MEDwave

**Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)**
*Medwave* 2016;16(Suppl5):e6795 doi: 10.5867/medwave.2016.6795

# Do branched chain amino acids improve hepatic encephalopathy in cirrhosis?

**Authors:** Maximiliano Vergara**[1,2]**, Victoria Castro-Gutiérrez**[1,2]**, Gabriel Rada**[2,3,4,5,6]**

**Affiliation:**
**[1]** Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
**[2]** Proyecto Epistemonikos, Santiago, Chile
**[3]** Programa de Salud Basada en Evidencia, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
**[4]** Departamento de Medicina Interna, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
**[5]** GRADE working group
**[6]** The Cochrane Collaboration

**E-mail:** radagabriel@epistemonikos.org

**Citation:** Vergara M, Castro-Gutiérrez V, Rada G. Do branched chain amino acids improve hepatic encephalopathy in cirrhosis?. *Medwave* 2016;16(Suppl5):e6795 doi: 10.5867/medwave.2016.6795
**Publication date:** 14/12/2016

## Abstract

There is controversy about the effectiveness of branched chain amino acids for treatment of hepatic encephalopathy. Searching in Epistemonikos database, which is maintained by screening multiple databases, we identified seven systematic reviews including 32 randomized controlled trials, of which 30 address the question of this article. We extracted results, combined the evidence using meta-analysis and generated a summary of findings following the GRADE approach. We concluded branched chain amino acids might improve hepatic encephalopathy, but they probably lead to little or no effect on mortality.

### Problem

Hepatic encephalopathy is a brain dysfunction associated to the presence of portal-systemic shunting, generally as consequence of liver insufficiency. The pathogenesis of hepatic encephalopathy is not completely understood, but it is accepted hyperammonaemia plays a central role, so most interventions for this condition are directed to a reduction of ammonia.
It is postulated the plasma ratio of aromatic and branched chain amino acids is altered in this condition, leading to an imbalance in neurotransmitter synthesis and accumulation of false neurotransmitters, which would contribute to hepatic encephalopathy.
Therefore, supplementation with branched chain amino acids could improve hepatic encephalopathy. However, it is unclear whether this is an effective intervention.

### Methods

We used Epistemonikos database, which is maintained by screening more than 30 databases, to identify systematic reviews and their included primary studies. With this information, we generated a structured summary using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

**Key messages**
- Branched chain amino acids probably lead to little or no effect on mortality in hepatic encephalopathy.
- Branched chain amino acids might improve hepatic encephalopathy, but the certainty of this evidence is low.

**About the body of evidence for this question**

| | |
|---|---|
| What is the evidence.<br>See evidence matrix in Epistemonikos later | We found seven systematic reviews [1],[2],[3],[4],[5],[6],[7] that include 32 trials reported in 61 references [8],[9],[10],[11],[12],[13],[14],[15],[16],[17],[18],[19],[20],[21],[22],[23],[24],[25],[26],[27],[28],[29],[30],[31], [32],[33],[34],[35],[36],[37],[38],[39],[40],[41],[42],[43],[44],[45],[46],[47],[48],[49],[50],[51],[52],[53],[54],[55],[56],[57],[58],[59],[60],[61],[62],[63],[64],[65],[66],[67], [68]. We excluded two trials evaluating liver transplantation [17],[68] since they did not directly evaluate the question of this summary. |
| What types of patients were included | In 27 trials, all of the participants had cirrosis [8],[13],[16],[20],[21],[24],[26],[30],[31],[32],[36],[39], [44],[46],[48],[50],[54],[55],[58],[59],[60],[61],[62],[64],[65],[66],[67], in one trial only 47% of participants had cirrhosis [27] and in three trials patients with portosystemic shunt were also included [55],[56],[67]. For one trial, it was not possible to extract this information from any review. [12]. |
| What types of interventions were included | Nine trials administered intravenous branched chain amino acids [8],[13],[30],[31],[32],[36],[46],[50],[56], 18 trials used oral branched chain amino acids [16],[20],[21],[24],[26],[39],[44],[48],[54],[55],[58],[59],[61],[62],[64],[65],[66],[67], one trial used oral or intravenous branched chain amino acids according to the condition of the patient [27] and one trial did not specify the route of administration [60]. For one trial, it was not possible to extract this information from any review. [12]. One trial used casein as cointervention [54].<br>All of the trials compared against placebo or standard treatment. |
| What types of outcomes were measured | The main outcomes addressed by the different systematic reviews were the following:<br>• Hepatic encephalopathy<br>• Mortality<br>Other outcomes evaluated were: development of ascites, resolution of ascites, gastrointestinal bleeding, resolution of encephalopathy, infections, bilirubin level, length of hospital stay, stay in intensive care unit, postoperative complications, intra-abdominal complications, postoperative pneumonia, operative wound infection, nitrogen balance, re-hospitalisation post liver transplantation,infections, changes in grade of hepatic encephalopathy, side effects (vomiting, diarrhoea), and time on mechanical ventilation. |

