Probiotics for Primary Prevention of *Clostridium difficile* Infection

April 24, 2015
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Objectives

• Review risk factors for *Clostridium difficile* infection (CDI)

• Describe guideline recommendations for CDI prevention

• Discuss available literature for probiotic use as primary prevention of CDI

• Provide a recommendation for primary prevention of CDI with probiotics
Definitions

**Antibiotic-associated diarrhea (AAD)**
- Unexplained diarrhea within 7 days of antibiotic initiation
- Typically self-limiting
- Caused by disruption of intestinal microbial flora
- Incidence depends on type of antibiotic used

**Clostridium difficile associated diarrhea (CDAD)**
- Defined by presence of symptoms with a positive diagnostic test for *C. difficile* toxin
- Most common nosocomial infection
- Accounts for 15-25% of AAD episodes

Epidemiology

Incidence
• Estimated incidence of 453,000 in 2011
• Outpatient onset in >50% of cases

Cost
• Increases hospital length of stay (LOS) by 2.8 to 5.5 days
• Estimated to increase US hospital costs $1-$4.9 billion per year

Mortality
• 5-10% each year
• Estimated 29,000 deaths in the US in 2011
Risk Factors

- Advanced age (≥ 65 years)
- ↑ duration of hospitalization
- Immunosuppression
- GI surgery or GI tract manipulation
- Gastric acid suppression
- Antibiotic exposure
  - Multiple antibiotics > single agent

<table>
<thead>
<tr>
<th>Common Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroquinolones</td>
</tr>
<tr>
<td>Ampicillin/Amoxicillin-clavulanate</td>
</tr>
</tbody>
</table>

**Any antibiotic agent can cause CDI**

CDI Development

- Interruption of normal gut flora
- *Clostridium difficile* colonization
- Toxin A and B production
- Symptom development

Predominant Normal Microflora

• Greater than 500 species of bacteria estimated to comprise the intestinal microflora

• Predominantly anaerobic organisms

• Common colonizing genera
  – *Bacteroides*
  – *Bifidobacterium*
  – *Eubacterium*
  – *Clostridium*
  – *Lactobacillus*
  – *Peptococcus*
  – *Peptostreptococcus*
Functions of Normal Microflora

Metabolic

- Salvage energy
- Dietary residue and endogenous mucus fermentation

Trophic

- Epithelial cell proliferation and differentiation
- Development and homeostasis of the immune system

Protective

- Barrier against pathogens

Proposed mechanism of disease suppression
- Binding site occupation
- Toxin neutralization
- Direct inhibition through toxic metabolites or bacteriocins

CDI Prevention

- Antimicrobial stewardship
- Hand hygiene
  - Soap and water
  - Alcohol based hand products are not effective at removing *C. difficile* spores
- Contact precautions
  - Full-barrier precautions
- Dedicated patient care items
- Decontamination with sodium hypochlorite
- Probiotics??

Contact Precautions

Anyone* entering this room MUST:

1. Perform **hand hygiene** (soap and water or foam)
2. Put on **gown** and **gloves** before entering room
3. Remove **gown** and **gloves** before leaving room
4. Wash **hands** with **soap and water**

* Visitors do not need to wear gloves and gown.

Questions?
Call Infection Control 444-5194 or Pager 21740

Probiotics

• “Live microorganisms that when administered in adequate amounts confer a health benefit on the host”

• Proposed mechanisms of action

  Anti-inflammatory effects → Prevent pathogen adherence → Gut microflora modification

• Preparations
  – Most well studied: *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Saccharomyces boulardii*, *Bifidobacterium*

Guideline Recommendations

• 2010 Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines for CDI in Adults
  – “Administration of currently available probiotics is not recommended to prevent primary CDI, as there are limited data to support this approach and there is a potential risk of bloodstream infection” (C-III)

• 2014 Society for Healthcare Epidemiology of America (SHEA) Strategies to Prevent Clostridium difficile Infections in Acute Care Hospitals
  – Unresolved issue

Literature Review

- November 2012
  - Annals of Internal Medicine Meta-analysis

- February 2013
  - Cochrane Review

- August 2013
  - PLACIDE Trial
Probiotics for the prevention of *Clostridium difficile*-associated diarrhea

