Canterbury District Health Board
Te Poari Hauora ō Waitaha

Antimicrobial Stewardship Bulletin

Departments of Pharmacy, Clinical Pharmacology & Infectious Diseases
Christchurch Hospital, Private Bag 4710, Christchurch
Antimicrobial pharmacist ext 80901, pager 8764

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Optimising flucloxacillin – probenecid, continuous infusions and more

Flucloxacillin has been the key antimicrobial used to treat susceptible staphylococcal infections in New Zealand for decades. However, its use is hampered by the need for frequent dosing and administration of the oral formulation away from food. This bulletin explores some options for optimising treatment for hospital discharge.

Optimising dosing

Penicillins have a time dependent bacterial kill – the time free (unbound) drug concentrations are above the minimum inhibitory concentration (MIC) of the organism is more important than the actual concentration achieved. Flucloxacillin has a short half-life (~1 h in 'normal' renal function) so four times daily dosing is required for most infections. As penicillins have a high therapeutic index the risk of underdosing (inadequately treated infection) is usually greater than the risk of overdosing (toxicity) **– see blue box.**

Going home – oral or iv?

Usual inpatient parenteral doses are 1 to 2 g q6h given by intermittent iv infusion. Dose adjustments for severity of infection and for renal impairment should be undertaken (fraction excreted unchanged renally is 0.7). If flucloxacillin is to continue at discharge, patients should ideally be converted to oral treatment (oral availability is ~0.8) for skin and soft tissue infections. For bacteraemias and deep infections (eg. bone/joint) continued iv administration may be needed. Note that risk factors for flucloxacillin hepatotoxicity include – female gender, > 55 years of age, high doses and courses > 14 days.

❖ **Oral flucloxacillin**

Two key dosing issues adversely affect compliance with oral flucloxacillin:

1. Four times daily dosing.
2. Empty stomach administration (1 hour before or 2 hour after food) to help absorption. Early studies showed food delayed the absorption of flucloxacillin, but it is not clear if the extent is affected. A study is underway locally to determine if flucloxacillin can be given with food without compromising efficacy.

Probenecid reduces renal elimination of flucloxacillin and increases plasma concentrations by ~2-fold. A local study suggested that adding probenecid 500 mg bd to flucloxacillin 1 g po bd (with food) obtains concentrations sufficient to treat skin & soft tissue infections. **Watch for interactions between probenecid and other drugs – see orange box**.

❖ **iv flucloxacillin as an outpatient**

This may be useful for stabilised patients who need long term treatment for conditions like osteomyelitis. Four times daily dosing is not practical at home so flucloxacillin is usually given by continuous infusion with an infusor device changed daily. Refer queries regarding this to the home iv team – ext. 81465.

Staphylococcus aureus bacteraemia

S. aureus bacteraemia has a high rate of metastatic infection, relapse and mortality. *S. aureus* comprises 20-25% of all blood culture isolates, and 90% of *S. aureus* isolates from blood cultures are clinically significant (it is unlikely to be a contaminant).

The mortality rate for *S. aureus* sepsis is 20%. Insufficient treatment duration contributes to early relapse rates of ~8%. Metastatic foci (eg. endocarditis, prosthetic joints) are seen in up to one-third of patients. Risk factors for *S. aureus* bacteraemia (and endocarditis) include immuno-suppression, iv drug use, liver disease and use of insulin and corticosteroids.

Initial pharmacological treatment

- Consult the Infectious Diseases department.
- Empiric treatment is flucloxacillin 2 g iv q6h (q4h if endocarditis suspected). There is no role for gentamicin synergy in this setting.
- Consider MRSA in situations such as known MRSA colonisation, contact with other hospitals, Polynesian ethnicity and contact sport exposure. Empiric therapy is vancomycin – see Pink Book 2014 p163.
- Repeat blood cultures after 48-72 hours as this may help guide the duration of treatment.
- Revisit history for metastatic foci
- Minimum treatment duration is 2 weeks iv therapy (longer if endocarditis, osteomyelitis etc)

PROBENECID – Watch for interactions

- Probenecid can be a useful adjunct to many β-lactams as it may delay their renal elimination and allow less frequent dosing.
- However, probenecid also increases the concentrations of many other drugs including NSAIDs, methotrexate and some benzodiazepines.
- If prescribing probenecid, the patient's concurrent drug therapy must be checked for interactions. Refer to your ward pharmacist, drug information (ext. 80901) or the Clinical Pharmacology intranet site for further information (probenecid bulletin).