**Summary of findings**

The information on the effects of branched chain amino acids in patients with hepatic encephalopathy is based on 23 randomized trials [8],[13],[16],[20],[21],[24],[26],[27],[30],[31],[32],[36],[39],[44],[46],[48],[50],[56],[58],[59],[60],[61],[62] including 1040 patients. The remaining trials did not provide data about relevant outcomes, or these were not suitable for meta-analysis. All of the trials measure the outcome hepatic encephalopathy and 19 trials (936 patients) measured mortality [8],[13],[16],[20],[21],[26],[27],[30],[32],[36],[39],[44],[46],[48],[50],[56],[58],[61],[62]. The summary of findings is the following:

- Branched chain amino acids probably lead to little or no effect on mortality in hepatic encephalopathy. The certainty of the evidence is moderate.
- Branched chain amino acids might decrease hepatic encephalopathy, but the certainty of this evidence is low.

| Branched chain amino acids for hepatic encephalopathy | | | | |
|---|---|---|---|---|
| **Patients** | Cirrhotic patients with hepatic encephalopathy | | | |
| **Intervention** | Branched chain amino acids (BCAA) | | | |
| **Comparison** | Standard therapy without BCAA or no intervention | | | |
| Outcomes | Absolute effect* | | Relative effect (95% CI) | Certainty of the evidence (GRADE) |
| | **WITHOUT BCAA** | **WITH BCAA** | | |
| | Difference: patients per 1000 | | | |
| Hepatic encephalopathy | 575 per 1000 | 448 per 1000 | RR 0.78 (0.68 to 0.89) | ⨁⨁◯◯[1,2] Low |
| | Difference: 127 patients less per 1000 (Margin of error: 63 to 184 less) | | | |
| Mortality | 218 per 1000 | 207 per 1000 | RR 0.95 (0.77 to 1.18) | ⨁⨁⨁◯[1,2] Moderate |
| | Difference: 11 patients less per 1000 (Margin of error: 50 less to 39 more) | | | |

RR= Risk ratio.
Margin of error = 95% confidence interval (CI).
GRADE: evidence grades of the GRADE Working Group (see later in this article)

* The risk **WITHOUT branched chain amino acids** is based on the risk in the control group of the trials. The risk **WITH branched chain amino acids** (and its margin of error) is calculated from relative effect (and its margin of error)

[1] The certainty of the evidence was downgraded in one level because many of the studies are at risk of bias.
[2] The certainty of the evidence was downgraded in one level because the funnel plot was highly indicative of publication bias. The certainty of the evidence was not downgraded by this factor for mortality because unpublished studies would probably reinforce the conclusion.

## About the certainty of the evidence (GRADE)*

⨁⨁⨁⨁
**High:** This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⨁⨁⨁◯
**Moderate**: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate

⨁⨁◯◯
**Low:** This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⨁◯◯◯
**Very low:** This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.
† Substantially different = a large enough difference that it might affect a decision.

## Other considerations for decision-making

**To whom this evidence does and does not apply**

- The evidence presented in this summary applies broadly to any patient with cirrhosis and hepatic encephalopathy.
- This evidence does not necessarily apply to other conditions associated to hepatic encephalopathy, such as hepatocellular carcinoma or liver surgery.

**About the outcomes included in this summary**

- The outcomes selected correspond to those critical for decision making according to the authors of this summary. They also agree with most systematic reviews and clinical guidelines.

**Balance between benefits and risks, and certainty of the evidence**

- Considering the level of uncertainty, it is not possible to provide a proper risk/benefit balance. However, considering it is a measure without significant adverse effects, the balance could be favorable.

