Arrhythmias and Electrolyte Imbalances as Consequences of Cancer

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Both arrhythmias and electrolyte imbalances are rather frequent consequences of cancer itself and of cancer treatments (and their side effects). Arrhythmias may be also a consequence of electrolyte imbalance.

5.1 Arrhythmias

(See Chap. 11 for more detailed information).

- **Sinus tachycardia** is frequently observed in patients with anemia, pleural or pericardial effusion, mediastinal masses, and lung tumors (both primary and secondary). It is a compensatory mechanism, which does not need any treatment as far as is well tolerated. However, a rest heart rate constantly >110/m', which raises >120–130 at any minimal effort, may be very uncomfortable for the patient.
  - **Treatment:**
    - Try to correct the underlying conditions (anemia, hypoxia…).
    - Low-dose beta-blockers (bisoprolol 1.25 mg/day or more).
    - If beta-blockers are not tolerated because of low blood pressure, ivabradine 5 or 7.5 mg, twice a day, is a good option.
- **Atrial fibrillation (AF)** is more frequent in patients with a cancer history in general, mostly with lung and colorectal cancer, after thoracic surgery, and in neoplastic involvement of the heart [1–4]. A condition possibly linking cancer to AF is chronic inflammation, which increases both cancer and AF risk [5–7]. An association of bisphosphonate use and risk of AF has been reported; bisphosphonate are used in high doses in treatment of bone metastasis and hypercalcemia. In a study of 3981 cancer patients exposed to intravenous bisphosphonate, 128 (3.2 %) developed AF/flutter [8].
- It should be reverted to sinus rhythm, if possible, to avoid the risk of thromboembolism and the need of anticoagulation. Moreover, in a recent prospective single-center study, AF after pulmonary lobectomy for lung cancer affected hospital morbidity and mortality, and long-term outcome in 5-year survivors [9].
  - **Treatment:**
    - In a study on lung cancer patients undergoing lung surgery and who had elevated N-terminal pro-brain natriuretic peptide levels in the perioperative period, both beta-blockers (BBs) and losartan significantly reduced the incidence of postoperative AF [10].
    - Amiodarone is able to lower the incidence of AF from 39.2 to 8.3 % and appeared to be safe with no major complications in patients undergoing lung surgery [11]. It is recommended in patients with low blood pressure.
    - Flecainide, dofetilide, propafenone, and IV ibutilide are useful for cardioversion of AF or atrial flutter, provided contraindications to the selected drug are absent [12].
    - Since many cancer patients are elderly, with possible comorbidities, amiodarone is the drug of choice in case of new onset AF if cardiac function is not known, and in older patients.
- **Ventricular arrhythmias (VA)** are most frequently observed as a consequence of some antineoplastic treatments (see Chap. 11 for more detailed information) or of electrolyte imbalances. Also ventricular tumors may present with VA. In presence of frequent VA, a careful assessment of both possible predisposing factors and risk of sudden death should be carried out [13].

- **Treatment**
  - Check serum electrolytes, including magnesium, and correct any abnormality (see below).
  - Beta-blockers are the first choice in case of frequent and/or symptomatic VA and in patients with ischemic heart disease. Advantages are the rapid effect, the short half-life (should the therapy be changed). The main disadvantage is that BBs are not well tolerated by hypotensive patients.
  - Amiodarone may be a therapeutic choice, unless in presence of QT interval prolongation or thyroid dysfunction. However, the long half-life may be a contraindication in some patients.

5.2 Electrolyte Imbalances

Wide, even rapid, changes in blood electrolytes are rather common in cancer patients, both as a consequence of the disease itself (malnutrition) and of the antineoplastic treatments, both surgical and pharmacological [14]. The sodium and potassium serum level are among the factors predictive of outcome after surgery for gastroesophageal cancer [15, 16].

Electrolyte abnormalities are among the most common causes of cardiac arrhythmias. Of all the electrolyte abnormalities, hyperkalemia and hypercalcemia are the most rapidly fatal.