**Methods**

- Meta-analysis
- Study inclusion: Randomized, controlled trials in adult or pediatric patients treated with antibiotics and any dose or strain of probiotics
- Two independent reviewers assessed quality of evidence and risk of bias

**Outcomes**

- 1°: Incidence of *Clostridium difficile* associated diarrhea

**Statistical Analysis**

- 80% power with 5% significance for relative risk reduction of 30% of *Clostridium difficile* infection
- Heterogeneity with $I^2$ statistic
- A priori subgroup analysis evaluating probiotic dose, species and number of species

Annals of Internal Medicine Studies (N=20)

Included Studies

Number of Patients

Study


- L. rhamnosus
- L. acidophilus
- S. boulardii
- Combination
- L. plantarum

### Annals of Internal Medicine Results

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Experimental Group, n</th>
<th>Control Group, n</th>
<th>Weight, %</th>
<th>Relative Risk (95% CI) M–H Random</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arvola et al, 1999 (32)</td>
<td>1/61</td>
<td>1/58</td>
<td>1.7</td>
<td>0.95 (0.06–14.85)</td>
</tr>
<tr>
<td>Beausoleil et al, 2007 (33)</td>
<td>1/44</td>
<td>7/45</td>
<td>3.0</td>
<td>0.15 (0.02–1.14)</td>
</tr>
<tr>
<td>Bravo et al, 2008 (34)</td>
<td>0/41</td>
<td>0/45</td>
<td>–</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Can et al, 2006 (35)</td>
<td>0/73</td>
<td>2/78</td>
<td>1.4</td>
<td>0.21 (0.01–4.37)</td>
</tr>
<tr>
<td>Duman et al, 2005 (36)</td>
<td>0/196</td>
<td>1/180</td>
<td>1.2</td>
<td>0.31 (0.01–7.47)</td>
</tr>
<tr>
<td>Gao et al, 2010 (37)</td>
<td>9/171</td>
<td>20/84</td>
<td>23.0</td>
<td>0.22 (0.11–0.46)</td>
</tr>
<tr>
<td>Hickson et al, 2007 (38)</td>
<td>0/56</td>
<td>9/53</td>
<td>1.6</td>
<td>0.05 (0.00–0.84)</td>
</tr>
<tr>
<td>Kotowska et al, 2005 (39)</td>
<td>3/119</td>
<td>10/127</td>
<td>7.9</td>
<td>0.32 (0.09–1.14)</td>
</tr>
<tr>
<td>Lönnermark et al, 2010 (40)</td>
<td>1/80</td>
<td>0/83</td>
<td>1.3</td>
<td>3.11 (0.13–75.26)</td>
</tr>
<tr>
<td>McFarland et al, 1995 (41)</td>
<td>3/97</td>
<td>4/96</td>
<td>5.9</td>
<td>0.74 (0.17–3.23)</td>
</tr>
<tr>
<td>Miller et al, 2008 (47)</td>
<td>4/95</td>
<td>7/94</td>
<td>8.9</td>
<td>0.57 (0.17–1.87)</td>
</tr>
<tr>
<td>Miller et al, 2008 (47)*</td>
<td>2/157</td>
<td>0/159</td>
<td>1.4</td>
<td>5.06 (0.25–104.63)</td>
</tr>
<tr>
<td>Plummer et al, 2004 (42)</td>
<td>2/69</td>
<td>5/69</td>
<td>4.9</td>
<td>0.40 (0.08–1.99)</td>
</tr>
<tr>
<td>Paraskevis et al, 2010 (48)</td>
<td>1/216</td>
<td>4/221</td>
<td>2.7</td>
<td>0.26 (0.03–2.27)</td>
</tr>
<tr>
<td>Rafiq et al, 2007 (49)</td>
<td>5/45</td>
<td>22/55</td>
<td>16.1</td>
<td>0.28 (0.11–0.67)</td>
</tr>
<tr>
<td>Ruszczyński et al, 2008 (43)</td>
<td>3/120</td>
<td>7/120</td>
<td>7.2</td>
<td>0.43 (0.11–1.62)</td>
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<tr>
<td>Safdar et al, 2008 (44)</td>
<td>0/23</td>
<td>1/17</td>
<td>1.3</td>
<td>0.25 (0.01–5.79)</td>
</tr>
<tr>
<td>Selinger et al, 2011 (50)</td>
<td>0/62</td>
<td>0/62</td>
<td>–</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Surawicz et al, 1989 (45)</td>
<td>3/116</td>
<td>5/64</td>
<td>6.5</td>
<td>0.33 (0.08–1.34)</td>
</tr>
<tr>
<td>Thomas et al, 2001 (46)</td>
<td>2/133</td>
<td>3/134</td>
<td>4.0</td>
<td>0.67 (0.11–3.96)</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

