Amino acid kinetics in patients with sepsis[1–3]

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ABSTRACT

Background: In patients with sepsis and systemic inflammatory response syndrome, amino acid extraction by the liver is enhanced, resulting in decreased plasma amino acid concentrations. Systematic investigations of the elimination of intravenously infused amino acids have not been performed.

Objective: The objective of this study was to compare the elimination of 17 amino acids in patients with sepsis and in healthy control subjects.

Design: Elimination of amino acids was evaluated in 9 patients with sepsis and in 8 healthy control subjects by using a combined loading and maintenance infusion of 375 mg amino acids/kg body wt for 60 min. Pharmacokinetic variables were analyzed from plasma curves.

Results: With the exception of lysine, methionine, glutamate, ornithine, phenylalanine, and tyrosine, plasma concentrations of amino acids were lower in the patients with sepsis than in the control subjects; phenylalanine was the only amino acid whose plasma concentration increased ($P < 0.001$). In patients with sepsis, whole-body clearance (Cl_{tot}) of total amino acids was 74% higher than in control subjects ($\bar{x} \pm$ SEM: 13161 $\pm$ 1659 and 7566 $\pm$ 91 mL/min, respectively; $P < 0.01$), the Cl_{tot} of essential amino acids was 64% higher ($P < 0.02$), that of nonessential amino acids was 82% higher ($P < 0.01$), and that of both branched-chain amino acids and glucogenic amino acids was 97% higher ($P < 0.001$). With the exception of phenylalanine, ornithine, proline, and glutamate, the Cl_{tot} of all amino acids was elevated. The Cl_{tot} of phenylalanine and ornithine decreased slightly (NS).

Conclusions: In patients with sepsis, plasma concentrations of most amino acids are greatly decreased and the elimination of amino acids from the intravascular space during intravenous infusion is greatly enhanced. *Am J Clin Nutr* 2001;73:908-13.

KEY WORDS Sepsis, hypermetabolism, amino acid metabolism, plasma amino acids amino acid elimination, amino acid clearance

INTRODUCTION

The systemic inflammatory response syndrome (SIRS) and sepsis syndrome are associated with hypermetabolism, increased oxygen consumption and energy expenditure, activation of peripheral protein catabolism, and, especially, augmented metabolic activity in the hepatosplanchnic region (1, 2). Amino acids are released from peripheral tissues and shifted to the liver for promotion of hepatic protein synthesis, gluconeogenesis, and urea synthesis (3). In fact, a major (if not predominant) portion of the hypermetabolism of the septic organism can be attributed to enhancement of hepatic and splanchnic metabolism (3).

Plasma amino acid concentrations in patients with sepsis are lower than in persons without sepsis (4). The extent of this difference has been used as a marker of the severity and prognosis of the disease process (5). The uptake of amino acids into the liver is elevated despite the reduced plasma amino acid concentration; thus, hepatic extraction of amino acids from the bloodstream is augmented (6–8). As a consequence, the metabolic clearance and turnover of endogenously released amino acids is enhanced.

Nevertheless, systematic investigations of clearance of individual amino acids in patients with sepsis have not been performed. A better knowledge of the pharmacokinetic behavior of individual amino acids is mandatory not only for more appropriate estimations of amino acid requirements but also for the formulation of more optimal amino acid mixtures than those currently available for parenteral or enteral nutrition in patients with sepsis or SIRS. In the present investigation we compared the pharmacokinetic behavior of 17 intravenously infused amino acids in patients with sepsis and in healthy control subjects.

SUBJECTS AND METHODS

Eight patients with microbiologically proven sepsis treated at a medical intensive care unit of a university hospital were investigated. The characteristics of the patients are presented in **Table 1**. The definition of septicemia was in accordance with the terminology of the American College of Chest Physicians and the Society of Critical Care Medicine, and only patients with positive blood cultures were enrolled in the study (9). The patients' body temperatures ranged between 38.0 and 39.5°C. Patients with sepsis who had respiratory or renal failure were included (7

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TABLE 1
Characteristics of patients with sepsis[1]

