**Impact of a Pharmacist-Driven Probiotic Protocol on the Incidence of Antibiotic- and *Clostridium difficile*-Associated Diarrhea in Hospitalized Patients Receiving Antibiotic Therapy**

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Abstract # 13
IRB Approved

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# Disclosure

- Mona Kamali
- Potential conflicts of interest: none
- Sponsorship: none
- Proprietary information or results of ongoing research may be subject to different interpretations
- Speaker's presentation is educational in nature and agrees to abide by the non-commercialism guidelines provided

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# Learning Objectives

1) Evaluate whether probiotics reduce the incidence of antibiotic-associated and *Clostridium difficile*-associated diarrhea in hospitalized patients on antibiotics
2) Describe the appropriate timing of initial probiotic administration, duration of probiotic administration, incidence of severe adverse effects, and potential associated healthcare cost savings

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# Background

- Antibiotics disrupt the normal intestinal flora
  - Common cause of antibiotic-associated diarrhea (AAD) and *Clostridium difficile*-associated diarrhea (CDAD)
- *Clostridium difficile* - leading cause of nosocomial outbreaks of diarrhea and colitis
- AAD and CDAD contribute to increased:
  - Hospital length of stay
  - Morbidity and mortality
  - Healthcare costs ($3,427 - $9,960 per episode of CDI)

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# Probiotics

- May reduce the incidence of AAD and CDAD and lead to significant cost savings
- Proposed mechanism of action:
  - Competition with pathogens for nutrients
  - Inhibition of pathogen adherence to the gastrointestinal mucosa
- 2017 IDSA Guidelines for *Clostridium difficile* Infection:
  - Insufficient data to support use of probiotics for primary prevention of CDI

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# Gao, et al.

- Objective: Determine incidence of AAD and CDAD in patients receiving Bio-K Plus® *(L. acidophilus* CL1285®, *L. casei LBC80R®, L. rhamnosus CLR2®*)
- Single-center, randomized, double-blind, controlled trial comparing placebo vs. Bio-K Plus® 50 billion CFU daily (Pro-1) vs BID (Pro-2).
- Results (Placebo vs. Pro-1 or Pro-2):
  - Incidence of AAD: 44.1% in placebo vs. 28.2 % in Pro-1 and 15.5% in Pro-2 ($p<0.001$)
  - Incidence of CDAD:
    - Pro-1: 23.8% in placebo vs. 9.4% ($p=0.03$)
    - Pro-2: 23.8% in placebo vs. 1.2% ($p=0.002$)

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## Shen, et al.

- Methods
  - Systematic review with meta-regression analysis of randomized controlled trials reporting CDI
- Results:
  - Risk of CDAD per 1,000 patients without probiotics vs. with probiotics
    - 39/1,000 vs. 16/1,000 [(RR: 0.42 (0.30-0.57)]
- Subgroup Analysis
  - Timing of probiotic administration was the only significant predictor of efficacy
    - Significantly more effective if given within 2 days

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## Norman Regional Health System

- Porter, HealthPlex, and Moore campuses
- Licensed for 387 beds
- Acute care community hospital

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## Study Objectives

- Primary outcomes
  - Incidence of AAD and healthcare-associated CDAD in hospitalized patients receiving antibiotics without probiotics vs. with probiotics
    - Healthcare Facility-Onset *C. difficile* Infection (HO CDI)
    - Community-Onset Healthcare Facility-Associated CDI (CO-HCFA CDI)
- Secondary outcomes
  - Timing of initial probiotic administration in patients with CDI
  - Incidence of severe adverse effects
  - Potential healthcare cost savings

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## Methods

- Multi-center quasi-experimental study of hospitalized patients 18 years of age and greater who received antibiotics
- Inclusion Criteria
  - Patients 18 years of age or older and receiving antibiotics while admitted to an acute care unit at Norman Regional Health System
- Exclusion Criteria
  - Pregnancy
  - Lactation
  - Receiving antibiotics for surgical prophylaxis
  - Unable to be fed through the gastrointestinal tract

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## Phase I Methods

- IRB-approved retrospective chart review of patients with a negative or positive *C. difficile* PCR test
  - July 1, 2017 to September 30, 2017

**Pre-Intervention Data Collection**

- Admission date
- Date and result of *C. difficile* PCR
- Antibiotics received during admission
- Probiotics received prior to admission

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## Phase II Methods

- Bio-K Plus® and Lactinex® approved for addition to hospital formulary
- Surveillance technology built to identify candidates and monitor safety and appropriate use of probiotics
- Pharmacist education of appropriate ordering of probiotics
- Nursing education of appropriate administration of probiotics
- Pharmacist-driven probiotic protocol implemented

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## Phase III Methods

- Pharmacists ordered probiotics for eligible patients
  - Bio-K Plus® 1 capsule (50 billion CFU) PO BID
  - Lactinex® (*L. acidophilus and bulgaricus)* 4 tabs (4 million CFU) PT QID
- Probiotic timing and duration
  - Administered at least 2 hours after initial antibiotic dose (preferably within 2 days)
  - Continued for 5 days after completion of antibiotics
- Clinical pharmacists monitored eligible patients daily through clinical surveillance system

