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Diabetic ketoacidosis associated with acute poisoning and drug exposure: a focused narrative review

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ABSTRACT

INTRODUCTION: Diabetic ketoacidosis (DKA) is usually precipitated by insulin deficiency, infection, or physiologic stress, but acute poisoning and drug exposure may precipitate, aggravate, or obscure DKA. Toxicologic conditions may also mimic or coexist with DKA.

OBJECTIVE: To review the association between acute poisoning or drug exposure and DKA, distinguish toxicologic precipitation from drug-associated DKA during therapeutic exposure, identify important non-DKA mimics of metabolic acidosis, and assess FDA Adverse Event Reporting System (FAERS) evidence.

METHODS: PubMed/MEDLINE was searched from January 1996 through August 2026 using terms related to DKA, ketoacidosis, poisoning, overdose, intoxication, toxic exposure, and drug-associated ketoacidosis, supplemented by drug-specific searches and reference screening. Of 505 records identified, 360 were excluded after title screening, 145 underwent further screening, and 15 publications were retained as core evidence. Additional references informed background, DKA management, toxicologic differential diagnosis, and pharmacovigilance. Findings were synthesized narratively due to substantial heterogeneity.

RESULTS: Poisoning may precipitate or aggravate DKA through insulin interruption, altered consciousness, vomiting, dehydration, starvation, catecholamine-mediated stress, infection, and seizures. Case reports involving salbutamol, psychotropic agents, and methadone illustrate these mechanisms, while observational evidence links cocaine exposure with recurrent DKA. Sodium-glucose cotransporter 2 (SGLT2) inhibitors have stronger evidence for drug-associated DKA, particularly euglycemic DKA, mainly during therapeutic use. FAERS analyses demonstrate substantial reporting signals for drug-associated ketoacidosis; a 2026 analysis identified 6,977 ketoacidosis reports among 22,375,298 adverse-event reports. Toxic alcohols, salicylates, lactic acidosis, alcoholic ketoacidosis, starvation ketoacidosis, and 5-oxoproline acidosis may mimic or coexist with DKA.

CONCLUSION: Acute poisoning and DKA are not mutually exclusive. Most evidence supports indirect precipitation or aggravation rather than a demonstrated direct pharmacologic induction of DKA. Patients with diabetes after poisoning require simultaneous assessment for DKA, insulin interruption, dehydration, starvation, and toxicologic causes of metabolic acidosis, particularly when DKA is euglycemic or intoxication compromises insulin administration

KEY WORDS: Diabetic ketoacidosis, acute poisoning, drug overdose, toxicology, euglycemic diabetic ketoacidosis, pharmacovigilance.

INTRODUCTION

Diabetic ketoacidosis (DKA) is a potentially fatal metabolic emergency characterized by inadequate effective insulin activity, increased counter-regulatory hormone activity, accelerated lipolysis, hepatic ketogenesis, and metabolic acidosis. The contemporary consensus definition recognizes DKA as a state of diabetes or hyperglycemia accompanied by elevated circulating ketones and metabolic acidosis and emphasizes that DKA may occur without marked hyperglycemia, particularly in patients receiving sodium-glucose cotransporter 2 (SGLT2) inhibitors [1].

Infection, insulin omission, newly diagnosed diabetes, myocardial infarction, cerebrovascular disease, and other physiologic stresses are established precipitants of DKA. Acute poisoning is a less systematically studied contributor, but intoxication may create several conditions that facilitate the development or progression of DKA. These include altered consciousness, vomiting, dehydration, prolonged fasting, inability to administer insulin, catecholamine excess, infection, seizures, myocardial ischemia, and other systemic complications. The relationship between poisoning and DKA should not be interpreted as a single phenomenon. At least three clinically distinct situations should be considered. First, acute poisoning may precipitate or aggravate DKA indirectly through impaired consciousness, interruption of insulin administration, dehydration, starvation, vomiting, infection, or physiologic stress. Second, some toxic exposures may have direct or biologically plausible metabolic effects that promote hyperglycemia or ketogenesis. Third, many medications are associated with DKA during therapeutic or chronic exposure and represent adverse drug reactions rather than acute poisoning. SGLT2 inhibitors and certain antipsychotic drugs are important examples [2-8].

A further diagnostic problem occurs when poisoning produces high-anion-gap metabolic acidosis that is incorrectly attributed to DKA. Hyperglycemia alone does not establish DKA, and metabolic acidosis in a poisoned patient may result from lactic acidosis, toxic alcohol poisoning, salicylate poisoning, alcoholic ketoacidosis, starvation ketoacidosis, renal failure, or acetaminophen-associated 5-oxoproline acidosis [9-14]. These conditions may also coexist with genuine DKA, further complicating diagnosis and management. Accordingly, the presence of a drug or toxin in a patient with DKA should be interpreted as a potential precipitating, aggravating, or coincidental factor unless clinical and mechanistic evidence supports a causal relationship.

The purpose of this focused narrative review is to examine the evidence for DKA occurring in association with acute poisoning or drug exposure, distinguish acute toxicologic precipitation from therapeutic drug-associated DKA, summarize pharmacovigilance evidence, and highlight non-DKA toxicologic mimics and alternative causes of high-anion-gap metabolic acidosis.