Patient	Sex	Age	Weight	BUN	Crea	Albumin	Glucose	Lactate	Temperature	Organ failing	Cause of septicemia	Bacteriology (blood culture)
		y	*kg*	*mmol/L*	*μmol/L*	*g/L*	*mmol/L*	*mmol/L*	*°C*			
1	M	47	63	16.4	159.1	28.8	6.5	0.6	39.4	Lung	Perforation of esophagus	*Staphylococcus aureus*
2	M	44	85	14.3	106.1	24	8.4	1.2	38.9	Lung	Meningo-encephalitis	*Streptococcus pneumoniae*
3	M	40	90	8.9	97.2	32.9	8.9	1.1	38.9	Lung	ARDS	*Candida albicans, Enterococci*
4	F	56	61	37.5	539.2	28.9	10.5	2.2	39.1	Lung, kidney	Cholangitis	*Escherichia coli*
5	F	70	60	51.8	565.8	30.4	8.2	1.0	38.0	Kidney	IgG deficiency	*E. coli*
6	M	62	66	17.8	141.4	24.6	4.4	1.0	39.3	Lung	Cholangitis	*Serratia marcescens*
7	M	65	50	19.6	777.9	21.9	8.4	1.8	38.0	Lung, kidney	Multiple trauma	*Klebsiella pneumoniae*
8	F	65	75	16.8	141.4	19.6	8.3	1.6	38.5	Lung	Burns	*Pseudomonas aeruginosa*
9	M	33	47	28.9	592.3	18.1	8.5	0.5	38.5	Kidney	Osteomyelitis	*S. aureus*
All	—	53.6 ± 4.3[2]	66.3 ± 4.8	23.6 ± 4.5	346.7 ± 89	25.5 ± 1.7	8.0 ± 0.6	1.2 ± 0.2	38.7 ± 0.15	—	—	—

[1] BUN, blood urea nitrogen; Crea, creatinine; ARDS, adult respiratory distress syndrome; IgG, immunoglobulin G.
[2] $\bar{x}$ ± SEM.

patients received ventilatory support and 4 patients received hemodialysis). Patients with circulatory shock (mean arterial blood pressure < 70 mm Hg), increased serum lactate concentration, metabolic acidosis (pH < 7.3), overt bleeding, body temperature > 39.5 °C, or arterial hypoxemia (P_aO_2 < 60 mm Hg) were excluded from the investigation. Patients with diabetes mellitus or chronic hepatic disease were also excluded.

The patients with sepsis received parenteral nutrition that provided 130% of basic energy expenditure and 1.2 g amino acids·kg^{-1}·d^{-1}. Intravenous nutrition was stopped 12 h before the study, and the investigation was conducted ≥18 h after the last hemodialysis therapy.

Eight healthy volunteers (6 men and 2 women; $\bar{x}$ ± SEM age: 24 ± 3.5 y) served as control subjects. These healthy control subjects were fed a mixed normal diet providing, on average, 8800 kJ/d and 80 g protein/d. In these subjects, the investigation was performed between 0800 and 1400 after the subjects had fasted overnight.

Amino acid clearance and other pharmacokinetic variables were evaluated from the time course of plasma amino acid concentrations with use of a combined loading and maintenance infusion protocol as described previously (10). A standard amino acid solution (Thomaeamin N 10%; Boehringer Ingelheim, Biberach, Germany) was infused with a precision infusion pump for 5 min at rate of 0.2 mL·kg^{-1}·min^{-1} (20 mg·kg^{-1}·min^{-1}) and then for 55 min at a rate of 0.05 mL·kg^{-1}·min^{-1} (5 mg·kg^{-1}·min^{-1}) into an antecubital vein; blood for amino acid analysis was taken from an indwelling arterial catheter in the radial artery.

Blood samples were drawn before the start of the infusion; 10, 20, 30, 40, 50, and 60 min during the infusion; and 5, 10, 20, 30, 60, 90, and 120 min after termination of the infusion. The blood samples were drawn into precooled heparin-containing test tubes and then centrifuged at 3000 × *g* for 15 min at 4 °C. The plasma was stored at −80 °C until analyzed.

The separation and measurement of amino acids was performed chromatographically by using an automated amino acid analyzer (Biotronic LC 6001; Kontron-Roche, Basel, Switzerland) connected to an automatic integrator (Autolab SP 4100; Kontron-Roche).

Pharmacokinetic analysis of the time course of changes in plasma concentrations of amino acids after intravenous administration was performed by using least-squares regression fitting to a biexponential function in an open two-compartment model (TOPFIT) (11). Inclusion of additional compartments or calculation with use of nonlinear models did not improve the accuracy of the fit. The elimination constant from the central compartment (k_{1e}), the whole-body clearance (Cl_{tot}, in mL/min), and the steady state distribution volumes (in L) were calculated.

