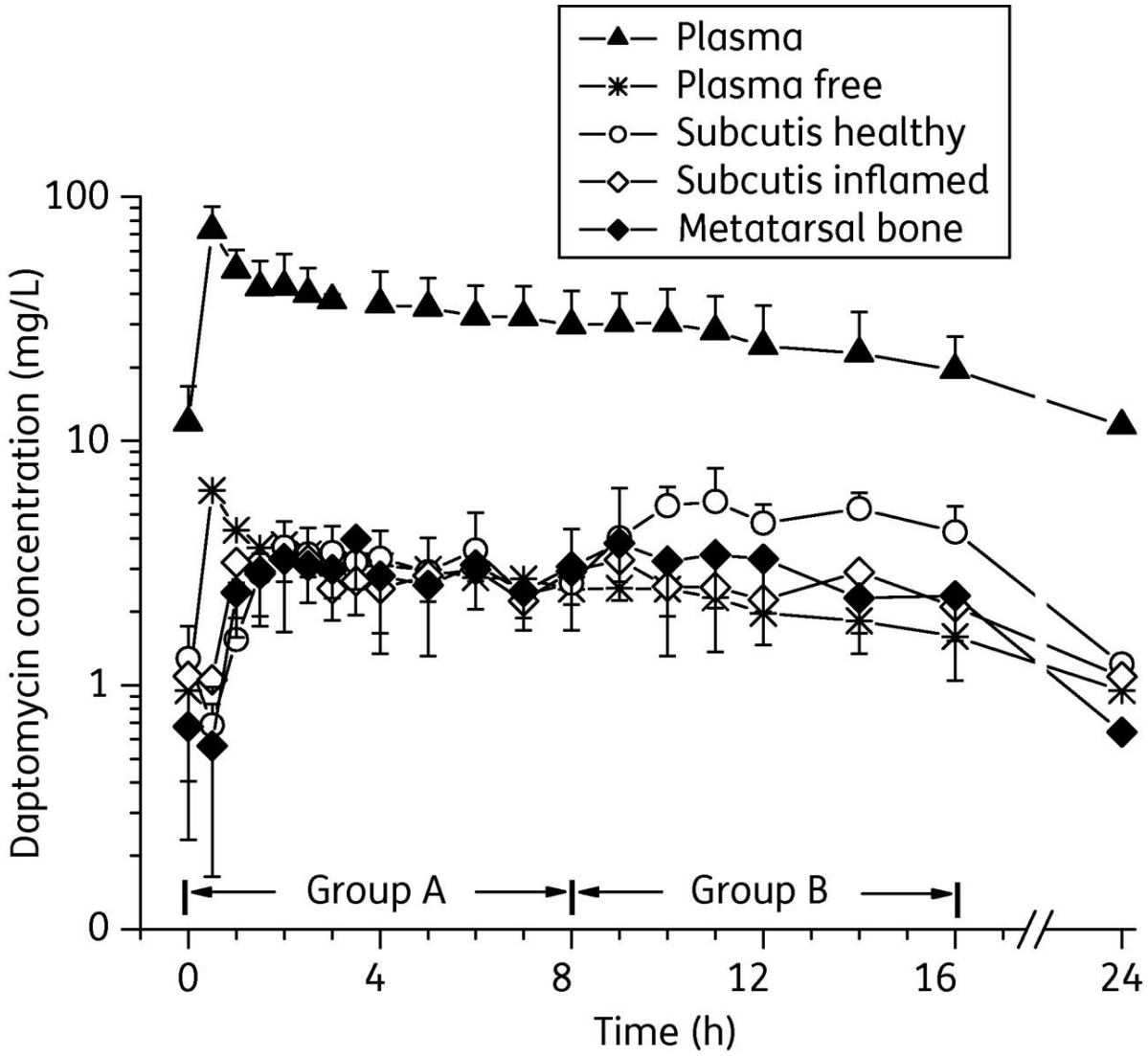


FIG 2 Representation of the daptomycin concentrations in plasma (C_{1HOUR} and C_{OP}) or in synovial fluid (C_{SF}) (µg/ml) and in bones ($C_{THIGHBONE}$ and $C_{SHINBONE}$) (µg/g) versus the sampling time.

Montange *et al. Antimicrobial agents and Chemotherapy,* 2014; 58: 3991-3996

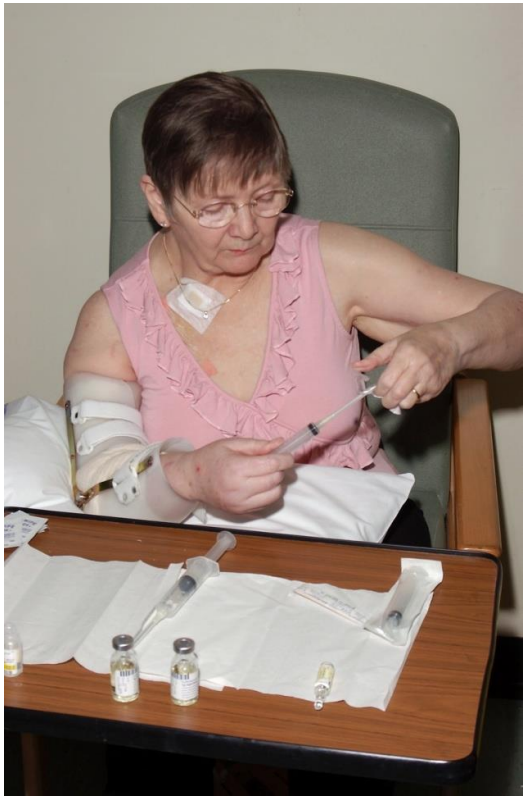
Daptomycin in bone (DFI)



Traunmüller F et al. J. Antimicrob. Chemother. 2010;65:1252-1257

Potential advantages of IV therapy

- Mode of delivery for Beta lactams, GPs, Daptomycin
- Acute: sepsis / infection beyond the bone
  - e.g. SAB, Endocarditis, severe SSTI
- Bioavailability
  - Reliable serum concentration following IV administration
  - Avoids problems with absorption
  - Ability to deliver bigger doses
  - Increased likelihood of achieving therapeutic concentration at site of infection
- Spectrum of activity (for certain agents)
- Chronic: compliance and tolerability
  - Missed doses are less likely



Good practice recommendations for outpatient parenteral antimicrobial therapy (OPAT) in adults in the UK: a consensus statement

1. OPAT team and service structure
2. Patient selection
3. Antimicrobial management and drug delivery
4. Monitoring of the patient during OPAT
5. Outcome monitoring and clinical governance

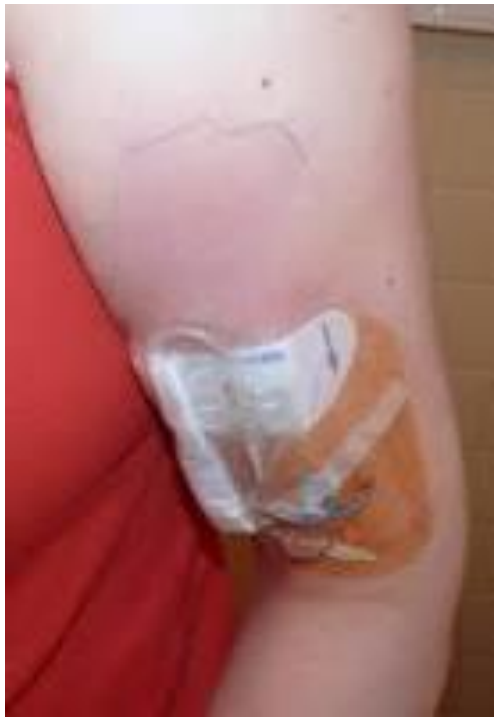
Journal of Antimicrobial Chemotherapy Advance Access published January 31, 2012

J Antimicrob Chemother
doi:10.1093/jac/dks003

Journal of Antimicrobial Chemotherapy

Potential disadvantages of IV therapy

- Requires an IV device
  - Painful to insert
  - Source of infection/ SAB
  - Thrombosis/ phlebitis / fracture
  - Inconvenient dosing regimens
- Requires hospitalisation or OPAT
  - Time consuming to administer
  - Restrictions of device / Hassle
  - Expensive
- Antimicrobial stewardship
  - Use of agents associated with CDI
  - May be unnecessarily broad spectrum

