RETROSPECTIVE REVIEW OF THE EFFICACY OF A PHARMACIST DRIVEN PROBIOTIC PROTOCOL FOR THE PREVENTION OF HOSPITAL ONSET *CLOSTRIDIUM DIFFICILE* INFECTIONS AMONG INPATIENTS RECEIVING HIGH-RISK ANTIMICROBIALS

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IRB status: received

Disclosure Statement

- Vivian Nguyen
- Conflict of interest – none
- Sponsorship - none
- Propriety information or results of ongoing research is subject to different interpretation
- Speaker’s presentation is educational in nature and abides by the non-commercial guidelines

Learning Objectives

- Explain the mechanisms of probiotics in the prevention of *Clostridium difficile* infections (CDI)
- Identify the most common risk factors of CDI
- State the percent reduction of antibiotic HO-CDI per 10,000 patient days with probiotic use found in this study

Providence Alaska Medical Center

- Tertiary care community medical center in Anchorage, AK
- Level II trauma center
- Largest hospital in the state of Alaska
  - 402 beds
  - 37 adult ICU beds
  - 62 ED beds
  - Primary referral center
  - Cardiac surgery
  - Dialysis

Pre-Test Assessment Questions

1. Which of the following are mechanisms of probiotics in the prevention of CDI?
   a) Inhibiting acid production in the stomach
   b) Creating toxins
   c) Interfering with toxin binding
2. Which of the following antibiotic(s) has been associated with CDI?
   a) Fluoroquinolones
   b) Clindamycin
   c) Carbapenems
3. Probiotics reduced the rate of antibiotic HO-CDI by ___ % compared to the control group?
   a) 20%
   b) 36%
   c) 75%

Study Objective

- To evaluate the efficacy of a pharmacist driven protocol for probiotic use in the prevention of *Clostridium difficile* infections (CDI) among inpatients who received high-risk antimicrobials
- Primary endpoint
  - Rate of CDI per 10,000 patient days
- Secondary endpoint
  - Rate of antibiotic associated diarrhea (AAD) per 10,000 patient days

Background

- *Clostridium difficile* (*C. difficile*) is an anaerobic, gram-positive, spore-forming bacterium which may infect human hosts after antibiotic disruption of normal gut flora
- Risk factors include advanced age, inpatient stay, chronic conditions, antibiotic use
- Probiotics may aid in preventing *C. difficile* colitis by several mechanisms:
  - producing substances with antimicrobial activity
  - modulating innate and adaptive intestinal barrier immune systems
  - producing acids that lower gut pH to prevent bacterial growth
  - interfering with the binding of C. difficile toxins A and B to intestinal epithelial cells
- Current literature evaluating the efficacy of probiotics in the prevention of CDI is conflicting[2,3,4,5,6,8,9]

Probiotic Protocol

- Adult and pediatric patients who are receiving high-risk antibiotics receive either *Lactobacillus rhamnosus* GG 1 capsule or *Lactobacillus acidophilus* and *bulgaricus* 1 packet by mouth twice daily
- Patients are not eligible for this protocol if they are NPO, neonates <1-year-old, pregnant, have cystic fibrosis, ventriculoperitoneal (VP) shunts in place, a prosthetic heart valve, or are immunocompromised (neutropenia, HIV with CD4 count <200 cells/mm^3, malignancy undergoing chemotherapy or radiation, transplant patients on current immunosuppression)
- Probiotics are given at the time of antibiotic initiation or as soon as possible thereafter
- Continued for 5 to 7 days after completion or discontinuation of the high-risk antimicrobial

Methodology

- Electronic health records of patients receiving high risk antibiotics will be reviewed retrospectively over two time periods:
  - Pre-protocol implementation (May 25, 2016 to May 24, 2017)
  - Post-protocol implementation (May 25, 2017 to May 24, 2018)
- Diarrhea defined as passage of ≥ 3 unformed stools (Type 6 or 7 on the Bristol Stool chart) in ≤ 24 consecutive hours
- Antibiotic associated diarrhea (AAD) defined as diarrhea negative for CDI

