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## An Evidence Based Appraisal of the Use of Probiotics to Prevent Antibiotic-associated Diarrhea in Intensive Care Settings

George Timothy Scott



Abstract:

(probiotics, antibiotic-associated diarrhea, prophylaxis, adults, critical care)  
It is estimated that between 5-25% of adults who receive antibiotic therapy develop antibiotic-associated diarrhea (AAD) (Cimperman et al., 2011; McFarland, 2009). When untreated, AAD can lead to dehydration, electrolyte imbalances, and skin breakdown, which may cause hospitalization. This paper provides a review of the literature related to the prophylactic use of probiotics to reduce the incidence of antibiotic-associated diarrhea. In addition, based on the findings, a set of recommendations are presented for the use of prophylactic probiotics to control ADD in intensive care populations. Sources were obtained from CINAHL plus with full text, MEDLINE (CSA), Health Reference Center Academic, MEDLINE (OVID), and Cochrane Reviews. Based on the available evidence, there is consensus that antibiotic-associated diarrhea is significantly decreased when higher doses of probiotics ( $10^{10}$  CFU, BID) are given within 36 hours of antibiotic administration. In addition, the probiotics should be continued for 4-6 weeks, using preparations of *Lactobacillus* or the strain *Saccharomyces boulardii*.

THE FLORIDA STATE UNIVERSITY  
COLLEGE OF NURSING

THE USE OF PROBIOTICS TO PREVENT ANTIBIOTIC-ASSOCIATED DIARRHEA  
IN INTENSIVE CARE SETTINGS

BY

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The members of the Defense Committee approve the thesis of Timothy Scott George Jr. defended on April 11, 2014.

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The Use of Probiotics to Prevent Antibiotic-Associated Diarrhea in  
Intensive Care Settings  
Timothy Scott George Jr.  
Florida State University

### **Abstract**

It is estimated that between 5-25% of adults who receive antibiotic therapy develop antibiotic-associated diarrhea (AAD) (Cimperman et al., 2011; McFarland, 2009). When untreated, AAD can lead to dehydration, electrolyte imbalances, and skin breakdown, which may cause hospitalization. This paper provides a review of the literature related to the prophylactic use of probiotics to reduce the incidence of antibiotic-associated diarrhea. In addition, based on the findings, a set of recommendations are presented for the use of prophylactic probiotics to control ADD in intensive care populations. Sources were obtained from CINAHL plus with full text, MEDLINE (CSA), Health Reference Center Academic, MEDLINE (OVID), and Cochrane Reviews. Based on the available evidence, there is consensus that antibiotic-associated diarrhea is significantly decreased when higher doses of probiotics ( $10^{10}$  CFU, BID) are given within 36 hours of antibiotic administration. In addition, the probiotics should be continued for 4-6 weeks, using preparations of *Lactobacillus* or the strain *Saccharomyces boulardi*.

“Within one linear centimeter of your lower colon there lives and works more bacteria (about 100 billion) than all humans who have ever been born. Yet many people continue to assert that it is we who are in charge of the world.”

– Dr. Neil deGrasse Tyson.

Antibiotics are a class of drugs that are used to treat bacterial infections. These chemical agents are effective at eliminating harmful pathogens that cause infections. However, they are non-discriminatory and will often kill helpful bacteria that reside in the body, such as the normal microflora of the gastrointestinal tract. Normal gut microbiota aid in the process of digestion in the intestine, and, when missing, can result in individuals developing diarrhea. It is estimated that between 5-30% of adults who receive antibiotic therapy develop antibiotic-associated diarrhea (AAD) (Cimperman, et al., 2011; Gaurino, Vecchio, & Canani, 2008; McFarland, 2009). Further, the use of extensive antibiotic therapy in critical care units has resulted in AAD that has been as high as 30% (Morrow, Gorgenini, & Malesker, 2012). Diarrhea associated with antibiotic use is caused by the ability of antibiotics to disrupt the normal balance of intestinal microflora. Other factors that have been identified as contributing to AAD include: the type and route of antibiotic administered, multiple, prolonged use of antibiotic therapy, exposure to nosocomial pathogens, and host factors (age and gender, and presence of immunosuppression, gastrointestinal conditions (e.g. surgery, ulcerative colitis)(Rhode, Bartolini, & Jones, 2009). According to the Food and Agriculture Organization of the World Health Organization, probiotics are microorganisms that have health benefits for humans. One of these benefits is the ability to establish or re-establish the balance of the gut microflora (Rhode, et al. 2009; Venugopalan, Shriner, & Wong-Beringer, 2010; & Hempel, et al., 2012).