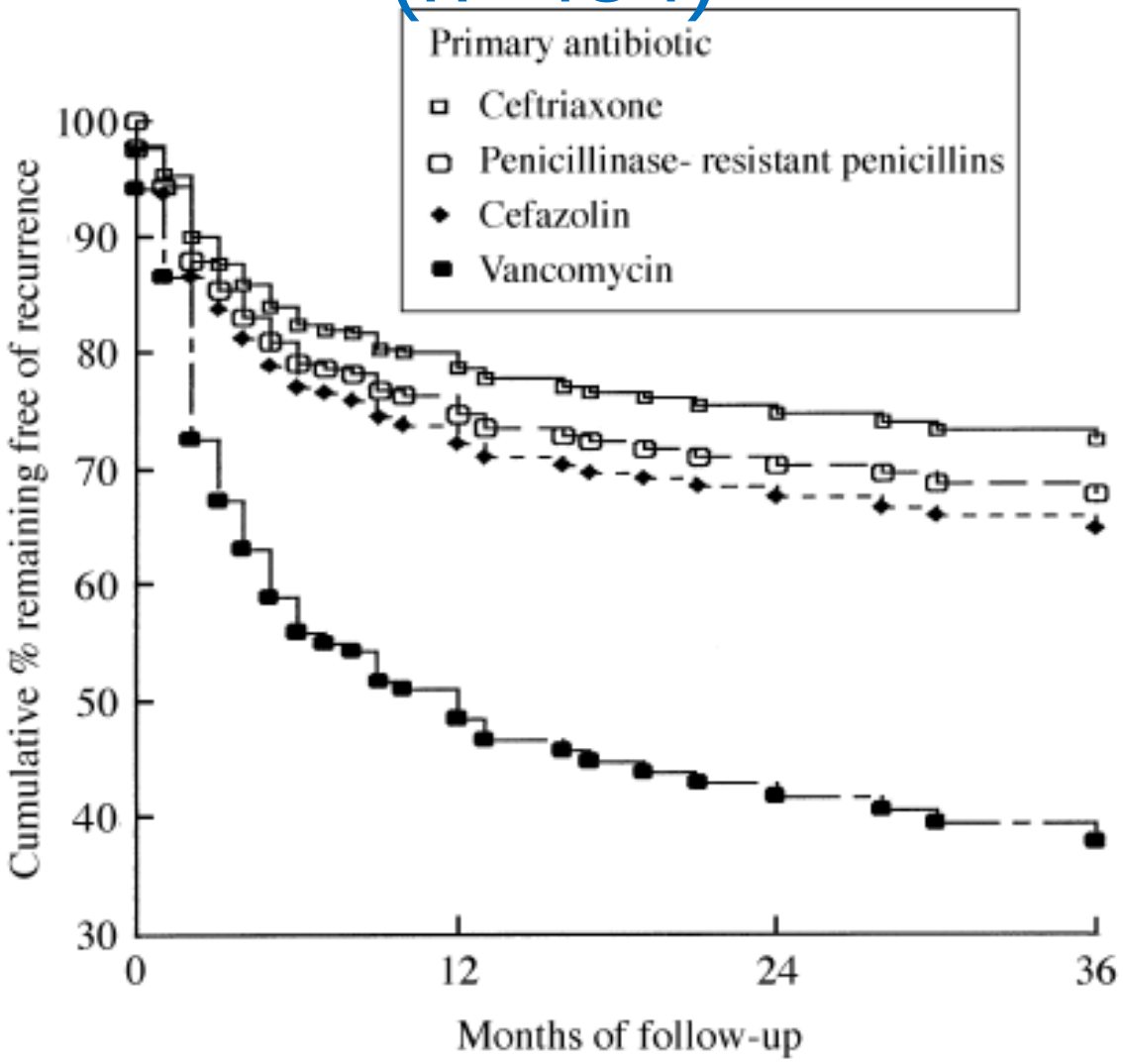


Wellsphere.com

Clinical outcome data

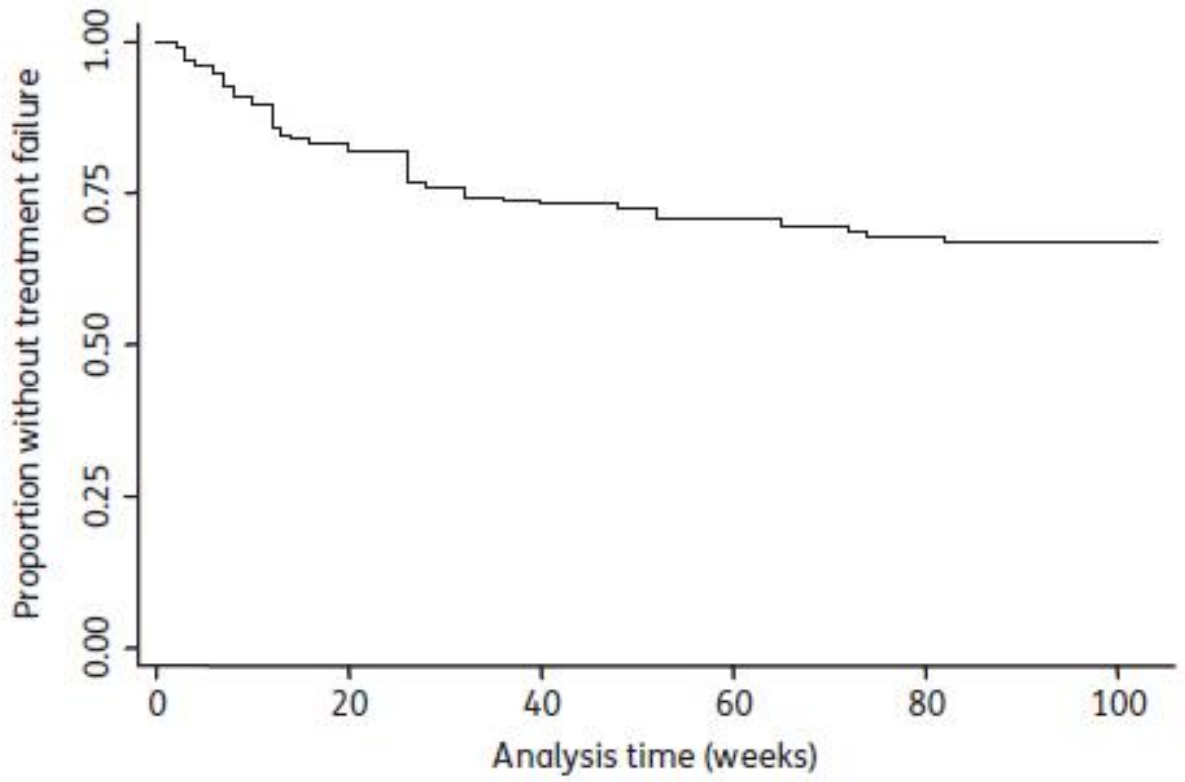
- Mainly observational studies with few RCTs
- Too many variables make comparisons between different IV agents difficult
  - Surgical approach
  - Variable methodology
  - Definitions of success
  - Length/ consistency of follow up

Outcomes in OPAT Rx Osteomyelitis (n=454)



Tice et al JAC 2003; 51: 1261

Outcomes in OPAT Rx OM (n=198)

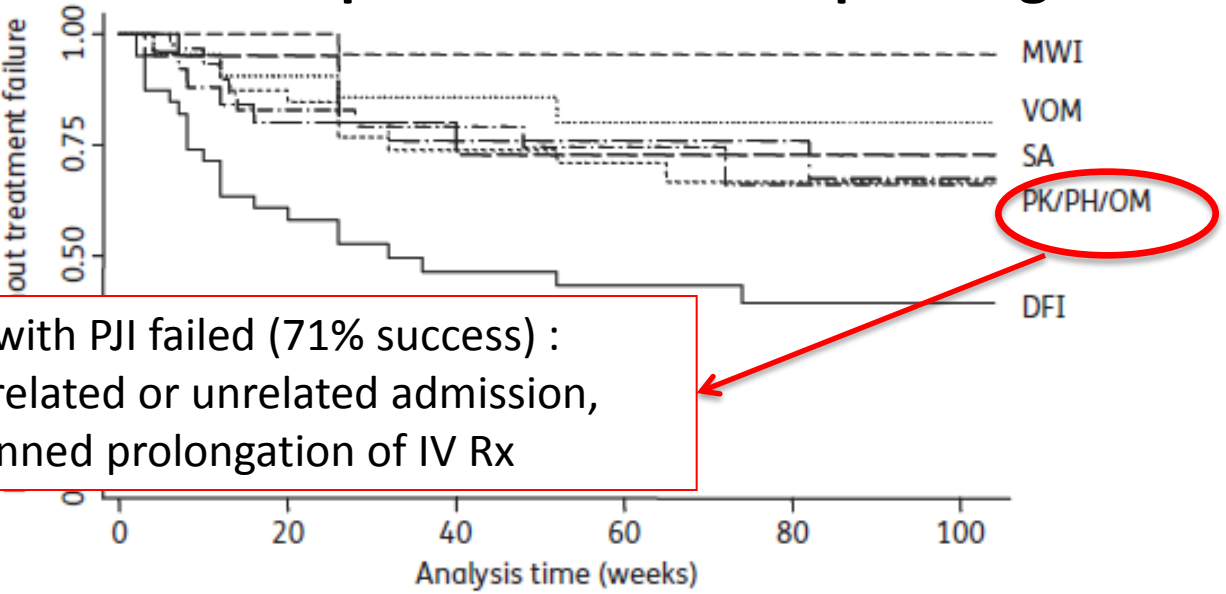


Numbers at risk	198	157	117	84	69	50
Numbers failing	0	35	51	55	58	59

Kaplan–Meier survival estimate of time to treatment failure for all patients showing all follow-up data available.

Mackintosh CL, White H.A, and Seaton R.A, JAC 2011

Kaplan-Meier survival estimate of time to treatment failure for all patients with OM per diagnosis



19 of 65 with PJI failed (71% success) :
Surgery, related or unrelated admission,
or unplanned prolongation of IV Rx

Weeks	0	20	40	60	80	100
Numbers at risk/numbers failing						
DFI	39/0	23/16	15/20	11/21	9/22	8/22
MWI	23/0	21/0	15/1	10/1	9/1	4/1
OM	30/0	24/5	18/6	10/7	6/8	5/8
PH	25/0	20/5	18/6	10/6	9/6	7/7
PK	40/0	32/6	26/10	17/11	13/12	11/12
SA	20/0	19/1	10/5	9/5	9/5	6/5
VOM	21/0	19/2	15/3	13/4	12/4	9/4

Mackintosh CL, White H.A, and Seaton R.A, JAC 2011

Teicoplanin for Bone infection in Glasgow OPAT

- Indications
  - Resistant staphylococcal infections (CoNS or MRSA)
  - Gram-positive infections with β-lactam allergy
  - Prior failure with β-lactams
- Dosing regimen
  - Loading: 20 mg/kg for 3 days (inpatient or outpatient)
  - Maintenance: 3×/week (butterfly)
  - TDM at longest interval (72 hours)
  - Target trough concentration for Bone infection: 20–30 μg/ml
    - <20 μg/ml: increase dose or reduce interval (alt. days)
    - >30 μg/ml: reduce dose or increase interval (2× or 1×/week)

Lamont E *et al. J Antimicrob Chemother* 2009;doi:10.1093/jac/dkp147

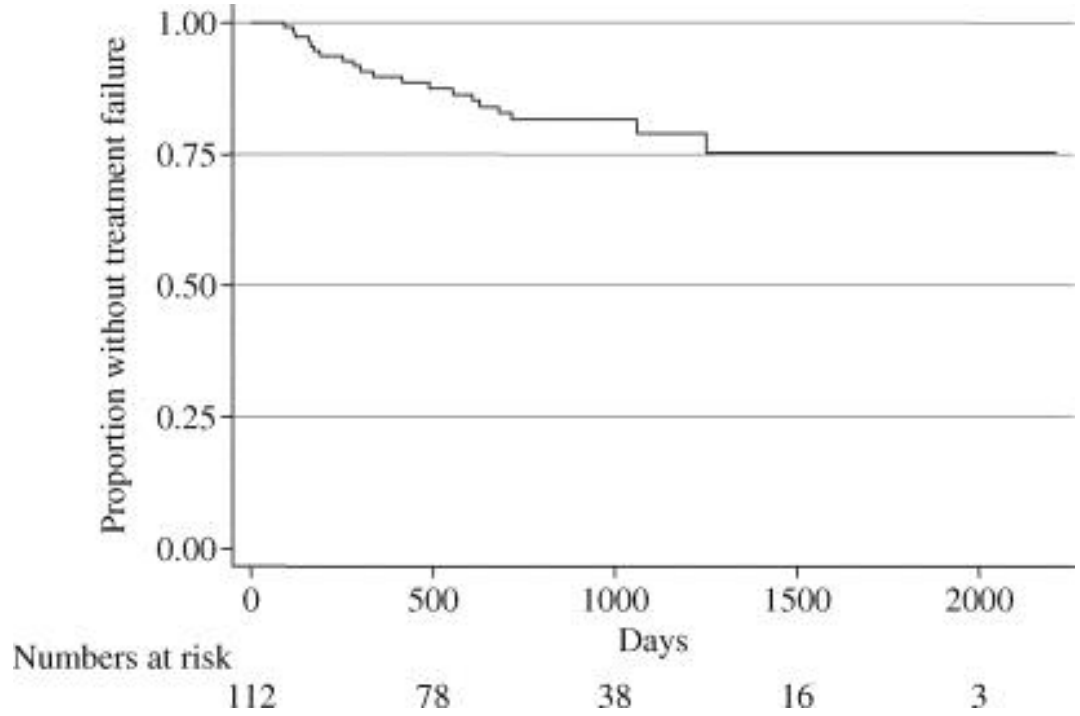
Hazard Ratio from Survival analysis (Cox regression) for the association of the initial IV Antibiotic with failure over the follow up period

Initial IV Rx	No.	No. Failing	Hazard ratio	CI	p
Teicoplanin	140	48 (34%)	1		
Ceftriaxone	51	10 (19.6%)	0.54	0.27-1.06	0.074
Other	5	1			

