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CRITICAL REVIEW ON SUPPORTIVE TREATMENT MEASURES IN ACUTE ALUMINUM PHOSPHIDE TOXICITY

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Abstract
Acute aluminum phosphide (AlP) poisoning represents one of the most challenging toxicological emergencies globally due to its high fatality rates and lack of a specific antidote. Phosphine gas, released upon AlP's exposure to moisture or gastric acid, disrupts mitochondrial oxidative phosphorylation, generating reactive oxygen species and precipitating systemic multi-organ failure. The primary management approach is supportive care, encompassing aggressive hemodynamic stabilization, respiratory support, and correction of severe metabolic acidosis. However, the rapid progression of toxicity, coupled with resource limitations in many affected regions, often leads to poor outcomes. Emerging interventions, including antioxidant therapies, mitochondrial protective agents, and advanced extracorporeal techniques such as extracorporeal membrane oxygenation (ECMO), show potential for improving survival. Concurrently, research into biomarkers for early severity prediction and the development of phosphine-neutralizing agents offers hope for more targeted approaches. Addressing the high mortality associated with AlP poisoning requires a multidisciplinary strategy, combining advancements in clinical care, stricter regulation of AlP distribution, and public health initiatives to mitigate its misuse, particularly for self-harm. Future innovations and equitable access to advanced medical interventions are essential to reducing the global burden of this highly lethal poisoning.

Keywords: Aluminum phosphide poisoning, Phosphine gas, Supportive care, Oxidative stress, Multi-organ failure, Mitochondrial dysfunction.

Introduction

Aluminum phosphide (AlP), a fumigant pesticide, has become a major public health problem because of its extreme toxicity. AlP is a potent cellular toxin, which disrupts essential metabolic pathways when exposed to moisture or gastric acid and liberates phosphine gas, a potent cellular toxin (Gurjar *et al*., 2011). The cytochrome c oxidase inhibition is the most important mechanism of toxicity. When the inhibition overwhelms the physiological limits of the system, the oxidation phosphorylation is

halted, the cellular energy failure is caused and reactive oxygen species (ROS) are initiated. Phosphine leads to a cascade of metabolic derangements which results in severe multi-organ dysfunction and death (in many cases). Acute AlP poisoning is therefore one of the most lethal forms of poisoning with no specific antidote available. This stark reality emphasizes the need for supportive care, the basic element of management. This wholly relies on supportive measures, evidencing that existing medical therapeutics have their limitations and that new therapeutic approaches are urgently required (Gupta & Ahlawat, 1995). The acute AIP tablet is illustrated in Figure 1.

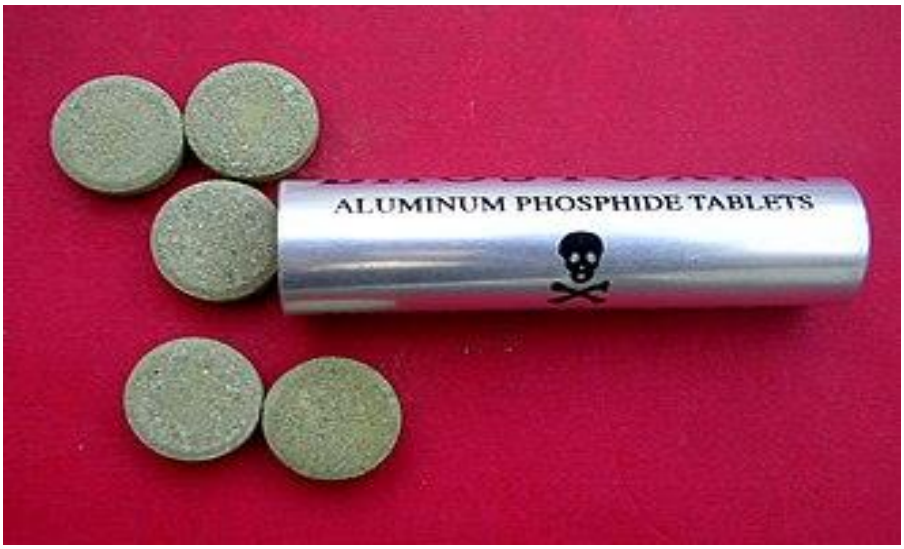

Figure 1: Acute Aluminum Phosphide

Source: https://en.wikipedia.org/wiki/Aluminium_phosphide_poisoning?utm_source=chatgpt.com

Epidemiology and Global Burden

In agricultural economies, where AlP is used as a cost-effective fumigant to protect stored grains, the burden of AlP poisoning is disproportionately high, especially in regions such as South Asia, the Middle East, and parts of Africa. However, this economic accessibility has, were unwanting of it, contributed to misuse, particularly for self-harm. AlP poisoning is reported to be a major cause of pesticide-related deaths in countries such as India and Iran, with case fatality rates of 40–80% (Mehrpour et al., 2012). An earlier finding of these chilling statistics speaks not only of the inherent toxicity of AlP but also of systemic factors: poor or no regulation, scant healthcare infrastructure, and no immediate medical resources in rural parts (Anbalagan *et al*., 2021).

For example, AlP is commonly used as an intentional poison in India because of its pervasive use and it's hard to access in rural markets. And many of these cases are thought to be due to socio-economic distress, mental health problems, and lack of awareness of its lethality. In Iran, as well, AlP has been extensively identified as the foremost cause of pesticide poisoning fatalities in agricultural societies (Anuradha *et al*., 2021). In Europe and North America, sporadic cases of AlP poisoning have been reported outside of these regions, usually through accidental or improper handling. However, the problem is most acute in developing countries, where regulatory oversight and mental health support systems are generally weak.

