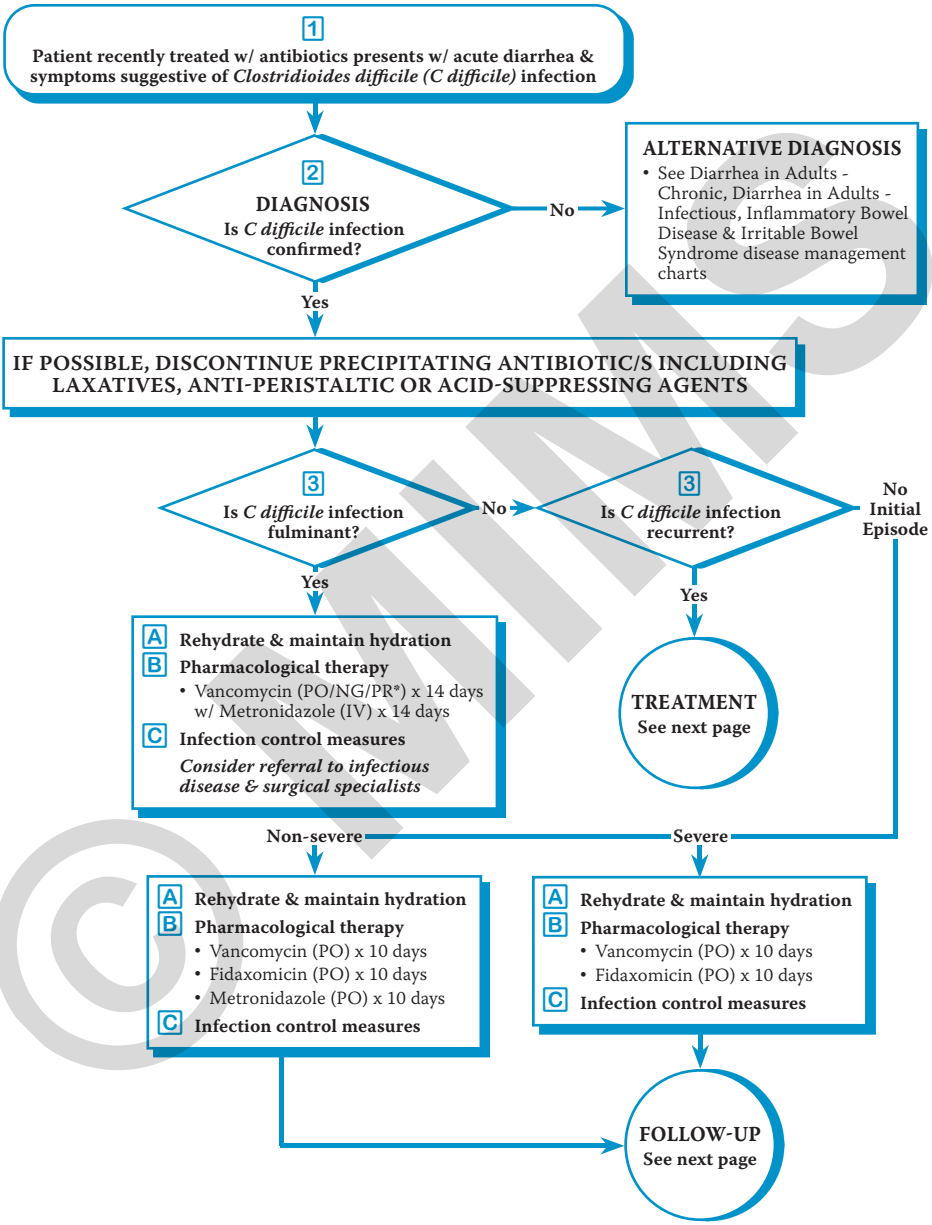
Clostridioides difficile Infection (1 of 9)



*Vancomycin may be given orally or by nasogastric tube if without significant abdominal findings. If w/ ileus, consider adding rectal instillation of Vancomycin.

