# DISORDERS of PURINE and PYRIMIDINE METABOLISM

CHI Formulary Development Project

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Related SOPs

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- o IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

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# Abbreviations

| | |
|---|---|
| ADA | Adenosine deaminase |
| ADAs | Adenosine deaminase superactivity |
| ADP | Adenosine diphosphate |
| ADSL | Aenylsuccinate lyase |
| AHS | Allopurinol hypersensitivity syndrome |
| AICAR | Aminoimidazole carboxamide ribotide |
| AICDA | Activation-induced CDA |
| AK | Adenylate kinase |
| AMP | Adenosine monophosphate |
| AMPD | Adenosine monophosphate deaminase |
| AOX | Aldehyde oxidase |
| APRT | Adenine phosphoribosyltransferase |
| ARF | Acute renal failure |
| Asp | Aspartate |
| ATIC | AICAR transformylase/IMP cyclohydrolase |
| ATP | Adenosine triphosphate |
| CDA | Cytidine deaminase |
| CMP | Cytidine monophosphate |
| CNS | Central nervous system |
| CRRT | Continuous renal replacement therapy |
| CSF | Cerebrospinal fluid |
| CSR | Class switch recombination |
| DBA | Diamond-Blackfan anemia |
| DGK | Deoxyguanosine kinase |
| DHODH | Dihydroorotate dehydrogenase |
| DNA | Deoxyribunucleic acid |
| DPD | Dihyropyrimidine dehydrogenase |
| DHP | Dihydropyrimidinase |
| DRESS | Drug reaction with eosinophilia and systemic symptoms |
| ERSD | End stage renal disease |
| FAICAR | Formylaminoimidazole carboxamide ribotide |

| | |
|---|---|
| FU | Fluorouracil |
| Fum | Fumarate |
| GMP | Guanosine monophosphate |
| HPRT | Hypoxanthine-guanine phosphoribosyltransferase |
| HRH | HPRT-related hyperuricemia |
| HRND | HPRT-related hyperuricemia with neurologic deficit without behavioral changes |
| HSCT | Hematopoietic stem cell transplantation |
| IEM | Inborn error of metabolism |
| IMP | Inosine monophosphate |
| IMPDH | Inosine monophosphate dehydrogenase |
| ITPA | Inosine triphosphate pyrophosphohydrolase |
| LND | Lesch-Nyhan disease |
| LNV | Lesch-Nyhan variants |
| MAD | Myoadenylate deaminase |
| MDDS | Mitochondrial DNA depletion syndrome |
| MNGIE | Mitochondrial neurogastrointestinal encephalomyopathy |
| MS/MS | Tandem mass spectrometry |
| MOCOD | Molybdenum cofactor deficiency |
| NAPDD | Nucleotidase associated pervasive developmental disorder |
| OA | Orotic acid |
| ODC | Orotidylic acid decarboxylase |
| OPRT | Orotate phosphoribosyltransferase |
| P/P | Purines, pyrimidines |
| PNP | Purine nucleoside phosphorylase |
| PRPP | Phosphoribosylpyrophosphate |
| PRPS | Phosphoribosylpyrophosophate synthetase |
| PRPSs | Phosphoribosylpyrophosophate synthase superactivity |
| P5'N-1 | Pyrimidine 5’-Nucleotidase-1 |
| RNA | Ribonucleic acid |
| S-Ado | Succinyl-adenosine |
| SAH | S-adenosylhomocysteine |
| SAHH | S-adenosylhomocysteine hydrolase |

| | |
|---|---|
| SAICA | Succinylaminoimidazole carboxamide |
| SAICAR | Succinylaminoimidazole carboxamide ribotide |
| SAM | S-adenosylmethionine |
| S-AMP | Adenulsuccinate |
| SCAR | Severe cutaneous adverse reactions |
| SCID | Severe combined immunodeficiency |
| SO | Sulfite oxidase |
| STS | Stevens-Johnson syndrome |
| TEN | Toxic epidermal necrolysis |
| TK | Thymidine kinase |
| TMPT | Thiopurine methyltransferase |
| UA | Uric acid |
| UMP | Uridine monophosphate |
| UMPH | Uridine monophosphate hydrolase |
| UMPHs | Uridine monophosphate hydrolase superactivity |
| UMPS | Uridine monophosphate synthase |
| UP | Ureidopropionase |
| XDH | Xanthine dehydrogenase |
| XMP | Xanthine monophosphate |
| XOD | Xanthine oxidase-dehydrogenase |

# Executive Summary

A decreased or an increased activity of an enzyme involved in the metabolism of purine and pyrimidine leads to abnormal concentrations of purines and pyrimidines (P/P) and/or their metabolites in cells or body fluids. More than 35 defects involved in the metabolism of purines and pyrimidines have been documented. Some are relatively benign and non-disease causing. Others may be responsible for severe, life-threatening, or devastating conditions. A total of 17 are known to cause human disease. Additional enzymatic defects remain to be characterized. Lethal in utero phenotypes may be caused by P/P variants implicated in the de novo synthesis but are not well understood. The actual prevalence of P/P disorders is unknown and most probably underestimated. Less than 1,000 patients had been diagnosed with purine or related pyrimidine disorders in the last survey in 1999, from a population of 435 million, spanning 18 European countries, of which 70% had been detected in only three countries where adequate laboratory facilities were available. Selective screening data from Poland suggests that these defects are not as rare as previously considered. The prevalence of purine and pyrimidine metabolic disorders in Middle Eastern countries, including Saudi Arabia, has not been extensively studied in terms of the epidemiological figures and clinical patterns[1].

Tables 1, 2, and 3 detail inborn errors of purines and pyrimidines metabolism with neurological, renal, and immunological and hematological manifestations[1]. Table 4 lists the pharmacogenetic syndromes of inborn errors of purine and pyrimidines metabolism[1].

**Table 1.** Inborn Errors of Purines and Pyrimidines Metabolism with Neurological Manifestations

Inborn errors of P/P metabolism with neurological manifestations.

| Defect (other names, OMIM) | Neurological manifestations | Other symptoms | Diagnostic metabolites (tests*) |
|---|---|---|---|
| Adenylosuccinate lyase (ADSL) deficiency (103050) | hypotonia, seizures often intractable, autistic featured, mild/moderate/severe PMR, behavioral disturbances, severe encephalopathy with hypotonia, seizures | dysmorphic features, microcephaly | S-Ado↑, SAICAr↑ |
| AICAR transformylase/IMP cyclohydrolase (ATIC) deficiency (AICAR-ribosiduria, 608688) | cognitive delay, epilepsy, congenital blindness | dysmorphic features | AICAr↑, SAICAr↑, S-Ado↑ |
| Deoxyguanosine kinase (DGK) deficiency (251880) | hepatocerebral form of mitochondrial DNA depletion syndrome (MDDS): hypotonia, nystagmus, cognitive/motor delay | early progressive liver failure, renal tubulopathy | glucose↓, lactate↑, mtDNA depletion |
| CAD deficiency | generalized seizures, global developmental delay | anemia with anisopoikylocytosis | |
| Dihydropyrimidinase (DHP) deficiency (dihydropyrimidinuria, 222748) | variable neurological symptoms: seizures, cognitive delay, delay in speech development, growth retardation, spastic quadriplegia / asymptomatic | dysmorphic features, microcephaly, congenital microvillus atrophy, toxicity to 5-fluorouracil | dhU↑, dhT↑, U↑, T↑ |
| Dihydropyrimidine dehydrogenase (DPD) deficiency (274270) | variable neurological symptoms: seizures, cognitive delay, acutely developed lethargy, cerebral palsy, hypertonia, growth retardation, autistic behavior, ocular anomalies / asymptomatic | microcephaly, toxicity to 5-fluorouracil | U↑, T↑ |
| Hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency (308000):<br>- Lesch-Nyhan disease (LND)<br>- HPRT-related hyperuricemia (HRH)<br>- HPRT-related hyperuricemia with neurologic deficit without behavioral changes (HRND) | choreoathetosis, dystonia, spastic quadriplegia, psychomotor retardation, self-mutilation (only LND), mild or no neurological symptoms in HRH | crystalluria, urolithiasis, acute renal failure, gouty arthritis, megaloblastic anemia | UA↑, hyp↑ |
| Molybdenum cofactor deficiency (AO/XDH/SO combined deficiency, MOCOD, 252150) | Neonatal: intractable seizures, feeding difficulties, profound developmental delay, alternations in muscle tone, ocular lens dislocation<br>Late presentation: motor or language delay, minor behavioral problems, lens dislocation | dysmorphic features, microcephaly, renal stones | (hypo-)xan↑, sulfite↑, thiosulfate↑, s-sulfocystine↑, cystine↓, UA↓ |
| Purine nucleoside phosphorylase (PNP) deficiency (164050) | variable neurological abnormalities: failure to thrive, cognitive/motor delay, ataxia, hyper/hypotonia | immunodeficiency (lymphocytes T), recurrent infections especially viral, malignancies, autoimmune disease | (d)Ino↑, (d)Guo↑, dGTP↑ (RBC), UA↓ |
| Phosphoribosylpyrophosphate synthase (PRPS) superactivity (PRPSs, 300661) | Early onset: severe neurodevelopmental impairment, sensorineural deafness | Early onset: dysmorphic features<br>Late juvenile: gouty arthritis, nephropathy, urolithiasis, no neurological deficit | UA↑ |
| Thymidine kinase 2 (TK2) deficiency (609560) | myopathic form of mitochondrial depletion syndrome (MDDS): isolated fatal myopathy, encephalomyopathy, spinal muscular atrophy | | lactic acid↑, mtDNA depletion |
| Thymidine phosphorylase (TP) deficiency (MNGIE, 603041) | symptoms mitochondrial neurogastrointestinal encephalomyopathy (MNGIE): severe failure to thrive, ptosis, leukoencephalopathy, peripheral neuropathy, myopathy | gastrointestinal dysmotility with symptoms of pseudo-obstruction | thymidine↑, uridine↑, deoxyuridine↑, mtDNA depletion |
| Uridine monophosphate hydrolase (UMPH) superactivity (UMPHs, 606224) | developmental delay, seizures, hyperactivity | alopecia, recurrent infections | UA↓ |
| Uridine monophosphate synthase (UMPS) deficiency (OPRT-ODC deficiency):<br>- orotate phosphoribosyltransferase (OPRT) deficiency (258900)<br>- orotidylic acid decarboxylase (ODC) deficiency (258920) | Hereditary orotic aciduria, megaloblastic anemia, occasional immunodeficiency<br>Neurological abnormalities, failure to thrive, crystalluria, no anemia | | - OA↑<br>- OA↑, Or↑ |
| Ureidopropionase (UP) deficiency (606673) | variable neurological symptoms: encephalopathy, hypo−/hypertonia, cognitive/motor delay, seizures, dystonia, optic atrophy / asymptomatic | scoliosis, congenital anomalies of urogenital and colorectal system | dhU↑, dhT↑, NC-BALA↑, NC-BAIB↑ |

Index metabolites increased (↑) or decreased (↓) in body fluids or in indicated cell types.
AICAr: aminoimidazolecarboxamide riboside; (d)GTP, (d)Guo, (d)Ino,: (deoxy) – guanosine triphosphate, – guanosine, –inosine; dhT: dihydroxythymine; dhU: dihydroxyuracil; (hypo-)xan: hypoxanthine; mtDNA: mitochondrial DNA; NC-BAIB: N-carbamyl-β-aminoisobutyric acid; NC-BALA: N-carbamyl-β-alanine; OA: orotic acid; Or: orotidine; RBC: red blood cells; S-Ado: succinlyadenosine; SAICAr: succinylaminoimidazolecarboxamide riboside; T: thymine; U: uracil; UA: uric acid.
* refers to high-performance liquid chromatography with UV detection, high performance liquid chromatography-mass spectrometry or tandem mass spectrometry.

**Table 2.** Inborn Errors of Purines and Pyrimidines Metabolism with Renal Manifestations

Inborn errors of P/P metabolism with nephrological manifestations.

| Defect (synonym, OMIM) | Clinical manifestations | Tests (diagnostic metabolites*) | Treatment |
|---|---|---|---|
| Aldehyde oxidase (AO) and xanthine dehydrogenase (XDH) deficiency (xanthinuria-II) | UTI, nephrolithiasis, acute renal failure | (hypo-)xan↑, UA↓ | inhibitors of XOR, high-fluid intake, low-purine diet |
| Adenine phosphoribosyltransferase (APRT) deficiency (2,8-diOH-adeninuria) | 2,8-dhAde renal lithiasis, crystalluria, acute renal failure, UTI | 2,8-dhAde↑, Ade↑ | inhibitors of XOR, high-fluid intake, low-purine diet, avoidance of dietary alkalis |
| Familial juvenile hyperuricemic nephropathy (FJHN, juvenile gout) | rapid progressive renal insufficiency, renal stones, renal failure, other: juvenile gout, hypertension | UA↑ | inhibitors of XOR, high fluid intake, low-puirne diet |
| Hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency:<br>- Lesch-Nyhan disease (LND)<br>- HPRT-related hyperuricemia (HRH)<br>- HPRT-related hyperuricemia with neurologic deficit without behavioral changes (HRND) | crystalluria, urolithiasis, acute renal failure, other: choreoathetosis, spastic quadriplegia, cognitive/growth delay, self-mutilation (only LND), gouty arthritis | UA↑, hyp↑ | inhibitors of XOR, high fluid intake, low-purine diet |
| Molybdenum cofactor deficiency (combined deficiency of AO, XDH and SO, xanthinuria-III, xanthinuria-sulfituria, MOCOD) | urolithiasis, other: intractable seizures, ocular lens dislocation, severe neurological abnormalities, sometimes microcephaly (neonatal presentation) | (hypo-)xan↑, sulfite↑, thiosulfate↑, s-sulfocystine↑, cystine↓, UA↓ | not established |
| Phosphoribosylpyrophpsphate synthase (PRPS) superactivity (PRPSs) | urolithiasis, other: severe neurodevelopmental impairment, dysmorphic features, sensorineural deafness (early onset) or gout, no neurological deficit (late onset) | UA↑ | inhibitors of XOR, high-fluid intake, low-purine diet, alkalisation of urine |
| Xanthine dehydrogenase (XDH) deficiency (xanthinuria-I) | xanthine lithiasis, acute renal failure, UTI, other: myopathy, arthritis, arthralgia, sometimes cognitive delay | (hypo-)xan↑, UA↓ | high fluid intake, low-purine diet |

Index metabolites increased (↑) or decreased (↓) in body fluids or in indicated cell types.
2,8-dhAde: 2,8-dihydroxyadenine; (hypo-)xan: hypoxanthine; UA: uric acid; UTI: urinary tract infection.
Urate stones are not radiopaque; computed tomography may permit detection of radiolucent stones that are not evident with other methods.
* refers to high-performance liquid chromatography with UV detection, high performance liquid chromatography-mass spectrometry or tandem mass spectrometry.

**Table 3.** Inborn Errors of Purines and Pyrimidines Metabolism with Immunological and Hematological Manifestations

Inborn errors of P/P metabolism with immunological and hematological manifestations.

| Defect (synonym, OMIM) | Clinical manifestations | Tests (diagnostic metabolites*) | Treatment |
|---|---|---|---|
| Activation-induced cytidine deaminase deficiency (hyper IgM syndrome type II) | recurrent bacterial infections, defective Ig class switching | none | control of infections |
| Adenosine deaminase (ADA) deficiency | Severe type: severe combined immunodeficiency (SCID), severe lymphopenia (T- and B-cells), recurrent chronic viral, fungal, protozoal and bacterial infections, candidiasis, persistent diarrhea, failure to thrive, other: behavior abnormalities, cognitive delay, hearing loss<br>Delayed type: recurrent, less severe infections, autoimmunity, allergy | dAdo↑, dATP↑ (RBC) | ERT with PEG-ADA, allogenic HSCT, GT |
| Purine nucleoside phosphorylase (PNP) deficiency | immunodeficiency (lymphocytes T), recurrent infections esp. viral, other: neurological abnormalities such as cognitive/motor delay, ataxia, hyper/hypotonia | (d)Ino↑, (d)Guo↑, dGTP↑ (RBC), UA↓ | HSCT |
| Adenine deaminase (ADA) superactivity (ADAs) | congenital aplastic anemia with anisopoikylocytosis and stomatocytosis (Diamond-Blackfan syndrome) | none | not established |
| Adenylate kinase (AK) deficiency | hemolytic anemia | none | supportive care |
| Cytidine diphosphate-choline phosphotransferase deficiency (ery CDP-CPT deficiency) | hemolytic anemia | CDP-choline + CDP-ethanolamine↑ (RBC) | not established |
| Hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency:<br>- Lesch-Nyhan disease (LND)<br>- HPRT-related hyperuricemia (HRH)<br>- HPRT-related hyperuricemia with neurologic deficit without behavioral changes (HRND) | - choreoathetosis, spastic quadriplegia, cognitive/growth delay, urolithiasis, acute renal failure, self-mutilation (only LND)<br>- gouty arthritis, crystalluria, urolithiasis, mild or nor neurological symptoms<br>- megaloblastic anemia frequently present, may range from mild to profound requiring treatment, microcytic anemia can also be present | UA↑, hyp↑ | inhibitors of XOR, high fluid intake, low-purine diet |
| Uridine monophosphate hydrolase (UMPH) deficiency (pyrimidine 5′-nucleotidase/Py-5′N deficiency) | non-spherocytic hemolytic anemia with basophilic stippling, splenomegaly mild to moderate in most patients, and severe in about 15%, inhibition of the UMPH enzyme is responsible for the hemolytic anemia associated with lead poisoning | pyrimidine nucleotides↑ (RBC, UTP, CTP, UDP-glucose, CDP-choline) | splenectomy |
| Uridine monophosphate synthase (UMPS) deficiency (orotic aciduria, OA):<br>- orotate phosphoribosyltransferase (OPRT) deficiency (OA type I)<br>- orotidylic acid decarboxylase (ODC) deficiency (OA type II) | Hereditary orotic aciduria, megaloblastic anemia combined with neutropenia and hypersegmented leukocytes, occasional immunodeficiency<br>Neurological abnormalities, failure to thrive, crystalluria, no anemia | - OA↑<br>- OA↑, Or↑ | uridine |

Index metabolites increased (↑) or decreased (↓) in body fluids or in indicated cell types.
dAdo; (deoxy)adenosine; (d)ATP, (d)GTP, (d)Guo, (d)Ino,: (deoxy) – adenosine triphosphate, −guanosine triphosphate, − guanosine, −inosine; ERT: enzyme replacement therapy; GT: gene therapy; HSCT: hematopoietic stem cell transplant; OA: orotic acid/orotic aciduria; RBC: red blood cells; UA: uric acid.
* refers to high-performance liquid chromatography with UV detection, high performance liquid chromatography-mass spectrometry or tandem mass spectrometry.

**Table 4.** Inborn Errors of Purines and Pyrimidines Metabolism - Pharmacogenetic Syndromes

Inborn errors of P/P metabolism – pharmacogenetic syndromes.

| Defect (synonym, OMIM) | Clinical manifestations | Tests (diagnostic metabolites*) | Treatment |
|---|---|---|---|
| Dihydropyrimidinase (DHP) deficiency (dihydropyrimidinuria, 222748) | variable neurological symptoms, epilepsy, dysmorphic features, cognitive delay, severe toxicity to 5-fluorouracil | dhU↑, dhT↑, U↑, T↑ | withdrawal of offending drug |
| Dihydropyrimidine (DPD) dehydrogenase deficiency (thymine-uraciluria, 274270) | variable neurological symptoms, spastic quadriplegia, microcephaly, severe toxicity to 5-fluorouracil | U↑, T↑ | withdrawal of offending drug |
| Ureidopropionase (UP) deficiency (NC-BALA amidohydrolase deficiency, ureidopropionic aciduria, 613161) | hypotonia, developmental delay, seizures, optic atrophy, scoliosis, acute life threatening events | dhU↑, dhT↑, NC-BALA↑, NC-BAIB↑ | withdrawal of offending drug |
| Thiopurine methyltransferase (TMPT) deficiency | 6-azatioprine and mercaptopurine toxicity | thiopurine nucleotides↑ (RBC) | dose adjustment |

Index metabolites increased (↑) or decreased (↓) in body fluids or in indicated cell types.
dhT: dihydroxythymine; dhU: dihydroxyuracil; NC-BAIB: N-carbamyl-β-aminoisobutyric acid; NC-BALA: N-carbamyl-β-alanine; RBC: red blood cells; T: thymine; U: uracil.
* refers to high-performance liquid chromatography with UV detection, high performance liquid chromatography-mass spectrometry or tandem mass spectrometry.