Mackintosh CL, White H.A, and Seaton R.A, JAC 2011

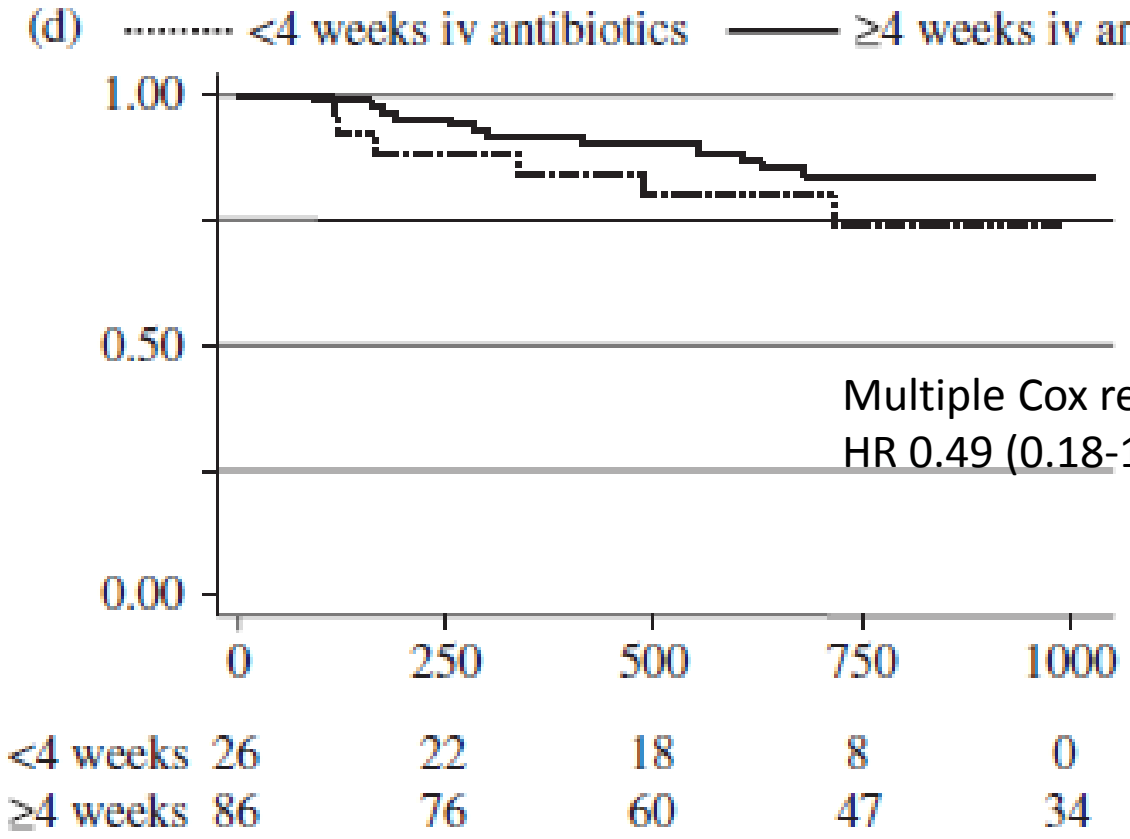
Debridement, Antibiotics and Implant Retention (DAIR)

- 6 weeks IV AB
  - Empiric
    - Vanc + Meropenem
  - Rationalized
    - Ceftriaxone
    - Teicoplanin
- ~12 months oral



Byren et al JAC 2009; 63: 1264

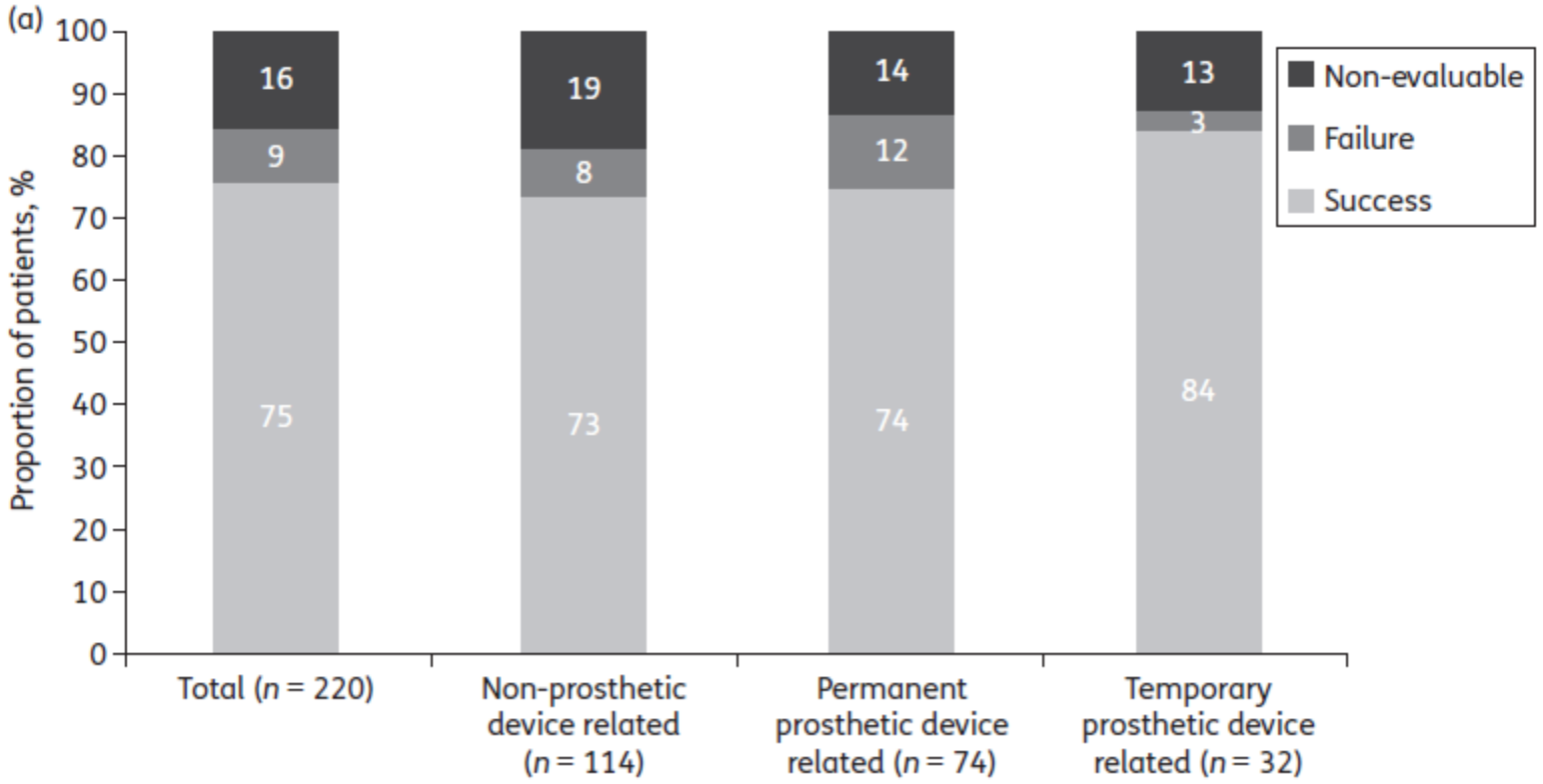
DAIR and duration of IV Rx



Multiple Cox repgression model
HR 0.49 (0.18-1.37), p=0.18

Byren et al JAC 2009; 63: 1264

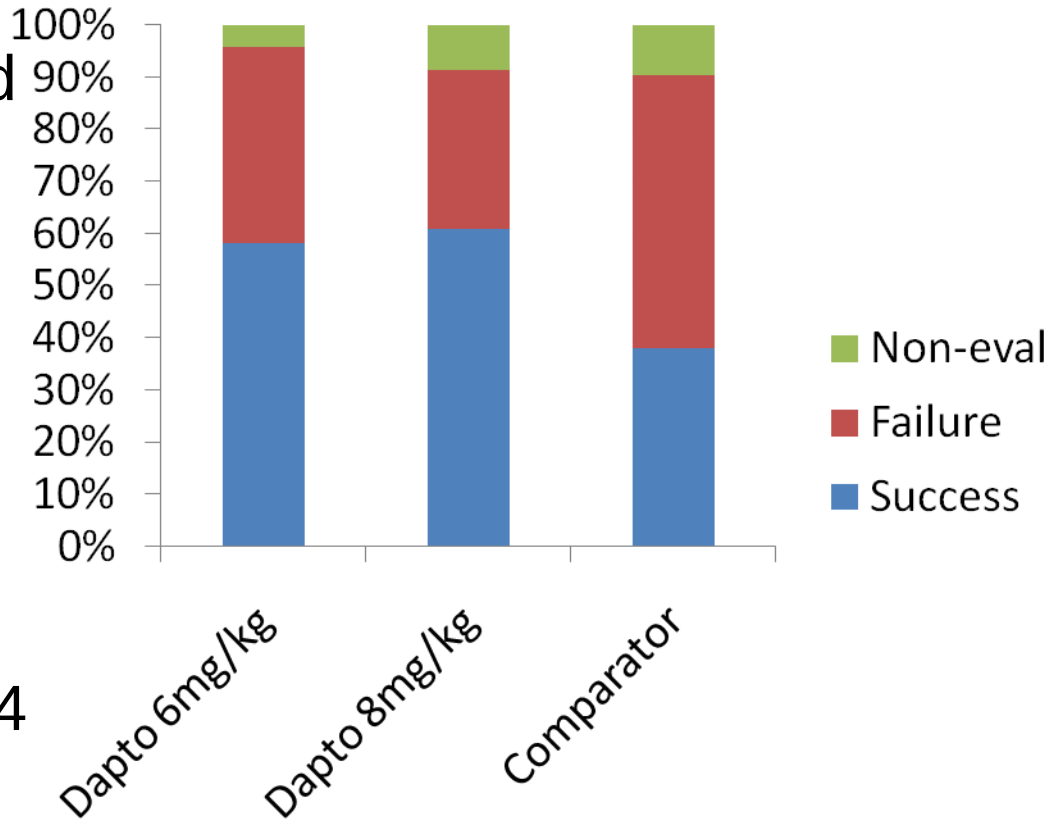
Daptomycin in Bone infection: Observational data to 30 days post-Rx



