

■ Specimens

When performing general screening for amino acid disorders, it is best to test both blood and urine. A decrease, or mild elevation, of amino acids can only be detected in blood. Conversely, accumulation of amino acids with very low renal threshold as well as the renal transport defects will be evident in the urine. The significance of a renal aminoaciduria is very different from that of an overflow aminoaciduria from blood. For instance, large increases in urine cystine, arginine, lysine and ornithine of renal origin are diagnostic of cystinuria. On the other hand, a similar urine pattern can be associated with three other metabolic diseases, in which there are elevations of plasma arginine, lysine or ornithine, respectively.

In contrast to metabolic defects of biogenic amine neurotransmitters, rarely is cerebrospinal fluid (CSF) preferred over blood and urine for diagnosis. It is often used to provide additional information, for confirmation of a diagnosis and to assess the degree of brain involvement. Vitreous fluid can be valuable in the post-mortem diagnosis of metabolic disorders when urine is often not available and blood is unsuitable due to post-mortem changes. Amino acid concentrations in vitreous fluid are in approximately the same range as found in plasma, except for glutamic acid, proline and glycine which are only one-tenth that in plasma.

Amniotic fluid has limited value in prenatal diagnosis for the aminoacidopathies. Unlike the organic acid disorders, in most amino acid disorders the metabolites do not accumulate before birth. Abnormal amino acid patterns in amniotic fluid have only been found in two of the urea cycle disorders, namely argininosuccinate lyase deficiency (argininosuccinic acidemia) and argininosuccinate synthetase deficiency (citrullinemia).

Tables B.1–B.4 list the amino acid values in blood, urine, CSF and vitreous fluid and are included as a guideline. However, it should be noted that even when using the same instrumentation the reference values may vary from laboratory to laboratory. Most often, each laboratory establishes its own reference ranges.

Table B.1. Amino acids in plasma ($\mu\text{mol/l}$)

Amino acid	Men (<i>n</i> = 50) ^a	Women (<i>n</i> = 15) ^a	Adolescents (<i>n</i> = 80) ^b	Children (<i>n</i> = 52) ^b	Infants <3mo (<i>n</i> = 17) ^c
Taurine	27–95	18–66	2–90	20–120	10–167
Aspartic acid	2–9	3–6	3–15	1–17	0–31
Threonine	92–180	93–197	102–246	40–204	46–222
Serine	89–165	78–166	92–196	70–194	92–178
Asparagine	32–92	26–74	34–94	15–83	38–121
Glutamic acid	6–62	6–38	17–69	14–78	8–179
Glutamine	466–798	340–696	457–857	333–809	402–776
Proline	97–297	112–220	58–324 ^d	40–332 ^c	97–254
Glycine	147–299	100–384	166–330	107–343	154–338
Alanine	146–494	218–474	242–594	120–600	142–421
Citrulline	19–47	10–58	19–52 ^d	8–47 ^c	8–36
α -Aminobutyrate	15–35	7–35	8–36 ^d	12–43 ^c	3–24
Valine	179–335	172–248	155–343	132–480	79–217
Cystine	24–54	31–49	36–58 ^d	23–68 ^c	6–43
Methionine	13–37	14–30	13–41	3–43	9–44
Isoleucine	46–90	39–67	34–106	6–122	12–77
Leucine	113–205	98–142	86–206	30–246	46–147
Tyrosine	37–77	26–78	35–107	19–119	13–91
Phenylalanine	46–74	42–62	34–86	26–98	25–74
Ornithine	55–135	36–96	47–195	20–136	41–129
Lysine	135–243	119–203	116–276	66–270	69–200
Histidine	72–108	68–104	68–108	47–135	37–83
Tryptophan	25–65	17–53	–	12–69 ^c	21–75
Arginine	28–96	28–108	1–81	12–112	7–128

Range = mean \pm 2SD^a Modified from ref. [1].^b Modified from ref. [2].^c Modified from ref. [5].^d Modified from ref. [6].^e Shih, unpublished data.

Table B.2. Amino acids in urine by age group (mmol per mol of creatinine)