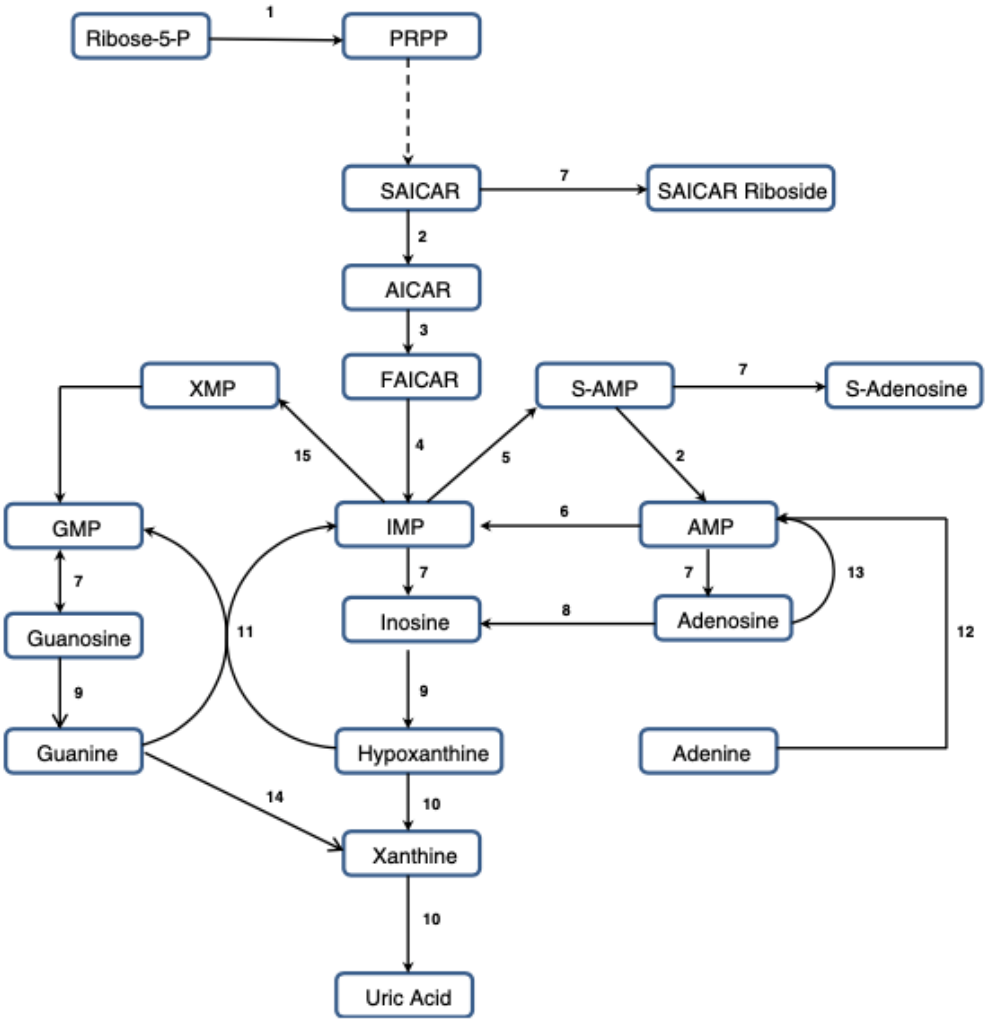



**Fig. 1** Pathways of purine metabolism. *PRPP*, phosphoribosylpyrophosphate; *SAICAR*, succinylaminoimidazole carboxamide ribotide; *AICAR*, aminoimidazole carboxamide ribotide; *FAICAR*, formylaminoimidazole carboxamide ribotide; *IMP*, inosine monophosphate; *GMP*, guanosine monophosphate; *AMP*, adenosine monophosphate; *S-AMP*, adenylosuccinate; *S-Ado*, succinyladenosine; *XMP*, xanthosine monophosphate. **Purine biosynthesis**: **1**, PRPP synthetase; **2**, adenylosuccinase (adenylosuccinate lyase); **3**, AICAR transformylase; **4**, IMP cyclohydrolase (3 and 4 form ATIC); **5**, adenylosuccinate synthetase; **Purine catabolism**: **6**, AMP deaminase; **7**, 5′-nucleotidase(s), **8**, adenosine deaminase; **9**, purine nucleoside phosphorylase; **10**, xanthine dehydrogenase; **Purine salvage**: **11**, hypoxanthine-guanine phosphoribosyltransferase; **12**, adenine phosphoribosyltransferase; **13**, adenosine kinase; **14**, guanase; 15, IMP dehydrogenase

***Figure 1.*** *Pathways of purine metabolism* [2]

**Table 5.** Main Presenting Clinical Signs and Laboratory Data in Inborn Errors of Purine and Pyrimidine Metabolism[3]

| Clinical signs | Diagnostic possibilities |
|---|---|
| Arthritis | PRPP synthetase superactivity |
| | HGPRT deficiency (partial) |
| Ataxia | PNP deficiency |
| | HGPRT deficiency (complete) |
| | Cytosolic 5′-nucleotidase superactivity |
| Autistic features | PRPP synthetase superactivity |
| | Adenylosuccinase deficiency |
| | Dihydropyrimidine dehydrogenase deficiency |
| | Cytosolic 5′-nucleotidase superactivity |
| Congenital blindness | AICA-ribosiduria (ATIC deficiency) |
| Convulsions | Adenylosuccinase deficiency |
| | Combined xanthine and sulfite oxidase deficiency |
| | Dihydropyrimidine dehydrogenase deficiency |
| | Dihydropyrimidinase deficiency |
| | Cytosolic 5′-nucleotidase superactivity |
| Deafness | PRPP synthetase superactivity |
| Dysmorphic features | AICA-ribosiduria (ATIC deficiency) |
| Growth retardation | Adenylosuccinase deficiency |
| | ADA deficiency |
| | UMP synthase deficiency |
| | Dihydropyrimidine dehydrogenase deficiency |
| | Cytosolic 5′-nucleotidase superactivity |
| Hypotonia | Adenylosuccinase deficiency |
| | Muscle AMP deaminase deficiency |
| | Ureidopropionase deficiency |
| Kidney stones: | |
| Uric acid | PRPP synthetase superactivity |
| | HGPRT deficiency (complete or partial) |
| Xanthine | Xanthine oxidase deficiency (isolated or combined with sulfite oxidase deficiency) |
| 2,8-Dihydroxyadenine | APRT deficiency |
| Orotic acid | UMP synthase deficiency |

| Clinical signs | Diagnostic possibilities |
|---|---|
| Muscle cramps | Muscle AMP deaminase deficiency |
| Muscle wasting | Adenylosuccinase deficiency |
| Psychomotor delay | PRPP synthetase superactivity |
| | Adenylosuccinase deficiency |
| | AICA-ribosiduria (ATIC deficiency) |
| | Combined xanthine and sulfite oxidase deficiency |
| | HGPRT deficiency (complete) |
| | UMP synthase deficiency |
| | Dihydropyrimidine dehydrogenase deficiency |
| | Dihydropyrimidinase deficiency |
| | Ureidopropionase deficiency |
| | Cytosolic 5′-nucleotidase superactivity |
| Recurrent infections | ADA deficiency |
| | PNP deficiency |
| | Cytosolic 5′-nucleotidase superactivity |
| Renal insufficiency | PRPP synthetase superactivity |
| | HGPRT deficiency (complete or partial) |
| | APRT deficiency |
| Self-mutilation | HGPRT deficiency (complete) |
| **Laboratory data** | **Diagnostic possibilities** |
| Anemia | |
| Megaloblastic | UMP synthase deficiency |
| Hemolytic | ADA superactivity |
| | Pyrimidine 5′-nucleotidase deficiency |
| Hyperuricemia | PRPP synthetase superactivity |
| | HGPRT deficiency (complete or partial) |
| Hypouricemia | PNP deficiency |
| | Xanthine oxidase deficiency (isolated or combined with sulfite oxidase deficiency) |
| Lymphopenia | |
| B and T-cells | ADA deficiency |
| T-cells | PNP deficiency |
| Orotic aciduria | UMP synthase deficiency |

*ADA*, adenosine deaminase; *APRT*, adenine phosphoriboysltransferase; *ATIC*, AICAR transformylase/IMP cyclohydrolase; *HGPRT*, hypoxanthine-guanine phosphoribosyltransferase; *PNP*, purine nucleoside phosphorylase; *PRPP*, phosphoribosyl pyrophosphate; *UMP*, uridine monophosphate.

## INBORN ERRORS IN PURINE METABOLISM

Inborn errors of purine metabolism comprise errors of[3]:

- Purine nucleotide synthesis.
- Purine catabolism.
- Purine salvage.

### 1. Phosphoribosyl Pyrophosphate Synthetase Superactivity

Clinical presentation

The main symptoms are gouty arthritis and/or uric acid lithiasis. Uricemia can be very high, reaching 10–15 mg/dl (0.60– 0.90 mmol/l) [normal adult values: 2.9–5.5 mg/dl (0.17– 0.32 mmol/l)]. The urinary excretion of uric acid is also increased, reaching up to 2400 mg (14 mmol)/24 h, or 2.5 mmol/mmol creatinine [normal adult values: 500 – 800 mg (3-4.7 mmol)/24 h, or 02–0.3 mmol/mmol creatinine]. Neurologic alterations usually occur with uric acid overproduction in infancy[4,5].

Metabolic derangement

Various genetic regulatory and catalytic defects lead to superactivity of phosphoribosyl pyrophosphate (PRPP) synthetase. This results in increased generation of PRPP from ribose-5-phosphate and ATP. PRPP amidotransferase (the rate-limiting enzyme of the de novo pathway) is not saturated by PRPP. Consequently, the synthesis of purine nucleotides and uric acid increases[4,5].

Genetics

The different forms of PRPP synthetase superactivity are inherited as X-linked traits. Heterozygous females have been found with gout and/or hearing impairment[5].

Diagnostic tests

Diagnosis is based on extensive kinetic studies of the enzyme, performed on erythrocytes and cultured fibroblasts. This disorder should be differentiated from partial HGPRT deficiency which may give similar clinical symptoms.

Treatment

**Allopurinol** is a xanthine oxidase inhibitor. Allopurinol use leads to decrease in the production of uric acid. Hypoxanthine, which replaces uric acid after allopurinol use, is about 10-fold more soluble. As is xanthine, which is also slightly more soluble than uric acid. Allopurinol therapy is started with an initial dosage of 10–20 mg/kg per day in children and 2–10 mg/kg per day in adults. Dosage is adjusted to maintain normal uricemia in plasma. **Febuxostat** is an effective alternative. Allopurinol therapy can lead to the formation of xanthine calculi. A low purine diet (free of organ meats, fishes, dried beans and peas) and high fluid intake can prevent crystallization. Urine

alkalinization should be considered, by administering sodium bicarbonate, potassium citrate or citrate mixtures to bring urinary pH to 6.0-6.5: indeed, uric acid and xanthine are more soluble at alkaline pH. Adequate control of uricemia prevents gouty arthritis and urate nephropathy. Dietary **S-adenosylmethionine (SAM) supplementation**, known to cross the blood–brain barrier, could lessen some neurologic symptoms in individuals with the severe phenotype by providing an oral source of purine nucleotide precursor that is not PRPP dependent[6].

### 2. Phosphoribosyl Pyrophosphate Synthetase Reduced Activity

PRPS1 gene mutations that reduce PRPP synthetase activity have been associated with Charcot–Marie–Tooth syndrome, type CMTX5. Symptoms include sensorineural hearing loss, optic neuropathy, and peripheral sensorimotor neuropathy[7]. Mutations that diminish PRPP synthetase activity have been found with Arts syndrome: it is characterized by recurrent infections, hearing and visual loss, and psychomotor retardation. **SAM supplementation** at a dose of 20 mg/kg per day has been used with some success for treatment in two Arts syndrome patients by replenishing purine nucleotides[8]. Among purines, SAM is unique in that it crosses both the gut and the blood–brain barrier, where it becomes a source of adenosine which can be salvaged to form purine nucleotides via adenosine kinase. Additionally, the external provision of SAM may diminish needs of cells that maintain an energy-dependent methylation cycle[9][10].

### 3. Adenylosuccinase Deficiency

Clinical picture

The Clinical spectrum of the deficiency of Adenylosuccinase (ADSL, also called adenylosuccinate lyase) is very broad ranging from fatal neonatal convulsions to mild psychomotor retardation and autistic behavior. Two types of deficiency exist. Type I deficiency (most common) manifests as moderate to severe psychomotor retardation, often accompanied by epilepsy and autistic features. Type II deficiency is characterized by only mild retardation, or profound muscle hypotonia with slightly delayed motor development[11–13].

Metabolic derangement

ADSL catalyzes two steps in purine synthesis. The first step is the conversion of succinylaminoimidazole carboxamide ribotide (SAICAR) into AICAR, and the second step is the conversion of adenylosuccinate (S-AMP) into AMP. ADSL deficiency results in accumulation in cerebrospinal fluid and urine of the succinylpurines, SAICA riboside and succinyl-adenosine (S-Ado), the products of dephosphorylation by 5-nucleotidase of the two substrates of the enzyme. In the most severe cases, S-Ado/ SAICA riboside ratios are around 1. In milder cases, the ratios are between 2 and 4[11,12]. Hence, SAICA riboside is assumed to be the offending compound, whereas S-Ado

could protect against its toxicity. ADSL defect is marked in liver and kidney, and variably expressed in erythrocytes, muscle, and fibroblasts. The higher S-Ado/SAICA riboside ratios might be explained by a deeper loss of activity of the enzyme toward S-AMP than toward SAICAR[14,15].

Genetics

The deficiency is transmitted as an autosomal recessive trait. ADSL gene is localized on chromosome 22. Forty mutations have been identified to date. Most of them are missense mutations, but a splicing error and a mutation in the 5UTR have also been identified. R462H mutation is the most frequent. R303C mutation, found in two independent type II patients with much less pronounced psychomotor retardation, is not readily deactivated by heat. It has a markedly lower activity with S-AMP than with SAICAR. This may explain why there are markedly higher ratios of S-Ado/SAICA-riboside, the dephosphorylated forms of the enzyme's substrates, in these patients[6].

Diagnostic tests

Diagnosis relies on the presence in cerebrospinal fluid and urine of SAICA riboside and S-Ado, normally undetectable. A modified Bratton-Marshall test, performed on urine, seems most practical for systematic screening. Several thin-layer chromatographic methods also exist. Final diagnosis requires HPLC with UV detection. Prenatal diagnosis of ADSL deficiency can be performed by target familial mutation analysis from chorionic villus sampling or amniocentesis[11,16,17].

Treatment

There is **no effective treatment currently available** for ADSL deficiency. Anticonvulsive drugs use is primarily aimed at controlling seizure frequency with minimal side effects. In cases of refractory epilepsy, a ketogenic diet has been proposed[1819]. This diet has been used as a therapeutic tool in several cases of severe ADSL deficiency. Survival prognosis is variable. Treatment with oral supplements of adenine (10 mg/kg per day) and allopurinol (5-10 mg/kg per day) are suggested to replenish decreased concentrations of adenine nucleotides in ADSL-deficient tissues. Adenine can be incorporated into the adenine nucleotides via adenine phosphoribosyltransferase (APRT)[11,15]. It is required to add allopurinol to avoid conversion of adenine by xanthine oxidase into minimally soluble 2,8-dihydroxyadenine, which forms kidney stones. Only some weight gain and acceleration of growth were noted. Oral administration of ribose (10 mmol/kg per day) has been reported to reduce seizure frequency[20]. Uridine (2 mmol/kg per day) also had a slight beneficial effect[21].

### 4. AICA-Ribosiduria

5-amino-4-imidazolecarboxamide (AICA)-riboside is the dephosphorylated counterpart of AICAR. A massive excretion of AICA-riboside was identified upon a positive urinary Bratton-Marshall test in a female infant presenting with severe mental retardation, marked dysmorphic features (prominent forehead and metopic suture, brachycephaly, wide mouth with thin upper lip, low-set ears, and prominent clitoris due to fused labia majora) and congenital blindness[16]. Assay of ATIC, the bifunctional enzyme catalyzing the two last steps of de novo purine biosynthesis, revealed a profound deficiency of AICAR transformylase, and a partial deficiency of IMP cyclohydrolase. A sequencing of the ATIC gene was performed and revealed a K426R change in the transformylase region in one allele, and a frameshift in the other. The discovery of this novel inborn error of purine synthesis emphasizes the need to perform a Bratton-Marshall test in all cases of unexplained mental retardation and/or neurological symptoms[22].

### 5. Inosine Monophosphate (IMP) Dehydrogenase Deficiency (IMPDD)

Mutations in the gene encode the IMP dehydrogenase (IDH) have been associated with retinitis pigmentosa type 10 and some cases of Leber congenital amaurosis. Genetic analyses carried out in families from various geographic origins revealed the presence of mutations in the IMPDH1 gene. Whole-exome sequencing was performed for the recent identification of IMPDH2 variants in dystonia-affected individuals and in a Finnish family affected by juvenile-onset dystonia-tremor disorder. The RNAi-mediated ablation of IMPDH1 transcripts in a murine model of RP10 appears to be promising. Gene therapies are under investigation for the treatment of certain types of Leber congenital amauriosis. However, no specific treatment for IMPDH1-associated RP and IMPDH2-associated neuropathy has been reported to date[6].

### 6. Muscle Adenosine Monophosphate (AMP) Deaminase Deficiency (mAMPD)

Clinical picture

Inherited myoadenylate deaminase (mAMPD) has variable clinical manifestations[23]. Most individuals with mAMPD deficiency are asymptomatic. Those who are symptomatic typically have exercise intolerance with muscle pain and cramping. Symptoms most commonly begin in adulthood, but they may begin in late childhood. They are usually nonprogressive. Increased serum creatine kinase and myoglobinuria has been found in approximately half of symptomatic individuals; however, in many cases, serum creatine kinase was normal at rest and abnormal only following exercise. Electromyography may be normal, but minor abnormalities have been described.

Though most individuals with mAMPD deficiency are asymptomatic, they may have measurable physiological abnormalities during exercise. Exercise studies in healthy population samples have revealed functional abnormalities in asymptomatic individuals homozygous for a common mutation in the AMPD1 gene, c.34C>T encoding Q12X. This suggests that these individuals are at risk of becoming symptomatic. Notably, mAMPD deficiency has been identified as a genetic risk factor in individuals who experience pain, weakness, and other symptoms of muscle dysfunction while on lipid-lowering drug therapy[24].

Due to its high incidence in the Caucasian population, mAMPD deficiency may also present coincidentally along with a wide array of other neuromuscular and rheumatological conditions. In these cases, it is unclear whether mAMPD deficiency contributes because symptoms are typically dominated by the associated disorder. Nevertheless, there is substantial evidence supporting a cause-and-effect relationship between mAMPD deficiency and myopathy. For example, c.34C>T appears to act synergistically with mutations in other genes known to be associated with other metabolic disorders of skeletal muscle to promote myopathic symptoms[25]. A subset of these individuals, named “double trouble”, exhibits complete deficiencies in both AMPD1 and a second metabolic gene, which in many cases is associated with a more severe phenotype than what is typically observed with either abnormality alone.

In a second subset of individuals with metabolic myopathy, heterozygosity for c.34C>T has been found secondary to complete genetic deficiencies in other metabolic pathways and may also contribute to clinical variability of the primary disorder, and in some cases deeper functional deficits may be evident. A third subset of metabolic myopathy comprises individuals who are carriers of mutations in more than one energy-generating pathway, or at multiple steps in the same pathway. These clinical presentations named “synergistic heterozygosity » may be similar to those with complete genetic deficiencies of the pathways involved[26]. Despite the absence of evidence for decreased exercise capacity in asymptomatic c.34C>T heterozygotes in the absence of another neuromuscular or rheumatological condition, increased hyperemia and decreased tissue damage have been reported in response to forearm ischemia in these individuals compared to normal homozygotes[27].

Metabolic derangement

AMP deaminase (AMPD; EC 3.5.4.6) catalyzes the irreversible deamination of AMP to IMP and is one component of the purine nucleotide cycle. In human tissues and cells, AMPD is a multigene family comprising three genes. Myoadenylate deaminase (mAMPD) deficiency affects mainly skeletal muscle adenine nucleotide catabolism.

Whether symptomatic or asymptomatic, when individuals with mAMPD deficiency exercise, their skeletal muscle does not accumulate IMP and NH3, as opposed to

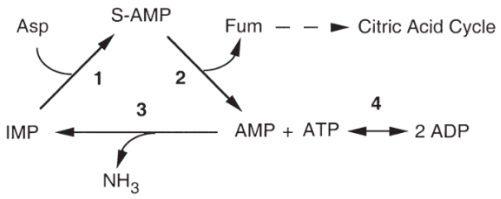
normal subjects. This abnormality is the basis for a commonly used lactate-ammonia test conducted during forearm exercise. This test is also used to detect glycolytic myopathies. Muscle biopsy examined by routine histochemical staining and electron microscopy showed variable images, from no pathologic findings to mild abnormalities in distribution of fiber size.

The mechanisms responsible for myopathic symptoms are thought to arise from interruption of the purine nucleotide cycle from AMP to IMP and back again. These series of reactions may function during exercise to maintain the adenylate energy charge of the myocyte, enhance the rate of glycolysis, and fuel the citric acid cycle.

The high prevalence of the c.34C>T allele in Caucasians suggests that this genetic variation is responsible for a selective advantage to the nearly 1/4 carriers of the mutation in this population. This hypothesis has led to a number of studies designed to explore correlations between AMPD1 genotype and clinical outcomes. The first retrospective studies identified the c.34C>T allele as a marker of improved clinical outcome in patients with heart failure and coronary artery disease. However, following retrospective studies with larger patient cohorts were unable to confirm these initial associations, with one demonstrating significantly poorer survival for c.34C>T heterozygotes in heart failure and following myocardial infarction. A single prospective study also failed to confirm a survival benefit among heart failure patients carrying the c.34C>T mutation. While survival data are conflicting, another retrospective study in both coronary artery disease and heart failure patients revealed that several indices of the metabolic syndrome (such as obesity, hyperglycemia and diabetes) were reduced in Q12X heterozygotes in comparison to those values in normal homozygotes with these clinical disorders.