J Antimicrob Chemother
doi:10.1093/jac/dkt067

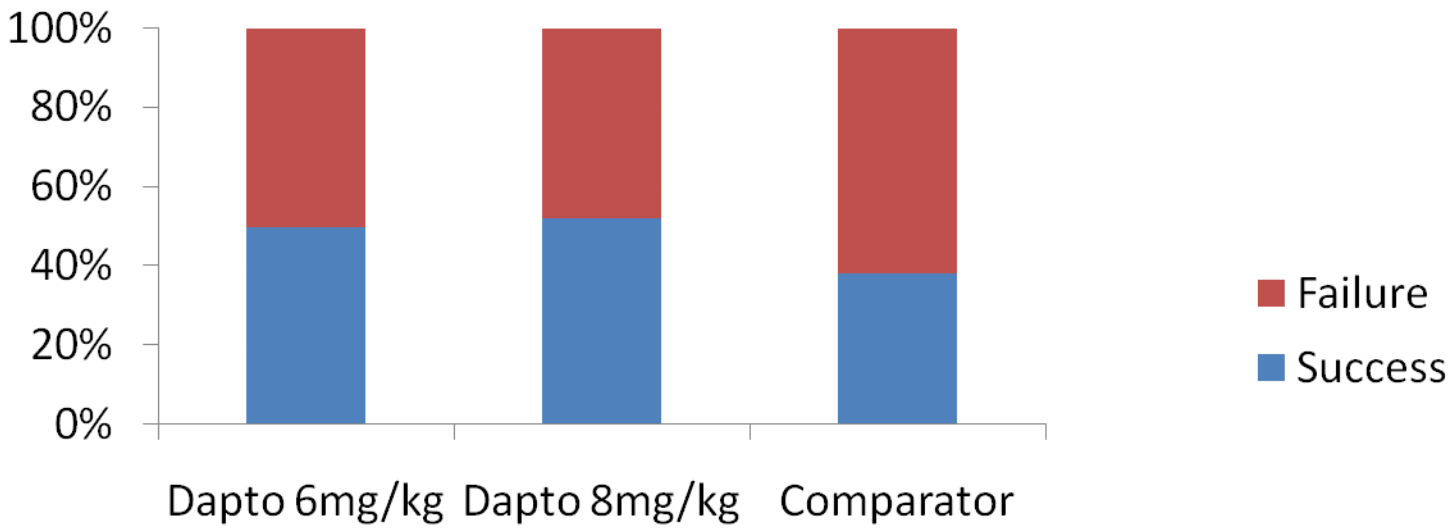
Daptomycin vs SOC in 2 Stage Revision (Phase II study)

- Microbiological confirmed PJI
- Randomised: 6-8mg/kg Dapto vs GP/SSP
- No oral agent
- 6 weeks post 1st stage
- TOC 2 weeks post 2nd stage
- If success reviewed @3-4 months
- 75 pts randomised



Byren et al ACC 2012; 56: 5626

Microbiological success



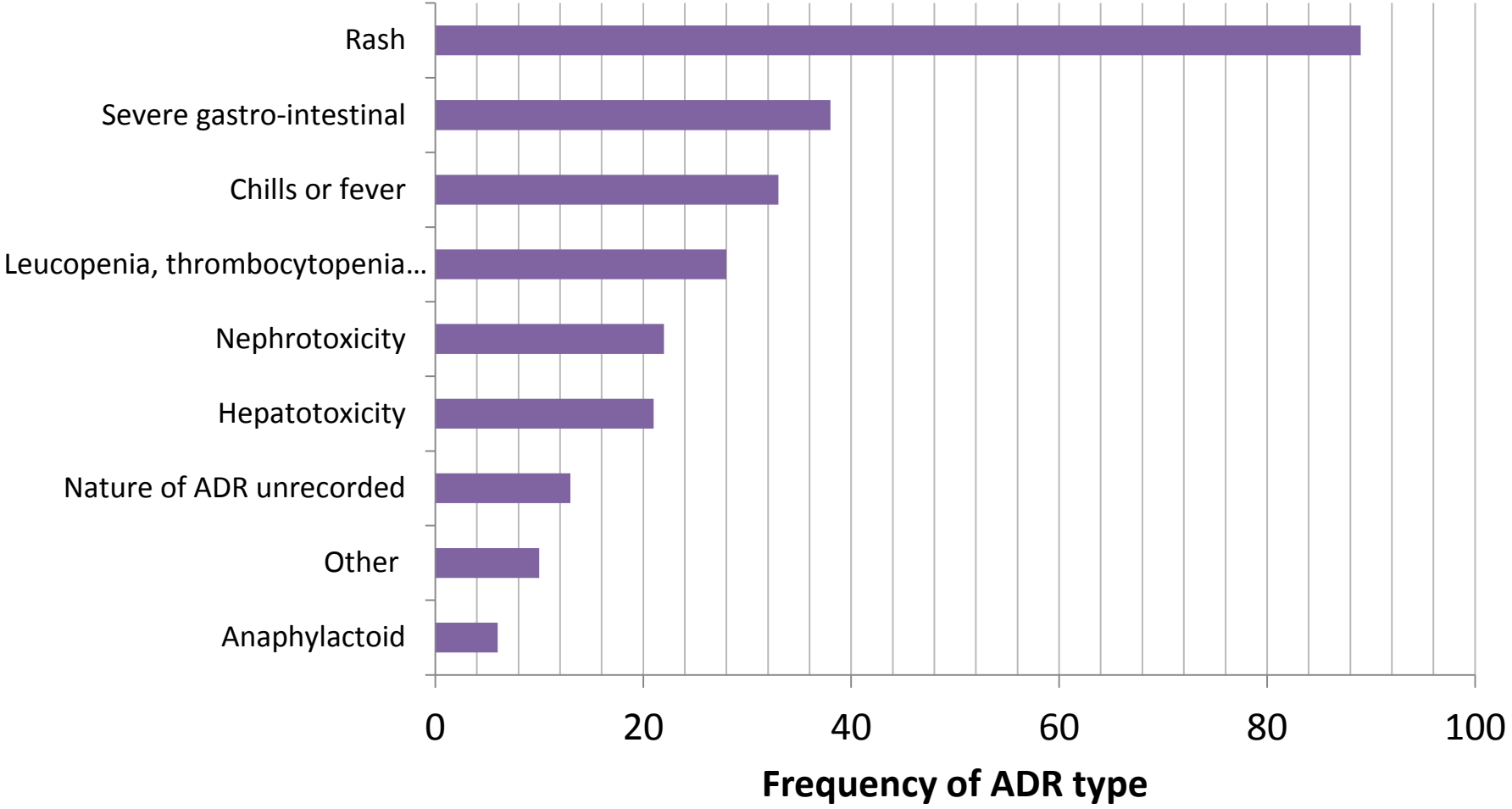
The MIC for daptomycin remained below the susceptibility breakpoint of ≤1 μg/ml for all staphylococcal isolates in patients with microbiological failure, with no increases in daptomycin MIC for isolates obtained at the first surgery compared with isolates obtained at reimplantation.

Byren et al ACC 2012; 56: 5626

Important Side-effects in OPAT agents

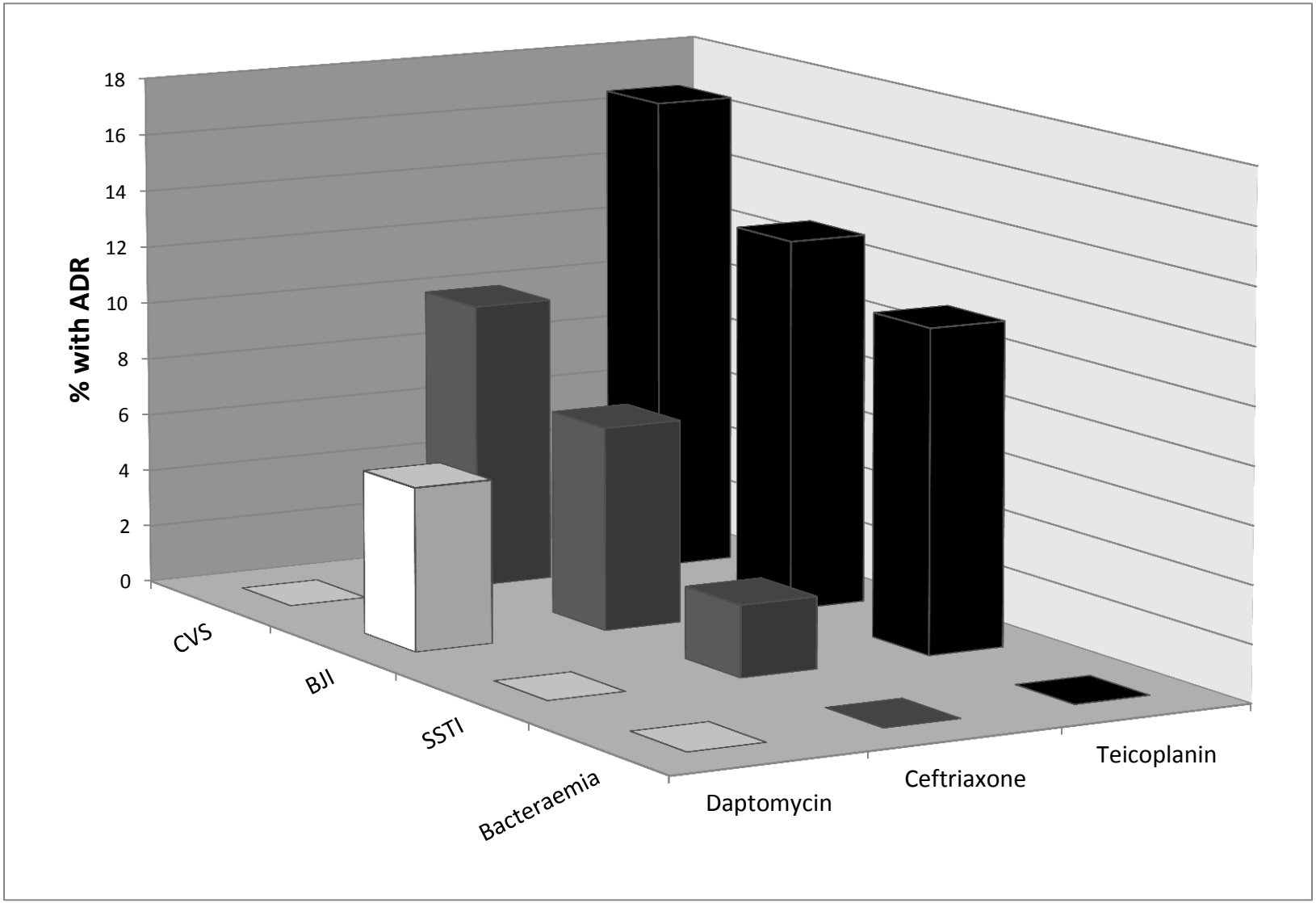
- Ceftriaxone: Rash, LFTs, diarrhoea, leucopenia
- Teicoplanin: Leucopenia, anaemia, TCP, fevers
- Daptomycin: CPK/ myotoxicity, Eosinophilic pneumonitis

Relative frequency of adverse drug reaction (ADR) types, in all first OPAT episodes over 10 year study period.



Note: An ADR in an individual patient in some instances involved multiple drug reaction types (e.g. rash and fever); each ADR type is counted separately in frequency bars even where they stem from one ADR event.