For statistical analysis, a repeated-measures analysis of covariance was performed to compare the time curves of amino acid concentrations between the groups. Results were compared by Mann-Whitney *U* test for unpaired data. $P < 0.05$ was regarded as significant. SAS (SAS Institute Inc, Cary, NC) was used for analysis. All values are expressed as means ± SEMs.

The study was performed in accordance with the Helsinki Declaration of Human Rights and was approved by the ethical committee of the University of Vienna. Informed, written consent was obtained from the patients or their respective relatives and from the volunteers.

RESULTS

The infusion of amino acids was not associated with any complications in the healthy control subjects or in the patients with sepsis. Two healthy control subjects experienced a slight flush after the initial bolus injection of the amino acid solution, a well-known consequence of the rapid intravenous infusion of amino acids.

The total basal amino acid concentration was 34% lower in the patients with sepsis than in the control subjects (**Table 2**).

TABLE 2
Plasma amino acid concentrations in patients with sepsis and in healthy control subjects[1]

Amino acid	Healthy control subjects (n = 8)	Patients with sepsis (n = 9)	P
	μmol/L		
Isoleucine	58 ± 3[2]	36 ± 4	<0.001
Leucine	140 ± 3	72 ± 7	<0.001
Lysine	106 ± 6	113 ± 12	0.6
Methionine	25 ± 2	29 ± 3	0.3
Phenylalanine	55 ± 3	103 ± 11	<0.001
Threonine	120 ± 10	59 ± 7	<0.001
Tryptophan	41 ± 3	27 ± 5	<0.035
Valine	202 ± 13	130 ± 5	<0.001
Arginine	84 ± 5	46 ± 6	<0.001
Histidine	86 ± 5	60 ± 4	<0.001
Proline	266 ± 35	124 ± 15	<0.001
Alanine	269 ± 35	165 ± 22	<0.02
Glutamic acid	52 ± 8	55 ± 12	0.8
Glycine	241 ± 13	124 ± 9	<0.001
Ornithine	48 ± 3	40 ± 4	0.14
Serine	124 ± 6	51 ± 5	<0.001
Tyrosine	52 ± 6	52 ± 6	1.0
Total AA	1969 ± 163	1292 ± 142	<0.01
EAA	747 ± 47	575 ± 59	<0.04
NEAA	1222 ± 116	717 ± 83	<0.004
BCAA	754 ± 64	399 ± 43	<0.001
Glucogenic AA	400 ± 23	244 ± 21	<0.001

[1] AA, amino acids; EAA, essential AA; NEAA, nonessential AA; BCAA, branched-chain AA.
[2] $\bar{x}$ ± SEM.

Concentrations of essential amino acids, nonessential amino acids, branched-chain amino acids, glucogenic amino acids, isoleucine, leucine, threonine, tryptophan, valine, arginine, histidine, proline, alanine, glycine, and serine were lower in the patients with sepsis; there were no significant differences in concentrations of lysine, methionine, glutamate, ornithine, or tyrosine. Phenylalanine was the only amino acid whose plasma concentration was higher in the patients with sepsis than in the control subjects.

Before, during, and after the infusion of the amino acid mixture, the total plasma concentration of amino acids was lower in the patients with sepsis than in the control subjects at all time points of investigation, and the net increase during the infusion was lower. Nevertheless, the patients with sepsis also achieved a steady state plasma concentration during the infusion (**Figure 1**).

Total clearance of the 17 amino acids was, on average, 74% higher (**Table 3**), that of essential amino acids was 64% higher, that of nonessential amino acids was 82% higher, and that of branched-chain amino acids and gluconeogenetic amino acids was 97% higher in the patients with sepsis than in the control subjects (**Figure 2**). Clearance of most individual amino acids was also higher. Clearance rates of proline and glutamate were higher, but not significantly so, because of large variations of individual values (Table 3). Phenylalanine and ornithine were the only amino acids whose clearances were lower in the patients with sepsis (NS). Calculated as a relative clearance rate (fraction of total clearance), the clearance of phenylalanine and ornithine was much lower.

The k_{le} for isoleucine, lysine, tryptophan, arginine, alanine, glutamate, and glycine was higher in the patients with sepsis than in the control subjects (**Table 4**). The distribution volume was higher for leucine and lower for tryptophan and ornithine (Table 4).