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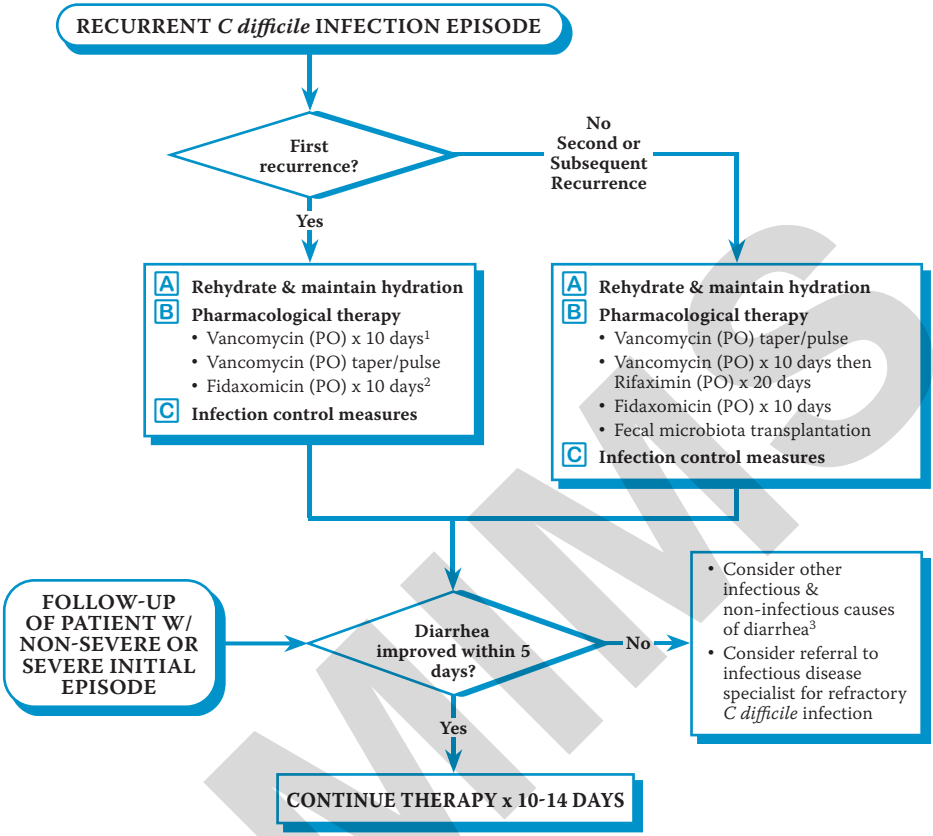
Specific prescribing information may be found in the latest MIMS.



[1]If Metronidazole was used for the initial episode
[2]If Vancomycin was used for the initial episode
[3]Medication-related side effects or recent initiation of enteral feeding

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1 *Clostridioides difficile* INFECTION

- *Clostridioides (*formerly *Clostridium) difficile* infection is commonly associated w/ antibiotic treatment & is one of the most common nosocomial infections
- Symptoms usually start on days 2-3 of antibiotic treatment, but may also occur up to 8-12 weeks after discontinuation of antibiotics
  - Acute diarrhea in an inpatient of ≥3 loose stools in ≤24 hours & in an outpatient of ≥3 loose stools in 24 hours for at least 2 consecutive days or ≥8 loose stools in 48 hours
  - Worsening of chronic diarrhea
  - Increasing output from an ostomy site after a recent antibiotic use
  - Severe pain & abdominal distension after an episode of diarrhea w/ no current stool output may indicate ileus or toxic megacolon

Risk Factors for *C difficile* Infection

- Antibiotic therapy
  - Antibiotics most commonly implicated are the cephalosporins, monobactams, carbapenems, fluoroquinolones, beta-lactamase inhibitor combinations & Clindamycin
  - Macrolides, aminoglycosides, sulfonamides & other penicillins are less commonly involved
  - Prolonged antibiotic administration increases the risk of *C difficile* colitis, but even a brief exposure to a single antibiotic may cause disease
- Intensive care unit (ICU) admission
- Prolonged stay in the hospital
- Sharing a hospital room w/ a *C difficile*-infected patient
- Recent surgery
- Advanced age
- Residing in a nursing home or long-term care facility
- Severe comorbid illnesses
- Immunosuppressive therapy
- Use of a nasogastric tube
- Use of antacids

2 DIAGNOSIS

Diagnostic Tests

- Submitted stool specimens which are formed should not be used for laboratory testing
  - There should be no recent initiation of enteral feeding or laxative use in the past 2 days
- When restrictions on sample submission are not implemented, multistep testing is recommended over single-step nucleic acid amplification tests (NAATs)
- Patients who are unable to produce stool specimens (eg those w/ ileus or toxic megacolon) may submit perirectal swabs for polymerase chain reaction testing

