UWTASP

tele-antimicrobial stewardship program

August 20, 2019

Agenda

- Prophylaxis for *C. difficile*
- Case Discussions
- Open Discussion

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Prophylaxis for *C. difficile* Infection (CDI)

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Agenda

Goal: Discuss the evidence for prophylaxis in CDI

1.) Primary prophylaxis

2.) Secondary prophylaxis

3.) Probiotics: a yogurt a day keeps *C. diff* away?

citations

C. difficile Fact Sheet

IMPACT

C. diff causes close to half a million illnesses each year and can affect people of all ages.[1]

1 in 5 patients will get *C. diff* at least once more.[1]

One in 11 people over 65 diagnosed with a healthcare-associated *C. diff* infection die within a month.[1]

RISK

People on antibiotics are 7 to 10 times more likely to get *C. diff* while on the drugs and during the month after.[2]

Extended stays in healthcare settings, especially hospitals and nursing homes, also increase risk.

More than 80% of *C. diff* deaths occur in people 65 and older.

cdc.gov/cdiff

[1] Table 3 from Lessa FC, Mu Yi, Bamberg WM et al. N Engl J Med 2015;372:825-34. DOI: 10.1056/NEJMoa1408913

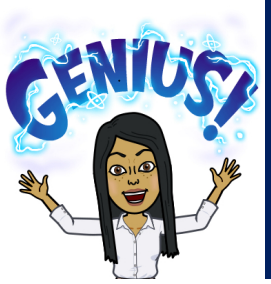
[2] Hensgens MPM, Goorhuis A, Dekkers OM, Kuijper EJ. J Antimicrob Chemother 2011. DOI: 10.1093/jac/dkr508