METHODS

A focused narrative literature review was performed using PubMed/MEDLINE from January 1996 through August 2026. Search concepts included combinations of “diabetic ketoacidosis,” “DKA,” “ketoacidosis,” “hyperglycemic crisis,” “poisoning,” “overdose,” “intoxication,” “toxic exposure,” “acute poisoning,” and “drug-induced ketoacidosis.” Additional drug-specific searches included salbutamol, β 2-agonists, cocaine, psychotropic drugs, methadone, antipsychotics, SGLT2 inhibitors, liraglutide, acetaminophen, salicylates, toxic alcohols, and alcoholic ketoacidosis. Reference lists of relevant publications were manually examined to identify additional reports.

The PubMed/MEDLINE search identified 505 records. After title screening, 360 records were excluded because they were clearly unrelated to the review question, leaving 145 records for further screening. Following abstract and, when available, full-text assessment, 130 records were excluded because they did not provide relevant evidence concerning acute poisoning, drug exposure, DKA, or important toxicologic mimics within the scope of the review. Fifteen publications were retained as core evidence addressing the relationship between acute poisoning or drug exposure and DKA. Additional publications were used for background, contemporary DKA definitions and management, toxicologic differential diagnosis, and pharmacovigilance context.

For this review, acute poisoning was defined as an intentional or unintentional excessive exposure to a drug or toxin associated with toxicologic manifestations. Drug-associated DKA occurring during prescribed or otherwise therapeutic exposure was considered separately and was not interpreted as evidence that acute poisoning commonly causes DKA.

Core evidence included case reports, case series, observational studies, forensic reports, and pharmacovigilance studies. Particular attention was paid to the timing and magnitude of exposure, baseline diabetic status, insulin use or interruption, gastrointestinal losses, dehydration, infection, altered consciousness, nutritional status, co-ingestants, and competing causes of metabolic acidosis.

FDA Adverse Event Reporting System (FAERS) studies were incorporated as complementary pharmacovigilance evidence. Because some FAERS analyses used the broader outcome “ketoacidosis” rather than DKA specifically, their findings were not treated as equivalent to DKA-specific clinical evidence. Spontaneous reporting systems can identify reporting associations or disproportionality signals but cannot establish incidence or causality. Because the available evidence was heterogeneous and predominantly observational or descriptive, quantitative meta-analysis was not considered appropriate.

The evidence was organized into four clinically distinct categories: acute poisoning with possible direct or indirect metabolic effects; recreational drug exposure associated with DKA; drug-associated DKA during therapeutic exposure; and non-DKA toxicologic mimics or alternative causes of high-anion-gap metabolic acidosis.

Conceptual Relationship Between Acute Poisoning and DKA

The development of DKA reflects an imbalance between effective insulin activity and counter-regulatory hormones. Reduced effective insulin activity promotes lipolysis and hepatic conversion of free fatty acids into ketone bodies, whereas glucagon, catecholamines, cortisol, and growth hormone promote hepatic glucose production and further stimulate ketogenesis [1]. Acute poisoning can interfere with this balance through several pathways. Severe intoxication may produce a stress response with increased catecholamine and cortisol activity. Vomiting, poor oral intake, osmotic diuresis, hyperthermia, and dehydration may reduce circulating volume and worsen metabolic instability. Altered consciousness may prevent patients from recognizing hyperglycemia or administering scheduled insulin. In patients dependent on exogenous insulin, interruption of insulin therapy may rapidly become clinically important when combined with toxicologic stress.