5.2.1 Hypokalemia

Hypokalemia is a common consequences of vomiting, diarrhea, fluid load, drugs, and some antineoplastic treatments [1]. It may be due to some neuroendocrine tumors [2, 3]. Hypokalemia increases the risk of ventricular arrhythmias [17].

Hypokalemia is defined as a serum potassium level <3.5 mEq/L.

Clinical Manifestations

Hypokalemia may cause weakness, paralysis, muscle cramps, respiratory failure, and constipation.

ECG changes including U waves, T-wave flattening, arrhythmias prevalently ventricular (especially if concomitant digoxin therapy), and asystolia.

Treatment

- Both enteral and parenteral potassium administration are equally effective in restoring serum potassium levels [18].
- Potential adverse effects with enteral administration include unpalatable taste, nausea, and abdominal discomfort.
- Adverse effects with intravenous administration include venous sclerosis, infusion-related pain, and phlebitis when delivered via peripheral vein and the risk of cardiac arrest due to excessive infusion rates when administered via a central intravenous catheter.
- Continuous ECG monitoring is essential during IV infusion, and the dose should be titrated after repeated sampling of serum potassium levels.

- If occurs ventricular arrhythmias or imminent arrest give infusion of 2 mEq/min, followed 10 mEq IV over 5–10 min.
- The mean dose–response per 20 mmol of potassium chloride is 0.25–0.27 mmol/L.

5.2.2 Hyperkalemia

Hyperkalemia may be due to renal insufficiency, tissue breakdown (rhabdomyolysis, tumor lysis, hemolysis), metabolic acidosis, drugs, abnormal erythrocytes, or thrombocytosis. It may cause severe ventricular arrhythmias and cardiac arrest; it is the most common electrolyte disorder associated with cardiopulmonary arrest.

Hyperkalemia is defined as a serum potassium >5.0 mEq/L.

Clinical Manifestations

Severe hyperkalemia may cause weakness, flaccid paralysis, depressed deep tendon reflexes, respiratory failure, and asystolic and cardiac arrest.

ECG changes including peaked T waves (tenting) and-when serum potassium increases-flattened or absent P waves, a prolonged PR interval, widened QRS complex, deepened S waves, merging of S and T waves, idioventricular rhythms, and asystolia.

Treatment [19, 20]

- **Mild hyperkalemia** (serum level <6 mEq/L):
  - Intravenous furosemide: 40–80 mg ev.
  - Potassium exchange resins, i.e., calcium resonium 15–30 g or sodium polystyrene sulfonate (Kayexalate®) 15–30 g in 50–100 mL of 20 % sorbitol, given either orally or by retention enema (onset in 1–3 h, maximal effect at 6 h).
  - Dialysis: hemodialysis is more efficient than peritoneal dialysis at removing potassium (immediate onset, 25–30 mmol potassium h^{-1} removed with hemodialysis).
- **Moderate forms** (serum level 6–7 mEq/L):
  - A solution of glucose 50 mg plus rapid acting insulin 10 units given intravenously over 15–30 min (onset in 15–30 min, maximal effect at 30–60 min; monitoring blood glucose).
  - Intravenous NaCO3 50 mEq ev in 5 min.
  - Use in addition to removal strategies above.
- **In more severe cases** (serum K+ >7 mEq/L):
  - Salbutamol, 5 mg nebulized. Several doses may be required (onset in 15–30 min).
  - Sodium bicarbonate plus glucose/insulin as above (onset in 15–30 min).
  - $CaCl^{-}$ 10 % (5–10 mL intravenously in 2–5 min) to prevent arrhythmias as membrane stabilizer (to be noticed: this does not lower K+ levels).
- **In case of cardiac arrest,** protect the heart first, then apply shifting and removal strategies using:
  - **Calcium chloride:** 10 mL of 10 % calcium chloride IV by rapid bolus injection to antagonize the toxic effects of hyperkalemia at the myocardial cell membrane.
  - **Sodium bicarbonate:** 50 mmol IV by rapid injection (if severe acidosis or renal failure).

