Learning Objectives:
- History/Pathogenesis/Epidemiology
- Diagnostic Algorithms – Stool Testing
- Prevention
- Treatment Acute/Recurrent Infections
- Role of Probiotics
- ? Association with Acid Suppression
- More Virulent Strains NAP1/BI/027

Clostridium Difficile:
- Anaerobic, Gram Positive Spore Forming Toxigenic Bacillus
- First Isolated 1935 Fecal Flora Healthy Neonates

Post-op Course:
- 9 Days – Diarrhea/Blood/Tenesmus
- 15 Days – Death
- Autopsy Findings: “Diphtheritic Colitis” Cecal Perforation

First Reported Case PMC:
22 Year Old Female, 3 Months Nausea & Vomiting, Epigastric Pain
Malnourished
Dilated Stomach – Palpable Mass
Surgery – Pyloric Ulcer
Rx Post-op Enema Saline & Whiskey

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Clostridia Difficile:

- Passed into Obscurity
- 1978 Association Toxin and Antibiotic Induced Pseudomembranous Colitis Reported


Clostridia Difficile:

- Incidence Risen Steadily Over Past Decade
- Primary Cause of Nosocomial Diarrhea in Developed Countries
- Rate Increase 31/100,000 in 1996 to 84/100,000 in 2005

Center for Disease & Control Atlanta Georgia

C Diff – Epidemiology & Pathogenesis – Requirements:

- Alteration Colonic Microflora by Antibiotics or Chemotherapeutic Agents
- Oral Ingestion of C Difficile or Its Spores with Colonization of Large Intestine
- Release of Toxin A & B into Lumen
- Binding and Intercalation of Toxins by Colonocyte
- Subsequent Colitis
- Host Factors – Immune Response – ? Carrier or Colitis

Kyne L, Farrell R, Kelly CP

Alteration of Colonic Microflora:

- Nearly All Who Develop C Diff Infection
- Colonization Resistance – Protective Barrier by Microflora
- Impaired by Antibiotics


Why Don’t Neonates & Infants Develop Colitis?

- Poor Colonization Resistance/No Stable Complex Microflora
- Colonization Rate C Diff 25 - 80% Infants
- Absence of Toxin Receptor Expression on Immature Colonic Epithelium- No Colitis

Alteration Microflora:

- Antibiotics
- Cancer Chemotherapy Agents
- Bowel Preparation Regimens


Antimicrobial Agents That Predispose to *Clostridium Difficile*-Associated Diarrhea and Colitis:

**Most Frequently**
- Ampicillin and Amoxicillin
- Cephalosporins
- Clindamycin
- Fluoroquinolones

Kelly CP, LaMont JT.

**Less Frequently**
- Macrolides (Including Erythromycin)
- Other Penicillins
- Sulfonamides
- Trimethoprim/Sulfamethoxazole

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**Rarely or Never**
- Bacitracin
- Carbapenems
- Chloramphenicol
- Daptomycin
- Metronidazole
- Parenteral aminoglycosides
- Rifampin
- Rifaximin
- Tetracyclines
- Tigecycline
- Vancomycin

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Other Risk Factors:

- Nursing Home or Rehab Center
- Age Greater Than 65
- Acid Suppression – Conflicting Data (Marker Comorbidity)
- White Race
- U.C. or Crohns
- HIV

Dial S et al. JAMA 2005; 294: 2985-2995

New Risk:

- Cirrhosis
- Pregnant – Small Series
- Increase Community Acquired
C Diff and Cirrhosis:
- Increase Mortality in Cirrhotic Patients
- Assoc of Antibiotics and PPI Usage


Why Increase Numbers?
- Crowded Hospitals with Older, Sicker Patients
- More Virulent Strains
- Widespread use of Quinolones
- Alcohol Hand Gel, Don’t Kill Spores
- H-2 Blockers & PPI’s?

