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Hydroxyurea Toxicity: Emergency Recognition, Clinical Management, and Nursing and Respiratory Care Considerations.

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Abstract

Background: Hydroxyurea is an antimetabolite medication used in the management of several hematological and oncological disorders, as well as sickle cell disease. Although generally well tolerated when prescribed and monitored appropriately, excessive exposure, dosing errors, impaired renal clearance, and prolonged treatment may result in clinically significant toxicity. Its major adverse effects include bone marrow suppression, gastrointestinal complications, mucocutaneous lesions, and, less frequently, neurological and pulmonary manifestations. Severe toxicity may lead to infection, bleeding, respiratory compromise, and other life-threatening complications.

Aim: This review aims to examine the clinical features, underlying mechanisms, diagnostic evaluation, and management of hydroxyurea toxicity, with particular attention to emergency recognition and the contributions of nursing and respiratory care professionals.

Methods: A narrative review approach was used to organize available clinical and pharmacological evidence concerning hydroxyurea toxicity. The review addresses its etiology, epidemiology, pathophysiology, toxicokinetics, clinical manifestations, diagnostic investigations, treatment strategies, differential diagnosis, and interprofessional management.

Results: Hydroxyurea toxicity primarily results from inhibition of ribonucleotide reductase, leading to impaired DNA synthesis and suppression of rapidly dividing cells, particularly bone marrow precursors. Clinical manifestations include anemia, neutropenia, thrombocytopenia, gastrointestinal disturbances, oral mucositis, skin ulceration, and neurological abnormalities. Evaluation requires medication and exposure history, complete blood counts, renal function assessment, and symptom-directed investigations. Management is mainly supportive and may include fluid replacement, blood product transfusion, growth factor administration, infection management, and treatment of specific complications.

Conclusion: Early recognition, appropriate monitoring, supportive treatment, and coordinated interprofessional care are essential to reducing complications and improving outcomes in patients with hydroxyurea toxicity.

Keywords: Hydroxyurea; hydroxyurea toxicity; drug overdose; myelosuppression; emergency management; nursing care; respiratory care.

Introduction

Hydroxyurea toxicity is a clinically significant condition that requires early recognition and coordinated management, particularly in emergency departments and acute care settings. Hydroxyurea, also known as hydroxycarbamide, is an antimetabolite and antineoplastic medication that interferes with DNA synthesis by inhibiting ribonucleotide reductase. This action reduces the production of deoxyribonucleotides required for DNA replication and cell proliferation. Although this mechanism provides therapeutic benefits in several hematological and oncological disorders, it can also affect rapidly dividing normal cells and produce dose-related adverse effects. Hydroxyurea is used alone or in combination with other chemotherapeutic agents or radiation therapy to treat selected resistant leukemias and carcinomas of the head and neck. It also has an established role in the management of sickle cell disease. By increasing fetal hemoglobin (HbF) concentration, hydroxyurea reduces the frequency of vaso-occlusive crises, decreases the occurrence of severe sickle cell complications, and may reduce the need for blood transfusions.

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Furthermore, hydroxyurea is used off-label in the treatment of several conditions, including polycythemia vera, essential thrombocythemia, psoriasis, acute myeloid leukemia, meningioma, melanoma, and ovarian cancer.[1][2] Despite its therapeutic benefits, hydroxyurea can cause clinically significant toxicity, particularly following excessive dosing, prolonged exposure, impaired drug elimination, or inadequate laboratory monitoring. Its major adverse effects include bone marrow suppression, anemia, neutropenia, thrombocytopenia, gastrointestinal disturbances, oral mucositis, and skin and nail changes. Severe toxicity may result in profound cytopenias, increasing the risk of serious infections, spontaneous bleeding, and complications requiring hospitalization. Patients with impaired renal function may be at increased risk because reduced drug clearance can contribute to higher systemic exposure.

The clinical presentation of toxicity varies according to the dose, duration of exposure, patient characteristics, and underlying medical conditions. Emergency clinicians must rapidly assess patients with suspected overdose or severe adverse reactions, identify complications, and initiate appropriate supportive management. Nursing care includes monitoring vital signs, assessing neurological status, identifying signs of infection and bleeding, administering prescribed treatment, and monitoring laboratory results. Respiratory specialists may contribute to the assessment and management of hypoxemia, respiratory distress, and pulmonary complications. Effective coordination among emergency physicians, nurses, hematologists, oncologists, pharmacists, and respiratory specialists is essential to improve patient safety, reduce complications, and support recovery.

