

# Sequential Intravenous High Dose Oral Antibiotics in the Treatment of Osteomyelitis in Children – A Randomised Controlled Trial

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## Background

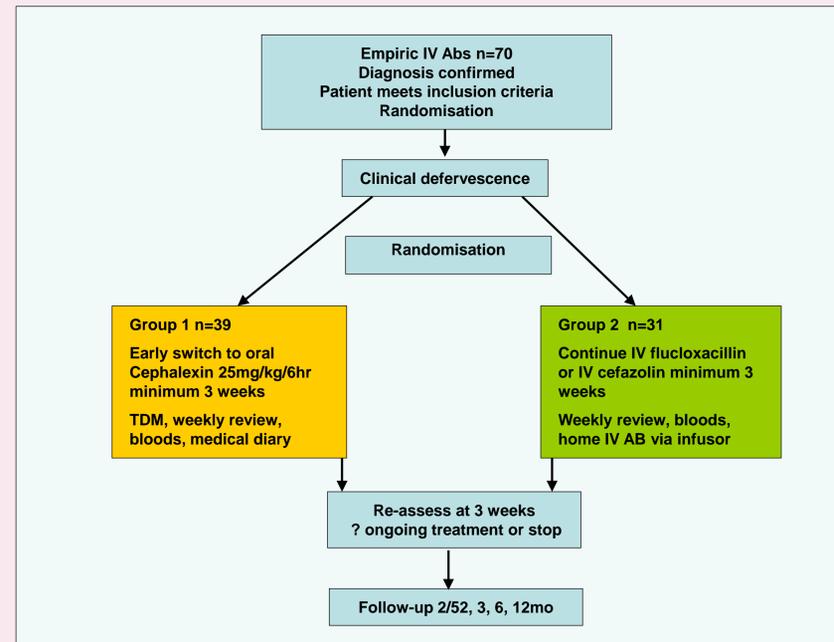
- Children in New Zealand have a high burden of acute osteomyelitis (OM).<sup>1</sup> Prolonged intravenous (IV) antibiotics is an effective treatment, however is associated with treatment related complications.
- Literature produced from systematic review and clinical trials indicate an early switch from IV to oral antibiotics may be feasible in treating osteoarticular infections in children, however, safety and efficacy of this modality have not been examined in a randomised controlled trial in this population.<sup>2,3,4</sup>

## Objectives

- To demonstrate in children with osteoarticular infection, sequential treatment with a short course of IV antibiotics followed by oral antibiotics can reduce the risk of adverse events, and reduce costs associated with treatment.
- To compare duration of hospitalisation and antibiotics from clinical defervescence between IV and sequential IV oral treatment.
- To document adverse events and adherence to treatment and assess infection recurrence rate 12 months from treatment.

## Methods

- Population:** From 2009 to 2015, 70 patients from Starship Children's Hospital and Kidz First Children's Hospital aged 0-14 years diagnosed with OM were included. Patients were excluded if they had a resistant organism, immunodeficiency, multifocal or vertebral OM, and allergy to penicillin.
- Clinical evaluation and management:** Children were randomised at the point of improvement of acute signs and symptoms and decreasing C-reactive protein (CRP) to receive high dose oral Cephalexin with trough level measured, or continue IV Flucloxacillin. A minimum of 3 weeks of antibiotics was given with weekly clinical, CRP and compliance monitoring, and until resolution of infection. Children were followed for 12 months post treatment.
- Statistical Method:** Patients were randomised by minimisation according to age, gender, and number of surgical procedures by the time clinical defervescence was achieved. Mann-Whitney U test was used to analysis the difference in hospital days and duration of antibiotics between the 2 groups.



## Results

### Population Characteristics (%)

	Intravenous N = 31	Oral N = 38
<b>Age at diagnosis</b>		
Median (range)	10 (0 – 14)	9 (0-14)
<b>Sex</b>		
Male	19 (62)	27 (71)
Female	12 (38)	11 (29)
<b>Race</b>		
NZ European	12 (39)	13 (34)
Maori	6 (19)	5 (13)
Pacific	10 (3)	13 (34)
Other	3 (10)	7 (19)
<b>Positive Microbiology</b>		
Yes	13 (42)	21 (55)
No	18 (58)	17 (45)
<b>Peak CRP (mg/L)</b>		
Median (range)	63 (2-243)	78 (4.9-270)
<b>Surgical Procedures</b>		
Mean (range)	0.8 (0-3)	2 (0-2)
Number of patients	15 (48%)	16 (43)
<b>Days to clinical defervescence</b>		
Median (range)	5 (2-12)	5 (1-10)
<b>Duration of Hospitalisation (days)</b>		
Median (range)	12 (5-104)	9 (5-22)
<b>Duration of Antibiotics from clinical defervescence (days)</b>		
Median	29 (16-103)	26 (18-44)
<b>Treatment failure</b>		
Number of patients	2 (8.8)	0 (0)

- One patient in the oral antibiotic arm was taken off study secondary to a subsequent diagnosis of chronic recurrent multifocal osteomyelitis.
- The total duration of hospitalisation was significantly shorter in the oral antibiotic group when compared with the IV group,  $p=0.02$ , whereas the duration of antibiotics post defervescence was not different.
- 29% of patients in the IV group developed a peripheral central catheter or antibiotic-related adverse event.
- 2 patients in the IV group had treatment failure and 4 patients (2 in the IV and 2 in the oral group) underwent modification of therapy due to increase symptoms without laboratory or imaging evidence of disease recurrence.

## Patients who had treatment failure

**Patient 1:** 10 year old male

**Diagnosis:** Left distal second and third distal metatarsal methicillin sensitive Staphylococcus aureus (MSSA) OM with surrounding soft tissue collection.

**Management:** Incision and drainage Day 3 and 5. Randomised to IV arm.

**Course:** Developed Flucloxacillin hypersensitivity rash on Day 20, changed to IV Clindamycin and completed 6 weeks of IV therapy with full adherence to medication. Xray demonstrated bony sclerosis.

**Relapse:** Returned 6 weeks post antibiotics with abscess at dorsum of foot and sinus tract. CRP <1mg/L. MRI showed worsening infection. Pus grew MSSA. Patient was treated with repeated washout and completed 3 months of IV Clindamycin. No long term bony or mobility sequelae.

**Patient 2:** 11 year old male

**Diagnosis:** Left fibula OM with positive blood culture presented initially as a draining infrapatellar abscess. Culture of abscess specimen was positive for MSSA and Group A streptococci.

**Management:** Randomised to IV arm and completed 4 weeks of Flucloxacillin with no missed dose. CRP 1mg/L at conclusion of therapy. No end of treatment xray was performed.

**Relapse:** Represented 2 weeks post treatment with fever, CRP 24 mg/L and localised pain. Imaging and microbiology confirmed relapsed MSSA OM. Treated with 6 weeks IV Flucloxacillin. No long term adverse effects.

## Conclusions

- Sequential intravenous high dose antibiotics appears to be a well-tolerated, safe and efficacious treatment in carefully selected population of children with OM with exclusions as outlined.
- In our population treatment failure occurred in 2/69 (3%) irrespective of antibiotic delivery route.
- Children randomised to the IV arm had a high rate of PICC or IV antibiotic-related adverse events.
- Clinical progress and antimicrobial adherence should be monitored regularly during treatment.

### References:

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