Left untreated, ADD can lead to dehydration, electrolyte imbalances, skin breakdown, and possible hospitalization or extended lengths of stay for hospitalized patients. All of these adverse events impact patient outcomes and, subsequently, healthcare costs. This paper provides a review of the literature related to the use of probiotics prophylactically to reduce the incidence of antibiotic-associated diarrhea. In addition, based on the findings, a set of recommendations are made for the use of prophylactic probiotics to control ADD in intensive care populations.

## **Methods**

### **Sources used**

Sources were obtained from CINAHL plus with full text, MEDLINE (CSA), Health Reference Center Academic, MEDLINE (OVID), and Cochrane Reviews. The search terms used included: probiotics, antibiotic-associated diarrhea, prophylaxis, adults, and critical care. The inclusion criteria for the articles required that they were written in the English language, peer-reviewed, published in national or international journals, and written in the last five years.

### **Review of the Literature**

In today's healthcare system, there is a concerted effort to provide care by using evidence-based practice (EBP). EBP is the "conscientious, judicious, and explicit use of current best evidence in making decisions about the care of individual patients" (Sackett, Rosenberg, Gray, Haynes, & Richardson, 1996, p.71-72). The following review of the literature was conducted with a focus on literature that would contribute to developing recommendations for best practice.

### **Antibiotics and Diarrhea**



At any point the human body can have over 40,000 bacterial species in the whole gastrointestinal tract (McFarland, 2006). Of those species, helpful symbiotic microbes are outnumbered by pathogenic bacteria at a ratio of 10 to 1 (Rhode et al., 2009). The microbes have more functions than protecting the gut by competitive inhibition. They also aid in the digestive process by breaking down non-absorbable carbohydrates into short chain fatty acids, fluid, and electrolytes. The products of this process are then absorbed by the colon for use in the body. The use of antibiotics can destroy the normal flora and disrupt this process. Undigested and non-absorbable carbohydrates, electrolytes, and fluid remain in the colon, resulting in the development of Antibiotic Associated Diarrhea (AAD). Additionally, the disruption of the normal flora can provide an opportunity for *Clostridium difficile* infection, which can cause *C. Difficile* associated Diarrhea (CDAD)(Kale-Pradman, Jassel & Wilhelm, 2010).

AAD affects one in every five people on antibiotics and about a third of those cases are CDAD. Risk factors for development of AAD/CDAD include age less than six, age greater than 65, length of hospitalization, use of nasogastric tubes, GI surgery or major surgery, acuter or chronic gastrointestinal illness, immunosuppression, history of AAD, use of broad spectrum antibiotics, and use of antibiotics in repetition or for a prolonged amount of time. Patients who develop CDAD remain in the hospital for an average of 3.6 days longer, costing an extra \$3,669.10 each day, up to 24% of those relapse within two months of their first episode of CDAD. Sadly one in ten patients who acquire *C. Difficile* die. (Avadhni & Miley, 2011; Rhode et al., 2009; Johnston et al., 2012; Kale-Pradman et al., 2009). The United States of America spends from \$1-3.2 billion dollars annually on the medical management of CDAD. However, if AAD not

associated with *C. Difficile* was factored into the cost, this number would be exponentially higher, considering that CDAD only constitutes a third of AAD cases.

### **Probiotics and AAD**

The mechanism of action for probiotics preventing AAD is not completely known. It has been theorized that they competitively inhibit the growth of pathogenic bacteria due to their ability to resist against gastric and bile acids, enhance the barrier functions of the goblet cells in the intestines, and stimulate the activation of the host-immune system (Cremonini & Videlock, 2013; Avadhani & Miley, 2011; Rohde et al., 2009). A great body of research has been growing about the use of probiotics concurrently with antibiotics to prevent the development of AAD. A majority of systemic reviews and meta-analyses have found that there is moderate quality evidence suggesting that probiotics are a safe and effective way to reduce the incidence of AAD (Hempel, et al., 2012; Butler, Duncan, Hood, 2012; Avadhani, Miley, 2011; Kale-Pradman, Jassel, Wilhelm, 2010; McFarland, 2010; Koretz, 2009; Goldenberg et al., 2013; Johnston et al., 2012), with effectiveness ranging from 30-60% reduction of the incidence. However, these results do not answer all questions about probiotic use.

