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EM - REVIEW

Progress in the management of acute colchicine poisoning in adults

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Abstract
Colchicine is a tricyclic, lipid-soluble alkaloid which has long been used to treat gout and many immunological diseases. Due to its narrow therapeutic window and long half-life of elimination, colchicine overdose occurs occasionally. Unfortunately, some patients lost their lives because of colchicine overdose or suicide. Acute colchicine poisoning can lead to original gastrointestinal disorders, shock, progressive multiple organ failure, and myelosuppression. Although many researchers in the world performed lots of research, there are currently no specific antidotes for colchicine poisoning. Meanwhile, there are no management guidelines to treat patients with acute colchicine poisoning until now. Herein, we systematically elaborate on the clinical features and progress in the management of acute colchicine poisoning in adults according to the previous literature. This paper will provide some valuable and available information for clinicians.

Keywords Colchicine poisoning · Multiple organ dysfunction · Myelosuppression · Management strategy · Blood perfusion · Extracorporeal life support

Introduction

Colchicine is a naturally occurring alkaloid extracted from the plants *Colchicum autumnale* and *Gloriosa superba* [1]. Colchicine is also an ancient drug which was originally used to treat gout for centuries. Due to its toxicity, the use of colchicine is clinically limited. In recent years, it has been approved by the Food and Drug Administration (FDA) to treat many autoinflammatory diseases including Behcet's disease, Familial Mediterranean fever, osteoarthritis, and certain spondyloarthropathy [2, 3]. Interestingly, new emerging evidence suggests that colchicine can significantly reduce the risk of mortality and hospitalization in patients with COVID-19 [3, 4]. The administration with a recommended dose of colchicine is safe for patients. The most common adverse effects of colchicine in a therapeutic dose are gastrointestinal disturbance including diarrhea, vomiting, and nausea, occurring in less than 10% of patients [1]. Excessive doses of colchicine would cause serious toxicity.

Acute toxicity by colchicine is not common but is followed by a high mortality rate. Although deaths resulting from the oral ingestion of overdose colchicine are reported every year, there are no management guidelines or specific antidotes currently. It is essential for clinicians to recognize and treat colchicine poisoning. Herein, the pharmacologic properties and toxic effects of colchicine are described. Meanwhile, the previous reports on acute colchicine overdose in adults were summarized and the management of colchicine poisoning was systematically illustrated. This paper would provide some valuable information for clinicians to treat patients with acute colchicine poisoning effectively.

Pharmacologic properties

Colchicine is a small molecule with a molecular weight of 399 Da. It exerts an anti-inflammatory effect due to the ability to suppress neutrophil activity. In addition, colchicine can impair mitosis by inhibiting microtubule devices which are necessary for the maintenance of cellular homeostasis and thereby causing cell injury [5, 6].

Colchicine can spread rapidly and widely to all tissues shortly after oral administration, accumulating in bone marrow, kidney, heart, liver, intestinal mucosa, and brain [7]. Colchicine is metabolized to 2- and 3-demethylcolchicine

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by the CYP 3A4 isoform of cytochrome P450 in hepatocytes, followed by biliary excretion [8]. Colchicine and its metabolites undergo significant enterohepatic re-circulation which may further lead to its retention in the body [9]. It has a short initial distribution phase, with a plasma half-life of 1–2.7 h. Its volume of distribution (V_d) can reach 7–10 L/kg in a therapeutic dose, which is significantly larger than the extracellular compartment [7]. Notably, its V_d can even reach up to 21 L/kg in overdose [10]. It indicates that colchicine can be distributed to nearly all tissues. Its binding to albumin is moderate (10–50%) in therapeutic doses [6, 11]. Colchicine and its metabolites are mainly eliminated through the liver. The kidneys contribute only 10–20% of the total colchicine clearance [12]. The elimination half-life of colchicine is 9.3–30 h in humans [11, 13]. In healthy volunteers given oral colchicine daily, the plasma levels of colchicine can reach the steady-state within a few days [13]. Therefore, the time to stable plasma levels is consistent with the long elimination half-life.

