

6.2 Enteral Nutrition (Other): Probiotics

June 28th, 2005

Recommendation:

There are insufficient data to make a recommendation on the use of probiotics in critically ill patients.

Discussion: The committee noted the lack of a treatment effect of probiotics on clinical outcomes and the inconsistency between studies in the method of reporting diarrhea. It was decided that the “number of patients with diarrhea” is a better outcome than “% total days with diarrhea” or “# of diarrhea days”. Given the variations in the type of probiotics used, in the use of prebiotics, and the potential for increased harm in critically ill patients with certain probiotics, specifically-saccharomyces boulardii ⁽¹⁾, the committee decided there was insufficient data to recommend their use.

⁽¹⁾ Lherm T, Monet C, Nougere B, Soulier M, Larbi D, Le Gall C, Caen D, Malbrunot C. Seven cases of fungemia with Saccharomyces boulardii in critically ill patients. Intensive Care Med. 2002 Jun;28(6):797-801.

| Values | Definition | Score: 0, +, ++, +++ |
|---------------------|---|----------------------|
| Effect size | magnitude of the absolute risk reduction attributable to the intervention listed--a higher score indicates a larger effect size | 1+ (diarrhea) |
| Confidence interval | 95% confidence interval around the point estimate of the absolute risk reduction, or the pooled estimate (if more than one trial)--a higher score indicates a smaller confidence interval | 1+ |
| Validity | refers to internal validity of the study (or studies) as measured by the presence of concealed randomization, blinded outcome adjudication, an intention to treat analysis, and an explicit definition of outcomes--a higher score indicates presence of more of these features in the trials appraised | 3+ |
| Homogeneity | similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials | 1+ |
| Safe | estimated probability of avoiding any significant harm that may be associated with the intervention listed--a higher score indicates a lower probability of harm | 2+ |
| Feasible | ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU | 2+ |
| Cost | estimated cost of implementing the intervention listed--a higher score indicates a lower cost to implement the intervention in an average ICU | 2+ |

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Question: Does the addition of probiotics to enteral feeding result in better outcomes in critically ill patients?

Summary of evidence: There were one level 1 and 3 level 2 studies that were reviewed. Two trials studied the effects of addition of *saccharomyces boulardii* to enteral nutrition on diarrhea, whereas the other two studied the effect of different probiotic combinations on gut barrier function and the systemic inflammatory response. The data from these studies were not aggregated in a meta-analysis due to the variations in the types of probiotics used. In two studies, patients received either enteral or parenteral nutrition, but no further details were provided.

Mortality: Three studies reported mortality and found no difference between the groups receiving probiotics or control.

Infections, LOS, ventilator days: Two studies looked at the incidence of septic morbidity and septic complications and there were no differences between the two groups.

Other: There were significantly fewer % total days with diarrhea in the *Saccharomyces boulardii* groups ($p < 0.001$) in the two studies, however Bleichner et al found there was no difference in the number of patients with diarrhea between the two groups ($p = 0.26$) while Tempe did not report on the # patients with diarrhea. In the study by Jain et al, gastric colonization with multiple organisms and potentially pathogenic bacteria was significantly reduced in the probiotic group. In one study, the administration of ProViva (L. Planatarum 299v) was associated with a late attenuation of the systemic inflammatory response when compared to the control group.

Conclusions:

- 1) The addition of probiotics i.e. *Saccharomyces boulardii* to enteral nutrition maybe associated with a reduction in the number of patients with diarrhea.
- 2) The use of probiotics has no effect on mortality or infectious complications.

Level 1 study: if all of the following are fulfilled: concealed randomization, blinded outcome adjudication and an intention to treat analysis.

