

Key Challenges of IV to Oral Switch & use of oral agents in OPAT

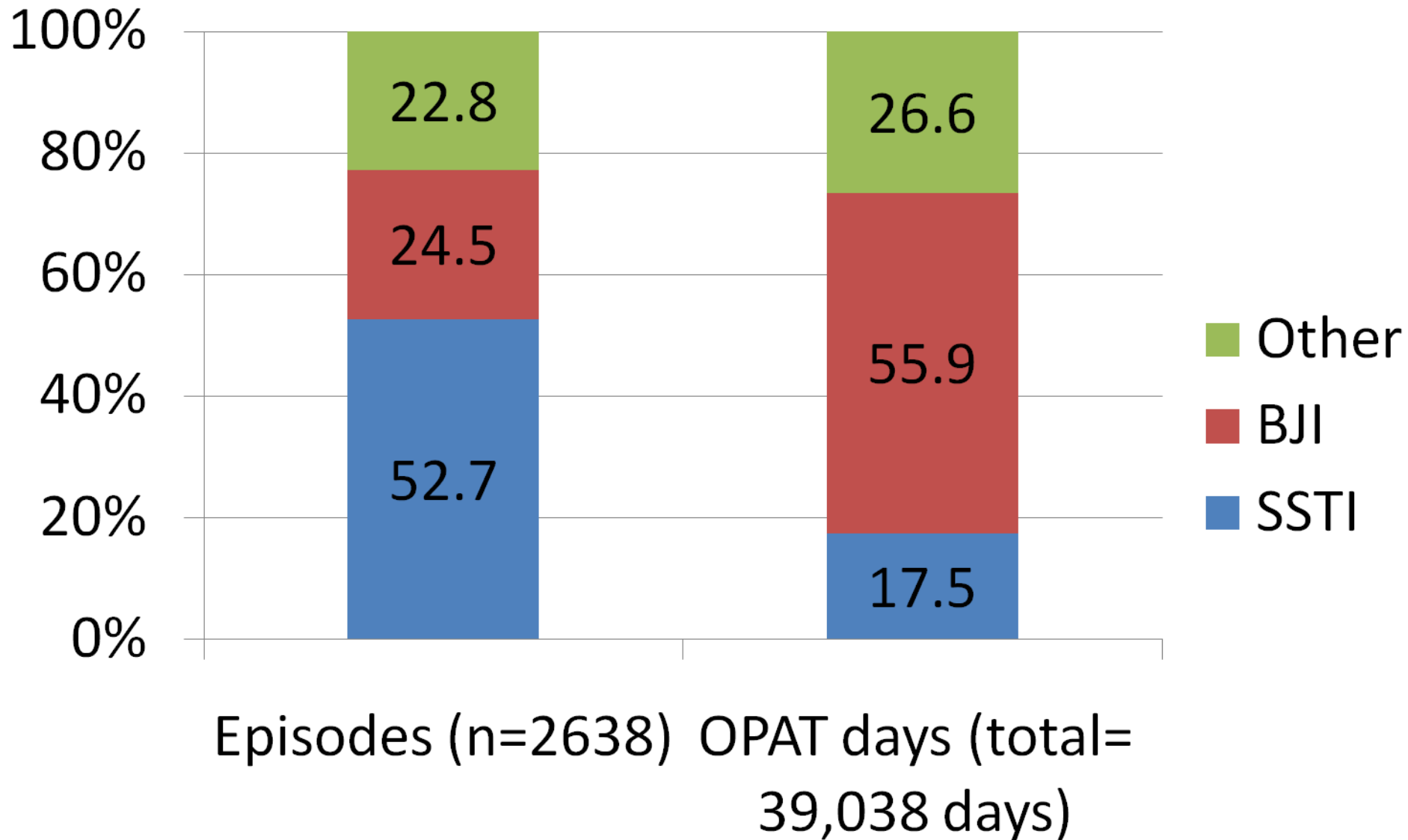
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Declarations of interest