Genetics

Deficiency of mAMPD is an inherited autosomal recessive disorder due to mutations in the AMPD1 gene. This gene is located on the short arm of chromosome 1. The prominent AMPD1 mutant allele in the Caucasian population includes a C to T transition at nucleotide (c.34C>T), which creates a nonsense codon, Q12X, in the mRNA. This results in an enzymatically inactive polypeptide. There are other rare mutations in the AMPD1 gene.  mAMPD deficiency is highest in Caucasians, intermediate in African Americans, and lowest in Asians. mAMPD deficiency penetrance is variable, potentially due to coinheritance of mutations in other energy-generating pathways, or to inter-individual differences in an alternative splicing event that removes the nonsense mutation from mRNA produced by the predominant mutant c.34C>T allele.[28,29]




IMP, inosine monophosphate; S-AMP, adenylosuccinate; AMP, adenosine monophosphate; ADP, adenosine diphosphate; ATP, adenosine triphosphate; Asp, aspartate; Fum, fumarate. 1, Adenylosuccinate synthetase; 2, adenylosuccinase; 3, AMP deaminase; 4, also shown is myokinase (adenylate kinase).

***Figure 2.*** *The purine nucleotide cycle*[3]

Diagnostic tests

Exercise tests serve for screening. Usually, a several-fold elevation of venous plasma ammonia is observed in normal subjects, but this elevation is absent in AMP-DA deficiency. A muscle biopsy with histochemical or biochemical assay is necessary for final diagnosis. In the primary defect, the activity of AMP-DA is below 2% of normal, and little or no immunoprecipitable enzyme is found. In the secondary defect, the activity is 2–15% of normal, and usually appreciable immunoreactivity is present. Diagnosis or confirmation of mAMPD deficiency can also be done via AMPD1 mutation analysis and AMPD enzyme assay[30].

Treatment

Symptoms may be gradually progressive, ultimately leading to the inability to dress and walk a few steps due to fatigue and myalgias. Patients should be advised to exercise cautiously to prevent rhabdomyolysis and myoglobinuria. Administration of **ribose** (2–60 g per day orally in divided doses) may improve muscular strength and endurance. In general, triggers such as exercise should be avoided[31].

## 7. Adenosine Deaminase 1 Deficiency

There are two isoforms of adenosine deaminase (ADA): ADA1 which is found in most cells, e.g., lymphocytes and macrophages, and ADA2 that is predominantly in plasma.

Clinical picture

The clinical spectrum of ADA1 deficiency is very broad ranging from a serious infancy illness to delayed and less sever later onset however, most patients (80-85%), present within the first weeks or months after birth, an important impairment of both humoral and cellular immunity, known as severe combined immunodeficiency disease (SCID)[32]. This leads to several recurrent infections, potentially life-threatening. These infections mainly localize to the skin, respiratory and gastrointestinal tract, and are caused by a broad variety of organisms. A suggestive sign of the disease in

children over 6 months of age is hypoplasia or apparent absence of lymphoid tissue. Bone abnormalities are present in about 50% of patients (clinically: prominence of the costochondral rib junctions; radiologically: cupping and flaring)[33]. Neurological abnormalities are found in a few children, including spasticity, head lag, movement disorders, nystagmus, and inability to focus. Hepatic dysfunction has also been reported[34].

Simple laboratory tests can confirm SCID: lymphopenia (< 500 total lymphocytes/mm3) involving both B and T cells, and hypogammaglobulinemia are almost invariably present. IgM deficiency can be detected early, but the IgG deficiency is seen only after the age of 3 months, after exhaustion of the maternal supply. More elaborate tests are available, showing a deficiency of antibody formation following specific immunization, and an absence or severe diminution of the lymphocyte proliferation induced by mitogens[33].

Metabolic derangement

The deficiency leads to the accumulation of adenosine in body fluids (normally undetectable) and deoxyadenosine, another substrate of adenosine deaminase (ADA), derived from the catabolism of DNA. Deoxyadenosine excess in lymphocytes leads to accumulation of dATP, which inhibits an essential enzyme for DNA synthesis: ribo-nucleotide reductase. dATP also triggers lymphoid progenitor cells apoptosis, and impair the generation of T, B, and NK lymphocytes. Deoxyadenosine can inactivate S-adenosylhomocysteine hydrolase, an enzyme implicated in methyl transfer[33].

Genetics

Approximately 1/3 of the cases of inherited SCID are X-linked, while 2/3 are autosomal recessive. ADA deficiency is found only in autosomal recessive cases, where it accounts for about 50% of the patients. The frequency of deficiency is estimated at 1 per 100,000-500,000 births. More than 70 mutations of the ADA gene have been found on chromosome 20, most of them being single nucleotide changes, leading to either an inactive or an unstable enzyme[33].

Diagnostic tests

Notably, only 15% of the patients with the clinical and hematologic picture of inherited SCID are ADA-deficient. In the remaining patients, SCID is caused by other mechanisms. The diagnosis is mostly performed on red blood cells. Despite the severity of the disease correlated with the loss of ADA1 activity, a few patients have been described with ADA deficiency in red blood cells, but normal immunocompetence. This is explained by the presence of residual ADA activity in their lymphocytes[33].

Treatment

Without treatment, ADA deficiency is **fatal** within the first year of life. Treatment became possible with bone marrow transplantation[35]. **Bone marrow/stem cell transplantation** is the therapeutic method of choice, with 70 % chance of complete immunological cure when an HLA-identical healthy donor is available. The graft provides stem cells, including T and B cells, which have enough ADA activity to prevent accumulation of adenosine and deoxyadenosine[36].

Other options include enzyme replacement therapies (ERT) with polyethylene glycol (PEG) modified bovine ADA or with erythrocyte encapsulated ADA[37]. They have been used successfully as primary therapy in certain cases: individuals lacking an HLA-identical donor, when the risks associated with a partially mismatched transplant, or when graft failure is high as in the delayed- or late-onset phenotypes. PEG-ADA has also been used as a secondary therapy in patients with graft failure or absence of acceptable recovery of immune function following experimental gene therapy. However, its use remains limited by the presence of neutralizing antibodies against the bovine enzyme, autoimmunity, and the high cost of lifelong therapy.

If no histocompatible bone marrow donor is available, enzyme replacement therapy can be given. Repeated partial exchange transfusions with normal erythrocytes result in marked clinical and immunological improvement in some patients, but is not sustained. PEG-ADA is a much more effective enzyme replacement therapy. Covalent attachment of PEG to bovine ADA results in marked extension of its half-life, and reduction of immunogenicity. Weekly to bi-weekly intramuscular injections of 15–30 units of PEG-ADA per kg result in mostly marked clinical improvement. In vitro immune function also significantly improves.

Finally, gene therapy is an option first performed in 1990 in two girls with ADA deficiency. Peripheral blood T cells were collected, cultured with interleukin-2, corrected by insertion of the ADA gene by means of a retroviral vector, and reinfused[38][39]. Total number of infusions was eleven or 12 infusions over two years in each patient. Normalization of the number of T cells was observed, as many cellular and humoral immune responses, without any adverse event. Expression of the retroviral remained present ten years after the last cell infusion[40]. Concomitant PEG-ADA treatment was administered. More recently, successful correction of ADA deficiency has been attained by gene therapy into hematopoietic stem cells, without concomitant PEG-ADA treatment. Gene therapy in X-linked not ADA deficient SCID has been suspended due to the development of leukemia in some cases. A gene therapy protocol consisting of low-intensity, non-myeloablative conditioning prior to the infusion of ADA vector-transduced hematopoietic stem cells, has induced a stable ADA1 expression in lymphoid cells, correction of metabolic abnormalities in erythrocytes and maintenance of good health without the need for ERT[41]. To date,

patients with ADA1 deficiency have not developed any lymphoproliferative disorder as a result of this method, as experienced with gene therapy for X-linked SCID.

### 8. Adenosine Deaminase 2 Deficiency

CECR1 (cat eye syndrome chromosome region, candidate 1) encodes ADA2, an ADA isoform with partial structural homology with human ADA1. Whole-exome sequencing allowed identification of loss-of-function mutations in CECR1 encode ADA2 in 3 unrelated patients with a syndrome of intermittent fevers, early-onset lacunar strokes and other neurovascular manifestations, hepatosplenomegaly, systemic vasculopathy, livedoid rash and mild immunodeficiency[42]. Subsequently, candidate-gene sequencing was performed in 3 patients with a similar phenotype, as well as 2 young siblings with polyarteritis nodosa and 1 patient with small-vessel vasculitis.

Biopsies were performed on skin, liver, and brain, and showed vasculopathic changes characterized by altered endothelial integrity, endothelial cellular activation and inflammation. Immunologic assessment showed mild abnormalities (hypogammaglobulinemia, increased B-cell death and reduced B-cell differentiation). A significant decrease in ADA2 activity in plasma was observed. Western blot analysis revealed reduced ADA2 protein levels in cell lysates, consistent with a loss of function. Preservation of ADA1 specific activity was noted.

ADA2 is a growth factor for endothelial and leukocyte development and differentiation, as supported by studies in patients and zebrafish. The data also suggest that ADA2 deficiency may compromise endothelial integrity while polarizing macrophage and monocyte subsets toward pro-inflammatory cells, creating a vicious circle of vasculopathy and inflammation.[43][44] Potential therapeutic strategies may include fresh-frozen plasma or recombinant ADA2 (ADA2 is found in plasma) and bone marrow transplantation (monocytes and macrophages, the main producers of ADA2, derive from bone marrow).

### 9. Adenosine Deaminase Superactivity

An autosomal dominant hereditary, 50-fold elevation of red cell ADA has been shown to cause non-spherocytic hemolytic anemia. This anemia can be explained by an increased catabolism of the adenine nucleotides, including ATP, because of the increase in ADA activity[45].

The possible role of ADA in the pathophysiology of Diamond-Blackfan anemia (DBA) remains uncertain. DBA is a ribosomopathy with genetic defects identified in nine different ribosomal genes: RPS19, RPL5, RPS26, RPL11, RPL35A, RPS10, RPS24, RPS7 and RPS17. Main features include reticulocytopenia, normochromic macrocytic anemia and nearly absent erythroid progenitors in the bone marrow. Patients display growth retardation, and 30 to 50 % have craniofacial, heart, upper limb and

urinary system congenital malformations. Most patients have increased mean corpuscular volume, elevated erythrocyte ADA activity and persistence of hemoglobin F[46].

### 10. Purine Nucleoside Phosphorylase (PNP) Deficiency

Clinical picture

It is characterized by recurrent infections, usually of later onset (from the end of the first year to 5-6 years of age). Susceptibility to viral diseases is increased, such as varicella, measles, cytomegalovirus, and vaccinia. Candida and pyogenic infections may occur as well. Anemia is found in 1/3 of the patients. Neurologic symptoms are present in 2/3 of patients and include spastic tetra- or diplegia, ataxia and tremor. Immunological studies show an increased deficiency of cellular immunity, reflected by a reduction in the number of T-cells. One third of patients also have B-lymphocyte function deficiency[47,48].

Metabolic derangement

This deficiency leads to the accumulation in body fluids of the 4 substrates of the enzyme which are normally undetectable: guanosine, inosine, and their deoxycounterparts (derived from DNA breakdown). Consequently, formation of uric acid is severely hindered. Accumulation of excess dGTP seems to explain the impairment of cellular immunity. It is formed from deoxyguanosine, inhibits ribonucleotide reductase, and hence cell division.

Genetics

The deficiency is autosomal recessive. The defect seems to be in the PNP gene, located on chromosome 14: several molecular defects have been found, among which a R234P mutation was most common[49].

Diagnostic tests

Deficiency of cellular immunity by marked reduction in the T-cell number and B-lymphocytes function were found in 1/3 of patients with PNP Deficiency. Additionally, marked decrease of the production of uric acid is frequently found, with plasma levels below 1 mg/dl and even undetectable. Nevertheless, in patients with residual PNP activity, plasma uric acid levels may be at the borderline of normal. The urinary excretion of uric acid is usually decreased as well. It is essential to rule out other causes of hypouricemia, such as xanthine oxidase deficiency and administration of certain drugs (acetylsalicylic acid, thiazide diuretics). Diagnosis of PNP deficiency is performed on red blood cells.

Treatment

Most initially diagnosed patients have died where viral or bacterial infections are responsible for most deaths. Treatments have consisted of bone marrow

transplantation and repeated transfusions of normal, irradiated erythrocytes. More recently, matched bone marrow transplantation has been reported successful[50].

### 11. Purine 5'-Nucleotidase

The family of 5'-nucleotidases comprises one ectosolic (eN) and six cytosolic (cN) enzymes. These enzymes catalyze the hydrolysis in the 5'-position of both ribo-and deoxyribo-nucleoside monophosphates. This results in the formation of an inorganic phosphate and the corresponding purine or pyrimidine nucleoside[51].

- Ectosolic 5'-nucleotidase: the first enzyme of this family to be purified and studied. The protein, which is strongly inhibited by ATP, is linked to the cell membrane through a glycosyl phosphatidylinositol anchor. It is responsible for the hydrolysis of both purine and pyrimidine extracellular nucleoside monophosphates, generating nucleosides. These nucleosides may act in the purinergic signaling, or may enter the cell through equilibrative or concentrative transporters. Inside the cell, nucleosides may be salvaged or further catabolized.
- Among cytosolic nucleotidases :
    - cN-IA : located mainly in skeletal muscle and the heart; preferentially hydrolyzes AMP, but also pyrimidine monophosphates.
    - CN-IB : expressed ubiquitously ; highly homologous to cN-IA ; its substrate is AMP.
    - CN-II : ubiquitous ; its expression is higher in proliferating tissues and low in muscle ; its preferential substrates are IMP and GMP, but also AMP which may be efficiently dephosphorylated, despite the high Km for this substrate.
    - CN-III : expressed in erythrocytes ; believed to regulate the degradation of pyrimidine nucleotides.
    - Cytosolic deoxynucleotidase (dNT-1) and mitochondrial deoxynucleotidase (mdN): preferentially act on pyrimidine deoxynucleotides.

All the above-described dephosphorylating activities are often simultaneously present in the same organ. Since they show a partially overlapping substrate specificity, it is difficult to identify the enzyme responsible for nucleotide degradation in different physiological situations. cN-I and cN-II are the major nucleotidases involved in the catabolism and recycling of purine compounds inside the cells.[52,53]

### *Ectosolic 5'-Nucleotidase*

Nucleotidase-associated pervasive developmental disorder (NAPDD) is a syndrome described in 1997 by Page et al[52,54]. The gene involved was not identified. However, in fibroblasts of one NAPDD patient, a hyperactivity of eN was found. The syndrome is very rare, and characterized by the following features:

- Extreme hyperactivity and impulsiveness
- Short attention span
- Poor social interaction
- Aggressiveness
- Delay in language (some patients are non-vocal)
- Neurological symptoms in all patients: seizures, ataxia, awkward gait, And impaired fine motor control.
- Infections of the sinuses and middle ear
- Low uricosuria, low immunoglobulins, and sometimes decreased T-cell function.

The relationship between the enzyme hyperactivity and the symptoms has not yet been elucidated.

A rare adult-onset vascular disease with calcification of joints and arteries has been associated with a mutation responsible for the loss of function of eN.

Diagnostic tests

The diagnosis of eN gain- or loss-of-function is based on the measurement of 5'-nucleotidase activity in cultured fibroblasts, in addition to the identification of the involved isoenzyme.

Treatment

Administration of uridine or UMP plus CMP or ribose was a successful treatment for the symptoms of NAPDD. In NAPDD patients, a slight decrease in uridylate is measured, and it may be corrected uridine. However, uridine is transported by the same system active on adenosine. Thus, an excess of the pyrimidine nucleoside might interfere with adenosine trafficking across the cell membranes and consequently with its function in neurodevelopment and inflammation.

### *Cytosolic 5'-Nucleotidase I*

cN-IA interacts with contractile elements in cardiac muscle. It is responsible for AMP hydrolysis and adenosine production in ischemic conditions, since it is activated by ADP. cN-IA plays a role in intracellular adenosine formation in the heart, but also in regulating pyrimidine deoxynucleotide pools in the tissues where it is expressed.

Although its expression has not been associated with specific diseases, anti cN-IA antibodies were also found in inclusion body myositis and other autoimmune diseases (e.g., Stevens–Johnson syndrome, systemic lupus erythematosus, juvenile dermatomyositis, and others), and even in healthy controls. The presence of these antibodies was associated with a decreased muscular cN-IA activity and with some mitochondrial dysfunction. It was hypothesized that decreased cN-IA activity leads to AMP accumulation, activation of the AMP-activated protein kinase, inhibition of the mechanistic target of rapamycin, and finally inhibition of protein synthesis and mitochondrial dysfunction, contributing to muscle weakness and degeneration.[53]

***Cytosolic 5'-Nucleotidase II***

Though not entirely clear, cN-II physiological role is the hydrolysis of relatively high concentrations of IMP and AMP, thus controlling purine intracellular concentrations and the regulatory functions of AMP and adenosine. To date, 9 mutations in the gene encoding for cN-II (NT5C2) have been associated with a diagnosis of hereditary spastic paraplegia 45 (HSP45). HSP is a group of rare neurodegenerative disorders, with various genetic origins and clinical presentations. It is characterized by a progressive lower limb spasticity and weakness, caused by the loss of corticospinal motor tract function. In many cases, the described mutations strongly impact the protein, leading to generation of shorter transcripts. This infers that HSP45 is associated with a complete lack of functional cN-II. Recently, a large consanguineous Saudi family was reported and allowed co-segregation of a novel homozygous splice site donor alteration in NT5C2. It was associated with a phenotype of spastic diplegic cerebral palsy, developmental delay, and microcephaly. More research is necessary to understand the link between the cN-II mutations and the described diseases. The observation alone clearly correlates cN-II and neurodevelopment. cN-II might be important for its ability to interact with other proteins (e.g. ICE protease-activating factor) in addition to its enzymatic activity. Several genome wide association studies (GWAS) suggest other clues on the impact of cN-II expression and function in physiological and pathological conditions: a strong association seems to exist between mutation in the locus containing the gene coding for cN-II and a variety of neurological disorders (e.g., schizophrenia and autism). In many cases, the frequency of single-nucleotide polymorphism (SNP) within, or nearby, the gene sequence was measured. In a meta-analysis from 17 independent studies, a specific SNP, inside the gene sequence, was first identified and associated with schizophrenia. This was confirmed within a validation set, and later in a South Chinese Han population. In a Latino cohort, the same SNP was found to be associated with bipolar disorders. Moreover, genetic variants in the cN-II locus have been associated with high blood pressure and body weight. Unfortunately, it remains unknown whether these variants affect the expression, activity, and/or binding capacity of cN-II. However, some genetic variants play a role in the regulation of the transcription of the

enzyme: this was demonstrated for schizophrenia risk variants affecting the miR-206 function in the regulation of cN-II expression.[53]

Diagnostic tests

Mutations in NT5C2 are associated with several diseases whose pathogenesis may also be ascribed to other factors. Therefore, genetic analysis is paramount for a specific diagnosis.

Treatment

As far as we know, there are no suggestions of therapies based on cN-II involvement.[53]

### 12. Hereditary Xanthinuria

Clinical picture

Three types of deficiencies of xanthine oxidase-dehydrogenase (XOD) are known: type I classical xanthinuria, caused by isolated XOD deficiency; type II classical xanthinuria, due to deficiencies of both XOD and aldehyde oxidase (AOX); and molybdenum cofactor deficiency resulting in combined deficiencies of XOD, AOX and sulphite oxidase[55,56].

Isolated xanthine oxidase deficiency (type I and II) can be completely asymptomatic. Some patients (~30%) suffer from urolithiasis, not visible on X-ray. Myopathy may be present. In the combined deficiency, sulfite oxidase deficiency dominates the xanthine oxidase deficiency. Symptoms include neonatal feeding difficulties and intractable seizures, myoclonus, increased or decreased muscle tone, eye lens dislocation and severe mental retardation[57].

Deficiency of molybdenum cofactor results in combined deficiencies of sulphite oxidase, XOD and AOX. The genetics of molybdenum cofactor deficiency are complex, but it typically presents with intractable neonatal seizures, feeding difficulties, myoclonus, axial hypotonia, limb hypertonia, diffuse cerebral atrophy or multicystic degeneration with psychomotor retardation and microcephaly. Physiopathology is marked by neuronal loss and white matter demyelination. Lens dislocation develops in patients who survive the neonatal period. Other ocular abnormalities include spherophakia, iris coloboma, nystagmus and enophthalmos. Cerebral blindness may also occur[56].

Metabolic derangement

Hypoxanthine and xanthine completely replace uric acid as purine catabolism end products. Hereditary xanthinuria can result from a deficiency of xanthine oxidase (type I) or of both xanthine oxidase and aldehyde oxidase (type II). The latter metabolizes synthetic purine analogues. In combined deficiency. Sulfite and sulfur-

containing metabolites accumulate. The combined defect is caused by the deficiency of a molybdenum cofactor, required for both enzymes.

Genetics

Inheritance is autosomal recessive. Studies of the xanthine oxidase gene (*XO* gene) on chromosome 2 identified, in type I, two mutations resulting in a nonsense substitution and a termination codon, respectively[58]. Xanthinuria type II might be caused by mutation of a molybdenum cofactor sulferase gene (*HMCS* gene) [59]. More than 30 different mutations have been identified[60].

Diagnostic tests

Both in isolated and combined xanthine oxidase deficiency, plasma uric acid is below 1 mg/dl (0.06 mmol/L); and may be undetectable on a low-purine diet. Urinary uric acid is reduced and replaced by hypoxanthine and xanthine. In the combined defect, these urinary changes are accompanied by an overexcretion of sulfite and other sulfur-containing metabolites. Diagnosis requires liver or intestinal mucosa. Sulfite oxidase and the molybdenum cofactor can be assayed in liver and fibroblasts, and can be confirmed by genetic testing.