Amino acid	0–1 month	1–6 months	6–12 months	1–2 years	2–4 years	4–7 years	7–13 years	Over 13 years
Taurine	8–226	6–89	9–123	12–159	13–200	17–230	18–230	16–180
Aspartic acid	2–12	2–16	3–12	3–10	2–8	2–8	1–10	2–7
Hydroxyproline	20–320	0–143	0–22	0–13	0–13	0–13	0–13	0–13
Threonine	20–138	17–92	14–56	15–62	10–48	9–36	8–28	7–29
Serine	80–282	42–194	50–137	45–124	32–94	38–93	23–69	21–50
Asparagine	0–84	0–58	0–36	0–32	0–30	0–29	0–24	0–23
Glutamic acid	0–30	2–29	0–18	0–11	0–10	0–8	0–9	0–12
Glutamine	52–205	63–229	74–197	62–165	45–236	52–133	20–112	20–76
Proline	21–213	0–130	0–14	0–13	0–9	0–9	0–9	0–9
Glycine	283–1097	210–743	114–445	110–356	111–326	91–246	64–236	43–173
Alanine	75–244	72–206	36–162	41–130	33–115	27–92	17–65	16–68
Citrulline	0–11	0–10	0–8	0–7	0–6	0–5	0–5	0–4
α -Aminobutyrate	0–9	0–7	0–8	0–8	0–6	0–5	0–5	0–4
Valine	3–26	4–19	6–19	7–21	6–20	3–15	3–17	3–13
Cystine	12–39	7–24	6–15	5–13	4–15	4–11	4–12	3–17
Methionine	7–27	6–22	8–29	7–29	5–21	5–20	3–17	2–16
Isoleucine	0–6	0–5	0–6	0–6	0–5	0–5	0–6	0–4
Leucine	3–25	4–12	4–16	3–17	4–18	3–13	3–16	2–11
Tyrosine	6–55	12–52	11–54	13–48	10–30	9–35	6–26	2–23
Phenylalanine	4–32	7–28	11–28	10–31	7–21	6–26	5–20	2–19
β -Aminoisobutyrate	0–87	0–216	0–226	0–206	0–175	0–59	0–85	0–91
Ornithine	0–19	0–13	0–8	0–8	0–7	0–7	0–6	0–5
Lysine	22–171	15–199	13–79	16–69	10–46	10–68	10–56	7–58
Histidine	80–295	72–342	92–278	87–287	68–255	61–216	43–184	26–153
3-Methylhistidine	20–39	19–40	20–47	22–57	20–59	21–61	18–59	19–47
Arginine	0–14	0–11	0–11	0–8	0–9	0–7	0–6	0–5

Modified from ref. [3].

Table B.3. Amino acids in CSF ($\mu\text{mol/l}$)

Amino acid	Men ($n=50$) ^a Range ($\pm 2\text{SD}$)	Women ($n=15$) ^a Range ($\pm 2\text{SD}$)	Children 3–18 yr ($n=50$) ^b Range ($\pm 2\text{SD}$)	Infants <12 mo ($n=12$) ^b Range ($\pm 2\text{SD}$)
Taurine	4.4–12.4	2.5–8.5	3.7–8.6	4.2–13.3
Aspartic acid	0.4–5.2	1.4–2.2	1.9–4.2	3.1–9.9
Threonine	22.2–52.6	22.3–47.1	10.3–39.5	<100.6
Serine	18.7–37.5	22.6–37.8	19.8–42.0	27.3–76.6
Asparagine	<17.9	0.6–17.4	2.7–7.4	3.5–14.5
Glutamic acid			<8.3	<7.8
Glutamine	356.0–680.0	284.0–566.0	333.5–658.4	363.0–785.1
Proline				
Glycine	2.2–14.2	0.7–14.7	2.9–7.9	3.7–7.6
Alanine	13.4–48.2	11.5–41.1	11.1–29.6	16.5–36.6
Citrulline	0.8–4.8	<6.4	0.9–2.4	<8.5
α -Aminobutyrate	1.5–7.1	<7.9	0.2–4.8	1.6–4.3
Valine	10.1–37.7	4.5–24.5	7.6–18.0	9.7–28.7
Cystine				
Methionine	<9.3	<8.8	0.9–3.5	0.7–6.0
Isoleucine	3.4–13.4	<11.1	2.2–6.2	3.9–11.3
Leucine	10.4–26.8	4.2–18.2	5.4–15.4	12.1–19.3
Tyrosine	5.3–13.3	1.9–13.9	4.3–11.7	6.7–20.4
Phenylalanine	6.7–18.3	2.4–19.2	0.5–15.9	0.6–22.6
Ethanolamine			7.8–23.8	<26.4
Ornithine	3–9	1.7–8.1	2.0–5.9	0.7–15.7
Lysine	20.1–42.9	15.1–36.3	9.1–25.5	9.1–33.6
Histidine	11.4–22.2	12.0–25.2	8.0–18.4	8.3–28.5
Arginine	13.1–35.1	14–34.4	11.3–29.5	10.1–29.9

^a Modified from ref. [1]; ^b modified from ref. [7].**Table B.4.** Amino acids in vitreous fluid ($\mu\text{mol/l}$)

Amino acid	Normal adults ($n=30$) ^a Mean	Postmortem ($n=3$) ^b Range
Taurine	66	485–590
Aspartic acid	–	8–11
Threonine	128	81–177
Serine	–	81–111
Asparagine	–	25–31
Serine + glutamine	824	–
Glutamic acid + glutamine	–	491–668
Glutamic acid	9	–
Proline	44	27–53
Glycine	24	45–181
Alanine	306	149–268
Valine	285	91–166
Cystine	7	4–18

Table B.4 (continued)

Amino acid	Normal adults ($n=30$) ^a Mean	Postmortem ($n=3$) ^b Range
Methionine	44	22–38
Isoleucine	65	29–63
Leucine	139	82–123
Tyrosine	91	39–59
Phenylalanine	93	52–54
Ornithine	–	14–32
Lysine	159	114–132
Histidine	67	38–40
Arginine	105	51–110
GABA	–	31–50
Ethanolamine	–	24–66

^a Modified from ref. [4].^b Shih and Atkins, unpublished.