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

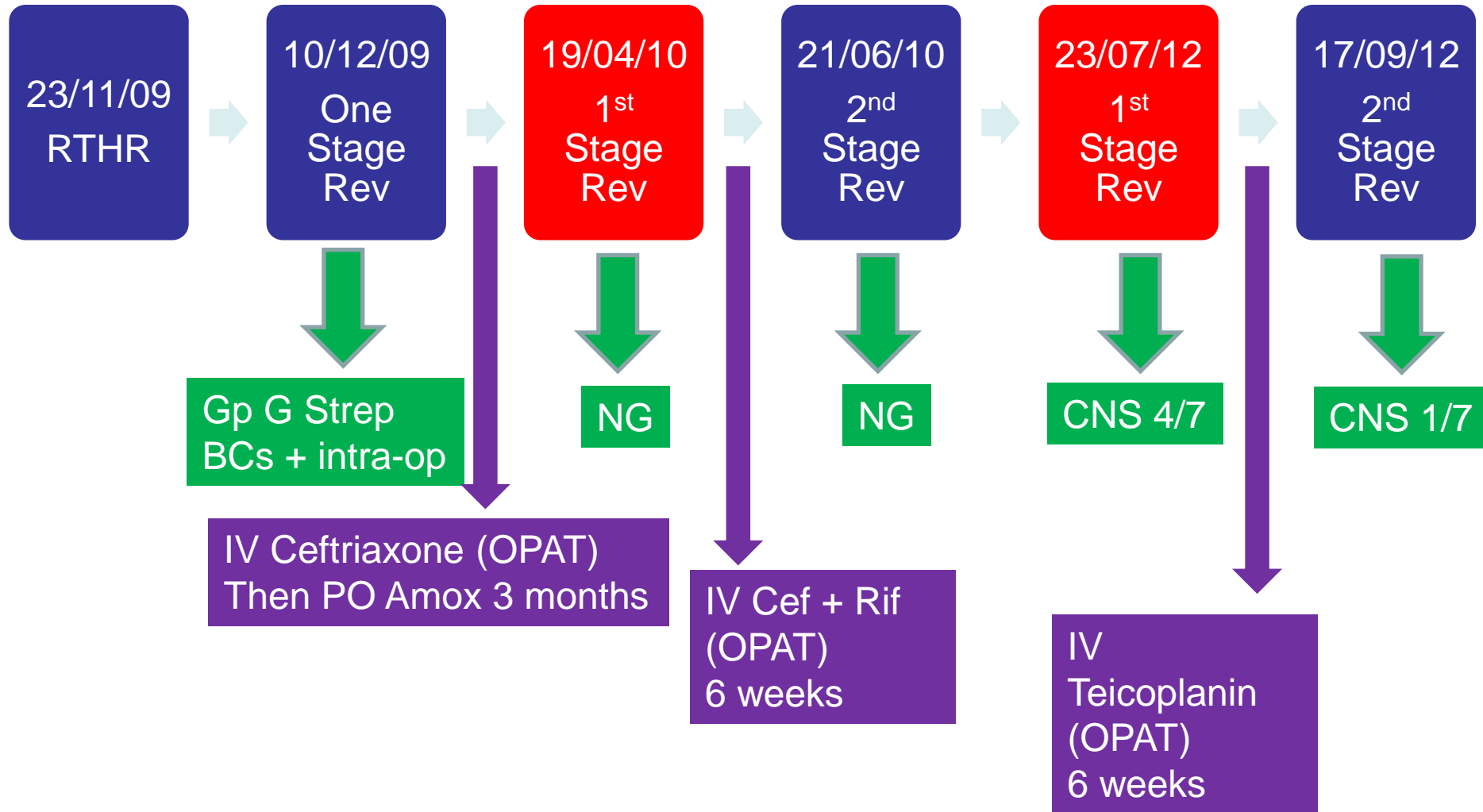
Key Patient Populations within OPAT



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

Complex Orthopaedic History



1st Stage Rev 26/01/15

(5th THR)

- GBS (7 samples)
 - **Sensitive:** Penicillin, Vancomycin, Teicoplanin, Ceftriaxone and Linezolid
 - **Resistant:** Doxycycline, Clindamycin, Levofloxacin
- Antibiotic Rx: Benzyl Penicillin
 - Then what?

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

“Current Practice”