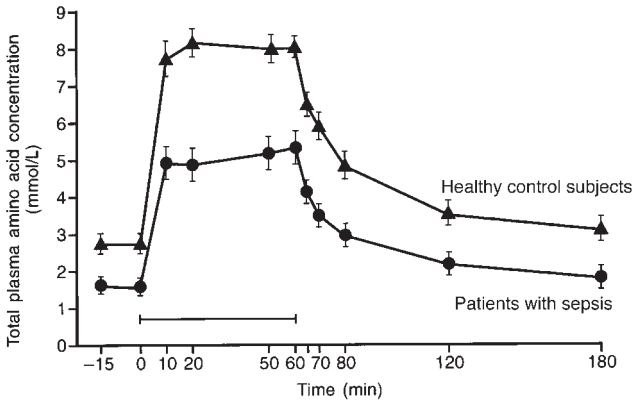

FIGURE 1. Mean (±SEM) total plasma amino acid concentrations before, during (from time 0 to 60 min), and after infusions of an amino acid solution providing 375 mg·kg body wt^{-1}·60 min^{-1} in patients with sepsis (n = 9) and in healthy control subjects (n = 8). The curves are significantly different at all time points, P < 0.001.

DISCUSSION

Our results show that the clearance of intravenously infused amino acids was greatly elevated in patients with sepsis. With the exceptions of phenylalanine, ornithine, proline, and glutamate, elimination of amino acids was ≈70% higher in these patients than in healthy control subjects. This was also reflected by substantially lower plasma concentrations of most amino acids. Thus, much higher infusion rates of amino acids are necessary to

TABLE 3
Clearance of amino acids in patients with sepsis and in healthy control subjects

Amino acid	Healthy control subjects (n = 8)	Patients with sepsis (n = 9)	Difference	P
	mL/min	*mL/min*	*%*	
Isoleucine	479 ± 54[1]	845 ± 78	76	<0.02
Leucine	321 ± 54	769 ± 68	139	<0.001
Lysine	401 ± 48	649 ± 61	62	<0.01
Methionine	513 ± 45	987 ± 155	92	<0.02
Phenylalanine	678 ± 83	546 ± 125	−20	NS
Threonine	351 ± 33	689 ± 79	96	<0.002
Tryptophan	378 ± 38	605 ± 48	60	<0.002
Valine	186 ± 37	325 ± 33	75	<0.02
Arginine	422 ± 57	874 ± 82	107	<0.001
Histidine	539 ± 56	1144 ± 135	112	<0.001
Proline	254 ± 43	395 ± 92	56	NS
Alanine	615 ± 89	1152 ± 137	87	<0.01
Glutamic acid	846 ± 66	1333 ± 216	58	NS
Glycine	522 ± 55	985 ± 101	89	<0.001
Ornithine	218 ± 27	163 ± 30	−25	NS
Serine	467 ± 56	1028 ± 114	120	<0.001
Tyrosine	376 ± 77	672 ± 105	79	<0.05
Total amino acids	7566 ± 918	13161 ± 1659	74	<0.01

[1] $\bar{x}$ ± SEM.

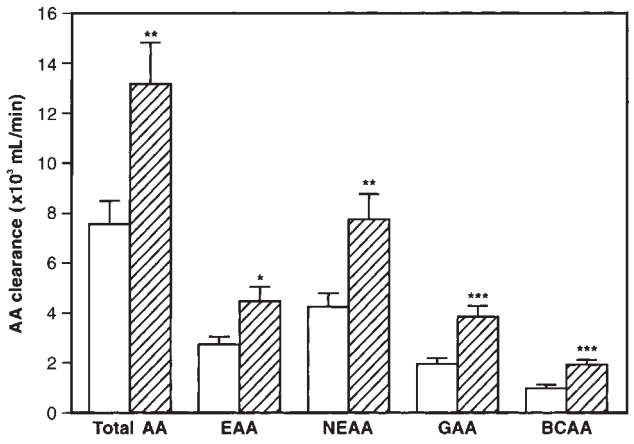

FIGURE 2. Comparison of the mean (±SEM) total clearance of all amino acids (total AA), essential AA (EAA), nonessential AA (NEAA), glucogenic AA (GAA), and branched-chain AA (BCAA) in healthy control subjects (open bars; $n = 8$) and in patients with sepsis (hatched bars; $n = 9$). *,**,***Significantly different from control subjects: $^{*}P < 0.02$, $^{**}P < 0.01$, $^{***}P < 0.001$.

raise plasma amino acid concentrations in patients with sepsis than in those without sepsis.