ADRs, Infection Type and AB Used

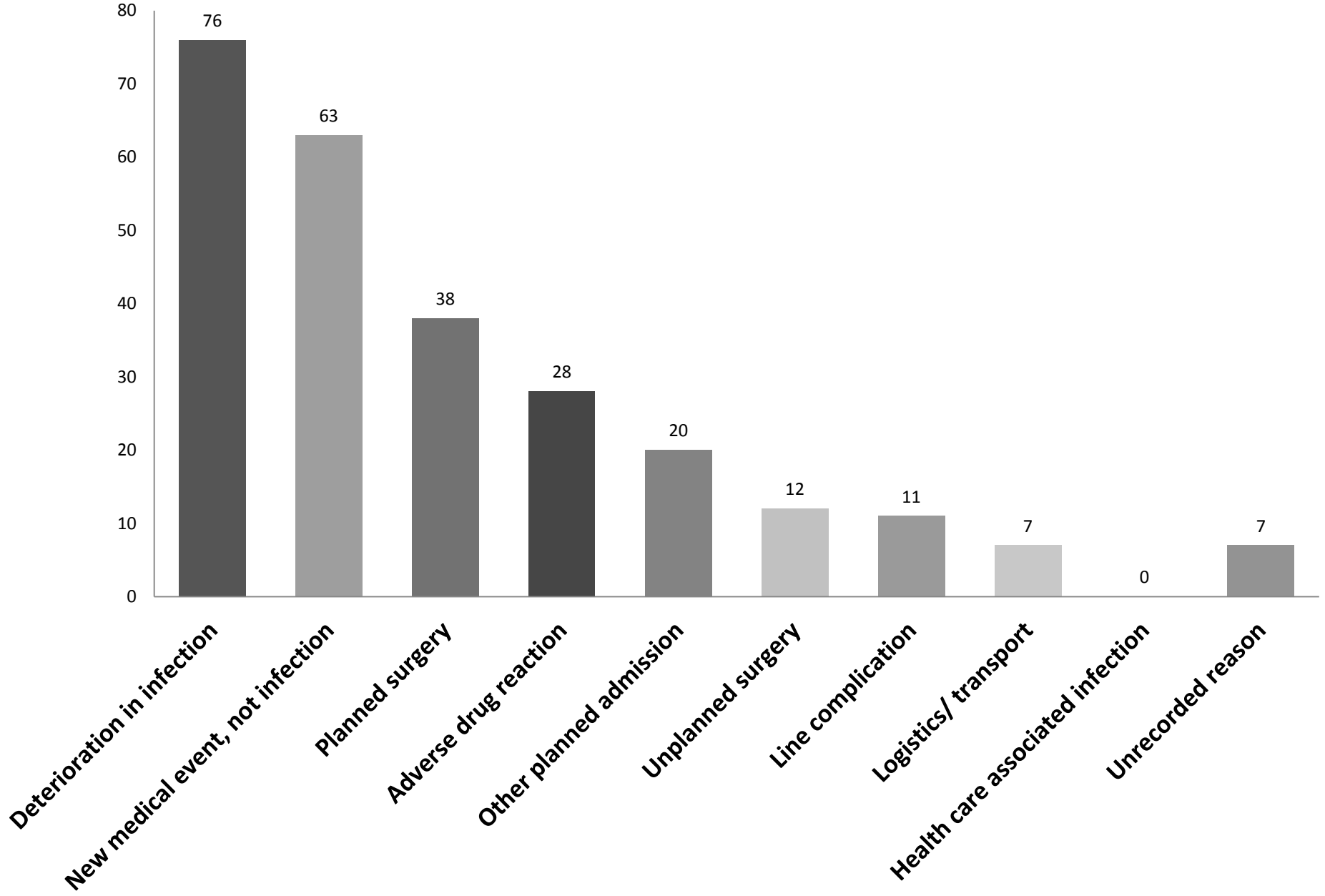


Line related complications in OPAT

- Infection: 0 to 3 per 1000 OPAT patient days
  - Associated with length of IV Rx
- Other line events
  - thrombosis, mechanical and chemical phlebitis: 5 to 50 per 1000 OPAT patient days
  - lowest risk in tunnelled central venous catheters
  - Highest risk when flucloxacillin primary OPAT agent
- No additional risk of patient/ carer administration

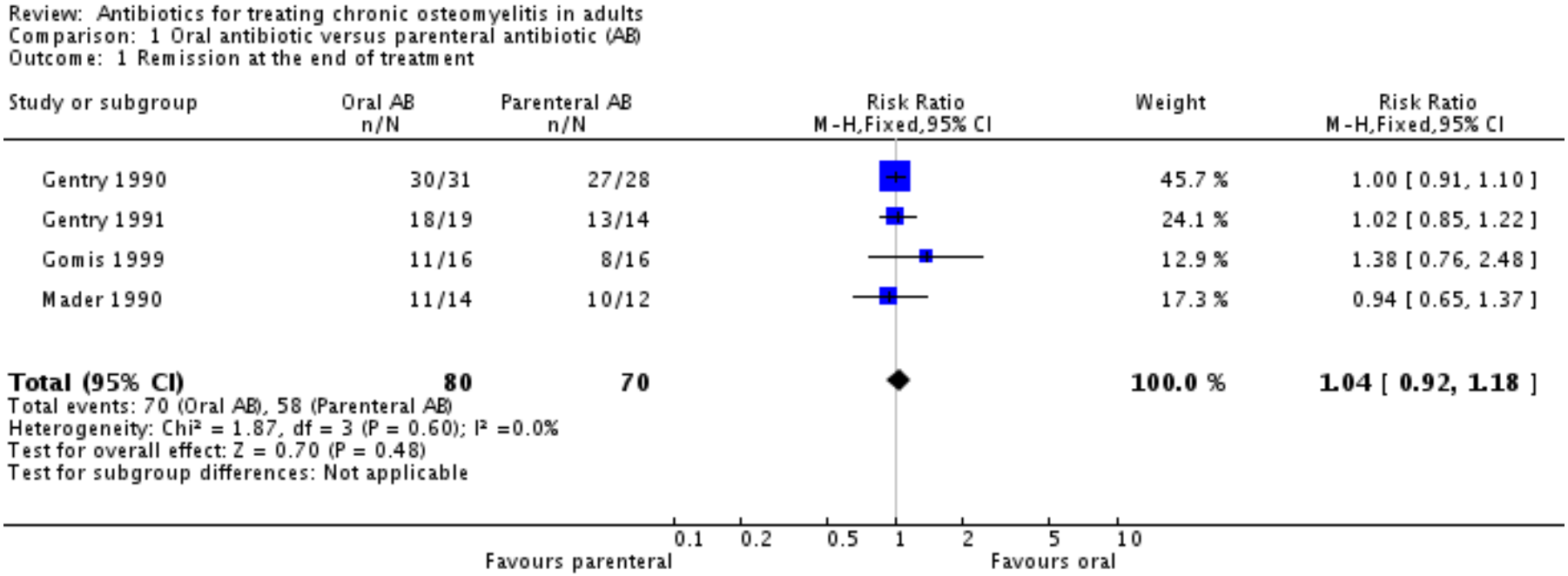
Barr DA et al EJCMID 2012;31:2611. Upton A et al NZMJ 2004;117:U1020.
Fisher DA et al IJAA 2006;28:545, Esposito S et al J Chemother 2007;19:417. Matthews PC et al JAC 2007;60:356

Reasons for admission from OPAT



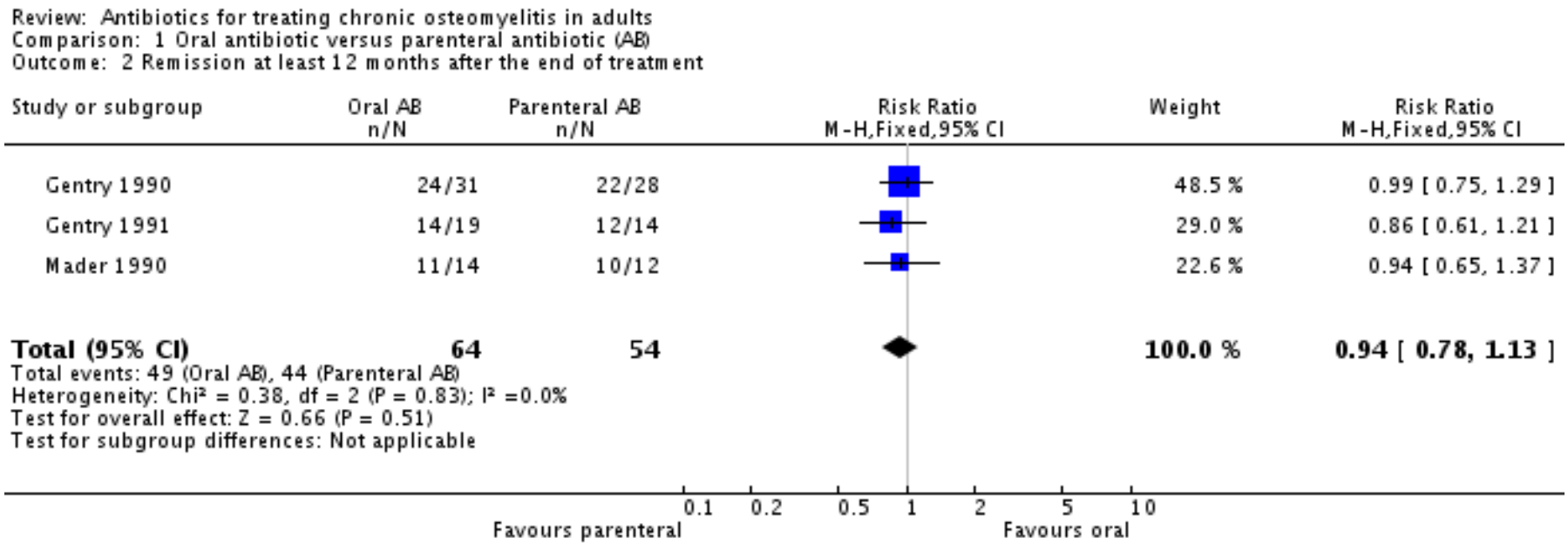
Oral Antibiotic Therapy

Comparison of IV s Oral Rx: End of Rx



Conterno, Turchi, Cochrane review Sep 2013

Comparison of IV s Oral Rx: ≥ 12 months post Rx



Conterno, Turchi, Cochrane review Sep 2013

Quinolones

- Cipro most studies but extrapolate for Levofloxacin
- High oral bioavailability
- Penetrates macrophages and neutrophils
- High bone: serum concentration (>7.3)
- Bone concentration is proportional to dose and in excess of MIC of sensitive organisms.
  - [Bone] 2-10 ug/g
- Effective vs MSSA, CNS, GNB
- In G+ve infection advisable to use 2nd agent to reduce R risk
- Beware QTc prolongation, drug interactions

Rifampicin

- High oral bioavailability
- Penetrates neutrophils
- Excellent bone penetration (1.7ug/g)
- Active in biofilm ++
- Synergistic with other agents
- R develops quickly ++
- Use only in combination (consider delay in administration)
- Drug interactions, LFTs