Hypervirulent C Diff:
- NAP1/BI/027 Strain
- Fluroquinolines Resistance
- Higher Level Toxin Production/Gene Deletion
- 3 Fold Higher Mortality Rate
- Epidemic Strain North America, Europe, Asia

Hypervirulent C Diff:
- Restriction Endonuclease Pattern BI
- Pulsed Field Gel Electrophoresis Pattern NAP1
- PCR Ribotype Designation 027

Clostridium Difficile Toxins:
- Toxin A and Toxin B
- Structurally Similar Protein Exotoxins
- Minority Produce (Less Than 10%)
  Binary Toxin (Iota Toxin C Perfringens)
- NAP1/BI/027 Binary Toxin Positive

Warny M, Kelly CP.
Clinical Features:

- Asymptomatic Carriage
- 10 - 21% Hospitalized Patients Receiving Antibiotics in High Risk Units are Carriers
- No Symptoms? Protective Immunity

Emerg Infect Dis 2006; 12: 409-415

Symptomatic C Diff:

- Incubation Period Less Than One Week
- Median Onset 2 Days
- 96% Patients Symptomatic C Diff Infection Received Antibiotics within 14 Days and All Received Antibiotics within 3 Months


C Diff Symptoms:

- Frequent Passage Loose/Watery Bowel Movements
- Mucus
- Occult Blood
- Melena or Hematochezia Uncommon

Abdominal Films – C Diff:

- Dilated Colon (> 7cm's)
- Toxic Megacolon
- Small Bowel Ileus with Air Fluid Levels

C Diff – Severe Disease:

- Colonic Ileus or Toxic Dilatation
- May Present NO Diarrhea
- High Fever
- Moderate or Marked (Leukemoid) PMN
- Diffuse Abdominal Pain
- Distention
Diagnosis of C Difficile:

- Neither Sigmoidoscopy nor Colonoscopy is Required for Diagnosis in Most Patients
- Helpful if Rapid Diagnosis Needed or Diagnosis in Doubt
- Colonic Pseudomembranes Pathognomonic
- May Be in Proximal Colon
Early Repeat C Diff Testing:

- 10,882 Patients Diarrhea
- 27% Positivity Rate Cytotoxic Assay
- Repeat Sample Testing Within 24-72 hrs Yielded 1 - 3% Positives
- Repeating Stool Cytotoxicity Assay in 1st 3 Days Not Beneficial

Kelly CP, LaMont JT.

Therapy Initial C Difficile Infection:

<table>
<thead>
<tr>
<th>Severity:</th>
<th>Clinical Manifestations:</th>
<th>Treatment:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrier</td>
<td><em>No discernible clinical symptoms or signs</em></td>
<td><em>No treatment is indicated</em></td>
</tr>
</tbody>
</table>

Linevsky JK, Kelly CP

Treatment of *Clostridium Difficile* Diarrhea and Colitis:

Discontinue the inciting antibiotic if possible
Provide supportive therapy
Confirm the diagnosis
Prescribe specific therapy if symptoms are moderately severe or persistent:
Metronidazole orally for 10-14 days (drug of choice for mild-to-moderate disease)
Vancomycin orally for 10-14 days if Diarrhea and colitis are severe
Diarrhea does not improve during metronidazole treatment
Patient cannot tolerate metronidazole
Patient is pregnant or younger than 10 yr of age

If the patient cannot tolerate oral medication, prescribe metronidazole 500 mg, every 6 hours intravenously

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<table>
<thead>
<tr>
<th>Severity:</th>
<th>Clinical Manifestations:</th>
<th>Treatment:</th>
</tr>
</thead>
</table>
| Mild to Moderate | *Mild diarrhea < 12 stools/day*  
*Abdome*  
*Mild-to-Moderate Abdominal Discomfort or Tenderness*  
*Nausea with Rare or Absent Vomiting*  
*With or Without Hospitalization*  
*Not in Intensive Care Unit*  
*Dysphagia*  
*Lukoyctosis >20,000*  
*SBN or Creatinine Above Baseline* | *Discontinuation of predisposing antibiotics*  
*Hydration*  
*Monitor Clinical Status*  
*Isolation*  
*Consider Probiotics*  
*Oral Metronidazole 500mg 3 Times Daily or Intravenously*  
*Metronidazole 500mg 3 Times Daily if Not Tolerating Oral Intake*  
*Oral Vancomycin 125mg 4 Times Daily if Intolerant Metronidazole* |

Linevsky JK, Kelly CP

<table>
<thead>
<tr>
<th>Severity:</th>
<th>Clinical Manifestations:</th>
<th>Treatment:</th>
</tr>
</thead>
</table>
| Severe    | *Severe or Bloody Diarrhea > 12 Stools a Day*  
Pseudomembranous colitis  
*Severe abdominal pain*  
*Nausea or vomiting*  
*Ilos*  
*Temperature >38.5°C*  
*Age > 60 years*  
*In intensive care unit*  
*Lukoyctosis > 20,000*  
*Albumin < 2.5mg/dL*  
*Renal failure* | *As above plus:*  
*Oral vancomycin 125 mg 4 times daily*  
*Consider addition of intravenous metronidazole 500 mg 3 times daily* |