**What would patients and their doctors think about this intervention**

- Patients and clinicians putting more value in an uncertain benefit could be inclined to use this intervention, especially considering this is consistent with the recommendations in the main guidelines.
- Those giving more importance to the associated costs would probably lean against its use while there is uncertainty.

**Resource considerations**

- This is an intervention that adds significant costs, especially if it is associated with some nutritional formula. It is not possible to perform a proper balance between benefits and costs due to the limitations in the certainty of the evidence. If we consider a possible benefit on encephalopathy, but not mortality, it would be a situation where the balance between costs and benefits would be highly dependent of the direct cost of branched chain amino acids in the specific scenario.

**Differences between this summary and other sources**

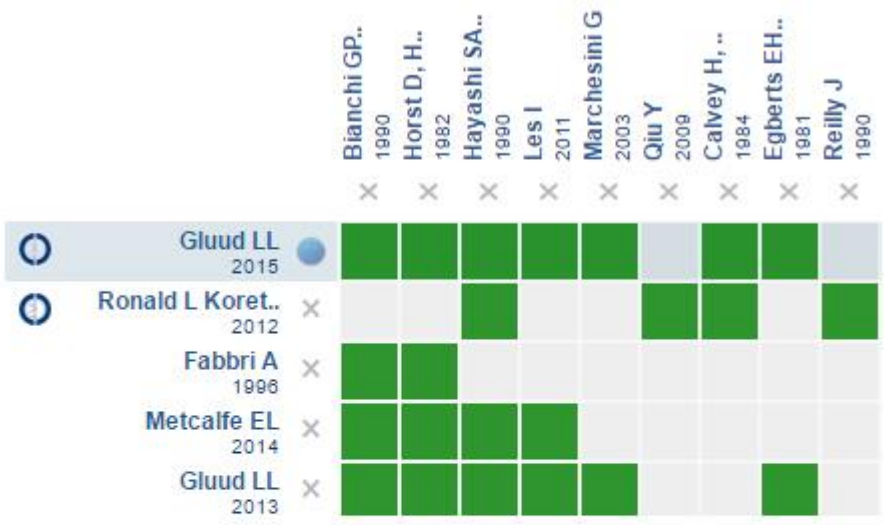
- The conclusions of this summary partially agree with the reviews identified, which generally conclude there is effect on encephalopathy but not in mortality, and that the evidence has limitations so more information is required. For example, the Cochrane review evaluating the specific question [2] reaches to the same conclusion that this summary regarding mortality, but gives greater certainty to the evidence for hepatic encephalopathy. Importantly, this review considered only a proportion of the trials identified in this summary.
- The conclusions of this summary partially agree with the main guidelines, which recommend the use of this intervention without putting emphasis on the limitations of the existing evidence [69].

**Could this evidence change in the future?**

- The probability that future evidence change the conclusions of this summary is high due to the associated uncertainty.
- There are at least four ongoing trials that could provide new information [70],[71],[72][73].

### How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.




Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database.
The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question.
The *rows* represent systematic reviews that share at least one primary study, and *columns* display the studies.
The boxes in green correspond to studies included in the respective reviews.

Follow the link to access the **interactive version**: Branched-chain amino acids for treatment of hepatic encephalopathy

## Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier. After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

The details about the methods used to produce these summaries are described here http://dx.doi.org/10.5867/medwave.2014.06.5997.

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org).

These summaries follow a rigorous process of internal peer review.