Methodology

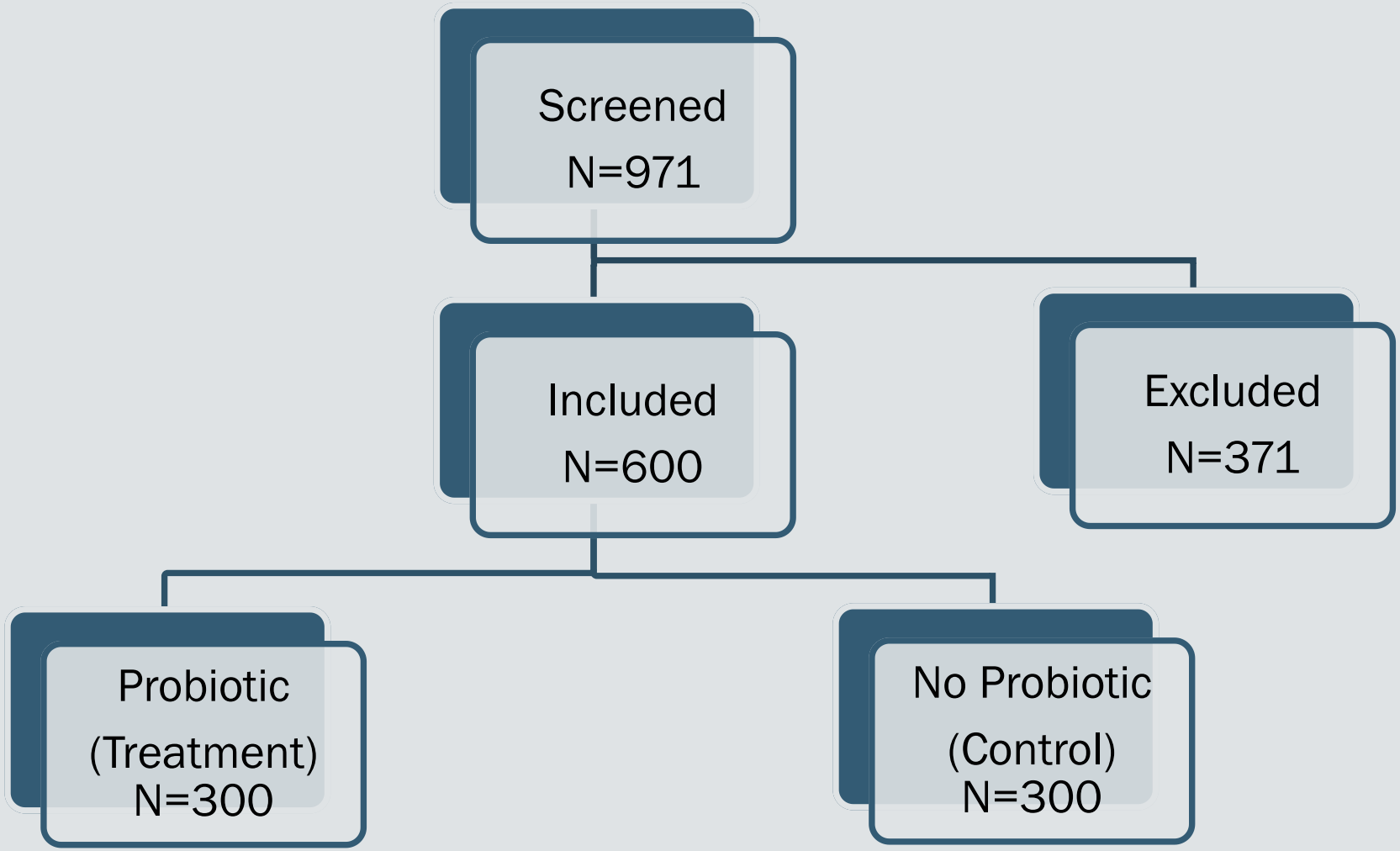
Inclusion Criteria

- ≥18 years of age
- Length of stay >48 hours
- Received high-risk antimicrobials for >48 hours
  - Clindamycin
  - 3rd or 4th generation cephalosporins
    - Ceftriaxone, cefoxitin, cefpodoxime, cefdinir, ceftazidime, and cefepime
  - Fluoroquinolones
    - Levofloxacin, ciprofloxacin, and moxifloxacin
  - Beta-lactam/beta-lactamase inhibitor combinations
    - Amoxicillin/clavulanate, ampicillin/sulbactam, and piperacillin/tazobactam
  - Carbapenems
    - Ertapenem, imipenem, meropenem, and doripenem