Etiology:

Hydroxyurea toxicity may result from excessive drug exposure, individual patient susceptibility, impaired drug elimination, or prolonged treatment without adequate monitoring. Hydroxyurea has a relatively narrow therapeutic index, meaning that the difference between therapeutic and toxic doses may be limited. Consequently, patients may develop significant adverse effects even when the medication is prescribed for appropriate clinical indications, particularly when dosing is not adjusted according to renal function or changes in clinical status. The primary mechanism underlying hydroxyurea toxicity is inhibition of ribonucleotide reductase, an enzyme responsible for converting ribonucleotides into deoxyribonucleotides required for DNA synthesis. By interfering with DNA replication, hydroxyurea suppresses the proliferation of rapidly dividing cells, including hematopoietic precursor cells in the bone marrow. This effect can produce myelosuppression, which represents one of the most important manifestations of toxicity. Reduced bone marrow activity may lead to neutropenia, thrombocytopenia, and anemia, increasing the patient's susceptibility to infections, bleeding, and reduced oxygen-carrying capacity.[1][2][3] Another consequence of hydroxyurea exposure is the development of megaloblastic changes in red blood cells. This occurs because hydroxyurea inhibits DNA synthesis without directly inhibiting RNA synthesis or cytoplasmic development to the same extent. Consequently, nuclear maturation becomes delayed while cytoplasmic maturation continues, resulting in enlarged erythroid precursor cells and macrocytic red blood cells. These hematological changes may be detected through complete blood count results and peripheral blood examination.[1][2][3] Additional factors may contribute to toxicity, including accidental overdose, medication administration errors, inappropriate dose escalation, and failure to perform regular blood count monitoring. Renal impairment is particularly relevant because hydroxyurea is substantially eliminated through the kidneys. Reduced renal clearance may increase systemic drug exposure and the risk of adverse reactions. Concomitant use of other myelosuppressive medications or chemotherapy may further increase bone marrow suppression. Therefore, identifying the underlying cause of excessive exposure and recognizing patient-related risk factors are essential for preventing severe toxicity and guiding appropriate clinical management.

Epidemiology

Epidemiological data on hydroxyurea toxicity, particularly acute overdose, remain limited. The available evidence is derived mainly from individual case reports and small clinical case series rather than large population-based studies. This limited evidence makes it difficult to establish the true incidence of acute poisoning, identify precise dose-toxicity relationships, or determine the frequency of severe outcomes. Nevertheless, reported cases demonstrate that hydroxyurea toxicity can occur in both pediatric and adult patients following accidental ingestion, intentional overdose, or administration of high therapeutic doses. One reported case involved a two-year-old child who accidentally received an excessive dose of hydroxyurea and subsequently developed mild myelosuppression.[3] The child was observed in the emergency department for eight hours before being discharged home. Outpatient monitoring of blood counts continued for two weeks to identify delayed hematological complications. This case highlights the importance of considering delayed bone marrow suppression following overdose, even when the patient initially appears clinically stable. It also demonstrates the importance of follow-up laboratory investigations after accidental pediatric exposure. Another reported case described a woman who developed severe neurological, cardiovascular, and hematological manifestations after ingesting 60

grams of hydroxyurea. Clinical findings included agitation, widespread myoclonic jerks, oculogyric crisis, sinus tachycardia, and myelosuppression. These manifestations indicate that substantial overdose may affect multiple physiological systems and require comprehensive emergency assessment and supportive management.

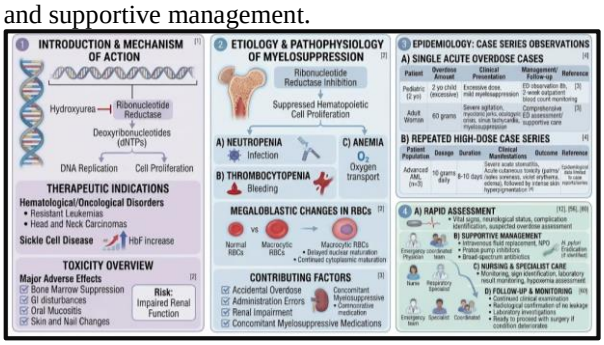


Figure-1: Overview of Hydroxyurea Toxicity.

Additional evidence comes from a case series involving three patients with advanced acute myelogenous leukemia who received high-dose oral hydroxyurea at 10 grams daily for eight to ten days.[4] All three patients developed severe acute stomatitis. Two also experienced acute cutaneous toxicity characterized by soreness, violet erythema, and edema affecting the palms and soles, followed by intense skin hyperpigmentation. These observations demonstrate that severe mucocutaneous reactions may develop during repeated high-dose exposure. Overall, the reported cases suggest that hydroxyurea toxicity varies according to the amount ingested, duration of exposure, patient age, underlying disease, and individual susceptibility. The limited epidemiological evidence emphasizes the need for accurate medication administration, appropriate dose adjustment, regular blood count monitoring, and prompt recognition of suspected overdose.