**Conflicts of interest**
The authors do not have relevant interests to declare.

## References


1. Koretz RL, Avenell A, Lipman TO. Nutritional support for liver disease. Cochrane Database Syst Rev. 2012 May 16;(5):CD008344 | CrossRef | PubMed |
2. Gluud LL, Dam G, Les I, Córdoba J, Marchesini G, Borre M, et al. Branched-chain amino acids for people with hepatic encephalopathy. Cochrane Database Syst Rev. 2015 Sep 17;(9):CD001939 | CrossRef | PubMed |
3. Metcalfe EL, Avenell A, Fraser A. Branched-chain amino acid supplementation in adults with cirrhosis and porto-systemic encephalopathy: systematic review. Clin Nutr. 2014 Dec;33(6):958-65 | CrossRef | PubMed |
4. Gluud LL, Dam G, Borre M, Les I, Cordoba J, Marchesini G, et al. Oral branched-chain amino acids have a beneficial effect on manifestations of hepatic encephalopathy in a systematic review with meta-analyses of randomized controlled trials. J Nutr. 2013 Aug;143(8):1263-8 | CrossRef | PubMed |
5. Zhu GQ, Shi KQ, Huang S, Wang LR, Lin YQ, Huang GQ, et al. Systematic review with network meta-analysis: the comparative effectiveness and safety of interventions in patients with overt hepatic encephalopathy. Aliment Pharmacol Ther. 2015 Apr;41(7):624-35 | CrossRef | PubMed|
6. Fabbri A, Magrini N, Bianchi G, Zoli M, Marchesini G. Overview of randomized clinical trials of oral branched-chain amino acid treatment in chronic hepatic encephalopathy. JPEN J Parenter Enteral Nutr. 1996 Mar-Apr;20(2):159-64 | PubMed |
7. Langer G, Großmann K, Fleischer S, Berg A, Grothues D, Wienke A, et al. Nutritional interventions for liver-transplanted patients. Cochrane Database Syst Rev. 2012 Aug 15;(8):CD007605 | CrossRef | PubMed |
8. Fiaccadori F, Ghinelli F, Pedretti G. Branched chain amino acid enriched solutions in the treatment of hepatic encephalopathy: a controlled trial. Italian Journal of Gastroenterology 1985;17:5–10. | Link |
9. Fiaccadori F, Ghinelli F, Pedretti G, Mancia D. Mental state course and biochemical findings in HE treated by BCAA-enriched mixtures. In: Holm E, Kasper H editor(s). Metabolism and Nutrition in Liver Disease Freiburg 1984: Proceedings of the 41st Falk Symposium. Lancaster: MTP Press, 1985:281–5. | Link |
10. Fiaccadori F, Ghinelli F, Pedretti G, Pelosi G, Sacchini D, Zeneroli ML, et al. Branched chain amino acid enriched solutions in the treatment of hepatic encephalopathy: a controlled trial. In: Capocaccia L, Fischer JE, Rossi-Fanelli F editor(s). Hepatic Encephalopathy in Chronic Liver Failure. New York: Plenum Press, 1984:323–33. | Link |
11. Fiaccadori F, Ghinelli F, Pelosi G, Sacchini D, Vaona GL, Zeneroli ML, et al. Selective amono acid solutions in hepatic encephalopathy treatment (a preliminary report). Ric Clin Lab. 1980 Apr-Jun;10(2):411-22 | PubMed |
12. Fiaccadori F, Elia GF, Lehndorff H, Merli M, Pedretti G, Riggio O, et al. The effect of dietary supplementation with branched-chain amino acids (BCAAs) versus casein in patients with chronic recurrent portal systemic encephalopathy: a controlled trial. In: Soeters P, Wilson J, et al., editors. Advances in ammonia metabolism and hepatic encephalopathy. Oxford: Excerpta Medica; 1988. pp. 489e97. | Link |