Exclusion Criteria

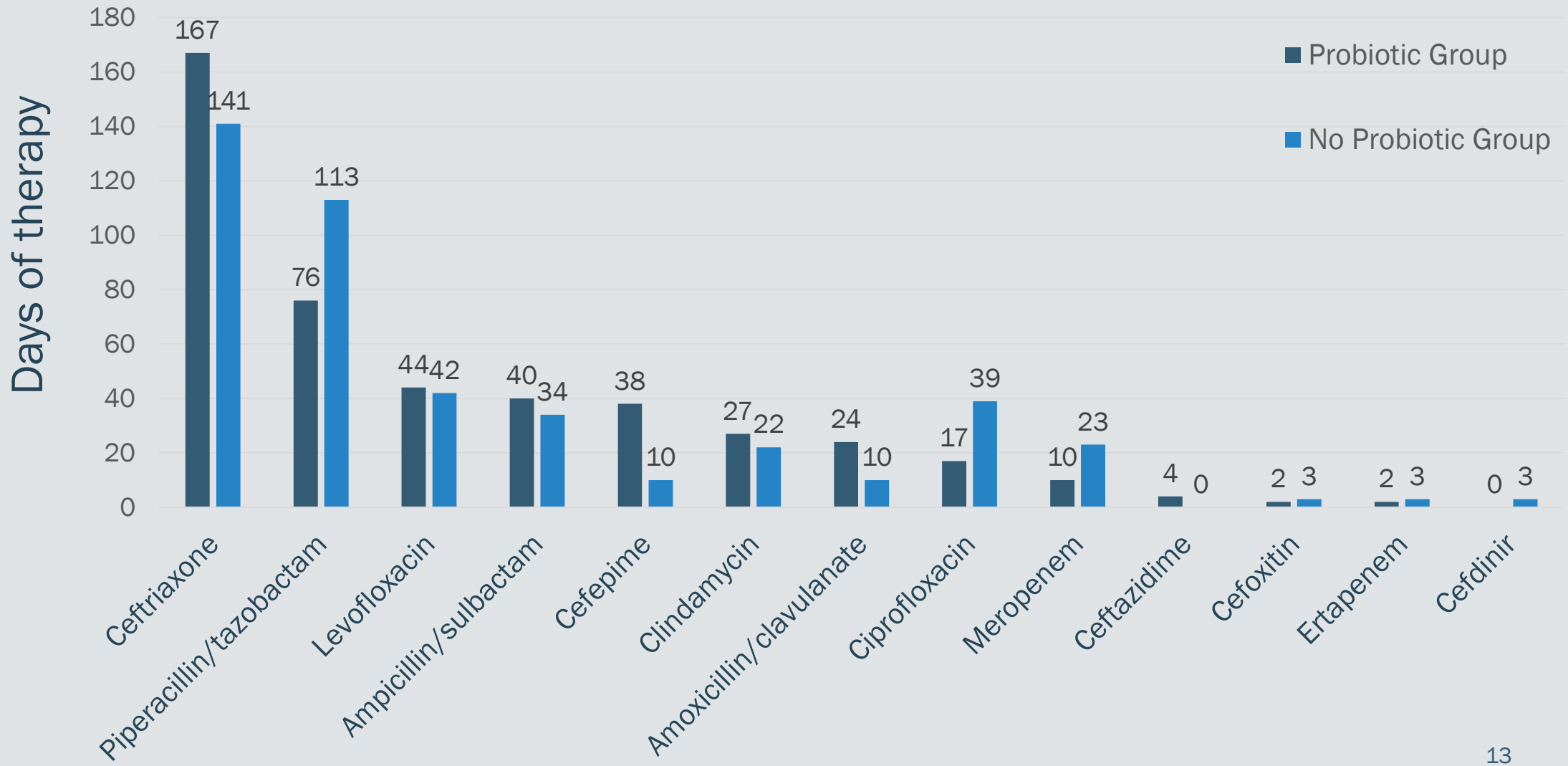
- Pregnant
- Incarcerated
- Previously taking probiotics prior to admission
- Probiotic administration not ordered as a result of protocol
- Probiotic orders initiated not by pharmacy
- Receipt of probiotics for <48 hours
- Previous infections with *C. difficile* in the previous 90 days
- Cystic fibrosis patients
- Patients with currently implanted VP shunts
- Patients with prosthetic heart valves
- Immunocompromised patients