Pathophysiology

Hydroxyurea is a hydroxylated analog of urea that produces its principal pharmacological effects by interfering with DNA synthesis. Its primary mechanism involves inhibition of ribonucleotide diphosphate reductase, an enzyme responsible for converting ribonucleotides into deoxyribonucleotides, which are essential building blocks for DNA replication. By reducing the intracellular availability of deoxyribonucleotides, hydroxyurea prevents normal DNA synthesis and limits cellular proliferation.[5][6] This mechanism explains its therapeutic activity against rapidly dividing malignant cells and its potential to produce toxicity in normal tissues with high cellular turnover. Hydroxyurea is considered a cell-cycle-specific medication because its inhibitory effects are most pronounced during the S phase, when DNA replication occurs. Exposure interferes with the progression of cells through the cell cycle, resulting in cell-cycle arrest at the transition from G1 to S phase and inhibition of DNA replication. Although this action is beneficial in controlling abnormal cellular proliferation, it also affects normal hematopoietic precursor cells within the bone marrow. Consequently, excessive exposure or prolonged treatment may cause myelosuppression, characterized by reduced production of erythrocytes, leukocytes, and platelets. These changes can lead to anemia, neutropenia, and thrombocytopenia, increasing the risks of fatigue, infection, and bleeding.

Hydroxyurea also produces several beneficial effects in patients with sickle cell disease. It increases fetal hemoglobin (HbF) concentration by stimulating HbF production, although the precise molecular mechanism responsible for this effect has not been fully established. Increased HbF reduces the polymerization of deoxygenated sickle hemoglobin, thereby limiting red blood cell sickling and improving blood flow through the microcirculation. In addition, hydroxyurea has antioxidant properties, modifies red blood cell membrane characteristics, increases erythrocyte deformability through greater intracellular water content, and reduces red blood cell adherence to vascular endothelial cells.[7][8][9] These effects contribute to its therapeutic benefits but do not eliminate the possibility of toxicity. At excessive concentrations, disruption of DNA synthesis may impair normal tissue function, particularly bone marrow activity and epithelial cell renewal. This may explain the development of mucositis, stomatitis, and other mucocutaneous manifestations during high-dose exposure. Understanding these mechanisms is important for emergency clinicians, nurses, and respiratory specialists because toxicity may produce systemic complications requiring laboratory surveillance, infection prevention, bleeding assessment, and supportive care.

Toxicokinetics

Understanding the toxicokinetic properties of hydroxyurea is important for evaluating drug exposure, predicting the development of toxicity, and determining appropriate management strategies following accidental or intentional overdose. Toxicokinetics describes how the body absorbs, distributes, metabolizes, and eliminates a substance, particularly when exposure exceeds the therapeutic range. Hydroxyurea is administered primarily through the oral route and is readily absorbed from the gastrointestinal tract. It has approximately 100% oral bioavailability, indicating that nearly the entire administered dose reaches the systemic circulation. This rapid and extensive absorption allows hydroxyurea to produce its therapeutic effects but also means that excessive oral ingestion can result in significant systemic exposure. Its plasma elimination half-life ranges from approximately 1.9 to 3.9 hours in adults and is about 1.7 hours in children.[10][11] However, a relatively short plasma half-life does not

exclude the development of prolonged toxicity because the consequences of DNA synthesis inhibition, particularly bone marrow suppression, may persist after circulating drug concentrations have declined.

Hydroxyurea is eliminated predominantly through renal excretion, making kidney function an important determinant of drug clearance. Patients with impaired renal function may experience reduced elimination and increased systemic exposure, potentially increasing the risk of adverse effects and hematological toxicity. Therefore, dose adjustment is recommended in patients with renal impairment to minimize drug accumulation and prevent excessive exposure. Assessment of renal function should form part of routine monitoring, particularly in older patients and those with pre-existing kidney disease. In suspected overdose, clinicians should consider the reported dose, time of ingestion, patient's age, renal function, and clinical manifestations. Initial laboratory assessment should include a complete blood count, renal function tests, and electrolyte measurements, with repeated blood counts when indicated to detect delayed myelosuppression. Because hematological complications may develop after the initial exposure, patients require appropriate follow-up even when early clinical findings are limited. These pharmacokinetic characteristics have important implications for emergency and nursing practice. Healthcare professionals should verify medication doses, identify potential administration errors, monitor renal function, and assess for delayed hematological complications. Respiratory specialists may also contribute when systemic toxicity is accompanied by infection, anemia-related respiratory symptoms, or respiratory compromise.