13. Cerra FB, Cheung NK, Fischer JE, Kaplowitz N, Schiff ER, Dienstag JL, et al. Disease-specific amino acid infusion (F080) in hepatic encephalopathy: a prospective, randomized, double-blind, controlled trial. JPEN J Parenter Enteral Nutr. 1985 May-Jun;9(3):288-95 | PubMed |
14. Cerra FB, Cheung NK, Fischer JE, Kaplowitz N, Schiff ER, Dienstag JL, et al. A multicenter trial of branched chain enriched amino acid infusion (F080) in hepatic encephalopathy (HE). Hepatology 1982;2:699. | Link |
15. Cerra FB, McMillen M, Angelico R, Cline B, Lyons J, Faulkenbach L, Paysinger, J. Cirrhosis, encephalopathy, and improved results with metabolic support. Surgery. 1983 Oct;94(4):612-9| PubMed |
16. Plauth M, Egberts E-H, Hamster W, Török M, Müller P, Brand O, et al. Long-term treatment with branchedchain amino acids (BCA) improves the portosystemic encephalopathy (PSE) in ambulant patients Results of a double blind, placebo controlled crossover study. Klinische Wochenschrift 1992;69:126. | Link |
17. Plauth M, Egberts EH, Hamster W, Török M, Müller PH, Brand O, et al. Long-term treatment of latent portosystemic encephalopathy with branched-chain amino acids. A double-blind placebo-crossover study. Journal of Hepatology 1993;17:308–14. | Link |
18. Reilly J, Mehta R, Teperman L, Cemaj S, Tzakis A, Yanaga K, Ritter P, Rezak A, Makowka L. Nutritional support after liver transplantation: a randomized prospective study. JPEN J Parenter Enteral Nutr. 1990 Jul-Aug;14(4):386-91. | PubMed |
19. Reilly J, Yanaga K, Tzakis A, Teperman L, Mehta R, Rezak A, et al. A randomized prospective study of nutritional support after liver transplant (Abstract). Journal Parenteral and Enteral Nutrition 1989;13:8S. | Link |
20. Marchesini G, Bianchi G, Merli M, Amodio P, Panella C, Loguercio C, et al. Nutritional supplementation with branched-chain amino acids in advanced cirrhosis: a double-blind, randomized trial. Gastroenterology. 2003 Jun;124(7):1792-801 | PubMed |
21. Bianchi GP, Marchesini G, Zoli M, Abbiati R, Ferrario E, Fabbri A, et al. Oral BCAA supplementation in cirrhosis with chronic encephalopathy: effects on prolactin and estradiol levels. Hepatogastroenterology. 1992 Oct;39(5):443-6. | PubMed |
22. Charlton M. Branched-chain amino acid-enriched supplements as therapy for liver disease: Rasputin lives. Gastroenterology. 2003 Jun;124(7):1980-2 | PubMed |
23. Marchesini G, Dioguardi FS, Bianchi GP, Zoli M, Bellati G, Roffi L, et al. Long-term oral branched-chain amino acid treatment in chronic hepatic encephalopathy. A randomized double-blind casein-controlled trial. The Italian Multicenter Study Group. J Hepatol. 1990 Jul;11(1):92-101 | PubMed |
24. Hayashi S, Aoyagi Y, Fujiwara K, Oka H, Oda T. A randomized controlled trial of branched-chain amino acid (BCAA)-enriched elemental diet (ED-H) for hepatic encephalopathy. Journal of Gastroenterology and Hematology 1991;6:191. | Link |

