Clostridium Difficile Associated Disease

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Introduction

• Which of the following is more common in community hospitals in the Southeast USA?
  • A) Clostridium difficile associated disease
  • B) Methicillin Resistant Staphylococcus aureus
Introduction

• Answer: CDAD
• Results
  • 3 million patient days 1/1/2008-12/31/2009
  • 847 cases CDAD
  • 680 cases MRSA
• Rates
  • CDAD 0.28/1000 pt d
  • MRSA 0.23/1000 pt d
Introduction

• Inferences
• Prescribing practices
• Geographic differences
• Improved infection control practices
• Patient factors

B. Miller, Duke, 2009
Case Presentation

- 80 yo female admitted with diarrhea and dehydration
- Recent treatment for diverticulitis with Levaquin® and Flagyl®
- C. difficile toxin positive
- Treated with Flagyl®/ Vancomycin
Case Presentation

- PMH- CAD/ Pancreatitis/Melanoma
- PSH- CABG/TAH/ APPY/ VV stripping
- Meds- Simvistatin/ Benicar®/ Atenolol
- MVIs/ASA/Creon®
Case Presentation

- GEN-AVSS
- HEENT- Neg. Scleral icterus
- Neck- supple
- Chest- CTA
- Cor- RRR
- Abd- Benign
- Labs- WBC-9.2
Background

• Incidence and severity of CDAD has increased dramatically
• Widespread regional outbreaks associated with a previously uncommon hypervirulent strain of C. diff in USA and Europe
• Suspected increased toxin production
• Other virulence factors
• Severe/Refractory disease
Background

- Complications
- ICU Admissions
- Colectomies
- Death
- Antibiotic Use
- Fluoroquinolones
- Cephalosporins
- High Resistance
Background

- Elderly Disproportionately Affected
- Recent Increase in Low Risk Populations
- Healthy Outpatients
- Peripartum Women
- ? Related to Epidemic Strain
Background

- Transmission within hospitals major source of acquisition
- Previous/Concurrent Use of Antimicrobials, Almost Universal among Cases
- Application of Evidence-Based Strategies for Management/Prevention is Critically Important
- Awareness Needed Re: Changing Epidemiology and Measures to Reduce Transmission of Disease
Pathogenesis

- Toxin Producing Strains of C. difficile
- Anaerobic Spore Forming Bacillus
- Illnesses:
  - Mild Diarrhea
  - Fulminant Colitis
  - Toxic Megacolon
  - Sepsis/ Death
Pathogenesis

- Essential Requirements:
- Exposure to Antimicrobials (Except IBD)
- New Acquisition of C. difficile
- ? Host Susceptibility
- ? Virulent Factors of Strain
- ? Asymptomatic Colonization
Pathogenesis/ Epidemiology

- Acquisition occurs by oral ingestion of spores
- Resist Acidity of Stomach
- Germinate into Vegetative form in small bowel
- Disruption of Commensal Flora of Colon
- Typically due to Antimicrobial Exposure
- Allows C. difficile to flourish
- Toxin Production leads to Colitis
Pathogenesis/ Epidemiology

• Primary Toxins A/B
• Large Exotoxins, Cause Inflammation/ Mucosal Damage
• Cytotoxic Effects-Disrupt Actin Cytoskeleton within cells
• Cytotoxin A Major Enterotoxin
• Recent Strains Producing cytotoxin B isolated in Pts with CDAD
Pathogenesis/Epidemiology

- Nearly all Antimicrobials implicated in CDAD
- Broad Spectrum have propensity to kill commensal colonic bacteria
- Cephalosporins
- Clindamycin
- Fluoroquinolones
Pathogenesis/ Epidemiology

- Risk Factors:
- Antimicrobial Exposure
- Advanced Age
- Hospitalization/ Institutionalization (Rehab/Extended Care Nursing)
- Severe Underlying Disease
- Immunocompromised State
Pathogenesis/Epidemiology

- Risk factors:
  - Chemotherapeutic Drugs
  - Gastrointestinal Surgery
  - Nasogastric Tubes
  - Gastric Acid Suppression (PPIs)
Pathogenesis/ Epidemiology

- Alleviating Factors:
- High Levels of IgG Antibodies to Toxin A
- Vigorous Antibody Response to Toxin A during initial infection leads to protection against recurrent disease
Pathogenesis/Epidemiology

- Community Acquired CDAD increasingly recognized
- 3% Healthy Adults Colonized
- 20-40% Hospitalized Patients Colonized
- Length of Stay Important
- Incubation Period Undefined
- High Level of Suspicion required for CDAD in diarrhea following hospital admission
Changing Epidemiology

• Incidence increased dramatically over last decade
• CDAD Rates increased:
  • ICU in > 500 Bed Hospitals
  • Hospital Discharges, Esp. Age > 64
Changing Epidemiology

- Hypervirulent Strain BI/NAP1/027
- 16 Fold Higher Toxin A Production
- 23 Fold Higher Toxin B Production
- Suspected Frameshift Mutation tcd C
Changing Epidemiology