It is commonly accepted that CYP3A4 plays a vital role in colchicine metabolism and elimination. In addition to CYP3A4, *P*-glycoprotein that is an ATPase efflux pump can extrude colchicine from the enterocytes to prevent gastrointestinal absorption [1]. Both CYP3A4 and *P*-glycoprotein are mainly responsible for colchicine metabolism. Therefore, the levels of CYP3A4 and *P*-glycoprotein would determine the content of colchicine in the human body. From another point of view, the drugs which inhibit or induce the activities of CYP3A4 and *P*-glycoprotein would affect the efficacy or toxicity of colchicine. The possible inducers and inhibitors of CYP 3A4 or *P*-glycoprotein [1, 14, 15] are shown in Table 1. Accordingly, when concurrent treatment with a strong inhibitor of CYP3A4 or P-glycoprotein is required, it is recommended that the colchicine dose should be reduced to prevent its toxicity.

Colchicine toxicity

Due to its narrow therapeutic window (1.2–2.4 mg/day in adults) [6] and long half-life of elimination mentioned above, the clinical application of colchicine is limited to some extent. The maximum oral doses of colchicine for familial Mediterranean fever (FMF) and acute gout recommended by the Food and Drug Administration (FDA) are 2.4 mg/day and 1.8 mg/day [6], respectively. Therefore, oral ingestion exceeding the maximum oral dose of 2.4 mg/day is commonly considered to be a colchicine overdose. Acute oral ingestion exceeding 0.5 mg − 0.8 mg/kg of colchicine is considered to be fatal [6, 16]. Nevertheless, there is no clear-cut line between nontoxic, toxic, and lethal doses of colchicine in human [6].

Colchicine overdose can inhibit cell division by fixing the intracellular tubulin and disrupting the mitosis and transport systems. Thus, the organs with active cell proliferation, such as the gastrointestinal tract, bone marrow, and hair follicles, are often the most susceptible to the toxic effects of colchicine [17, 18]. Moreover, colchicine overdose can lead to multiple organ dysfunction by inhibiting cell mitosis progress, particularly in the liver and kidneys. According to previous reports, the fatality rate of acute colchicine poisoning may range from 14.3 to 25.6% [19, 20].

Table 1 Drugs affecting colchicine toxicity

Interactions with colchicine	Representative drugs
CYP3A4 inhibitors (↑ toxicity)	Almorexant, alpha, amiodarone, amprenavir, aprepitant, atazanavir, boceprevir, casopitant, ceritinib, chloramphenicol, cimetidine, ciprofloxacin, clarithromycin, clotrimazole, cobicistat, conivaptan, crizotinib, cyclosporine, dalfopristin, danazol, darunavir, dasatinib, deferasirox, delavirdine, diltiazem, dronedarone, erythromycin, fluconazole, fluoxetine, fluvoxamine, fosamprenavir, fosaprepitan, fusidic acid, grapefruit juice, idelalisib, imatinib, indinavir, interferon alpha, isoniazid, itraconazole, ketoconazole, lapatinib, lopinavir, lomitapide, miconazole, natural, nefazodone, nelfinavir, paroxetine, posaconazole, propoxyphene, quinupristin, ritonavir, saquinavir, simeprevir, telaprevir, telithromycin, tipranavir, troleandomycin, verapamil, voriconazole, etc
P-glycoprotein inhibitors (↑ toxicity)	Atorvastatin, budesonide, clarithromycin, cyclosporine, diltiazem, erithromycin, grapefruit juice, hydrocortisone, itraconazole, ketoconazole, lovastatin, propafenone, quinidine, ranolazine, saquinavir, simvastatin, tacrolimus, verapamail, etc
CYP3A4 inducers (↓ toxicity)	Aminoglutethimide, armodafinil, barbiturates, bexarotene, bosentan, carbamazepine, dabrafenib, dexamethasone, efavirenz, enzalutamide, eslicarbazepine, etravirine, fosamprenavir, fosphenytoin, griseofulvin, lumacaftor, modafinil, nafcillin, nevirapine, oxcarbazepine, phenytoin, primidone, rifabutin, rifampin, rifapentine, St. John's wort, etc
P-glycoprotein inducers (↓ toxicity)	Phenytoin, curcumin, carbamazepine, genistein, St. John's wort extract, quercetin, rifabutin, etc

Literature review

Clinical reports in adults between January 2001 and December 2021 were sought in PubMed and Web of Science using the following search terms: ("colchicine poisoning " OR "colchicine overdose".) Data concerning the dosage of colchicine, clinical manifestations, management, and outcomes were extracted in this paper. Meanwhile, case series of acute colchicine poisoning were also reviewed. The reports which met any of the following criteria were included in this study: (1) age ≥ 18 years old; (2) patients had a definite history of suicidal poisoning with colchicine or overdose after colchicine misuse treatment; (3) time interval between ingestion and admission to hospital ≤ 72 h. The reports were excluded based on the following criteria: (1) colchicine poisoning was confirmed by autopsy; (2) patients suffered from accidental poisoning with the plants containing colchicine; (3) with other drugs or toxicants poisoning; (4) incomplete description of the clinical manifestations and therapeutic strategy of colchicine poisoning.