The large difference in the clearance of amino acids is a consequence of the augmentation of hepatic extraction of amino acids in sepsis, which was well-defined in several studies (6, 7). This is especially obvious for glucogenic amino acids, which expectedly showed the highest increase in elimination. Nevertheless, branched-chain amino acids, which supposedly escape hepatic extraction and are taken up mainly by peripheral tissues, showed a doubling of clearance rates.

An exception is phenylalanine, which, together with ornithine, was the only amino acid with a decreased clearance rate in subjects with sepsis. Similar observations were made in subjects with renal and hepatic failure (12). It is also known that phenalylanine concentrations increase in patients with sepsis or burns. The exact mechanisms of these findings remain to be elucidated. An increase in phenylalanine release during catabolism from skeletal muscle was proposed as a potential cause (13). Alternatively, it was suggested that interconversion to tyrosine is inadequate in several disease states and that tyrosine might become a conditionally essential amino acid (14). Certainly, this cannot represent a global dysfunction of the liver because hepatic protein synthesis was shown to be greatly increased in patients with sepsis (15). The "falsely" low clearance rate of ornithine might reflect overactivity of the urea cycle because amino acid catabolism and flux through the urea cycle are greatly increased and endogenous ornithine formation is augmented in catabolic disease (15).

Stimulation of hepatic protein synthesis, gluconeogenesis from amino acids, and ureagenesis, together with augmented skeletal muscle catabolism, present constitutive elements of the sepsis syndrome (16). However, these metabolic alterations are not specific to sepsis but present a more basic pattern of reaction of the organism to various insults and stress factors; it is also characteristic of SIRS, acute renal failure, and postoperative states and, surprisingly, is even present with nontraumatic pain (17–20).

Causes of this typical metabolic scenario might be manifold. Catabolic hormones, inflammatory mediators, and prostaglandins all have been implicated (21, 22). As a final pathway, the ubiquitin proteasome system accounts for a major fraction of catabolism and glucocorticoids appear to play a permissive action in this process (23). However, the ultimate trigger remains to be elucidated. Similarly, the exact causes of the augmented hepatic amino acid extraction and protein synthesis in patients with sepsis are not known. Nevertheless, it was shown that inflammatory mediators and especially tumor necrosis factor α can both

TABLE 4
Elimination of amino acids in patients with sepsis and in healthy control subjects[1]

	Elimination constant k_{1e}		Distribution volume	
Amino acid	Healthy control subjects ($n = 8$)	Patients with sepsis ($n = 9$)	Healthy control subjects ($n = 8$)	Patients with sepsis ($n = 9$)
			L	
Isoleucine	5.1 ± 0.7	7.5 ± 0.5[2]	6.3 ± 0.8	7.1 ± 0.6
Leucine	5.0 ± 1.7	7.0 ± 0.5	4.7 ± 0.6	6.7 ± 0.4[2]
Lysine	2.7 ± 0.6	7.2 ± 0.8[3]	8.3 ± 1.3	5.7 ± 0.5
Methionine	5.1 ± 1.0	8.4 ± 1.5	7.2 ± 1.2	7.5 ± 0.7
Phenylalanine	6.3 ± 0.7	4.0 ± 1.5	7.8 ± 1.2	10.5 ± 2.4
Threonine	4.3 ± 0.9	6.8 ± 1.2	6.1 ± 1.2	7.6 ± 1.7
Tryptophan	3.4 ± 0.7	9.5 ± 1.5[4]	7.8 ± 1.1	4.0 ± 0.5[4]
Valine	1.7 ± 0.5	2.7 ± 0.2	7.2 ± 0.8	7.6 ± 0.9
Arginine	5.1 ± 1.1	9.9 ± 1.2[2]	5.8 ± 1.1	5.5 ± 0.3
Histidine	4.6 ± 1.1	7.9 ± 1.4	9.0 ± 1.8	9.9 ± 1.6
Proline	2.4 ± 0.5	3.9 ± 0.9	6.7 ± 1.1	6.4 ± 0.8
Alanine	5.3 ± 1.1	13.8 ± 2.6[2]	8.8 ± 2.2	5.7 ± 0.9
Glutamic acid	11.0 ± 2.0	16.2 ± 1.5[5]	5.3 ± 4.0	6.0 ± 0.7
Glycine	5.2 ± 0.9	12.1 ± 2.0[4]	7.3 ± 1.0	5.5 ± 0.7
Ornithine	2.4 ± 0.5	1.7 ± 0.2	6.7 ± 0.9	4.5 ± 0.5[5]
Serine	5.0 ± 1.0	8.7 ± 2.0	6.9 ± 1.4	9.9 ± 2.3
Tyrosine	2.4 ± 0.2	5.0 ± 2.2	9.4 ± 1.8	14.7 ± 4.9