■ Patient Status/Patient Information

Clinical information is an integral part of laboratory diagnosis of inherited amino acid disorders. Common presenting clinical features in different age groups as indications for amino acid studies are listed in Table B.5. Blood chemistry such as gases, pH, electrolytes, anion gap, glucose and ammonia provides clues to the kind of metabolic disorder. These laboratory data along with a brief clinical resume should be made available to the laboratory for better interpretation of the metabolic screening results.

Table B.5. Indications for amino acid studies

Common presenting clinical features in different age groups			
System	Neonatal	Infancy/Childhood	Adolescence/Adulthood
CNS	Hypotonia Lethargy Seizures Coma	Microcephaly Developmental delay Episodic ataxia Hypotonia Choreoathetosis Spastic paraparesis Movement disorder Learning disorder Behavior disorder Awkward gait Coma Speech defect Stroke ADHD	Mental retardation Episodic stupor or ataxia Altered mental status Spastic diplegia Coma Neuropsychiatric symptoms Stroke
GI	Poor feeding, vomiting	Intolerance to feeding, failure to thrive	Unusual dietary habits
Liver	Hepatomegaly	Hepatomegaly/liver disease, pancreatitis	Hepatomegaly
Cardiovascular	–	Recurrent venous thrombosis; arrhythmia	Premature vascular occlusive diseases
Respiratory	Tachypnea	–	–
Renal	–	Urinary stones, renal tubular dysfunction	Familial urinary stones
Eye/Vision	Optic lens dislocation	Optic lens dislocation, optic atrophy, night blindness/myopia; corneal ulceration	Optic lens dislocation, retinitis pigmentosa; corneal ulceration
Skeletal	–	Skeletal changes	Skeletal changes
Hair/Skin	Acrodermatitis enteropathica	Hair loss/unusual hair, hair/skin pigmentary changes, skin lesions, recurrent skin ulcers; acrodermatitis enteropathica	Recurrent skin ulcers; abnormal hair
Other	Unusual odor	Unusual odor	Unusual odor
Other	Dysmorphism	Acute illness precipitated by stress, e.g. infection or surgery	Acute illness precipitated by stress, e.g. infection, surgery, postpartum status

Table B.5 (continued)

Common presenting clinical features in different age groups			
System	Neonatal	Infancy/Childhood	Adolescence/Adulthood
Family history	Parental consanguinity Diagnosis of an inborn error in a family member Family history of siblings with similar clinical features or of infant deaths		
Laboratory findings	Positive newborn screening test Metabolic acidosis Hyperammonemia Hypoglycemia Ketonuria Increased anion gap Positive urine reducing substance Neutropenia Megaloblastic changes Low B12 and folate levels Coagulopathy Abnormal liver function tests High serum IgG Increased α -fetoprotein Increased ferritin Low serum uric acid Low serum and urine creatinine Urinary crystals		
Other findings	Abnormal bone density (osteoporosis) Decreased ERG response Abnormal neuroimaging Pulmonary fibrosis		

Amino acid levels in body fluids are influenced by a number of factors, such as age, physiological changes, nutritional status, illness and disease, medications and toxins. It is notable that medications can cause artifacts that interfere with the analysis or can disrupt the body's metabolism of amino acids, leading to an abnormal amino acid pattern which, although suggestive of an inborn error, is actually an acquired condition. These factors are discussed below.

■ Specimen Collection

Specimen collection is a very important step in the detection of metabolic disorders. In acutely ill patients, the blood and urine specimens on admission are likely to be most revealing and most appropriate for metabolic screening. It is good practice to save these specimens from all patients in whom the diagnosis is unclear. Table B.6 provides a rough guide for the volume of specimen needed for amino acid analysis. For the minimum amounts required, contact the specific testing laboratory.

Table B.6. Guide to specimen collection for amino acid analysis

Specimen type	Quantity (ml) ^a	Transport	Handling/storage
Blood	3	On ice	Centrifuge, remove plasma or serum (−20 °C)
Plasma	1	Frozen	Frozen (−20 °C)
Serum	1	Frozen	Frozen (−20 °C)
CSF	1	Frozen	Frozen (−20 °C)
Urine	4	Frozen	Frozen (−20 °C)
Vitreous fluid (eye)	0.5	Frozen	Frozen (−20 °C)

^a Most laboratories are able to perform quantitative analysis with 1 ml of sample. Consult your laboratory for the quantity needed for a specific analysis.

For the diagnosis of most amino acid disorders, morning fasting blood specimens are preferred. Samples from young infants, who are fed at frequent intervals, should be collected immediately before the next scheduled feeding. For hyperammonemia screening, postprandial blood is more suitable since an elevation of blood ammonia may be intermittent and present only in the fed state.