Enzyme-Linked Immunoassay for Toxin

- Most common test used to detect *C difficile* toxins A & B
- Has moderate specificity, rapid turnaround time (TAT), & is inexpensive but is not used alone due to its low sensitivity
  - Results are available within 2-6 hours
- The test may need to be repeated in patients who initially had negative test results, but in whom *C difficile* infection is highly suspected

Glutamate Dehydrogenase (GDH)

- Detects *C difficile* common antigen but does not differentiate between toxigenic & non-toxigenic strains
- Used as a screening tool for *C difficile* infection detection w/ good sensitivity but low specificity, has a rapid TAT, & is widely available & inexpensive

Nucleic Acid Amplification Tests (NAATs)

- Detects *C difficile* toxin genes by identifying toxigenic organisms in the stool
- May be used alone or as part of a multistep testing when toxin & GDH tests are indeterminate
  - False positives are of concern in single-step testing
- Has high sensitivity but low to moderate specificity

Stool Cytotoxin Assay

- Gold standard for the diagnosis of *C difficile*-mediated infection
- Highly sensitive & specific
- Disadvantages: Expensive, results only available after 24-48 hours, requires a tissue culture facility

Stool Culture

- Not helpful in diagnosis because the test is not specific for pathogenic toxin-producing strains of *C difficile*
- May be used for epidemiological typing & strain characterization

2 DIAGNOSIS (CONT'D)

Other Laboratory Tests

White Blood Cell (WBC) Count

- May show leukocytosis

Blood Chemistry

- Eg serum creatinine, albumin, electrolytes
- May show electrolyte imbalance & evidence of dehydration
- Serum lactate may serve as indicator of disease severity before performing surgical treatment

Stool Exam

- Grossly bloody stools are rare, but occult blood may be present in severe colitis

Endoscopy

- Indications
  - If there is a delay or difficulty in lab tests for *C difficile*
  - When lab exams for *C difficile* are negative but suspicion of the infection remains high
  - When there is a need for rapid diagnosis, ie fulminant disease
  - In a patient who cannot produce stool because of ileus
  - As part of testing for other colonic diseases
- The pseudomembranous finding on bowel mucosa or on examination of a biopsy sample is pathognomonic of *C difficile* colitis
- Findings may be normal in mild disease or may show only nonspecific colitis in moderate cases
- Sigmoidoscopy alone may not detect abnormalities when lesions are confined to the right colon
- Colonoscopy & sigmoidoscopy may be contraindicated in patients w/ fulminant colitis because of the risk of perforation

Computed Tomography (CT) Scan

- Not useful in confirming the diagnosis of early or mild colitis
- May be used as a confirmatory procedure for suspected *C difficile* infection when thickening of colonic mucosa is seen
- Can quickly diagnose fulminant disease
  - Abdominal & pelvic CT scan may be done in patients w/ complicated infection, ie abdominal distension w/ signs & symptoms of ileus or toxic megacolon
- In cases involving the right colon, it may reveal bowel wall edema & inflammation

3 STAGES OF *C difficile* INFECTION

Non-severe Infection

- Diarrhea w/ mild abdominal pain & cramping
- Dehydration & electrolyte imbalance w/ mild to moderate infection
- Systemic inflammatory response symptoms (eg fever, fatigue)
- WBC count <15,000/µL **&** serum creatinine <1.5 mg/dL

Severe Infection

- Diarrhea w/ increased abdominal pain & cramping including systemic inflammatory response symptoms
- Hypoalbuminemia <2.5 g/dL, WBC count ≥15,000/µL **or** serum creatinine >1.5 mg/dL & not caused by pre-existing comorbidities

Fulminant Infection

- Hypotension or shock due to *C difficile* infection **or**
- Clinical & radiographic evidence of ileus not due to another disease process **or** toxic megacolon **or**
- Peritonitis on exam, radiographic finding of free air in abdomen **&/or**
- Colonic perforation

Recurrent Infection

- *C difficile* infection meeting the above diagnostic criteria after initial resolution of symptoms following treatment completion **&** occurring within 8 weeks of prior episode or after new use of systemic antibiotic
- 10-30% of patients w/ *C difficile* infection will experience a recurrent infection
- Recurrences are not usually due to development of antibiotic-resistant organisms
  - Usually due to germination of persistent spores in the colon after treatment or reinfection because of reingestion of the pathogen
- Risk factors for recurrence include advanced age, severe infection or disease, immunocompromised state & concomitant use of other antibiotics for another infection