Level 2 study: if any one of the above characteristics are unfulfilled

Table 1. Randomized studies evaluating probiotics in critically ill patients

| Study | Population | Methods (score) | Intervention | Mortality # (%) | | Other | | RR (CI)** |
|-------------------|-------------------------|--|---|-----------------|------------|--|--------------|------------------|
| | | | | | | | | |
| 1) Bleichner 1997 | Mixed ICU N=128 | C.Random: not sure ITT: yes Blinding: double (13) | EN + saccharomyces boulardii (SB) vs EN + placebo | NA | NA | EN + SB | EN + placebo | 0.75 (0.45-1.24) |
| | | | | | | # patients with diarrhea 18/64 (28) | 24/64 (38) | NA |
| | | | | | | # days with diarrhea 91 (14) | 134 (20) | |
| 2) Tempe 1983 | ICU patients N=40 | C.Random: yes ITT: yes Blinding: double (10) | EN + saccharomyces boulardii (SB) vs EN + placebo | 3/20 (15) | 3/20 (15) | EN + SB | EN + placebo | NA |
| | | | | | | # days with diarrhea 34/389 (9) | 63/373 (17) | |
| 3) Jain 2004 | ICU patients N = 90 | C.Random: no ITT: yes Blinding: double (10) | Trevis™ (Lactobacillus acidophilus La5, Bifidobacterium lactis Bb12, Streptococcus thermophilus, Lactobacillus bulgaricus) + Raffitose (prebiotic oligofructose) vs. placebo. All patients received EN or PN. | 22/45 (49) | 20/45 (45) | Trevis™ | Placebo | |
| | | | | | | Hospital LOS 14 (9-29) | 15 (9-26) | |
| | | | | | | ICU LOS 7 (3-16) | 5 (3-14) | |
| | | | | | | Septic Complications 33/45 (73) | 26/45 (58) | |
| | | | | | | # multiple organisms Day 8 9/23 (39) | 18/24 (75) | |
| | | | | | | # potentially pathogenic organisms day 8 10/23 (43) | 18/24 (75) | |
| 4) McNaught 2005 | ICU patients N = 103 | C.Random: no ITT: no Blinding: no (5) | Proviva (Lactobacillus plantarum 299v) vs. standard care. All patients received EN or PN as needed. | 18/52 (35) | 18/51 (35) | Septic morbidity 21/52 (40) | 22/51 (43) | |

C.Random: concealed randomization
 ITT: intent to treat
 SB: saccharomyces boulardii
 NA: not available
 LOS days, Ventilator days and Cost: not reported
 ** RR= relative risk, CI= Confidence intervals

TOPIC: 6.2 Probiotics

(Reviewers: Shannon MacKenzie & Deborah Schroter Noppe)

Article inclusion log

Criteria for study selection

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|--|
| Type of study: RCT or Meta-analysis |
| Population: critically ill, ventilated patients (no elective surgery patients) |
| Intervention: TPN and /or EN |
| Outcomes: mortality, LOS, QOL, functional recovery, complications, cost. Exclude studies with only biochemical, metabolic or nutritional outcomes. |

| | Author | Journal | I | E | why rejected |
|----|-----------|--------------------|---|---|---------------------------|
| 1. | Bleichner | Int Care Med 1997 | √ | | |
| 2. | Tempe | Sem Hop Paris 1983 | √ | | |
| 3. | Olah | Br J Surgery 2002 | | √ | Not ICU pts |
| 4. | Lherm | Int Care Med 2002 | | √ | Not RCT |
| 5. | Jain | Clin Nut 2004 | √ | | |
| 6. | McNaught | Clin Nut 2005 | √ | | |
| 7. | Anderson | Gut 2004 | | √ | Elective surgery patients |
| | | | | | |
| | | | | | |

I = included, E = excluded

References

1. Bleichner G, Blehaut H, Mentec H, Moysé D. *Saccharomyces boulardii* prevents diarrhea in critically ill tube-fed patients. A multicenter, randomized, double-blind placebo-controlled trial. *Intensive Care Med.* 1997 May; 23(5): 517-23.
2. Tempe JD, Steidel AL, Blehaut H, Hasselmann M, Lutun P, Maurier F. [Prevention of diarrhea administering *Saccharomyces boulardii* during continuous enteral feeding] *Sem Hop.* 1983 May 5; 59(18): 1409-12.
3. Olah A, Belagyi T, Issekutz A, Gamal ME, Bengmark S. Randomized clinical trial of specific lactobacillus and fibre supplement to early enteral nutrition in patients with acute pancreatitis. *Br J Surg.* 2002 Sep; 89(9): 1103-7.
4. Lherm T, Monet C, Nougier B, Soulier M, Larbi D, Le Gall C, Caen D, Malbrunot C. Seven cases of fungemia with *Saccharomyces boulardii* in critically ill patients. *Intensive Care Med.* 2002 Jun; 28(6): 797-801.
5. Jain PK, McNaught CE, Anderson AD, MacFie J, Mitchell CJ. Influence of synbiotic containing *Lactobacillus acidophilus* La5, *Bifidobacterium lactis* Bb 12, *Streptococcus thermophilus*, *Lactobacillus bulgaricus* and oligofructose on gut barrier function and sepsis in critically ill patients: a randomised controlled trial. *Clin Nutr.* 2004 Aug; 23(4): 467-75.
6. McNaught CE, Woodcock NP, Anderson AD, MacFie J. A prospective randomised trial of probiotics in critically ill patients. *Clin Nutr.* 2005 Apr; 24(2): 211-9.
7. Anderson AD, McNaught CE, Jain PK, MacFie J. Randomised clinical trial of synbiotic therapy in elective surgical patients. *Gut.* 2004 Feb; 53(2): 241-5.