- **Dextrose/insulin:** 10 units short-acting insulin and 50 g glucose IV by rapid injection.
- **Hemodialysis:** consider this for cardiac arrest induced by hyperkalemia, which is resistant to medical treatment.

5.2.3 Hypercalcemia

Hypercalcemia is the most common life-threatening metabolic disorder associated with cancer, occurring in approximately 10–30 % of all patients with neoplastic disease especially with skeletal metastases [21]. It may be humoral due to secretion of the parathormone-like 1,25-dihydroxy vitamin D or PTH-related protein (PTHrP), or secondary to extensive bone lysis (in multiple myeloma, breast cancer bone metastases). PTHrP-secreting tumors may be lymphomas; squamous cancer of the lung, esophagus, head, and neck; gynecologic malignancies, breast cancer, and renal carcinomas. A serum calcium >14 mg/dL may cause acute renal failure and cardiac arrest. It should be promptly treated even in absence of any symptom [22].

Hypercalcemia is defined as serum calcium concentration >10.5 mEq/L.

Clinical Manifestations

Hypercalcemia may cause somnolence, confusion, depression, psychosis, muscle weakness, coma; constipation, anorexia, nausea, abdominal pain, peptic ulcer disease, pancreatitis, polyuria, polydipsia, nephrolithiasis, nephrocalcinosis, and renal failure; hypertension and digitalis sensitivity; and osteoporosis, fracture, and bone pain.

ECG changes including QT interval shortening, atrioventricular block, prolonged PR and QRS intervals, and increased QRS voltage.

Treatment [19, 20]

- **Intravenous isotonic saline** solutions to reverse volume depletion will often lower the serum calcium 1–2 mg/dL as a consequence of expanding the intravascular space. Approximately 3–6 L of intravenous fluid during the initial 24-h period have been recommended.
  - Caution should be exercised in administering large volumes and high rates of intravenous fluid because of the likelihood of producing congestive heart failure and third spacing, particularly in malignancy-associated hypercalcemia, where patients tend to be quite ill and often have concomitant hypoalbuminemia.
- Some authors recommend rehydration with no more than 75–150 mL/h of 0.9 % sodium chloride in this patient population and avoidance of saline-induced diuresis [23].
- Further decreases in the serum calcium can be achieved by infusing intravenous saline to induce a diuresis, though this is not a consistent finding.
- **Furosemide** was used in the past to reduce calcium reabsorption in the loop of Henle and thus augment calciuresis. However it is no longer recommended (unless needed to reverse overly aggressive fluid replacement) as excessive diuresis may lead to volume depletion, hypokalemia, and worsening hypercalcemia.
- **Bisphosphonates** are pyrophosphate analogues that are deposited in bone and lower serum calcium levels via multiple effects on osteoclasts, one of which is inhibition of osteoclastic bone resorption. They are the most used treatment for cancer hypercalcemia, mostly if due to bone lysis.

- Zoledronic acid (3–4 mg intravenously in 100 mL of saline over 15–30 min) is the most powerful biphosphonate and has a rapid and durable effect. In several studies, it performed better than other agents, by reducing the number of skeletal-related events, preventing recurrence of hypercalcemia and exhibiting a longer duration of response. Adverse effects are pyrexia, skeletal pain, nausea, and asthenia [24].
- Pamidronate is also highly effective and show a durable response. It is given at doses of 60–90 mg intravenously in 2–24 h. Its effect is not as prompt as zoledronic acid.
- Salmon calcitonin is useful for treatment of severe hypercalcemia irrespective of etiology, given its early onset of action and relatively mild adverse effects. It begins working within several hours and lowers plasma calcium levels by 1–2 mg/dL only. However, when calcitonin is given along with intravenous fluid therapy, the combination may be sufficient to reverse the immediate risks of severe hypercalcemia. It may be considered in the emergency setting, as an early intervention if biphosphonate are not available. Recommended doses are 4–8 units subcutaneously (or intranasal, less used) every 6–12 h. Side effects include nausea, vomiting, flushing, and injection site reactions, while intranasal form can be associated with rhinitis. Hypersensitivity reactions can occur.