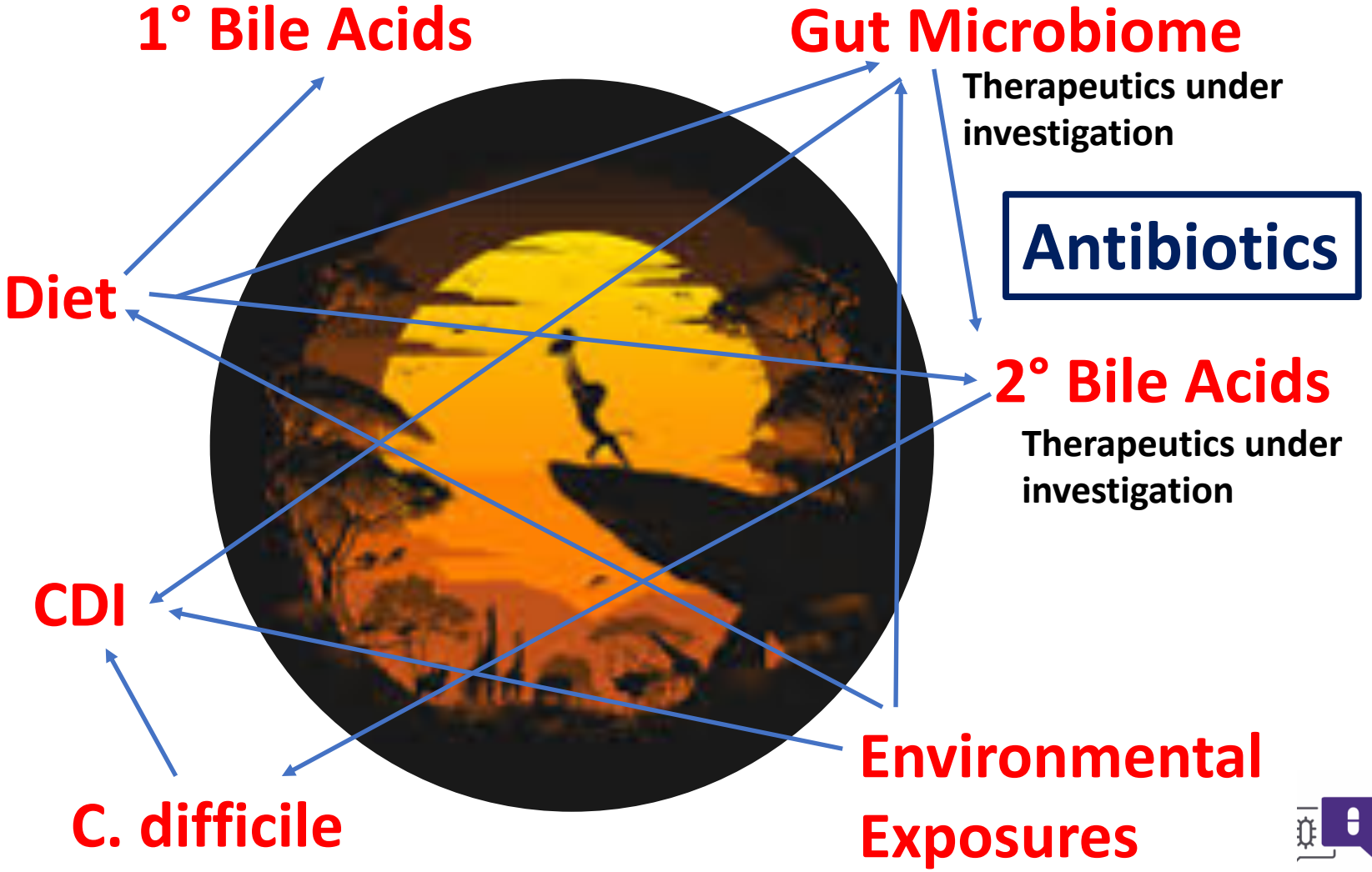
CS292825

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

citations

Everything is connected





Indications for Primary Prophylaxis

- *C.* difficile incidence in hematopoietic stem cell transplant (HSCT) recipients are 5 to 9 folder higher than general hospitalized population

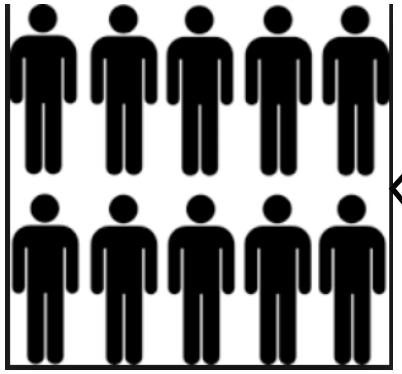
- CDI occurs in 5-15% of autologous and 12-34% of allogeneic HSCT recipients

- Contributing factors:
  - Cytotoxic chemotherapy
  - Prolonged neutropenia
  - **Broad spectrum antibiotics**
  - Possibly graft vs host disease (GVHD)

citations

Primary Prophylaxis – Fidaxomicin

Adults stem cell transplant with FQ prophylaxis



59% Autologous
41% Allogeneic

	Day 30 Failure	Day 30 CDI
PLACEBO (N = 299)	**30.8%**	**10.7%**
FIDAXOMICIN 200mg QD (N = 301)	**28.6% (NS)**	**4.3% p<0.05**

Primary Endpoint : Prophylaxis failure
Confirmed CDI, use of antibiotics effective against CDI for any reason, missing CDI assessments

citations

Mullane KM, et al. CID 2019;68:196-203.

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America

hivma hiv medicine association

OXFORD

Oral Vancomycin Prophylaxis Is Highly Effective in Preventing *Clostridium difficile* Infection in Allogeneic Hematopoietic Cell Transplant Recipients

Alex Ganetsky,[1] Jennifer H. Han,[2,3] Mitchell E. Hughes,[1] Daria V. Babushok,[4] Noelle V. Frey,[4] Saar I. Gill,[4] Elizabeth O. Hexner,[4] Alison W. Loren,[4] Selina M. Luger,[4] James K. Mangan,[4] Mary Ellen Martin,[4] Jacqueline Smith,[4] Craig W. Freyer,[1] Cheryl Gilmar,[3] Mindy Schuster,[2] Edward A. Stadtmauer,[4] and David L. Porter[4]

