CLOSTRIDIUM DIFFICILE INFECTION/COLITIS

Background
1. Definition – inflammation of large bowel, usually associated with diarrhea, caused by toxins of Clostridium difficile
2. General Information 1, 2
   o Clostridium difficile (C. difficile) - anaerobic spore-forming bacillus
   o Toxin-producing strains cause illnesses ranging from mild diarrhea to fulminant colitis and megacolon
   o Sepsis and death can occur
   o C. difficile is leading cause of antibiotic-associated nosocomial diarrhea (also called CDAD – C. difficile-associated diarrhea/CDAC – C. difficile-associated colitis)

Pathophysiology
1. Pathology of Disease 1, 2, 4, 5
   o Two essential requirements for CDAD to occur
     ▪ Exposure to antimicrobials
     ▪ New acquisition of C. difficile by oral ingestion of vegetative organisms or spores
   o Spores resist stomach acid and germinate in small intestine
   o Disruption of normal colonic flora by antimicrobials allows C. difficile to flourish and produce toxins
   o Toxins A and B cause mucosal damage and attract inflammatory mediators/white blood cells
   o Binary toxin also implicated in pathology (associated only with hypervirulent, NAP1/BI/027 strain
   o Disease spectrum: 5
     ▪ Asymptomatic carriers
     ▪ CDAD – mild to moderate diarrhea and lower abdominal cramps
     ▪ CDAC – most common clinical manifestation is without pseudomembranous formation; more serious symptoms/signs than CDAC
     ▪ Fulminant colitis – very sick patients with numerous clinical complications
2. Incidence, Prevalence 2, 4
   o Approximately 3 million cases of CDAD/CDAC (Clostridium difficile-associated colitis) annually in US
   o C. difficile implicated in the following:
     ▪ 10-25% of patients with antibiotic-associated diarrhea
     ▪ 50-75% of those with antibiotic-associated colitis
     ▪ 90-100% of those the antibiotic-associated pseudomembranous colitis
   o Incidence and severity increased over the past decade
   o About 3% of healthy adults and 20%-40% of hospitalized patients colonized with C. difficile, which metabolically inactive in spore form in healthy persons
   o In long-term care facilities (LTCF’s), carrier rate may be as high as 50%
   o Fulminant colitis develops in 3%-8% of patients
3. Risk Factors
   - Antibiotic exposure (#1 risk factor) – essentially all antibiotics implicated, especially cephalosporins and clindamycin
     - Newer fluoroquinolones associated with increased risk for hypervirulent 027/BI/NAP1 strain
   - Age >65 y/o
   - Duration of hospitalization
   - Exposure to other patients with CDAD
   - Chronic proton pump inhibitor (PPI) use

4. Morbidity / Mortality
   - Overall mortality rate: 1-2.5%
   - Mortality ranges from 6-30% with pseudomembranous colitis
   - Hospital costs >$4000 per case

Diagnostics
1. History
   - Diarrhea, usually less than 10 watery bowel movements per day
   - History of recent antibiotic exposure
   - Rarely, hx of bloody stools
   - May be non-specific and include: nausea, vomiting, dehydration, lethargy, and tachycardia
   - More severe forms:
     - Increased abdominal cramping
     - Systemic inflammation symptoms – fever
     - Lack of diarrhea due to lieus

2. Physical Examination
   - May be relatively normal or consistent with history
   - May be indicative of patient going into sepsis or toxic megacolon

3. Diagnostic Testing
   - Most widely used laboratory assays for C. difficile infection involve toxin A and/or toxin B detection
   - Stool culture for C difficile is sensitive, but may take up to 48 hours

4. Laboratory evaluation
   - Overall, no laboratory test is ideal
   - Cell cytotoxicity assays considered gold standard; sensitive to <10 picograms of toxin; may give false negative if toxins allowed to degrade in sample
   - ELISA/ enzyme immunoassays or immunochromatography capable of detecting both toxin A (Tcd A) and toxin B (Tcd B) highly recommended; most common test used in US.
     - Relatively specific but less sensitive; reported to have false-negative rates up to 40%
     - Allow for results to be available within hours
   - CBC, Albumin
   - Stool culture for C. difficile
Use of cell cytotoxicity assay or ELISA with stool culture allows for sensitive and specific detection of toxigenic organism, but requires prolonged time and is labor intensive.

5. Diagnostic imaging
   - Plain abdominal films may be used if suspect toxic megacolon; otherwise generally non-specific findings
   - CT may show bowel wall thickening

6. Other studies
   - Direct endoscopic visualization of the colonic mucosa can be useful in making diagnosis of CDAD/CDAC.
   - Endoscopy is not indicated in patients with classic clinical findings and a positive stool toxin assay.
   - Greater than 95% of patients identified with pseudomembranes have C difficile infection
   - However, 10% false negative rate and increased risk for perforation constrain use to patient with severe disease and negative laboratory results in whom there is need for rapid diagnosis

7. Diagnostic “Criteria” (If indicated)
   - No published “criteria”; however, presence of Tcd A and/or Tcd B on cytotoxicity assay or EIA in clinical setting c/w CDAD/CDAC considered diagnostic

8. Evidence-based Recommendations
   - Testing for C. difficile or toxins should be performed only on diarrheal (unformed) stool, unless ileus due to C. difficile suspected (SOR:B, LOE II).
   - Stool culture most sensitive test and is essential for epidemiological studies (SOR:A, LOE II).
   - Repeat testing during same episode of diarrhea of limited value and should be discouraged (SOR:B, LOE II).
   - C. difficile toxin A and B enzyme immunoassay (EIA) testing rapid but less sensitive than cell cytotoxin assay; suboptimal alternative diagnosis approach (SOR:B, LOE II)