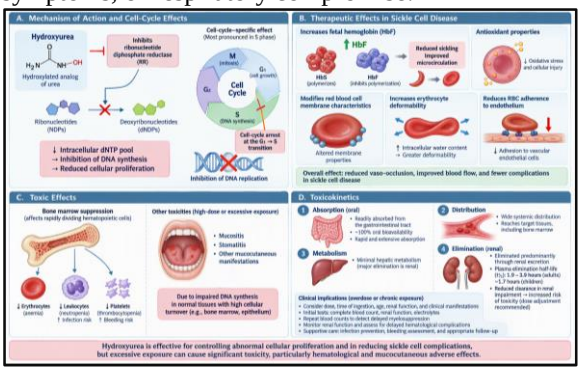


Figure-2: Pathophysiology and Toxicokinetics of Hydroxyurea.

History and Physical

The clinical manifestations of hydroxyurea toxicity vary according to the administered dose, duration of treatment, patient characteristics, renal function, and underlying medical conditions. A comprehensive history and physical examination are essential for identifying suspected toxicity, evaluating the severity of adverse effects, and determining the need for emergency intervention. Assessment should include medication history, prescribed dosage, recent dose changes, possible accidental or intentional overdose, treatment duration, concomitant medications, and previous hematological or organ-related complications. Particular attention should be given to symptoms suggesting bone marrow suppression, gastrointestinal injury, skin toxicity, respiratory complications, and neurological abnormalities.

Hematology-Oncology

Bone marrow suppression is one of the most important adverse effects of hydroxyurea and may occur during therapeutic use or following excessive exposure. Myelosuppression results from inhibition of DNA synthesis in rapidly dividing hematopoietic precursor cells. Clinical manifestations include anemia, leukopenia, and thrombocytopenia. Leukopenia, particularly neutropenia, is a common manifestation and increases susceptibility to bacterial, viral, and fungal infections. Patients may present with fever, recurrent infections, sore throat, oral lesions, and general weakness. Thrombocytopenia increases the risk of spontaneous bleeding, bruising, petechiae, and mucosal hemorrhage, whereas anemia may cause fatigue, pallor, dizziness, tachycardia, and reduced exercise tolerance. Hydroxyurea-associated myelosuppression is generally reversible following interruption of treatment. In patients receiving therapeutic doses, withholding the medication for approximately two weeks may allow bone marrow recovery, after which treatment may be resumed at a reduced dose when clinically appropriate. However, the duration of recovery depends on the severity of suppression and the patient's underlying condition. Regular complete blood count monitoring is essential to identify declining cell counts and guide treatment adjustments. Another hematological effect is macrocytosis, which may develop early during hydroxyurea treatment. It is characterized by an increase in mean corpuscular volume and may resemble the hematological changes associated with pernicious anemia. However, hydroxyurea-induced macrocytosis is generally unrelated to vitamin B12 or folic acid deficiency. Folic acid supplementation may be recommended during treatment, although macrocytosis alone does not establish a nutritional deficiency.[12]

Long-term hydroxyurea treatment in patients with myeloproliferative disorders has also raised concerns about secondary hematological malignancies. A reported case series described leukemic transformation in three patients with essential thrombocythemia who had received continuous hydroxyurea treatment for 47, 81, and 90 months, respectively.[13] The contribution of hydroxyurea to this transformation may be difficult to distinguish from the natural progression of the underlying myeloproliferative disease and other treatment-related factors. Furthermore, prolonged

exposure has been associated with an increased risk of cutaneous malignancies, including squamous cell carcinoma and other skin cancers. These complications may develop after several years of treatment.[14] Long-term surveillance should include examination of the skin, assessment of suspicious lesions, and referral for dermatological evaluation when indicated.

Gastrointestinal

Gastrointestinal adverse effects are common during hydroxyurea treatment and may range from mild digestive disturbances to clinically significant mucosal injury. Patients may experience nausea, vomiting, abdominal discomfort, gastric distress, gastritis, oral mucositis, and ulceration of the oral mucosa.[15][16] These manifestations may interfere with eating, drinking, medication adherence, and nutritional status. Severe oral mucositis can cause painful swallowing, difficulty maintaining oral hygiene, reduced food intake, and dehydration. Physical examination should include inspection of the oral cavity for erythema, ulceration, bleeding, and evidence of secondary infection. Nurses should assess pain intensity, swallowing ability, nutritional intake, and hydration status. Patients with extensive mucosal injury may require supportive treatment, oral care, nutritional interventions, and evaluation for infection. Elevations in serum hepatic enzyme concentrations have also been reported in patients receiving hydroxyurea. Although clinically significant hepatotoxicity is uncommon, severe and occasionally fatal hepatic failure has been described in patients with HIV infection receiving hydroxyurea in combination with antiretroviral medications. These cases occurred particularly among patients receiving hydroxyurea, didanosine, and stavudine together. Patients receiving such combinations require careful assessment of hepatic function and clinical manifestations of liver injury. Both fatal and nonfatal pancreatitis have also been reported in patients with HIV infection treated with hydroxyurea and didanosine, with or without stavudine. Clinical manifestations may include severe upper abdominal pain, nausea, vomiting, and abdominal tenderness. Serum lipase and other appropriate investigations should be considered when pancreatitis is suspected. Hydroxyurea should be permanently discontinued in patients who develop pancreatitis associated with treatment, according to the reported recommendations.

