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**Clinical Scenario:** Mother of 7 month old white male with no significant past medical history presents with the complaint of irritability, decreased appetite and pulling at left ear for 4 days. Mother states that patient has become more irritable and fussy over the last 2 days. She states that he did have an ear infection at 3 months of age, which was treated with Amoxicillin. The infant developed severe diarrhea from the antibiotic, therefore the mother did not complete the full course of the antibiotic treatment.

**Clinical Question:** Among children ages 0 to 18 who suffer from antibiotic-associated diarrhea (AAD) is there evidence supporting that the use of probiotics is clinically proven to reduce the occurrence of AAD?

**Articles:**

(1)Johnston, B.C., Goldenberg, J.Z., Vandvik, P.O., Sun, X., & Guyatt, G.H. (2011). Probiotics for the prevention of pediatric antibiotic-associated diarrhea. *Cochrane Database of Systematic Reviews* (11).

(2)Szajewska, H., Ruczynski, M., & Radzikoski, A. (2006). Probiotics in the prevention of antibiotic associated diarrhea in children: A meta-analysis of randomized controlled trials. *The Journal of Pediatrics*, 149(3)367-372.

**Summary and Appraisal of Key Evidence:**

In a level 1 grade A study conducted by Johnston, Goldenberg, Vandvik, Sun and Guyatt (2011) probiotics were investigated in regards to a) co-administered with antibiotics reduce the incidence of antibiotic-associated diarrhea in children; b) caused any adverse events when co-administered with antibiotics in children; c) co-administered with antibiotics reduce the duration of diarrhea; d) co-administered with antibiotics reduce the daily stool frequency. Selection criteria consisted of randomized, parallel, controlled trials in children (0 to 18 years) receiving antibiotics that compare probiotics to placebo, active alternative prophylaxis, or no treatment and measure the incidence of diarrhea secondary to antibiotic use were considered for inclusion. In a level 1 grade A study conducted by Szajewska, Ruczynski, and Radikoski (2006) probiotics were investigated in regards to being a) influential on preventing antibiotic-associated diarrhea; b) more effective than a placebo in treating antibiotic-associated

diarrhea; c) decreased the incidence of antibiotic-associated diarrhea. Randomized controlled trials (RCTs) in children who had received antibiotics for any reason in any setting (out-or inpatient) in which the use of probiotics at any dose or time schedule was assessed and compared with placebo or with no additional intervention.

#### Article Analysis

In the study conducted by Johnston, Goldenberg, Vandvik, Sun and Guyatt in 2011, the Cochrane Complementary Medicine Field's Register of Controlled Trials, CENTRAL, MEDLINE, EMBASE, CINAHL and AMED were searched to May 2010. This was a meta-analysis. Cochrane review that validates the information provided. In the study conducted by Szajewska, Ruczynski, and Radikoski in 2006, several randomized controlled studies were searched and analyzed from 1999-2009. The authors also searched the databases of MEDLINE, EMBASE, and The Cochrane Library up to December 2005, (Szajeweska, Ruczynski, & Radikoski, 2006). The downfall to the evidence is that there are no published articles of information available within the last year. This validates that there needs to more research on this topic. This was a meta-analysis. Study limitations included a small sample size in some trials and no widely agreed upon definition of diarrhea. Finally all meta-analyses contain heterogeneity.

Information was extracted on patients, interventions, methods and results; and assessed risk of bias and quality of the probiotic intervention. Outcomes extracted included incidence of diarrhea, adverse events, mean duration of diarrhea, and mean stool frequency (Johnston et al., 2011). The second meta-analysis extracted the same patient information. The primary outcomes extracted included both incidence of diarrhea or AAD (as defined by investigators) and the incidence of *C. difficile* diarrhea. The secondary outcomes: mean duration of diarrhea, the need for discontinuation of the antibiotic treatment, hospitalization to manage the diarrhea (in outpatients) or intravenous rehydration in any of the study groups, and adverse events (Szajeweska, Ruczynski, & Radikoski, 2006).

Johnston et al., (2011) included 16 studies with 2941 participants that met inclusion criteria. Fifteen studies reported on the incidence of diarrhea. None of the studies specifically defined adverse events. Five studies recorded the mean duration of diarrhea. Four RCTs reported mean stool frequency. Six of the 15 trials provided adequate details regarding the antibiotic agent administered with the probiotic. In a subgroup of patients given beta-lactams/penicillins only, a statistically significant difference emerged between the probiotic treatment and the control group. Two trials reported AAD incidence rates in patients who were administered cephalosporins and macrolides, both demonstrated a non-significant difference (Johnston et al., 2011). In the second study 6 trials with a total of 766 participants who met the inclusion criteria. All studies were placebo controlled. Five studies reported on the effects of evaluating only lactic acid bacteria. Two RCTs evaluated the effect of probiotics in the preventions of *C. difficile* diarrhea in children. This trial found statistically significant and clinically significant benefits of a trend to lower risk of *C. difficile* diarrhea in the probiotic group when compared to the placebo group (Szajeweska, Ruczynski, & Radikoski, 2006).

**Critical Bottom Line:**

In previous reviews of the effectiveness of probiotics in preventing antibiotic-associated diarrhea or decreasing the duration and frequency of *C. difficile* was considered promising and substantial (2). While the trials did have a slight variation in a definition for diarrhea, all the trials did show a statistically significant impact of AAD. The daily dosage of probiotic(s) varied greatly throughout the trails (200 million to 40 billion CFU/day), which demonstrated an impact on the overall success rate of the probiotic in the reduction of AAD. This represents an important finding as dosage recommendations for products containing probiotics available in pharmacies and health food stores have a wide range (1 to 450 billion CFU/day); and dosages less than 5 billion have shown a reduced preventative effect on AAD (1). None of the trials within the studies found any adverse effects associated with the use of probiotics for AAD in this vulnerable population. Confidence interval 95%, systematic review of RCTs, so I give the evidence level 1A.

**Relevance to Clinical Practice:**

Without any hesitation or reservation I would recommend or offer probiotics, at least 5 billion CFU/day, for pediatric patients whom I prescribe antibiotic therapy. Probiotics would probably be most beneficial for my patients receiving beta-lactams/penicillins. Evidence based information like this vital and gives professional health care providers an exceptional knowledge base to have for patients. I believe that there are several parents who would gladly embrace and incorporate probiotics into their child's treatment plan. For patients who have suffered from AAD there is likely to be compliance with finishing the complete course of prescribed antibiotic therapy, which in turn will hopefully lead to the development of less resistant microorganisms.