Favors Experimental Group

Favors Control Group

Relative Risk (95% CI) M–H Random

Heterogeneity: $\chi^2 = 0.00$; chi-square = 12.09; $P = 0.79$; $I^2 = 0\%$

Test for overall effect: $Z = 5.87$; $P < 0.001$

Annals of Internal Medicine - Subgroup Analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Events/Patients, n/n</th>
<th>Relative Risk (95% CI)</th>
<th>P Value for Test of Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probiotic Group (n = 1974)</td>
<td>Control Group (n = 1844)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>33/1674</td>
<td>90/1539</td>
<td>0.22 (0.23–0.49)</td>
</tr>
<tr>
<td>Children</td>
<td>7/300</td>
<td>18/305</td>
<td>0.40 (0.17–0.96)</td>
</tr>
<tr>
<td>Probiotic dosage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;10 billion CFU/d</td>
<td>36/1775</td>
<td>98/1634</td>
<td>0.34 (0.23–0.49)</td>
</tr>
<tr>
<td>≤10 billion CFU/d</td>
<td>4/199</td>
<td>10/210</td>
<td>0.61 (0.08–4.60)</td>
</tr>
<tr>
<td>Species</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (mixed) species</td>
<td>8/335</td>
<td>37/339</td>
<td>0.30 (0.15–0.61)</td>
</tr>
<tr>
<td>L. acidophilus + L. casei</td>
<td>11/431</td>
<td>31/350</td>
<td>0.21 (0.11–0.42)</td>
</tr>
<tr>
<td>L. rhamnosus</td>
<td>12/566</td>
<td>18/565</td>
<td>0.63 (0.30–1.33)</td>
</tr>
<tr>
<td>S. boulardii</td>
<td>9/642</td>
<td>22/590</td>
<td>0.39 (0.19–0.82)</td>
</tr>
<tr>
<td>Risk of bias</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>17/695</td>
<td>52/613</td>
<td>0.27 (0.16–0.46)</td>
</tr>
<tr>
<td>High or unclear</td>
<td>23/1279</td>
<td>56/1231</td>
<td>0.42 (0.26–0.68)</td>
</tr>
<tr>
<td>Species</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>21/1208</td>
<td>40/1155</td>
<td>0.50 (0.29–0.84)</td>
</tr>
<tr>
<td>Multiple</td>
<td>19/766</td>
<td>68/689</td>
<td>0.25 (0.15–0.41)</td>
</tr>
</tbody>
</table>
Annals of Internal Medicine Discussion

• Probiotics for primary prevention may cause a reduction in CDAD rates
  – Moderate quality evidence
  – Three studies found clinical benefit

• Probiotic dose and type of species did not impact outcome

• Potential difference in outcome for number of species in probiotic preparation

• Other considerations
  – CDAD diagnosis based on definition used in each study
  – Significant variability in the type of probiotics and patient populations
Lactobacilli and bifidobacteria in the prevention of antibiotic-associated diarrhea and *Clostridium difficile* diarrhea in older inpatients (PLACIDE)

**Methods**
- Prospective, multicenter, double-blind, randomized placebo-controlled
- Inclusion: ≥65 years, exposure to ≥1 PO or IV antibiotic in ≤7 days or about to start antibiotic therapy
- Exclusion: Existing diarrhea or IBD, immunocompromised, ICU admission, prosthetic heart valve, CDI ≤3 months, pancreatitis, jejunal feeds, mesenteric vessel abnormality