Dermatology

Cutaneous toxicity is an important complication of prolonged hydroxyurea exposure. Patients may develop painful skin ulcers, aphthous ulcers, erythema, skin infiltration, and other changes affecting the skin and mucous membranes.[17] Ulcers commonly affect the lower extremities and may be associated with delayed wound healing, persistent pain, and secondary infection. These lesions can significantly impair mobility and quality of life, particularly in patients with underlying vascular disorders. Long-term treatment has also been associated with rare but serious complications, including gangrene affecting the toes and fingers.[18][19] Patients may present with pain, discoloration, tissue breakdown, ulceration, and progressive ischemic changes. Physical examination should assess skin integrity, peripheral circulation, wound characteristics, and signs of infection. Persistent or severe hydroxyurea-associated skin ulcers and gangrenous changes may require discontinuation of the medication and specialist evaluation. Nursing care includes regular skin inspection, wound assessment, pain management, infection prevention, and patient education regarding early reporting of new skin lesions.

Reproductive

Hydroxyurea can adversely affect reproductive function because of its ability to interfere with DNA synthesis and cellular division. In males, treatment has been associated with reduced sperm count and impaired sperm motility, potentially affecting fertility.[20] Patients who may wish to have children should receive counseling regarding reproductive risks and available fertility-preservation options before prolonged treatment when appropriate. Hydroxyurea also presents potential risks during pregnancy because of its effects on cellular development. The medication has historically been classified as pregnancy category D under the former US Food and Drug Administration classification system, indicating evidence of fetal risk. Pregnancy status and reproductive plans should therefore be discussed before treatment initiation. Effective contraception should be considered during therapy according to current prescribing recommendations. Breastfeeding is not recommended during hydroxyurea treatment because of potential exposure of the infant to the medication.[20]

Pulmonary

Pulmonary toxicity is an uncommon but potentially life-threatening complication of hydroxyurea treatment. The medication has been associated with severe interstitial pneumonitis, which may develop even after several years of treatment.[21] This delayed presentation can complicate diagnosis because respiratory symptoms may initially be attributed to infection, underlying malignancy, cardiovascular disease, or other pulmonary conditions. Clinical manifestations may include progressive dyspnea, persistent dry cough, fever, tachypnea, and reduced oxygen saturation. Physical examination may reveal inspiratory crackles and signs of respiratory distress. Further evaluation may include pulse oximetry, arterial blood gas analysis, chest radiography, high-resolution computed tomography, and pulmonary function testing, depending on clinical severity. If drug-

induced interstitial pneumonitis remains unrecognized or untreated, persistent inflammation may progress to pulmonary fibrosis and respiratory failure. Early identification is therefore essential. Suspected hydroxyurea-induced pneumonitis requires prompt medical evaluation and discontinuation of the medication when the association is established. Emergency clinicians should assess respiratory stability, while respiratory specialists contribute to oxygenation assessment, respiratory support, and evaluation of pulmonary impairment.

Cardiology

Cardiovascular complications associated with hydroxyurea are less clearly established than its hematological and mucocutaneous adverse effects. A published case described a patient with chronic myelogenous leukemia who developed acute myocardial infarction while receiving hydroxyurea treatment.[22] However, the pathophysiological relationship between hydroxyurea exposure and myocardial infarction remains uncertain. The underlying malignancy, cardiovascular risk factors, and other concurrent treatments may also contribute to cardiovascular events. Patients presenting with chest pain, dyspnea, palpitations, or unexplained hemodynamic instability require prompt cardiovascular assessment. Evaluation may include electrocardiography, cardiac biomarkers, blood pressure monitoring, and additional investigations according to clinical findings. Emergency teams should avoid assuming that cardiovascular symptoms are necessarily caused by hydroxyurea and should investigate other potentially life-threatening causes.

Neurology

Neurological adverse effects associated with hydroxyurea are relatively uncommon but may occur during treatment or following substantial overdose. Reported manifestations include headache, dizziness, disorientation, hallucinations, and seizures. Severe overdose may produce neurological abnormalities such as agitation, myoclonic jerks, and oculogyric crisis. These findings require urgent assessment to identify medication-related toxicity and exclude alternative causes, including metabolic disturbances, infection, cerebrovascular events, and complications of the underlying disease. Neurological assessment should include the level of consciousness, orientation, pupil responses, motor activity, and seizure activity. Vital signs, blood glucose, electrolyte concentrations, renal function, and other relevant investigations should be evaluated. Patients experiencing seizures or altered consciousness require immediate stabilization and appropriate supportive management. Continuous observation may be necessary in severe cases to identify deterioration and prevent secondary injury. Overall, the history and physical examination of patients with suspected hydroxyurea toxicity should follow a systematic, multisystem approach. Emergency physicians, nurses, hematologists, pharmacists, and respiratory specialists have complementary responsibilities in identifying adverse effects, monitoring organ function, preventing complications, and supporting recovery.