Linevsky JK, Kelly CP
Severity:

<table>
<thead>
<tr>
<th>Clinical Manifestations</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fulminant</td>
<td></td>
</tr>
<tr>
<td>*Toxic megacolon</td>
<td>*As above plus:</td>
</tr>
<tr>
<td>*Peritonitis</td>
<td>*Surgical consultation</td>
</tr>
<tr>
<td>*Albumin &lt; 2.5mg/dL</td>
<td>*Oral vancomycin 125 mg 3 times daily and intravenous metronidazole 500 mg 3 times daily</td>
</tr>
<tr>
<td>*Renal failure</td>
<td>*Consider IVIG</td>
</tr>
<tr>
<td>*Respiratory distress</td>
<td></td>
</tr>
<tr>
<td>*Hemodynamic instability</td>
<td></td>
</tr>
</tbody>
</table>

Fulminant Toxicity:

- Metallic Taste
- Headache
- Nausea
- Coagulopathy with Coumadin
- Disulfiram – Like Effect Alcohol
- Peripheral Neuropathy
- Ataxia

Metronidazole:

- First Line Treatment
- Parenteral, Rectal, Oral
- AntiInflammatory/Antioxidant/Immunomodulatory

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Vancomycin:

- Tricyclic Glycopeptide Inhibits Cell Wall Synthesis
- Oral Administration Reaches Colon Intact
- Parenteral Vancomycin Does Not Reach Colonic Lumen

PREVENTION IS BETTER THAN CURE


<table>
<thead>
<tr>
<th>Point</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt; 80 years</td>
</tr>
<tr>
<td></td>
<td>&gt; 101°F (38.3°C)</td>
</tr>
<tr>
<td></td>
<td>Albumin &lt; 2.5 mg/dL</td>
</tr>
<tr>
<td></td>
<td>WBC &gt; 10,000 cells/mm³</td>
</tr>
<tr>
<td>2</td>
<td>PMN at colonoscopy</td>
</tr>
<tr>
<td></td>
<td>ICU patient</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Severity</th>
<th>Rate of Cure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>80%</td>
</tr>
<tr>
<td>Severe</td>
<td>60%</td>
</tr>
</tbody>
</table>

*Prevnocillin Methadiazole*
Prevention:
- Limit the use of antimicrobial drugs
- Wash hands between contacts with all patients
- Use enteric (stool) isolation precautions for patients with C. Difficile Diarrhea
- Wear gloves when contacting patients with C. Difficile diarrhea or their environment
- Disinfect objects contaminated with C. Difficile with sodium hypochlorite, alkaline glutaraldehyde, or ethylene oxide
- Educate the medical, nursing, and other appropriate staff members about the disease and its' epidemiology

Alternative Antibiotics – Rifaximin:
- Nonabsorbable Antibiotic Similar to Rifampin Inhibits Bacterial RNA Synthesis
- Efficacy in Initial and Recurrent Infection
- ? Resistance
- Pregnancy Class C

Alternative – Rifampin:
- Increase Mortality in Conjunction with Flagyl Compaired to Flagyl Alone

Acute Fulminant Infection:
- Case fatality Rate >2%
- 1st Recurrence or Initial Infection
- Hemodynamic Collapse Mean 9 Days

To O.R.:
- Increase Lactate > 5
- Increase WBC > 20
- Shock/Pressors
  - Age > 75

Recurrent C Difficile Infection:
- 15-30% Patients Symptomatic Recurrence
- Older Patients and Previous C Diff Higher Risk
- Most Recurrence Within 2 Weeks Stopping Therapy
Treatment of Recurrent *C. Difficile* Infection:

**Initial recurrence**
- 14-day course of oral metronidazole or vancomycin
- Consider probiotics

**Second recurrence**
- Tapered pulse dose oral vancomycin
  - 125 mg 4 times daily for 1 week
  - 125 mg twice daily for 1 week
  - 125 mg daily for 1 week
  - 125 mg every other day for 1 week
  - 125 mg every third day for 2 weeks
- Consider 1-month course of probiotics starting in the final 2 weeks of antibiotic therapy