### **Probiotics in Critical Care Units**

In 2010, a survey of 100 physicians (86% gastroenterologists) was conducted regarding the safety of probiotics. 100% deemed probiotics to be safe, but 6% cautioned their use in immunocompromised patients (Williams et al, 2010). The majority of existing studies on the use of probiotics to prevent AAD have been conducted outside of critical care settings (Morrow, Gogineni & Malesker, 2012). This was primarily due to concerns about the safety of use in patients who are critically ill. Many existing studies

have excluded patients who are in critical care from their trials. At present, it remains unclear if probiotics are beneficial in this patient population (Koretz, 2009).

The existing research does show that there are no documented reports of bacteremia or fungemia associated with probiotic use in patients who are not immunosuppressed, have prosthetic heart valves, or uncontrolled diabetes (Morrow, 2012). In addition, the Agency for Healthcare Research and Quality released a systemic review concluding that there is no clear increase in adverse events with the administration of probiotics, but also noted issues with heterogeneity in RCT's (Hempel et al., 2011). Further research is warranted on the use of probiotics to prevent the occurrence of AAD in the critically ill population.

### **Summary**

The existing research suffers from low powered RCT's and inconsistencies in the strain of probiotics used, dosing of probiotics, length of time between start of antibiotic and probiotic administration, and duration of follow up with probiotics after cessation of antibiotic therapy (Hempel et al., 2012, Rhode et al., 2009; Gao, Mubasher, Fang, Reifer & Miller, 2010). (These factors will be discussed later.) "Meta-analysis is simply a mathematical manipulation that is used to combine data from multiple trials" (Koretz R, 2009). The heterogeneity that is present from study to study only enables allows meta-analyses to provide draw conclusions about the general effectiveness of probiotics (Verna & Lucak, 2010; McFarland, 2006). Thus, it is not possible to draw clear-cut recommendations of effectiveness to be used in clinical practice. Considering this fact it is possible to theorize that probiotics could be more effective than the literature suggests but is lowered by these inconsistencies. At present, there are few studies

specifically addressing the use of probiotics to prevent AAD in critical care populations. Further research is warranted on the subject.

### **Recommendations and Conclusion**

Despite the uncertainty in existing systemic reviews and meta-analyses, it is possible to draw some direction for clinical use of probiotics from this review of the literature. The following is a discussion of those recommendations.

#### **Dosing Amount and Frequency**

Existing meta-analyses that have examined the efficacy of probiotics on the reduction of AAD have not discriminated on the dosing amount of the probiotic in regards to Colony Forming Units (CFU's). The ranges of daily dosing amount in current RCT's have ranged from  $10^7$ -  $10^{11}$  (McFarland, 2009, Kale-Pradman et al., 2010). Many probiotic trials have failed to show significant efficacy due to the use of sub-therapeutic doses of probiotics (McFarland 2009, 2006). When probiotics are ingested, much of the oral dose is destroyed by the host's defenses. For the surviving dose to be effective stool levels must be above  $10^8$  organisms per stool. Due to this phenomenon several studies have recommended for doses to be greater than  $10^{10}$  CFU daily with patients on antibiotic treatment (Butler, Duncan & Hood, 2012; McFarland 2009). A study demonstrating the dose-response efficacy of probiotics further illustrates this point. Probiotic capsules of 50 billion CFU or placebo capsules were given twice a day to three groups; 1) one group receiving two probiotic capsules, 2) a second group receiving one placebo capsule and one probiotic capsule, and 3) the last group receiving two placebo capsules. The results were as follows: AAD occurred in 15.5% of patients receiving two probiotic capsules, compared to 28.2% of those receiving one probiotic capsule, also

compared to 44.1% of those receiving just placebo capsules. The duration of symptoms was 2.8 days in the group receiving two probiotic capsules, compared to 4.1 days in group 2, and 6.4 days in group 3 (Gao et al., 2010). The study of 255 patients demonstrated a dose efficacy response from 100 billion to 50 billion CFU daily, but it is important to note that the results could be drug specific, had a statistical power of 86%, and the population was only of Asian descent.

