Canterbury District Health Board
Te Poari Hauora o Waitaha

Antimicrobial Stewardship Bulletin

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Metronidazole - twice daily oral dosing for most indications (adults)

Key messages for metronidazole at CDHB

1. **Oral administration.** Avoid the IV route except when GI absorption is compromised, or the patient is "nil by mouth",
2. **Twice daily dosing for most indications** i.e. 600 mg PO BD or 500 mg IV q12h,
3. **Avoid unnecessary doubling up of anaerobic cover.** If unsure about antimicrobial choice, consult Infectious Diseases or Clinical Microbiology.

BACKGROUND

- Metronidazole is our antimicrobial of choice for empiric treatment of suspected anaerobic bacterial infections. It has many desirable features including:
  - rapid bactericidal activity against anaerobic bacteria,
  - excellent oral availability (> 0.9) and tissue penetration,
  - low rates of resistance, despite extensive usage.
- Local prescribing regimens for metronidazole (eg. 500 mg IV 8 hourly) do not reflect current understanding of antimicrobial concentration-effect relationships. Several properties of metronidazole suggest outcomes might be improved by giving larger doses less frequently (more in line with aminoglycoside than β-lactam dosing):
  - concentration-dependent bacterial kill,
  - long half-life (by antimicrobial standards) of ~8 hours,
  - suppression of bacterial growth even after metronidazole concentrations have declined to very low levels (post-antibiotic effect).
- Review of metronidazole pharmacokinetics, minimum inhibitory concentrations of anaerobic bacteria, clinical studies and international guidelines have resulted in new recommendations for metronidazole dosing at CDHB:

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For most indications prescribe metronidazole orally as 600 mg PO BD*

500 mg IV 12 hourly may be used when gastrointestinal absorption is compromised or the patient is "nil by mouth"

**Exceptions exist – see pink box*

PRESCRIBE ORALLY

- Metronidazole has excellent oral availability (> 0.9).
- Only prescribe metronidazole IV when the oral route is not feasible. Unnecessary use of the IV route increases complication risk (eg. catheter-related infections), reduces mobility and comfort, and inflates administration costs.

TWICE DAILY DOSING FOR MOST INDICATIONS

- Effective metronidazole concentrations are achieved with twice daily dosing of 600 mg PO or 500 mg IV. A lower IV dose per 24 hours (1000 vs 1500 mg used previously) may reduce complications without compromising efficacy.
- Give a 600 mg oral dose as 3 x 200 mg tablets, with food.
- Dosage recommendations for some indications have not changed (see pink box).

Metronidazole
600 mg PO or 500 mg IV 12 hourly

BD dosing for most indications:

- acute peritonitis
- cellulitis – complicated/ulcers
- deep neck space infections
- septicaemia
- bite infections
- cholecystitis/cholangitis
- pelvic inflammatory disease (severe)

TDS dosing remains important for *C. difficile* diarrhoea and parasitic gastrointestinal infections to ensure adequate luminal concentrations.

There has been **no change to dosing recommendations** for indications such as *H. pylori,* bacterial vaginosis and trichomoniasis.

See Pink Book 2015 online
(October release includes metronidazole dose changes)

Doubling up on anaerobic cover

- Anaerobic bacteria are normal flora of the mouth and GI tract. Oral anaerobes are mainly Gram-positive cocci (eg. *Peptostreptococcus spp.,*) and are usually susceptible to penicillins. Intestinal anaerobes include Gram-negative bacilli such as *Bacteroides* spp., which exhibit variable susceptibility to antianaerobic agents but are usually metronidazole susceptible.
- At CDHB, metronidazole is the first choice antimicrobial for anaerobic cover of intra-abdominal infections, gynaecological infections and soft tissue infections.
- **Metronidazole should not usually be added to another agent with good anaerobic cover** such as:
  - amoxicillin/clavulanate
  - clindamycin
  - piperacillin/tazobactam
  - carbapenems eg. meropenem
  - moxifloxacin
- In line with this, Pink Book guidelines for severe/life-threatening aspiration pneumonia have been changed to monotherapy with piperacillin/tazobactam only (metronidazole is not required).
- An exception is the treatment of *C. difficile* diarrhoea in patients already receiving antibiotics with anaerobic activity for other infections (see Pink Book), and liver abscesses where amoeba are thought to be involved (consult Infectious Diseases).
- Unnecessary doubling up with antimicrobials increases the risk of adverse effects without added benefit.
- Susceptibility testing of anaerobic bacteria is not undertaken routinely. Treatment failure with anaerobic infections is more likely due to inadequate source control than resistance. Metronidazole has excellent tissue penetration and reliable activity against *B. fragilis*, which may be advantageous if surgical drainage is incomplete. **If uncertain about antimicrobial choice – discuss with Infectious Diseases or Clinical Microbiology**.