As shown in Fig. 1, a total of 67 cases were collected in the examined period. Forty-seven patients were excluded based on the exclusion criteria. Consequently, a total of 20 cases extracted from nineteen articles were summarized in Tables 2 and 3. Among the enrolled cases, four cases were extracted from case series of three articles [5, 16, 21]. The average age of the patients enrolled in this study was 35.75 ± 14.83 years shown in Table 3. The male to female ratio of the patients was 12/8, but there was no gender-dependent effect using Fisher's exact test ($P > 0.05$) according to the collected data. In terms of the patient's living area, half of them were from Asian countries (Table 2).

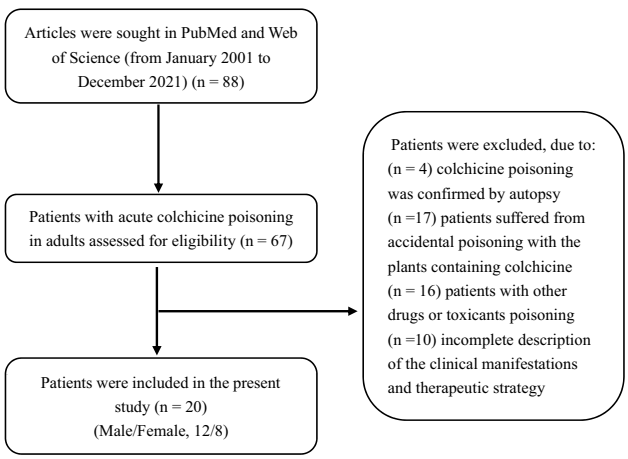

Fig. 1 Flow diagram illustrating the patient selection process

Clinical features

As described in the previous literatures, the typical symptoms of acute colchicine poisoning can be separated into three sequential and overlapping phases [22]. Phase I (within 24 h post-ingestion) reflects gastrointestinal mucosal damage characterized by abdominal pain, severe vomiting, diarrhea, and gastrointestinal hemorrhage. Phase II (generally 1–7 days post-ingestion) is characterized by metabolic acidosis, shock, myelosuppression, and multi-organ dysfunction including oliguric renal failure, liver dysfunction, and respiratory failure. Phase III (7–21 days post-ingestion) is characterized by bone marrow hematopoietic recovery and resolution of organ system derangements. It is worth noting that most of the deaths occur 7–10 days after oral ingestion [23]. Metabolic acidosis and multiple organ dysfunction are closely associated with substantial morbidity and mortality. Once multiple organ failure occurs, the mortality rate would be close to 100% [5, 16].

As shown in Tables 2 and 3, approximately 70% of patients developed gastrointestinal symptoms and metabolic acidosis; most patients suffered from multiple organ dysfunction including acute kidney injury (75%), acute respiratory failure (80%), hepatic dysfunction (60%), and acute myocardial injury (80%); myelosuppression including anemia, leucopenia, and thrombocytopenia occurred in around half of the patients. The mortality rate for patients with colchicine poisoning is 50%.

Management

Due to the high mortality rate of acute colchicine poisoning, prompt and effective treatment is essential with the aim of ameliorating the toxic effects of colchicine. Considering that there are no specific antidotes for colchicine, the management strategy for acute colchicine poisoning including prevention of colchicine absorption, blood purification, and supportive therapy is described in detail as follows.

Prevention of colchicine absorption

Gastric lavage is effective within the first 1–2 h post-ingestion to remove residual toxic substances in the stomach [24]. In addition, gastric decontamination with activated charcoal is recommended in most guidelines for acute toxicant poisoning. It was demonstrated that 5 g of activated charcoal can effectively bind up to 90% of approximately 10 mg of colchicine [25]. Activated charcoal with a small volume of liquid may be administered through the orogastric tube to

Table 2 Summary of acute colchicine poisoning in adults (2001–2021)