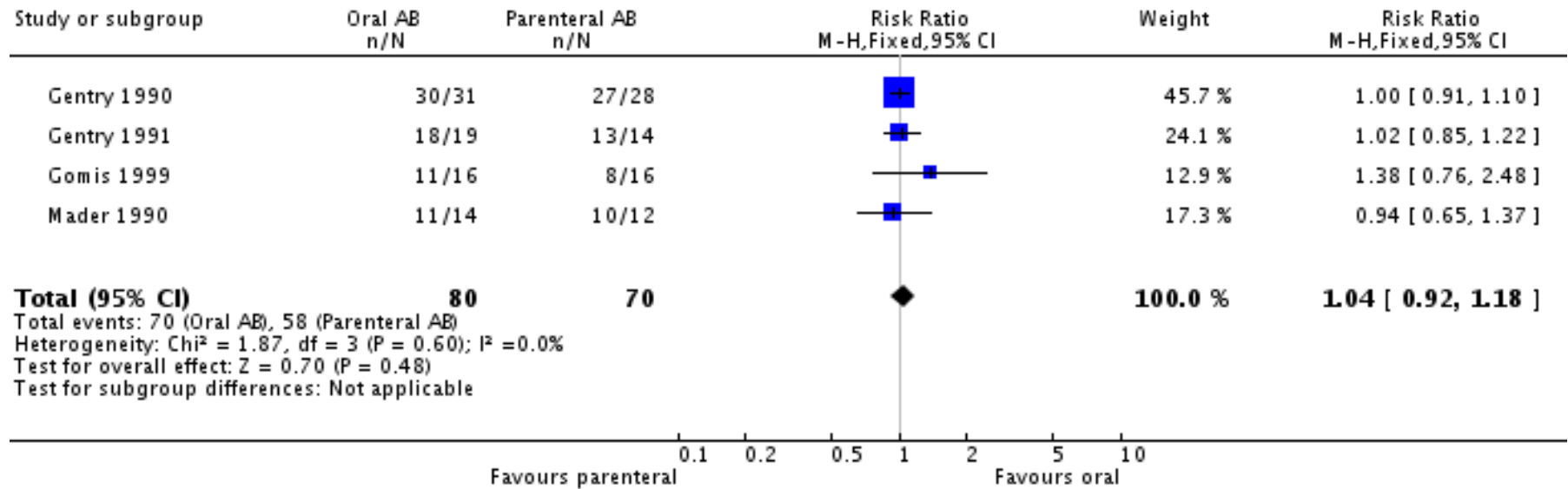
“Osteomyelitis is rarely controlled without the combination of careful, complete surgical debridement and **prolonged parenteral antibiotic therapy at high dosage**”

Waldvogel et al

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

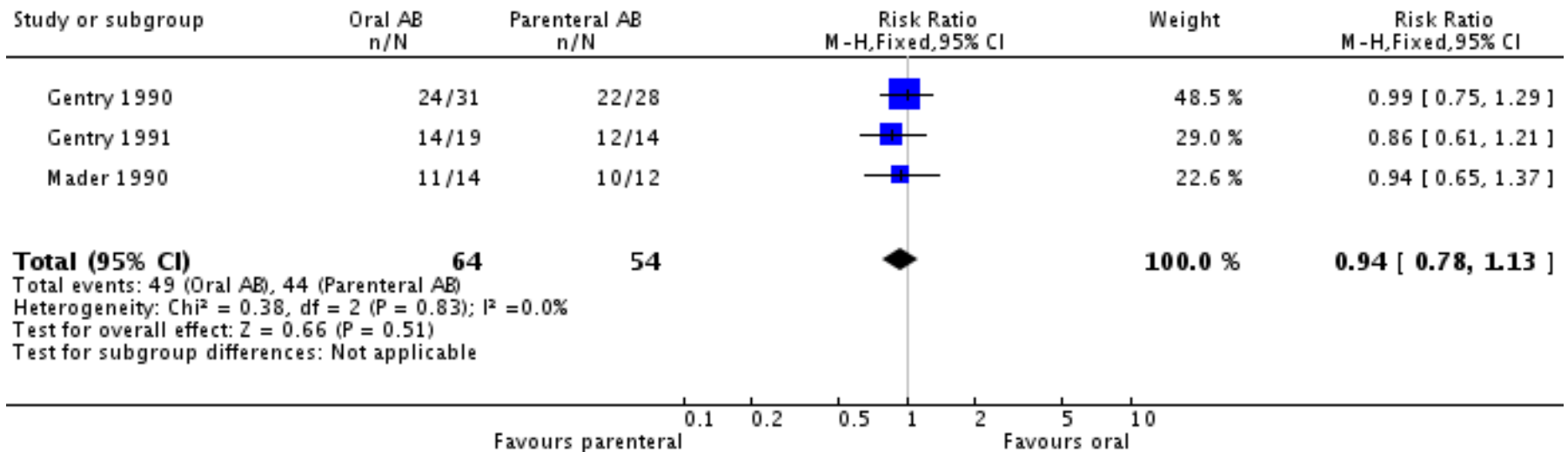
Comparison of IV s Oral Rx: End of Rx

Review: Antibiotics for treating chronic osteomyelitis in adults
 Comparison: 1 Oral antibiotic versus parenteral antibiotic (AB)
 Outcome: 1 Remission at the end of treatment



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

Review: Antibiotics for treating chronic osteomyelitis in adults
 Comparison: 1 Oral antibiotic versus parenteral antibiotic (AB)
 Outcome: 2 Remission at least 12 months after the end of treatment



When may it be appropriate to IVOST in BJI?