The delayed recognition of clinical manifestations of AlP poisoning, the rapid progression to critical illness, and the difficulty in obtaining timely and appropriate medical care further increase the global burden of AlP poisoning. In addition to its toxicological profile, the high mortality rates with AlP poisoning are not just a consequence of the toxicological profile, since the affected regions suffer also from healthcare disparities. To solve this problem, there need to be strict regulatory measures in place, education and information regarding public health, and better delivery of healthcare (Farahani *et al*., 2016).

Challenges in Management

AlP poisoning is one of the most complex toxicological emergencies to manage, due to the clinical and systemic challenges posed by its management. The rapid onset of severe toxicity following ingestion of AlP often exceeds the ability of healthcare systems to provide rapid results and effective treatment (Katwal *et al*., 2021). Patients may rapidly develop profound hypotension, metabolic acidosis, and multiorgan failure within minutes to hours and require immediate intervention and aggressive measures. Nevertheless, since there is no specific antidote for AlP poisoning clinicians only have the option of supportive care to stabilize the patient and prevent the systemic effect (Xu *et al*., 2016).

While supportive care is critically important, it is resource-intensive and requires the use of intensive care units (ICUs), mechanical ventilation, and hemodynamic support. However, these resources are not available in low- and middle-income countries where AlP poisoning is most prevalent. In particular, rural healthcare settings are ill-equipped to handle such cases, and delays in treatment and increased mortality rates are the result. In addition to this, healthcare providers in these regions are often not specialized in toxicology and this further contributes to the problem. Suboptimal care of AlP poisoning is due to many frontline healthcare workers being unfamiliar with the pathophysiology of AlP poisoning and the nuances of its management (Moghadamnia, 2012).

Another major obstacle is the uncertain or nonavailability of a history of ingestion which renders the AlP poisoning difficult to diagnose. The clinical presentation of AlP poisoning can be similar to sepsis or myocardial infarction and therefore can be misdiagnosed and treated inappropriately. Biochemical markers, such as elevated lactate levels and severe metabolic acidosis, can be helpful, but are nonspecific and must be correlated with clinical history and other findings. Diagnostic tools are advanced, but not widely available, and the diagnostic process is further complicated by the lack of advanced diagnostic tools, such as phosphine gas detection methods (Agrawal *et al*., 2015).

In addition to these clinical challenges, systemic issues contributing to the misuse of AlP include a lack of regulatory controls on the sale and distribution of AlP. AlP is sold over the counter in many countries without restrictions and is easily available to people who want to harm themselves. Its sale has been resisted by efforts to regulate it and promote safer alternatives because of economic and logistical concerns. Furthermore, many societies are still stigmatizing mental health issues which discourages many people from asking for help thereby perpetuating the chain of self-harm (Pannu *et al*., 2020).

There is also a paucity of robust clinical research and evidence-based guidelines for the management of AlP poisoning. There is little high-quality evidence to support specific interventions, and most treatment protocols are based on small observational studies or expert opinion (Shadnia *et al*., 2005). Variability in the standards of care results in this variability of outcomes and can object to the accumulation of additional trials to increase survival rates if even one patient fails to survive with a particular policy of care. Well-designed clinical trials to evaluate the efficacy of emerging therapies, such as antioxidants and mitochondrial protective agents, in the management of AlP poisoning, are urgently needed (Abd-Allah *et al*., 2022).

Finally, the psychological and social dimensions of AlP poisoning are not well addressed. Many AlP poisonings are intentional, demonstrating underlying mental health issues that need to be addressed (Yadav *et al*., 2021). Nevertheless, attention is frequently confined to the physical treatment of poisoning rather than to psychological support or preventive action. However, the root causes of this issue as well as a decrease in the incidence of AlP poisoning in the long term require the integration of mental health services into the management framework. Finally, although supportive care remains the mainstay of management for AlP toxicity, it is surprising that the delivery of timely and effective care is proving to be both difficult and complex. To address these challenges, clinicians, policymakers, and public health practitioners must work together to expand access to care, increase the means of diagnostic and therapeutic processing, and put in place preventative measures. Addressing these will limit the amount of AlP that is burdened on people afflicted with the disease (Babu *et al*., 2021).

Pathophysiology of Aluminum Phosphide Toxicity

Aluminum phosphide (AlP) poisoning is a major cause of morbidity and mortality, largely because it can generate phosphine gas when it comes into contact with water or gastric acid. Phosphine is a potent cellular toxin that blocks mitochondrial cytochrome c oxidase, an essential enzyme of the electron transport chain. Inhibition of this interferes with oxidative phosphorylation, creating a very serious energy crisis in the cell. Along the same lines, phosphine also generates ROS that causes oxidative damage to lipids, proteins, and DNA, all of which compounds pile upon cellular injury (Wadia *et al*., 2018). The clinical presentation and diagnosis are illustrated in Figure 2. The Systemic toxicity observed in AlP poisoning is due to the combination of energy depletion and oxidative stress.