### **Timing and Duration for Administration**

Another issue that needs to be addressed is the timing of the medication administration. In the study by Gao et al. (2010) study administered the probiotics were administered two hours after breakfast and two hours after antibiotic administration. It could be prudent to follow the same timing for administration, to evenly distribute the administration of the probiotic with food and after antibiotic administration. Therefore it is recommended to administer doses of probiotics twice daily, at least 2 hours after antibiotic administration, totaling to over 100 billion CFU daily.

The optimal duration for probiotic treatment is not known due to heterogeneity in studies leading to inconsistent data (Verna & Lucak, 2010). It is not known how long a specific strain of probiotic takes to colonize in a host and alter the microflora, and could vary due to type, dose, and duration of antibiotic used, and host characteristics. What is known is that AAD can be delayed in onset by 4-6 weeks (McFarland, 2009). This phenomena might also contribute to inconsistent findings from study to study which have ranged from 3-30 days. With this in mind it would be prudent to continue to administer probiotics from the end of the antibiotic course until the patient is no longer susceptible to redeveloping AAD, which could be in the 6-8 week range (Kale-Pradham, 2010).

Another aspect of this issue to examine is the initiation of probiotic administration after antibiotic therapy has begun. Again, there are no clear guidelines for practice due to heterogeneity among studies. Existing RCT's have begun probiotic administration as early as just after antibiotic administration and as late as seven days after its initiation. The timeline of administration could play an important role in the prevention of AAD. An example of this is a study published by the National Health Service of Great Britain in 2013. A multicenter RCT examined the use of probiotics to reduce AAD in 3000 patients over the age of 65 and found no statistically significant evidence of effectiveness (Allen 2013). 60 billion CFU's of a mixture of *Lactobacillus acidophilus* and *Bifidobacterium bifidum* were given once a day and followed up for 21 days after antibiotic cessation. However, the window of recruitment was seven days after antibiotic administration. The normal flora in the patient receiving antibiotic treatment may have already been killed off at this point, which could have lead to higher incidence of AAD. Gao et al. (2010) administered their probiotic therapy within 36 hours of beginning antibiotic treatment. With this in mind, when administering probiotics prophylactically to prevent AAD it would be prudent to administer them within 36 hours of the start of antibiotic therapy as well or ideally two hours after the start of therapy.

### **Strain and Preparation of Probiotic**

The systemic review and meta-analysis of 63 RCT's with 11, 811 participants by Hempel et al (2012) showed a statistically significant association between probiotic administration and the reduction of AAD (relative risk, 0.58; 95% CI, 0.50 to 0.68;  $P_{.001}$ ;  $I^2$ , 54%; [risk difference,  $-0.07$ ; 95% CI,  $-0.10$  to  $-0.05$ ], [number needed to treat, 13; 95% CI, 10.3 to 19.1]). However, “the analysis found no evidence that the

effectiveness varies systematically even by probiotic genus.” This was one of the first studies to go against the speculation that the effectiveness of probiotic strains was specific to the strain used (Koretz, 2009; McFarland, 2010). This discrepancy warrants more research on different strains of probiotics to determine which one has the greatest efficacy.

At present, there are two types of probiotics that have been researched and show the most promise. The first are *Lactobacillus* based formulations (Hempel et al., 2012; Kale-Pradhan et al., 2010; Butler et al., 2012; Verna & Lucak, 2010). Fifty-seven out of 82 RCT’s examined in the meta-analysis by Hempel et al. (2012) used *Lactobacillus* based probiotic interventions. However, 41 of 82 did not state the exact strain used which illustrates the heterogeneity in the existing research. Many RCT’s have only reported the genus and species of *Lactobacillus* interventions but not the strain. Therefore, it is not possible to recommend an exact strain or formulation of *Lactobacillus* to use.

The second type of probiotic that has been shown to be effective is *Saccharomyces boulardi*, a strain of yeast related to yeast commonly used in baking and brewing. McFarland’s 2010 meta-analysis found that *S. boulardi* was significantly effective in preventing AAD (RR=0.47, 95% CI: 0.35-0.63, P<0.001), and no adverse reactions occurred in any of the studies analyzed. *S. boulardi* shows promise for use due to the body of evidence indicating its efficacy (Butler et al., 2012; Verna, 2010). However, several authors have suggested that studies that have found no significant protective effect have suffered from lack of follow-up time after antibiotic administration or low power in the study (Zocco, Garcovich & Gasbarrini, 2012; McFarland, 2010).