- High Resistance to Fluoroquinolones
- Host Factors:
  - Age > 65 years
  - Nursing Homes
  - Recent Emergence:
  - Healthy Outpatients
  - Peripartum Women
  - Children
  - Patients without antibiotic exposure
Diagnosis

- High Degree of Clinical Suspicion
- Anymore- Anyone with Chronic Diarrhea
- Recent Antimicrobial Exposure/Hospitalization
- Enzyme immunoassay for Toxin A/B
Diagnosis

- Immunoassay
- Highly Specific
- Lower Sensitivity (70-87%)
- Test Two-Three Specimens, Increase Yield by 10%
- Culture Rarely Performed
Treatment

- New Guidelines from Society for Healthcare Epidemiology (SHCEA) and Infectious Disease Society of America (IDSA)
- Mild/Moderate CDAD
  - Metronidazole 500 mg TID x 10-14 days
- Severe CDAD
  - Vancomycin 125 mg QID x 10-14 days
Treatment

• First Recurrence:
• Same Regimen for initial episode
• Stratisfy for Disease Severity
• Mild/ Moderate
• Severe
• Severe/Complicated
• Avoid Metronidazole beyond first recurrence due to neurotoxicity
Treatment

- Second/ Later Recurrence Utilize:
- Vancomycin Tapered/ Pulse Regimen:
  - 125 mg QID x 10-14 d
  - 125 mg BID x 7 d
  - 125 mg QD x 7 d
  - 125 mg Q 2-3 d x 14-35d
Treatment

- No evidence Cholestyramine/ Rifampin beneficial
- Resins Bind Vancomycin
- Uncontrolled data Re: Rifaximin (Xifaxan®)
- 400 mg BID x 14 d
- “Cured” 7/8 pts after last Vancomycin dose before recurrent symptoms
Diagnosis

- Endoscopy Recommended When:
  - Rapid Diagnosis Needed
  - Test Results Delayed
  - Insensitive Tests Used
  - Ileus/ Stool Unavailable
  - Other Colonic Diseases can be diagnosed with endoscopy
Treatment

- Infection Control Measures/ Universal Precautions
- Hand Hygiene/ Hand Washing
- Contact Precautions:
  - Glove Use
  - Gowns
  - Isolation/ Private room
- Environmental Cleaning
- Use of Disposables
- Disinfection “Terminal Cleaning”
Treatment

- Stop Offending Microbials (if possible)
- Treatment orally if possible
- Avoid anti-peristaltic agents (Narcotics)
- Toxic Megacolon/Ileus:
  - Vancomycin orally
  - NG Tube
  - Rectal Enemata
Treatment

- Fulminant Disease
- Surgery/ Colectomy (STC)
- Monitor Lactate
- WBC > 50K - Severe Mortality
Treatment

• Probiotics- Inconclusive
• Saccromyceses buolardii
• Lactobacillus/ Acidophyllus
• Avoid immunocompromised patients
• Central Venous Line (CVL)
• Critically ill
• Immunomodulation
• Serum IgG
• ? Vaccines
Treatment

- Novel Agents
- Fidaxomicin
- REP3123
- Oritavancin
- NUB302
- Nitazoxamide
Fidaxomicin

- Macrocyclic Antibiotic
- 18 membered molecule
- Activity against gram positive Aerobes and Anaerobes, including C. difficile
- Microbiologic studies comparing in Vitro activity of Fidaxomicin with Metronidazole and Vancomycin
- Good activity against all strains of C. diff
- Except MIC consistently lower
Fidaxomicin

- Fidaxomicin lacks activity against gram negative pathogens
- Preserves normal flora
- Low plasma concentration
- High concentrations in stool
- Post antibiotic effect > 24 Hr
- Data: 2 phase 2A/ 1 phase 3
- Dose 200 mg every 12 hours
Fidaxomicin

- Inhibits RNA polymerase
- Results in cell death of specific bacteria (C. diff.)
- Phase 3 trials to date:
  - Recurrence rates Fidaxomicin 12.8%
  - Recurrence rates Vancomycin 25.3%
  - Recurrence rates measured @ 3 weeks, ? 3 mos
- Safe as Vancomycin
Treatment

- Fecal Bacteriotherapy
- Refractory to traditional therapy
- Purpose: Introduce normal flora esp. Bacteroides
- Informed Consent
- Concerns:
  - Hepatitis A/B/C
  - HIV
  - Other fecal / oral agents
Case Presentation

- 80 year old female treated with Vancomycin and Metronidazole, now with recurrent C. diff, which of the following are appropriate treatment options?
  - A) Repeat Vancomycin and Metronidazole
  - B) Pulse therapy Vancomycin
  - C) Colectomy
  - D) Fecal Bacteriotherapy
  - E) None of the above
Case Presentation

- Correct Answer
- B or D
Case Presentation

• Actual Therapy:
• Fecal Transplant with complete resolution of symptoms at 4 week follow up