Authors	Gender	Age (Y)	Cause	Dosage (serum colchicine level)	Time interval between ingestion and admission (h)	Clinical symptoms	Organ dysfunction	Therapy	Outcome	Country
Maxwell, M. J. et al. [26]	M	41	Overdose	26.5 mg	24–48	Abdominal pain, diarrhea, vomiting,	Acute myocardial injury, acute respiratory failure, AKI, metabolic acidosis	Mechanical ventilation	Death	UK
Arroyo, M. P. et al. [58]	M	48	Overdose	18 mg	30	Diarrhea, nausea, vomiting	Acidosis, acute myocardial injury, acute respiratory failure, AKI, anemia, coagulation disorders, leucopenia, rhabdomyolysis, thrombocytopenia	Antibiotics, blood component transfusion, fluid therapy, G-CSF, hemodialysis, mechanical ventilation	Death	USA
Jayaprakash, V. et al. [21]	M	20	Suicide	40 mg	12	Abdominal pain, diarrhea	Acute myocardial injury, acute respiratory failure, AKI, coagulation disorders	Activated charcoal, mechanical ventilation	Death	New Zealand
Huang, W.H., et al. [59]	M	48	Overdose	> 10 mg	72	Abdominal pain, diarrhea	AKI, liver damage	Fluid therapy	Recovery	China
Iosfina, I., et al. [55]	F	47	Suicide	90 mg	1	Abdominal pain, diarrhea, nausea, positive blood / sputum culture, vomiting	Acidosis, acute myocardial injury, acute respiratory failure, AKI, anemia, coagulation disorders, leucopenia, liver damage, rhabdomyolysis, thrombocytopenia	Activated charcoal, antibiotics, blood component transfusion, fluid therapy, gastric lavage, G-CSF, hemodialysis, NAC	Recovery	Canada
Herrán-Monge, R., et al. [60]	M	52	Overdose	40 mg	8	Abdominal pain, diarrhea, positive blood/urine culture	Acidosis, acute myocardial injury, acute respiratory failure, AKI, coagulation disorders, leucopenia, liver damage, rhabdomyolysis, thrombocytopenia	Activated charcoal, antibiotics, antifungal therapy, gastric lavage, G-CSF, hemodialysis, mechanical ventilation	Death	Spain
Jouffroy, R., et al. [46]	M	51	Suicide	17 mg (9.7 nmol/L)	24	Shock	Acute myocardial injury, acute respiratory failure, AKI	ECLS, hemodialysis, mechanical ventilation	Recovery	France

Table 2 (continued)

Authors	Gender	Age (Y)	Cause	Dosage (serum colchicine level)	Time interval between ingestion and admission (h)	Clinical symptoms	Organ dysfunction	Therapy	Outcome	Country
Erden, A., et al. [16]	F	23	Suicide	50 mg	4	Abdominal pain, diarrhea, nausea, vomiting	Acidosis, acute myocardial injury, acute respiratory failure, AKI, coagulation disorders, rhabdomyolysis	Activated charcoal, blood component transfusion, gastric lavage, hemodialysis, mechanical ventilation	Death	Turkey
Fernández, S., et al. [61]	M	34	Suicide	30 mg	12	Abdominal pain, vomiting, positive blood culture	Acidosis, acute myocardial injury, acute respiratory failure, AKI, coagulation disorders, leucopenia, liver damage, rhabdomyolysis, thrombocytopenia	Antibiotics, fluid therapy, G-CSF, hemodialysis, mechanical ventilation	Death	Spain
Aghabiklooei, A., et al. [5]	F	37	Suicide	38 mg	8	Abdominal pain, nausea, vomiting	Acidosis, acute myocardial injury, acute respiratory failure	Activated charcoal, gastric lavage, mechanical ventilation	Death	Iran
	F	25	Suicide	25 mg	4	Vomiting	Leucopenia, thrombocytopenia	Activated charcoal, blood component transfusion, G-CSF	Recovery	Iran
Shuttleworth, E. et al. [51]	M	19	Suicide	50 mg	2	Vomiting	Anemia, coagulation disorders, leucopenia, thrombocytopenia	Antibiotics, fluid therapy	Recovery	UK
Lev, S., et al.[53]	F	18	Suicide	18 mg	72	Abdominal pain, diarrhea, vomiting	Acidosis, acute respiratory failure, anemia, coagulation disorders, leucopenia, liver damage, rhabdomyolysis, thrombocytopenia	Antibiotics, blood component transfusion, G-CSF, mechanical ventilation, NAC	Recovery	Israel

Table 2 (continued)