- Clinical
 - No sepsis (resolved)
 - Surgical control
 - No acute SSTI
 - No *S. aureus* bacteraemia
 - Oral route not compromised
 - No malabsorption
- Appropriate agent available

Antibiotic considerations

- Activity vs organism
- Penetration to site of infection
- (Activity in biofilm)
- Drug-Drug-Host interactions
- Side effects

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

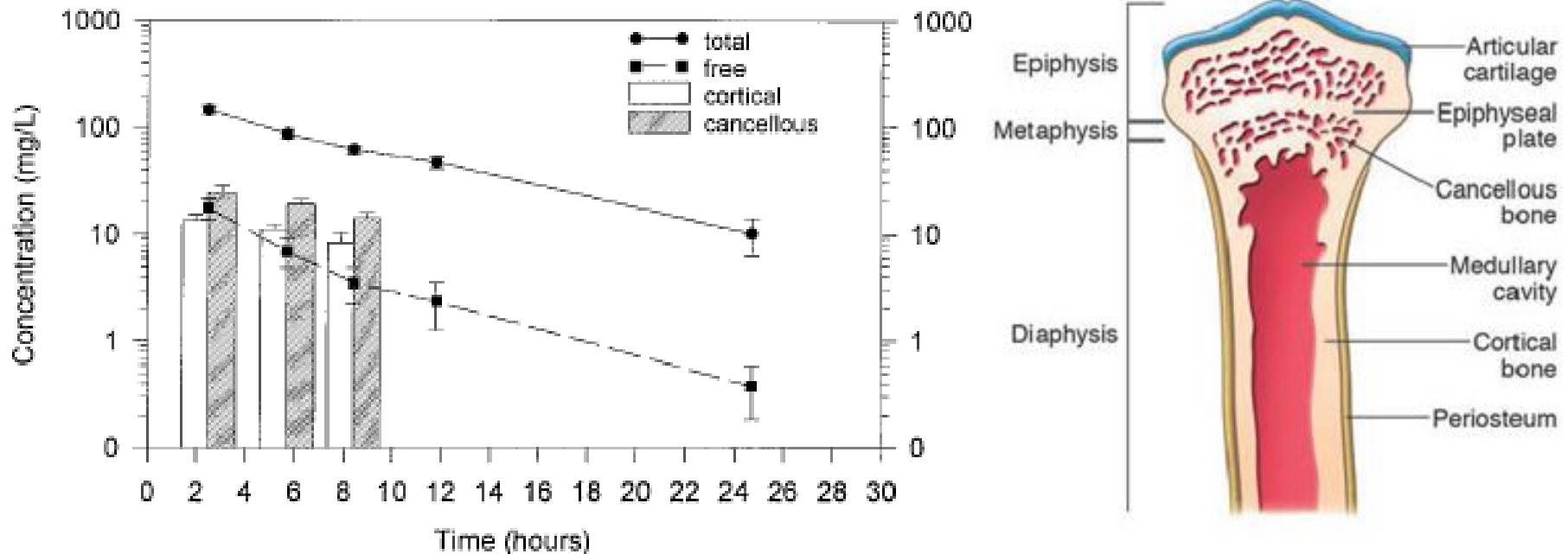


FIG. 2. Mean concentrations of ceftriaxone in serum (total and free levels) and in cancellous and cortical bone.

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

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- Alternative oral switch options following IV Rx?
 - Linezolid?

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

Linezolid

- Excellent bone penetration
- Prolonged use associated with
 - Thrombocytopenia
 - Anaemia
 - Peripheral neuropathy
- Careful monitoring required
- MAO-A inhibitor

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.

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- GBS (7 samples)
 - **Sensitive:** Penicillin, Vancomycin, Teicoplanin, Ceftriaxone and Linezolid
 - **Resistant:** Doxycycline, Clindamycin, Levofloxacin
- No alternative oral switch options following IV Rx
- **Conclusion:** Prolonged IV Rx justified (Ben Pen, Ceftriaxone, Teicoplanin, Daptomycin)

When is it appropriate to IVOST in BJI?