Certain amino acids are maintained at higher concentration in blood cells compared to plasma. This is the case for taurine, glutamate, aspartate, glutathione and for argininosuccinate, when present. Thus, hemolysis often increases the levels of these amino acids in plasma or serum. Hemolysis also releases the enzyme arginase, which hydrolyzes arginine to ornithine.

Improper handling of specimens can result in artifactual changes in the amino acid contents.

Unspun blood specimens left at room temperature can show artifactual changes in several amino acids. The combination of increased ornithine and decreased arginine is the result of arginine hydrolysis by erythrocytic arginase and can occur in unspun blood even without hemolysis. Free cystine and homocystine are lost to protein binding. Glutamine is unstable and breaks down during prolonged storage. Low serine in urine may be due to bacterial contamination, and the presence of hydroxyproline can be due to fecal contamination. Tubes used for blood collection can also be the

source of artifacts (see Table B.7). Homocysteine values are approximately 10% higher in serum compared to EDTA plasma.

Table B.7. Collection, handling, and storage artifacts

Factor/Condition	Source	Amino acid(s) affected	Value	
Contamination, bacterial	U	Ala, Gly, Pro	↑	H
Contamination, bacterial	U	Trp, aromatic amino acids, Ser	↓	L
Contamination, fecal	U	Pro, Glu, Leu, Ile, Val, OH-proline	↑	H
Contamination, protein	U	Cys	↓	L
Contamination, RBC	U	Orn	↑	H
Contamination, unwashed skin	B	most amino acids	↑	H
Contamination, WBC	U	Tau	↑	H
Contamination, WBC	B	Asp, Glu, Tau	↑	H
Hemolysis	B	Asp, Glu, Gly, Orn	↑	H
Hemolysis	B	Arg, Gln	↓	L
Serum vs. plasma	B	Serum Tau >plasma Tau		
Serum vs. plasma	B	serum homocysteine >plasma homocysteine		
Storage	U	Glu, Asp, GABA	↑	H
Storage	U	Gln, Asn, phosphoethanolamine	↓	L
Storage	B	Gln, Cys, homocyst(e)ine	↓	L
Storage	B	Glu	↑	H
Tube artifact, thrombin	B	Gly	↑	H
Tube artifact, EDTA	B	Ninhydrin positive artifact		
Tube artifact, metasulfite	B	S-sulfocysteine	↑	H
Unspun blood left at rm. temp.	B	Orn, total homocysteine	↑	H
Unspun blood left at rm. temp.	B	Arg, Cys, homocystine	↓	L

To minimize specimen artifacts, specimens should be kept on ice for local transport or processed and kept frozen during overnight shipping. When processing blood samples for analysis, keep samples cold, centrifuge the blood as soon as possible and separate the plasma or serum. If the analysis cannot be performed right away, deproteinize the sample and store it frozen. For urine amino acid analysis, a 24-h collection is preferable to a random spot urine, although this is often not practical, especially with children. Urine creatinine is widely used as a reference, however, the amino acid excretion on a per creatinine basis in a very dilute urine may not be as accurate as that obtained using a more concentrated urine specimen.

Routine metabolic screening for amino acid disorders usually includes several simple general preliminary tests and chromatographic analysis of amino acids. Because of the wide availability of amino acid analyzers, semi-quantitative amino acid screening is now used less often. One-dimensional paper or thin-layer chromatographic screening for amino acids is

now obsolete since it gives poor resolution, will miss mild changes, and requires confirmation by quantitative analysis. For blood, quantitative amino acid analysis is recommended. Although two-dimensional chromatographic separation of amino acids in urine by high-voltage electrophoresis and chromatography is less expensive and is still being used for routine screening in some laboratories, the current trend is to perform quantitative amino acid analysis.

Quantitative analysis of amino acids can be performed by an amino acid analyzer with ion-exchange column, a HPLC system with a reverse phase column, or gas chromatography. The amino acid analyzer has been the most popular method in clinical laboratories. Most of the normal and pathological values in the literature were obtained by this technique. Analysis by HPLC is now being used by an increasing number of laboratories.

The technique for quantifying blood amino acids should be sensitive enough to measure concentrations as low as a few micromoles/liter. This limit is important because a low citrulline level is a diagnostic criterion for certain defects in urea synthesis. Special processing of the specimen may be necessary, depending on the clinical application. For instance, free argininosuccinate in blood and amniotic fluid can be difficult to detect and quantify since it often co-elutes with other compounds. Conversion of the free acid to its stable anhydrides increases the sensitivity and allows more accurate results. In addition, measurement of total (free+protein-bound) homocysteine rather than only free homocystine is a more sensitive diagnostic test for mild homocyst(e)inemia and in risk assessment for vascular occlusive diseases. Urine screening by nitroprusside test or amino acids analysis is not useful for this purpose as these individuals do not excrete homocystine.

For proper interpretation of screening results it is important to consider the effects of many factors, some of which are listed in Tables B.8–B.11.