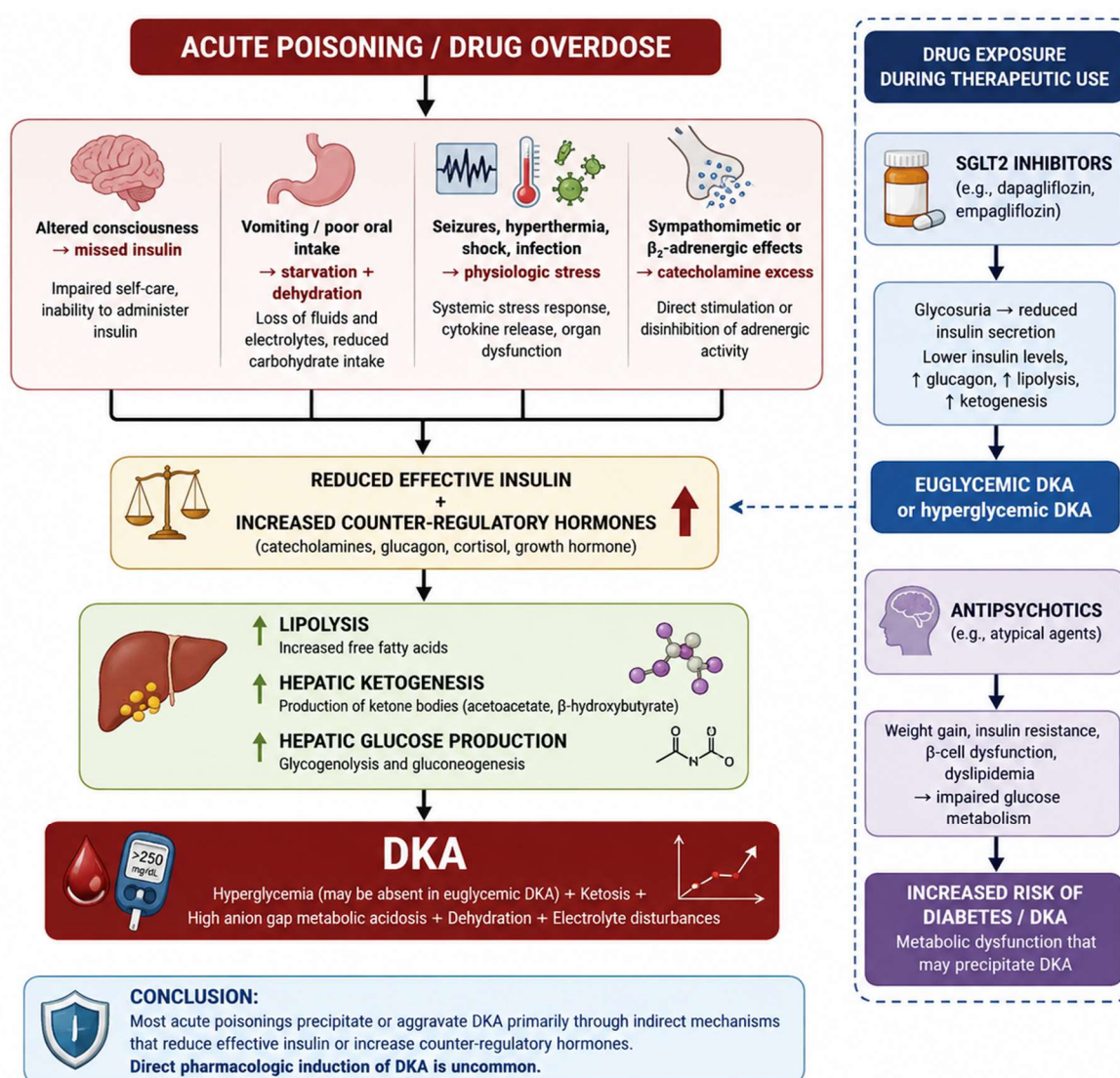


Figure 1. Proposed pathophysiological pathways through which acute poisoning and drug exposure may precipitate or aggravate diabetic ketoacidosis. DKA: diabetic ketoacidosis; SGLT2: sodium-glucose cotransporter 2. Illustration generated using ChatGPT (OpenAI) and reviewed and edited by the author.

Poisoning may also precipitate DKA indirectly through aspiration, pneumonia, sepsis, seizures, rhabdomyolysis, myocardial ischemia, or other complications. Consequently, the presence of a toxin in a patient with DKA should not automatically be interpreted as evidence of a direct pharmacologic induction of DKA. The exposure may instead have initiated a sequence involving impaired consciousness, missed insulin doses, starvation, dehydration, infection, or systemic stress.

This distinction is particularly important in forensic cases. Byard and colleagues described two fatal cases in which significant drug toxicity coexisted with severe DKA in insulin-dependent patients. In both cases, the authors concluded that intoxication likely impaired insulin administration and that death resulted from interacting toxicologic and metabolic processes rather than from isolated drug toxicity or isolated DKA [15] (**Figure 1**).

EVIDENCE FROM ACUTE DRUG OVERDOSE

Salbutamol Overdose

Salbutamol is a β 2-adrenergic agonist capable of increasing glycogenolysis, gluconeogenesis, lipolysis, and lactate production. Excessive exposure may therefore produce substantial metabolic disturbances. Habib and colleagues reported DKA temporally associated with oral salbutamol overdose [16]. The case provides a biologically plausible example in which marked β 2-adrenergic stimulation may have contributed to hyperglycemia and DKA. However, the evidence consists of an individual case report, and a direct causal relationship cannot be established. Dehydration, physiologic stress, underlying insulin deficiency, and other factors may have contributed. Salbutamol overdose should therefore be regarded as a possible precipitant or amplifier of DKA rather than an established direct cause.

Psychotropic Overdose

Psychotropic overdose provides another example of DKA occurring in temporal association with acute poisoning. Kawashita and colleagues described a patient with type 1 diabetes who developed severe DKA, shock, coma, and subsequent persistent vegetative state following excessive consumption of psychotropic agents [17]. The clinical course illustrates a plausible indirect mechanism in which intoxication caused prolonged unconsciousness, impaired oral intake, and prevented appropriate insulin administration. The report should not be interpreted as demonstrating that the psychotropic agents directly induced DKA. Rather, it illustrates how severe intoxication may disrupt the behavioral and physiologic conditions required to maintain metabolic control.

Methadone and Mixed Drug Toxicity

Byard and colleagues described two fatal cases in which DKA complicated significant drug toxicity [15]. One patient had a lethal sertraline concentration together with an elevated methadone concentration, whereas another had a potentially lethal methadone concentration. Severe DKA was present in both cases. The authors concluded that intoxication likely impaired the patients' ability to administer insulin and that death resulted from a combination of drug toxicity and DKA [15].