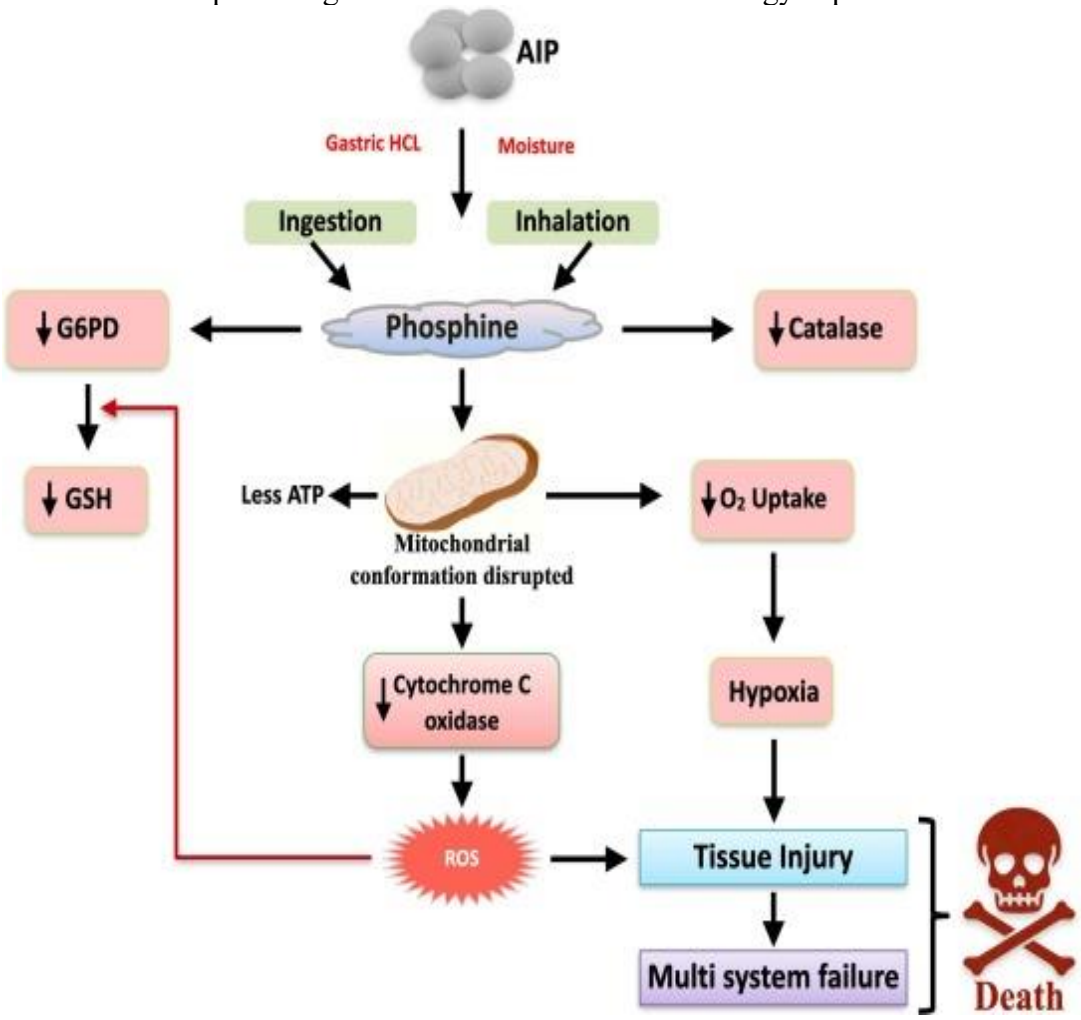

Figure 2: Clinical Presentation and Diagnosis

Source: https://www.sciencedirect.com/science/article/abs/pii/S0009898121001820

Pathophysiological pathway of aluminum phosphide toxicity illustrating the liberation of phosphine gas, mitochondrial dysfunction, and subsequent multi-system failure.

Phosphine gas primarily affects the cardiovascular system at the organ level, causing profound myocardial depression, arrhythmias, and peripheral vascular collapse. Often, these changes lead to refractory shock, a hallmark of severe AlP poisoning (Elgarhy *et al*., 2021). Many patients also develop pulmonary edema and acute respiratory distress syndrome (ARDS) of the respiratory system. It is thought to be mediated by increased pulmonary vascular permeability and systemic inflammation caused by ROS. These metabolic disturbances include severe electrolyte abnormalities (like hyperkalemia and hypocalcemia) as well as profound acidosis, caused by the accumulation of lactate, which further exacerbates the already present clinical picture (Anuradha *et al*., 2021).

AlP is one of the most lethal poisoning agents in the world because of its rapid onset and severity of toxicity. Factors that affect outcomes include the amount of AlP ingested, the time to initiation of treatment, and the degree of metabolic derangement. Poor outcomes are associated with high levels

of lactate and severe metabolic acidosis. Although research on the specific biomarkers, such as oxidative stress or mitochondrial dysfunction markers, for the early severity prediction, is ongoing but not yet finalized in the clinical practice.

3. Clinical Presentation and Diagnosis

Symptoms and Severity Assessment

Symptoms of AlP poisoning usually occur rapidly because phosphine gas is generated. Phosphine is corrosive and the initial clinical manifestations are nausea, vomiting, and abdominal pain. At this stage, as the toxin disseminates systemically cardiovascular collapse is a defining feature. Common are hypotension, often refractory to fluid resuscitation, and arrhythmias, with patients often progressing to shock (Zeng *et al*., 2018). Dyspnea, cyanosis, and pulmonary edema are also common and frequently lead to acute ARDS illustrated in Figure 3. Hypoxia and severe metabolic acidosis lead to neurological manifestations such as altered sensorium, agitation, and seizures (Æbelø *et al*., 2019). Guiding treatment and predicting outcomes are dependent on severity assessment. Higher mortality is associated with clinical parameters, including refractory hypotension, persistent metabolic acidosis, and significant electrolyte disturbance (hyperkalemia; hypomagnesemia; (Sobh *et al*., 2023). Prognosis in these patients has been estimated using scoring systems, such as the Simplified Acute Physiology Score (SAPS) and Sequential Organ Failure Assessment (SOFA) (Anuradha *et al*., 2021).