Table B.8. Effects of age/physiological changes/toxins on amino acid values

Factor/Condition	Source	Amino acid(s) affected	Value	
Age, first week of life	U	Tau	↑	H
Age, first 6 months of life	U	Pro, hydroxyproline, Gly	↑	H
Age, prematurity	U	Cystathionine	↑	H
Age, prematurity	B	Tyrosine	↑	H
Circadian rhythm	B	Tyr, Phe, Trp		
Exercise, prolonged heavy	B	Val, Ile, Leu, Ala	↓	L
Hypoglycemic infants of diabetic mothers	B	Ser, Tyr, Met, Asp, Gly, Ala	↓	L
Hypoglycemic SGA infants	B	Ala, Gly, Pro, Val	↑	H
Poisoning, ethylene glycol	U	Glycine	↑	H
Poisoning, lead	U	Delta-aminolevulinic acid	↑	H
Menstrual cycle, second half	B	Ser, Thr, Glu, Pro, Lys, Orn	↓	L
Pregnancy	U	His, Arg, Thr	↑	H

Table B.9. Nutritional status and amino acid values

Factor/Condition	Source	Amino acid(s) affected	Value	
Diet, canned formula or milk	U	Homocitrulline	↑	H
Diet, gelatin	U	Gly	↑	H
Diet, high protein (infants)	B	Met, Tyr	↑	H
Diet, shellfish	U	Taurine	↑	H
Diet, white meat from fowl	U	Anserine, 1-methylhistidine, carnosine	↑	H
Folate deficiency	B	Homocyst(e)ine	↑	H
Kwashiorkor	B	Pro, Ser, Gly, Phe	↑	H
Kwashiorkor	B	Leu, Ile, Val, Trp, Met, Thr, Arg	↓	L
Obesity	B	Branched chain amino acids, Phe, Tyr	↑	H
Obesity	B	Gly	↓	L
Starvation, 1–2 days	B	Branched chain amino acids, Gly	↑	H
(with or without vomiting)				
Starvation, 1–2 days	B	Alanine	↓	L
(with or without vomiting)				
Vitamin B12 deficiency	B	Homocyst(e)ine	↑	H
Vitamin B6 deficiency	U	Cystathionine	↑	H

Table B.10. Effects of illness/disease on amino acid values

Factor/Condition	Source	Amino acid(s) affected	Value	
Burn >20% of surface area (0–7 days after injury)	B	Phe	↑	H
Burn >20% of surface area (0–7 days after injury)	U	Ala, Gly, Thr, Ser, Glu, Gln, Orn, Pro	↓	L
Diabetes	B	Leu, Ile, Val	↑	H
Hepatic disease	B	Tyr, Phe, Met, Orn, GABA	↑	H
Hepatic disease	B	Branched chain amino acids	↓	L
Hepatoblastoma	U	Cystathionine	↑	H
Hyperinsulinism	B	Leu, Ile, Val	↓	L
Hypoparathyroidism, primary	U	All amino acids	↑	H
Infection	B	All amino acids	↓	L
Infection	B	Phe/Tyr ratio	↑	H
Infection	U	All amino acids	↑	H
Ketosis	B	Leu, Ile, Val	↑	H
Ketotic hypoglycemia	B	Ala	↓	L
Leukemia, acute	U	Advanced disease: all amino acids	↑	H
Leukemia, acute	U	On therapy: gly, asp, thr, ser	↑	H
Neuroblastoma	U	Cystathionine	↑	H
Renal failure	U	Phe, Val	↓	L
Renal failure	U	His	↑	H
Renal failure	B	Phe, Cit, Cys, Gln, homocyst(e)ine	↑	H
Renal failure	B	Leu, Val, Ile, Glu, Ser	↓	L
Respiratory distress on oxygen	B	Cysteine	↓	L
Rickets	U	Gly	↑	H

B = blood; U = urine; H = increased; L = decreased.

Table B.11. Effect of medications on amino acid values

Factor/Condition	Source	Amino acid(s) affected	Value	
Acetaminophen	U	Acetaminophen-cysteine disulfide may interfere with determination of Phe	↑	H
N-acetylcysteine	U	Acetylcysteine-cysteine disulfide	↑	H
Ampicillin/amoxicillin	U	Interferes with determination of Met, Phe, argininosuccinate	↑	H
Arginine infusion	B	Arg	↑	H
Arginine infusion	U	Arg, Lys, Orn, Cys	↑	H
Bile acid sequestrants (colestipol, niacin)	B	Homocyst(e)ine	↑	H
Cephalexin	U	Ninhydrin reactive metabolite		
Cyclosporine A	B	Total homocysteine	↑	H
2-Deoxycoformycin	B	Homocyst(e)ine	↓	L
Lysine aspirin	U	Lys	↑	H
Methotrexate therapy	B	Homocyst(e)ine	↑	H
Methotrexate therapy	B	Phe/Tyr ratio	↑	H
Nitrous oxide anaesthesia	B	Homocyst(e)ine	↑	H
oral contraceptives	B	Pro, Gly, Ala, Val, Leu, Tyr	↓	L
Penicillamine	U	Penicillamine disulfide, penicillamine-cysteine disulfide	↑	H
D-Phenylalanine	U	Phe	↑	H
Tamoxifen	B	Homocyst(e)ine	↓	L
Tetracycline, renal toxicity	U	All amino acids	↑	H
Valproate	B,U	Gly	↑	H
Vigabatrin/vinyl-GABA	U	β -alanine, β -aminoisobutyrate, GABA	↑	H
Vigabatrin/vinyl-GABA	CSF	GABA, β -alanine	↑	H
Vigabatrin/vinyl-GABA	B,U	2-Aminoadipic acid	↑	H

B = blood; U = urine; H = increased; L = decreased.