Authors	Gender	Age (Y)	Cause	Dosage (serum colchicine level)	Time interval between ingestion and admission (h)	Clinical symptoms	Organ dysfunction	Therapy	Outcome	Country
Hirayama, I., et al. [62]	F	18	Overdose	15 mg	<24	Abdominal pain, diarrhea	Acidosis, acute myocardial injury, acute respiratory failure, AKI, anemia, coagulation disorders, leucopenia, liver damage, thrombocytopenia	Antibiotics, antifungal therapy, blood perfusion, CRRT, Fluid therapy, G-CSF, mechanical ventilation	Recovery	Japan
Zhong, H., et al. [63]	F	19	Suicide	40 mg	44	Abdominal pain, diarrhea, vomiting	Acidosis, acute myocardial injury, acute respiratory failure, AKI, anemia, coagulation disorders, liver damage, thrombocytopenia	Antibiotics, blood components transfusion, CRRT, fluid therapy, hemoperfusion	Recovery	China
Fu, M., et al. [64]	M	56	Overdose	12 mg	40	Abdominal pain, diarrhea, nausea, vomiting	Acidosis, acute myocardial injury, acute respiratory failure, AKI, coagulation disorders, liver damage, rhabdomyolysis	Antibiotics, blood components transfusion, CRRT, fluid therapy, gastric lavage, G-CSF, mechanical ventilation	Death	China
Sun, Y. et al. [65]	M	38	Suicide	80 mg	4	Diarrhea, nausea, vomiting	Acute myocardial injury, coagulation disorders, liver damage, leucopenia, thrombocytopenia	Antibiotics, blood component transfusion, CVVHDF, fluid therapy, gastric lavage, hemoperfusion, recombinant human thrombopoietin, Vitamin K	Recovery	China

Table 2 (continued)

Authors	Gender	Age (Y)	Cause	Dosage (serum colchicine level)	Time interval between ingestion and admission (h)	Clinical symptoms	Organ dysfunction	Therapy	Outcome	Country
Jiang, Q. et al. [66]	F	23	Suicide	50 mg	48	Abdominal pain, diarrhea, nausea, vomiting positive blood/sputum culture, rhabdomyolysis,	Acidosis, acute myocardial injury, acute respiratory failure, AKI, anemia, coagulation disorders, leucopenia, liver damage, thrombocytopenia	Antibiotics, antifungal therapy, blood component transfusion, CVVHDF, fluid therapy, G-CSF, hemoperfusion, mechanical ventilation, plasma exchange, recombinant human thrombopoietin	Recovery	China
Cozza, J., et al. [22]	M	32	Overdose	32.4 mg (9.6 ng/mL)	44	Abdominal pain, diarrhea, nausea, positive blood culture, vomiting	Acidosis, acute myocardial injury, acute respiratory failure, AKI, anemia, coagulation disorders, leucopenia, liver damage, rhabdomyolysis, thrombocytopenia	Activated charcoal, antibiotics, blood component transfusion, fluid therapy, gastric lavage, G-CSF, hemodialysis, mechanical ventilation, NAC	Death	USA
Seixas, R., et al. [52]	M	66	Suicide	90 mg	12	Dizziness	Acidosis, acute myocardial injury, acute respiratory failure, AKI, coagulation disorders, liver damage	Activated charcoal, antibiotics, CVVH, gastric lavage, mechanical ventilation, NAC	Death	Portugal

AKI acute kidney injury, *CRRT* continuous renal replacement therapy, *CVVH* continuous venous-venous hemofiltration, *CVVHDF* continuous venous-venous hemodiafiltration, *ECLS* extracorporeal life support, *G-CSF* granulocyte-colony stimulating factor, *NAC N*-acetylcysteine

Table 3 Characteristics of acute colchicine poisoning in adults ($n=20$)