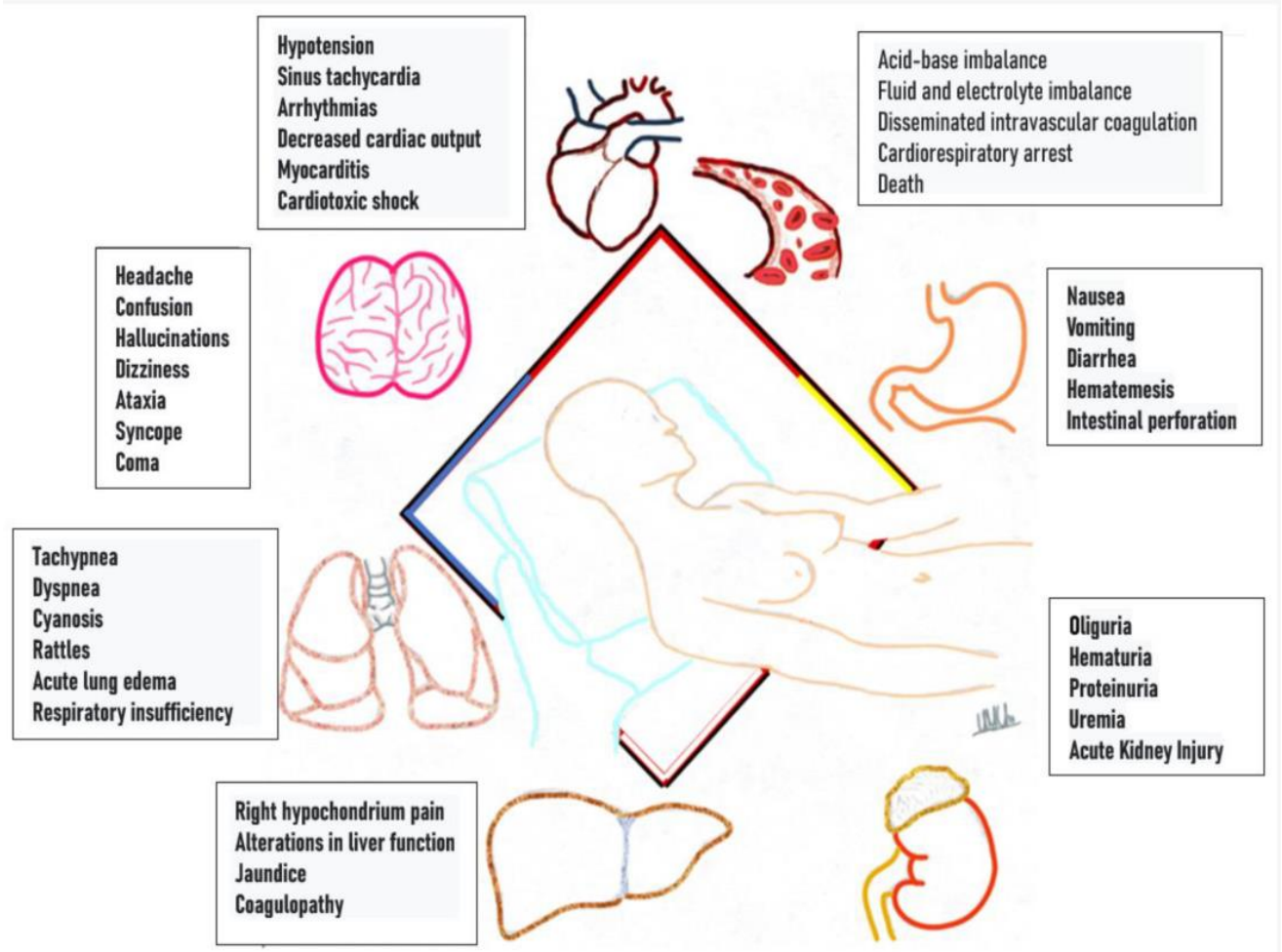

Figure 3: Systemic manifestations of aluminum phosphide poisoning, highlighting the involvement of multiple organ systems, including the cardiovascular, respiratory, gastrointestinal, renal, hepatic, and neurological systems

Sources: https://www.mdpi.com/2305-6304/11/7/555

Diagnostic Challenges

AlP poisoning is difficult to diagnose because there are no specific clinical signs and no universally available confirmatory laboratory tests. The majority of cases depend on a detailed clinical history and circumstantial evidence of exposure, such as ingestion of tablets used in grain preservation. In settings where intentional self-poisoning is common, the lack of disclosure by patients or families can further delay diagnosis (Zeng *et al*., 2018).

Typically, biochemical investigations show severe metabolic acidosis, with elevated lactate and an increased anion gap. Myocardial injury (Aimo *et al*., 2019).

is indicated by electrocardiographic changes such as ST-T abnormalities and conduction blocks. Features of pulmonary edema may be seen in imaging studies, such as chest X-rays, and echocardiography can show reduced myocardial contractility depicted in Figure 4.