Treatment

Isolated xanthine oxidase deficiency (type I and II) is mostly benign. To prevent renal stones, a low purine diet should be prescribed, and fluid intake should be increased. The prognosis is very poor. Low-sulfur diets, the administration of sulfate and molybdenum, and trials to bind sulfite with thiol-containing drugs, have all been unsuccessful. No effective therapy for molybdenum cofactor deficiency was available. Cyclic pyranopterin monophosphate in a neonate resulted in near-normalization of biochemical markers and significant clinical improvement.

### 13. Hypoxanthine-Guanine Phosphoribosyltransferase Deficiency

Clinical picture

With a wide clinical spectrum that determined by the residual enzyme activity, patients with near-complete deficiency of hypoxanthine-guanine phosphoribosyltransferase (HGPRT) display the Lesch-Nyhan syndrome. Neurologic symptoms including delayed motor development, choreo-athetoid movements and spasticity with hyperreflexia start to manifest at the age of 3 to 4 months[61]. Progressively, patients develop compulsive self-destructive behavior and severe action dystonia. Speech is hampered by athetoid dysarthria IQ is around 50. Half of the patients have seizures. Uric acid stones can manifest. Untreated, nephrolithiasis leads to renal failure.

Gouty arthritis is common in partial HGPRT deficiency. Most are normal neurologically. Spasticity, dysarthria, and a spinocerebellar syndrome can be found[62].

Metabolic derangement

Uric acid overproduction can be explained by the following: PRPP is available in increased quantities for the rate limiting enzyme, PRPP amidotransferase. Its activity increases lead to the overproduction of uric acid. HGPRT defect leads to the deficit of the dopaminergic system which probably results in the neuropsychiatric manifestations of Lesch-Nyhan patients.

Genetics

Both the Lesch-Nyhan syndrome and the partial deficiencies of HGPRT are transmitted in a X-linked recessive manner. Studies of the HGPRT gene have revealed a variety of defects, ranging from point mutations, to extensive deletions. Henceforth, enzymes become unstable. Their kinetic properties differ. Suppression of enzyme synthesis is possible[63].

Over 250 mutations of the HGPRT gene have been described, and molecular studies have led to precise prenatal diagnosis and efficient carrier testing of at-risk females[64].

Diagnostic tests

Patients excrete excessive amounts of uric acid, ranging from 25 to 140 mg (0.15 to 0.85 mmol)/kg of body weight per 24 h, as compared to an upper limit of 18 mg (0.1 mmol)/ kg per 24 h in normal children. Screening tests are possible via the determination of the ratio of uric acid to creatinine (mg/mg) in morning samples of urine[65]. In HGPRT deficiency, this ratio is much higher than the normal upper limits of 2.5, 2.0, 1.0 and 0.6 for infants, 2 years, 10 years, and adults, respectively. Increased ratios are also found in other disorders with uric acid overproduction, such as PRPP synthetase superactivity, glycogenosis type I, lymphoproliferative diseases, and after fructose loading. Uric acid overproduction is usually accompanied by an increase of serum urate, reaching 18 mg/dl (1 mmol/L). However, particularly before puberty, uricemia may be in the normal or high normal range.

Lesch-Nyhan patients display nearly undetectable HGPRT activity in red blood cells. In partial deficiencies, similar low or higher values may be found.

Treatment

Inhibitors of XOR, such as **allopurinol** and **febuxostat**, effectively lower UA but induce hypoxanthine and xanthine accumulation[66,67]. The latter may form stones with frequent renal failure. Increased hypoxanthine and xanthine concentrations in LND cerebrospinal fluid have been related to neurological manifestations. **Rasburicase**, a recombinant urate oxidase converting UA into allantoin, is also sporadically used for the rapid prevention of renal failure. Alternative treatments avoiding hypoxanthine accumulation have been recently proposed, based on recombinant enzyme therapy restoring the uricolytic pathway, or on upstream PNP inhibition to slower purine breakdown. Treatment with allopurinol or other

hypouricemic drugs has no effect on the neurological or behavioral manifestations of the disease. Dopamine replacement therapy in LND patients was proven insufficient[68]. Current treatments are mainly symptomatic, either by drugs or the chronic deep brain stimulation of the globus pallidus[69]. Appropriate restraints and measures should be taken to help diminish self-mutilation. Diazepam, haloperidol and barbiturates may sometimes improve choreoathetosis. Dosage is based on control of symptoms and patient tolerance profile.

Bone marrow transplantation can restore erythrocyte HGPRT activity[70].

### 14. Adenine Phosphoribosyltransferase Deficiency

Clinical picture

The clinical expression is heterogenous, with variable onset of symptom. Symptoms include urinary passage of gravel, small stones, and crystals, frequently accompanied by abdominal colic, dysuria, hematuria, and urinary tract infection. Some patients may experience acute anuric renal failure. The urinary precipitates are composed of 2,8-dihydroxyadenine, radiotranslucent, and cannot be distinguished from uric acid stones[71].

Metabolic derangement

The deficiency can be complete or partial, resulting in suppression of the salvage of adenine. Consequently, adenine is oxidized by xanthine oxidase into 2,8-dihydroxyadenine, a very poorly soluble compound. Activities range from 10 to 30% of normal at supraphysiological concentrations of PRPP. However, a 20- to 30-fold decrease in the affinity for PRPP results in near inactivity under physiological conditions[72].

Genetics

APRT deficiency is autosomal recessive. c.2069T C substitution in exon 5 is present in all type II Japanese patients, resulting in a M136T change. Approximately 80% are homogenous, with two other mutations accounting for nearly all the other cases. Thirty mutations have been found in Caucasians[72].

Diagnostic tests

Complex analyses are required to identify 2,8-dihydroxyadenine. For instance, UV and infrared spectrography, mass spectrometry and X-ray cristallography are used. APRT activity measure in red blood cells seems easier[71].

Treatment

**Allopurinol** should be given, as detailed under PRPP synthetase superactivity, in order to inhibit the formation of 2,8-dihydroxyadenine. Even in asymptomatic patients, dietary purine restriction and high fluid intake are recommended. It is not

advised to alkalinize urine. Ultimate prognosis depends on renal function at the time of diagnosis.

### 15. Adenosine kinase deficiency

Adenosine kinase catalyzes the phosphorylation of adenosine to produce AMP. Adenosine kinase is an important regulator of extracellular and intracellular adenine nucleotides. Adenosine kinase deficiency is a methionine cycle defect resulting in hypermethionenemia, severe slowly progressive encephalopathy. Almost all had neonatal onset liver dysfunction with variable severity and microvesicular steatosis, furthermore global psychomotor delay, sparse or absent language, poorly controlled epilepsy, hypotonia with muscular weakness, dysmorphic features, and relative macrocephaly are associated symptoms[73]. Biochemical parameters include raised methionine, S-adenosylmethionine (SAM), S-adenosylhomocysteine (SAH) in plasma and CSF. Urinary adenosine excretion is increased. Recent studies demonstrate that accumulation of adenosine kinase substrate e.g., AICA riboside and succinyl AICA riboside occur in this condition. So far there is no effective treatment for this condition. Methionine restriction has shown some promising results in some patients[73].

### 16. S-Adenosylhomocysteine hydrolase (SAHH) deficiency

SAHH deficiency is also a methionine cycle defect resulting in a clinical picture similar to that of adenosine kinase deficiency. Findings show hypermethionenemia, severe and slowly progressive encephalopathy, global psychomotor delay, sparse or absent language, poorly controlled epilepsy, hypotonia with muscular weakness, liver dysfunction, dysmorphic features, and relative macrocephaly. Biochemical features included raised aminotransferases, creatine kinase, methionine and specifically raised S-adenosylmethionine (SAMe), S-adenosylhomocysteine (SAH) in plasma and CSF. Limitation of dietary methionine and phosphatidylcholine, and/or creatine supplementation may be beneficial. SAM and SAH levels decreased but remained over the normal range. Creatine kinase and liver function remained unchanged. Some patients showed clinical improvements in muscle strength and mental alertness. Developmental delay persisted. Early treatment ameliorates the outcome[74].

### 17. Adenylate kinase 1 (AK1) deficiency

Adenylate kinase 1 (AK1) modulates the interconversion of adenine nucleotides. Deficiency of this enzyme results in chronic nonspherocytic hemolytic anemia associated with hepatosplenomegaly and psychomotor retardation[75].

### 18. Adenylate kinase isoenzyme 2 (AK2) deficiency

Adenylate kinase 2 (AK2) is located within the mitochondrial intermembrane space that is uniquely expressed in some tissues. It has an important role in regulating energy metabolism by reversibly catalyzing the transfer of a phosphoryl group from ATP to ADP. AK1, a cytoplasmic enzyme, has a similar function. Human mitochondrial AK2 mutations are responsible for reticular dysgenesis, a form of SCID characterized by absence of granulocytes and almost complete deficiency of lymphocytes in peripheral blood, hypoplasia of the thymus, secondary lymphoid organs, and lack of innate, adaptive humoral and cellular immune functions, with increased apoptosis, reactive oxygen species formation and decreased mitochondrial membrane potential. Moreover, AK2 deficiency has also been associated with deep hematopoietic defects and sensorineural deafness[76]. While most tissues express both AK1 and AK2 enzymes, neutrophils, T lymphocytes, and cells of the stria vascularis in the inner ear uniquely express AK2, which explains the phenotype observed in reticular dysgenesis[77]. Omenn syndrome has been described in a Kuwaiti male infant, whose parents were consanguineous and whose sister had reticular dysgenesis and homozygous missense AK2 mutations[78]. Bioinformatic analyses have shown transcriptional insufficiencies due to AK2 mutations, which reduce proteosomal activity and proteins of mitochondrial and hematopoietic translational systems by lowering ATP levels and inhibiting NF-kβ activity while activating growth factor independence 1.

### 19. Deoxyguanosine Kinase Deficiency

Deoxyguanosine Kinase (DGUOK) Deficiency also known as mitochondrial DNA depletion syndrome was found to be caused by a deficiency of mitochondrial deoxyguanosine kinase in the hepatocerebral cells. This autosomal recessive syndrome is characterized by liver failure, neurological abnormalities, hypoglycemia, and increased lactate. Deoxyguanosine kinase phosphorylates the deoxycounterpart of guanosine into deoxyGMP, particularly in liver and brain[79].

### 20. Inherited defects of uric acid transport

Uric acid does not have specific renal excretion transporters. It uses other anion transporters, so that competition between urate and natural substrates for transporters can lead to reduced urate clearance (e.g., GLUT9/SLC2A9, URAT1/SLC22A12 and ABCG2/BCRP)[80,81].

Familial juvenile hyperuricemic nephropathy (FJHN) is an autosomal dominant defect of uric acid transport. It is associated with early-onset hyperuricemia due to a low fractional excretion of uric acid, usually leading to interstitial nephropathy and end-stage renal failure. Mutations in at least four unrelated genes seem to be responsible for FJHN: the gene encoding uromodulin (or Tamm-Horsfall protein),

UMOD on 16p12; the renin gene REN on chromosome 1q32.1; hepatocyte nuclear factor-1beta (HNF1B) on chromosome 17q1 (rarer presentation of FJHN with diabetes); for the fourth locus, HNFJ3, in chromosome 2p22.1-p21, the causative gene is yet to be identified. On the other hand, approximately 10 % of common familial hyperuricemia/ gout in Caucasians has been shown to be associated with a functional polymorphism, p.Gln141Lys, in the multidrug ATP-binding cassette ABCG2[81]. More recently, a large GWAS of 140,000 individuals determined another 18 genes associated with high uricemia[82].

Hereditary renal hypouricemia types I and II (RHUC1 and RHUC2), arising from renal hyperuricosuria, have been associated with mutations in the transporter genes SLC22A12 and SLC2A9 respectively. More than 150 patients with a loss-of-function mutation in SLC22A12 have been identified until now, mainly in Asia. Loss of function mutations in SLC2A9 are responsible for severe hypouricemia. Previously considered a benign disorder, hypouricemia has now been associated with frequent complications such as acute kidney injury arising from urate nephrolithiasis, which is treatable by allopurinol if detected early[83].

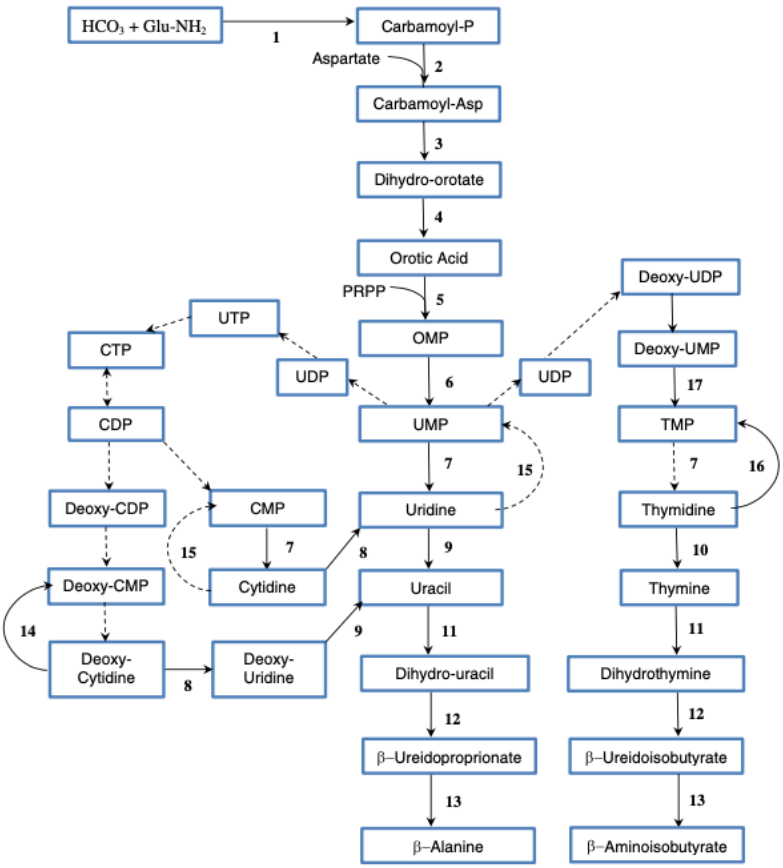



**Fig. 1** Pathways of pyrimidine metabolism. *Glu-NH2*, glutamine; *Carbamoyl-P*, carbamoyl-phosphate; *Carbamoyl-Asp*, carbamoyl-aspartate; *OMP*, orotidine monophosphate; *PRPP*, phosphoribosyl-pyrophosphate; *UMP*, uridine monophosphate; *CMP*, cytidine monophosphate; *CTP*, cytidine triphosphate; *TMP*, thymidine monophosphate. **De novo pyrimidine synthesis**: **1**, carbamoylphosphate synthetase II; **2**, ATCase; **3**, dihydroorotase (1, 2 and 3 comprise CAD); **4**, dihydroorotate dehydrogenase; **5**, orotate phosphoribosyl-transferase; **6**, OMP decarboxylase (5 and 6 comprise UMP synthase). **Pyrimidine catabolism**: **7**, pyrimidine-5′-nucleotidase; **8**, cytidine deaminase; **9**, uridine phosphorylase; **10**, thymidine phosphorylase; **11**, dihydropyrimidine dehydrogenase; **12**, dihydropyrimidinase; **13**, ureidopropionase. **Pyrimidine Salvage**: **14**, deoxy-cytidine kinase; **15**, uridine/cytidine kinase; **16**, thymidine kinase. Steps known to be associated with metabolic or pharmacogenetic disorders are shown as solid lines, other steps are shown as dashed lines. Synthesis of deoxy-nucleotides proceeds via ribonucleotide reductase; deoxy-CTP and TTP for DNA synthesis are formed from deoxy-CMP/deoxy-CDP and TMP/TDP respectively

***Figure 3.*** *Pathways of pyrimidine metabolism*[2]

## INBORN ERRORS OF PYRIMIDINE METABOLISM

Inborn errors of pyrimidine metabolism include defects of the synthesis of pyrimidine nucleotides and inborn errors of pyrimidine catabolism.[3]

### 1. UMP Synthase Deficiency (Hereditary Orotic Aciduria)

Clinical presentation

Megaloblastic anemia appears first after birth. Blood smears show anisocytosis, poikilocytosis, and hypochromia. Bone marrow examination reveals erythroid hyperplasia and megaloblastic erythroid precursors[84].

Metabolic derangement

Uridine monophosphate (UMP) synthase is a bifunctional enzyme of the de novo synthesis. Orotate phosphoribosyltransferase (OPRT) turns orotic acid into OMP. Then, orotidine decarboxylase (ODC) decarboxylates OMP into UMP. Orotic acid overproduction results from the enzymatic defect. The overproduction is caused by the weakened inhibition feedback on the first enzyme, the cytosolic carbamoyl phosphate synthetase II. The deficiency of pyrimidine nucleotides leads to impairment of cell division. This explains the megaloblastic anemia and the growth retardation[84].

Genetics

Hereditary orotic aciduria is characterized by an autosomal recessive inheritance due to mutation in *UMPS* gene.

Diagnostic tests

Urinary analysis is characterized by an over excretion of orotic acid, reaching, in infants, sometimes 1000-fold the normal adult value of 1–1.5 mg per 24 h. Crystalluria can be noted. Enzymatic diagnosis can be performed on red blood cells. Type I hereditary orotic aciduria is defined by a deficiency of both OPRT and ODC. Type II is when the activity of ODC was initially only deficient[84].

Treatment and prognosis

This anemia is not responding the folic, iron or even Vitamin B12 treatment. However, the enzyme defect can be bypassed by **uridine**, which is converted into UMP. An initial dose of 100-150 mg/kg can help with a better hematologic response, acceleration of growth and psychomotor development. One should aim to reach the lowest possible output of orotic acid.

### 2. Dihydroorotate dehydrogenase (DHODH) deficiency

DHODH catalyzes the oxidation of dihydroorotate (DHO) to orotic acid (OA). DHODH deficiency causes Miller syndrome[85]. The clinical distinctive features of Miller syndrome (postaxial acrofacial dysostosis) include severe micrognathia, cleft lip and/or palate, hypoplasia, or aplasia of the posterior elements of the limbs, coloboma of the eyelids and supernumerary nipples. Elevated DHO has recently been confirmed in plasma of a Miller syndrome patient. It is assumed that other dehydrogenase enzymes may convert DHO to orotate during secretion into urine. Intracellular DHO (or a byproduct of DHO from another pathway) may inhibit pyrimidine synthesis in the limb and facial buds. This may affect the potential response to fibroblast growth factor signaling, resulting in malformations of these structures.

Supplementation with OA or uridine should bypass the enzymatic block. This approach would be unlikely to correct the phenotypic abnormalities because the main and first damage occurs before birth.

### 3. Dihydropyrimidine Dehydrogenase Deficiency

Clinical picture

Two forms occur. The first in children. Most display epilepsy, motor and mental retardation with generalized hypertonia, hyperreflexia, growth delay, dysmorphic features including microcephaly and autistic features. Dihydropyrimidine dehydrogenase (DPD) deficiency can be complete. Asymptomatic cases have been identified. The second in adults who receive the pyrimidine analog, 5-fluorouracil, a classic treatment of various cancer. DPD deficiency leads in these cases to severe toxicity when administered 5-fluorouracil. Findings show neutropenia, stomatitis, diarrhea and neurologic symptoms, including ataxia, paralysis and stupor[86].

Metabolic derangement

DPD plays a role in the catabolism of uracil and thymine into dihydrouracil and dihydrothymine, respectively. DPD deficiency leads to the accumulation of the former compounds. Decreased alanine may have a role in the manifestation of symptoms. A block of the catabolism via DPD of the anticancer drug 5-fluorouracil may explain its marked toxicity[86].

Genetics

DPD gene is localized on chromosome 1. DPD deficiency in infancy is inherited via an autosomal recessive trait. Forty mutations have been identified. Approximately 25% of patients are heterozygotes for the IVS14+1G>A mutation in DPD deficiency in adults[87].

Diagnostic tests

Patients excrete high amounts of uracil (56–683 mmol/mol creatinine, as compared to 3–33 in control urine) and of thymine (7–439 mmol/mol creatinine, as compared to 0–4 in control urine). The pyrimidine catabolites can be detected by high-performance liquid chromatography and gas chromatography mass spectrometry[87].

With the exception of red blood cells, the enzyme defect can be found in fibroblasts, liver and other blood cells. DPD deficiency in infancy can be either partial or complete. However, in adults, DPD deficiency is partial[87].

Treatment

No treatment is available for pediatric patients. In the adult cancer patients, **discontinuation of 5-fluorouracil** is advised[87].

### 4. Dihydropyrimidinase Deficiency

Clinical picture

Various symptoms can be present: from psychomotor retardation with epilepsy, dysmorphic features, or microcephaly to completely asymptomatic patients[88].

Metabolic derangement

Dihydropyrimidinase (DHP) catalyzes the cleavage of dihydrouracil and dihydrothymine into, repectively, -ureidopropionate and -ureidoisobutyrate. DHP deficiency results in urinary excretion of important quantities of dihydrouracil and dihydrothymine. Uracil and thymine excretion is increased. Decreased alanine concentration may have a role in symptom generation. Patients seem more sensible to 5-fluorouracil[88].

Genetics

Inheritance is autosomal recessive. *DHP* gene is localized on chromosome 8. Studies identified one frameshift and five missense mutations[89].

Diagnostic tests

Increased urinary dihydrouracil and dihydrothymine levels can be detected. Enzyme assay requires liver biopsy[90].

Treatment

There is no therapy, and the prognosis seems unpredictable. Complete recovery is possible. Some progressive neuro-degenerative cases have been reported[90].