5.2.4 Hypocalcemia

Hypocalcemia may occur in acute pancreatitis, tumor lysis syndrome, rhabdomyolysis, and toxic shock syndrome. Hypocalcemia can exacerbate digitalis cardiotoxicity.

Hypocalcemia is defined as a serum calcium concentration <8 mg/dL.

Clinical Manifestations

Hypocalcemia may cause tetany, seizures, and cardiac arrest.

ECG changes including prolonged QT interval, T-wave inversion, AV heart block, and ventricular fibrillation.

Treatment

- Calcium chloride 10 %: 10–40 mL intravenously
- Magnesium sulfate 50 %: 2–4 g if needed

5.2.5 Hypomagnesemia

Hypomagnesemia is a common consequence of decreased absorption or increased loss of magnesium from the kidneys or intestines such as diarrhea, abnormalities of thyroid hormones, or some drugs (e.g., pentamidine, diuretics, alcohol) and malnourishment.

Hypomagnesemia is defined as a serum magnesium concentration <1.3 mEq/L.

Clinical Manifestations

Hypomagnesemia may cause muscle tremor, nystagmus, tetany, and mental status alterations.

ECG changes including prolonged PR and QT interval, T-wave inversion, widening of QRS, torsades de pointes, and ventricular tachycardias.

Treatment [19, 20]

- 1–2 g of MgSO4 bolus IV in 15 min
- If there are convulsions 2 g of MgSO4 iv in 10 min
- Calcium gluconate when associated hyocalcemia

5.2.6 Hypermagnesemia

Hypermagnesemia is the most common consequences of renal failure but may be iatrogenic with intake of food or continuous use of laxative.

Hypermagnesemia is defined as a serum magnesium concentration >2.2 mEq/L.

Clinical Manifestations

Hypermagnesemia may cause muscular weakness, paralysis, ataxia, drowsiness, confusion, and hypotension. High serum magnesium levels may induce a depressed level of consciousness, hypoventilation, and cardiac arrest.

ECG changes including prolonged PR and QT intervals, bradycardia, block AV, and cardiac arrhythmias.

Treatment

- $CaCl^{-}$ 10 % (5–10 mL intravenous) to prevent arrhythmias as membrane stabilizer.
- Dialysis is the treatment of choice in severe hypermagnesemia.
- Saline solution 0.9 %.
- Forced diuresis with furosemide 1 mg/kg.

5.2.7 Hyponatremia

Hyponatremia is a common electrolyte disorder representing an excess of water relative to total body solute, may be due to heart failure, liver cirrhosis, renal failure, hypothyroidism, and non-osmotic vasopressin activity determined by malignancies, infections, and drugs as diuretics but also antineoplastic agents as cyclophosphamide, cisplatin, vincristine, and ifosfamide [25–27].

Hyponatremia is defined as a serum sodium concentration <135 mEq/L.

Clinical Manifestations

It is usually asymptomatic, but acute or serious hyponatremia can cause brain edema with severe symptoms as decreased consciousness, seizures, and muscle rigidity. Other symptoms are nausea and vomiting, headache, muscle weakness, cramps, and spasm.

Treatment [25, 26]

Different strategies have been proposed to treat hyponatremia.

- In the setting of severe symptoms, infusion of hypertonic saline intravenous is recommended, having a concentration of 3 % infused at 1 mEq/L/h until restoring neurological symptoms then continue at 0.5 mEq/L/h.