- Quality improvement initiative at U of Pennsylvania
- All allogeneic HSCT received oral vancomycin 125mg twice daily starting on hospital admission until discharge
- Primary outcome: CDI confirmed by 2-step testing
- Results:
  - Pre-implementation: No prophylaxis: 20% (11/55)
  - Post-implementation: Vancomycin prophylaxis: 0% (0/90)
  - P<0.001

citations

Fidaxomicin vs. Vancomycin

- No head to head comparison
- Vancomycin
  - Limited to observational studies
- Fidaxomicin
  - Narrower spectrum
  - Inhibits production of toxin A and B
  - Potent inhibitors of *C. difficile* spore formation
  - Post-hoc analyses suggested higher sustained clinical responses without recurrence in cancer patients

- Consider primary prophylaxis given high risk of CDI in HSCT transplant recipients.

citations Cornely OA, et al. J of Clin Oncology 2013

Audience Survey Question

59 yo male with history of previous CDI, admitted to your hospital with osteomyelitis requiring 6 weeks of antibiotics. Would you start oral vancomycin for CDI prophylaxis?

1) For sure
2) No way
3) Don’t know

citations

Audience Survey Question

What dose and frequency of oral vancomycin would you recommend?

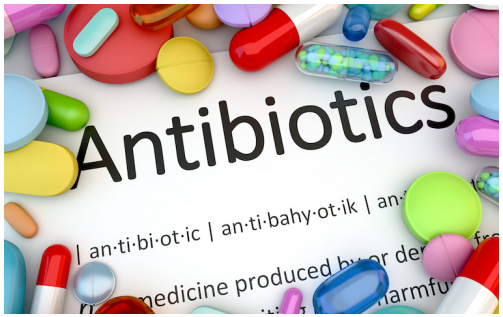
1) 125mg qdaily
2) 125mg twice daily
3) 125mg four times daily
4) 250mg twice daily

citations

Secondary Prophylaxis

- **Suppressive Therapy:**
  - Concurrent CDI while on systemic **antibiotics**
  - Extension of CDI suppressive therapy when concomitant systemic **antibiotics** can not be discontinued

- **Secondary Prophylaxis:**
  - Initiation of CDI prophylaxis in patients with previously treated CDI who systemic **antibiotics** are re-introduced



citations

Suppressive Therapy

- Retrospective study
  - 228 patients with incident CDI
  - regul
  - exten
- The two
  - Age, s
- Primary
  - CDI re treatment)
- CDI relapse rate
  - Regular (17%) vs. Extended (23%)
  - Adjusted OR 1.4 (95% CI: 0.7-2.7)

citations

Kaki R et al. The internet Journal of Infectious Diseases 2016

Oral Vancomycin Prophylaxis (OVP)

- Retrospective study
  - ≥ 18 yo with previous CDI and re-hospitalized requiring systemic antibiotics
  - 71 patients receiving OVP 125-250mg bid
  - 132 patients (control)

- Primary endpoint:
  - Recurrent CDI defined as PCR positive c. difficile within 4 wks of completion of systemic abx

- CDI recurrence:
  - 4.2% OVP vs. 26.6% control ($p<0.001$)

citation Van Hise et al, CID 2016;63:651-653

Secondary Prophylaxis (Incident vs. Recurrent CDI)

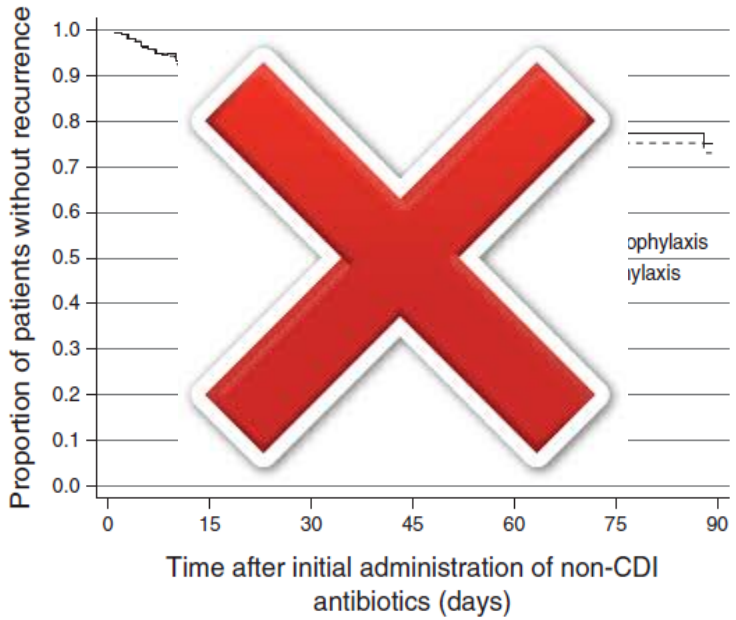
	Carignan (Canada)	Caroff (USA)
Inclusion Criteria	Previous CDI requiring systemic abx within 90 days after CDI diagnosis during a hospital admission or a visit to a hospital outpatient clinic.	Previous CDI requiring systemic abx within 150 days after CDI diagnosis during a hospital stay.
Primary Endpoints	CDI recurrence within 90d	CDI recurrence within 90d
Study population	551 patients OVP: 227 (41%) No OVP: 324 (59%) Age: 50% with ≥ 75yo	760 patients OVP: 193 (25%) No OVP: 567 (75%) Avg age = 59-64 yo
CDI relapse	32.9%	9.5%
Median abx exposure	14 days	5-6 days
Median duration of OVP	7 days	2.3 days