These forensic observations provide important evidence that drug toxicity and DKA can coexist and interact in fatal cases. They do not establish that methadone or sertraline directly induces DKA. Instead, altered consciousness and interruption of insulin therapy provide plausible mechanisms by which intoxication may permit otherwise manageable metabolic abnormalities to progress to fatal DKA.

Liraglutide Overdose

A 2026 case report described severe DKA temporally associated with supratherapeutic liraglutide exposure in a patient with type 2 diabetes who administered approximately 18 mg over 3 days and subsequently developed severe metabolic abnormalities, including a reported pH of 6.9 [18]. Because this represents an isolated observation, causality remains uncertain. Potential contributors include gastrointestinal effects, reduced food intake, dehydration, and underlying insulin deficiency. The case is noteworthy as a single observation of severe DKA following excessive exposure, but additional clinical and mechanistic evidence is required before liraglutide overdose can be considered an established cause of DKA.

Cocaine and Other Sympathomimetic Exposures

Cocaine deserves particular attention in patients with recurrent or unexplained DKA. Warner and colleagues retrospectively evaluated admissions for DKA at an urban teaching hospital between 1985 and 1994. Among 720 adult DKA admissions, 27 cocaine users accounted for 102 admissions. These patients were compared with 85 non-cocaine-user controls accounting for 154 admissions [19]. Cocaine users had more recurrent DKA admissions than controls and were significantly more likely to have omitted insulin before admission. They were also less likely to have an identifiable intercurrent systemic illness as a precipitant. The investigators proposed that cocaine might contribute through both insulin omission and increased counter-regulatory hormone activity [19]. These findings support an association between cocaine exposure and recurrent DKA but do not establish a purely direct pharmacologic mechanism. Cocaine increases catecholamine activity and may promote glycogenolysis, gluconeogenesis, lipolysis, and ketogenesis, while behavioral factors may simultaneously result in missed insulin doses [19].

A 2025 report by Wu and colleagues described four patients with cocaine-associated hyperglycemic crises and identified several potentially interacting factors, including missed insulin, infection, pulmonary injury, dehydration, and possible insulin resistance [20]. Because the report concerned hyperglycemic crises rather than a uniformly defined DKA cohort, its findings should be interpreted as supportive contextual evidence rather than as definitive proof of cocaine-induced DKA. The relationship should therefore be interpreted as multifactorial. Cocaine exposure may function as a precipitant, amplifier, or marker of several concurrent risk factors rather than as an isolated direct cause of DKA. Similar mechanisms may plausibly occur with other sympathomimetic exposures, although extrapolation should be cautious because stimulant toxicity more commonly produces lactic acidosis, hyperthermia, seizures, or rhabdomyolysis than true DKA.

DRUG-ASSOCIATED DKA DURING THERAPEUTIC EXPOSURE

SGLT2 Inhibitors

SGLT2 inhibitors require separate consideration because their association with DKA is supported by substantially stronger evidence than that available for most acute overdoses. These agents promote urinary glucose excretion and may reduce plasma glucose while increasing susceptibility to ketogenesis in settings of insulin deficiency, carbohydrate restriction, dehydration, acute illness, or insulin dose reduction. DKA may consequently occur with only modest hyperglycemia, producing euglycemic DKA [2].

FAERS analyses have demonstrated substantial reporting associations between SGLT2 inhibitors and DKA, including euglycemic DKA. He and colleagues identified 10,195 FAERS reports associated with SGLT2 inhibitors, including 1,680 reports of euglycemic DKA and 8,515 reports of DKA, with marked disproportionality compared with other glucose-lowering agents [3]. An earlier FAERS analysis likewise identified more than 2,500 DKA reports in which an SGLT2 inhibitor was listed as a suspect or concomitant medication [4]. A 2025 FAERS analysis of newer glucose-lowering agents also identified DKA reporting signals involving SGLT2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors, with the strongest signal observed for SGLT2 inhibitors [5].

The relevance of these findings to toxicology is primarily diagnostic rather than evidentiary for overdose. A patient presenting after an unexplained medication exposure may develop euglycemic DKA that is overlooked if clinicians rely on marked hyperglycemia as a diagnostic requirement. However, most SGLT2-associated DKA reports represent adverse drug reactions during therapeutic exposure rather than acute poisoning [2-5].

Antipsychotic Drugs

Antipsychotic-associated DKA represents another important category of drug-associated DKA. Evidence now extends beyond isolated case reports. A 2026 systematic review of clinical case reports identified 151 reports involving antipsychotic-associated diabetic complications, including 121 DKA cases, 28 HHS cases, and 2 cases involving both conditions. Olanzapine was associated with the largest number of reported DKA cases, followed by clozapine [6].

A separate 2026 systematic review of observational studies included 15 studies and found additional evidence supporting an association between atypical antipsychotic exposure and DKA, although the studies varied substantially in design, populations, case definitions, and outcomes [7]. These findings complement earlier evidence associating antipsychotic exposure with disturbances in glucose metabolism and development of diabetes [8]. Forensic literature has also documented fatal DKA in patients receiving second-generation antipsychotics [21]. The mechanisms are likely multifactorial and may involve weight gain, insulin resistance, altered glucose regulation, direct metabolic effects, and development or unmasking of diabetes.