Evaluation

The evaluation of suspected hydroxyurea toxicity requires a systematic assessment of medication exposure, clinical manifestations, and potential organ dysfunction. Initial assessment should establish the indication for hydroxyurea treatment, prescribed dosage, duration of therapy, time of the last dose, and possibility of accidental or intentional overdose. Clinicians should also review recent dose adjustments, medication administration errors, renal impairment, and concurrent use of other medications, particularly chemotherapeutic agents that may produce similar adverse effects. Laboratory investigations play an important role in identifying hematological and metabolic complications. A complete blood count with differential and platelet count is essential for detecting myelosuppression, including anemia, leukopenia, neutropenia, and thrombocytopenia. Patients with reduced neutrophil counts require close monitoring for fever, chills, sore throat, oral lesions, and other signs of infection. Similarly, patients with thrombocytopenia should be assessed for bruising, petechiae, mucosal bleeding, and other manifestations of impaired hemostasis. Repeated blood count measurements may be necessary because hematological complications can become apparent after the initial exposure.[22] Renal function and serum electrolyte concentrations should also be monitored, particularly in patients experiencing severe nausea, vomiting, or diarrhea. These gastrointestinal symptoms can cause dehydration, electrolyte disturbances, and reduced renal perfusion. Assessment should include serum creatinine, blood urea nitrogen, sodium, potassium, and other electrolytes according to the patient's clinical condition. Urine output and fluid balance should be documented to identify early signs of renal impairment.

Additional investigations should be guided by presenting symptoms. Liver function tests may be appropriate in patients with suspected hepatic injury, while serum lipase should be measured when pancreatitis is suspected. Patients presenting with respiratory symptoms may require pulse oximetry, arterial blood gas analysis, and chest imaging to evaluate hypoxemia or pulmonary complications. Neurological assessment is necessary in patients with confusion, agitation, abnormal movements, or seizures. A complete physical examination should assess vital signs, hydration status, skin integrity, oral mucosa, respiratory function, cardiovascular stability, and neurological status. Nurses play an essential role in documenting clinical changes, monitoring laboratory results, identifying deterioration, and communicating abnormal findings to the medical team. Early recognition of complications allows

clinicians to initiate supportive treatment and reduce the risk of severe toxicity.

Treatment / Management

The management of hydroxyurea toxicity is primarily symptomatic and supportive. Treatment depends on the amount ingested, time since exposure, severity of clinical manifestations, and presence of complications. Patients with suspected overdose require prompt assessment and stabilization, with particular attention to airway protection, breathing, and circulation. The initial management approach should identify life-threatening manifestations, including respiratory compromise, severe myelosuppression, seizures, and hemodynamic instability. Gastrointestinal decontamination is generally not recommended in the prehospital setting. Activated charcoal may be considered following a recent overdose when the patient can protect the airway, is not experiencing persistent vomiting, and has no contraindication to its administration. It should only be administered after appropriate clinical assessment and consideration of aspiration risk. Inducing vomiting is not recommended. Patients with altered consciousness or an inability to maintain airway protection require appropriate airway management before considering any gastrointestinal intervention. Respiratory support should be provided according to clinical requirements. Patients with respiratory distress or inadequate airway protection may require oxygen therapy and advanced airway management, including endotracheal intubation when indicated. Respiratory specialists may assist with oxygenation assessment, ventilatory support, and monitoring of patients with suspected pulmonary toxicity [22].

Gastrointestinal symptoms such as nausea and vomiting should be treated with appropriate antiemetic medications. Intravenous fluids may be required to correct dehydration and maintain adequate renal perfusion. Electrolyte abnormalities should be identified and corrected according to laboratory findings. Management of myelosuppression depends on the affected blood cell line and the severity of the abnormality. Patients with clinically significant neutropenia may require granulocyte colony-stimulating factors when indicated. Severe thrombocytopenia accompanied by significant bleeding or other clinical indications may require platelet transfusion. Packed red blood cell transfusion may be necessary in patients with severe or symptomatic anemia. Patients with suspected infection require prompt assessment and appropriate antimicrobial treatment. Seizures should be managed with standard emergency seizure protocols and appropriate antiepileptic medications. Continuous neurological and respiratory monitoring may be necessary in patients with recurrent seizures or altered consciousness. Oral mucositis requires supportive treatment based on severity. Mild cases may be managed with bland oral rinses containing 0.9% normal saline, sodium bicarbonate, or water. Moderate mucositis associated with pain may require the addition of topical anesthetic preparations. Moderate to severe cases may require local anesthetics and systemic analgesics. Antimicrobial mouthwashes may help reduce the risk of secondary oral infection when clinically appropriate.[12][22] Hydroxyurea should be withheld when significant toxicity is suspected, with subsequent treatment decisions guided by clinical recovery, laboratory findings, and specialist recommendations. Continued monitoring is essential because bone marrow suppression and other complications may persist after the initial exposure.

