ECHO Antibiotic Stewardship Program: Are probiotics money down the C. diff toilet?

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What is a probiotic?

- Definition: “Live microorganisms which when administered in adequate amounts confer a health benefit on the host”
- Is there any evidence these supplements deserve to be called “probiotics”?
“Probiotic” supplements- in the U.S., consumers spent $2.4 billion on them last year alone!

• What’s in them:
  • Lactinex©- lactobacillus species found in unpasteurized milk- *L. acidophilus* and *L. helviticus*
  • Kefir, Activia, Greek yogurts – contain various species of Lactobacillus, Strep. Thermophilus, bifidobacteria
Some earlier studies in hospitals with very high HO-CDI incidence (>23% in some facilities) showed reduced CDI rate while using lactobacillus containing probiotic supplements. These studies, however, may not be applicable to most hospitals now where 1% to 2% baseline rates of CDI are common.

- More recent large randomized double blind study PLACIDE (2 lactobacillus strains and bifidobacteria probiotic regimen vs placebo) showed no benefit.

- These updated CDI Guidelines recommend caution in applying study results from institutions with abnormally high baseline HO-CDI incidence, and conclude there is insufficient data at this time to recommend probiotics for primary prevention of HO-CDI outside of clinical trials.
Based on the probiotic regimen used in older studies which claimed positive results, Scripps developed a combination supplement with L. acidophilus, L. casei, and L. rhamnosus.

- Large 400 bed community hospital
- Made it available for physicians, at their discretion, to prescribe this probiotic regimen for their patients on IV antibiotics. 1576 patients – about half on probiotics - in the study
- Multi-variate analysis to correct for severity of illness, length of antibiotic treatment, but not by actual antibiotic used.
- No difference in HO-CDI rate (1.8%) in either group

Conclusion:

• “Antibiotic use is the most important modifiable risk factor for HO-CDI in acute care hospitals. The CDC estimates that at least 30% of antibiotic use is unnecessary. Based on these findings, our institution **removed all probiotics from the formulary**. Instead, we **endorse strong antimicrobial stewardship practices** that are shown to be efficacious and caution that probiotics may consume health care resources without adding additional benefit”
“Risk of *C. difficile* Infection with Systemic Antimicrobial Therapy Following Successful Stool Transplant: Should we recommend Anti-*C. difficile* Antibiotic Prophylaxis?”
Alegretti et al, Digestive Diseases and Sciences January 10 2019 online

- Looked at long term risks of relapse in patients 1 to 2 years after Fecal transplant (FMT) who were in need of antibiotics. Is there any evidence to suggest the prophylactic use of either oral vancomycin or probiotics reduce risk of relapse when given with antibiotics in these high risk patients.

- This study surprisingly found that in this group of patients with prior FMT receiving antibiotics these interventions had either no benefit (vancomycin) or actually increased the risk (with probiotics) of CDI developing!

- Doesn’t make sense- Why would probiotics actually be detrimental to these patients ??

- Israeli GI Researchers asked the following 2 questions: **To what extent can probiotics colonize the healthy human gut** (this first study), and **what effects do probiotics have on the gut when taken after a course of antibiotics** (the second study)?

- 19 healthy volunteers took a 11-strain probiotic supplement (that included the 4 major bacterial groups used in most probiotic compounds around the world) or placebo, twice daily for 4 weeks

- Traditionally, gut microbiome studies **rely solely on study participants stool culture results** to analyze changes of the probiotics on the microbiome

- This study was different- using colonoscopy and upper endoscopic techniques, they **collected samples and biopsies all along the intestinal tract** for genetic sequencing to determine microbiome content

- Found that participants given probiotics fell into 2 groups: “**permissive**”- these people had significant changes in their microbiome versus others that were “**resistant**”- no significant colonization of the microbiome by the probiotics. Likely related to the healthy already established microbiome somehow blocking the ability of the probiotic to set up shop in the intestines

- Surprisingly, there was no significant difference in the amount of probiotics found in the stool cultures between the 2 groups despite their distinct intestinal results- and both of these groups shed more probiotics in their stool than then placebo group. Therefore, depending on only stool culture results did not accurately reflect what was going on in the intestines
Placebo vs probiotic supplement in healthy volunteers—some were resistant to intestinal colonization by the bacteria, despite finding the bacteria in their stool.
Conclusions from this first study in healthy people who were not on antibiotics and consumed supplemental probiotics

• Author states “our currently applied one size fits all probiotic approach is probably incorrect”.