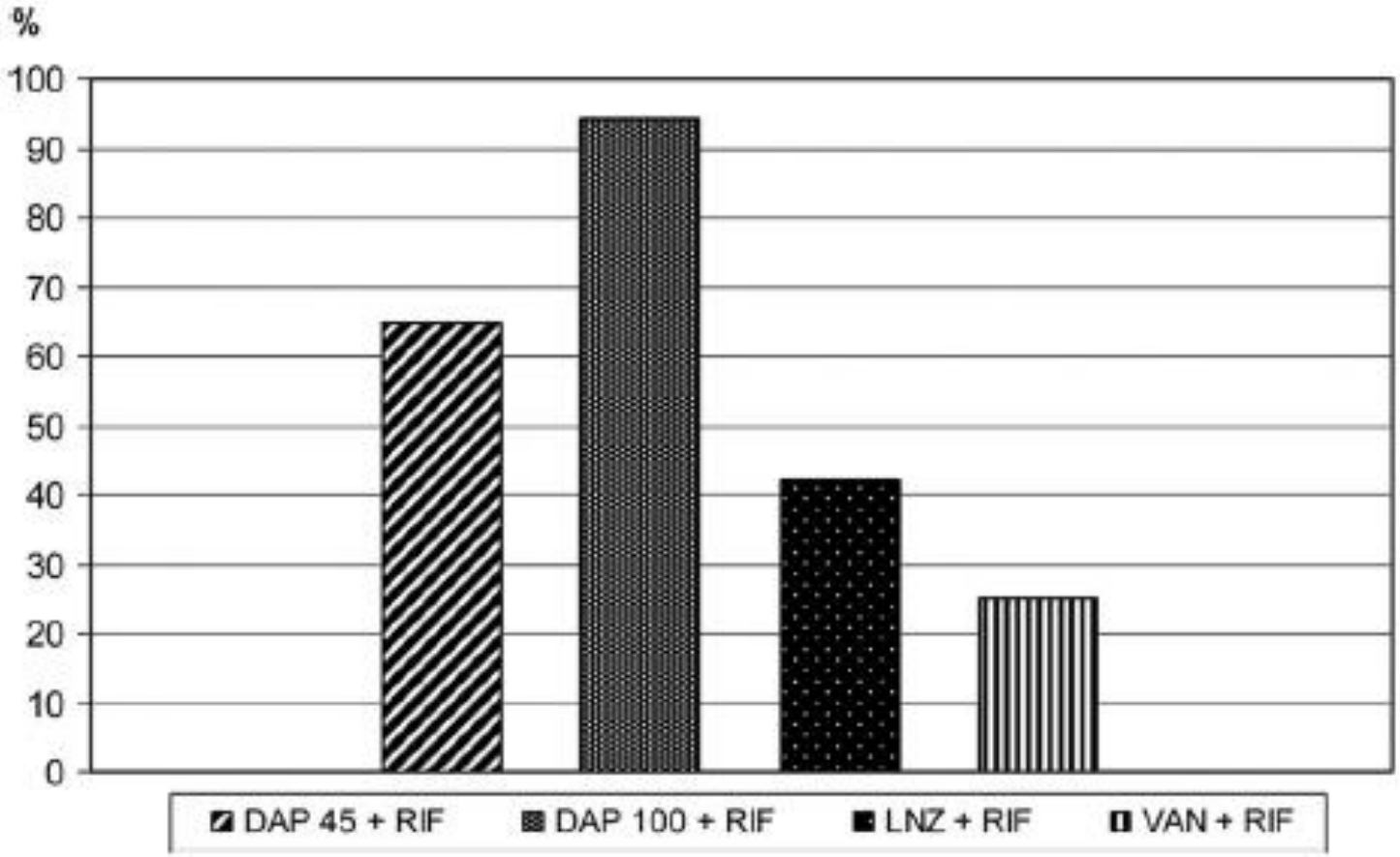


FIG. 2. Cure rates of infection for antibiotic combinations with rifampin at day 11. Data for antibiotics alone are not shown. LNZ, linezolid; VAN, vancomycin; RIF, rifampin; DAP45, daptomycin at 45 mg/kg/day; DAP100, daptomycin at 100 mg/kg/day.

Garirgos et al, AAC, 2010: 54; 5241

Other Oral Antibiotics useful in PJI

- Sodium fusidate: caution statins, LFTs
- Trimethoprim: caution CKD, K+
- Doxycycline: chelated by Fe, Ca, ant acids
- Clindamycin: CDI, LFTs
- Linezolid: Haem toxicity, neuropathy. Caution with RIF, other D-DIs
- Pristinamycin (unlicensed)

Table 2. Percentage penetration of linezolid in osteo-articular tissue and fluid for corresponding serum concentration

	SF (%)	Synovium (%)	Muscle (%)	Bone (%)
Case 1	84.4	48.4	64.5	17.7
Case 2	133.7	107.9	161.8	97.8
Case 3	70.1	49.8	65.3	15.5
Case 4	107.3	98.9	82.1	43.6
Case 5	93.2	102.8	104	43
Case 6	125.3	121.1	59.6	47
Case 7	64.5	62.7	70.5	24.9
Case 8	88	94.3	100	52.8
Case 9	85.8	92.7	81.8	37.1
Case 10	66.4	43	45.1	22
Mean	91.9	82.2	83.5	40.1
±S.D.	23.8	28.4	32.9	24.1

Journal of Antimicrobial Chemotherapy (2002) **50**, 747–750
DOI: 10.1093/jac/dkf207

IDSA PJI Guidelines

Procedure	Organism	IV Antibiotic		Duration
DAIR	Staph	Flucloxacillin Ceftriaxone Or Vancomycin Daptomycin Linezolid (IV/PO)	With Rifampicin	2-6 weeks then oral combination Rx including RIF Total 3 months: THR, other 6 months: TKR
DAIR	Other	Pathogen specific IV or highly bio available oral combination		4-6 weeks then potentially indefinite suppressive Rx (?avoid RIF)
Amputation	Any	Pathogen specific IV or highly bio available oral combination		24-48 hrs post amputation unless sepsis 4-6 weeks if residual infection

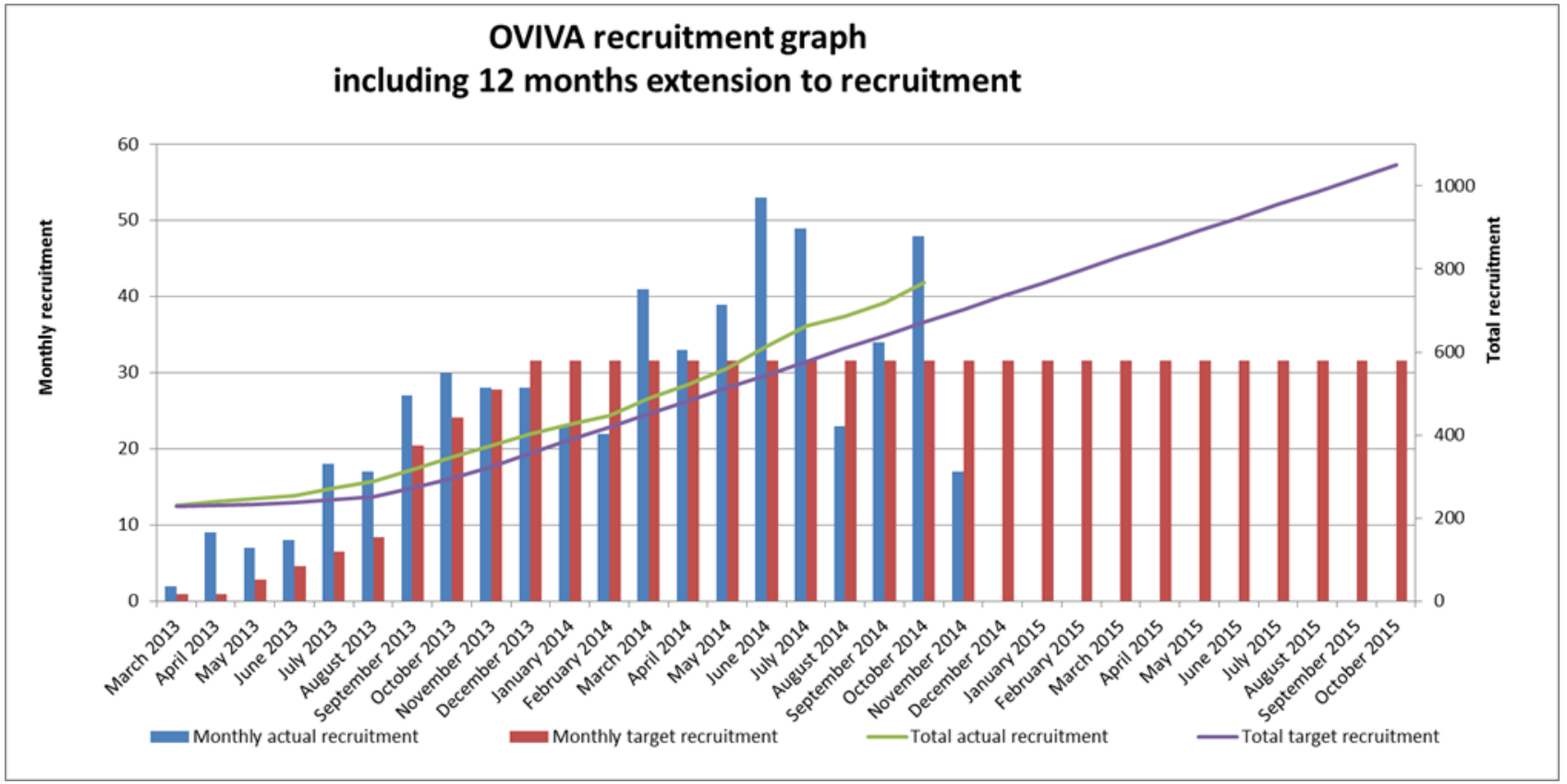
Osman et al CID 2013; 56: 1

IDSA PJI Guidelines

Procedure	Organism	IV Antibiotic		Duration
One Stage Revision	Staph	Flucloxacillin Ceftriaxone Or Vancomycin Daptomycin Linezolid (PO)	With Rifampicin	2-6 weeks then oral Rx Total 3 months: Rif + other Longer if required
One Stage Revision	Other	Pathogen specific IV or highly bio available oral combination		4-6 weeks then potentially indefinite suppressive Rx (?avoid RIF)
Resection arthroplasty / 1st of 2 stage revision	Any	Pathogen specific IV (without Rifampicin) or highly bio available oral combination		4-6 weeks then stop
				Osman et al CID 2013; 56: 1

OVIVA study

- Comparing IV vs oral approach in OM (including PJI) 6/52 Rx
- Randomisation within 7 days of surgery or commencement of IV Abx



Conclusions

- Use a best guess/tailored IV antibiotic which will cover the likely/proven organisms
  - Empirical and acute settings
- Use high dose therapy for optimum PK/PD
- Combine with Rifampicin if Staphylococcal infection and the aim is “cure” (timing)
- Duration dependent on surgery and availability of highly orally bio-available agents
  - Resistance
  - Drug interactions (including QTc)
- OPAT use is safe: Follow Good Practice Recommendations for OPAT
- IV Beta lactams probably more effective than GPs
- “Equipoise” in IV vs oral for longer term Rx

New Developments

OPAT trends over 10 yrs in NHS GGC

	Trend over time		
Referral from non-local hospital	↑	X^2_{trend} = 72.92	p < 0.0001
Referral from secondary care	↑	X^2_{trend} = 26.07	p < 0.0001
Co-morbidity	↑	X^2_{trend} = 24.07	p < 0.0001
Non-SSTI infection	↑	X^2_{trend} = 97.14	p < 0.0001
MRSA infections (as % of *S. aureus*)	↓	X^2_{trend} = 6.682	p = 0.0097
G-ve infections (% of +ve cultures)	↑	X^2_{trend} = 10.491	p = 0.0012
Self / carer antibiotic admin	↑	X^2_{trend} = 48.49	p < 0.0001