Antipsychotic-associated DKA generally represents a drug-related adverse event during therapeutic or chronic exposure rather than acute poisoning. Consequently, the presence of an antipsychotic in a patient presenting after intentional overdose should not automatically be interpreted as evidence of direct acute induction of DKA. The chronic medication may instead represent a background metabolic risk factor, while the acute overdose contributes through altered consciousness, reduced intake, dehydration, or interruption of diabetes management.

FAERS PHARMACOVIGILANCE EVIDENCE

FAERS provides complementary evidence for identifying drug-associated metabolic safety signals but should be interpreted differently from clinical case reports and epidemiologic studies. Spontaneous reporting systems can identify disproportionate reporting of adverse events but cannot establish incidence or causality.

The 2025 FAERS analysis by Thaibah and colleagues evaluated reports from the first quarter of 2019 through the third quarter of 2024 and identified DKA reporting signals associated with SGLT2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors. The strongest signal was observed with SGLT2 inhibitors [5]. These findings provide real-world pharmacovigilance support for drug-associated DKA but do not establish absolute risk or prove causation.

The 2026 analysis by Du and colleagues provides a broader pharmacovigilance assessment of drug-associated ketoacidosis, rather than a DKA-specific analysis. The investigators analyzed FAERS reports submitted from the first quarter of 2004 through the second quarter of 2025. Among 22,375,298 adverse-event reports, 6,977 were related to the broader outcome of ketoacidosis. The drugs with the greatest numbers of reports included metformin, quetiapine, empagliflozin, canagliflozin, and dapagliflozin, whereas the highest reporting odds ratios were predominantly observed with SGLT2 inhibitors [22].

These findings reinforce the value of pharmacovigilance for identifying uncommon or previously underrecognized drug-associated metabolic toxicities. However, the 6,977 reports should **not** be interpreted as 6,977 confirmed DKA cases because the analyzed outcome was ketoacidosis rather than DKA specifically. Furthermore, report counts should not be interpreted as incidence, and a disproportionality signal does not establish causality. FAERS reports may contain incomplete clinical information, multiple concomitant medications, underlying diabetes, infection, dehydration, nutritional abnormalities, and other potential explanations for metabolic acidosis. Reporting may also be influenced by regulatory warnings, publicity, and changes in prescribing patterns [3-5,22].

Accordingly, FAERS should be regarded as hypothesis-generating evidence that complements clinical and epidemiologic evidence. This distinction is particularly important in the present review because most FAERS evidence concerns drug-associated adverse-event reporting rather than acute poisoning or intentional overdose.

TOXICOLOGIC MIMICS AND ALTERNATIVE CAUSES OF METABOLIC ACIDOSIS

One of the most important diagnostic problems after poisoning is distinguishing true DKA from other causes of high-anion-gap metabolic acidosis. Hyperglycemia alone does not establish DKA, and a poisoned patient with metabolic acidosis should not automatically be assumed to have DKA [1,9]. Alcoholic ketoacidosis is an important non-DKA differential diagnosis, particularly in patients with chronic alcohol exposure, vomiting, reduced nutritional intake, and volume depletion. Glucose may be normal or only mildly elevated. Treatment differs from conventional DKA and generally emphasizes dextrose-containing fluids, volume and electrolyte replacement, and thiamine rather than insulin as the primary intervention [9].

Starvation ketoacidosis is another non-DKA cause that may occur after prolonged fasting, vomiting, poor oral intake, or severe intoxication. It is particularly relevant to poisoning because intoxicated patients may remain unable to eat for prolonged periods. Ketosis can become substantial despite normal or mildly elevated glucose. The clinical context, degree of insulin deficiency, glucose concentration, β -hydroxybutyrate level, and overall metabolic profile are important in distinguishing starvation ketoacidosis from DKA [1,9].

Lactic acidosis is another major alternative or coexisting process. It may occur with seizures, shock, hypoperfusion, hyperthermia, severe sympathomimetic toxicity, cyanide poisoning, metformin-associated toxicity, and other toxicologic conditions. Lactate may also be elevated in genuine DKA. Measurement of both lactate and β -hydroxybutyrate can therefore be useful when the clinical picture is complex [10]. Salicylate poisoning may produce a mixed respiratory alkalosis and metabolic acidosis and can coexist with ketosis in patients with vomiting or poor intake [11]. An unexplained high-anion-gap acidosis accompanied by tachypnea, neurologic symptoms, or a mixed acid-base disturbance should therefore prompt consideration of salicylate exposure rather than automatic attribution to DKA.

Toxic alcohol poisoning is another critical non-DKA mimic. Methanol and ethylene glycol produce high-anion-gap metabolic acidosis through toxic metabolites and may be accompanied by an increased osmolal gap. These conditions require specific antidotal treatment and, in selected cases, extracorporeal therapy rather than insulin-centered management [12]. Acetaminophen exposure may cause high-anion-gap metabolic acidosis through accumulation of 5-oxoproline, particularly in patients with malnutrition, renal dysfunction, chronic acetaminophen exposure, or other predisposing factors [13,14]. Measurement of β -hydroxybutyrate, lactate, renal function, and exposure history can help distinguish this process from DKA.