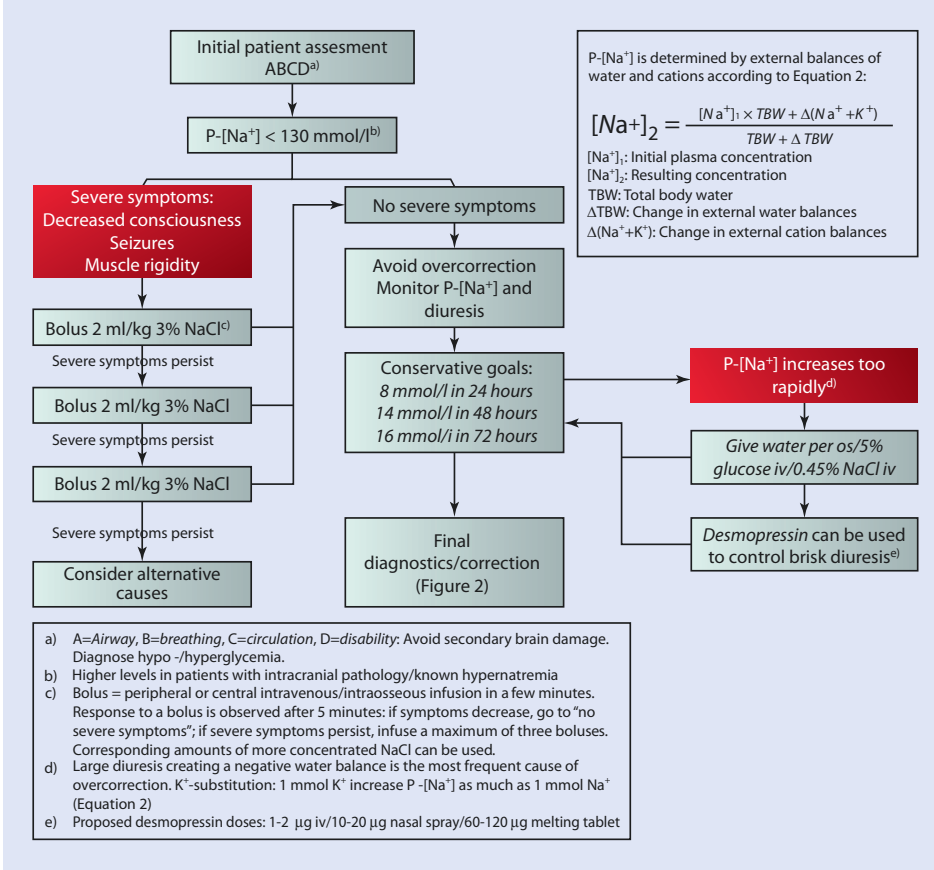

Fig. 5.1 Reproduced from Overgaard-Steensen and Ring [25], published under CC BY 4.0 license
► http://ccforum.biomedcentral.com/articles/10.1186/cc11805

- For euvolemic and hypervolemic asymptomatic hyponatremia fluid restriction are recommended as first treatment.
- Saline solution 0.9 % infusion is recommended calculated with Adrogue–Madias formula (Fig. 5.1).
- Infusion usually varied between 8 and 12 mmol/L during the first 24 h and 18 mmol/L during the first 48 h regardless if hyponatremia was acute or chronic.
- Stricter limit of <8 mmol/L during the first 24 h in cases where the patient was believed to be high risk for developing osmotic demyelination syndrome.

5.2.8 Hypernatremia

Hypernatremia is a rare electrolyte imbalances resulting in three situations [25, 28]:

(a) **Water and solute loss** occurs when hypovolemia is present due to critical illness, sedation, neurological impairment, fever, and gastrointestinal loss of hypotonic fluid.

(b) **Pure water loss** occurs when water balance is negative with reduced water intake as in patients with critical illness and occasionally diabetes insipidus and infants.
(c) **Increased total body solutes** are rare, usually due to infusion of hypertonic potassium-containing solutions, hypertonic saline, and NaHCO3 treatment.

Hypernatremia is defined as a serum concentration above the normal range of 135 to 145 mEq/L.

Clinical Manifestations

Hypernatremia may cause cerebral symptoms as decreased level of consciousness, irritability, hyperreflexia, spasticity, and seizures.