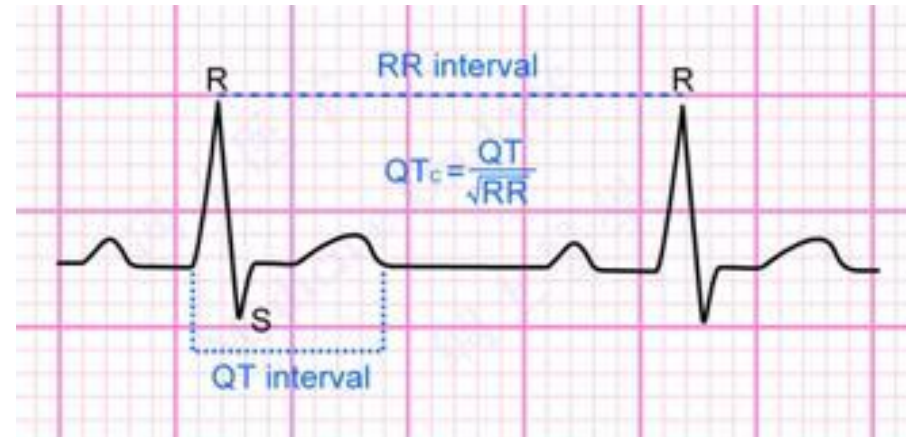
- Clinical
 - No sepsis (resolved)
 - Surgical control
 - No acute SSTI
 - No *S. aureus* bacteraemia
 - Oral route not compromised
 - No malabsorption
- **Appropriate agent available**

Quinolones

- Cipro most studied but extrapolate for Levofloxacin
- High (100%) 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

Quinolones

- In G+ve infection advisable to use 2nd agent to reduce R risk
- Beware QTc prolongation, drug interactions
 - Amitriptyline, Citalopram
- If RFs for QTc prolongation repeat ECG @ steady state



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)
- CYP3A4 inhibition: Drug interactions (timing)
- LFTs

Other Oral Antibiotics useful in BJI

- 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)

Oral Switch Options in BJI

	Considerations	MSSA	MRSA	CNS	BHS	GNB
Ciprofloxacin	QTc, D-Dis	+	-	+	-	+
Clindamycin	CDI	+	+/-	+/-	+	-
Doxycycline	Chelators	+	+/-	+	+	-
Fusidate	Myotox, LFTS, Statins	+	+/-	+	-	-
Levofloxacin	QTc, D-Dis	+	-	+	+	+
Linezolid	Toxicity, D-Dis	+	+	+	+	-
Pristinamycin	Nausea, D-Dis	+	+	+	+	-
Rifampicin	D-DIs, LFTs	+	+	+	-	-
Trimethoprim	AKI, K+	+	+/-	+	-	+/-

