Safety of PROBIOTICS

SITUATION:

- To compile list of contraindications to probiotics based on literature review and SHC experience.

BACKGROUND:

Please see Background at end of SBAR for findings of literature review.

ASSESSMENT:

- The potential benefits of probiotics seem to outweigh the potential risks, especially in relatively healthy, immunocompetent hosts.
- However, as an effort to ensure that safety measures are in place, we recommend that probiotics be avoided in certain populations due to either a documented or theoretical increased risk of severe adverse events.
- These recommendations should not replace provider's clinical judgment during decision making.

RECOMMENDATION:

- The following were derived from literature evaluating probiotic capsules, tablets, etc and may not be applicable to probiotic yogurts where concentrations of microorganisms is often less than that found in capsules/tablets.
- **Contraindications to probiotics at SHC:**
    - Severely immunocompromised state, including
        - Neutropenia (ANC <500)
        - Post-transplant, receiving induction immunosuppression or within 1 year
        - HIV patients with CD4 <200
        - Active malignancy receiving chemotherapy with expected or impending neutropenia
    - Patients at increased risk for bacterial translocation and resultant bacteremia, including
        - Strict NPO for bowel rest
        - Bowel perforation
        - Short-gut syndrome
        - Ileus or small bowel obstruction
        - Bowel resection during current hospitalization or within last 30 days if current hospitalization >30 days
        - Valve replacement or pacemaker lead placement during current hospitalization or within last 30 days if current hospitalization >30 days
        - Inflammatory bowel disease, unless directed by a GI specialist
    - Severe allergy to any component of the probiotic product

- Healthcare workers handling probiotics should wear gloves during preparation and administration. Workers should be aware of and avoid any central line or ports during probiotic administration. Opening of probiotic capsules or packets should be done in a confined space, away from patients, to avoid aerosolization of spores and contamination of sterile sites.

BACKGROUND:

- Probiotics are live microorganisms, which when administered in adequate amounts, may confer health benefits, such as positive effects in Clostridium difficile-associated colitis, inflammatory bowel disease, etc on the host.
- Drawing strong conclusions from scientific evidence remains a challenge, because existing studies are usually limited by heterogeneity in probiotic strains, dosages, duration of administration, multiple comorbidities, nature and dose of offending antibiotics, small sample sizes, and trial design. Results of various studies are even contradictory.
- Safety concerns with the use of probiotics are present not only in patients receiving probiotics but potentially also neighboring patients and healthcare workers responsible for probiotics administration if infection control practices are not adhered to.[6]
    - There is a theoretical potential for these viable organisms to translocate from the gastrointestinal tract and cause localized or systemic bacterial and fungal (in cases of Saccharomyces) infections, especially in immunocompromised patients.
        - There have been **no reports of bacteremia or fungemia associated with probiotic administration in otherwise healthy patients. Moreover, bacteremia or fungemia have not been reported as adverse effects in clinical trials of probiotics, despite being tested in different populations, including many high risk groups.[6]** There have been many controlled clinical trials on the use of probiotics that demonstrate safe use.[12]
        - Cases of *Lactobacillus*-related bacteremia from 1950 to 2003 were reported in patients with underlying immunosuppression due to cancer, transplantation, DM, or use of broad-spectrum antimicrobials.[6,7]
        - **AHRQ** published in 2011 their evaluation of the available evidence on the presence or absence of adverse health outcomes with probiotics, and they found that although case studies suggest that those with immunocompromised health are more likely to experience adverse events, they found **no evidence of significantly increased risk of adverse outcomes in RCTs done in medium-risk and critically ill patients**. They concluded that current literature was not well equipped to answer questions on the safety of probiotics with confidence.[11]
        - There have been studies on the proposed benefits of probiotics in the setting of **pancreatitis**. However, in 2008, one RCT (PROPATRIA, N=296) evaluating patients with severe acute pancreatitis (SAP) found an unexpected significant increase in mortality and bowel ischemia in probiotic-treated patients vs. placebo (packets of cornstarch and maltodextrins). A multi-species probiotic preparation containing *L. acidophilus, L. casei, L. salivarius, L. lactis, B. bifidum* and *B. lactis* (plus cornstarch and maltodextrins) was given via small bowel feeding tube combined with soluble and insoluble fibers, with a