25. Hayashi, S. A randomized controlled study of an elementary diet (ED-H) in cirrhotic with hepatic encephalopathy. JJPEN 1990 | Link |
26. Les I, Doval E, García-Martínez R, Planas M, Cárdenas G, Gómez P, et al. Effects of branched-chain amino acids supplementation in patients with cirrhosis and a previous episode of hepatic encephalopathy: a randomized study. Am J Gastroenterol. 2011 Jun;106(6):1081-8 | CrossRef| PubMed |
27. Calvey H, Davis M, Williams R. Controlled trial of nutritional supplementation, with and without branched chain amino acid enrichment, in treatment of acute alcoholic hepatitis. J Hepatol. 1985;1(2):141-51 | PubMed |
28. Calvey H, Davis M, Williams R. Prospective study of nasogastric feeding via East Grinstead or Viomedex tubes compared with oral dietary supplementation in patients with cirrhosis. Clin Nutr. 1984 Jul;3(2):63-6 | PubMed |
29. Williams R, Calvey H, Davis M. Controlled trial of nutritional supplementation in acute alcoholic hepatitis. In: Holm E, Kasper H editor(s). Metabolism and nutrition in liver disease. Lancaster, England: MTP Press, Ltd., 1985: 361–8. | Link |
30. Hwang SJ, Chan CY, Wu JC, Lee SD, Huan YS, Tsai YT, et al. A randomized controlled trial for the evaluation of the efficacy of branched chain amino acid-enriched amino acid solution in the treatment of patients with hepatic encephalopathy. Chinese Journal of Gastroenterology 1988;5: 185–92. | Link |
31. Hasse J, Crippin J, Blue L, Huang K, DiCecco S, Francisco-Ziller N, et al. Does nutrition supplementation benefit liver transplant candidates with a history of encephalopathy? (Abstract). J Parenter Enter Nutr 1997;21(1). S16(91). | Link |
32. Riggio O, Cangiano C, Cascino A, Merli M, Stortoni M, Rossi-Fanelli F, et al. Long term dietary supplement with branched chain amino acids: a new approach in the prevention of hepatic encephalopathy: results of a controlled study in cirrhotics with porto-caval anastomosis. In: Associazione Italiana per Lo Studio del Fegato. Congress, editor(s). Hepatic Encephalopathy in Chronic Liver Failure. New York: Plenum Press, 1984:183–92. | Link |
33. Rossi Fanelli F, Cangiano C, Capocaccia L, Cascino A, Ceci F, Muscaritoli M, et al. Use of branched chain amino acids for treating hepatic encephalopathy: clinical experiences. Gut. 1986 Nov;27 Suppl 1:111-5 | PubMed |
34. Rossi-Fanelli F, Cangiano C, Cascino A, Merli M, Riggio O, Stortoni M, et al. Branched-chain amino acids in the treatment of severe hepatic encephalopathy. In: Capocaccia L, Fischer JE, Rossi-Fanelli F editor(s). Hepatic Encephalopathy in Chronic Liver Failure. New York: Plenum Press, 1984:335–44 | Link |
35. Rossi-Fanelli F, Riggio O, Cangiano C, Cascino A, De Conciliis D, Merli M, et al. Branched-chain amino acids vs lactulose in the treatment of hepatic coma: a controlled study. Dig Dis Sci. 1982 Oct;27(10):929-35 | PubMed |
36. Gluud C, Dejgaard A, Hardt F, Kristensen M, Køhler O, Melgaard B, et al. Preliminary treatment results with balanced amino acid infusion to patients with hepatic encephalopathy. Scandinavian Journal of Gastroenterology 1983;18:19. | Link |
37. Vilstrup H, Gluud C, Hardt F, Kristensen M, Køhler O, Melgaard B, et al. Branched chain enriched amino acid versus glucose treatment of hepatic encephalopathy. A double-blind study of 65 patients with cirrhosis. J Hepatol. 1990 May;10(3):291-6 | PubMed |
38. Vilstrup H, Gluud C, Hardt F, Kristensen M, Melgaard B, Køhler O, et al. Branched chain enriched amino acid nutrition does not change the outcome of hepatic coma in patients with cirrhosis of the liver. Journal of Hepatology 1985;1:S347. | Link |
39. Egberts EH, Hamster W, Schomeerus H, Jürgens P. Effect of branched chain amino acids on latent porto-systemic-encephalopathy (PSE). JPEN. Journal of Parenteral and Enteral Nutrition 1981;5:5. | Link |
40. Egberts EH, Schomeerus H, Hamster W, Jürgens P. Effective treatment of latens porto-systemic encephalopathy with oral branched chain amino acids. In: Capocaccia L, Fischer JE, Rossi-Fanelli F editor(s). Hepatic Encephalopathy in Chronic Liver Failure. New York: Plenum Press, 1984: 351–7. | CrossRef |
41. Egberts EH, Schomerus H, Hamster W, Jürgens P. Branched chain amino acids in the treatment of latent portosystemic encephalopathy. A double-blind placebo-controlled crossover study. Gastroenterology. 1985 Apr;88(4):887-95. | PubMed |
42. Egberts EH, Schomerus H, Hamster W, Jürgens P. [Branched-chain amino acids in the treatment of latent porto-systemic encephalopathy. A placebo-controlled double-blind cross-over study]. Z Ernahrungswiss. 1986 Mar;25(1):9-28. German. | PubMed |
43. Hamster W, Egberts EH, Hamster H. Treatment with branched-chain amino acids and effect on psycho-physical capacity functions in latent porto-systemic encephalopathy [Behandlung mit verzweigtkettigen aminosäuren und ihre auswirkung auf psychophysische leistungsfunktionen bei latenter portosystemischer enzephalopathie].Arzneimittelforschung 1982;32:901–2. | Link|
44. Muto Y, Sato S, Watanabe A, Moriwaki H, Suzuki K, Kato A, et al. Effects of oral branched-chain amino acid granules on event-free survival in patients with liver cirrhosis. Clin Gastroenterol Hepatol. 2005 Jul;3(7):705-13 | PubMed |
45. Sato S, Watanabe A, Muto Y, Suzuki K, Kato A, Moriwaki H, et al. Clinical comparison of branched-chain amino acid (l-Leucine, l-Isoleucine, l-Valine) granules and oral nutrition for hepatic insufficiency in patients with decompensated liver cirrhosis (LIV-EN study). Hepatol Res. 2005 Apr;31(4):232-40 | PubMed |
46. Strauss E, Cartapatti Da Silva E, Lacet CM, Capacci MLL, Bernardini AP. Treatment of hepatic encephalopathy: a randomized clinical trial comparing a branched chain enriched amino acid solution to oral neomycin. Nutritional Support Services 1986;6:18–21. | Link |
47. Strauss E, Santos WR, Da Silva EC, Lacet CM, Capacci LL, Bernardini AP. A randomized controlled clinical trial for the evaluation of the efficacy of an enriched branched-chain amino-acid solution compared to