Infants less than 6 months of age excrete large amounts of proline, hydroxyproline and glycine, but this pattern is abnormal when present in older individuals. Homocitrulline in the urine of infants is usually from infant formula and is only rarely due to a metabolic disorder. Taurine is normally excreted in large amounts in the first week of life and decreases to a minimum thereafter in the first and probably the second year of life. However, the urine from infants less than 1 year of age often contains taurine from breast milk and/or taurine-supplemented formula, and the amount can fluctuate widely depending on the time of urine collection in relation to the time of feeding. Taurine is not detected in urine from infants fed unsupplemented formulas. Another aminoaciduria of dietary origin, generally seen in older children and adults, is an iminopeptiduria of anserine, 1-methyl-histidine and carnosine from eating the white meat of fowl. Parenteral nutrition and parenteral amino acid treatment are also causes of altered blood and urine amino acid patterns.

Urinary excretion of glycine is quite variable. It can be of dietary origin (e.g. gelatin) as well as secondary to medication (e.g. valproate). Persistent isolated hyperglycinuria suggests carrier status for familial renal iminoglycinuria and is only rarely associated with other hereditary syndromes. Urine histidine is increased during pregnancy.

In young infants, particularly in preterm infants, the quantity and quality of protein feeding has a direct effect on the plasma amino acid concentrations. The postprandial rise of total amino acids is more pronounced in infants on higher protein feeding. Transient hypertyrosinemia and hypermethioninemia have resulted from excessive protein load.

Circadian rhythm is a physiological basis for higher amino acid concentrations, up to 10–15%, in the blood in the afternoon. A mild generalized increase in urine amino acids is a relatively common finding in hospitalized children. Vomiting and starvation of 1–2 days' duration may cause mild elevations (two- to threefold) of the plasma branched-chain amino acids, and this should not be mistaken as a disease pattern.

Amino acid changes can be of a secondary nature and a clue to other types of metabolic disorders such as galactosemia, organic acidopathies and pyruvate metabolic disorders.

Gross elevations of many amino acids, particularly glutamine and alanine in blood, have been reported in moribund children, however, elevations of the branched-chain amino acids, citrulline and arginine are probably secondary to hypoxia and liver failure. Post-mortem blood shows similar but more pronounced amino acid changes.

Table B.12 lists the amino acids and the disorders in which the amino acid level is abnormal. An abnormal concentration of an amino acid may be suggestive of several different inborn errors. Conversely, some disorders are characterized by abnormalities in several different amino acids. This table serves as a quick guide to more detailed information found in other chapters in this book.

Table B.12. Pathological values/differential diagnosis of inborn errors

Amino acid	Source	Value	Value	Disorder(s)
All amino acids	U	↑	H	Classic galactosemia
All amino acids	U	↑	H	Fanconi syndrome
All amino acids	U	↑	H	Fumarylacetoacetase deficiency (Tyrosinemia I)
All amino acids	U	↑	H	Glutamylcysteine synthetase deficiency
All amino acids	U	↑	H	Hereditary fructose intolerance
All amino acids	U	↑	H	Lowe syndrome
All amino acids	U	↑	H	Vitamin D-dependent rickets
Neutral amino acids	U	↑	H	Hartnup disorder
Alanine	B	↑	H	Hyperammonemic syndromes
Alanine	B	↑	H	Mitochondrial disorders

Table B.12 (continued)