Treatment [28]

(a) **Water and solute loss.**
- Restoring extracellular volume by infusing intravenous saline (see above).

(b) **Pure water loss.**
- Restoring of the water loss.

(c) **Increased total body solutes.**
- Reduce input and increase output with diuretics or rarely dialysis (with caution!). No optimal correction rate has been determined, but it has been suggested that it should not exceed 0.5 mmol/L/h.

5.2.9 Hyperphosphatemia

Hyperphosphatemia may be observed in chronic kidney disease and after cancer treatments; it has been associated to a poorer cancer prognosis [29]. Its more severe form is observed in the tumor lysis syndrome (see below).

Clinical Manifestations

Arrhythmias, lethargy, seizures, nausea, and vomiting.

Treatment

- Diet with no added phosphate in replacement fluids.
- Use of phosphate binders.
- Prevention of oliguria.
- Using diuretics to minimize the risk for calcium phosphate precipitation in renal tubules.
- Dialysis is useful in phosphate removal and continuous venovenous hemofiltration are the therapy of choice.

5.3 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is a potentially life-threatening metabolic disorder occurring after massive lysis of tumor cells. It is more frequent after antineoplastic treatments, but it may develop also spontaneously in tumors with rapid tumor cell turnover, such as Burkitt's

Table 5.1 Definitions of laboratory tumor lysis syndrome (LTLS)

Author	Cairo–Bishop	Montesinos	Howard	
			Adults	Children
Uric acid	$x \geq 476$ µmol/L or 25 % increase from baseline	>7.5 mg/dL	>8 mg/dL	>ULN
Potassium	$x \geq 6.0$ mmol/L or 25 % increase from baseline	>5 mEq/L	>6 mmol/L	
Phosphate	$x \geq 2.1$ mmol/L (children), $x \geq 1.45$ mmol/L (adults) or 25 % increase from baseli	>5 mg/dL	>4.5 mg/dL	>6.5 mg/dL
Calcium	$x \leq 1.75$ mmol/L or 25 % decrease from baseline	<8 mg/dL	Corrected <7 mg/dL; ionized <1.12	
Creatinine	–	>1.4 mg/dL		

Note: Cairo–Bishop's clinical classification has 5 grades: grade 5 (not reported here) includes death. Data from Cairo and Bishop [35], Montesinos et al. [37], and Howard et al. [36]
UNL = upper normal limits (for laboratory and/or according to age)

lymphoma and acute leukemias [30–33]. This syndrome may develop in patients with hematologic malignancies or solid tumors, mostly in highly chemosensitive tumors and when the tumor burden is large; also the presence of preexisting renal disease, the use of nephrotoxic drugs, and the presence of disseminated intravascular coagulation are risk factor for TLS [34, 35]. Treatment-induced TLS usually occurs 12–72 h after starting therapy.

- The incidence varies according to the diagnostic method used to define the TLS: laboratory versus clinical presentation; several criteria have been proposed [35–39] (Tables 5.1 and 5.2).
  - Two or more laboratory abnormalities (hyperuricemia, hyperphosphatemia, hyperkalemia, hypocalcemia) are necessary for diagnosis.

It is characterized by the rapid development of:

- **Hyperuricemia,** from rapid release and catabolism of intracellular nucleic acids
- **Hyperkalemia,** caused by the rapid release of potassium from malignant cells and by the renal failure
- **Hyperphosphatemia** from the rapid release of intracellular phosphorous from malignant cells
- **Acute renal failure** as a consequence of calcium phosphate precipitation in the renal tubules

Frequently observed are also:

- **Hypocalcemia**, as a consequence of hyperphosphatemia calcium phosphate precipitation
- **Uremia**, due to uric acid crystal formation in the renal tubules secondary to hyperuricemia, calcium phosphate deposition, tumor infiltration in the kidney, tumor-associated obstructive uropathy, drug associated-nephrotoxicity, and/or acute sepsis.

