
LETTERS TO THE EDITORS

BRANCHED-CHAIN AMINO ACIDS IN HEPATIC ENCEPHALOPATHY

Continuing Controversy

To the Editors:

In December 1990, the *Journal* published a technology assessment report (6) from the American College of Physicians covering, inter alia, the role of parenteral nutrition in hepatic encephalopathy (HE). In the 2 years since that report was prepared, there has been further debate about this controversial therapy.

Our group's conclusions were based on a meta-analysis (7) of trials appraising solutions enriched with branched-chain amino acids (BCAA). In aggregate, patients receiving BCAA were more likely to show partial or complete clearing of HE. However, uncertain effects on mortality, together with the short duration of all studies, led us to suggest that routine use of BCAA could not be endorsed and to call for a new randomized trial with a longer follow-up period to settle the matter definitively.

The above-noted effect on HE has since been questioned by Ferenci (5) because dropouts and crossovers in one trial were not tallied in a way that most strongly favored the null hypothesis. We therefore aggregated results using a more negative interpretation for crossover and drop-out data from two of the trials, and again demonstrated a significant relative improvement in recovery rates (+22%, 95% CI: +3-37%, $p = .02$) (8).

Independent of our meta-analysis, Eriksson and Conn (3) published a nonquantitative review, concluding that BCAA had no effect on mental status. They located the same trials, but obtained data on additional randomized patients from final reports and one unpublished manuscript. Adding these new data to our original pooled analysis left the findings with respect to HE unchanged (9). Only by aggregating the new data with the most conservative interpretation of two trials, as noted above, was the level of significance reduced. However, there remained a clear trend to benefit (odds ratio, 1.50; 95% CI: 0.95, 2.45, $p = .088$). Other interpretive points are dealt with in a lengthy exchange between the two groups that is published elsewhere (4;8).

For short-term mortality (rather than HE per se), DerSimonian (2) has used the additional data from Eriksson and Conn and found no aggregate effect on mortality, with reasonably narrow confidence bounds. However, that interpretation hinges in part on how one counts events in the largest trial, a multicenter study reported by Cerra et al. (1). Cerra et al. found that 22 of 40 patients initially assigned to the BCAA group were discharged alive, as opposed to 9 of 35 in the control group ($p = .02$). The issue is whether such an intention-to-treat analysis can be meaningful when there were liberal provisions for crossover up to 4 days after randomization.

On balance, I believe the case for a definitive trial remains strong. Potential outcome measures could be: (a) all-cause mortality, with perhaps 6 months' follow-up; and (b) effect on HE, measured as mean time to a predefined recovery point and/or

proportion of patients who have recovered by any given day postrandomization. The interventions – for example, with or without lipid enrichment, composition of the amino acid solutions, or type of control solutions, if any – will have to be debated by many clinical experts. So too will the design. Although those who are persuaded that BCAA improves mental status may favor a cross-crossover design on ethical grounds, the mortality data probably justify a standard parallel design that would obviate further interpretive controversy.

A few general lessons can also be drawn. First, even when several RCTs have been performed, technology assessment can be controversial. In this instance, a number of small trials of disparate design with differing cointerventions created a situation in which an interpretive consensus remains elusive. Second, reporting standards are needed for interim analyses and multiple publications from ongoing RCTs. The multiple publications (unreferenced here for diplomatic reasons) in this field include interim analyses yielding abstracts for two of the RCTs; three and possibly four publications from one trial, with conflicting dates reported for the actual duration of the study or studies; and a single center report split off from a larger multicenter trial. Small wonder that debate arose between groups of reviewers about the extent of overlap in patients and data (4;8). Third, several issues in meta-analysis are illustrated. These include the importance of comprehensive literature search strategies, uncertainty about handling data from abstracts and unpublished manuscripts, and the need to update any aggregate analysis as more data become available. Although there are obvious advantages to quantitative approaches, methods of counting and attributing events will have a strong influence on any overview (2;8). Judgment therefore remains crucial in determining what data are used in a meta-analysis, and sensitivity analyses are mandatory to test the robustness of conclusions with differing interpretive and analytical frameworks.

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COST-EFFECTIVENESS OF EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY

To the Editors:

In Volume 6, Number 4, Hatziandreu, Carlson, Mulley, and Weinstein have written an interesting and useful article on the cost-effectiveness of extracorporeal shock wave lithotripsy (ESWL).

Their observations on per-case costs and sequelae are no doubt valid, but they may miss a most important point in comparing noninvasive therapies to invasive alternatives. When a new procedure is much safer, less traumatic, and less disabling, it will likely be used more frequently than the procedure it replaces. ESWL versus surgical lithotomies is a case in point.

At Blue Cross and Blue Shield of the National Capital Area, we are able to compare the number of open lithotomies we covered in our nonfederal population to the number of ESWL procedures after the new technology became available locally in midyear 1986:

	Lithotomies	ESWL procedures
1986	3	63
1987	1	107
1988	0	124
1989	1	114
1990	0	57

We have confirmed in discussions with urologic surgeons that ESWL, an essentially painless and safe procedure, made it appropriate to treat a great many patients with kidney stones who would never have been considered for the open surgical procedure. Most stones, after all, eventually pass naturally, albeit very painfully.

Any evaluation of "cost-effectiveness," it seems to me, must look not only at per-case data but also at changes in the incidence of therapy. We are spending enormously more for ESWL than we ever did for surgical open lithotomies.

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