### 5. Ureidopropionase Deficiency

Ureidopropionase catalyzes the conversion of β-ureidopropionate and β-ureidoisobutyrate to β-alanine and β-aminoisobutyric acid, respectively. The catalytic conversion is accompanied by concomitant production of ammonia and carbon dioxide. Symptoms are dominated by muscle hypotonia, dystonic movements and severe developmental delay. In vitro H-NMR spectroscopy of urine reveal elevated ureidopropionic acid (also called N-carbamyl-alanine) and ureidoisobutyric acid (also called N- carbamyl-aminoisobutyric acid). The cause seem to be liver ureidopropionase deficiency (also termed-alanine synthase).

### 6. Pyrimidine 5’-Nucleotidase Deficiency

P5'N-1 dephosphorylates uridine monophosphate (UMP) and cytidine monophosphate (CMP) to their corresponding nucleosides. P5’N-1 deficiency is restricted to erythrocytes. Pyrimidine nucleotides accumulation resulting in basophilic stippling and chronic hemolytic anemia occur. The clinical pattern is exaggerated when associated with HbE[91].

### 7. Cytosolic 5’-Nucleotidase Superactivity

Clinically, superactivity results in a syndrome including developmental delay, growth retardation, seizures, ataxia, recurrent infections, autistic features, and hypouricosuria. Patients’ fibroblasts showed 20-fold elevations of the activity of

cytosolic 5-nucleotidase. This increased catabolism might cause a deficiency of pyrimidine nucleotides. Uridine at the dose of 1 g/kg per day can help developmental improvement, and a decrease in frequency of seizures and infections[52].

### 8. Thymidine Phosphorylase Deficiency

Deficiency in thymidine phosphorylase, which results in accumulation of thymidine, causes mitochondrial neurogastrointestinal encephalomyopathy (MNGIE). MNGIE is an autosomal recessive disease associated with multiple deletions of skeletal muscle mitochondrial DNA[92]. Hemodialysis and platelet infusions have been used unsuccessfully. Allogenic hematopoietic stem cell transplantation (HSCT) has been more successful in halting the clinical course through normalization of cellular nucleotide pools. The main challenges with HSCT appear to be frequent engraftment failure, high mortality rates of up to 50 % and limited matched donor availability.

In some reported cases, enzyme replacement therapy using erythrocyte encapsulated recombinant Escherichia coli TP (EE-TP), has successfully reduced plasma nucleoside concentration with clinical improvement. EE-TP should be considered as a rescue or maintenance therapy. EE-TP should be administered while waiting for an allogeneic HSCT donor or as an alternative therapy for patients who have end-stage disease[93].

Lentiviral-mediated hematopoietic gene therapy offers a promising alternative treatment. Pre-clinical data shows restoration of thymidine phosphorylase activity in mice[94].

### 9. Thymidine Kinase Deficiency

Two mutations of the gene encoding thymidine kinase-2, the mitochondrial form of the thymidine salvage enzyme, have been reported. Findings show isolated myopathy, and depletion of muscular mitochondrial DNA. The defect provokes imbalance of the mitochondrial nucleotides which impairs the mitochondrial DNA[95].

### 10. Activation-induced cytidine deaminase (CDA) deficiency (hyper-IgM syndrome type II)

CDA catalyzes the conversion of cytidine to uridine. Patients with autosomal recessive hyper-IgM syndrome type 2 are found to have mutations of the activation-induced cytidine deaminase (AICDA). Findings show normal or elevated serum IgM levels, an absence of IgG, IgA and IgE. These abnormalities indicate that the AICDA deficiency results in defective class switch recombination (CSR) process. AICDA generation of hyper-mutations in the immunoglobulin variable region genes results in impaired antibody affinity maturation.

Patients with hyper-IgM syndrome present with recurrent infections, lymphoid hyperplasia, autoimmune and related inflammatory disorders. Intravenous immunoglobulin therapy and antibiotic prophylaxis improve the clinical scenario in most cases[96].

This report compiles all clinical and economic evidence related to P/P metabolism disorder according to the relevant sources. The ultimate objective of issuing P/P metabolism disorders guidelines by the Council of Health Insurance is to update the IDF (CHI Drug Formulary) with the best available clinical and economic evidence related to drug therapies, ensuring timely and safe access to P/P metabolism disorder patients in Saudi Arabia. The focus of the review was on Saudi, American, European and International guidelines issued within the last ten years.

Several classes and drugs can be used for the management of inborn errors of P/P metabolism and are summarized in the table below.

**Table 6.** SFDA-Registered Drugs for Disorders of Purines and Pyrimidines Metabolism

| Drug | Indication | Dose | Level of evidence and HTA recommendation |
|---|---|---|---|
| ***XANTHINE OXYDASE INHIBITORS*** | | | |
| **Allopurinol** | Hyperuricemia associated with inborn errors of purine metabolism. | **Pediatric population:** 5 to 10 mg/Kg/day; adjust to maintain a high-normal serum uric acid concentration and a urinary uric acid/creatinine ration <1; reported rand: 3.7 to 9.7 mg/Kg/day.<br>**Maximum daily dose:** 600 mg/day. | N/A |
| **Febuxostat** | Hyperuricemia associated with inborn errors of purine metabolism. | **Adult population:** 40 mg once daily; may increase to 80 mg once daily in patients who do not achieve a serum uric acid level <6 mg/dL after 2 weeks. The dose may be increased further to 120 | N/A |

| | | | |
|---|---|---|---|
| | | mg once daily if clinically indicated.<br>**Maximum daily dose:**<br>120 mg/day. | |
| **Rasburicase** | Hyperuricemia associated with inborn errors of purine metabolism. | N/A | N/A |
| **ALKALANIZING AGENTS** | | | |
| **Sodium bicarbonate** | Urine alkalinization for PRPP superactivity | **Adult population:**<br>Oral: Initial: 48 mEq (4 g), then 12 to 24 mEq (1 to 2 g) every 4 hours; dose should be titrated to desired urinary pH; doses up to 186 mEq/day (15.6 g/day) in patients <60 years of age and 92.9 mEq/day (7.8 g/day) in patients >60 years of age. Administration of 48 mEq (4 g) every 8 hours has also been shown to achieve a urinary pH of at least 7 after a period of 10 hours in one study of healthy volunteers.<br><br>IV (off label):<br>Initial: Note: May consider use of initial bolus doses prior to initiation of a continuous infusion, especially in patients with preexisting acidemia.<br>IV: 50 to 100 mEq or 1 to 2 mEq/kg over 1 to 2 minutes; repeat as needed to achieve a urinary pH of 7.5 to 8.5 and a serum pH | N/A |

| | | | |
|---|---|---|---|
| | | of 7.45 to 7.55. Initiate a continuous infusion following initial bolus therapy (if used).<br>Continuous infusion:<br>IV: Initiate a continuous infusion using sodium bicarbonate (8.4%) 150 mEq in 1 L D5W. Administer at a rate of ~150 mL/hour to maintain a urinary pH of 7.5 to 8.5 and a serum pH of 7.45 to 7.55. Avoid fluid overload. | |
| **Potassium citrate** | Urine alkalinization for PRPP superactivity | | N/A |

**Other Drugs, Measures and Treatment Options**

**Adenine**

Adenylosuccinate lyase (ADSL) deficiency

There is no effective treatment currently available for ADSL deficiency. Survival prognosis is variable. Treatment with oral supplements of adenine (10 mg/kg per day) is suggested to replenish decreased concentrations of adenine nucleotides in ADSL-deficient tissues. Adenine can be incorporated into the adenine nucleotides via APRT. It is required to add Allopurinol, to avoid conversion of adenine by xanthine oxidase into minimally soluble 2,8-dihydroxyadenine, which forms kidney stones. Only some weight gain and acceleration of growth were noted.

**Erythrocyte encapsulated ADA**

Adenosine deaminase (ADA) deficiency

Without treatment, ADA deficiency is fatal within the first year of life. Treatment became possible with bone marrow transplantation. Bone marrow/stem cell transplantation is the therapeutic method of choice, with 70 % chance of complete immunological cure when an HLA-identical healthy donor is available. The graft provides stem cells, including T and B cells, which have enough ADA activity to prevent accumulation of adenosine and deoxyadenosine.

Other options include enzyme replacement therapies (ERT) with polyethylene glycol (PEG) modified bovine ADA or with erythrocyte encapsulated ADA. They have been used successfully as primary therapy in certain cases: individuals lacking an HLA-identical donor, when the risks associated with a partially mismatched transplant, or when graft failure is high as in the delayed- or late-onset phenotypes.

**Orotic acid**

Dihydroorotate Dehydrogenase (DHODH) Deficiency.

Supplementation with OA or uridine should bypass the enzymatic block. This approach would be unlikely to correct the phenotypic abnormalities because the main and first damage occurs before birth.

**PEG-ADA**

Adenosine deaminase (ADA) deficiency

Without treatment, ADA deficiency is fatal within the first year of life. Treatment became possible with bone marrow transplantation.

Other options include enzyme replacement therapies (ERT) with polyethylene glycol (PEG) modified bovine ADA or with erythrocyte encapsulated ADA. They have been used successfully as primary therapy in certain cases: individuals lacking an HLA-identical donor, when the risks associated with a partially mismatched transplant, or when graft failure is high as in the delayed- or late-onset phenotypes. PEG-ADA has also been used as a secondary therapy in patients with graft failure or absence of acceptable recovery of immune function following experimental gene therapy. However, its use remains limited by the presence of neutralizing antibodies against the bovine enzyme, autoimmunity, and the high cost of lifelong therapy.

If no histocompatible bone marrow donor is available, enzyme replacement therapy can be given. Repeated partial exchange transfusions with normal erythrocytes result in marked clinical and immunological improvement in some patients but is not sustained. Covalent attachment of PEG to bovine ADA results in marked extension of its half-life, and reduction of immunogenicity. Weekly to bi-weekly intramuscular injections of 15–30 units of PEG-ADA per kg result in mostly marked clinical improvement. In vitro immune function also significantly improves.

**Recombinant ADA2**

Adenosine deaminase 2 (ADA2) deficiency

ADA2 is a growth factor for endothelial and leukocyte development and differentiation, as supported by studies in patients and zebrafish. The data also suggests that ADA2 deficiency may compromise endothelial integrity while polarizing macrophage and monocyte subsets toward pro-inflammatory cells,

creating a vicious circle of vasculopathy and inflammation. Potential therapeutic strategies may include fresh-frozen plasma or recombinant ADA2 (ADA2 is found in plasma) and bone marrow transplantation (monocytes and macrophages, the main producers of ADA2, derive from bone marrow).

**Ribose**

Adenylosuccinate lyase (ADSL) deficiency

There is no effective treatment currently available for ADSL deficiency. Oral administration of ribose (10 mmol/kg per day) has been reported to reduce seizure frequency.

Ectosolic 5'-Nucleotidase

The diagnosis of eN gain- or loss-of-function is based on the measurement of 5'-nucleotidase activity in cultured fibroblasts, in addition to the identification of the involved isoenzyme. Administration of uridine or UMP plus CMP or ribose was a successful treatment for the symptoms of NAPDD. In NAPDD patients, a slight decrease in uridylate is measured, and it may be corrected uridine. However, uridine is transported by the same system active on adenosine. Thus, an excess of the pyrimidine nucleoside might interfere with adenosine trafficking across the cell membranes and consequently with its function in neurodevelopment and inflammation.

Muscle AMP deaminase deficiency

Symptoms may be gradually progressive, ultimately leading to the inability to dress and walk a few steps due to fatigue and myalgias. Administration of ribose (2–60 g per day orally in divided doses) may improve muscular strength and endurance. In general, triggers such as exercise should be avoided.

**SAM supplementation**

Phosphoribosylpyrophosphate (PRPP) synthetase superactivity

Dietary S-adenosylmethionine (SAM) supplementation, known to cross the blood–brain barrier, could lessen some neurologic symptoms in individuals with the severe phenotype by providing an oral source of purine nucleotide precursor that is not PRPP dependent.

Phosphoribosylpyrophosphate (PRPP) synthetase reduced activity

SAM supplementation has been used with some success for treatment in two Arts syndrome patients by replenishing purine nucleotides. Among purines, SAM is unique in that it crosses both the gut and the blood–brain barrier, where it becomes a source of adenosine which can be salvaged to form purine nucleotides via

adenosine kinase. Additionally, the external provision of SAM may diminish needs of cells that maintain an energy-dependent methylation cycle.

**UMP + CMP**

Ectosolic 5'-Nucleotidase

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**Uridine**

ADSL deficiency

There is no effective treatment currently available for ADSL deficiency. Uridine (2 mmol/kg per day) also had a slight beneficial effect.

Cytosolic 5'-Nucleotidase superactivity

Uridine at the dose of 1 g/kg per day can help developmental improvement, and a decrease in frequency of seizures and infections.

DHODH deficiency

Supplementation with OA or uridine should bypass the enzymatic block. This approach would be unlikely to correct the phenotypic abnormalities because the main and first damage occurs before birth.

Ectosolic 5'-Nucleotidase

The diagnosis of eN gain- or loss-of-function is based on the measurement of 5'-nucleotidase activity in cultured fibroblasts, in addition to the identification of the involved isoenzyme. Administration of uridine or UMP plus CMP or ribose was a successful treatment for the symptoms of NAPDD. In NAPDD patients, a slight decrease in uridylate is measured, and it may be corrected uridine. However, uridine is transported by the same system active on adenosine. Thus, an excess of the pyrimidine nucleoside might interfere with adenosine trafficking across the cell membranes and consequently with its function in neurodevelopment and inflammation.

UMP Synthase Deficiency (Hereditary Orotic Aciduria)

The enzyme defect can be bypassed by uridine, which is converted into UMP. An initial dose of 100-150 mg/kg can help with a better hematologic response, acceleration of growth and psychomotor development. One should aim to reach the lowest possible output of orotic acid.

# Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

## 1.1 KSA Guidelines

There are no specific guidelines for the treatment of inborn errors of purine and pyrimidine metabolism in Saudi Arabia.

## 1.2 European Guidelines

There are no specific guidelines for the treatment of inborn errors of purine and pyrimidine metabolism in Europe.

## 1.3 North American Guidelines

There are no specific guidelines for the treatment of inborn errors of purine and pyrimidine metabolism in North America.

## 1.4 International Guidelines

There are no specific guidelines for the treatment of inborn errors of purine and pyrimidine metabolism internationally.

# Section 2.0 Drug Therapy

## 2.1 Xanthine Oxidase Inhibitors

### 2.1.1 Allopurinol

Information on Allopurinol is detailed in the table below.

**Table 7.** Allopurinol Drug Information

| SCIENTIFIC NAME<br>ALLOPURINOL | |
|---|---|
| **SFDA Classification** | Prescription |
| **SFDA** | No |
| **US FDA** | No |
| **EMA** | No |
| **MHRA** | Yes |
| **PMDA** | No |
| **Indication (ICD-10)** | E79 |
| **Drug Class** | XANTHINE OXYDASE INHIBITORS/PYRAZOLOPYRIMIDINES |
| **Drug Sub-class** | PYRAZOLO[3,4-d] PYRIMIDINES |
| **ATC Code** | M04AA01 |
| **Pharmacological Class (ASHP)** | Antigout agents |
| **DRUG INFORMATION** | |
| **Dosage Form** | Oral solution |
| **Route of Administration** | Oral use |
| **Dose (Adult) [DDD]*** | Hyperuricemia associated with inborn errors of purine metabolism<br>2 to 20 mg/Kg/day |
| **Maximum Daily Dose Adults*** | N/A |
| **Dose (pediatrics)** | Hyperuricemia associated with inborn errors of purine metabolism<br>Initial: 5 to 10 mg/Kg/day; adjust to maintain a high-normal serum uric acid concentration and a urinary uric acid/creatinine ration <1; reported rand: 3.7 to 9.7 mg/Kg/day. |
| **Maximum Daily Dose Pediatrics*** | 600 mg/day. |

<table>
<tr><td>Adjustment</td><td>In adult patients<br>Allopurinol: Suggested Initial Doses in Kidney Impairment[a]<table><tr><th>eGFR mL/minute/1.73 m²</th><th>Suggested initial dose</th></tr><tr><td colspan="2">[a]ACR (FitzGerald 2020); Perez-Ruiz 2022; Stamp 2012; Vargas-Santos 2017.</td></tr><tr><td>>30 to 60</td><td>50 mg daily</td></tr><tr><td>>15 to 30</td><td>50 mg every other day</td></tr><tr><td>5 to 15</td><td>50 mg twice weekly</td></tr><tr><td><5</td><td>50 mg once weekly</td></tr></table>In pediatric patients<br>GFR 30 to 50 mL/minute/1.73 m2: Administer 50% of normal dose.<br>GFR 10 to 29 mL/minute/1.73 m2: Administer 50% of normal dose.<br>GFR <10 mL/minute/1.73 m2: Administer 30% of normal dose.<br>Intermittent hemodialysis: Administer 30% of normal dose.<br>Peritoneal dialysis: Administer 30% of normal dose.<br>Continuous renal replacement therapy (CRRT): Administer 50% of normal dose.</td></tr>
<tr><td>Prescribing edits*</td><td>N/A</td></tr>
<tr><td>AGE (Age Edit):</td><td>N/A</td></tr>
<tr><td>CU (Concurrent Use Edit):</td><td>N/A</td></tr>
</table>

| | |
|---|---|
| **G (Gender Edit):** | N/A |
| **MD (Physician Specialty Edit):** | N/A |
| **PA (Prior Authorization):** | N/A |
| **QL (Quantity Limit):** | N/A |
| **ST (Step Therapy):** | N/A |
| **EU (Emergency Use Only):** | N/A |
| **PE (Protocol Edit):** | N/A |
| **SAFETY** | |
| **Main Adverse Drug Reactions (Most common and most serious)** | Acute gout attacks, delayed hypersensitivity reactions (often termed allopurinol hypersensitivity syndrome [AHS]) ranging from mild maculopapular rash to severe cutaneous adverse reactions (SCAR), including Stenvens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS), gastrointestinal (nausea, vomiting), hepatotoxicity (most associated with DRESS and AHS), renal failure syndrome. |
| **Drug Interactions** | **Category X:**<br>• Didanosine<br>• Fluorouracil Products<br>• Pegloticase |
| **Special Population** | N/A |
| **Contraindications** | Severe hypersensitivity reaction to allopurinol or any component of the formulation. |
| **Monitoring Requirements** | • CBC<br>• LFTs<br>• Renal function<br>• Prothrombin time<br>• Hydration status<br>• Signs/symptoms of hepatotoxicity<br>• Signs/symptoms of hypersensitivity reaction |

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| **Precautions** | Hydration: For tumor lysis prevention, administer aggressive fluids sufficient to maintain adequate output. For other indications, fluid intake sufficient to yield a daily urinary output at least 2L and maintenance of a neural or (preferably) a slightly alkaline urine, are desirable in order to avoid possible formation of xanthine calculi due to allopurinol therapy and to help prevent renal urate precipitation in patients receiving concomitant uricosuric agents. |
| **Black Box Warning** | N/A |
| **REMS*** | N/A |

## HEALTH TECHNOLOGY ASSESSMENT (HTA)

A search for clinical economic recommendations from the HTA bodies didn't yield any guidance for allopurinol in disorders of purine and pyrimidine metabolism.

## CONCLUSION STATEMENT – Allopurinol

**Allopurinol is a xanthine oxidase inhibitor, used to lower uric acid levels.** It is sometimes utilized in the treatment of hyperuricemia associated with inborn errors of purine metabolism, particularly in Phosphoribosyl Pyrophosphate Synthetase superactivity, Adenylosuccinase deficiency, Hypoxanthine-Guanine Phosphoribosyltransferase deficiency and Adenine Phosphoribosyltransferase deficiency. Typically, oral allopurinol may be prescribed at a dosage of 5 to 10 mg/kg/day in pediatric patients; to maintain a high-normal serum uric acid concentration. However, it's crucial to note that the use of allopurinol should be carefully monitored by a healthcare professional, as it can have potential side effects, particularly when there is renal impairment. There are no recommendations issued by the HTA bodies for allopurinol.