**Intervention**
- Probiotic=*Lactobacillus acidophilus* and bifidobacterium
  - Dose=6x10^{10} live bacteria
  - Placebo=identical capsules filled with inert maltodextrin powder
  - Regimen: 1 capsule daily x 21 days
  - Continued after hospital discharge

PLACIDE Trial

- Primary outcomes
  - AAD at week 8
    - Estimated occurrence of 20% in placebo-treated patients
  - CDAD at week 12
    - Estimated occurrence of 4% in placebo-treated patients
  - Power analysis
    - 2478 individuals needed to detect a 50% reduction in CDAD in the treatment group

<table>
<thead>
<tr>
<th>Secondary outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity and duration</td>
</tr>
<tr>
<td>Serious adverse events</td>
</tr>
<tr>
<td>Microbial preparation tolerability</td>
</tr>
</tbody>
</table>

PLACIDE Trial

17,420 patients assessed for eligibility

2981 randomized

14,439 not recruited

3202 excluded

9068 declined participation

1493 probiotic group
1470 analyzed

1488 placebo group
1471 analyzed

## PLACIDE Trial: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Probiotic N=1470</th>
<th>Placebo N=1471</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age (years)</strong></td>
<td>77.2 (70.8-83.6)</td>
<td>77 (71.3-83.5)</td>
</tr>
<tr>
<td><strong>Gender (male)</strong></td>
<td>777 (52.9%)</td>
<td>679 (46.2%)</td>
</tr>
<tr>
<td><strong>White ethnicity</strong></td>
<td>1459 (99.9%)</td>
<td>1461 (99.8%)</td>
</tr>
<tr>
<td><strong>Admitted from</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Home</td>
<td>1345 (91.6%)</td>
<td>1334 (90.9%)</td>
</tr>
<tr>
<td>- Residential care</td>
<td>58 (3.9%)</td>
<td>67 (4.6%)</td>
</tr>
<tr>
<td>- Other hospital</td>
<td>37 (2.5%)</td>
<td>39 (2.7%)</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- HTN</td>
<td>779 (53.5%)</td>
<td>812 (55.7%)</td>
</tr>
<tr>
<td>- COPD</td>
<td>350 (24%)</td>
<td>354 (24.2%)</td>
</tr>
<tr>
<td>- DM</td>
<td>357 (24.4%)</td>
<td>314 (21.4%)</td>
</tr>
<tr>
<td><strong>Hospital admission ≤ 8 weeks</strong></td>
<td>488 (33.2%)</td>
<td>448 (30.5%)</td>
</tr>
<tr>
<td><strong>Live bacteria consumption ≤ 2 weeks</strong></td>
<td>72 (4.9%)</td>
<td>45 (3.1%)</td>
</tr>
</tbody>
</table>

All data reported as n (%)
## PLACIDE Trial: Antibiotic Therapy

<table>
<thead>
<tr>
<th>Antibiotic class</th>
<th>Probiotic N=1470</th>
<th>Placebo N=1471</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>1052 (71.6%)</td>
<td>1061 (72.1%)</td>
</tr>
<tr>
<td>Cephalosporin</td>
<td>359 (24.4%)</td>
<td>356 (24.2%)</td>
</tr>
<tr>
<td>Quinolones</td>
<td>185 (12.6%)</td>
<td>180 (12.2%)</td>
</tr>
<tr>
<td>Macrolides</td>
<td>249 (16.9%)</td>
<td>251 (17.1%)</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>171 (11.6%)</td>
<td>142 (9.7%)</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>18 (1.2%)</td>
<td>14 (1%)</td>
</tr>
</tbody>
</table>