Probiotics on the commercial market are available in a large array of preparations ranging from juices, milk, and yogurts, to powders and tablets (Verna, 2010) These preparations are often freeze dried, heat dried, or lyophilized, and there is some concern about the quality of the products due to lack of standards (McFarland, 2010). It is important to consider the preparation due to the need for over  $10^{10}$  CFU's to ensure effectiveness. However, it may be more important to be mindful about the ease of use for the patient for whom they are prescribed. Patients over the age of 65 often take several medicines, and may not adhere to a probiotic regimen for enough time to ensure a significant follow up, if the probiotics require a large amount of additional preparation (Allen, 2013). Thus, it is recommended to prescribe probiotics in the pill/capsule form for ease of use and consumption.

### **Conclusion**

There is a consensus, based on the available evidence, that antibiotic-associated diarrhea is significantly decreased with higher doses of probiotics ( $10^{10}$  CFU, BID) given within 36 hours of antibiotic administration. In addition, the probiotics should be continued for 4-6 weeks, using preparations of *Lactobacillus* or the strain *Saccharomyces boulardi* (Gao et al., 2010; Psaradellis, 2009; Avadhani, 2011). Probiotics offer a cheap and promising solution to antibiotic-associated diarrhea, and further research is warranted due to inconsistent dosing, administration, and strains of existing research (Butler, 2012).



## References

- Allen, S.J., Wareham, K., Wang, D., Bradley, C., Hutchings, H., Harris, H., Dhar, A., Brown, H., Foden, A., Gravenor, M.B. & Mack, D. (2013). 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. *Lancet*, 382, 1249–1257.
- Avadhani, A. & Miley, H. (2011). Probiotics for prevention of antibiotic-associated diarrhea and *Clostridium difficile*-associated disease in hospitalized adults—A meta-analysis. *Journal of the American Academy of Nurse Practitioners*, 23, 269–274.
- Butler, C.C., Duncan, D., & Hood, K. (2012). Does taking probiotics routinely with antibiotics prevent antibiotic associated diarrhoea? *British Medical Journal*, 344:e682.
- Cimperman, L. Bayless, J., Best, K., Diligente, A., Mordarski, B., Oster, M., Smith, M., Vatakis, F., Wiese, D., Steiber, A., and Katz, J. , (2011). A randomized, double-blind, placebo-controlled pilot study of *Lactobacillus reuteri* ATCC 55730 for the prevention of antibiotic-associated diarrhea in hospitalized adults. *Journal of Clinical Gastroenterology*, 45, 785-789.
- Cremonini, F., & Videlock, E.J. (2013). Probiotics are associated with a decreased risk of antibiotic-associated diarrhea. *Evidence-Based Medicine*, 18 (2).
- Gao XW, Mubasher M, Fang CY, Reifer C, Miller LE. (2010). Dose-response efficacy of a proprietary probiotic formula of *Lactobacillus acidophilus* CL1285 and *Lactobacillus casei* LBC80R for antibiotic-associated diarrhea and *Clostridium*

- difficile* -associated diarrhea prophylaxis in adult patients. *American Journal of Gastroenterology*, 105, 1636-1641.
- Goldenberg, J.Z., Ma, S.S.Y., Saxton, J.D., Martzen, M.R., Vandvik, P.O., Thorlund, K., Guyatt, G.H., & Johnston, B.C. (2013). Probiotics for the prevention of *Clostridium difficile*-associated diarrhea in adults and children (Review). *Cochrane Library*, 5
- Guarino, A., Lo Vecchio, A., & Canani, R.B. (2008). Probiotics as prevention and treatment for diarrhea. *Current Opinion in Gastroenterology*, 25:18–23
- Hempel, S., Newberry, S., Ruelaz, A., Wang, Z., & Miles, J. Agency for Healthcare Research and Quality, (2011). *Safety of probiotics to reduce risk and prevent or treat disease executive summary*(Pub. No. 11-E007-1)
- Hempel, S. , Newberry, S.J., Maher, A.R., Wang, Z., Miles, J.N.V., Shanman, R., Johnsen, B., & Shekelle, P.J., (2012). Probiotics for the prevention and treatment of antibiotic-associated diarrhea: A systematic review and meta-analysis. *Journal of the American Medical Association*, 307 ( 18).
- Psaradellis, E., & Sampalis, J. (2010). Efficacy of BIO K+CL1285 in the reduction of antibiotics-associated diarrhea- a placebo controlled double blind randomized, multi-center study. *Archives of Medical Science*, 6 (1) 56-64.
- Johnston, B. C., Ma, S. S., Goldenberg, J. Z., Thorlund, K., Vandvik, P. O., Loeb, M., & Guyatt, G. H. (2012). Probiotics for the prevention of *clostridium difficile*-associated diarrhea: A systematic review and meta-analysis. *Annals of Internal Medicine*, 157(12), 878-888.