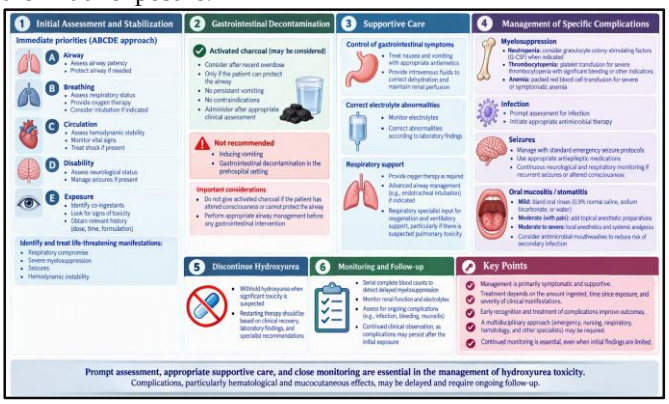


Figure-3: Management and Treatment of Hydroxyurea toxicity.

Differential Diagnosis

The differential diagnosis of hydroxyurea toxicity is important because its clinical manifestations are not specific and may overlap with adverse effects caused by other medications, complications of underlying diseases, and independent medical conditions. This is particularly relevant in patients with malignancies or hematological disorders who receive hydroxyurea in combination with other chemotherapeutic or supportive medications. Myelosuppression is a major manifestation of hydroxyurea toxicity. However, anemia, leukopenia, neutropenia, and thrombocytopenia may also result from other antineoplastic agents, radiation therapy, bone marrow infiltration by malignant cells, or progression of the underlying hematological disease. Therefore, clinicians should review the complete medication history, treatment schedule, previous blood count results, and timing of symptom development. The presence of multiple myelosuppressive medications may increase the likelihood of combined drug-related bone marrow toxicity.[22] Infection is another important consideration, particularly in patients presenting with fever and neutropenia. Bacterial sepsis, viral infections, and opportunistic fungal infections may produce fever, weakness,

hypotension, and deterioration in general condition. In these patients, infection may occur as a consequence of hydroxyurea-induced neutropenia rather than representing a direct manifestation of the medication itself. Gastrointestinal symptoms also require careful differentiation. Nausea, vomiting, abdominal pain, gastritis, and mucositis may be associated with hydroxyurea, but similar manifestations can occur with other chemotherapeutic agents, gastrointestinal infections, peptic ulcer disease, pancreatitis, and hepatic disorders. Patients with severe abdominal pain should undergo appropriate assessment to exclude acute abdominal conditions. Neurological manifestations such as confusion, agitation, dizziness, and seizures may be associated with drug toxicity but can also result from electrolyte abnormalities, hypoglycemia, central nervous system infection, cerebrovascular disease, or other medication effects. Respiratory symptoms require differentiation between drug-induced interstitial pneumonitis, pneumonia, pulmonary embolism, pulmonary edema, and complications associated with the underlying disease. A detailed history, physical examination, medication reconciliation, complete blood count, renal and hepatic function tests, electrolyte measurements, and symptom-directed investigations help distinguish hydroxyurea toxicity from alternative diagnoses. Identifying the possibility of combined medication effects is particularly important when patients receive multiple anticancer or antiretroviral agents.

Consultations

Consultation with a poison control center is recommended whenever hydroxyurea toxicity is suspected, particularly following accidental or intentional overdose, uncertain medication exposure, or the development of significant adverse effects. Poison control specialists can assist with exposure assessment, evaluation of potential complications, recommendations regarding gastrointestinal decontamination, and decisions concerning observation or hospital admission. Their involvement is particularly valuable when the ingested dose is uncertain or the clinical presentation does not clearly establish the cause of toxicity. Emergency medicine physicians should be involved in the initial assessment and stabilization of patients presenting with acute overdose. Their responsibilities include evaluating airway protection, respiratory function, circulation, neurological status, and the need for immediate supportive interventions. Medical toxicologists may provide additional guidance in severe or complicated cases, especially when patients develop multiple organ manifestations or when the diagnosis remains uncertain. Hematology and oncology consultation is important because hydroxyurea is frequently prescribed for hematological malignancies and myeloproliferative disorders. Specialists can assess the severity of myelosuppression, determine whether the medication should be withheld, interpret changes in blood counts, and recommend appropriate treatment adjustments. They can also guide decisions regarding restarting therapy after recovery and the need for alternative treatment strategies. Nephrology consultation may be appropriate in patients with significant renal impairment or acute kidney injury because renal function affects hydroxyurea elimination. Infectious disease specialists may be required when patients develop severe neutropenia, febrile neutropenia, or suspected systemic infection. Gastroenterology consultation may be useful in cases involving severe mucositis, gastrointestinal complications, or suspected pancreatitis. Respiratory specialists should participate in the management of patients with hypoxemia, respiratory distress, or suspected hydroxyurea-induced interstitial pneumonitis. They may assist with respiratory investigations, oxygen therapy, ventilatory support, and assessment of pulmonary complications. Critical care consultation is necessary when patients develop severe respiratory failure, hemodynamic instability, septic shock, recurrent seizures, or multiple organ dysfunction. Early involvement of the appropriate specialists supports coordinated decision-making and timely treatment. The consultation process should include clear communication of the exposure history, clinical findings, laboratory results, and response to initial interventions.