citations

Carignan et al. Am J Gastroenterol 2016
Caroff et al. ICHE 2019

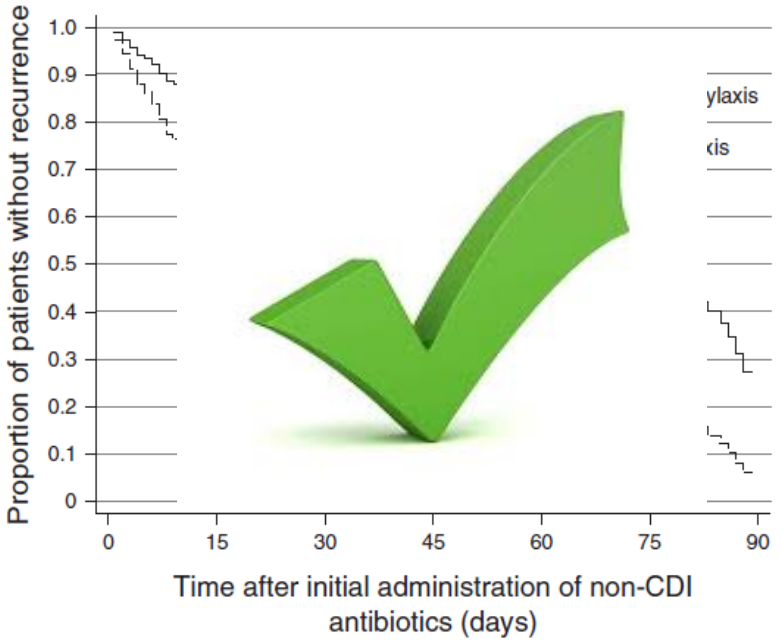
Vancomycin prophylaxis only beneficial in recurrent CDI

Incident CDI (1 previous CDI)



Number at risk							
No vancomycin prophylaxis	242	184	139	111	91	60	0
Vancomycin prophylaxis	137	115	95	84	75	58	0

Recurrent CDI (>1 episode)



Number at risk							
No vancomycin prophylaxis	82	47	34	19	16	8	0
Vancomycin prophylaxis	90	81	61	41	29	18	0

Carignan et al. Am J Gastroenterol 2016

citations

Vancomycin prophylaxis only effective in incident CDI

	Incident CDI (1 previous episode)		Recurrent CDI (>2 episodes)	
	No OVP (n=353)	OVP (n=118)	No OVP (n=118)	OVP (n=353)
CDI relapse (%)	10.5	8.5	7.8	10.9
Adjusted OR (95% CI)	---	0.42 (0.19-0.93)	---	1.19 (0.42-3.33)