Differential Diagnosis
1. Key Differential Diagnoses
   - Diarrhea from other causes:
     - Food poisoning
     - Viral infection
     - Other bacteria, such as Klebsiella and Staphylococcus
     - Candida species

Therapeutics
1. Acute Treatment
   - Stop offending antibiotic if possible
     - Up to 25% of symptomatic patients will resolve with this alone
   - If not possible, use antibiotic with lower risk of CDAD/CDAC: macrolides, aminoglycosides, sulfamethoxazole, tetracyclines or vancomycin
Avoid use of antiperistaltic agents: loperamide, paregoric, diphenoxylate hydrochloride and opioids

Begin empiric therapy, orally if possible, with either metronidazole (preferred for mild/moderate disease due to cost) or vancomycin based on clinical response and disease classification

- Mild to moderate disease (mild to moderate diarrhea, leukocytosis <15,000/µl)
  - Metronidazole 500 mg orally 3 times/day for 10 to 14 days
- Severe disease (fever, profuse diarrhea, abdominal pain, leukocytosis =15,000/µl, elevated creatinine)
  - Vancomycin 125 to 500 mg orally 4 times/day for 10 to 14 days
- Severe disease, complicated (hypotension, shock, toxic megacolon, ileus)
  - Vancomycin 500 mg enterally by nasogastric tube and/or rectal enema 4 times/day with or without intravenous metronidazole 500 mg every 8 hours

2. Further Management/Long-Term Care

- Between 15% and 35% of patients with a first episode of CDAD relapse within two months
- Recommended treatment for first recurrence is second course of initial therapy with either metronidazole or vancomycin.
- Commonly used treatment strategy for subsequent recurrences - prolonged, tapering course of oral vancomycin, which may be followed by pulsed dosing
- No evidence of benefit for treating asymptomatic carriers

3. Evidence-based Recommendations

- Discontinue therapy with suspected causative antimicrobial agent(s) as soon as possible; this may influence risk of CDAD/CDAC recurrence (SOR:A, LOE II).
- Metronidazole drug of choice for initial episode of mild-to-moderate CDAD/CDAC. Dosage - 500 mg orally 3 times per day for 10–14 days. (SOR:A, LOE I)
- Vancomycin drug of choice for an initial episode of severe CDAD/CDAC. Dosage - 125 mg orally 4 times per day for 10–14 days. (SOR:B, LOE I)
- Consider colectomy for severely ill patients. Monitoring serum lactate level and the peripheral blood white blood cell count may be helpful in prompting decision to operate; serum lactate level rising to 5 mmol/L and white blood cell count rising to 50,000 cells per µL associated with greatly increased perioperative mortality. If surgical management necessary, perform subtotal colectomy with preservation of rectum. (SOR:B, LOE II)
- Treat first CDAD/CDAC recurrence with same regimen as for initial episode (SOR:A, LOE II)
- Do not use metronidazole beyond first recurrence of CDAD/CDAC or for long-term chronic therapy - potential for cumulative neurotoxicity (SOR:B, LOE II)
- Treat second or later CDAD/CDAC recurrence with vancomycin therapy using tapered and/or pulse regimen (SOR:B, LOE III)

Follow-Up

1. Return to Office
No specific recommendations following hospital discharge
F/U if symptoms recur

2. Refer to Specialist
   If more than mild signs/symptoms, or high risk for complications, consider admission and consulting hospitalist or Infectious Disease provider
   If fulminant colitis, likely need GI and/or Surgery consultation

3. Admit to Hospital
   Asymptomatic patients and carriers usually never know they have C diff on board, and are not tested
   Community-acquired CDAD/CDAC does occur, but is rare; if more than mild signs/symptoms, or high risk for complications, consider admission

Prognosis
   Between 15% and 35% of patients with a first episode of CDAD relapse within two months
   Having one recurrence puts patients at high risk for subsequent recurrences
   Most patients do well with mild/moderate disease
   Increased co-morbidities or increased severity of disease portends higher recurrence rate and higher morbidity/mortality
   Mortality for fulminant C difficile infection ranges from 30% to 90%.

Prevention
   Prevention of C difficile infections requires appropriate infection control practices and avoidance of unnecessary antibiotics
   Measures for Healthcare Workers, Patients, and Visitors
   Healthcare workers and visitors must use gloves (SOR:A, LOE 1) and gowns (SOR:B, LOE 3) on entry to room of patient with CDI.
   Emphasize compliance with hand hygiene (SOR:A, LOE 2).
   If outbreak or increased CDI rate, instruct visitors and healthcare workers to wash hands with soap/antimicrobial soap and water after caring for or contacting CDI patients (SOR:B, LOE 3)
   Accommodate CDI patients in private room with contact precautions (SOR:B, LOE 3)
   Routine identification of asymptomatic carriers (patients or healthcare workers) for infection control purposes not recommended (SOR:A, LOE 3) and treatment of such identified patients not effective (SOR:B, LOE 1)
   Environmental Cleaning and Disinfection
   Identification and removal of environmental sources of C. difficile, including replacement of electronic rectal thermometers with disposables, can reduce the CDI incidence (SOR:B, LOE 2).
   Use chlorine-containing cleaning agents or other sporicidal agents to address environmental contamination in areas associated with increased CDI rates (SOR:B, LOE 2).
   Antimicrobial Use Restrictions
   To reduce CDI risk, minimize frequency and duration of antimicrobial therapy and number of antimicrobial agents prescribed (SOR:A, LOE 2)
- Implement antimicrobial stewardship program (SOR:A, LOE 2).

5. Use of Probiotics
   - Administration of currently available probiotics not recommended to prevent primary CDI; limited data to support this approach and potential risk of bloodstream infection (SOR:C, LOE 3).

Patient Education

References

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