Methodology



Baseline Characteristics	Probiotic (N=300)	No Probiotic (N=300)	P-value (95% CI)
Male	148 (49.3%)	149 (49.7%)	0.935
Age (years) Mean ± SD	62±18	63±18	0.57 (-2.08 to 3.77)
Comorbidities • Diabetes • Irritable bowel syndrome • Inflammatory bowel disease • Chronic kidney disease	 103 (34.3%) 1 (0.3%) 3 (1.0%) 65 (21.7%)	 103 (34.3%) 3 (1.0%) 12 (4.0%) 64 (21.3%)	 1.000 0.616 0.036 0.921
≥2 comorbidities	43 (14.3%)	48 (16.0%)	0.649
ALF or nursing home prior to admission	22 (7.3%)	25 (8.3%)	0.761
CrCl (mL/min) Mean ± SD	94.9±74	89.9±66	0.382 (-6.23 to 16.25)
Hypoalbuminemia (<2.7 g/dL)	30 (10.0%)	41 (13.7%)	0.206
PPI use prior to admission	67 (22.3%)	78 (26.0%)	0.008
H2RA use prior to admission	18 (6.0%)	11 (3.7%)	0.253
Mean number of previous hospital admissions ± SD	1.05±1.64	1.06±2.00	0.947 (-0.30 to 0.28)

High-Risk Antibiotic Days of Therapy



Results

	Probiotic (N=300)	No Probiotic (N=300)	P-value (95% CI)
PPI use during admission	115 (38.3%)	139 (46.3%)	0.057
H2RA use during admission	86 (28.7%)	89 (29.7%)	0.857
GI procedures	54 (18.0%)	61 (20.3%)	0.534
Enteral tube feeds	40 (13.3%)	49 (16.3%)	0.358
Mean number of high-risk antibiotics ± SD	1.5±0.73	1.5±0.73	0.911 (-0.11 to 0.12)
Mean duration of hospitalization (days)	18±66	11±13	0.103 (-1.29 to 14.05)
Mean duration of high-risk antibiotic therapy ±SD	6.67±4.84	6.68±4.39	0.977 (-0.75 to 0.73)
Mean days of high-risk antibiotic therapy ± SD	7.10±5.13	7.16±5.15	0.874 (-0.89 to 0.76)

Results

	Probiotic (N=300)	No Probiotic (N=300)	P-value (95% CI)
Total days of hospitalization	5351	3435	
Number of CDI	16 (5.3%)	16 (5.3%)	1.000
Total number of antibiotic associated diarrhea (AAD)	67 (22.3%)	91 (30.3%)	0.033
CDI within 12 weeks of admission date	13	9	0.515
Therapy included metronidazole	74 (24.7%)	74 (24.7%)	1.000
Endpoints	**Probiotic (N=300)**	**No Probiotic (N=300)**	**RR (95% CI)**
CDI rate per 10,000 patient days	30	47	0.64 (0.32 to 1.28) P = 0.2099
AAD rate per 10,000 patient days	125	170	0.47 (0.34 to 0.65) P <0.0001

Results

Compliance with Probiotic Protocol	Probiotic (N=300)
Mean time to initiation of probiotic in relation to start of antibiotic	30 hours
Mean duration of probiotics	6 days
Probiotic continued for 5-7 days after antibiotic therapy	44 (14.7%)
Probiotic not continued for 5-7 days after antibiotic therapy	58 (19.3%)
Probiotic not continued due to discharge	198 (66.0%)

Discussion

- Study design - retrospective chart review
- Not generalizable
  - Single institution
  - Patient population
- Confounding variable: PPIs
- Compliance with probiotic protocol
- Small sample size
- Not powered to detect a difference in outcomes

Conclusions/Future Direction

- Preliminary data indicates reduction of CDI and AAD
- Optimize adherence to the probiotic protocol
- Larger patient population needed to determine difference
- There are other ways to prevent the spread CDI:
  - Hand hygiene
  - Patient isolation
  - Personal Protective Equipment
  - Antimicrobial stewardship
  - Cleaning high contact surfaces

Post-Test Assessment Questions

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