Importantly, these conditions are not always mutually exclusive. A patient with diabetes may simultaneously have DKA and lactic acidosis, alcoholic ketoacidosis and hyperglycemia, or DKA with an additional toxic alcohol exposure. The diagnostic goal is therefore not merely to identify one cause of the anion gap but to determine whether multiple processes are present.

Table 1. Representative evidence linking acute poisoning and drug exposure with DKA.

Evidence category	Exposure	Study design	Principal finding and interpretation
Acute poisoning	Salbutamol	Case report	DKA after oral overdose; β 2-adrenergic stimulation, stress, and dehydration may have contributed. Very low causal strength [16].
Acute poisoning	Psychotropic agents	Case report	DKA after overdose in a patient with type 1 diabetes; impaired insulin administration, poor intake, dehydration, and stress provide a plausible indirect mechanism [17].
Acute/mixed toxicity	Methadone $\pm$ sertraline	Forensic case reports	DKA complicated two fatal intoxications, plausibly through altered consciousness and inability to administer insulin. Very low causal strength [15]
Recreational drug exposure	Cocaine	Observational study/case series	Recurrent DKA and insulin omission were reported among cocaine users; sympathetic effects and insulin omission may contribute. Causality remains uncertain [19,20].
Therapeutic exposure	Antipsychotic drugs	2026 systematic review of case reports	121 DKA cases among 151 reports of antipsychotic-associated diabetic complications; olanzapine and clozapine were prominent. Supports an association [6].
Therapeutic exposure	Antipsychotic drugs	2026 systematic review of observational studies	Fifteen observational studies provided additional evidence of an association with DKA, although definitions and populations varied substantially [7].
Therapeutic exposure	SGLT2 inhibitors	FAERS analysis	10,195 DKA reports, including euglycemic DKA, with strong disproportionality. Supports a pharmacovigilance signal rather than overdose causation [3].
Therapeutic exposure	SGLT2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors	FAERS analysis	DKA signals were identified across several glucose-lowering drug classes, strongest for SGLT2 inhibitors. Pharmacovigilance association does not establish incidence or causality [5].
Acute excessive exposure	Liraglutide	Case report	Severe DKA after approximately 18 mg over 3 days; reduced intake, dehydration, gastrointestinal effects, and metabolic vulnerability were possible contributors. Very low causal strength [18].

Table note: Acute-poisoning reports generally support indirect precipitation or aggravation of DKA through insulin interruption, altered consciousness, poor intake, dehydration, vomiting, infection, or physiologic stress. Therapeutic drug exposures, particularly SGLT2 inhibitors and antipsychotic drugs, have stronger evidence for an association with DKA. Case reports and pharmacovigilance signals do not establish incidence or causality.

DIAGNOSTIC APPROACH IN THE POISONED PATIENT

When a patient with diabetes presents after suspected poisoning, DKA should be evaluated simultaneously with the toxicologic differential rather than considered an alternative diagnosis. Initial assessment should include plasma glucose, venous or arterial blood gas analysis, serum electrolytes, bicarbonate, renal function, β -hydroxybutyrate, lactate, and, when appropriate, measured serum osmolality and urinalysis [1].