Barr et al, IJAA 2012

ESBL Resistant E. coli Implant infections

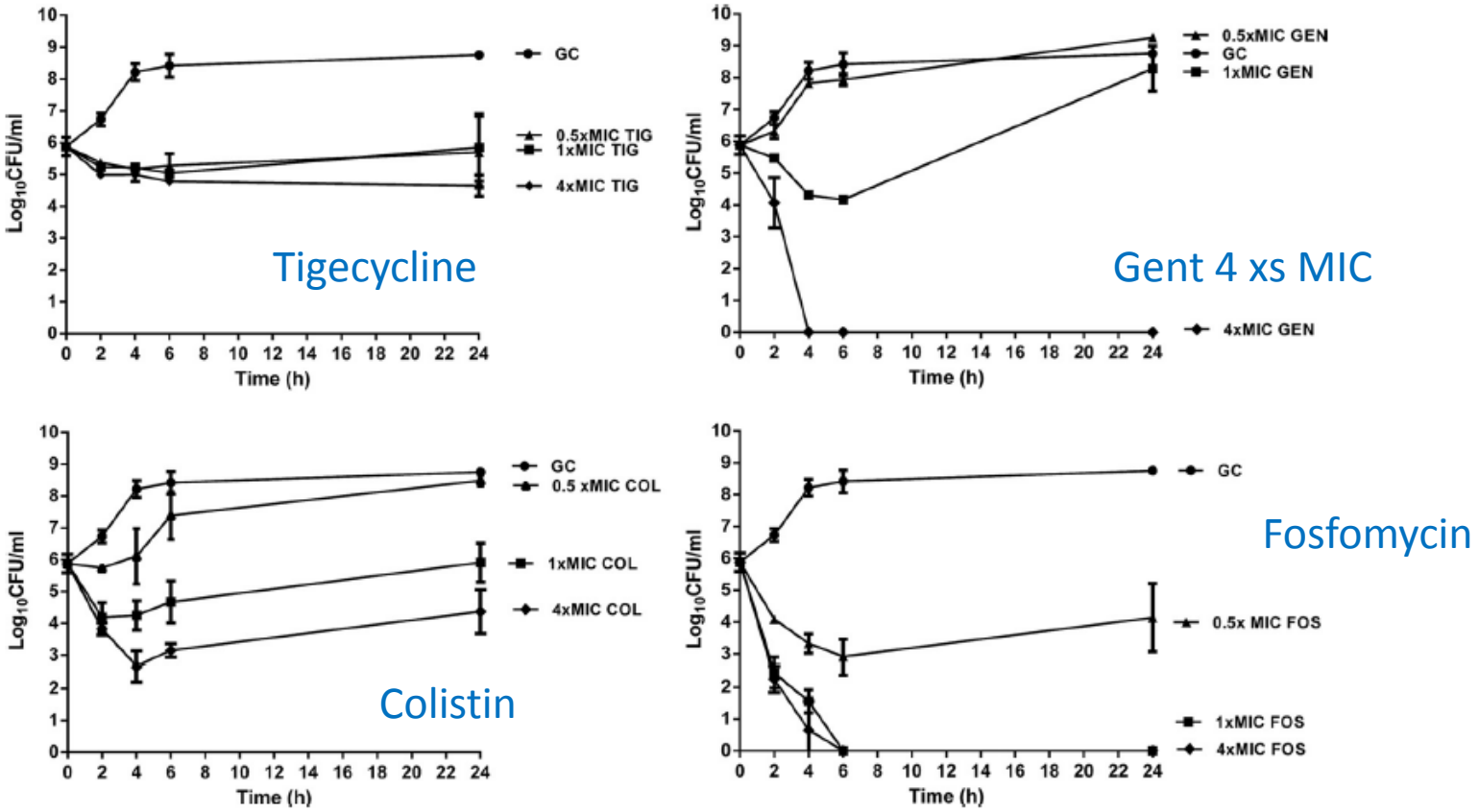


FIG 1 Time-kill curves with 0.5, 1, and 4× the MIC of tigecycline (TIG), colistin (COL), fosfomycin (FOS), and gentamicin (GEN) against *E. coli* in log growth phase (inoculum, 10^6 CFU/ml). Values are means ± SD. The experiments were performed in triplicate. GC, growth control.

Corvec et al, AAC, 2013; 57: 1421

Synergy between Fosfomycin and Colistin

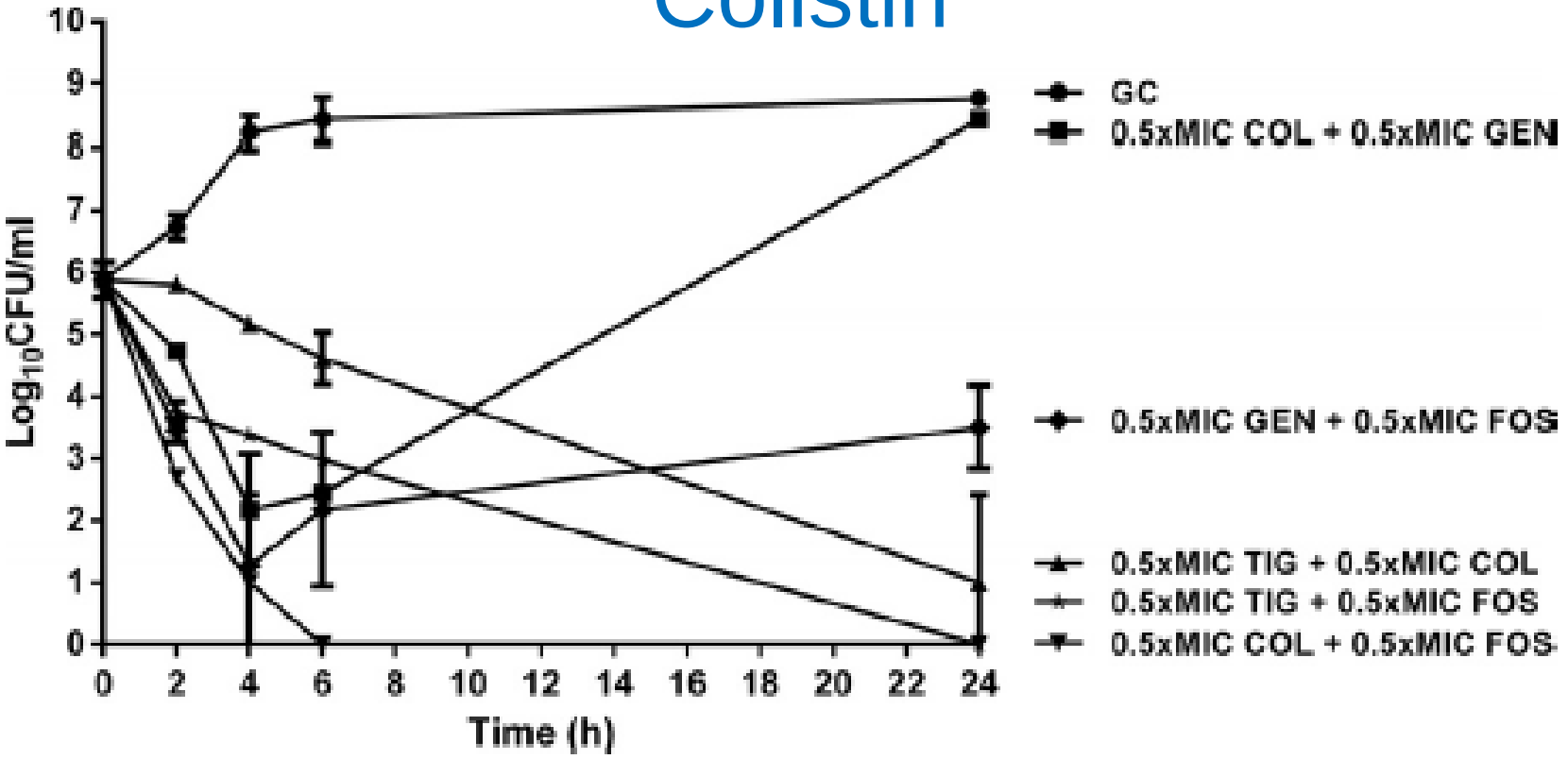


FIG 2 Time-kill curves with 0.5× the MIC of tigecycline (TIG), colistin (COL), fosfomycin (FOS), and gentamicin (GEN) in combinations against *E. coli* in log growth phase (inoculum, 10^6 CFU/ml). Values are means ± SD. The experiments were performed in triplicate. GC, growth control.

Corvec et al, AAC, 2013; 57: 1421

Growth during Rx and 5 days post Rx

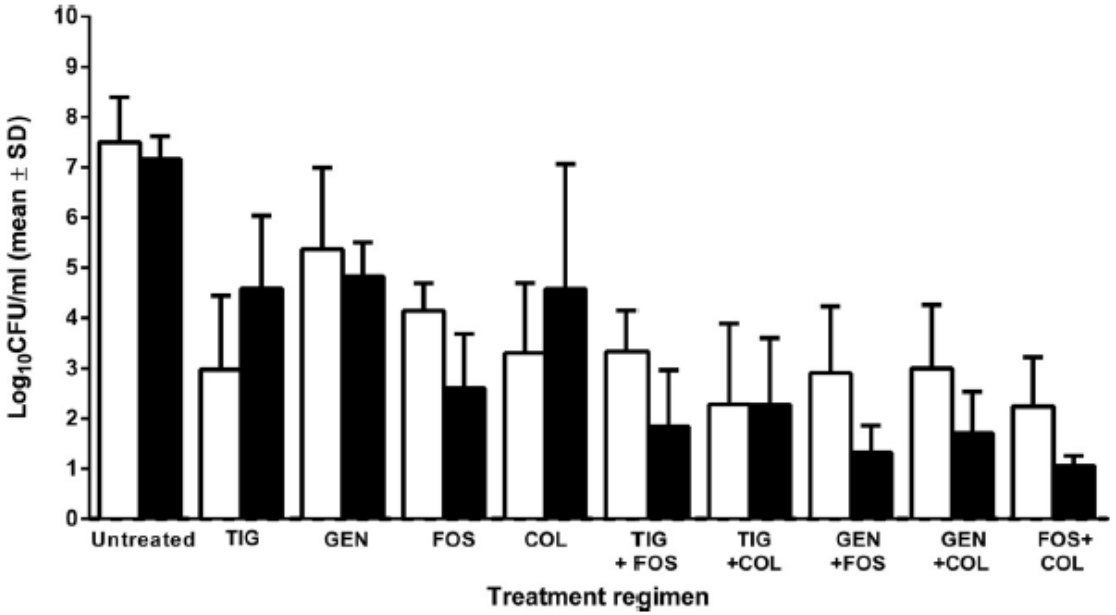


FIG 3 Activities against planktonic bacteria in cage fluid aspirated during treatment (i.e., day 5; open bars) and 5 days after end of treatment (i.e., day 10; closed bars). In each group, fluid from 12 cages (from 3 animals) was investigated. The *y* axis shows $\log_{10}$ CFU/ml in aspirated cage fluid, expressed as means ± standard deviations (SD).