Multiply Recurrent Infection

- ≥2 recurrences of *C difficile* infection occurring after the initial episode w/ each episode meeting the above diagnostic criteria

A REHYDRATE & MAINTAIN HYDRATION

- Administer fluids & electrolytes to rehydrate & maintain hydration
  - *Please see Diarrhea in Adults - Infectious disease management chart for specific therapy*
- Diarrhea may resolve w/ conservative management in approximately 15-23% of otherwise healthy patients
- Provide albumin supplementation to all patients w/ severe infection
- Aggressive resuscitation & invasive monitoring may be needed in patients w/ fulminant colitis

PRINCIPLES OF THERAPY

- The first step in otherwise healthy patients is to stop the offending antibiotic as soon as possible
  - May be the only measure needed for patients w/ only mild diarrhea, no fever, no abdominal pain nor a high WBC count
  - Cessation of antibiotics allows for reconstitution of the normal colonic microflora & markedly reduces the risk of recurrence
- Treatment for *C difficile* should be started if colitis is evident & diarrhea continues despite discontinuation of precipitating antibiotic
  - If w/ fulminant *C difficile* infection & clinical condition deteriorates despite antibiotic therapy, surgical treatment w/ total abdominal colectomy or a diverting loop ileostomy w/ colonic lavage is recommended
- Antibiotic therapy specific for *C difficile* should be given to the following:
  - Patients w/ severe diarrhea or colitis
  - Elderly patients
  - Patients w/ multiple concomitant illnesses
  - Patients in whom antibiotics cannot be discontinued
- Empiric antibiotic therapy may be initiated in cases where there is a delay in laboratory confirmation or for patients w/ fulminant infection
- Oral route of administration is preferred because *C difficile* remains within the lumen of the colon & does not invade the mucosa
- Other medications that also need to be stopped & avoided include laxatives (to decrease the risk of prolonged diarrhea), opiates & antidiarrheal/anti-peristaltic medications (because impaired intestinal motility can worsen toxin-mediated disease) & unnecessary proton pump inhibitors
- Asymptomatic toxigenic *C difficile* colonization requires no treatment

Duration of Therapy

- Antibiotics are generally given for 10-14 days
  - Normalization of stool consistency & frequency may take weeks after clinical response
- Prolonged treatment may be necessary for patients w/ severe colitis or those w/ underlying gastrointestinal (GI) conditions

B PHARMACOLOGICAL THERAPY

Vancomycin

- Recent data suggest that Vancomycin is superior to Metronidazole in all cases of *C difficile* infection
- 1st-line agent for both non-severe & severe initial cases & for first recurrence in patients previously treated w/ Metronidazole
- Oral Vancomycin is poorly absorbed from the intestines which results in high concentrations in the gut lumen along w/ fewer adverse effects
- For fulminant cases, it may be given orally or via nasogastric tube w/ IV Metronidazole
  - May be administered as retention enema in patients w/ ileus
- IV Vancomycin has no effect on *C difficile* infection as it is not excreted into the colon

Fidaxomicin

- A treatment option for patients w/ both non-severe & severe initial cases, for first recurrence in patients previously treated w/ Vancomycin & for patients w/ multiple recurrences
- As effective as Vancomycin but w/ fewer secondary recurrences
  - May be given to patients at high risk for recurrence
- Has intestinal microbiota-sparing effect
- May be considered if patient is allergic or intolerant to Vancomycin

B PHARMACOLOGICAL THERAPY (CONT'D)

Metronidazole

- No longer recommended as 1st-line agent due to data showing poor rates of initial cure (resolution of diarrhea after 10 days of treatment) & sustained cure (clinical cure & absence of recurrence within 1 month posttreatment)
- Recommended only if patient is allergic or intolerant to or cannot afford Vancomycin or Fidaxomicin, or if Vancomycin or Fidaxomicin is unavailable
- Oral Metronidazole is an alternative agent for non-severe initial cases; IV Metronidazole is used in combination w/ oral & rectal Vancomycin for fulminant infection
- Not to be used in severe or recurrent infection
- Avoid prolonged or repeated treatment courses due to risk of neurotoxicity