### 2.1.2 Febuxostat

Information on Febuxostat is detailed in the table below

**Table 8.** Febuxostat Drug Information

| SCIENTIFIC NAME FEBUXOSTAT | |
|---|---|
| **SFDA Classification** | Prescription |
| **SFDA** | No |
| **US FDA** | Yes |
| **EMA** | No |
| **MHRA** | No |
| **PMDA** | No |
| **Indication (ICD-10)** | E79 |
| **Drug Class** | XANTHINE OXYDASE INHIBITORS/AZOLES |
| **Drug Sub-class** | THIAZOLES |
| **ATC Code** | M04AA03 |
| **Pharmacological Class (ASHP)** | Antigout agents |
| **DRUG INFORMATION** | |
| **Dosage Form** | Oral solution |
| **Route of Administration** | Oral use |
| **Dose (Adult) [DDD]*** | Initial: 40 mg once daily; may increase to 80 mg once daily in patients who do not achieve a serum uric acid level <6 mg/dL after 2 weeks. The dose may be increased further to 120 mg once daily if clinically indicated. |
| **Maximum Daily Dose Adults*** | 120 mg. |
| **Dose (pediatrics)** | N/A |
| **Maximum Daily Dose Pediatrics*** | N/A |
| **Adjustment** | In the adult population:<br>Altered kidney function:<br>CrCl ≥30 mL/minute: No dosage adjustment necessary.<br>CrCl <30 mL/minute: Initial: 20 to 40 mg once daily. Note: Observational studies in patients with hyperuricemia have |

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| | reported safety and tolerability of 60 and 80 mg/day; careful titration may be considered in patients unresponsive to standard doses.<br><br>Hemodialysis, intermittent (thrice weekly): Unlikely to be dialyzed (highly protein bound): Initial: 20 to 40 mg once daily; no supplemental dose necessary. Note: A small, retrospective, observational study in patients with hyperuricemia reported safety and tolerability of doses up to 80 mg/day; careful titration may be considered in patients unresponsive to standard doses.<br><br>Peritoneal dialysis: Unlikely to be dialyzed (highly protein bound): Initial: 20 to 40 mg once daily. Note: A small, retrospective, observational study in patients with hyperuricemia reported safety and tolerability of doses up to 80 mg/day; careful titration may be considered in patients unresponsive to standard doses.<br><br>CRRT: Dose as for CrCl <30 mL/minute.<br><br>PIRRT (e.g., sustained, low efficiency diafiltration): Dose as for CrCl <30 mL/minute.<br><br>Dosing: Hepatic Impairment: Adult Preexisting hepatic impairment:<br><br>Mild to moderate impairment (Child-Pugh class A or B): No dosage adjustment necessary. |

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| | Severe impairment (Child-Pugh class C): There are no dosage adjustments provided in the manufacturer's labeling (has not been studied); use caution.<br><br>Hepatotoxicity during treatment:<br><br>ALT or AST >3 times ULN (in the clinical context of potential liver injury [eg, fatigue, anorexia, right upper quadrant pain, dark urine, jaundice]): Interrupt febuxostat therapy and evaluate. Do not reinitiate febuxostat if liver injury is confirmed or no alternate etiology for liver test abnormalities is identified.<br><br>ALT or AST >3 times ULN and serum total bilirubin >2 times ULN without alternative etiology: Permanently discontinue. |
| **Prescribing edits*** | **ST** |
| **AGE (Age Edit):** | N/A |
| **CU (Concurrent Use Edit):** | N/A |
| **G (Gender Edit):** | N/A |
| **MD (Physician Specialty Edit):** | N/A |
| **PA (Prior Authorization):** | N/A |
| **QL (Quantity Limit):** | N/A |
| **ST (Step Therapy):** | Second line treatment, reserved for cases of failure or intolerance to allopurinol. |
| **EU (Emergency Use Only):** | N/A |
| **PE (Protocol Edit):** | N/A |
| **SAFETY** | |
| **Main Adverse Drug Reactions (Most common and most serious)** | Acute gout attacks have been reported during the early stages of urate-lowering therapy, including febuxostat, even when normal or optimal serum uric acid levels have been attained. Gout attacks generally decrease in duration and |

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| | severity after several months of urate-lowering therapy.<br>Delayed hypersensitivity reactions may occur, including morbilliform skin rash and SCARs. SCARs include DRESS, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Other delayed reactions include eosinophilic polymyositis.<br>Dermatologic: Skin rash (0.5% to 2%).<br>Gastrointestinal: Nausea (1%).<br>Hepatic: Hepatic insufficiency (5% to 7%), increased serum alanine aminotransferase (3%), increased serum aspartate aminotransferase (2%).<br>Neuromuscular & skeletal: Arthralgia (≤1%). |
| **Drug Interactions** | **Category X:**<br>• Azathioprine<br>• Didanosine<br>• Mercaptopurine<br>• Pazopoanib<br>• Pegloticase<br>• Topotecan |
| **Special Population** | **Pregnancy Considerations**<br>Adverse events were observed in some animal reproduction studies.<br>**Breastfeeding Considerations**<br>It is not known if febuxostat is present in breast milk. According to the manufacturer, the decision to continue or discontinue breastfeeding during therapy should take into account the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother. |
| **Contraindications** | Concurrent use with azathioprine or mercaptopurine.<br>Significant drug interactions exist, requiring dose/frequency adjustment or |

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| | avoidance. Consult drug interactions database for more information.<br>Canadian labeling: Additional contraindications (not in US labeling): Hypersensitivity to febuxostat or any component of the formulation. |
| **Monitoring Requirements** | • LFTs at baseline, periodically, and if signs/symptoms of hepatic injury (eg, fatigue, anorexia, right upper quadrant pain, dark urine, jaundice)<br>• For gout, monitor serum uric acid levels (as early as 2 weeks after initiation, after each dosage titration), then every 6 months (symptomatic patients or tophi) or every 12 months (all patients on urate-lowering therapy, regardless of symptoms)<br>• Monitor for signs/symptoms of cardiovascular events and signs/symptoms of hypersensitivity or severe skin reactions. |
| **Precautions** | Disease-related concerns:<br>• Secondary hyperuricemia: Use in secondary hyperuricemia has not been studied; avoid use in patients at increased risk of urate formation (eg, malignancy and its treatment; Lesch-Nyhan syndrome).<br>Dosage forms specific issues:<br>• Lactose: Contains lactose. |
| **Black Box Warning** | Gout patients with established cardiovascular (CV) disease treated with febuxostat had a higher rate of CV death compared to those treated with allopurinol in a CV outcomes study. Consider the risks and benefits of febuxostat when deciding to prescribe or continue patients on febuxostat. Febuxostat should only be used in patients who have an inadequate |

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| | response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable. |
| **REMS*** | N/A |

## HEALTH TECHNOLOGY ASSESSMENT (HTA)

A search for clinical economic recommendations from the HTA bodies didn't yield any guidance for febuxostat in disorders of purine and pyrimidine metabolism. This is probably because treatment paradigms haven't much changed in the last decade, with no new drugs introduced in the management landscape.

However, on January 20, 2022, the Haute Autorité de Santé (HAS) issued a favorable opinion regarding the maintenance of febuxostat reimbursement in the treatment of chronic hyperuricemia. Febuxostat is indicated in the treatment of chronic hyperuricemia only when urate deposition has already occurred. It is a second line treatment, reserved for cases of failure or intolerance to allopurinol. It is not recommended in case of ischemic disease or congestive heart failure and should be avoided in patients with cardiovascular risk factors unless there is no alternative treatment.

## CONCLUSION STATEMENT – Febuxostat

**Febuxostat is a xanthine oxidase inhibitor, used to low uric acid levels.** It is sometimes utilized in the treatment of hyperuricemia associated with inborn errors of purine metabolism, particularly in Phosphoribosyl Pyrophosphate Synthetase superactivity and Hypoxanthine-Guanine Phosphoribosyltransferase deficiency. There are no studies establishing the recommended dose in hyperuricemia associated with inborn errors of purine metabolism. However, oral febuxostat may be prescribed at a dosage to maintain a high-normal serum uric acid concentration. It is crucial to note that the use of febuxostat should be carefully monitored by a healthcare professional, as it can have potential side effects. Particularly, gout patients with established CV disease treated with febuxostat had a higher rate of CV death compared to those treated with allopurinol in a CV outcomes study. The results of this study cannot be extrapolated to patients with purine metabolism disorder. On January 20, 2022, the HAS issued a favorable opinion regarding the maintenance of febuxostat reimbursement in the treatment of chronic hyperuricemia. Febuxostat is indicated in the treatment of chronic hyperuricemia only when urate deposition has already occurred. It is a second line treatment, reserved for cases of failure or intolerance to allopurinol. It is not recommended in case of ischemic disease or congestive heart failure and should be avoided in patients with cardiovascular risk factors unless there is no alternative treatment.

### 2.1.3 Rasburicase

Information on Rasburicase is detailed in the table below.

**Table 9.** Rasburicase Drug Information

| SCIENTIFIC NAME<br>Rasburicase | |
|---|---|
| **SFDA Classification** | Prescription |
| **SFDA** | No |
| **US FDA** | No |
| **EMA** | No |
| **MHRA** | No |
| **PMDA** | No |
| **Indication (ICD-10)** | E79 |
| **Drug Class** | XANTHINE OXYDASE INHIBITORS/ Carboxylic Acids and Derivatives |
| **Drug Sub-class** | Amino Acids, Peptides, and Analogues |
| **ATC Code** | V03AF07 |
| **Pharmacological Class (ASHP)** | Antigout agents |
| **DRUG INFORMATION** | |
| **Dosage Form** | Intravenous solution |
| **Route of Administration** | IV |
| **Dose (Adult) [DDD]*** | **Hyperuricemia**: 0.1 to 0.2 mg/kg |
| **Maximum Daily Dose Adults*** | N/A |
| **Dose (pediatrics)** | N/A |
| **Maximum Daily Dose Pediatrics*** | N/A |
| **Adjustment** | N/A |
| **Prescribing edits*** | N/A |
| **AGE (Age Edit):** | N/A |
| **CU (Concurrent Use Edit):** | N/A |
| **G (Gender Edit):** | N/A |
| **MD (Physician Specialty Edit):** | N/A |
| **PA (Prior Authorization):** | N/A |
| **QL (Quantity Limit):** | N/A |
| **ST (Step Therapy):** | N/A |

| | |
|---|---|
| **EU (Emergency Use Only):** | N/A |
| **PE (Protocol Edit):** | N/A |
| **SAFETY** | |
| **Main Adverse Drug Reactions (Most common and most serious)** | **>10%:**<br>Cardiovascular: Peripheral edema (adults: 50%)<br>Dermatologic: Skin rash (13%; serious: <1%)<br>Endocrine & metabolic: Hypervolemia (adults: 12%), hypophosphatemia (adults: 17%)<br>Gastrointestinal: Abdominal pain (20% to 22%), constipation (20%), diarrhea (20%), nausea (27% to 58%), stomatitis (15%), vomiting (38% to 50%)<br>Hepatic: Hyperbilirubinemia (16%), increased serum alanine aminotransferase (adults: 11%)<br>Immunologic: Antibody development (infants, children, and adolescents: 11%; adults [IgE]: 6%), development of IgG antibodies (adults: 18%; neutralizing 8%)<br>Infection: Sepsis (adults: 12%)<br>Nervous system: Anxiety (adults: 24%), headache (26%)<br>Respiratory: Pharyngolaryngeal pain (adults: 14%)<br>Miscellaneous: Fever (46%)<br><br>**1% to 10%:**<br>Endocrine & metabolic: Hyperphosphatemia (adults: 10%)<br>Hypersensitivity: Hypersensitivity reaction (adults: 4%) |
| **Drug Interactions** | **Category X:**<br>N/A |
| **Special Population** | N/A |
| **Contraindications** | History of anaphylaxis or severe hypersensitivity to rasburicase or any |

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| | component of the formulation; history of hemolytic reaction or methemoglobinemia associated with rasburicase; glucose-6-phosphatase dehydrogenase (G6PD) deficiency. |
| **Monitoring Requirements** | • Plasma uric acid levels<br>• CBC<br>• G6PD deficiency screening (in patients at high risk for deficiency).<br>• Monitor for signs/symptoms of hypersensitivity reactions, hemolysis, and methemoglobinemia. |
| **Precautions** | • Hemolysis: Rasburicase may cause hemolysis (<1%). Severe hemolytic reactions occurred within 2 to 4 days of rasburicase initiation. Screen patients at higher risk for G6PD deficiency (eg, patients of African or Mediterranean descent) prior to therapy.<br>• Hypersensitivity: Serious and fatal hypersensitivity reactions (including anaphylaxis) have been reported. Reactions may occur at any time during treatment (including the initial dose); signs and symptoms may include bronchospasm, chest pain/tightness, dyspnea, hypotension, hypoxia, shock, or urticaria. The safety and efficacy of more than one course of administration has not been established.<br>• Methemoglobinemia: Methemoglobinemia has been reported (<1%), including cases of serious hypoxemia requiring medical intervention. Initiate appropriate treatment (eg, transfusion, methylene blue) if methemoglobinemia occurs. |

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| | • Hydration: Patients at risk for tumor lysis syndrome should receive appropriate IV hydration as part of uric acid management; however, alkalinization (with sodium bicarbonate) concurrently with rasburicase is not recommended.<br>• Multiple courses: Rasburicase is immunogenic and can elicit an antibody response; efficacy may be reduced with subsequent courses of therapy.<br>• Uric acid degradation: Enzymatic degradation of uric acid in blood samples will occur if left at room temperature, which may interfere with serum uric acid measurements; specific guidelines for the collection of plasma uric acid samples must be followed, including collection in prechilled tubes with heparin anticoagulant, immediate ice water bath immersion and assay within 4 hours (sample should remain on ice until analyzed). |
| **Black Box Warning** | Rasburicase may cause serious and fatal hypersensitivity reactions, including anaphylaxis. Immediately and permanently discontinue rasburicase in patients who experience a serious hypersensitivity reaction.<br>Do not administer rasburicase to patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Immediately and permanently discontinue rasburicase in patients developing hemolysis. Screen patients at higher risk for G6PD deficiency (eg, patients of African or Mediterranean ancestry) prior to starting rasburicase. |

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| | Rasburicase can result in methemoglobinemia in some patients. Immediately and permanently discontinue rasburicase in patients developing methemoglobinemia. Rasburicase enzymatically degrades uric acid in blood samples left at room temperature. Collect blood samples in prechilled tubes containing heparin and immediately immerse and maintain sample in an ice water bath. Assay plasma samples within 4 hours of collection. |
| **REMS*** | N/A |

## HEALTH TECHNOLOGY ASSESSMENT (HTA)

A search for clinical economic recommendations from the HTA bodies didn't yield any guidance for rasburicase in disorders of purine and pyrimidine metabolism. This is probably because treatment paradigms haven't much changed in the last decade, with no new drugs introduced in the management landscape.

## CONCLUSION STATEMENT – Rasburicase

**Rasburicase is a Xanthine oxidase inhibitor, used to low uric acid levels.** It is sometimes utilized in the treatment of hyperuricemia associated with inborn errors of purine metabolism, particularly in Hypoxanthine-Guanine Phosphoribosyltransferase deficiency. There are no studies establishing the recommended dose in hyperuricemia associated with inborn errors of purine metabolism. However, intravenous rasburicase may be prescribed at a dosage to maintain a high-normal serum uric acid concentration. It is crucial to note that the use of rasburicase should be carefully monitored by a healthcare professional, as it can have potential side effects. Particularly, rasburicase may cause serious and fatal hypersensitivity reactions, including anaphylaxis. Rasburicase is contraindicated in patients with G6PD deficiency. Rasburicase can result in methemoglobinemia in some patients. There are no recommendations issued by the HTA bodies for rasburicase.

## 2.2 Alkalinizing Agents

### 2.2.1 Sodium Bicarbonate

Information on Sodium Bicarbonate is detailed in the table below.

**Table 10.** Sodium Bicarbonate Drug information

| SCIENTIFIC NAME<br>SODIUM BICARBONATE | |
|---|---|
| **SFDA Classification** | Prescription |
| **SFDA** | No |
| **US FDA** | No |
| **EMA** | No |
| **MHRA** | Yes |
| **PMDA** | No |
| **Indication (ICD-10)** | E79 |
| **Drug Class** | Alkalinizing agents |
| **Drug Sub-class** | N/A |
| **ATC Code** | B05CB04 |
| **Pharmacological Class (ASHP)** | Alkalinizing agents |
| **DRUG INFORMATION** | |
| **Dosage Form** | Oral solution – IV solution |
| **Route of Administration** | Oral use – IV use |
| **Dose (Adult) [DDD]*** | Oral: Initial: 48 mEq (4 g), then 12 to 24 mEq (1 to 2 g) every 4 hours; dose should be titrated to desired urinary pH; doses up to 186 mEq/day (15.6 g/day) in patients <60 years of age and 92.9 mEq/day (7.8 g/day) in patients >60 years of age. Administration of 48 mEq (4 g) every 8 hours has also been shown to achieve a urinary pH of at least 7 after a period of 10 hours in one study of healthy volunteers.<br><br>IV (off label): |

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| | Initial: Note: May consider use of initial bolus doses prior to initiation of a continuous infusion, especially in patients with preexisting acidemia.<br>IV: 50 to 100 mEq or 1 to 2 mEq/kg over 1 to 2 minutes; repeat as needed to achieve a urinary pH of 7.5 to 8.5 and a serum pH of 7.45 to 7.55. Initiate a continuous infusion following initial bolus therapy (if used).<br>Continuous infusion: IV: Initiate a continuous infusion using sodium bicarbonate (8.4%) 150 mEq in 1 L D5W. Administer at a rate of ~150 mL/hour to maintain a urinary pH of 7.5 to 8.5 and a serum pH of 7.45 to 7.55. Avoid fluid overload. |
| **Maximum Daily Dose Adults*** | N/A |
| **Dose (pediatrics)** | N/A |
| **Maximum Daily Dose Pediatrics*** | N/A |
| **Adjustment** | N/A |
| **Prescribing edits*** | N/A |
| **AGE (Age Edit):** | Doses up to 186 mEq/day (15.6 g/day) in patients <60 years of age and 92.9 mEq/day (7.8 g/day) in patients >60 years of age. |
| **CU (Concurrent Use Edit):** | N/A |
| **G (Gender Edit):** | N/A |
| **MD (Physician Specialty Edit):** | N/A |
| **PA (Prior Authorization):** | N/A |
| **QL (Quantity Limit):** | N/A |
| **ST (Step Therapy):** | N/A |
| **EU (Emergency Use Only):** | N/A |
| **PE (Protocol Edit):** | N/A |
| **SAFETY** | |
| **Main Adverse Drug Reactions (Most common and most serious)** | Cardiovascular: Cardiac failure (exacerbation), edema |

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|---|---|
| | Central nervous system: Cerebral hemorrhage<br><br>Endocrine & metabolic: Acidosis (intracranial), hypernatremia, hypocalcemia, hypokalemia, metabolic alkalosis, milk-alkali syndrome (especially with renal dysfunction)<br><br>Gastrointestinal: Abdominal distention, eructation, flatulence (oral administration)<br><br>Neuromuscular & skeletal: Tetany<br><br>Respiratory: Pulmonary edema |
| **Drug Interactions** | **<u>Category X:</u>**<br>• Cefditoren<br>• Levonadifloxacin |
| **Special Population** | Contains sodium; use with caution, especially in patients with concomitant hypertension, heart failure, or volume overload.<br><br>**Pediatric:** Rapid administration in neonates, infants, and children <2 years of age has led to hypernatremia, decreased CSF pressure, and intracranial hemorrhage. |
| **Contraindications** | Injection: Chloride loss due to vomiting or from continuous GI suction; concomitant use of diuretics known to produce a hypochloremic alkalosis.<br><br>Neutralizing additive (dental or IV use): Not for use as a systemic alkalizer.<br><br>OTC labeling: When used for self-medication, do not use if on low-sodium diet. |

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| | Significant drug interactions exist, requiring dose/frequency adjustment or avoidance. Consult drug interactions database for more information. |
| **Monitoring Requirements** | • Serum electrolytes (including bicarbonate, potassium, sodium, calcium)<br>• Urinary pH<br>• Arterial blood gases (if indicated) |
| **Precautions** | Concerns related to adverse effects:<br><br>· Extravasation: Vesicant (at concentrations ≥8.4%); ensure proper catheter or needle position prior to and during infusion. Avoid extravasation (tissue necrosis may occur due to hypertonicity and alkalinity).<br><br>Disease-related concerns:<br><br>· Cirrhosis: Use with caution in patients with cirrhosis.<br><br>· Edema: Use with caution in patients with edema.<br><br>· Heart failure: Use with caution in patients with heart failure.<br><br>· Peptic ulcer disease: Not to be used in treatment of peptic ulcer disease.<br><br>· Kidney impairment: Use with caution in patients with kidney impairment; may cause sodium retention.<br><br>Special populations: |

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| | • Older adult: potential for systemic alkalosis.<br><br>• Pediatric: Rapid administration in neonates, infants, and children <2 years of age has led to hypernatremia, decreased CSF pressure, and intracranial hemorrhage.<br><br>Dosage form specific issues:<br><br>• Injection: Use of IV sodium bicarbonate should be reserved for documented severe metabolic acidosis and for severe/emergent hyperkalemia (eg, cardiotoxicity or cardiac arrest). Routine use in cardiac arrest is not recommended.<br><br>• Powder/Tablets: Completely dissolve in water prior to administration; severe stomach irritation may occur. |
| **Black Box Warning** | N/A |
| **REMS*** | N/A |

## HEALTH TECHNOLOGY ASSESSMENT (HTA)

A search for clinical economic recommendations from the HTA bodies didn't yield any guidance for sodium bicarbonate in disorders of purine and pyrimidine metabolism. This is probably because treatment paradigms haven't much changed in the last decade, with no new drugs introduced in the management landscape.

## CONCLUSION STATEMENT – Sodium bicarbonate

**Sodium bicarbonate is an Alkalinizing agent, used to alkalinize urine.** It is sometimes utilized in the treatment of PRPP superactivity. There are no studies establishing the recommended dose in PRPP superactivity. However, for urinary alkalinization regardless of cause, the following dosing regimen is suggested.
Oral: Initial: 48 mEq (4 g), then 12 to 24 mEq (1 to 2 g) every 4 hours; dose should be titrated to desired urinary pH; doses up to 186 mEq/day (15.6 g/day) in patients <60 years of age and 92.9 mEq/day (7.8 g/day) in patients >60 years of age.

Administration of 48 mEq (4 g) every 8 hours has also been shown to achieve a urinary pH of at least 7 after a period of 10 hours in one study of healthy volunteers.
IV (off label): Initial: Note: May consider use of initial bolus doses prior to initiation of a continuous infusion, especially in patients with preexisting acidemia.
IV: 50 to 100 mEq or 1 to 2 mEq/kg over 1 to 2 minutes; repeat as needed to achieve a urinary pH of 7.5 to 8.5 and a serum pH of 7.45 to 7.55. Initiate a continuous infusion following initial bolus therapy (if used).
Continuous infusion: IV: Initiate a continuous infusion using sodium bicarbonate (8.4%) 150 mEq in 1 L D5W. Administer at a rate of ~150 mL/hour to maintain a urinary pH of 7.5 to 8.5 and a serum pH of 7.45 to 7.55. It is crucial to note that the use of sodium bicarbonate should be carefully monitored by a healthcare professional, as it can have potential side effects. Particularly, sodium bicarbonate contains sodium; use with caution, especially in patients with concomitant hypertension, heart failure, or volume overload. There are no recommendations issued by the HTA bodies for sodium bicarbonate.