Skin and Soft Tissue Infection

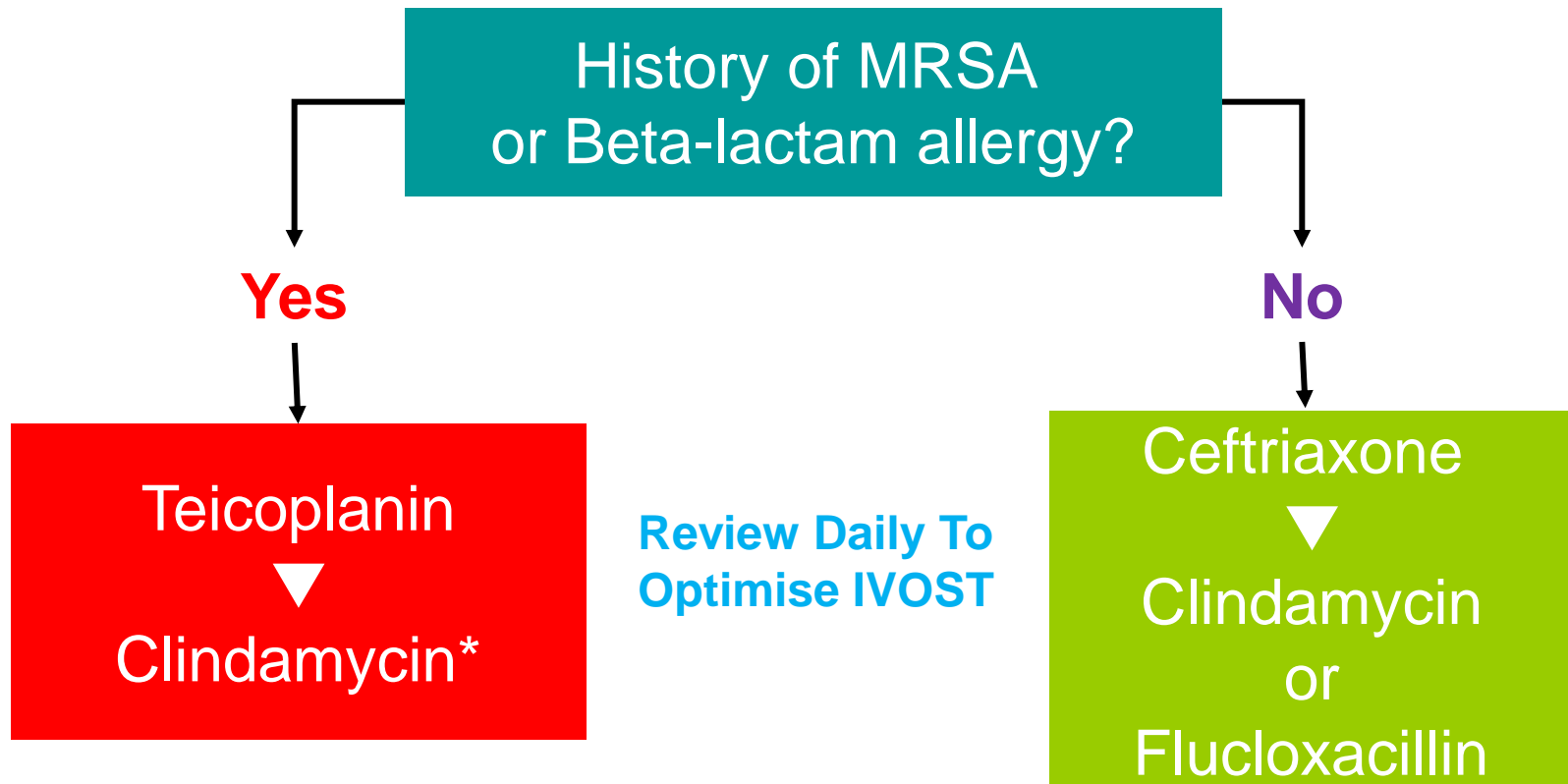


Good Practice Recommendations

- **SSTI should be reviewed daily** by the OPAT team to optimize speed of intravenous to oral switch.

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OPAT Patient Group Direction for SSTIs: empiric antibiotic Rx



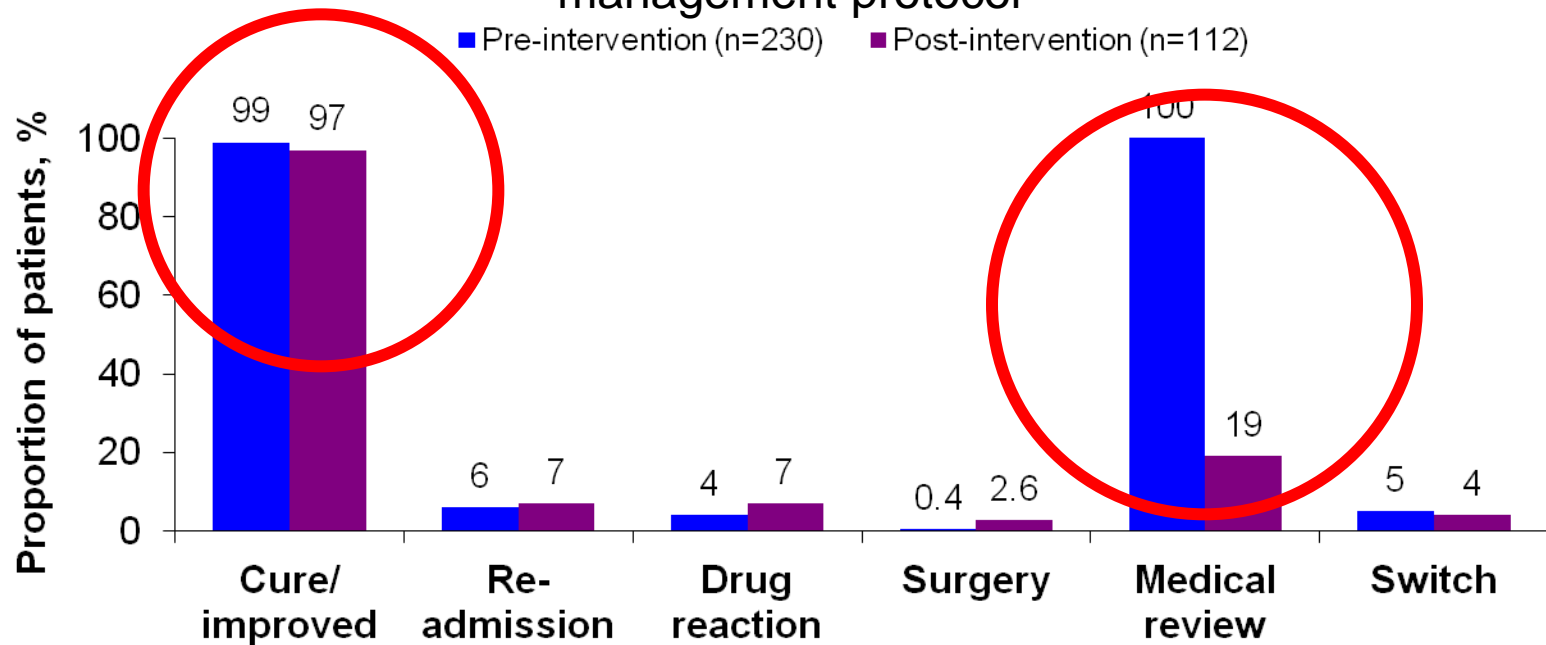
*If Beta-lactam allergy or sensitive MRSA