[1] $\bar{x}$ ± SEM.
[2–5] Significantly different from healthy control subjects: [2] $P < 0.02$, [3] $P < 0.001$, [4] $P < 0.01$, [5] $P < 0.05$.

augment peripheral muscle catabolism and stimulate amino acid uptake into hepatocytes (22).

Evidence is increasing that protein catabolism in sepsis is not a primary event at skeletal muscle level but is directed by the metabolic demands of the liver, ie, that the central tissues and especially the hepatosplanchnic bed "drag" amino acids from the periphery. A popular hypothesis suggests that peripheral protein catabolism and release of amino acids into the circulation are triggered by the low plasma amino acid concentration. This implies that infusion of exogenous amino acids could reverse or spare endogenous protein catabolism. In fact, it was shown in patients with sepsis that hepatic gluconeogenesis from amino acids can be mitigated but, in contrast with healthy subjects, cannot be suppressed in the postabsorptive state by exogenous infusion (17).

Enhanced peripheral protein catabolism and concomitant stimulation of hepatic metabolism must be viewed as an indispensable element in acute phase reactions and SIRS. Augmented availability of amino acids through stimulation of muscle protein catabolism might present a necessary and crucial prerequisite for coping with an acute disease process. There is a tight relation between central clearance of amino acids and prognosis (24). This may be one explanation for the increased frequency of development of multiple organ failure in critically ill patients treated with recombinant human growth hormone, which suppresses peripheral proteolysis and the release of amino acids (25). In this context it seems logical to raise plasma amino acid concentrations and to reassess conventional nutritional concepts that have been recently neglected in favor of growth factors and other endocrine interventions. In support, it was shown that endogenous glutamine was spared when intravenous glutamine was supplied (26). Moreover, plasma concentrations of amino acids were shown to be a major determinant of protein synthesis, so a combined effect of a reduction in catabolism and a stimulation of anabolism could result in an amelioration of nitrogen balance (27–30).

Certainly, no direct conclusions can be drawn from these pharmacokinetic investigations regarding recommendations for amino acid or protein intake for patients with sepsis. Nevertheless, there are both quantitative and qualitative points of consideration. If elevating plasma concentrations of amino acids can spare endogenous protein and stimulate protein synthesis, higher amounts of protein or amino acids should be provided to patients with sepsis than to noncatabolic subjects. In fact, isotopic investigation in patients with sepsis clearly showed that amino acid requirements are higher in these patients than in healthy subjects and that $\approx$1.5 g amino acids$\cdot$kg body wt$^{-1}\cdot$d^{-1} should be provided (17). Nevertheless, it must be stressed that there is little support for the assumption that higher or even excessive doses of amino acids will exert an additional effect on protein catabolism (17, 31, 32).

However, there is also a qualitative aspect to be considered. The renewed interest in conventional nutritional concepts will stimulate the search for more optimal compositions of amino acid solutions, which are adapted to the specific metabolic alterations in patients with sepsis. Most currently available amino acid solutions are composed according to a reference protein in oral nutrition. Unbalanced amino acid infusions, especially those with high phenylalanine concentrations, can impair protein synthesis (33). Obviously, there are fundamental differences in the disposition of amino acids between oral (enteral) and parenteral amino acid infusion (34); thus, evaluations of pharmacokinetic behavior of amino acids after intravenous infusion might be a more appropriate approach to designing adapted amino acid solutions. Nevertheless, qualitatively, there are many similarities in the pattern of amino acid elimination between patients with sepsis, SIRS, or renal failure. Thus, newer amino acid solutions for parenteral administration in patients with renal failure might also be appropriate for patients with sepsis (35).

In conclusion, in patients with sepsis, amino acid clearance is greatly enhanced, plasma amino acid concentrations are significantly depressed, and much higher infusion rates of amino acids are necessary to increase plasma concentrations. Investigations of phamacokinetic behavior of amino acids might serve as a basis for designing more optimal amino acid solutions with respect to stimulation of protein synthesis and reduction of muscle catabolism for parenteral nutrition in patients with sepsis.

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