### 2.2.2 Potassium Citrate

Information on Potassium Citrate is detailed in the table below.

**Table 11.** Potassium Citrate Drug Information

| SCIENTIFIC NAME<br>POTASSIUM CITRATE | |
|---|---|
| **SFDA Classification** | Prescription |
| **SFDA** | No |
| **US FDA** | No |
| **EMA** | No |
| **MHRA** | No |
| **PMDA** | No |
| **Indication (ICD-10)** | E79 |
| **Drug Class** | Alkalinizing agents |
| **Drug Sub-class** | N/A |
| **ATC Code** | A12BA02 |
| **Pharmacological Class (ASHP)** | Alkalinizing agents |
| **DRUG INFORMATION** | |
| **Dosage Form** | Oral solution - powder |
| **Route of Administration** | Oral use |

| | |
|---|---|
| **Dose (Adult) [DDD]*** | Powder: Oral: One packet dissolved in cool water or juice 4 times daily; adjust dose to urinary pH.<br><br>Solution: Oral: 10 to 30 mL 4 times daily; adjust dose based on urinary pH. |
| **Maximum Daily Dose Adults*** | N/A |
| **Dose (pediatrics)** | Urine alkalinization, urolithiasis (cystinuria, uricosuria, hypocitraturia):<br><br>Fixed dosing: Children and Adolescents: Oral: 10 to 30 mEq bicarbonate/dose after meals and at bedtime; typical adult doses do not exceed 60 mEq bicarbonate/dose (manufacturer's labeling).<br><br>Weight-directed dosing: Limited data available: Infants, Children, and Adolescents: Oral: Reported range: 0.5 to 4 mEq bicarbonate/kg/day in 4 divided doses; titrate to target pH (dependent on stone composition). Per the manufacturer, in adults, when used for urine alkalinization, doses of 20 to 30 mEq bicarbonate administered 4 times daily typically maintain urinary pH 7 to 7.6. |
| **Maximum Daily Dose Pediatrics*** | N/A |
| **Adjustment** | N/A |
| **Prescribing edits*** | N/A |
| **AGE (Age Edit):** | N/A |
| **CU (Concurrent Use Edit):** | N/A |
| **G (Gender Edit):** | N/A |
| **MD (Physician Specialty Edit):** | N/A |
| **PA (Prior Authorization):** | N/A |
| **QL (Quantity Limit):** | N/A |
| **ST (Step Therapy):** | N/A |
| **EU (Emergency Use Only):** | N/A |

| | |
|---|---|
| **PE (Protocol Edit):** | N/A |
| **SAFETY** | |
| **Main Adverse Drug Reactions (Most common and most serious)** | The following adverse drug reactions and incidences are derived from product labeling unless otherwise specified.<br>Frequency not defined.<br>Endocrine & metabolic: Hyperkalemia<br><br>Gastrointestinal: Abdominal distress, diarrhea, nausea, vomiting. |
| **Drug Interactions** | **Category X:**<br>• Anticholinergic Agents<br>• Spironolactone<br>• Triamterene |
| **Special Population** | N/A |
| **Contraindications** | Renal insufficiency (GFR <0.7 mL/kg/minute); patients with hyperkalemia or with conditions predisposing to hyperkalemia (eg, chronic renal failure, acute dehydration, adrenal insufficiency, uncontrolled diabetes mellitus, tissue breakdown, strenuous physical exercise in unconditioned individuals); patients with delayed gastric emptying, esophageal compression, or intestinal obstruction or stricture; patients with active urinary tract infection; peptic ulcer disease.<br>Hypersensitivity to any ingredient of the formulation, severe renal insufficiency with oliguria or azotemia; untreated Addison disease; adynamia episodica hereditaria; acute dehydration; heat cramps; anuria; severe myocardial damage; hyperkalemia. |
| **Monitoring Requirements** | • Serum electrolytes (potassium, chloride, sodium)<br>• Bicarbonate<br>• Serum creatinine |

| | |
|---|---|
| | • CBC every 4 months (more frequently with cardiac/renal disease or acidosis)<br>• Urinary citrate and/or urinary pH at initiation or dose change and every 4 months<br>• ECG (periodically)<br>• BUN<br>• LFTs |
| **Precautions** | Concerns related to adverse effects:<br><br>• GI effects: May cause GI upset (eg, nausea, vomiting, diarrhea, abdominal pain, discomfort) and lead to GI ulceration, bleeding, perforation and/or obstruction requiring surgical intervention. Some fatal cases have been reported. Discontinue immediately if abdominal pain, distension, nausea, vomiting or GI bleeding occurs.<br><br>• Hyperkalemia: Close monitoring of serum potassium concentrations is needed to avoid hyperkalemia; severe hyperkalemia may lead to muscle weakness/paralysis and cardiac conduction abnormalities (eg, heart block, ventricular arrhythmias, asystole).<br><br>Disease-related concerns:<br><br>• Acid/base disorders: Use with caution in patients with acid/base alterations; changes in serum potassium concentrations can occur during acid/base correction, monitor closely.<br><br>• Cardiovascular disease: Use with caution in patients with cardiovascular disease (eg, heart failure, cardiac arrhythmias); patients may be more |

| | |
|---|---|
| | susceptible to life-threatening cardiac effects associated with hyper/hypokalemia.<br><br>• Hepatic impairment: Citrate is converted to bicarbonate in the liver; this conversion may be impaired in patients in hepatic failure.<br><br>• Potassium-altering conditions/disorders: Use with caution in patients with disorders or conditions likely to contribute to altered serum potassium and hyperkalemia.<br><br>• Renal impairment: Use with caution in patients with renal impairment; monitor serum potassium concentrations closely. Contraindicated in severe renal impairment with oliguria or azotemia.<br><br>• Severely ill: Citrate is converted to bicarbonate in the liver; this conversion may be impaired in patients who are severely ill or in shock.<br><br>Dosage form specific issues:<br><br>• Benzyl alcohol and derivatives: Some dosage forms may contain sodium benzoate/benzoic acid; benzoic acid (benzoate) is a metabolite of benzyl alcohol; large amounts of benzyl alcohol (≥99 mg/kg/day) have been associated with a potentially fatal toxicity ("gasping syndrome") in neonates; the "gasping syndrome" consists of metabolic acidosis, respiratory distress, gasping respirations, CNS dysfunction (including convulsions, intracranial hemorrhage), hypotension, and cardiovascular |

| | |
|---|---|
| | collapse; some data suggests that benzoate displaces bilirubin from protein binding sites; avoid or use dosage forms containing benzyl alcohol derivative with caution in neonates. See manufacturer's labeling.<br><br>• Propylene glycol: Some dosage forms may contain propylene glycol; large amounts are potentially toxic and have been associated hyperosmolality, lactic acidosis, seizures and respiratory depression; use caution.<br><br>Other warnings/precautions:<br><br>• Administration: Dilute with water to minimize GI injury; administer after meals to minimize saline laxative effect.<br><br>Pediatric considerations:<br>Some dosage forms may contain propylene glycol; in neonates, large amounts of propylene glycol delivered orally, intravenously (eg, >3,000 mg/day), or topically have been associated with potentially fatal toxicities which can include metabolic acidosis, seizures, renal failure, and CNS depression; toxicities have also been reported in children and adults including hyperosmolality, lactic acidosis, seizures, and respiratory depression; use caution. |
| **Black Box Warning** | N/A |
| **REMS*** | N/A |

## HEALTH TECHNOLOGY ASSESSMENT (HTA)

A search for clinical economic recommendations from the HTA bodies didn't yield any guidance for potassium citrate in disorders of purine and pyrimidine metabolism. This is probably because treatment paradigms haven't much changed in the last decade, with no new drugs introduced in the management landscape.

## CONCLUSION STATEMENT – Potassium citrate

**Potassium citrate is an Alkalinizing agent, used to alkalinize urine.** It is sometimes utilized in the treatment of PRPP superactivity. There are no studies establishing the recommended dose in PRPP superactivity. However, Potassium citrate may be prescribed based on the following regimen:

For adult patients:
Powder: Oral: One packet dissolved in cool water or juice 4 times daily; adjust dose to urinary pH. Solution: Oral: 10 to 30 mL 4 times daily; adjust dose based on urinary pH.

For pediatric patients:

Urine alkalinization, urolithiasis (cystinuria, uricosuria, hypocitraturia):
Fixed dosing: Children and Adolescents: Oral: 10 to 30 mEq bicarbonate/dose after meals and at bedtime; typical adult doses do not exceed 60 mEq bicarbonate/dose (manufacturer's labeling). Weight-directed dosing: Limited data available: Infants, Children, and Adolescents: Oral: Reported range: 0.5 to 4 mEq bicarbonate/kg/day in 4 divided doses; titrate to target pH (dependent on stone composition). Per the manufacturer, in adults, when used for urine alkalinization, doses of 20 to 30 mEq bicarbonate administered 4 times daily typically maintain urinary pH 7 to 7.6.

It is crucial to note that the use of potassium citrate should be carefully monitored by a healthcare professional, as it can have potential side effects. Particularly, potassium citrate may cause serious and fatal hypersensitivity reactions to any ingredient of the formulation, severe renal insufficiency with oliguria or azotemia; untreated Addison disease; adynamia episodica hereditaria; acute dehydration; heat cramps; anuria; severe myocardial damage; hyperkalemia. Cautious use of potassium citrate should be considered in renal insufficiency (GFR <0.7 mL/kg/minute); in patients with hyperkalemia or with conditions predisposing to hyperkalemia (eg, chronic renal failure, acute dehydration, adrenal insufficiency, uncontrolled diabetes mellitus, tissue breakdown, strenuous physical exercise in unconditioned individuals); in patients with delayed gastric emptying, esophageal compression, or intestinal obstruction or stricture; in patients with active urinary tract infection; peptic ulcer disease. There are no recommendations issued by the HTA bodies for potassium citrate.

## 2.3 Other Drugs, Measures and Treatment Options

The following section details other management options in disorders of P/P. These suggestions are based on the literature from the review articles mentioned in the references table. Since disorders of P/P are rare pathologies, there are no established guidelines. Some of the following drugs are SFDA registered and some are not. For the sole purpose of simplifying this report, the SFDA registered drugs mentioned below are detailed as such because no elaborated data other than that mentioned in the corresponding paragraph was found.

**Adenine**

ADSL deficiency

There is no effective treatment currently available for ADSL deficiency. Survival prognosis is variable. Treatment with oral supplements of adenine (10 mg/kg per day)) is suggested to replenish decreased concentrations of adenine nucleotides in ADSL-deficient tissues. Adenine can be incorporated into the adenine nucleotides via APRT. It is required to add Allopurinol, in order to avoid conversion of adenine by xanthine oxidase into minimally soluble 2,8-dihydroxyadenine, which forms kidney stones. Only some weight gain and acceleration of growth were noted.

**Anticonvulsive drugs**

ADSL deficiency

There is no effective treatment currently available for ADSL deficiency. Anticonvulsive drugs use is primarily aimed at controlling seizure frequency with minimal side effects.

**Antibiotic prophylaxis**

Activation-induced cytidine deaminase (CDA) deficiency (hyper-IgM syndrome type II)

Patients with hyper-IgM syndrome present with recurrent infections, lymphoid hyperplasia, autoimmune and related inflammatory disorders. Intravenous immunoglobulin therapy and antibiotic prophylaxis improve the clinical scenario in most cases.

**Benzodiazepines**

LND

Treatment with allopurinol or other hypouricemic drugs has no effect on the neurological or behavioral manifestations of the disease. Dopamine replacement therapy in LND patients was proven insufficient. Current treatments are mainly symptomatic. Appropriate restraints and measures should be taken to help diminish

self-mutilation. Diazepam, haloperidol, and barbiturates may sometimes improve choreoathetosis.

**Bone marrow transplantation**

ADA deficiency

Without treatment, ADA deficiency is fatal within the first year of life. Treatment became possible with bone marrow transplantation. Bone marrow/stem cell transplantation is the therapeutic method of choice, with 70 % chance of complete immunological cure when an HLA-identical healthy donor is available. The graft provides stem cells, including T and B cells, which have enough ADA activity to prevent accumulation of adenosine and deoxyadenosine.

ADA2 deficiency

ADA2 is a growth factor for endothelial and leukocyte development and differentiation, as supported by studies in patients and zebrafish. The data also suggest that ADA2 deficiency may compromise endothelial integrity while polarizing macrophage and monocyte subsets toward pro-inflammatory cells, creating a vicious circle of vasculopathy and inflammation. Potential therapeutic strategies may include fresh-frozen plasma or recombinant ADA2 (ADA2 is found in plasma) and bone marrow transplantation (monocytes and macrophages, the main producers of ADA2, derive from bone marrow).

LND

Bone marrow transplantation can restore erythrocyte HGPRT activity.

PNP deficiency

Viral or bacterial infections are responsible for most deaths. Treatments have consisted of bone marrow transplantation and repeated transfusions of normal, irradiated erythrocytes. More recently, matched bone marrow transplantation has been reported successful.

**Chronic deep stimulation of the globus pallidus**

LND

Treatment with allopurinol or other hypouricemic drugs has no effect on the neurological or behavioral manifestations of the disease. Dopamine replacement therapy in LND patients was proven insufficient. Current treatments are mainly symptomatic, either by drugs or the chronic deep brain stimulation of the globus pallidus.

**Discontinuation of 5-Fluorouracil**

DPD deficiency

In adult cancer patients, discontinuation of 5-fluorouracil is advised.

**EE-TP**

Thymidine phosphorylase deficiency

Deficiency in thymidine phosphorylase, which results in accumulation of thymidine, causes MNGIE. MNGIE is an autosomal recessive disease associated with multiple deletions of skeletal muscle mitochondrial DNA. Hemodialysis and platelet infusions have been used unsuccessfully. Allogenic hematopoietic stem cell transplantation (HSCT) has been more successful in halting the clinical course through normalization of cellular nucleotide pools. In some reported cases, enzyme replacement therapy using erythrocyte encapsulated recombinant Escherichia coli TP (EE-TP), has successfully reduced plasma nucleoside concentration with clinical improvement. EE-TP should be considered as a rescue or maintenance therapy. EE-TP should be administered while waiting for an allogeneic HSCT donor or as an alternative therapy for patients who have end-stage disease.

**Erythrocyte encapsulated ADA**

ADA deficiency

Without treatment, ADA deficiency is fatal within the first year of life. Treatment became possible with bone marrow transplantation. Bone marrow/stem cell transplantation is the therapeutic method of choice, with 70 % chance of complete immunological cure when an HLA-identical healthy donor is available. The graft provides stem cells, including T and B cells, which have enough ADA activity to prevent accumulation of adenosine and deoxyadenosine.

Other options include enzyme replacement therapies (ERT) with polyethylene glycol (PEG) modified bovine ADA or with erythrocyte encapsulated ADA. They have been used successfully as primary therapy in certain cases: individuals lacking an HLA-identical donor, when the risks associated with a partially mismatched transplant, or when graft failure is high as in the delayed- or late-onset phenotypes.

**Exercise restriction**

Muscle AMP deaminase deficiency

Symptoms may be gradually progressive, ultimately leading to the inability to dress and walk a few steps due to fatigue and myalgias. Patients should be advised to exercise cautiously to prevent rhabdomyolysis and myoglobinuria.

**FFP**

ADA2 deficiency

ADA2 is a growth factor for endothelial and leukocyte development and differentiation, as supported by studies in patients and zebrafish. The data also suggest that ADA2 deficiency may compromise endothelial integrity while polarizing macrophage and monocyte subsets toward pro-inflammatory cells, creating a vicious circle of vasculopathy and inflammation. Potential therapeutic strategies may include fresh-frozen plasma or recombinant ADA2 (ADA2 is found in plasma) and bone marrow transplantation (monocytes and macrophages, the main producers of ADA2, derive from bone marrow).

**Gene therapy**

ADA deficiency

Without treatment, ADA deficiency is fatal within the first year of life. Treatment became possible with bone marrow transplantation.

Other options include enzyme replacement therapies (ERT) with polyethylene glycol (PEG) modified bovine ADA or with erythrocyte encapsulated ADA. They have been used successfully as primary therapy in certain cases.

Finally, gene therapy is an option first performed in 1990 in two girls with ADA deficiency. Peripheral blood T cells were collected, cultured with interleukin-2, corrected by insertion of the ADA gene by means of a retroviral vector, and reinfused. Total number of infusions was eleven or 12 infusions over two years in each patient. Normalization of the number of T cells was observed, as many cellular and humoral immune responses, without any adverse event. Expression of the retroviral remained present ten years after the last cell infusion. Concomitant PEG-ADA treatment was administered. More recently, successful correction of ADA deficiency has been attained by gene therapy into hematopoietic stem cells, without concomitant PEG-ADA treatment. Gene therapy in X-linked not ADA deficient SCID has been suspended due to the development of leukemia in some cases. A gene therapy protocol consisting of low-intensity, non-myeloablative conditioning prior to the infusion of ADA vector-transduced hematopoietic stem cells, has induced a stable ADA1 expression in lymphoid cells, correction of metabolic abnormalities in erythrocytes and maintenance of good health without the need for ERT. To date, patients with ADA1 deficiency have not developed any lymphoproliferative disorder as a result of this method, as experienced with gene therapy for X-linked SCID.

**Hematopoietic stem cell transplantation**

Thymidine phosphorylase deficiency

Deficiency in thymidine phosphorylase, which results in accumulation of thymidine, causes MNGIE. MNGIE is an autosomal recessive disease associated with multiple

deletions of skeletal muscle mitochondrial DNA. Hemodialysis and platelet infusions have been used unsuccessfully. Allogenic hematopoietic stem cell transplantation (HSCT) has been more successful in halting the clinical course through normalization of cellular nucleotide pools. The main challenges with HSCT appear to be frequent engraftment failure, high mortality rates of up to 50 % and limited matched donor availability.

**High fluid intake**

Adenine Phosphoribosyltransferase deficiency

Allopurinol should be given, as detailed under PRPP synthetase superactivity, in order to inhibit the formation of 2,8-dihydroxyadenine. Even in asymptomatic patients, dietary purine restriction and high fluid intake are recommended. It is not advised to alkalinize urine. Ultimate prognosis depends on renal function at the time of diagnosis.

PRPP synthetase superactivity

A low purine diet (free of organ meats, fishes, dried beans and peas) and high fluid intake can prevent crystallization.

SAHH deficiency

Limitation of dietary methionine and phosphatidylcholine, and/or creatine supplementation may be beneficial. SAM and SAH levels decreased but remained over the normal range. Creatine kinase and liver function remained unchanged. Some patients showed clinical improvements in muscle strength and mental alertness. Developmental delay persisted. Early treatment ameliorates the outcome.

**IVIG**

Activation-induced cytidine deaminase (CDA) deficiency (hyper-IgM syndrome type II)

Patients with hyper-IgM syndrome present with recurrent infections, lymphoid hyperplasia, autoimmune and related inflammatory disorders. Intravenous immunoglobulin therapy and antibiotic prophylaxis improve the clinical scenario in most cases.

**Ketogenic diet**

ADSL deficiency

There is no effective treatment currently available for ADSL deficiency. Anticonvulsive drugs use is primarily aimed at controlling seizure frequency with minimal side effects. In cases of refractory epilepsy, a ketogenic diet has been proposed. This diet has been used as a therapeutic tool in several cases of severe ADSL deficiency. Survival prognosis is variable.

**Low purine diet**

Adenine Phosphoribosyltransferase deficiency

Allopurinol should be given, as detailed under PRPP synthetase superactivity, in order to inhibit the formation of 2,8-dihydroxyadenine. Even in asymptomatic patients, dietary purine restriction and high fluid intake are recommended. It is not advised to alkalinize urine. Ultimate prognosis depends on renal function at the time of diagnosis.

PRPP synthetase superactivity

A low purine diet (free of organ meats, fishes, dried beans and peas) and high fluid intake can prevent crystallization.

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**Orotic acid**

DHODH deficiency

Supplementation with OA or uridine should bypass the enzymatic block. This approach would be unlikely to correct the phenotypic abnormalities because the main and first damage occurs before birth.

**PEG-ADA**

ADA deficiency

Without treatment, ADA deficiency is fatal within the first year of life. Treatment became possible with bone marrow transplantation.

Other options include enzyme replacement therapies (ERT) with polyethylene glycol (PEG) modified bovine ADA or with erythrocyte encapsulated ADA. They have been used successfully as primary therapy in certain cases: individuals lacking an HLA-identical donor, when the risks associated with a partially mismatched transplant, or when graft failure is high as in the delayed- or late-onset phenotypes. PEG-ADA has also been used as a secondary therapy in patients with graft failure or absence of acceptable recovery of immune function following experimental gene therapy. However, its use remains limited by the presence of neutralizing antibodies against the bovine enzyme, autoimmunity and the high cost of lifelong therapy.

If no histocompatible bone marrow donor is available, enzyme replacement therapy can be given. Repeated partial exchange transfusions with normal erythrocytes

result in marked clinical and immunological improvement in some patients, but is not sustained. Covalent attachment of PEG to bovine ADA results in marked extension of its half-life, and reduction of immunogenicity. Weekly to bi-weekly intramuscular injections of 15–30 units of PEG-ADA per kg result in mostly marked clinical improvement. In vitro immune function also significantly improves.