Other Agents

Teicoplanin

- As effective as Vancomycin but there is concern regarding the development of resistant enterococcal strains

Bacitracin (Oral)

- Less effective than Vancomycin or Metronidazole
- Given at 25,000 u PO 6 hourly x 10 days

Cholestyramine, Colestipol

- Binds *C difficile* toxins
- Results of studies have been variable
- Binds Vancomycin & should therefore not be used concomitantly w/ this drug

Biologic Agents & Other Therapies

- Include Ridinilazole, immunoglobulins, monoclonal antibodies (Actoxumab), bacteriophages & probiotics *Saccharomyces boulardii*, *Lactobacillus* spp & *Bifidobacterium* spp
  - Probiotics appeared to be effective & safe w/ short-term use together w/ antibiotics in patients who are not severely debilitated or immunocompromised; may also be an effective adjunct in preventing recurrent infection
  - More studies are needed before these can be recommended

Treatment of Recurrent Infection

- Mild recurrences often resolve spontaneously & do not require antibiotics
- For first recurrence, drug previously given may be reused, eg oral Vancomycin or Fidaxomicin
- For first recurrence in patients initially treated w/ Vancomycin or in second/subsequent recurrences, give Vancomycin in a tapered &/or pulse regimen
- For recurrent fulminant disease (regardless if initial or second/subsequent recurrence), treatment is the same as the initial fulminant disease followed by a Vancomycin tapered regimen
  - If first fulminant *C difficile* infection episode is not recurrent, complete treatment course without subsequent tapering if patient is improving; if w/ slow resolution of infection or significant abdominal findings, consider referring to an infectious disease specialist to extend treatment course for >14 days

Other Regimens

- Vancomycin taper
  - 125 mg PO 6 hourly x 10-14 days, 12 hourly x 1 week, 24 hourly x 1 week, & then every 2 or 3 days x 2-8 weeks
  - Taper inhibits *C difficile* vegetative cells but preserves colonic flora
- Vancomycin pulse therapy
  - 125 mg PO every 2 days or 500 mg PO every 3 days x 3 weeks
  - Used for the second recurrence of *C difficile* infection
- Vancomycin 125 mg PO 6 hourly x 10 days followed by Rifaximin 400 mg PO 8 hourly x 20 days is a treatment option for patients w/ multiple recurrences
  - A case series had suggested that Fidaxomicin, instead of Rifaximin, may be given for 20 days
- Vancomycin 250-500 mg PO 6 hourly x 10 days followed by *S boulardii* 500 mg PO 12 hourly x 4 weeks
- Metronidazole 500 mg PO 6 hourly x 10 days followed by Cholestyramine 4 g PO 8 hourly + *Lactobacillus* 1 g PO 6 hourly x 4 weeks
- Patients w/ >10 episodes of recurrent diarrhea may need long-term therapy

B PHARMACOLOGICAL THERAPY (CONT'D)

Treatment of Recurrent Infection (Cont'd)

Bezlotoxumab

- A human monoclonal antibody which binds to *C difficile* toxin B that is used to prevent recurrence in high-risk adults receiving antibacterial therapy for *C difficile* infection
  - Risk of recurrent *C difficile* infection is decreased by approximately 40% when given during the first episode
- Not an antibacterial drug & thus should only be used in conjunction w/ *C difficile* infection antibacterial treatment
  - May be administered at any time during the 10-14-day antibacterial treatment course

Fecal Microbiota Transplantation or Fecal Bacteriotherapy

- An effective treatment for recurrent *C difficile* infection
- A stool in a liquid suspension is transplanted in the patient's GI tract
- May be administered via a nasogastric tube, nasojejunal tube, upper endoscopy, colonoscopy, enema or encapsulated preparations
- It restores a healthier intestinal microbiota in patients w/ recurrent *C difficile* infection
- Consider a fecal microbiota transplant in patients w/ at least 2 recurrences (3 episodes of *C difficile* infection) who have failed appropriate antibiotic therapy
  - Consult infectious disease & gastroenterology specialists for evaluation