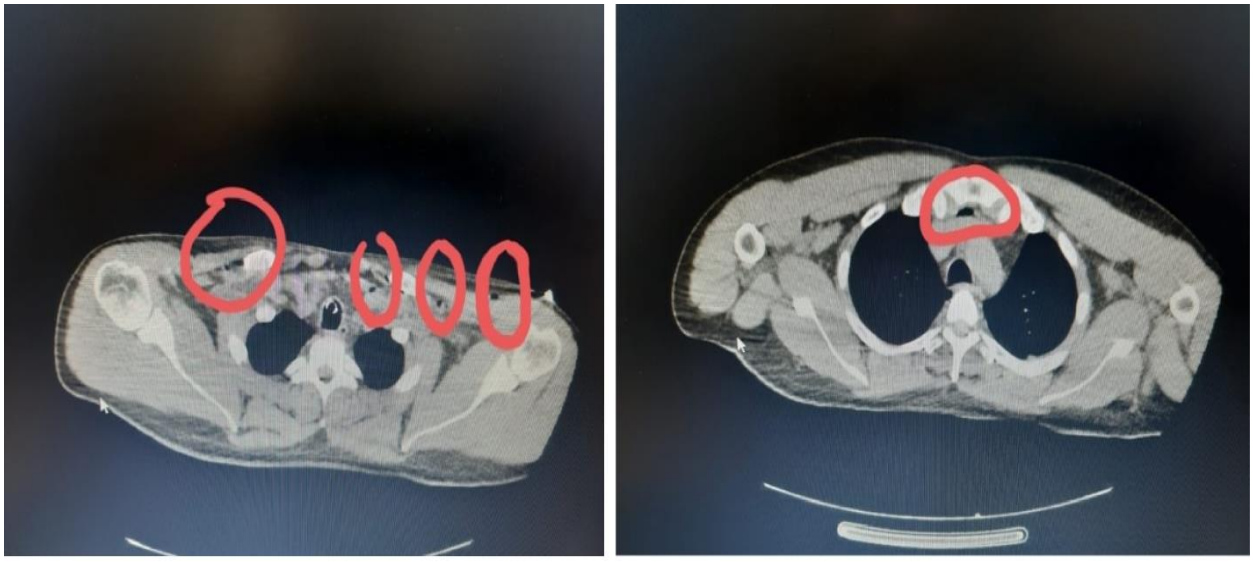

Figure 4: CT scans showing multiple air bubbles in the anterior chest wall and mediastinum (red circles), indicative of complications such as pneumomediastinum or emphysema in severe aluminum phosphide poisoning

Source: https://intjem.biomedcentral.com/articles/10.1186/s12245-024-00591-8/figures/3

Role of Biomarkers

The potential role of biomarkers in AlP poisoning early diagnosis and severity assessment is attracting attention. A strong correlation between Systemic toxicity exists between elevated serum lactate and high anion gap metabolic acidosis and worse outcomes. Studies have indicated that oxidative stress markers, including thiobarbituric acid reactive substances (TBARS) and low levels of antioxidants (glutathione), can predict prognosis and to some extent can also reflect the extent of cellular damage (Rathod & Garg, 2017). Research using portable gas analyzers on exhaled phosphine detection also shows promise for rapid diagnosis in emergency settings, but this availability is limited (Hrubešová *et al*., 2019).

Principles of Supportive Care in Toxicity Management

Supportive Care Definition and Goals

Supportive care is the various interventions designed to stabilize the patient's physiological and systemic damage especially if the patient has no specific antidote. Supportive care in the case of AlP poisoning emphasizes hemodynamic stabilization, correction of metabolic derangements, and addressing organ dysfunctions. The over-arching goal is to sustain life long enough so that the body can naturally get rid of the toxin and the aftereffects (Karanth & Nayyar, 2020).

The principles of supportive care in AlP poisoning include:
Hemodynamic Stabilization: The toxin has a propensity to cause refractory hypotension and shock, and preventing circulatory collapse is critical.
Oxygenation and Ventilation: Oxygen delivery to tissues and control of respiratory complications such as ARDS.
Metabolic and Electrolyte Correction: Hallmarks of severe toxicity are addressed by addressing metabolic acidosis, hypocalcemia, and hyperkalemia.
Monitoring and Prevention of Organ Failure: Prevent irredeemable damage (continuous monitoring of cardiac, renal, and respiratory function.

Importance in Aluminum Phosphide Poisoning
The management of AlP poisoning is entirely reliant on supportive care due to the absence of a definitive antidote. The rapid systemic effects of phosphine necessitate immediate and aggressive interventions to counteract its life-threatening impact. Cardiovascular collapse is the leading cause of mortality in AlP poisoning, making early initiation of vasoactive drugs and fluid resuscitation critical (Reddy *et al*., 2018).
Supportive care also plays a crucial role in managing complications such as ARDS, where mechanical ventilation and high-flow oxygen therapy may be required. Early correction of severe metabolic acidosis with sodium bicarbonate has shown potential in improving outcomes by stabilizing cellular metabolism (Aimo *et al*., 2019).
Moreover, the use of magnesium sulfate as a membrane stabilizer has been explored, as it potentially mitigates phosphine-induced cardiac toxicity, though its efficacy remains debated (Dewan *et al*., 2017).
In resource-limited settings, where advanced facilities such as ECMO are unavailable, effective supportive care can significantly influence survival outcomes. Prompt triage, monitoring, and timely administration of supportive measures are critical for improving prognosis in such contexts (Verma *et al*., 2020). The mechanism of toxicity caused by AIP tablets is well illustrated in Figure 5 below highlighting various dysfunctions and impairments.

