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**STUDY LEVELS OF EVIDENCE (LOE)**

From the Centre for Evidence-Based Medicine, Oxford. For the most up-to-date levels of evidence, see www.cebm.net/levels\_of\_evidence.asp)

*Therapy/Prevention/Etiology/Harm:*

- 1a: Systematic reviews of randomized controlled trials
- 1b: Individual randomized controlled trials
- 1c: All or none randomized controlled trials
- 2a: Systematic reviews of cohort studies
- 2b: Individual cohort study or low-quality randomized controlled
- 2c: "Outcomes" research, ecological studies

*Diagnosis:*

- 1a: Systematic review of level-1 diagnostic studies
- 1b: Independent blind comparison of an appropriate spectrum of consecutive patients, all of whom have undergone both the diagnostic test and the reference standard, or a clinical decision rule not validated on a second set of patients
- 1c: Absolute SpPins and SnNouts
- 2a: Systematic review of level >2
- 2b: Independent blind or objective comparison, study confined to a narrow spectrum of study individuals, or a diagnostic clinical rule not validated in a test set

*Prognosis:*

- 1a: Systematic review of inception cohort studies
- 1b: Individual inception cohort study with >80% follow-up, or a clinical rule not validated on a second set of patients
- 1c: All or none case series
- 2a: Systematic review of either retrospective cohort studies or untreated control groups in RCTs
- 2b: Retrospective cohort study or follow-up of untreated control patients in an RCT, or clinical rule not validated in a test set
- 2c: "Outcomes" research

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**Probiotics Effective in Preventing Acute, but Not Traveler’s, Diarrhea**

**Clinical Question**

Are probiotics effective in the prevention of acute diarrhea?

**Bottom Line**

Probiotics reduce the risk of antibiotic-associated diarrhea and other types of acute diarrhea—but not the risk of traveler’s diarrhea—in both children and adults. The protective effect does not vary among different probiotic strains or by mode of delivery. (LOE=1a)

**Study Design**

Meta-analysis (randomized controlled trials)

**Funding**

Government

**Setting**

Various (meta-analysis)

**Synopsis**

Probiotics are effective in the treatment of acute infectious diarrhea in adults and children. However, evidence for the role of probiotics in preventing acute diarrhea is less certain. These investigators thoroughly searched multiple databases—including Medline®, the Cochrane Registry and references of published review articles—and personally contacted researchers known to be working in the field. Only randomized double-blind placebo-controlled trials in either English or French were included in the analysis. Three individuals separately evaluated articles for eligibility and quality; disagreements were resolved by consensus discussion. A total of 34 trials, including 4,844 patients, aged 6 months to 71 years, met the inclusion criteria. Overall, probiotics reduced the risk of acquiring diarrhea by 33% (95% CI: 22–44%; number needed to treat=15, 11–22). In subgroup analyses, probiotics signifi-

cantly reduced the risk of antibiotic-associated diarrhea and acute diarrhea of other types but did not reduce the risk of traveler’s diarrhea. Probiotics were more effective in children than in adults, and the protective effect did not vary significantly among different probiotic strains or by mode of delivery (i.e., capsules, tablets, granules or powder). A formal analysis found no evidence of significant publication bias.

**REFERENCE**

Sazawal S, Hiremath G, Dhingra U, et al. Efficacy of probiotics in prevention of acute diarrhea: a meta-analysis of masked, randomized, placebo-controlled trials. *Lancet Infect Dis.* 2006;6: 374-382.

**Pneumonia: Three Days of Antibiotics for Uncomplicated Course**

**Clinical Question**

In patients hospitalized for treatment of community-acquired pneumonia, can treatment be stopped after three days if the patient has substantially improved?