Table 5.2 Definitions of clinical tumor lysis syndrome (CTLS)

	Cairo–Bishop					Montesinos	Howard
	Grade 0	Grade 1	Grade2	Grade 3	Grade 4		
Renal failure	Creatinine ≤1.5 × UNL	Creatinine >1.5 × UNL	Creatinine >1.5–3 × UNL	Creatinine >3–6 × UNL	Creatinine >6 × UNL	Urine output ≤800 mL/day	Urine output <0.5 mL/kg/h for 6 h
						Dialysis	Increase in serum creatinine of 0.3 mg/dL or >1.5 × ULN
Cardiac arrhythmia	None	No intervention required	Non urgent medical intervention	Symptomatic, incompletely controlled with drugs	With syncope, shock, or life-threatening	Any	If caused by hyperkalemia or hypocalcemia
						ECG signs of hyperkalemia	Hypotension, heart failure
Neuromuscolar irritability	None		One brief seizure; well controlled with anticonvulsivants, focal	Seizure with altered consciousness, poorly medically controlled; generalized	Status epilepticus, intractable epilepsy	Seizures	Seizures
						Tetany	Tetany, paresthesias, carpopedal spasm, Trousseau's sign, laryngospasm, bronchospasm

Note: Cairo–Bishop's clinical classification has 5 grades: grade 5 (not reported here) includes death. Data from Cairo and Bishop [35], Montesinos et al. [37], and Howard et al. [36]
UNL upper normal limits (for laboratory and/or according to age)

5.3.1 Clinical Manifestations

- Renal failure, oliguria
- Seizures, neuromuscular irritability, laryngospasm, bronchospasm
- Cardiac arrhythmias/death
- Heart failure

5.3.2 Treatment [38–40]

- Vigorous hydratation is recommended: target fluid intake of 3 L/day
- Prevent (especially for high risk patients) and treat hyperuricemia choosing amongst these drugs:
  - **Allopurinol** is commonly used in treatment of hyperuricemia. However, it has been associated with several hypersensitivity syndromes. An interaction between allopurinol and azathioprine (often used for immunosuppression in patients with transplants or autoimmune conditions) can lead to severe and life-threatening bone marrow suppression.
  - **Febuxostat** is a novel xanthine oxidase inhibitor that does not appear to have the hypersensitivity profile of allopurinol. In addition, it is metabolized to inactive metabolites in the liver, obviating the need for specific kidney dosing. Its routine use is limited by the higher cost compared to allopurinol.
- **Rasburicase** is an *Aspergillus*-derived recombinant urate oxidase and catalyzes the conversion of uric acid to allantoin, carbon dioxide, and hydrogen peroxide. Recommended dose is 0.15–0.2 mg/kg as a daily intravenous (i.v.) infusion for up to 5 days. It reduces uric acid levels within 4 h, both in pediatric and adult patients, catalyzing the oxidation of uric acid into allantoin, rapidly excreted by the kidneys. It was approved in the EU and in the USA for the management of acute hyperuricemia. *Warning*: it can lead to devastating methemoglobinemia and hemolytic anemia in individuals with glucose-6-phosphate dehydrogenase deficiency [41]. The routine use of Rasburicase in children with cancer is still questionable [42].
- Urine alkalinization, the solubility of uric acid is highly pH dependent. At a typical acidic urine pH of 5.0, the solubility of uric acid is 15 versus 200 mg/dL at a pH of 7.0. *However*, alkalinization of the urine (or serum) can favor the precipitation of calcium phosphate salts in soft tissues and renal tubules, potentially worsening kidney failure. Urinary alkalinization should only be considered in cases of severe hyperuricemia in which recombinant urate oxidase is unavailable.
- Use of diuretics remain controversial.
- Dialysis may be necessary in case of severe renal insufficiency. Continuous modalities are often preferred to intermitted hemodialysis to reduce the risk of "rebound" hyperkalemia or hyperphosphatemia.

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