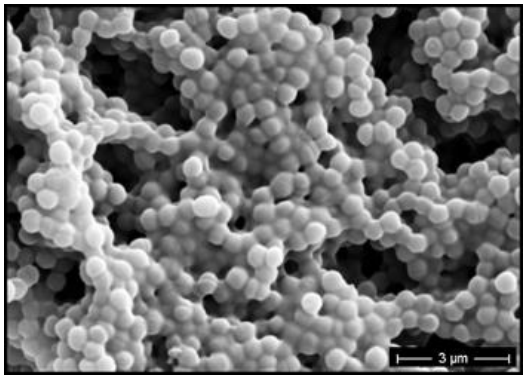
Corvec et al, AAC, 2013; 57: 1421

Background

- c.180 K TKR or THRs / year in UK
  - 14 K in Scotland (2013)
- c. 0.5-5% of all joint replacements Hip > knee
- Diagnosis
  - Acute post-op vs Acute infection of established prosthesis: Heat, erythema, pain, swelling +/-wound
  - Sub-acute: pain and radiological loosening
- Multiple tissue sampling w/o contamination
  - Sonication (when available)
  - Microbiological (PCR when available)
  - Histological

Common organisms

- *Staph.aureus* inc MRSA (40.6%)
- Coagulase negative staphylococci (15.9%)
- Coliforms (15.6%)
- Enterococci (9.6%)
- Streptococci
- Diphtheroids
- Pseudomonas
- Anaerobes
- Polymicrobial



(Fifth Report of the Mandatory Surveillance of Surgical Site Infection in Orthopaedic Surgery)

Decline in inpatient SSI in TKR and TKR in Scotland

FIGURE 5: Trends in the annual inpatient incidence of SSI in hip arthroplasty procedures with upper and lower 95% confidence intervals, 2003 to 2013

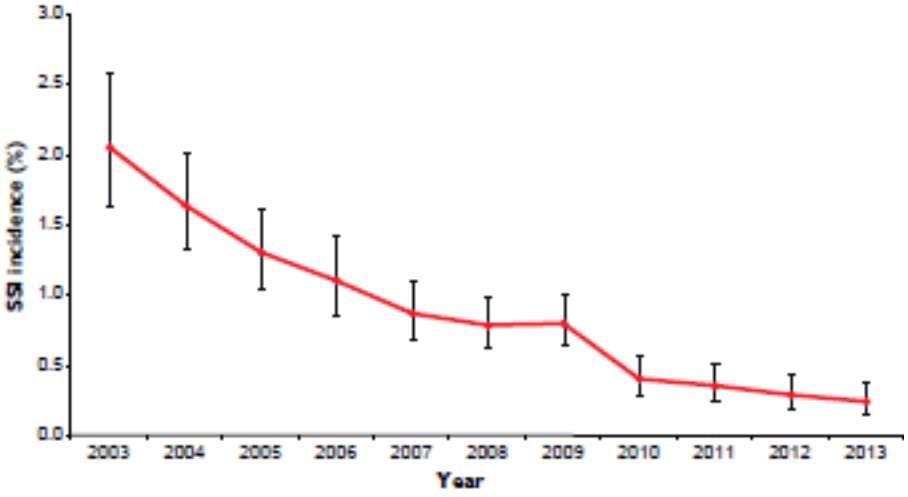


FIGURE 6: Trends in the annual inpatient incidence of SSI in knee arthroplasty procedures with upper and lower 95% confidence intervals, 2003 to 2013

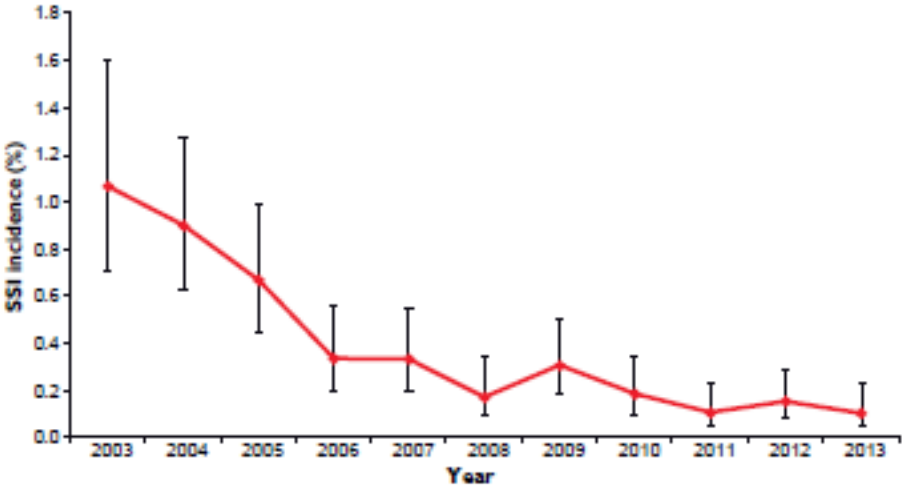
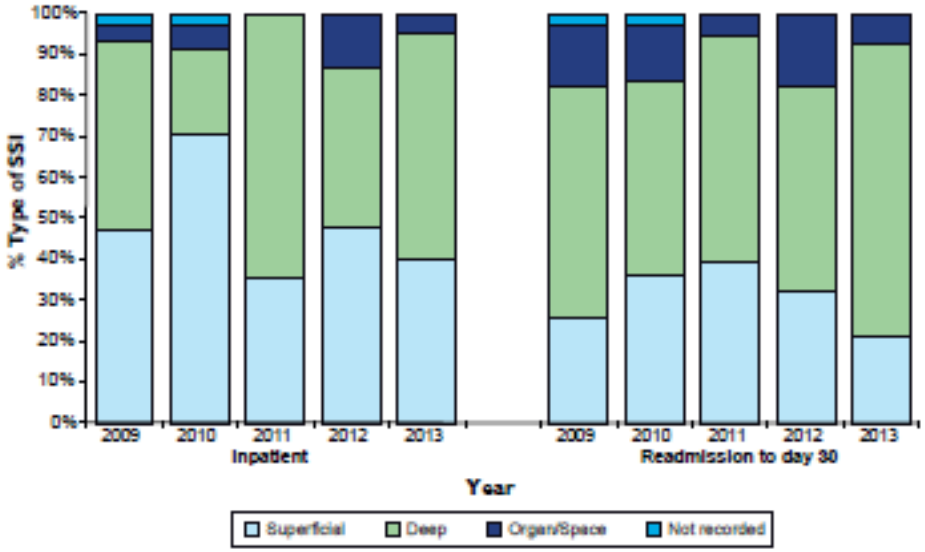


FIGURE 10: Proportion of SSI involving superficial or deep or organ space infections, for hip arthroplasty procedures (inpatient and readmission to day 30), 2009 to 2013



Hip arthroplasty enhanced SSI surveillance:
0.76% by day 30
Majority are deep seated SSI

SSHAIP, HPS, 2014

Fosfomycin + Colistin: Cure in biofilm

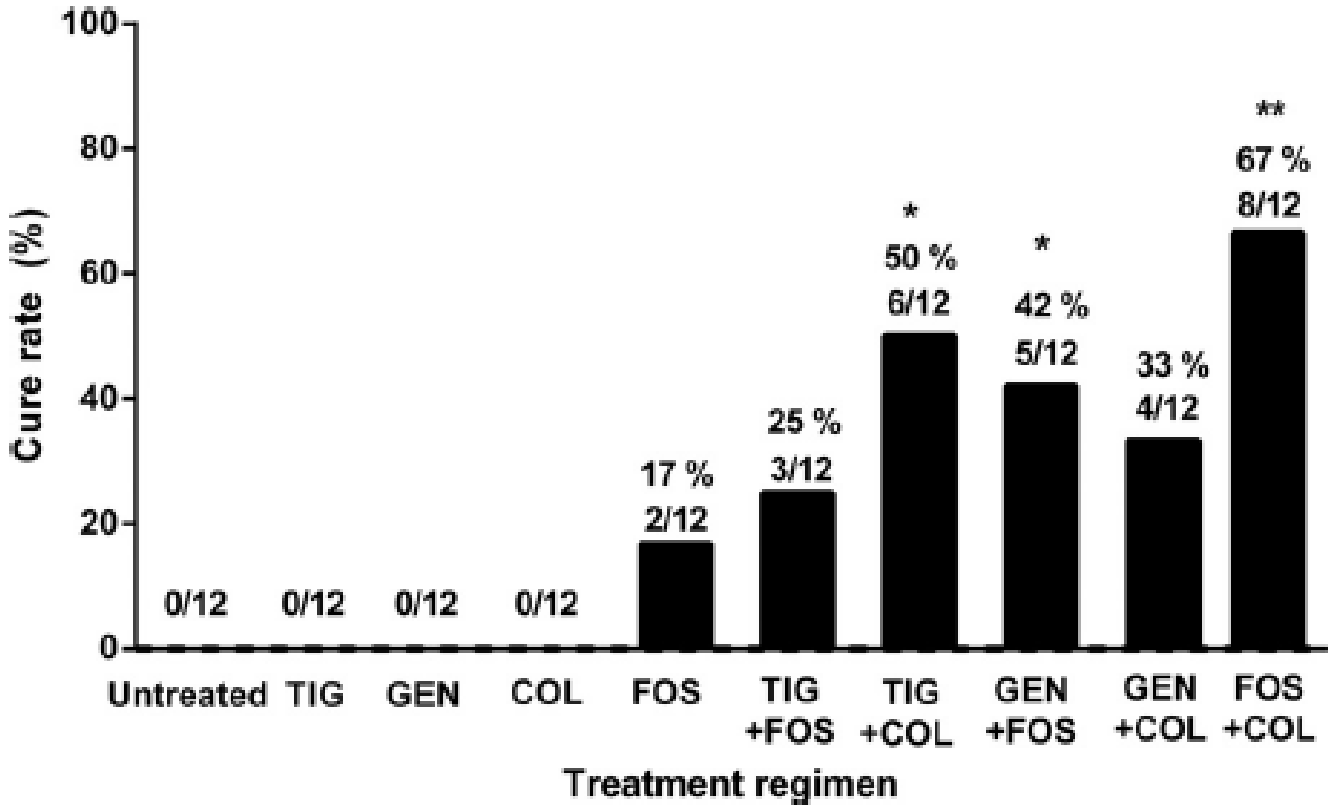


FIG 4 Rate of cure of cage-associated infection. The values are numbers of cage cultures without growth of *E. coli* divided by the total number of cages in the treatment group ($n = 12$). Significant differences compared to untreated controls are indicated with asterisks (*, $P < 0.05$; **, $P < 0.01$).

Corvec et al, AAC, 2013; 57: 1421

Pharmacokinetic parameters of daptomycin at steady-state (Day 4 or 5) from 9 patients with diabetic foot infections treated with 6 mg/kg daptomycin

	Cmax (mg/l)	**Half life (h)**	**AUC_{0-24}***
Plasma	72.9	10.05	619.30
Subcutis inflamed	4.0	10.98	54.47
Metatarsal bone	4.7	10.72	60.24

* Steady state concentrations at baseline were used for concentrations at 24 hours

•The EUCAST breakpoint for staphylococci is 1 mg/L