**Recombinant ADA2**

ADA2 deficiency

ADA2 is a growth factor for endothelial and leukocyte development and differentiation, as supported by studies in patients and zebrafish. The data also suggest that ADA2 deficiency may compromise endothelial integrity while polarizing macrophage and monocyte subsets toward pro-inflammatory cells, creating a vicious circle of vasculopathy and inflammation. Potential therapeutic strategies may include fresh-frozen plasma or recombinant ADA2 (ADA2 is found in plasma) and bone marrow transplantation (monocytes and macrophages, the main producers of ADA2, derive from bone marrow).

**Repeated transfusions of normal irradiated erythrocytes**

PNP deficiency

Viral or bacterial infections are responsible for most deaths. Treatments have consisted of bone marrow transplantation and repeated transfusions of normal, irradiated erythrocytes. More recently, matched bone marrow transplantation has been reported successful.

**Ribose**

ADSL deficiency

There is no effective treatment currently available for ADSL deficiency. Oral administration of ribose (10 mmol/kg per day) has been reported to reduce seizure frequency.

Ectosolic 5'-Nucleotidase

The diagnosis of eN gain- or loss-of-function is based on the measurement of 5'-nucleotidase activity in cultured fibroblasts, in addition to the identification of the involved isoenzyme. Administration of uridine or UMP plus CMP or ribose was a successful treatment for the symptoms of NAPDD. In NAPDD patients, a slight decrease in uridylate is measured, and it may be corrected uridine. However, uridine is transported by the same system active on adenosine. Thus, an excess of the pyrimidine nucleoside might interfere with adenosine trafficking across the cell membranes and consequently with its function in neurodevelopment and inflammation.

Muscle AMP deaminase deficiency

Symptoms may be gradually progressive, ultimately leading to the inability to dress and walk a few steps due to fatigue and myalgias. Administration of ribose (2–60 g per day orally in divided doses) may improve muscular strength and endurance. In general, triggers such as exercise should be avoided.

**SAM supplementation**

PRPP synthetase superactivity

Dietary S-adenosylmethionine (SAM) supplementation, known to cross the blood–brain barrier, could lessen some neurologic symptoms in individuals with the severe phenotype by providing an oral source of purine nucleotide precursor that is not PRPP dependent.

PRPP synthetase recuced activity

SAM supplementation has been used with some success for treatment in two Arts syndrome patients by replenishing purine nucleotides. Among purines, SAM is unique in that it crosses both the gut and the blood–brain barrier, where it becomes a source of adenosine which can be salvaged to form purine nucleotides via adenosine kinase. Additionally, the external provision of SAM may diminish needs of cells that maintain an energy-dependent methylation cycle.

**UMP + CMP**

Ectosolic 5'-Nucleotidase

The diagnosis of eN gain- or loss-of-function is based on the measurement of 5'-nucleotidase activity in cultured fibroblasts, in addition to the identification of the involved isoenzyme. Administration of uridine or UMP plus CMP or ribose was a successful treatment for the symptoms of NAPDD. In NAPDD patients, a slight decrease in uridylate is measured, and it may be corrected uridine. However, uridine is transported by the same system active on adenosine. Thus, an excess of the pyrimidine nucleoside might interfere with adenosine trafficking across the cell membranes and consequently with its function in neurodevelopment and inflammation.

**Uridine**

ADSL deficiency

There is no effective treatment currently available for ADSL deficiency. Uridine (2 mmol/kg per day) also had a slight beneficial effect.

Cytosolic 5’-Nucleotidase superactivity

Uridine at the dose of 1 g/kg per day can help developmental improvement, and a decrease in frequency of seizures and infections.

DHODH deficiency

Supplementation with OA or uridine should by-pass the enzymatic block. This approach would be unlikely to correct the phenotypic abnormalities because the main and first damage occurs before birth.

Ectosolic 5'-Nucleotidase

The diagnosis of eN gain- or loss-of-function is based on the measurement of 5'-nucleotidase activity in cultured fibroblasts, in addition to the identification of the involved isoenzyme. Administration of uridine or UMP plus CMP or ribose was a successful treatment for the symptoms of NAPDD. In NAPDD patients, a slight decrease in uridylate is measured, and it may be corrected uridine. However, uridine is transported by the same system active on adenosine. Thus, an excess of the pyrimidine nucleoside might interfere with adenosine trafficking across the cell membranes and consequently with its function in neurodevelopment and inflammation.

UMP Synthase Deficiency (Hereditary Orotic Aciduria)

The enzyme defect can be bypassed by uridine, which is converted into UMP. An initial dose of 100-150 mg/kg can help with a better hematologic response, acceleration of growth and psychomotor development. One should aim to reach the lowest possible output of orotic acid.

**Urine alkalinization**

PRPP superactivity

Urine alkalinization should be considered, by administering sodium bicarbonate, potassium citrate or citrate mixtures to bring urinary pH to 6.0-6.5: indeed, uric acid and xanthine are more soluble at alkaline pH. Adequate control of uricemia prevents gouty arthritis and urate nephropathy.

## Section 3.0 Key Recommendations Synthesis

A decreased or an increased activity of an enzyme involved in the metabolism of purine and pyrimidine leads to abnormal concentrations of P/P and/or their metabolites in cells or body fluids. More than 35 defects involved in the metabolism of purines and pyrimidines have been documented. Some are relatively benign and non-disease causing. Others may be responsible for severe, life-threatening or devastating conditions.

There are no specific guidelines for the treatment of inborn errors of purine and pyrimidine metabolism in Saudi Arabia, in Europe, in the United States of America or internationally.

Treatment is tailored to each enzymatic defect.

Hyperuricemia, associated with P/P metabolism disorders, is treated with Xanthine oxidase inhibitors.

Non-hyperuricemic inborn errors require other specific treatment measures, drugs or supplementation.

Here is a brief summary:

**Adenine**

ADSL deficiency
Adenine replenishes decreased concentrations of adenine nucleotides in ADSL-deficient tissues.

**Anticonvulsive drugs**

ADSL deficiency
Anticonvulsive drugs control seizure frequency with minimal side effects.

**Antibiotic prophylaxis**

Activation-induced cytidine deaminase (CDA) deficiency (hyper-IgM syndrome type II)

Antibiotic prophylaxis improves the clinical scenario in most cases.

**Benzodiazepines**

LND

Diazepam, haloperidol and barbiturates may sometimes improve choreoathetosis.

**Bone marrow transplantation**

ADA deficiency

The graft provides stem cells which have enough ADA activity to prevent accumulation of adenosine and deoxyadenosine.

ADA2 deficiency

Potential therapeutic strategies may include bone marrow transplantation.

LND

Bone marrow transplantation can restore erythrocyte HGPRT activity.

PNP deficiency

Treatments have consisted of bone marrow transplantation. More recently, matched bone marrow transplantation has been reported successful.

**Chronic deep stimulation of the globus pallidus**

LND
Current treatments are mainly symptomatic by the chronic deep brain stimulation of the globus pallidus.

**Discontinuation of 5-Fluorouracil**

DPD deficiency

In the adult cancer patients, discontinuation of 5-fluorouracil is advised.

**EE-TP**

Thymidine phosphorylase deficiency

Enzyme replacement therapy using erythrocyte encapsulated recombinant Escherichia coli TP (EE-TP), has successfully reduced plasma nucleoside concentration with clinical improvement.

**Erythrocyte encapsulated ADA**

ADA deficiency

ERT with PEG modified bovine ADA or with erythrocyte encapsulated ADA.

**Exercise restriction**

Muscle AMP deaminase deficiency

Patients should be advised to exercise cautiously to prevent rhabdomyolysis and myoglobinuria.

**FFP**

ADA2 deficiency

Potential therapeutic strategies may include fresh-frozen plasma.

**Gene therapy**

ADA deficiency

A gene therapy protocol consisting of low-intensity, non-myeloablative conditioning prior to the infusion of ADA vector-transduced hematopoietic stem cells, has induced a stable ADA1 expression in lymphoid cells, correction of metabolic abnormalities in erythrocytes and maintenance of good health without the need for ERT.

**Hematopoietic stem cell transplantation**

Thymidine phosphorylase deficiency

HSCT has been more successful in halting the clinical course through normalization of cellular nucleotide pools.

**High fluid intake**

Adenine Phosphoribosyltransferase deficiency

Even in asymptomatic patients, high fluid intake is recommended.

PRPP synthetase superactivity

A low purine diet (free of organ meats, fishes, dried beans and peas) and high fluid intake can prevent crystallization.

SAHH deficiency

Early treatment ameliorates the outcome.

**IVIG**

Activation-induced cytidine deaminase (CDA) deficiency (hyper-IgM syndrome type II)

Intravenous immunoglobulin therapy improves the clinical scenario in most cases.

**Ketogenic diet**

ADSL deficiency

A ketogenic diet has been proposed. This diet has been used as a therapeutic tool in several cases of severe ADSL deficiency.

**Low purine diet**

Adenine Phosphoribosyltransferase deficiency

Dietary purine restriction is recommended.

PRPP synthetase superactivity

A low purine diet (free of organ meats, fishes, dried beans and peas) and high fluid intake can prevent crystallization.

SAHH deficiency

Early treatment ameliorates the outcome.

**Orotic acid**

DHODH deficiency

Supplementation with OA or uridine should by-pass the enzymatic block.

**PEG-ADA**

ADA deficiency

ERT with PEG modified bovine ADA or with erythrocyte encapsulated ADA has been used successfully as primary therapy in certain cases.

**Recombinant ADA2**

ADA2 deficiency

Potential therapeutic strategies may include recombinant ADA2.

**Repeated transfusions of normal irradiated erythrocytes**

PNP deficiency

Treatments have consisted of repeated transfusions of normal, irradiated erythrocytes.

**Ribose**

ADSL deficiency

Oral administration of ribose has been reported to reduce seizure frequency.

Ectosolic 5'-Nucleotidase

Administration of uridine or UMP plus CMP or ribose was a successful treatment for the symptoms of NAPDD.

Muscle AMP deaminase deficiency

Administration of ribose may improve muscular strength and endurance. **SAM supplementation**

PRPP synthetase superactivity

Dietary S-adenosylmethionine (SAM) supplementation could lessen some neurologic symptoms in individuals with the severe phenotype by providing an oral source of purine nucleotide precursor that is not PRPP dependent.

PRPP synthetase recuced activity

SAM supplementation has been used with some success for treatment in two Arts syndrome patients by replenishing purine nucleotides.

**UMP + CMP**

Ectosolic 5'-Nucleotidase

Administration of uridine or UMP plus CMP or ribose was a successful treatment for the symptoms of NAPDD.

**Uridine**

ADSL deficiency
Uridine had a slight beneficial effect.

Cytosolic 5'-Nucleotidase superactivity

Uridine can help developmental improvement, and a decrease in frequency of seizures and infections.

DHODH deficiency

Supplementation with uridine should by-pass the enzymatic block.

Ectosolic 5'-Nucleotidase

Administration of uridine or UMP plus CMP or ribose was a successful treatment for the symptoms of NAPDD.

UMP Synthase Deficiency (Hereditary Orotic Aciduria)

The enzyme defect can be by-passed by uridine, which is converted into UMP.

**Urine alkalinization**

PRPP superactivity

Urine alkalinization should be considered, by administering sodium bicarbonate, potassium citrate or citrate mixtures to bring urinary pH to 6.0-6.5.

## Section 4.0 Conclusion

The recommendations provided in this report are intended to assist in the management of inborn errors of P/P metabolism.

These recommendations should be used to support and not supplant decisions in individual patient management.

## Section 5.0 References


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# Section 6.0 Appendices

## Appendix A. Prescribing Edits Definition

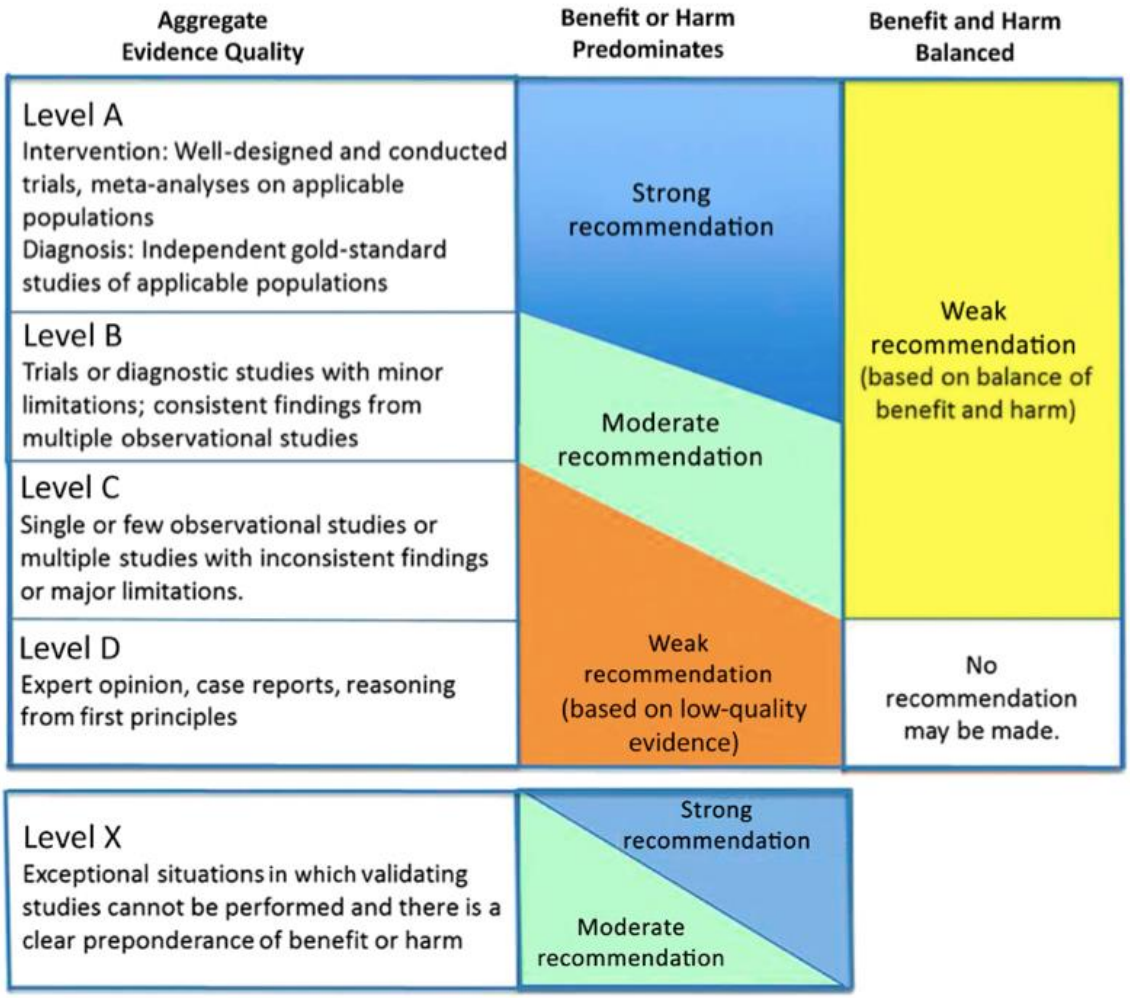
Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

| Prescribing edits Tools | Description |
|---|---|
| **AGE (Age):** | Coverage may depend on patient age |
| **CU (Concurrent Use):** | Coverage may depend upon concurrent use of another drug |
| **G (Gender):** | Coverage may depend on patient gender |
| **MD (Physician Specialty):** | Coverage may depend on prescribing physician's specialty or board certification |
| **PA (Prior Authorization):** | Requires specific physician request process |
| **QL (Quantity Limits):** | Coverage may be limited to specific quantities per prescription and/or time period |
| **ST (Step Therapy):** | Coverage may depend on previous use of another drug |
| **EU (Emergency Use only):** | This drug status on Formulary is only for emergency use |
| **PE (Protocol Edit):** | Use of drug is dependent on protocol combination, doses and sequence of therapy |

## Appendix B. PubMed Search Methodology Terms

| Query | Filters | Search Details | Results |
|---|---|---|---|
| (((((((((Severe Combined Immunodeficiency[MeSH Terms]) OR (Combined Immunodeficiency, Severe[Title/Abstract])) OR (Immunodeficiencies, Severe Combined[Title/Abstract])) OR (Severe Combined Immunodeficiencies[Title/Abstract])) OR (Immunodeficiency Syndrome, Severe Combined[Title/Abstract])) OR (Severe Combined Immunodeficiency Syndrome[Title/Abstract])) OR (Severe Combined Immunologic Deficiency[Title/Abstract])) OR (Severe Combined Immune Deficiency[Title/Abstract])) OR (Familial Reticuloendothelioses[Title/Abstract])) OR (Syndrome, Omenn[Title/Abstract]) | In the last 5 years | ("severe combined immunodeficiency"[MeSH Terms] OR "combined immunodeficiency severe"[Title/Abstract] OR "immunodeficiencies severe combined"[Title/Abstract] OR "severe combined immunodeficiencies"[Title/Abstract] OR "immunodeficiency syndrome severe combined"[Title/Abstract] OR "severe combined immunodeficiency syndrome"[Title/Abstract] OR "severe combined immunologic deficiency"[Title/Abstract] OR "severe combined immune deficiency"[Title/Abstract] OR (("familialities"[All Fields] OR "familiality"[All Fields] OR "familially"[All Fields] OR "familials"[All Fields] OR "familie"[All Fields] OR "family"[MeSH Terms] OR "family"[All Fields] OR "familial"[All Fields] OR "families"[All Fields] OR "family s"[All Fields] OR "familys"[All Fields]) AND "Reticuloendothelioses"[Title/Abstract]) OR "syndrome omenn"[Title/Abstract]) AND (y_5[Filter]) | 686 |

## Appendix C. Level of Evidence




| Statement | Definition | Implication |
|---|---|---|
| Strong recommendation | A particular action is favored because anticipated benefits clearly exceed harms (or vice versa), and quality of evidence is excellent or unobtainable. | Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present. |
| Moderate recommendation | A particular action is favored because anticipated benefits clearly exceed harms (or vice versa), and the quality of evidence is good but not excellent (or is unobtainable). | Clinicians would be prudent to follow a moderate recommendation but should remain alert to new information and sensitive to patient preferences. |
| Weak recommendation (based on low-quality evidence) | A particular action is favored because anticipated benefits clearly exceed harms (or vice versa), but the quality of evidence is weak. | Clinicians would be prudent to follow a weak recommendation but should remain alert to new information and sensitive to patient preferences. |
| Weak recommendation (based on balance of benefits and harms) | A weak recommendation is provided when the aggregate database shows evidence of both benefit and harm that appears to be similar in magnitude for any available courses of action. | Clinicians should consider the options in their decision-making, but patient preference may have a substantial role. |

# Appendix D. Summary Table of Treatable Purine and Pyrimidine Metabolism Disorders

Treatable inborn errors of P/P metabolism.

| Disease group | P/P defects | Treatment | Outcomes |
|---|---|---|---|
| Severe combined immunodeficiency (SCID) | • Adenosine deaminase deficiency (ADA deficiency)<br>• Purine nucleoside phosphorylase deficiency (PNP deficiency) | • ERT with PEG-ADA<br>• allogenic HSCT<br>• autologous GT | • ERT with PEG-ADA: improves endogenous immune function and helps in recovery from infections, however only suboptimal immune reconstitution<br>• HSCT: better overall survival<br>• GT: reduced rate of infections, robust immune reconstitution |
| Disorders associated with overexcretion of insoluble purines and nephrological consequences | Uric acid:<br>• Hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency complete & partial<br>• Phosphoribosylpyrophosphate synthase (PRPS) superactivity<br>2,8-dihydroxyadenine:<br>• Adenine phosphoribosyltransferase (APRT) deficiency (2,8-diOH-adeninuria)<br>Xanthine:<br>• Xanthine dehydrogenase (XDH) deficiency (xanthinuria-I) | • XOR inhibitors (*e.g.*, allopurinol)<br>• high-fluid intake<br>• alkalization of the urine by administration of bicarbonate or citrate (not successful in APRT deficiency)<br>• low-purine diet | • prevention of renal failure from crystal nephropathy<br>• improvement of renal function |
| Disorders associated with hematological manifestations | Uridine monophosphate synthase (UMPS) deficiency (orotic aciduria) | • supplementation with uridine | • induces prompt hematological response and acceleration of growth<br>• does not prevent suboptimal physical and mental development |
| Pharmacogenetic syndromes | • Dihydropyrimidinase (DHP) deficiency (dihydropyrimidinuria)<br>• Dihydropyrimidine dehydrogenase (DPD) deficiency (thymine-uraciluria)<br>• Ureidopropionase (UP) deficiency (NC-BALA amidohydrolase deficiency, ureidopropionic aciduria)<br>• Thiopurine methyltransferase (TPMT) deficiency | • withdrawal of offending drug<br>• dose adjustment | • prevention of pharmacogenetic syndrome |
| Other | • CAD deficiency | • uridine supplementation | • immediate cessation of seizures<br>• resolution of anisopoikylocytosis<br>• improved development |
| | • TP deficiency (MNGIE) | • HSCT<br>• OLT | • effective in permanently restoring the biochemical imbalance<br>• risk for complications and mortality related to HSCT<br>• metabolic complications chronic kidney insufficiency, diabetes or cardiovascular disease related to life-long immunosuppressive therapy |

ERT: enzyme replacement therapy; GT: gene therapy; HSCT: hematopoietic stem cell transplant; OLT: orthotopic liver transplantation; PEG-ADA: polyethylene glycol-conjugated adenosine deaminase; XOR: xanthine oxidoreductase.

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