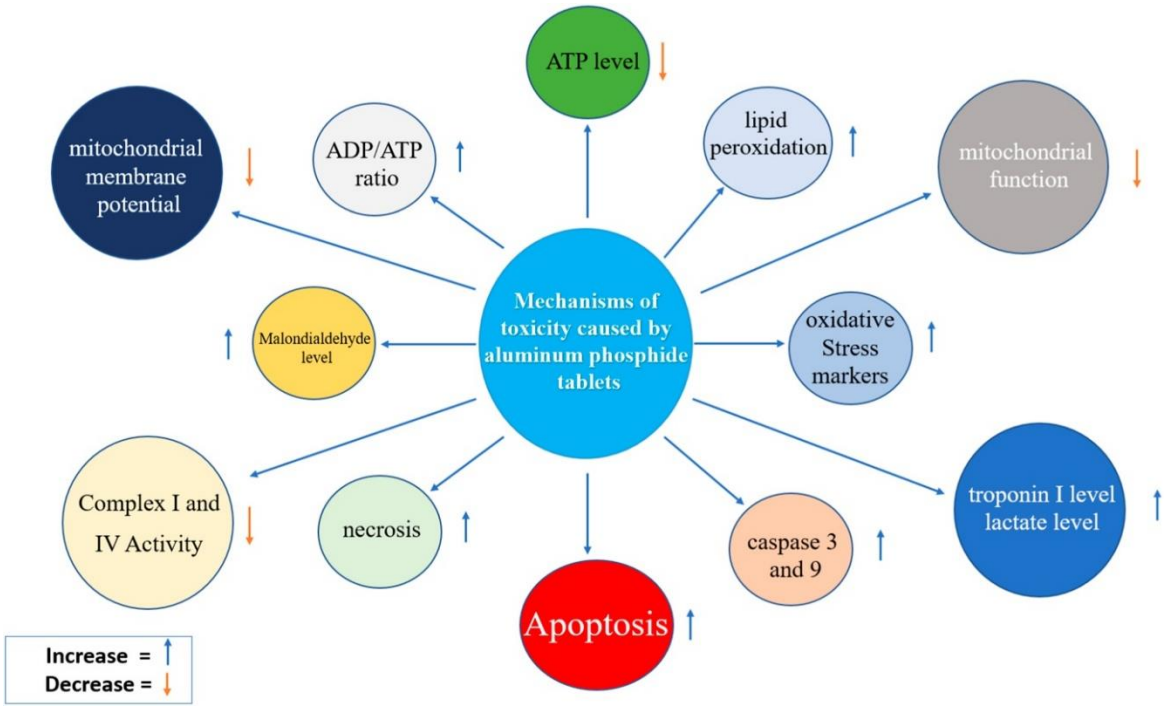

Figure 5: Mechanisms of toxicity caused by aluminum phosphide tablets, highlighting mitochondrial dysfunction, ATP depletion, oxidative stress, and systemic damage leading to apoptosis and necrosis5. Key Supportive Care Interventions
Source: https://journals.sagepub.com/doi/10.1177/09603271241290922

Respiratory and Airway Support

AlP poisoning is managed with effective respiratory support because of the rapid progression to hypoxemia and respiratory failure. Supplementation with early oxygen is crucial to reduce tissue hypoxia. Protective lung strategies with mechanical ventilation are often needed in the setting of ARDS, and high-flow oxygen is often necessary. Invasive mechanical ventilation for severe cases of respiratory insufficiency ARDS or respiratory failure was recommended (Garg *et al*., 2019), however, may consider non-invasive ventilation for mild to moderate cases of respiratory insufficiency. In patients with decreased consciousness, escaping the world beyond the patient is critical to prevent aspiration, and this is with airway protection through endotracheal intubation.

Cardiovascular Management

A hallmark of severe AlP poisoning is refractory hypotension which requires immediate aggressive management. The restoration of intravascular volume should be made initially using isotonic crystalloid fluid resuscitation, but it should not be overhydrated to decrease the risk of pulmonary edema (Ahmad *et al*., 2020). Commonly used vasopressors to maintain blood pressure when hypotension persists despite adequate fluid administration include norepinephrine. Dopamine may be considered as an adjunct, but its use is limited by its arrhythmogenic potential. Mehta *et al*. (2021) suggest that hemodynamic stability and reduced mortality can be improved by early initiation of vasoactive drugs.

Metabolic and Acid-Base Correction

A critical feature of AlP poisoning is severe metabolic acidosis secondary to lactate accumulation and mitochondrial dysfunction. Normally, excess hydrogen ions are buffered using cycling the use of ions that insert and transit within the mitochondria and by intravenous administration of sodium bicarbonate to correct acidosis. In critically ill patients, this intervention also helps to stabilize myocardial function and improve hemodynamics. However, the use should use, be judicious to avoid complications like hypernatremia, and hypokalemia (Anuradha *et al*., 2021). Emerging therapies such as dichloroacetate and L-carnitine are being investigated for their ability to overcome metabolic derangements (Pandey *et al*., 2020).

Gastrointestinal Decontamination

Initiation of gastrointestinal decontamination is most effective within an hour of ingestion. AlP poisoning is commonly treated with gastric lavage to remove unabsorbed tablets, especially when the ingestion is recent. This procedure, however, should be done with care to avoid aspiration (Kumar *et al*., 2019). AlP poisoning is less responsive to activated charcoal because phosphine gas is rapidly released, but activated charcoal may be used as an adjunct. Lavage using oxidizing agents such as potassium permanganate to neutralize the phosphine, however, has been explored but with only weak evidence (Aimo *et al*., 2019).

Renal Support

AlP poisoning is a potential cause of acute kidney injury (AKI), which is usually secondary to systemic hypoperfusion and toxin-induced cellular damage. Fluid balance is important to prevent renal function and careful monitoring is needed to prevent fluid overload. Renal replacement therapies, including hemodialysis, may be used in cases of severe AKI or refractory metabolic acidosis (Rana *et al*., 2021). It also allows severe electrolyte imbalances, such as hyperkalemia, which frequently occur in critically ill patients with AlP poisoning, to be corrected.

6. Adjunct Therapies and Emerging Interventions

Antioxidant Therapies

The critical role of oxidative stress in the pathophysiology of aluminum phosphide (AlP) poisoning has led to the emergence of antioxidant therapies as a promising adjunct to its management. Phosphine gas generates ROS that leads to lipid peroxidation, mitochondrial dysfunction, and systemic cellular

injury. Reducing oxidative damage has been shown by antioxidants such as N-acetylcysteine (NAC). NAC replenishes intracellular stores of glutathione and directly scavenges ROS protecting cellular membranes and mitochondrial function. Early NAC treatment, plus supportive care, is reported to provide improved survival (Goswami *et al*., 2021). Other antioxidants are also being studied for their potential to trump phosphine-induced oxidative stress, and although the evidence remains limited, vitamin E and selenium are other antioxidants that are being investigated (Prasad *et al*., 2020).