C INFECTION CONTROL MEASURES

- Isolate patients w/ *C difficile*-associated diarrhea
- Use precautions (eg gloves, gowns) when in contact w/ the infected patient & the environment
  - Maintain contact precautions until diarrhea has resolved
- Proper handwashing between patient contacts must be observed
- Reusable devices & equipment must be properly disinfected
- Educate patient & hospital staff regarding the disease
- Judicious use of antibiotics (ie proper antibiotic stewardship) must be exercised to prevent further cases of infection

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Dosage Guidelines

ANTIDIARRHEAL MICROORGANISM

Drug	Dosage	Remarks
Saccharomyces boulardii	250-500 mg PO 12-24 hrly **or** 282.5 mg PO 12-24 hrly	**Adverse Reactions** • Dermatologic effects (rash, urticaria, pruritus); Other effects (flatulence, angioedema, shock) **Special Instructions** • Use w/ caution in diarrhea >2 days, pregnancy, lactation • Contraindicated in patients allergic to yeast, immunocompromised patients

MACROLIDE

Drug	Dosage	Remarks
Fidaxomicin	200 mg PO 12 hrly x 10 days	**Adverse Reactions** • GI effects (N/V, abdominal pain, GI hemorrhage); Hematologic effects (anemia, neutropenia); Other effects (pruritus, rash, increased liver enzymes & serum alkaline phosphatase level, dyspnea) **Special Instructions** • Not to be used for systemic infection

OTHER ANTIBIOTICS

Drug	Dosage	Remarks
Glycopeptides		
Teicoplanin	100-200 mg PO 12 hrly x 7-14 days	**Adverse Reactions** • Fever, chills, skin rash, pruritus, occasionally anaphylaxis or bronchospasm have been reported • Other hypersensitivity reactions can occur (Stevens-Johnson syndrome); GI effect (GI disturbances); CNS effects (dizziness, headache); Hematologic effects; Hepatic effects **Special Instructions** • Use w/ caution in patients w/ preexisting renal dysfunction • Monitor renal & auditory function if on prolonged therapy • Periodic monitoring of CBC & LFTs are advised

All dosage recommendations are for non-pregnant & non-breastfeeding women, & non-elderly adults w/ normal renal & hepatic function unless otherwise stated.

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Dosage Guidelines

OTHER ANTIBIOTICS (CONT'D)		
Drug	**Dosage**	**Remarks**
Glycopeptides (Cont'd)		
Vancomycin	**First episode** **Non-severe:** 125 mg PO 6 hrly x 10 days May increase to 500 mg PO 6 hrly x 10 days for severe cases **Max dose:** 2,000 mg/day **Multiple recurrences** 125 mg PO 6 hrly x 10 days followed by either dose tapering (gradually decreasing dose until 125 mg/day) or pulse regimen (125-500 mg/day every 2-3 days for at least 3 wk)	**Adverse Reaction** • Hypersensitivity reactions (can range from mild to severe eg anaphylactoid reactions, Stevens-Johnson syndrome); Hematologic effects have occurred; Renal effect (nephrotoxicity may occur especially at high doses or in patients w/ predisposing factors); Ototoxic effects (ototoxicity which is more likely w/ high plasma concentrations or in renal impairment may be irreversible; tinnitus may precede hearing loss & can be used as a sign to discontinue treatment) **Special Instructions** • Avoid in patients w/ a history of impaired hearing • Use w/ caution in patients w/ impaired renal function & the elderly • Monitoring of serum concentrations may be done to help avoid renal & otic toxicity - Monitoring of CBC & renal function during treatment is suggested along w/ monitoring of auditory function
Nitroimidazole Derivative		
Metronidazole	**Non-severe:** 500 mg PO 8 hrly **Fulminant:** 500 mg IV 8 hrly **Duration of therapy:** 10-14 days	**Adverse Reactions** • GI effects (N/V, metallic taste, diarrhea, constipation) • CNS effects have been reported (weakness, dizziness, headache, mood changes); Hematologic & hepatic effects have occurred; Rarely hypersensitivity reactions; may cause darkening of urine; Other effect (candidal infection) • High dose or prolonged use has caused peripheral neuropathy & epileptiform seizures **Special Instructions** • When given w/ alcohol a Disulfiram-like reaction can occur • Use w/ caution in patients w/ severe hepatic impairment • If given >10 days recommend monitoring CBC & clinical monitoring for CNS effects

All dosage recommendations are for non-pregnant & non-breastfeeding women, & non-elderly adults w/ normal renal & hepatic function unless otherwise stated.

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