IVOST criteria for SSTI in OPAT

- Regression of infection
 - Reduction in heat, erythema, induration, extent
- No SIRS
- Oral route not compromised
- No malabsorption
- CRP should not determine IVOST

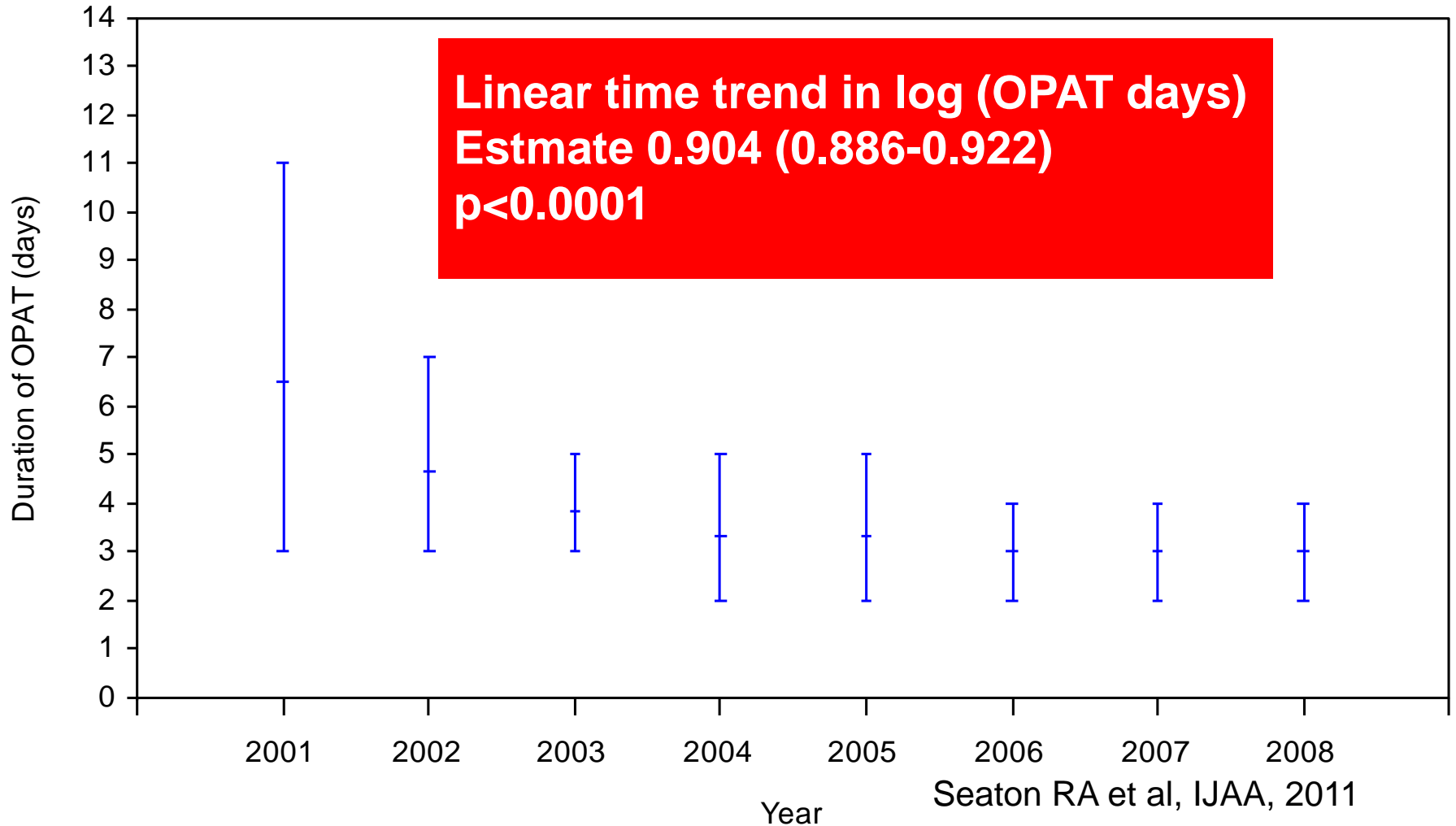
Nurse-led Mx for OPAT SSTIs

Comparison of patients pre- and post-introduction of a nurse-led management protocol