Chelation Agents

AlP poisoning is a relatively underexplored area of chelation therapy. Chelation agents could theoretically bind to aluminum ions and make them less bioavailable and, consequently, less toxic. Deferoxamine, a commonly prescribed chelating agent for iron toxicity, has been evaluated in some experimental studies for protecting individuals from oxidative damage induced by AlP toxicity (Yadav *et al*., 2019). Preliminary results indicate that deferoxamine may inhibit free radical generation by interfering with iron-mediated Fenton reactions. Its safety and efficacy in the setting of AlP poisoning remain to be established by clinical trials. There are no current clinical guidelines recommending the routine use of chelation agents because their therapeutic benefits have not been proven.

Extracorporeal Membrane Oxygenation (ECMO): role.

More and more, ECMO is being considered in the management of severe AlP poisoning, especially in the setting of refractory cardiogenic shock or ARDS. ECMO pumps blood to and from the body bypassing the heart and lungs in an attempt to also cleanse the body of the toxin is given to allow time for it to be metabolized and excreted. Early initiation of ECMO has been demonstrated in case reports to stabilize hemodynamics and improve survival when these cases are otherwise fatal (Raja *et al*., 2022). ECMO, however, is resource intensive and requires specialized expertise, and is therefore only available in high-resource settings. Its widespread adoption is limited by high costs and potential complications (bleeding, infections). However, for selected patients with severe AlP toxicity, ECMO may be a lifesaving intervention when conventional supportive measures fail.

7. Prognostic Indicators and Outcomes

Role of Early Intervention

Early intervention is important in improving outcomes for patients with AlP poisoning. Phosphine-induced systemic toxicity has a rapid onset and immediate stabilization of the airway, breathing, and circulation, as well as aggressive management of metabolic derangements, is required. Reduction in mortality rates is greatest if treatment is initiated in the “golden hour” (first hour) of exposure (Aggarwal *et al*., 2021). Particularly beneficial is early gastric decontamination, fluid resuscitation, and correction of metabolic acidosis. Delayed intervention, even by a few hours, is associated with increased morbidity from irreversible cellular injury, multi-organ failure, and refractory shock. Better outcomes occur in hospitals that are equipped with emergency care protocols specific to toxicology cases because there is quick access to trained personnel and the required resources (Kumar *et al*., 2019).

Predictive Scoring Systems

Several scoring systems have been adapted to predict the prognosis of AlP poisoning. Acute Physiologic Assessment and Chronic Health Evaluation (APACHE II) and Simplified Acute Physiology Score (SAPS II) are the two common scoring methods to determine the risk of physiologic derangement and organ failure by mortality (Gupta *et al*., 2020). These systems also yield a quantitative view, enabling clinician prioritization of intensive care and resource allocation.

Recent research has suggested AlP-specific scoring systems based on lactate levels, arterial blood gas (ABG) findings, and serum magnesium concentrations. To demonstrate, the ALP Specific Severity Index (ASSI), which includes cardiovascular and metabolic indicators to predict outcomes with high sensitivity, has been used (Raj *et al*., 2021). High lactate above 5 mmol/L, persistent hypotension, and very severe acidosis (pH <7.2) are bad prognostic factors. In addition to guiding clinical decision-

making, these tools enhance communication among healthcare teams about what to expect from the disease.

Factors Influencing Recovery

Recovery from AlP poisoning depends on several factors, including:

Ingested Dose: Increased mortality is directly correlated with a higher quantity of AlP that causes greater phosphine release and its systemic toxicity (Hrubešová *et al*., 2019).

Time to Treatment: It is also rapid initiation of care that minimizes systemic damage, specifically to the cardiovascular and respiratory systems.

Metabolic Stability: Recovery depends on the correction of metabolic acidosis and electrolyte imbalances. Poor outcomes (Mehta *et al*. 2020) are associated with severe hyperkalemia and acidosis.

Age and Comorbidities: Patients younger than 50 and without underlying medical problems such as diabetes or chronic heart disease are more likely to survive.

Organ Involvement: Prognosis is greatly influenced by the degree of organ dysfunction, especially cardiac and renal failure. Often, multi-organ failure portends a fatal outcome.

Healthcare Setting: This markedly improves survival rates with access to advanced supportive care (mechanical ventilation or ECMO).

Despite improvements in supportive care, mortality rates for severe AlP poisoning remain high, 30–80%. Thus, future outcomes will improve through the development of targeted therapies and biomarkers for early detection and intervention (Sharma *et al*., 2022).

Challenges in Implementing Supportive Care

Resource Limitations in Low Resource Settings

In low-resource settings, access to critical care infrastructure is limited, and supportive care for AlP poisoning is a challenge. Advanced monitoring systems, including continuous arterial blood gas analysis and bedside hemodynamic monitoring, are often not available in facilities and are critical for the management of patients with severe metabolic derangements and cardiovascular collapse. In addition, resource constraints prevent the availability of life-saving interventions such as ECMO or advanced ventilatory support in refractory cases (Verma *et al*., 2021). Mortality rates are also raised by the lack of intensive care unit beds in many rural and semi-urban hospitals. For example, patient transfers from peripheral centers to critical care often lead to worse outcomes (Rai *et al*., 2020).

Lack of Specific Antidotes

The biggest problem in controlling AlP poisoning is that there is no specific antidote. AlP management is entirely supportive care, unlike poisoning cases with established antidotes, such as NAC for acetaminophen toxicity. However, current experimental therapies, including magnesium sulfate and antioxidant supplements, have shown little clinical success to date, and lack robust validation (Anuradha *et al*., 2021). Clinical management is complicated by the absence of a targeted therapy, which requires medical teams to rely on symptomatic treatment and wait for spontaneous detoxification. Efforts in research of specific antidotes, for example, compounds that inhibit phosphine gas, or those that neutralize reactive oxygen species, are still in the preclinical or experimental stage (Prakash *et al*., 2020).