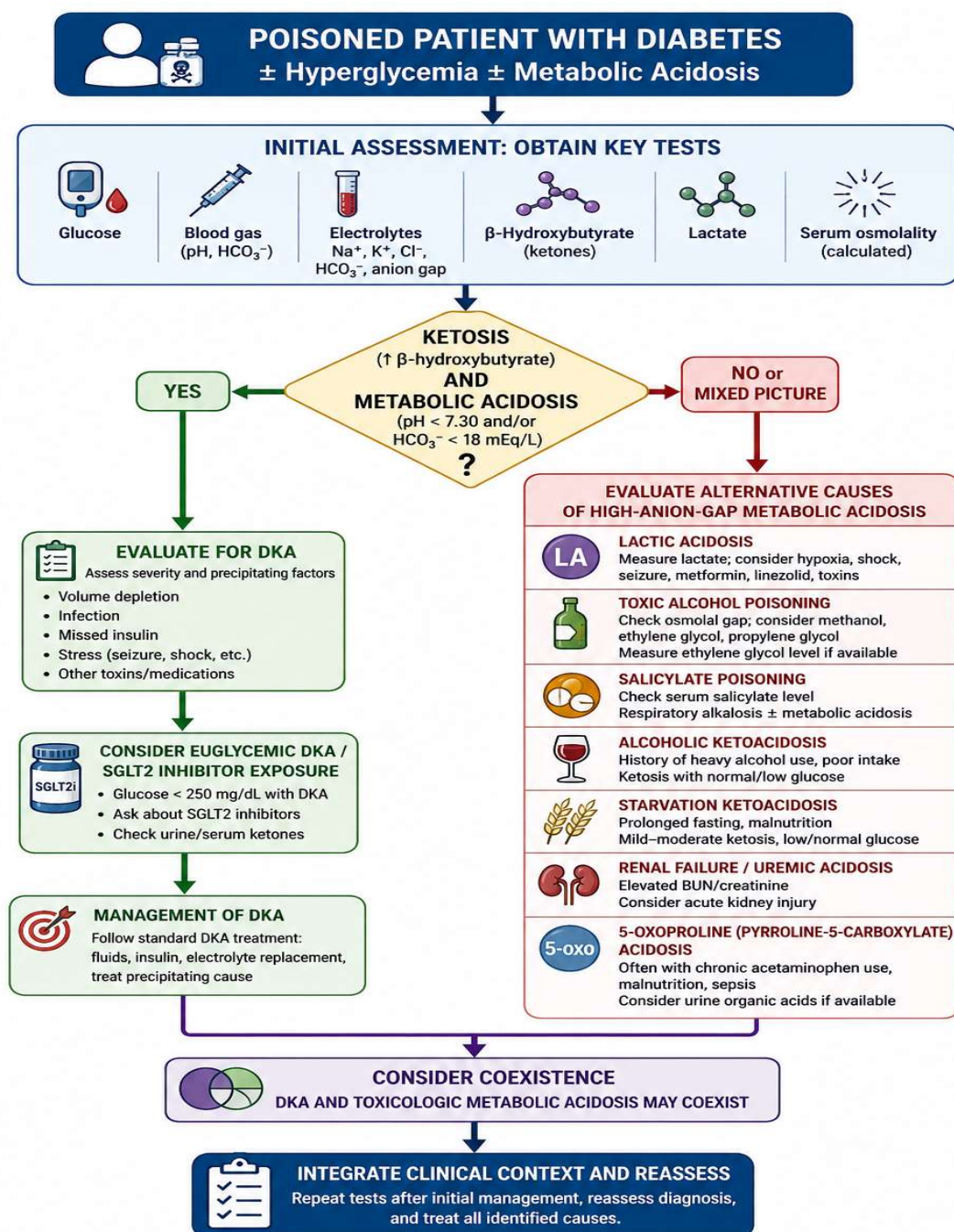


Figure 2. Diagnostic approach to metabolic acidosis and suspected diabetic ketoacidosis in patients with acute poisoning or drug exposure. Illustration generated using ChatGPT (OpenAI) and reviewed and edited by the author.

DKA should not be diagnosed on the basis of hyperglycemia alone. Appropriate diagnosis requires evidence of ketonemia or ketosis together with metabolic acidosis in the relevant clinical context [1]. Direct measurement of β -hydroxybutyrate is preferable to reliance on urinary ketones because β -hydroxybutyrate is the predominant ketone body during DKA [1].

The history should establish baseline diabetic status, diabetes type, usual insulin regimen, recent insulin administration, oral intake, vomiting, alcohol exposure, prescribed medications, recreational drug use, and the circumstances and timing of the suspected exposure. Medication reconciliation is particularly important for SGLT2 inhibitors, atypical antipsychotics, glucocorticoids, sympathomimetics, and other agents capable of altering glucose metabolism.

In unconscious or unreliable patients, collateral history and scene information may be decisive. In insulin-dependent patients, clinicians should specifically consider whether intoxication prevented insulin administration. This mechanism was central to the forensic cases reported by Byard and colleagues [15]. Normal or only mildly elevated glucose does not exclude DKA. This is particularly important with SGLT2 inhibitors and other circumstances associated with euglycemic DKA [1-3].

Conversely, marked hyperglycemia does not prove DKA. A poisoned patient with hyperglycemia and high-anion-gap acidosis should be evaluated for β -hydroxybutyrate, lactate, toxic alcohol exposure, salicylates, alcoholic ketoacidosis, starvation ketoacidosis, renal failure, and acetaminophen-associated 5-oxoproline acidosis according to the clinical circumstances [9-14,23] (**Figure 2**).

MANAGEMENT CONSIDERATIONS

When DKA is confirmed, treatment should follow established DKA principles while the poisoning and its complications are managed simultaneously. Intravenous fluids, insulin, electrolyte replacement, glucose when necessary, and close monitoring of metabolic and ketone resolution remain central to treatment [1,23].

The toxicologic context may modify immediate priorities. Clinicians should assess for dehydration, altered consciousness, seizures, hyperthermia, rhabdomyolysis, infection, myocardial ischemia, and shock while treating DKA. In SGLT2 inhibitor-associated euglycemic DKA, the drug should be discontinued and insulin continued despite relatively modest glucose concentrations; dextrose may be required to permit continued insulin administration until ketogenesis resolves [1-3].

A concurrent toxicologic cause of metabolic acidosis must be actively considered. Suspected salicylate or toxic alcohol poisoning requires appropriate antidotal and, when indicated, extracorporeal treatment [11,12]. Alcoholic and starvation ketoacidosis should not automatically be managed as conventional DKA. Thus, treatment should address both DKA and the underlying toxicologic process rather than focusing solely on the anion gap.

FORENSIC AND MEDICOLEGAL CONSIDERATIONS

The coexistence of DKA and poisoning creates particular challenges in death investigation. Toxicologic detection of a drug does not establish that poisoning was the sole cause of death, and the presence of DKA does not exclude fatal drug toxicity. The cases reported by Byard and colleagues demonstrate how drug toxicity and DKA may interact to produce death [15].