Caroff et al. ICHE 2019

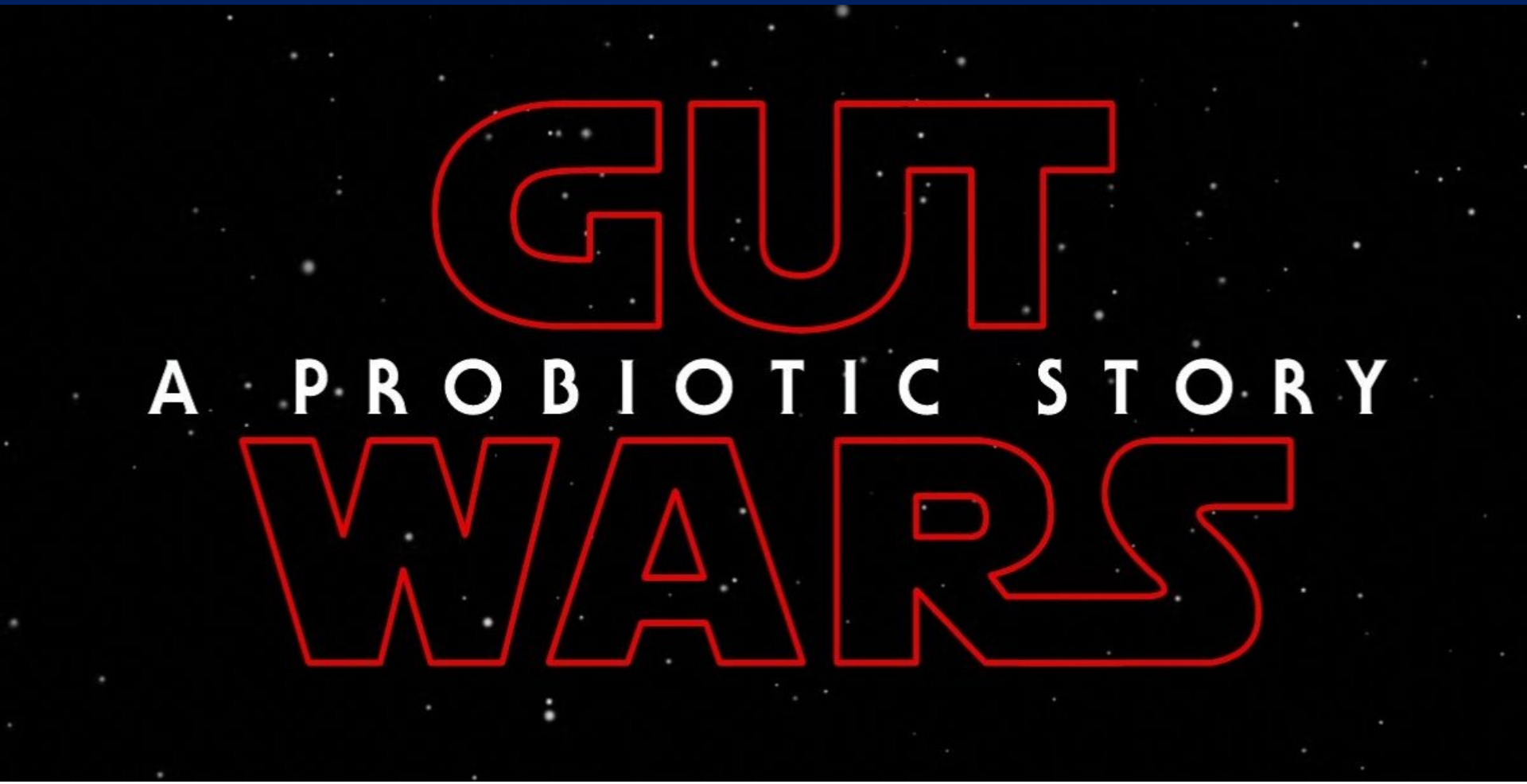
citations

Secondary Prophylaxis

- Data are limited
- Gaps in knowledge
  - Targeted population
  - Optimal dose and duration
  - How long?
- Vancomycin is not harmless
  - Deleterious effects to indigenous microbiota of the colon
  - Promote colonization with VRE, KPC, and E. coli
  - 125mg Qdaily is probably sufficient

citations

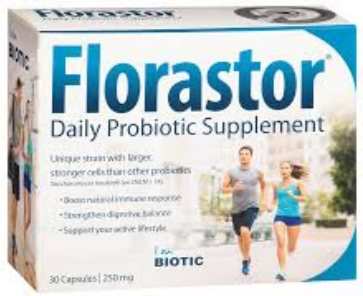
In a galaxy not so far away…….



citations

What are Probiotics?