**Bottom Line**

Dogma successfully challenged: in patients who respond well to initial treatment, stopping antibiotic therapy after three days is just as effective as continuing treatment for the standard eight days. (LOE=1b)

**Study Design**

Randomized controlled trial (double-blinded)

**Funding**

Industry

**Allocation**

Uncertain

**Setting**

Inpatient (any location)

**Synopsis**

The treatment of pneumonia for 7–10 days is based on tradition, not scientific evidence. The researchers conducting

this study challenged the status quo by enrolling 119 adults with mild-to-moderate/severe community-acquired pneumonia with a severity index score of  $\leq 110$ . On admission, all patients were started on intravenous amoxicillin, the preferred empirical treatment in the Netherlands. After 72 hours of treatment, patients who showed improvement in symptoms, had a temperature of  $< 38^{\circ}\text{C}$  and could take oral drugs were randomized to treatment with placebo or amoxicillin 750 mg three times daily for five days. Using modified intention-to-treat analysis, after 10 days, 89% of patients in both groups were clinically cured. In follow-up at 28 days, clinical cure rates were also similar between the two approaches, as was bacteriologic success and radiologic success. This study was designed to find a difference in success rates of  $\geq 10\%$ . There are a couple of notable limitations to this study. First, the patients in the short-treatment group had a median age of 54 years compared with 60 years in the eight-day group, and these younger patients may be more likely to respond to the short course, thus skewing the results. Second, the study was conducted in the Netherlands, where resistance patterns may be different than in other countries. Finally, the study was conducted in nine hospitals over three years, which works out to  $< 5$  patients per hospital per year recruited into the study. Given the imbalance in age and this sparse representation, these patients could be highly selected and not representative of the typical patient admitted to a community hospital.

## REFERENCE

el Moussaoui R, de Borgie CA, van den Broek P, et al. Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study. *BMJ*. 2006;332:1355-1358.

## Neuropsychologic Scores Marginally Predict Alzheimer's Risk

### Clinical Question

Does cognitive performance predict the subsequent development of Alzheimer's disease?

## Bottom Line

Baseline scores on the Mayo Cognitive Factor Scales (MCFS) are somewhat predictive of developing Alzheimer's disease after six years. (LOE=2b)

### Study Design

Cohort (prospective)

### Funding

Government

### Setting

Outpatient (specialty)

### Synopsis

These authors recruited 102 patients with and without cognitive complaints and followed up with them repeatedly until they died. At baseline, all patients completed a variety of neuropsychiatric tests, including the age- and education-adjusted MCFS. The clinical diagnosis of dementia was made according to the most recent *Diagnostic and Statistical Manual of Mental Disorders*. However, the authors don't report if this assessment was made with the knowledge of baseline MCFS results. The main outcome was a neuropathologic diagnosis of Alzheimer's disease, which, the authors report, was not influenced by the initial neuropsychiatric testing. All patients had an average of nearly six years of follow-up. The MCFS detected 75% of patients with a neuropathologic diagnosis of Alzheimer's disease and was 73.9% specific (positive likelihood ratio=2.9; negative likelihood ratio=0.34). These numbers suggest that the MCFS is of limited use in ruling out or ruling in Alzheimer's disease.

## REFERENCE

Powell MR, Smith GE, Knopman DS, et al. Cognitive measures predict pathologic Alzheimer disease. *Arch Neurol*. 2006;63:865-868.

## Multiple Cesareans Increase Risk of Maternal Morbidity

### Clinical Question

For women undergoing cesarean delivery without labor, does the number of prior cesareans influence the risk of maternal morbidity?

## Bottom Line

Maternal morbidity increases with the number of cesarean deliveries. Women should be made aware of these risks during their family planning. The implications are especially important for women contemplating elective primary cesarean delivery and for those considering a pregnancy after  $\geq 2$  previous cesarean births. (LOE=1b)

### Study Design

Cohort (prospective)

### Funding

Government

### Setting

Inpatient (ward only)

### Synopsis

Maternal morbidity was documented in this prospective cohort of 30,132 women from 19 academic medical centers. All women were undergoing cesarean delivery (CD) without labor. There were 6201 first, 15,808 second, 6,324 third, 1,452 fourth, 258 fifth and 89 sixth or more CDs. Placenta accrete was documented in 0.24% of primary CDs and increased progressively with the number of prior CDs, surpassing 2% with the fourth and reaching almost 7% at the sixth or more. Hysterectomy was required in 0.65% of first CDs, 0.9% of second, 2.4% of third and reached 9% with  $\geq 6$ . Bowel, bladder and ureteral injuries, need for blood transfusion, need for intensive care admission, and hospital length of stay all increased with increasing numbers of CDs. However, there were no differences in maternal deaths or infectious complications associated with number of CDs.

## REFERENCE

Silver RM, Landon MB, Rouse DJ, et al, for the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Maternal morbidity associated with multiple repeat cesarean sections. *Obstet Gynecol*. 2006;107:1226-1232.