Postmortem assessment may require integration of clinical history, scene evidence, toxicology, vitreous glucose, β -hydroxybutyrate where available, renal and hepatic findings, and evidence of chronic diabetes. In the Byard cases, markedly elevated vitreous glucose and β -hydroxybutyrate supported severe DKA, while toxicologic findings demonstrated significant drug exposure [15].

Postmortem hyperglycemia and ketones should therefore be interpreted in conjunction with the circumstances of death, evidence of chronic diabetes, toxicologic findings, and other postmortem observations rather than in isolation. The forensic diagnosis should recognize that DKA and drug toxicity may represent interacting contributors rather than mutually exclusive causes of death.

LIMITATIONS OF THE EVIDENCE

The principal limitation of the literature is the low level of causal evidence directly linking acute poisoning to DKA. Most reports of DKA after acute poisoning are case reports or small case series. Such reports are useful for identifying unusual associations and plausible mechanisms but cannot establish incidence or reliably distinguish direct pharmacologic effects from indirect pathways such as insulin omission, starvation, dehydration, infection, or systemic stress. The heterogeneity of the published evidence also limits direct comparison. Reports vary substantially in diabetes type, baseline treatment, exposure dose, timing, nutritional status, insulin administration, co-ingestants, clinical severity, and methods used to define DKA. The observational cocaine literature provides stronger evidence of association than isolated overdose reports, but it remains vulnerable to confounding by behavioral and clinical factors. The original Warner study found more frequent insulin omission among cocaine users, making it difficult to separate the pharmacologic effects of cocaine from treatment interruption [19].

Therapeutic drug-associated DKA should also not be extrapolated directly to overdose. SGLT2 inhibitors and antipsychotics have substantially stronger evidence for association with DKA during therapeutic exposure than most acutely poisoned drugs, but these findings do not demonstrate that overdose commonly causes DKA [2-8]. FAERS provides a much larger evidence base but has important limitations, including underreporting, stimulated reporting, duplicate reports, missing clinical information, confounding by indication, concomitant medications, and reporting bias. Disproportionality measures identify whether an event is reported more frequently than expected; they do not establish absolute risk, incidence, or causality [3-5,22].

Finally, the PubMed/MEDLINE search and citation-based supplementary searching were designed for a focused narrative review rather than a formal systematic review. The reported record numbers therefore describe the screening process used for this review and should not be interpreted as evidence of exhaustive identification of every publication on the subject.

CONCLUSIONS

Acute poisoning and drug overdose may precipitate, aggravate, or obscure DKA. For most acute poisoning cases, the available evidence supports indirect mechanisms involving insulin interruption, altered consciousness, dehydration, vomiting, starvation, infection, catecholamine excess, or other systemic stress rather than a demonstrated direct pharmacologic induction of DKA. Salbutamol overdose, psychotropic overdose, methadone-associated toxicity, and cocaine exposure illustrate different possible pathways, but the strength of evidence varies substantially among these exposures [15-20].

Cocaine exposure has been associated with recurrent DKA and more frequent insulin omission, while case reports demonstrate that severe drug toxicity can impair insulin administration and contribute to fatal DKA [15,19,20]. These observations support the concept of poisoning as a precipitating or amplifying factor rather than establishing a uniform direct toxic mechanism.

SGLT2 inhibitors represent the strongest pharmacovigilance evidence for drug-associated DKA, particularly euglycemic DKA. Antipsychotic drugs also have increasing clinical and observational evidence for association with DKA [2-8]. These drug-associated events, however, primarily occur during therapeutic or chronic exposure and should be distinguished from acute poisoning.

The 2026 FAERS analysis demonstrates substantial reporting of drug-associated ketoacidosis, including 6,977 reports among 22,375,298 adverse-event reports and strong disproportionality signals predominantly involving SGLT2 inhibitors [22]. Because the FAERS outcome was broader ketoacidosis rather than DKA specifically, these findings should not be interpreted as 6,977 confirmed DKA cases or as evidence of incidence.

For emergency physicians and medical toxicologists, the central practical message is that DKA and poisoning are not mutually exclusive diagnoses. A poisoned patient with diabetes, hyperglycemia, and metabolic acidosis requires simultaneous evaluation for true DKA and alternative toxicologic causes of the anion gap. β -Hydroxybutyrate measurement, careful assessment of insulin interruption, detailed medication and exposure history, and targeted evaluation for lactate, toxic alcohols, salicylates, alcoholic ketoacidosis, starvation ketoacidosis, renal failure, and 5-oxoproline acidosis can prevent major diagnostic errors. Particular vigilance is required when DKA is euglycemic or when intoxication has impaired the patient's ability to administer insulin.

Future research should move beyond isolated case reports toward well-characterized multicenter studies that distinguish acute overdose from therapeutic drug exposure and systematically document exposure timing, dose, insulin interruption, dehydration, nutritional status, co-ingestants, and competing causes of metabolic acidosis. Such studies are needed to determine whether selected toxins have direct pharmacologic effects that can induce DKA or primarily precipitate DKA through indirect toxicologic, behavioral, and physiologic pathways.

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