neomycin in hepatic encephalopathy. Hepatology 1983;3:862. | Link|
48. Horst D, Grace N, Conn HO, Schiff E, Schenker S, Viteri A, et al. A double-blind randomized comparison of dietary protein and an oral branched chain amino acid (BCAA) solution in cirrhotic patients with chronic portal-systemic encephalopathy (PSE) [IASL abstract]. Hepatology 1982;2: 184 | Link |
49. Horst D, Grace ND, Conn HO, Schiff E, Schenker S, Viteri A, et al. Comparison of dietary protein with an oral, branched chain-enriched amino acid supplement in chronic portal-systemic encephalopathy: a randomized controlled trial. Hepatology. 1984 Mar-Apr;4(2):279-87 | PubMed |
50. Michel H, Bories P, Aubin JP, Pomier-Layrargues G, Bauret P, Bellet-Herman H. Treatment of acute hepatic encephalopathy in cirrhotics with a branched-chain amino acids enriched versus a conventional amino acids mixture. A controlled study of 70 patients. Liver. 1985 Oct;5(5):282-9 | PubMed |
51. Michel H, Pomier-Layrargues G, Aubin JP, Bories P, Mirouze D, Bellet-Herman H. Treatment of hepatic encephalopathy by infusion of a modified amino acid solution: results of a controlled study in 47 cirrhotic patients. In: Capocaccia L, Fischer JE, Rossi-Fanelli F editor(s). Hepatic Encephalopathy in Chronic Liver Failure. New York: Plenum Press, 1984:301–10. | Link |
52. Michel H, Pomier-Layrargues G, Duhamel O, Lacombe B, Cuilleret G, Bellet-Hermann H. Intravenous infusion of ordinary and modified amino-acid solutions in the management of hepatic encephalopathy (controlled study, 30 patients). Gastroenterology 1980;79:1038. | Link |
53. Pomier-Layrargues G, Duhamel O, Lacombe B, Cuilleret G, Bellet H, Michel H. Intravenous infusion of ordinary and modified amino-acid solutions in the management of hepatic encephalopathy. Liver 1981;1:140 | Link |
54. Christie ML, Sack DM, Pomposelli J, Horst D. Enriched branched-chain amino acid formula versus a casein-based supplement in the treatment of cirrhosis. JPEN J Parenter Enteral Nutr. 1985 Nov-Dec;9(6):671-8 | PubMed |
55. Sieg A, Walker S, Czygan P, Gärtner U, Lanzinger-Rossnagel G, Stiehl A, et al. Branched-chain amino acid-enriched elemental diet in patients with cirrhosis of the liver. A double blind crossover trial. Z Gastroenterol. 1983 Nov;21(11):644-50 | PubMed |
56. Ceriati F, Cavicchioni C, Marino IR, De Luca G, Puglionisi A. Management of hepatic encephalopathy in cirrhotic patients after derivative surgery [Trattamento dell'encefalopatia epatica nei pazienti cirrotici sottoposti ad intervento chirurgico derivativo]. Acta Medica Romana 1985;23(1):69–76. | Link |
57. Puglionisi A, Ceriati F, Marino IR, Cavicchioni C, De Luca G, Roncone A, et al. Prophylaxis of hepatic encephalopathy after porta-caval anastomosis using branched chain amino acid mixtures. In: Capacaccio L, Fischer JE, Rossi-Fanelli F editor(s). Hepatic Encephalopathy in Chronic Liver Failure. New York: Plenum Press, 1984:345–50 | Link |
58. Ichikawa T, Naota T, Miyaaki H, Miuma S, Isomoto H, Takeshima F, Nakao K. Effect of an oral branched chain amino acid-enriched snack in cirrhotic patients with sleep disturbance. Hepatol Res. 2010 Oct;40(10):971-8 | CrossRef | PubMed |
59. Simko V. Long-term tolerance of a special amino acid oral formula in patients with advanced liver disease. Nutrition Reports International 1983;27(4):765–73 | Link |