• In healthy people, the idea that probiotics somehow promote gut health by edging out “bad” bugs is dubious.

• In this second study, researchers wanted to know what happens in the gut when a person follows up a course of antibiotics with probiotic supplements, and how long does the gut microbiome take to get back to a healthy balance after that.

• 21 healthy volunteers took one week of broad spectrum anti-microbial therapy with oral ciprofloxacin and metronidazole to severely disrupt the gut microbiome. They then were assigned to 1 of 3 study arms:

1. 4 weeks of the same BID probiotic supplement used in first study
2. Autologous FMT with their own stool collected prior to the antibiotic course
3. No intervention- watchful waiting

Which group recovered their healthy microbiome the quickest?
Which group took the longest by a long shot to recover and why?
Second study results

• With their own microbiome now wiped out, everyone in group 1 who took the probiotic became fully colonized by the probiotics. There was none of the resistance seen in people with healthy colon flora
• As expected, the FMT group had quick restoration of their normal microbiome
• The watchful waiting group had recovery of their microbiome, but at a slower pace than the FMT
• But the probiotic group- took far longer to return to a normal fecal microbiome than the other 2 groups- even after the 6 month f/u period of the study. So the probiotic actually delayed, not enhanced, microbiome recovery
• Could that be why in the earlier study the use of probiotics actually increased the risk of C. diff in FMT patients treated with antibiotics?
Study Conclusion: Probiotics given after a course of antibiotics significantly delays return of the healthy colon microbiome compared to not taking them at all or after receiving a FMT.

Intestinal culture-probiotics block recovery of healthy colon microbiome.
Comments taken from the July 2018 CR magazine article on Probiotics. They may not only not work, but can themselves be a cause of infection in vulnerable patients:

- For generally healthy people, the risk is low and consuming probiotics is unlikely to have severe negative effects
- But for other groups—such as people who are critically ill, people who are immune-compromised (with HIV or undergoing chemotherapy, for example), and premature babies—probiotics may not be so benign
- “Certain populations are more vulnerable to infection and may not be able to fight off an infection caused by a probiotic. There have been tragic cases reported of deaths resulting from infection in patients being given probiotics. There is huge uncertainty about the safety of these interventions in the elderly, critically sick patients, including infants, and those who are immune compromised”

comment by Aida Bafeta, Ph.D. (author of meta-analysis of 340 studies of probiotic studies, only 9 of which addressed potential risks of probiotics)
Case presentation - 68 year old male cancer patient presents with fever, diarrhea and bacteremia

- patient has metastatic colon cancer and is undergoing intensive chemotherapy through a portacath. Just finished cycle #10 of planned 12, has been getting diarrhea with each cycle. Has been on long-term daily OTC probiotic supplements at his wife’s request.

- This cycle he has the usual post-chemo diarrhea, but now accompanied by onset of fever and rigors. Admitted to hospital.

- WBC 34,000. C-diff test negative

- Initially started on empiric broad spectrum antibiotics, then all blood cultures (drawn both via portacath and peripheral sites) become positive for *Lactobacillus* species. We suspect bacterial translocation of the inflamed colon by probiotic supplement

- Porta Cath pulled and patient completes course of ampicillin therapy.

- He and his wife agree he will stop taking “probiotics”
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<td>Is there any role for “probiotics” for</td>
<td>No evidence that prophylactic use of presently available probiotic</td>
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<td>prevention or treatment of C. diff</td>
<td>formulations reduces risk of antibiotic associated C. diff colitis</td>
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<td>colitis?</td>
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<td>Not recommended in latest 2017 Guidelines</td>
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<td>Can cause lactobacillus bacteremia when colitis develops</td>
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<td>Can delay recovery of normal fecal microbiome after antibiotic exposure.</td>
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<td>Can increase risk of recurrent C. diff in Fecal transplant patients</td>
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