PHARMACY & THERAPEUTICS COMMITTEE
Pharmacotherapy Directive

Title: Metronidazole Dosing Frequency

Purpose: To change the standard dosing interval of metronidazole to every 12 hours for most anaerobic or mixed anaerobic infections.

Therapeutic Class (AHFS Class & Code): 8:12 Antibacterials

Disease State Class/ ICD-10 Code: N/A

Summary & Procedure:
Patients prescribed metronidazole will receive the doses every 12 hours, compared to the traditional every 8 hours. Pharmacokinetic and clinical outcome data support dosing every 12 hours. Additionally, dosing metronidazole every 12 hours can potentially reduce the overall medication costs and waste for the health system.

Procedure:

1. Identify patient receiving metronidazole for presumed anerobic or mixed anerobic infection
2. Confirm no exclusion criteria:
    a. Patient with *C. difficile* infection
    b. Patient with CNS infection
    c. Patient receiving metronidazole for surgical prophylaxis
    d. Patient with parasitic/amoebic infection
    e. Pediatric patient
3. Convert metronidazole dosing interval to every 12 hours

PHARMACIST RESPONSIBILITY

1. Convert metronidazole dosing interval to every 12 hours if patient meets criteria
2. Orders will be entered using "Per Protocol: Cosign Required" mode

Background:

Traditionally, metronidazole dosing regimens utilized an every-8-hour dosing strategy to treat anaerobic and mixed anaerobic infections. When closely examining the pharmacokinetic data of metronidazole in the serum, the half-life is 8-12 hours, with serum concentrations exceeding the *in vitro* MIC for most anaerobic organisms at 12 hours post-dose, including *Bacteroides fragilis*.

Clinical Studies:

Several studies examined the impact of changing from an every 8-hour dosing regimen to an every-12-hour dosing regimen for metronidazole. Bunz and colleagues first explored this idea in 1990 for patients receiving metronidazole for both prophylaxis and treatment post-operatively to prevent and/or treat infection.[1] The authors concluded that there was no change in post-operative infection rate or death between the every-12-hour dosing group and the every-8-hour dosing group. They also commented that an every 12-hour dosing regimen resulted in a cost savings of approximately $28,000 per year.

Soule and colleagues demonstrated that there was no significant differences in clinical cure for every 12 hours versus every 8 hours metronidazole dosing regimens, where clinical cure was defined as improvement or resolution of the principle sign/symptom of infection with normalization of white blood cells (WBCs >4000 and <12,000 cells/µl) and temperature (>96.8°F and <100.4°F) at the end of therapy or at discharge, whichever occurred first.[2] There were 100 patients included in each group, and 80% of patients in each cohort achieved cure (p = 1.00). Additionally, there was no difference in duration of antibiotic therapy in days between groups (5.9 versus 5.8, respectively) (p = 0.891).

The most recently published study was conducted in multiple sites and included patients with proven anaerobic bacteremia, comparing metronidazole 500mg every 8 hours with 500mg every 12 hours.[3] Eighty-five patients were included in this study with 32 patients receiving every 8-hour dosing and 53 with every 12-hour dosing. Patients who received 500mg every 8 hours had no significant difference in all cause 30-day mortality (15.6% vs 9.4%; p=0.49), post-infection days of hospitalization [9 (6–12.8) vs 8 (4–10); p=0.27], or escalation of antimicrobial therapy (12.5% vs 5.7%; p=0.42) compared to those who received 500 mg every 12 hours.

Financial Impact of Proposed Therapeutic Directive:

In 2023, Our Lady of Lourdes Health (3 campuses, adult patients only) used 4502 doses of metronidazole IV. Current cash price of metronidazole is $3.00/ IV bag.[4] This would equate to a total cost spent of $13,506 in 2022. Reducing to every 12-hour dosing would translate to ~3000 doses dispensed and a total cost spent of ~$9000. This could yield a potential cost savings of $4500 per year.

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Medical Executive Committee Approved on:

References:

1. Bunz D, Gupta S, Jewesson P. Hosp Formul 1990; 25(11):1167-1169, 1177.
2. Soule AF, Green SB, Blanchette LM. Clinical efficacy of 12-H metronidazole dosing regimens in patients with anaerobic or mixed anaerobic infections. Ther Adv Infect Dis 2018; 5(3):57-62.
3. Shah S, Adams K, Merwede J, McManus, Topal J. Three is a crowd: clinical outcomes of a twice daily versus thrice daily metronidazole dosing strategy from a multicenter study. Anaerobe 2021; 71:102378.
4. Lexicomp Online, Lexi-Drugs Online. Waltham, MA: UpToDate, Inc.; January 25, 2022. https://online.lexi.com. Accessed January 25, 2022.