### Duration of antibiotic therapy

<table>
<thead>
<tr>
<th>Duration</th>
<th>Probiotic N=1470</th>
<th>Placebo N=1471</th>
</tr>
</thead>
<tbody>
<tr>
<td>One dose</td>
<td>133 (9.5%)</td>
<td>123 (8.8%)</td>
</tr>
<tr>
<td>1-6 days</td>
<td>389 (27.7%)</td>
<td>398 (28.5%)</td>
</tr>
<tr>
<td>7-13 days</td>
<td>402 (28.6%)</td>
<td>426 (30.5%)</td>
</tr>
<tr>
<td>≥14 days</td>
<td>482 (34.3%)</td>
<td>451 (32.3%)</td>
</tr>
</tbody>
</table>

All data reported as n (%)
## PLACIDE Trial: Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Probiotic N=1470</th>
<th>Placebo N=1471</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAD</td>
<td>159 (10.8%)</td>
<td>153 (10.4%)</td>
<td>0.72</td>
</tr>
<tr>
<td>CDAD</td>
<td>12 (0.8%)</td>
<td>17 (1.2%)</td>
<td>0.35</td>
</tr>
<tr>
<td>CDAD duration (days)</td>
<td>5 (3-8)</td>
<td>9 (6-13)</td>
<td>N/A</td>
</tr>
<tr>
<td>CDAD severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Mild</td>
<td>7 (63.6%)</td>
<td>7 (50%)</td>
<td>N/A</td>
</tr>
<tr>
<td>• Moderate</td>
<td>1 (9.1%)</td>
<td>2 (14.3%)</td>
<td></td>
</tr>
<tr>
<td>• Severe</td>
<td>3 (27.3%)</td>
<td>5 (35.7%)</td>
<td></td>
</tr>
<tr>
<td>Hospital LOS</td>
<td>4 (1-11)</td>
<td>4 (1-11)</td>
<td>0.87</td>
</tr>
</tbody>
</table>

All data reported as n (%) or median (IQR), as appropriate

- No gastrointestinal symptoms or serious adverse events attributed to probiotic preparation
- No differences in quality of life or tolerability of preparation

PLACIDE Trial: Discussion

• Stool sample collection for patients with AAD
  – 93/159 (59%) in probiotic group
  – 88/153 (58%) in placebo group

• Adherence to 21 days of therapy
  – ~50% in both groups
  – ~75% took ≥14 days of therapy

• Power
  – CDAD occurred at lower rate in the placebo group than estimated 4%
  – 7750 patients needed to detect a 50% reduction in CDAD with an incidence of 1.2% in placebo-treated patients
PLACIDE Trial: Conclusions

- Probiotic preparation of lactobacilli and bifidobacteria not effective for AAD or CDAD prevention
  - Low incidence rates of both primary outcomes

- No difference in severity and duration of CDAD

- Similar hospital LOS in both groups

- No difference in tolerability or adverse events

Probiotic Safety Considerations

• Risk factors

<table>
<thead>
<tr>
<th>Major</th>
<th>Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Immunocompromised</td>
<td>• Central venous catheter</td>
</tr>
<tr>
<td>• Prematurity</td>
<td>• Impaired epithelial barrier</td>
</tr>
</tbody>
</table>

• Case reports

  – Fungal sepsis with *Saccharomyces boulardii* (N=24)
  – Bacterial sepsis
    – *Lactobacillus rhamnosus* (N=7)
    – *Bacillus subtilis* (N=5)

• No reported cases in otherwise healthy individuals

Unanswered Questions

• Role of probiotics outside of primary prevention of CDI?

• Studying the right patient populations?

• Appropriate doses studied?

• Are we looking at the right probiotics?

• Role of microbial ecosystem therapeutics?
Summary

**Efficacy**
- Meta-analyses show potential benefit
- Largest RCT found no benefit

**Safety**
- Potential for sepsis
- Increased with certain risk factors
- ↑ safety concerns with *Saccharomyces boulardii*

**Cost**
- Inexpensive
- Increased pill burden for patients
Conclusions

• Many studies currently being conducted
  – Elderly
  – Critically ill
  – Hospitalized

• PLACIDE study questioned the efficacy of probiotics

• Current lack of data to support routine use of probiotics for primary prevention of CDI
Probiotics for Primary Prevention of \textit{Clostridium difficile} Infection

April 24, 2015
Sarah Petite, Pharm.D.
PGY-2 Pharmacotherapy Resident