60. Sievert W, Gibson PR, Colman JC, Kronborg I, Crawford DH, Keogh J, et al. Energy and amino acid supplements in a malnourished patients with cirrhosis: a randomised controlled trial. 50th Annual Meeting American Association for the Study of Liver Disease (Published in: . Hepatology. 1999;30(Supp 4):434A. 1999 | Link |
61. Humbert P, Pintó A, Johnston S, Fábrega C, Planas R, Boix J, et al. Effect of oral administration of branched-chain amino acids for the treatment of nutrition disturbances and for the prophylaxis of encephalopathy in cirrhotic patients [Efecto de la administración oral de aminoácidos ramificados en el tratamiento de los trastornos nutricionales y en la prevención de la encefalopatía de pacientes cirróticos.]. Gastroenterología y Hepatología 1989;12(1): 9–13. | Link |
62. Nakaya Y, Okita K, Suzuki K, Moriwaki H, Kato A, Miwa Y, et al. BCAA-enriched snack improves nutritional state of cirrhosis. Nutrition. 2007 Feb;23(2):113-20 | PubMed |
63. Nakaya Y, Okita K, Kato A, Miwa Y, Suzuki K, Moriwaki H. Randomized trial of branched chain amino acid rich supplement against carbohydrate-rich snacks as a late evening snack in patients with liver cirrhosis (Abstract). Hepatology 2005;42 Suppl 1(4):699A–700A. | Link |
64. McGhee A, Henderson JM, Millikan WJ Jr, Bleier JC, Vogel R, Kassouny M, et al. Comparison of the effects of Hepatic-Aid and a Casein modular diet on encephalopathy, plasma amino acids, and nitrogen balance in cirrhotic patients. Ann Surg. 1983 Mar;197(3):288-93 | PubMed |
65. Panella C, Guglielmi F, Laddaga L, Reale L, Polimeno L, DiLeo A. Oral branched-chain amino acids in the treatment of low portosystemic encephalopathy: a long term multicentric trial. Liver and Hormones 1992 Volume 43, Pages 97-106 | Link |
66. Guarnieri GF, Toigo G, Situlin R, Pozzato G, Faccini L. Muscle biopsy studies on malnutrition in patients with liver cirrhosis: Preliminary results of long-term treatment with a branched-chain amino acid enriched diet. Hepatic Encephalopathy in Chronic Liver Failure, Capocaccia L, Fischer JE, Rossi-Fanelli F (eds). Plenum Press, New York 1984 | Link |
67. Eriksson LS, Persson A, Wahren J. Branched-chain amino acids in the treatment of chronic hepatic encephalopathy. Gut. 1982 Oct;23(10):801-6 | PubMed |
68. Qiu Y, Zhu X, Wang W, Xu Q, Ding Y. Nutrition support with glutamine dipeptide in patients undergoing liver transplantation. Transplant Proc. 2009 Dec;41(10):4232-7 | CrossRef | PubMed |
69. Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the

European Association for the Study of the Liver. Hepatology. 2014 Aug;60(2):715-35 | CrossRef | PubMed |
70. Won Young Tak. Branched-chain Amino Acid (BCAA) on Progression of Advanced Liver Disease (BRAVE) | Link |
71. Keiding S. Effects of Branched-Chain Amino Acids on Muscle Ammonia Metabolism in Patients With Cirrhosis and Healthy Subjects | Link |
72. Torre A. Branched chain aminoacid supplementation in patients with liver cirrhosis | CrossRef | Link |
73. Córdoba J. Effects of proteins in patients with cirrhosis and prior hepatic encephalopathy. ClinicalTrials.gov identifier: NCT00955500 | Link |

**Author address:**
**[1]** Facultad de Medicina
Pontificia Universidad Católica de Chile
Lira 63
Santiago Centro
Chile