**Third or subsequent recurrence**
- Tapered pulse dose oral vancomycin
  - 125 mg 4 times daily for 1 week
  - 125 mg twice daily for 1 week
  - 125 mg daily for 1 week
  - 125 mg every other day for 1 week
  - 125 mg every third day for 2 weeks

**Followed by**
- 14-day course of rifaximin, nitazoxanide, or toxin-binding resins
- Consider 1-month course of probiotics starting in the final 2 weeks of antibiotic therapy
- Consider intravenous immunoglobulin or fecal bacteriotherapy
- Consider chronic low-dose suppressive therapy with oral vancomycin for elderly patients and those with multiple comorbidities

### Treatment Options for *C. Difficile* Infection:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Regimen</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole</td>
<td>250–500 mg 3 times daily or 4 times daily by mouth or intravenously</td>
<td>First-line therapy or in combination with vancomycin in severe disease</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>125–500 mg 3 times daily or 4 times daily by mouth</td>
<td>First-line therapy for severe disease</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>400–800 mg twice daily or 3 times daily by mouth</td>
<td>Adjunctive in recurrent <em>C. difficile</em> infection</td>
</tr>
<tr>
<td>Binding resins, cholestyramine</td>
<td>4 g 3 times daily or 4 times daily</td>
<td>Adjunctive with antibiotics, must be taken ≥2 hours apart from vancomycin</td>
</tr>
<tr>
<td>Nitazoxanide</td>
<td>500 mg twice daily by mouth</td>
<td>Adjunctive in recurrent <em>C. difficile</em> infection</td>
</tr>
<tr>
<td>Immunoglobulin</td>
<td>300–500 mg/kg daily until resolution or maximum of 8 doses</td>
<td>Adjunctive with antibiotics in severe refractory or recurrent <em>C. difficile</em> infection</td>
</tr>
<tr>
<td>Probiotics</td>
<td>Variable doseholding</td>
<td>Adjunctive with antibiotics for treatment or prevention of recurrent <em>C. difficile</em> infection</td>
</tr>
<tr>
<td>Surgery</td>
<td>Subtotal colectomy with ileostomy</td>
<td>Early surgical consultation recommended in severe disease</td>
</tr>
</tbody>
</table>

### Probiotics:
- S. boulardii
- Lactobacillus Plantarum
- Lactobacillus GG
- Lactobacillus Acidophilus
- Flora Q
- Allign
Probiotics:
- Recent Meta-Analysis Reviewed 31 Studies of Probiotics for Prophylaxis Showing Reduction of Subsequent C Diff Infection
- Varying Data for Treatment of Recurrent Infection
  
  Am J Gastroent 101: 812-822

Probiotic – Risks:
- Lactobacillus GG
  - Bacteremia
  - Liver Abscess
- S boulardii
  - Fungemia Imunosuppressed and ICU Patients Central Lines

Restoring Fecal Flora:
- Emulsified Stool from Healthy Donor
- Delivery Through Colonscope
- Delivery Through NG Tube
- Fecal Enemas

Prevention:
- C Difficile is Managed Better by Prevention Than Cure
- Appropriate Use of Antibiotics
- Vaccine Development

Guidelines for the Prevention of C Difficile Infection:

<table>
<thead>
<tr>
<th>Individual patient</th>
<th>Institution</th>
<th>Regional</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Limit antibiotics</td>
<td>- Hand washing after all patient contact</td>
<td>- Educate medical staff and at-risk populations about C difficile</td>
</tr>
<tr>
<td></td>
<td>- Isolation for patients known to be infected with C difficile</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Use of gloves and gowns when in contact with patients known or suspected to be infected with C difficile</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Disinfect contaminated objects with appropriate agents, including sodium hypochlorite, glutaraldehyde, or ethylene oxide</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions:
- Explosion of C Diff Infection Since 2000 with a Health Care Cost of 1 Billion Dollars Per Year
- There Are an Increasing Number of Patients Resistant to Metronidazole, Although This Remains 1st Line Therapy
- Failure to Develop Antibody Response may lead to Treatment Failure
- Epidemic Virulent Strains Including NAP1/B1027 Are Increasing in Number
- Cytotoxin Assay and Glutamate Dehydrogenase Remain Gold Standard for Diagnosis
- Vancomycin, Binding, Resins, Bacterotherapy, Rifaximin and Probiotics may be used in Recurrent Infection
- Prevention is Better Than Cure