Training and Awareness Needed

A major yet overlooked barrier to effective supportive care is the absence of training for healthcare providers in the management of AlP poisoning. Phosphine toxicity is associated with the swift onset of toxicity that arises from disruption of organ function, and despite this, many frontline healthcare workers are unfamiliar with phosphine pathophysiology and rapid systemic effects, and thus many delay diagnosis and initiation of therapy. A frequent complication with these settings is mismanagement of fluid resuscitation, which leads to pulmonary edema (Bhardwaj *et al*., 2019). Furthermore, little awareness exists regarding the importance of early metabolic correction, the source of vasopressor administration, and the monitoring of continuous hemodynamics.

There is an urgent need for such education and training programs especially in regions that have frequently encountered toxicology emergencies, for example, due to the exposure to pesticides. Clinical decision-making and errors in critical care settings can be improved using simulation-based training and workshops on AlP management (Kapoor *et al*., 2022). The poisoning burden could also be reduced through public health campaigns intended to curtail the misuse of AlP as a suicide agent and greater regulation of its sale.

Future Directions

Advances in Therapeutic Strategies

Even though the management of AlP poisoning is largely supportive, recent advances in therapeutic strategies are promising. Neutralizing phosphine gas, mitigating oxidative stress, and improving mitochondrial function are the focus of emerging therapies. Investigation is ongoing of compounds such as dichloroacetate and L-carnitine, which increase mitochondrial energy production and have shown promise in animal studies (Mohan *et al*., 2021). Moreover, intravenous lipid emulsion therapy (ILE), a standard form of intravenous lipophilic drug toxicity treatment, has been employed to admit systemic toxicity resulting from phosphine gas by sequestering it. According to initial case reports, ILE is likely to improve survival in severe cases, but this needs to be validated by randomized clinical trials (Rao *et al*., 2020).

Antioxidant therapies, including high-dose NAC, selenium, and vitamin C, have been evaluated for reducing oxidative damage from phosphine. NAC has been shown to reduce mortality but the optimal dosing and timing of NAC remains to be determined (Gupta *et al*., 2022). In addition, extracorporeal therapies, such as ECMO and high-volume hemofiltration, are being incorporated into management protocols for refractory cases, although they are available only in high-resource settings (Kumar *et al*., 2022).

Research Gaps and Innovations

Although progress has been made, much remains to be studied in the understanding and treatment of AlP toxicity. The mechanisms of phosphine toxicity are not fully elucidated, especially its effects on non-cardiac tissues. Targeted therapy development requires a deeper understanding. Second, there are no specific biomarkers for early diagnosis and prognostication. Intervention is delayed by current reliance on nonspecific parameters, such as lactate levels and metabolic acidosis. Rapid phosphine gas assays could dramatically change diagnostics (Prasad *et al*., 2020).

For these reasons, innovative approaches, such as gene expression profiling and proteomic studies, are being explored to identify molecular targets and biomarkers for early severity prediction. In addition, the development of phosphine-neutralizing agents, such as nanoparticle-based adsorbents, is an exciting area of research. Theoretically, these agents could reduce phosphine bioavailability before systemic absorption, greatly improving outcomes (Sharma *et al*., 2021).

Multidisciplinary Approaches Importance

The management of AlP poisoning necessitates a multidisciplinary (toxicologists, critical care specialists, emergency physicians, and mental health professionals) approach. Among the specialties in hospitals, a collaboration of all specialties helps in providing timely as well as comprehensive care of stabilization to long-term recovery. This includes, for example, critical care teams who focus on hemodynamic and respiratory support, and toxicologists who contribute expertise in emerging therapies and antidotal research (Verma *et al*. 2021).

Many cases of AlP ingestion are intentional and mental health professionals are key to preventing repeat poisonings. Risk factors could be alleviated by early psychological interventions and community mental health programs including depression and sociocultural stressors. Public health initiatives to regulate the sales of AlP and promote better pest control substitutes would decrease availability and misuse (Anuradha *et al*., 2021). Further outcomes could be achieved through global collaboration and the establishment of specialized toxicology centers. Such centers would standardize care protocols, allow for multicentric research, and train healthcare professionals in high-risk areas.

Conclusion

Acute aluminum phosphide (AlP) poisoning represents a significant global health challenge, particularly in regions with widespread agricultural use and limited healthcare resources. Its lethality stems from the rapid release of phosphine gas, which disrupts mitochondrial function, generates oxidative stress, and leads to systemic multi-organ failure. The absence of a specific antidote underscores the critical importance of supportive care, which remains the cornerstone of management. Hemodynamic stabilization, respiratory support, metabolic corrections, and advanced interventions like extracorporeal therapies are vital components of care in severe cases. However, resource limitations, especially in low-income settings, significantly hinder access to such measures, contributing to poor outcomes. Emerging therapeutic strategies, including antioxidants and mitochondrial protectors, provide hope but require further clinical validation. The development of early diagnostic biomarkers and predictive scoring systems is essential to improve outcomes through timely and targeted interventions. Additionally, public health initiatives aimed at regulating AlP distribution and addressing the psychosocial determinants of intentional poisoning are imperative. Addressing the challenge of AlP toxicity requires a multidisciplinary approach, combining advancements in clinical care with public health strategies. Ongoing research and global collaboration are critical to overcoming current limitations and reducing the burden of this highly fatal poisoning. Enhanced awareness and resource allocation can significantly improve survival rates and patient outcomes.

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