Amino acid	Source	Value	Value	Disorder(s)
Alanine	B	↑	H	Pyruvate/lactate disorders
β -alanine	B, U	↑	H	β -Alaninemia
β -alanine	CSF	↑	H	GABA-transaminase deficiency
β -alanine	U	↑	H	Methylmalonate semialdehyde dehydrogenase deficiency
β -alanine	U	↑	H	Pyrimidine disorders
Allo-isoleucine	B, U	↑	H	E ₃ Lipoamide dehydrogenase deficiency
Allo-isoleucine	U	↑	H	Ethylmalonic aciduria
Allo-isoleucine	B, U	↑	H	Maple syrup urine disease
α -aminoadipic acid	U	↑	H	α -Aminoadipic/ α -ketoadipic aciduria
α -aminoadipic acid	U	↑	H	Kearns-Sayre syndrome
β -aminoisobutyric acid	U	↑	H	β -Alaninemia
β -aminoisobutyric acid	U	↑	H	β -Aminoisobutyric acid aminotransferase deficiency (benign genetic marker)
δ -Aminolevulinic acid	U	↑	H	Hereditary tyrosinemia I
Arginine	B	↓	L	Creatine deficiency
Arginine	U	↑	H	Cystinuria
Arginine	U	↑	H	Dibasic aminoaciduria
Arginine	B	↓	L	HHH syndrome
Arginine	B	↑	H	Hyperargininemia
Arginine	U	↑	H	Lysinuric protein intolerance
Arginine	B	↓	L	Ornithine aminotransferase deficiency (gyrate atrophy)
Argininosuccinate	B, U, AF	↑	H	Argininosuccinic aciduria (argininosuccinate lyase deficiency)
Aspartic acid	U	↑	H	Dicarboxylic aminoaciduria
Aspartylglucosamine	B, U	↑	H	Aspartylglucosamidase deficiency
Carnosine	U	↑	H	Carnosinemia
Citrulline	B	↑	H	Argininosuccinic aciduria (argininosuccinate lyase deficiency)
Citrulline	B	↑	H	Citrullinemia
Citrulline	B	↓	L	Δ^1 -Pyrroline-5-carboxylate synthase deficiency
Citrulline	B	↓	L	Lysinuric protein intolerance
Citrulline	B	↓	L	NAGS, CPS, OTC deficiencies
Citrulline	B	↑	H	Pyruvate carboxylase deficiency type B
Citrulline	B	↓	L	Respiratory chain disorders
Citrulline	B, U	↑	H	Saccharopinuria
Cystathionine	B, U	↑	H	Cobalamin disorder
Cystathionine	B, U	↑	H	Cystathionase deficiency
Cystathionine	B, U	↓	L	Cystathionine β -synthase deficiency
Cystathionine	B, U	↑	H	Methylene tetrahydrofolate reductase deficiency
Cystine	U	↑	H	Cystinuria
Cystine	U	↑	H	Hyperlysinemia
Cystine	U	↑	H	Hyperornithinemia
Cystine	U	↑	H	Lysinuric protein intolerance
Cystine	B	↓	L	Molybdenum cofactor deficiency
Cystine	B	↓	L	Sulfite oxidase deficiency

Table B.12 (continued)

Amino acid	Source	Value	Value	Disorder(s)
Ethanolamine	U	↑	H	Ethanolaminosis
Formiminoglutamic acid	U	↑	H	Formiminoglutamic aciduria
GABA	B, U	↑	H	β -Alaninemia
GABA	CSF, B, U	↑	H	GABA transaminase deficiency
Glutamic acid	U	↑	H	Dicarboxylic aminoaciduria
Glutamic acid	P	↑	H	Glutamic acidemia
Glutamine	CSF	↑	H	Adenosine deaminase deficiency
Glutamine	B, U	↑	H	CPS & OTC deficiencies
Glutamine	B, U, CSF	↑	H	Hyperammonemic syndromes
Glutamine	B	↓	L	Maple syrup urine disease
Glutathionine	U	↑	H	γ -Glutamyl transpeptidase deficiency
Glycine	U, B, CSF	↑	H	Cobalamin disorders
Glycine	U, B, CSF	↑	H	D-Glyceric aciduria
Glycine	U	↑	H	Familial renal iminoglycinuria
Glycine	U	↑	H	Hyperprolinemia I & II
Glycine	U, B, CSF	↑	H	Methylmalonic acidemia
Glycine	U, B, CSF	↑	H	Nonketotic hyperglycinemia
Glycine	U, B, CSF	↑	H	Propionic acidemia
Glycine	B, CSF	↓	L	Serine deficiency disorders
Glycylproline	U	↑	H	Prolidase deficiency
Hawkinsin	U	↑	H	Hawkinsinuria
Histidine	B, U	↑	H	Histidinemia
Homoarginine	B, U	↑	H	Hyperlysinemia
Homocarnosine	CSF	↑	H	Homocarnosinosis
Homocitrulline	U	↑	H	HHH syndrome
Homocitrulline	B, U	↑	H	Saccharopinuria
Homocyst(e)ine	U	↑	H	Adenosine deaminase deficiency
Homocyst(e)ine	B, U	↑	H	Cobalamin disorders
Homocyst(e)ine	B, U	↑	H	Cystathionine β -synthase deficiency
Homocyst(e)ine	B, U	↑	H	Folate disorders
Homocyst(e)ine	B	↑	H	Methionine adenosyltransferase deficiency
Homocyst(e)ine	B	↑	H	Nonketotic hyperglycinemia
Homocysteine-cysteine disulfide	B	↑	H	Cystathionine β -synthase deficiency
Homocysteine-cysteine disulfide	U	↑	H	Cystinuria
Homocysteine-cysteine disulfide	B	↑	H	Hyperhomocysteinemia
Hydroxylysine	U	↑	H	Hydroxylysineuria
Hydroxyproline	U	↑	H	Familial renal iminoglycinuria
Hydroxyproline	U	↑	H	Hydroxyprolinuria
Hydroxyproline	U	↑	H	Hyperprolinemia I & II
Imidodipeptides	U	↑	H	Prolidase deficiency
Isoleucine	B, U	↑	H	E ₃ Lipoamide dehydrogenase deficiency
Isoleucine	B, U	↑	H	Maple syrup urine disease
Leucine	B, U	↑	H	E ₃ Lipoamide dehydrogenase deficiency
Leucine	B, U	↑	H	Maple syrup urine disease