Enhancing Healthcare Team Outcomes

Effective management of hydroxyurea toxicity requires coordinated collaboration among emergency physicians, nurses, pharmacists, internists, hematologists, oncologists, respiratory specialists, medical toxicologists, and critical care professionals. Each member of the healthcare team contributes to early recognition, clinical stabilization, treatment selection, and prevention of complications. An interprofessional approach is particularly important because hydroxyurea toxicity may affect several organ systems and require different forms of supportive care. Emergency medicine physicians are responsible for the initial assessment and stabilization of patients with suspected toxicity. They should evaluate airway patency, respiratory function, circulation, neurological status, and evidence of severe hematological complications. Patients with respiratory depression, altered consciousness, or severe respiratory distress may require advanced airway management and ventilatory support. Emergency physicians should also coordinate early laboratory investigations and seek guidance from poison control centers or medical toxicologists when the exposure history or diagnosis is unclear. Nurses have a central role in continuous patient assessment and monitoring. They should regularly evaluate vital signs, oxygen saturation, neurological status, fluid balance, urine output, skin condition, oral mucosa, and signs of infection or bleeding. Monitoring complete blood counts and reporting significant

changes are essential responsibilities, particularly in patients with neutropenia or thrombocytopenia. Nurses should also administer prescribed medications, provide supportive care, assess treatment responses, and document clinical changes. Oncology and critical care nurses may be particularly important when patients require prolonged observation or management of severe complications.

Pharmacists contribute through medication reconciliation, verification of prescribed doses, identification of administration errors, and assessment of potential drug-drug interactions. They should review concomitant medications that may increase bone marrow suppression or contribute to hepatic and pancreatic toxicity. Pharmacists can also support dose adjustment recommendations in patients with renal impairment and provide counseling regarding safe medication administration and storage. Hematologists and oncologists should evaluate the underlying disease, assess the severity of hematological toxicity, and determine the appropriate timing for withholding or restarting hydroxyurea. Respiratory specialists should assess patients with pulmonary symptoms and contribute to the management of hypoxemia, interstitial pneumonitis, and respiratory failure. Internists and critical care physicians may assist in managing associated metabolic disturbances, infection, and multiple organ dysfunction. Patient and caregiver education is another essential component of care. Nurses and pharmacists should explain the prescribed dosage, the importance of adherence, and the need for regular laboratory monitoring. Patients should be informed about symptoms requiring medical attention, including fever, unusual bruising, bleeding, persistent vomiting, oral ulcers, severe abdominal pain, and new respiratory symptoms. They should also understand the importance of avoiding unsupervised dose changes and informing healthcare professionals about all medications they use. This coordinated approach improves medication safety, supports early identification of complications, and promotes appropriate treatment decisions. Effective communication, accurate documentation, medication reconciliation, and patient education are essential for improving outcomes in individuals receiving hydroxyurea and those presenting with suspected toxicity.[22]

Conclusion:

Hydroxyurea toxicity is a clinically important adverse drug condition that requires early recognition and appropriate management. Its effects extend beyond bone marrow suppression and may involve the gastrointestinal tract, skin, nervous system, and respiratory system. Accurate assessment of medication exposure, renal function, clinical manifestations, and hematological parameters supports timely diagnosis and treatment. Management relies primarily on supportive interventions, correction of hematological abnormalities, prevention and treatment of infection, and management of organ-specific complications. Nurses play a central role in monitoring vital signs, detecting clinical deterioration, identifying bleeding and infection, and educating patients about medication adherence and warning symptoms. Pharmacists, emergency physicians, hematologists, respiratory therapists, and critical care teams contribute to safe and coordinated care. Regular laboratory monitoring, appropriate dose adjustment, and patient education remain essential preventive measures. An interprofessional approach can reduce treatment-related complications, support recovery, and improve patient safety.

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