totally daily dose of 10^{10} for up to 28 days. Majority of the deaths (N = 20 of 24, 83%) in the probiotic group was deemed due to multi-organ failure, and all 9 cases of bowel ischemia (including 8 with fatal outcome), were seen in patients who had early onset of organ failure.[13] Criticisms regarding the study design and conduct of the trial came out shortly after this trial was published. It was thought that this result was multifactorial, given that the probiotic group had a higher incidence of organ failure, pancreatic necrosis, and transmural necrosis of the bowel near the site of probiotic delivery. Some explained that local fermentation of the soluble fibers by the bacteria in the relatively immobile small bowel may have been a major risk factor for localized acidosis and bowel wall injury.[6] In 2014, a **meta-analysis of six RCT's (including the PROPATRIA trial) comparing probiotics to placebo in the setting of SAP showed neither beneficial nor adverse effects** (ie. infection of necrotic pancreas tissue, total infection, operation, hospital stay, and mortality) with probiotics use. It was felt that the use of different types and duration of probiotic treatment seemed to play an important role in the heterogeneity between trials in this meta-analysis.[14c]

- *CHEST*, in 2013, published a meta-analysis evaluating RCT's in **critically ill patients** admitted in the ICU who received probiotics. Data from **9 RCTs reported no infection or bacteremia** due to a probiotics strain used, **and no occurrence of ischemic bowel disease**.[4]

- Probiotic use in **HIV patients** is generally safe as probiotics have been used to supplement HAART to improve GI tract immunity and function with no reported adverse events although data in use in patients with uncontrolled HIV or AIDS is relatively lacking.[15]
- Another concern of probiotics use is the spread of antimicrobial resistance genes from probiotics to other bacteria. These genes appear to be chromosomally located and are not easily transferred to other genera. While there have been studies showing *Lactobacillus* vancomycin or aminoglycoside resistance genes conjugated in other strains of bacteria, it has yet to be determined if probiotics truly contribute to this ongoing problem.[6,7]

REFERENCES:

1. Fijan, S. Microorganisms with Claimed Probiotic Properties: An Overview of Recent Literature. *Int. J. Environ. Res. Public Health* 2014;11;4745-4767
2. Kligler B, Cohrssen A. Probiotics. *Am Fam Physician*. 2008;78(9):1073-1078
3. Williams NT. Probiotics. *Am J Health-Syst Pharm* 2010; 67:449-58
4. Barraud D, et al. Impact of the Administration of Probiotics on Mortality in Critically Ill Adult Patients. *CHEST* 2013; 143(3):646–655
5. Evans CT, Johnson S. Prevention of *Clostridium difficile* Infection With Probiotics. *Clinical Infectious Diseases* 2015;60(S2):S122–8
6. Urben LM, et al. Bugs or Drugs: Are Probiotics Safe for Use in the Critically Ill? *Curr Gastroenterol Rep* 2014;16:388
7. Borriello SP, et al. Safety of Probiotics That Contain Lactobacilli or Bifidobacteria. *Clinical Infectious Diseases* 2003; 36:775–80
8. Donohue DC. Safety of probiotics. *Asia Pac J Clin Nutr* 2006;15(4):563-569
9. Hammerman C, Bin-Nun A, Kaplan M. Safety of probiotics: comparison of 2 popular strains. *BMJ* 2006;333:1006-8
10. Liong Min-Tze. Safety of probiotics: translocation and infection. *Nutrition Reviews* 2008;66(4):192–202
11. Hempel S, et al. Safety of Probiotics to Reduce Risk and Prevent or Treat Disease. Agency for Healthcare Research and Quality, US Department of Health and Human Services. AHRQ Publication No. 11-E007. April 2011
12. Syndman DR. The Safety of Probiotics. *Clinical Infectious Diseases* 2008; 46:S104–11
13. Besselink MG, et al. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. PROPATRIA. *Lancet* 2008; 371: 651–59
14. Gou S, et al. Use of probiotics in the treatment of severe acute pancreatitis: a systematic review and meta-analysis of randomized controlled trials. *Critical Care* 2014, 18:R57
15. D'Ettorre G, et al. Probiotics Reduce Inflammation in Antiretroviral Treated, HIV-Infected Individuals: Results of the "Probio-HIV" Clinical Trial. PLoS One 2015, 10