- Kale-Pradman, P.B., Jassel, H.K., & Wilhelm, S.M. (2010). Role of lactobacillus in the prevention of antibiotic-associated diarrhea: A meta-analysis. *Pharmacotherapy*, *30* (2) 119-126.
- Koretz, R.L. (2009). Probiotics, critical illness, and methodologic Bias. *Nutrition in Clinical Practice*, *24* (1) 45-49.
- McFarland, L.V. (2006). Meta-analysis of probiotics for the prevention of antibiotic – associated diarrhea and the treatment of Clostridium difficile disease. *American Journal of Gastroenterology*, *101*, 812–822.
- McFarland, L.V. (2009). Evidence-based review of probiotics for antibiotic-associated diarrhea and Clostridium difficile infections. *Anaerobe*, *15*, 274–280.
- McFarland, L.V. (2010). Systematic review and meta-analysis of Saccarhomyces boullardi in adult patients. *World Journal of Gastroenterology*, *16* (18). 2002-2222.
- Morrow, L.E., Gogineni, V., & Malesker, M.A. (2012). Probiotic, prebiotic, and synbiotic use in critically ill patients. *Current Opinion in Critical Care*, *18*, 186–191.
- Newhouse, R., Dearholt, S., Poe, S., Pugh, L. C., & White, K. M. (2005). Evidence-based practice: A practical approach to implementation. *Journal of Nursing Administration*, *35*(1), 35-40.
- Rohde, C.L., Bartolini, V. & Jones, N. (2009). The use of probiotics in the prevention and treatment of antibiotic-associated diarrhea with special interest in clostridium difficile-associated diarrhea. *Nutrition in Clinical Practice*, *24* (1) 33-40.

Sackett, D. L., Rosenberg, W., Gray, J., Haynes, R. B., & Richardson, W. S. (1996).

Evidence based medicine: What it is and what it isn't. *BMJ: British Medical*

*Journal (International Edition)*, 312(7023), 71-72. doi:10.1136/bmj.312.7023.71

Williams, M.D, Ha, C.Y., & Ciorba, M.A. (2010). Probiotics as therapy in

gastroenterology-A study of physician opinions and recommendations. *Journal of*

*Clinical Gastroenterology*; 44, 631–636.

## Table

*Meta-Analyses in the Literature*

Citation	Number of Studies	Intervention: daily dose and organism used	Outcomes (risk ratio) for AAD
Hempel 2012	82 RCTs met inclusion criteria, 63 RCTs used, 11,811 children and adults	57 of 82 used <i>lactobacillus</i> based formulations, 16 of 82 used <i>S boulardii</i> , ranging from $7 \times 10^6$ to $3 \times 10^{10}$	Combined 0.58 (95% CI, 0.50 to 0.68) Children 0.55 (95% CI, 0.38 to 0.80) Adults (age 18 to 65) 0.54 (95% CI, 0.34 to 0.85) Elderly adults (age $65 \leq X$ ) 0.81 (95% CI, 0.40 to 1.63) Many studies had combined age groups
McFarland 2010	10 RCTs, 1825 adults	<i>S boulardii</i> , ranging from $4 \times 10^9$ to $4 \times 10^{10}$	0.47 (95% CI, 0.35 to 0.63)
Avadhani 2010	8 RCTs, 1220 adults	3 trials <i>S boulardii</i> , 6 trials <i>L ramnosus</i> , 6 other single strains, and 7 mixed strains, ranging from $1 \times 10^7$ to $1 \times 10^{11}$ (mean dose $3 \times 10^9$ )	0.56 (95% CI, 0.44 to 0.71)
Kale-Pradham 2010	10 RCTs, 1862 children and adults	Single agent <i>lactobacillus</i> , ranging from $2 \times 10^9$ to $4 \times 10^{10}$	Combined 0.35 (95% CI, 0.19 to 0.67) Adults 0.24 (95% CI, 0.08 to 0.75) Children 0.44 (95% CI, 0.18 to 1.08)