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## Phase III Methods

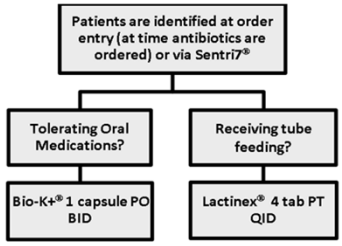


Figure 1: Process for pharmacist ordering of probiotics

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## Phase III Results

- Data Collection
  - Two groups:
    - Group 1 (July 1 to September 30, 2017)
      - Pre-implementation of probiotic protocol
    - Group 2 (January 16 to April 17, 2018)
      - Post-implementation of probiotic protocol

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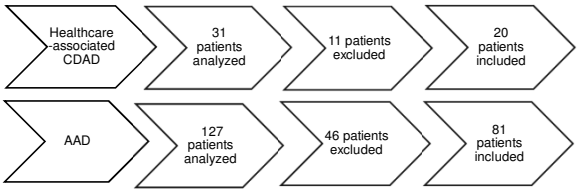
## Phase III Results

- Group 1 (July 1 to September 30, 2017)
  - Pre-implementation of probiotic protocol

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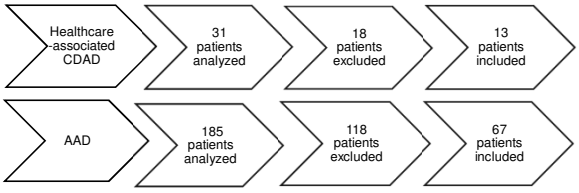
## Phase III Results

- Group 2 (January 16 to April 17, 2018)
  - Post-implementation of probiotic protocol

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## Phase III Results: AAD

| | Group 1 | Group 2 | Difference in Incidence |
|---|---|---|---|
| Patient Days | 12354 | 14649 | 18.6% |
| AAD Cases | 81 | 67 | -17.3% |
| AAD Incidence (per 10,000 patient days) | 65.6 | 45.7 | -30.3% |

- Potential cost savings for reduced incidence of AAD (reduced number of *C. difficile* PCR tests)
  - $\frac{\sim 20\ tests}{90\ days} = \frac{\sim 81\ \text{tests}}{365\ days}$
  - 81 tests/year x \$60/test = \$4,860/year

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## Phase III Results: HO and CO-HCFA CDI

| | Group 1 | Group 2 | Difference in Incidence |
|---|---|---|---|
| Patient Days | 12354 | 14649 | 18.6% |
| Number of Patient Admissions | 2960 | 3515 | 18.8% |
| HO CDI Cases | 17 | 10 | -41.2% |
| HO CDI Incidence (per 10,000 patient days) | 13.8 | 6.8 | -50.7% |
| CO-HCFA CDI Cases | 3 | 3 | 0% |
| CO-HCFA-CDI Incidence (per 1,000 patient admissions) | 1.0 | 0.85 | -15.0% |
| Total: HO and CO-HCFA CDI Cases | 20 | 13 | -35.0% |
| Total: HO and CO-HCFA CDI Incidence (per 10,000 patient days) | 16.2 | 8.9 | -45.0% |

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## Phase III Results: Group 2

- Potential healthcare cost savings
  - Reduction of HCA CDI (HO CDI + CO-HCFA CDI Incidence)
    - $\frac{7\ patients}{90\ days} = \frac{\sim 28\ patients}{365\ days}$
    - 28 patients x ($3,427 - $9,960 per episode)
    - **Annual cost savings = $95,956 - $278,880**
  - Reduced incidence of AAD (reduced number of PCR tests)
    - **Annual cost savings = $4,860**
  - Annual probiotic cost:
    - $\frac{\$10,881}{48\ \text{days}} \times \frac{X}{365\ \text{days}} = \$82,741$
  - **Total annual cost savings = $18,075 - $200,999**

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## Phase III Results: Group 2

- Timing of initial probiotic administration in relation to initial antibiotic dose for patients with AAD + HO CDI + CO-HFCA CDI
  - Mean: 27 hours and 3 minutes (SD: 19 hours and 5 minutes)
  - Range: 104 hours and 19 minutes
- Incidence of severe adverse effects: None

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## Limitations

- Significant number of doses (~10 doses) missed for some patients
- Patients may not have continued probiotics through 5 days following completion of antibiotics after discharge
- Bio-K Plus® is not readily available for purchase outpatient
- Restrictions initiated in Phase III for CDI PCR tests ordered after the 3rd calendar day of admission

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## Conclusions

- Probiotics may be effective in reducing both AAD and healthcare-associated CDAD in hospitalized patients receiving antibiotics
- Probiotics should be initiated within 2 days of antibiotics for effective prevention of *Clostridium difficile*-associated diarrhea
- A pharmacist-driven probiotic protocol may result in substantial healthcare cost savings

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## Future Directions

- Protocol has been modified to allow administration of Bio-K+® to patients with a feeding tube
- Results of 3-month data will be presented to Medicine Executive Committee for approval to continue protocol
- Dependent upon approval:
  - Incorporation of probiotics into standard order sets containing antibiotics
  - Expansion of the probiotic protocol to other patient populations

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# References


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# Acknowledgements


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# Self-Assessment Questions

1) In the study by Gao, et al., a dose-response relationship was demonstrated as increased probiotic dosage resulted in a lower incidence of both AAD and CDAD.
   a. True
   b. False
2) According to the study by Shen, et al., when should probiotics be initiated in patients receiving antibiotics for effective prevention of *Clostridium difficile*-associated diarrhea?
   a) Within 24 hours of the first antibiotic dose
   b) Within 2 days of the first antibiotic dose
   c) Within 3 days of the first antibiotic dose
   d) Within 36 hours of the first antibiotic dose

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