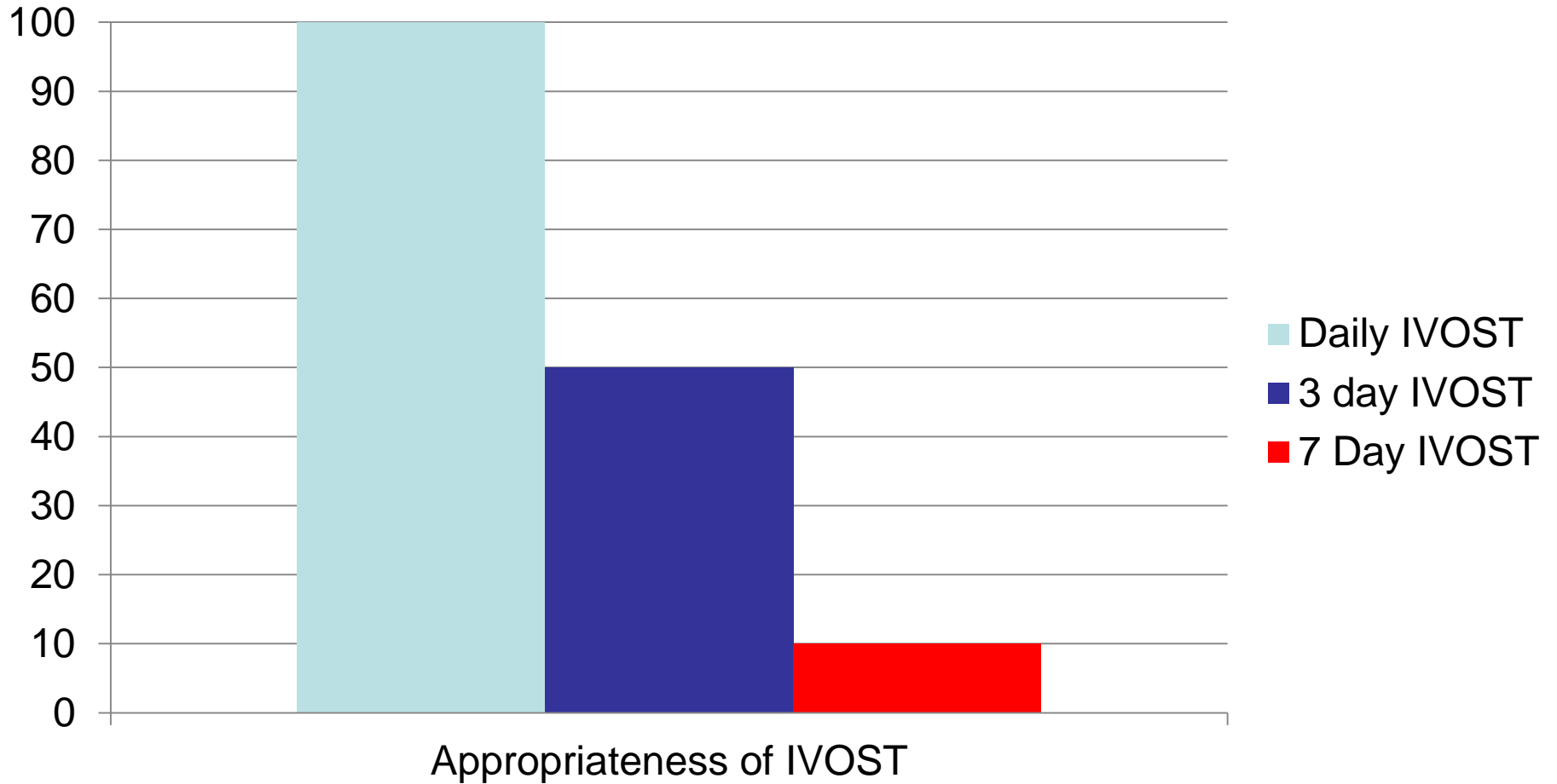


- Protocol management was associated with reduced duration of outpatient i.v. therapy (from 4 to 3 days, $P=0.02$)

SSTI: Median duration of OPAT (days)



Appropriateness of Timing of IVOST for SSTI in OPAT



Summary and Conclusions

- IVOST in BJI in OPAT is possible if:
 - Post acute setting (Sepsis, surgical etc.)
 - Agent with good penetration to site of infection is selected and is available:
 - Sensitive organism/ Lack of D-DIs/
Manageable toxicity profile
- IVOST in SSTI in OPAT
 - Review daily not at 3 or 7 days

Acknowledgements

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