Table B.12 (continued)

Amino acid	Source	Value	Value	Disorder(s)
Lysine	B	↓	L	Creatine deficiency
Lysine	U	↑	H	Cystinuria
Lysine	U	↑	H	Dibasic aminoaciduria
Lysine	B	↓	L	HHH syndrome
Lysine	B, U	↑	H	Hyperlysinemia
Lysine	U	↑	H	Lysinuric protein intolerance
Lysine	B	↓	L	Ornithine aminotransferase deficiency (gyrate atrophy)
Lysine	B	↑	H	Pyruvate carboxylase deficiency type B
Lysine	B, U	↑	H	Saccharopinuria
β -Mercaptolactate- cysteine disulfide	U	↑	H	β -mercaptolactate-cysteine disulfiduria
Methionine	P, CSF	↑	H	Adenosine deaminase deficiency
Methionine	B	↓	L	Cobalamin disorders
Methionine	B, U	↑	H	Cystathionine β -synthase deficiency
Methionine	B	↑	H	Hypermethioninemias
Methionine	CSF	↓	L	Methylenetetrahydrofolate reductase deficiency
Methionine sulfoxide	B	↑	H	Cystathionine β -synthase deficiency
Methionine sulfoxide	B	↑	H	Hypermethioninemias
Ornithine	B	↑	H	Creatine deficiency
Ornithine	U	↑	H	Cystinuria
Ornithine	B	↓	L	Δ^1 -Pyrroline-5-carboxylate synthase deficiency
Ornithine	U	↑	H	Dibasic aminoaciduria
Ornithine	B	↑	H	HHH syndrome
Ornithine	U	↑	H	Hyperlysinemia
Ornithine	U	↑	H	Lysinuric protein intolerance
Ornithine	B	↑	H	Ornithine aminotransferase deficiency (gyrate atrophy)
Phenylalanine	B	↑	H	Hereditary tyrosinemia I
Phenylalanine	B, U	↑	H	Hyperphenylalaninemia
Phenylalanine	B	↑	H	Neonatal transient tyrosinemia
Phenylalanine	B, U	↑	H	PKU
Phenylalanine	B, U	↑	H	Pterin disorders
Phosphoethanolamine	U	↑	H	Hypophosphatasia (rickets)
o-Phosphohydroxyly- sine	U	↑	H	o-Phosphohydroxylysinuria
Pipecolic acid	B	↑	H	Hyperlysinemia
Pipecolic acid	U	↑	H	Hyperprolinemia II
Pipecolic acid	B, U	↑	H	Peroxisomal disorders
Proline	B	↓	L	Δ^1 -Pyrroline-5-carboxylate synthase deficiency
Proline	U	↑	H	Familial renal iminoglycinuria
Proline	B, U	↑	H	Hyperprolinemia I & II
Proline	B	↑	H	Pyruvate carboxylase deficiency type B
Saccharopine	B, U	↑	H	Saccharopinuria
Sarcosine	B, U	↑	H	Glutaric acidemia II
Sarcosine	B, U	↑	H	Mitochondrial disorders
Sarcosine	B, U	↑	H	Sarcosinemia
Serine	B	↓	L	Cystathionine β -synthase deficiency

Table B.12 (continued)

Amino acid	Source	Value	Value	Disorder(s)
Serine	B, CSF	↓	L	Serine deficiency disorders
S-Sulfocysteine	B, U	↑	H	Molybdenum cofactor deficiency
S-Sulfocysteine	B, U	↑	H	Sulfite oxidase deficiency
Taurine	U	↑	H	β-Alaninemia
Taurine	U	↑	H	Molybdenum cofactor deficiency
Taurine	U	↑	H	Sulfite oxidase deficiency
Tryptophan	U	↑	H	Tryptophanuria
Tyrosine	B, U	↑	H	4-Hydroxyphenylpyruvate dioxygenase deficiency (Tyrosinemia III)
Tyrosine	B, U	↑	H	4-Hydroxyphenylpyruvate oxidase deficiency
Tyrosine	B, U	↑	H	Fumarylacetoacetase deficiency (Tyrosinemia I)
Tyrosine	B, U	↑	H	Neonatal transient tyrosinemia
Tyrosine	B	↓	L	PKU
Tyrosine	B	↓	L	Pterin disorders
Tyrosine	B, U	↑	H	Tyrosine aminotransferase deficiency (Tyrosinemia II)
Valine	B, U	↑	H	E3 Lipoamide dehydrogenase deficiency
Valine	B, U	↑	H	Hypervalinemia
Valine	B, U	↑	H	Maple syrup urine disease

B, blood; U, urine; CSF, cerebrospinal fluid; H, high; L, low.

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