- Live microorganisms
  - Active when reach the intestine
- Confer benefit on the host
  - When administered in adequate amounts
- Common probiotics:
  - *Lactobacillus rhamnosus* GG
  - *Lactobacillus acidophilis*
  - *Bifidobacterium bifidum*
  - *Saccharomyces boulardii*



citations

Lactobacilli and bifidobacteria in the prevention of antibiotic-associated diarrhoea and *Clostridium difficile* diarrhoea in older inpatients (PLACIDE): a randomised, double-blind, placebo-controlled, multicentre trial

Stephen J Allen, Kathie Wareham, Duolao Wang, Caroline Bradley, Hayley Hutchings, Wyn Harris, Anjan Dhar, Helga Brown, Alwyn Foden, Michael B Gravenor, Dietrich Mack

- Inpatients ≥65 yo, exposed to ≥ 1 antibiotics
- 1493 received multi-strain lactobacilli & bifidobacteria (6 x 10^{10} organisms), once daily x 21 days; 1488 received placebo
- Primary outcome:
  - Antibiotic associated diarrhea OR *C. difficile* infection (CDI) within 12 wks
- No difference in primary outcome (10.4% vs. 10.8%)
- No difference in risk reduction of CDI
  - CDI occurred in 0.8% probiotics arm vs. 1.2% in placebo arm

citations

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Goldenberg JZ, et al. Cochrane Database Systematic Review 2017

Probiotics compared to control for preventing *C. difficile* associated diarrhea

Patient or population: preventing *C. difficile* associated diarrhea
Setting: inpatient and outpatient
Intervention: probiotics
Comparison: control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with control	Risk with probiotics			
Incidence CDAD: complete case	Study population		RR 0.40 (0.30 to 0.52)	8672 (31 RCTs)	⊕⊕⊕◯ MODERATE [1]
	40 per 1,000	16 per 1,000 (12 to 21)			
CDAD (baseline risk 0-2%)	Study population		RR 0.77 (0.45 to 1.32)	5845 (15 RCTs)	⊕⊕⊕◯ MODERATE [2]
	11 per 1,000	8 per 1,000 (5 to 14)			
CDAD (baseline risk 3-5%)	Study population		**RR = 0.53 (95% CI: 0.16-1.77)**		
	38 per 1,000	20 per 1,000 (6 to 67)	**Evidence : Low grade based on 3 RCTs**		
CDAD (baseline risk >5%)	Study population		RR 0.30 (0.21 to 0.42)	2454 (13 RCTs)	⊕⊕⊕◯ MODERATE [5]
	116 per 1,000	35 per 1,000 (24 to 49)			
Incidence of *C. difficile* infection: complete case	Study population		RR 0.86 (0.67 to 1.10)	1214 (15 RCTs)	⊕⊕⊕◯ MODERATE [6]

Safety Consideration

- FDA: Generally Recognized as Safe (GRAS) when added to food as a dietary supplement
- Fungemia:
  - 33 case reports of *S. cerevisiae/boulardii*
- Bacteremia:
  - 8 cases of *lactobacilli*
- Sepsis:
  - 9 cases with *S. boulardii, Lactobacillus G, Bacillus subtilis, Bifidobacterium breve*, or combination
- Endocarditis:
  - 2 cases with *Lactobacillus* & *Streptococcus*

Doron S et al. Clin Infect Dis. 2015 May 15;60 Suppl 2:S129-34

citations

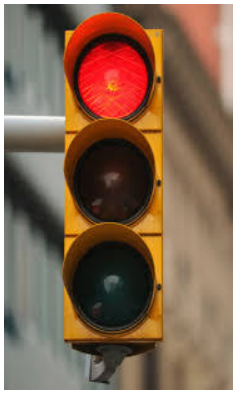
A yogurt a day keeps C. diff away?

citations

Summary

- **Primary prophylaxis:**
  - HSCT transplant recipients
  - Fidaxomicn vs. vancomycin?

- **Secondary prophylaxis:**
  - Many unanswered questions
  - Vancomycin 125mg qdaily probably sufficient



- **Probiotics:**
  - IDSA: insufficient data

citations