Age (years)	
Mean ± standard deviation	35.75 ± 14.83
Male/female	12/8
Dosage (mg)	
Median (interquartile range)	35.2 (18.00, 50.00)
Time interval between ingestion and admission (h)	
Median (interquartile range)	18.0 (5.00, 43.00)
Clinical symptoms, *n* (%)	
Abdominal pain	14 (70%)
Diarrhea	14 (70%)
Dizziness	1 (5%)
Nausea	8 (40%)
Shock	1 (5%)
Vomiting	14 (70%)
Positive blood culture	5 (25%)
Positive sputum culture	2 (10%)
Positive urine culture	1 (5%)
Organ dysfunction, *n* (%)	
Acute myocardial injury	16 (80%)
Acidosis	14 (70%)
Acute kidney injury	15 (75%)
Acute respiratory failure	16 (80%)
Anemia	8 (40%)
Coagulation disorders	15 (75%)
Leucopenia	11 (55%)
Liver damage	12 (60%)
Rhabdomyolysis	9 (45%)
Thrombocytopenia	12 (60%)
Therapy, *n* (%)	
Activated charcoal	8 (40%)
Antibiotics	13 (65%)
Antifungal therapy	3 (15%)
Blood component transfusion	8 (40%)
Continuous renal replacement therapy	13 (65%)
Extracorporeal life support	1 (5%)
Fluid therapy	11 (55%)
Gastric lavage	8 (40%)
Granulocyte-colony stimulating factor	10 (50%)
Hemoperfusion	3 (15%)
Mechanical ventilation	14 (70%)
N-acetylcysteine	5 (25%)
Plasma exchange	1 (5%)
Recombinant human thrombopoietin	2 (10%)
Vitamin K	1 (5%)
Outcome	
Death/recovery	10/10

promote the efficiency of decontamination via absorption. Hence, once the history of colchicine overdose or suicide with colchicine is definite, gastric lavage with activated charcoal should be used promptly after oral ingestion. Gastric lavage should be performed if a high dose of colchicine is ingested, preferably within < 60 min of the ingestion [26]. More importantly, blood drug concentration vs time curve displaying two peaks within 6 h of administration is present [27]. It is possibly associated with a second absorption site or enterohepatic recirculation. Considering the rapid absorption in the gastrointestinal tract and extensive enterohepatic recirculation, gastric lavage and catharsis with multiple doses of activated charcoal can be repeatedly used to continuously remove residual toxicants in the gastrointestinal tract for 48–96 h [28]. The elimination of colchicine in the gastrointestinal tract can prevent intestinal mucosal cell injury from long-time exposure to colchicine.

Fluid supportive therapy

In addition to gastric lavage and activated charcoal, early and active fluid resuscitation are essential for the treatment of patients with colchicine poisoning due to gastrointestinal fluid loss [29]. Severe dehydration may result in the reduction of renal perfusion leading to acute kidney injury (AKI) with electrolyte and acid–base imbalances. Fluid and electrolyte supplementation can promote the removal of colchicine through the kidneys and improve renal perfusion/hemodynamics [30].

Fluid resuscitation was emphasized in many cases of reports of colchicine poisoning, but the management strategies of fluid supportive therapy were not described in detail. It is accepted the main goals of fluid resuscitation are to restore lost fluid volume and provide adequate tissue perfusion. Both balanced crystalloids (e.g., lactated Ringer's, Plasma-Lyte) and saline are widely used in clinical practice. Balanced crystalloids are solutions in which including sodium, potassium, chloride, and bicarbonate buffers closer to that of extracellular fluid [31]. According to the previous literatures [32–34], the routine use of balanced crystalloids is greatly beneficial for critically ill patients. Compared with saline, the intravenous fluid administration of balanced crystalloids may cause a decrease in all-cause mortality and incidence of renal insufficiency [33]. Particularly, hyperkalemia is a relative contraindication to the use of balanced crystalloids [32]. Colloids are conventionally used in a 1:3 ratio of colloids to crystalloids to maintain intravascular volume [35]. However, the optimal fluid and volume that should be administered to a specific patient is still the focus of debate. Determination of the fluid volume during resuscitation requires a complicated balance of benefits and risks for each patient. It is reasonable to administer up to 2–3 L of balanced crystalloid to critically ill adult patients [36]. Notably, rapid infusion of fluids may increase the risk of pulmonary edema [33]. The vital signs should be regularly

monitored including blood pressure, body temperature, pulse rate, respiration rate, and mental state. The application of available hemodynamic monitoring may guide further fluid administration [36]. In addition, special attention should be paid to the complications arising from fluid resuscitation mainly including hypothermia, acid/base imbalance, hyperkalaemia, hypocalcaemia, and clotting problems. Taken together, the fluid resuscitation strategies for the patients with acute colchicine poisoning need to be further explored.

Intravenous lipid emulsion

Colchicine is a lipophilic compound. In theory, lipophilic substances can be removed from the blood using Intravenous lipid emulsion (IVLE). Although it was reported that IVLE was successfully administered to facilitate colchicine clearance in a dog with colchicine overdose [30], there are no clinical reports in human studies. Further studies are needed to certify the efficacy of IVLE.

Diuresis

In addition to the liver, the kidney contributes to < 20% of the clearance. According to the retrospective study reported by Lu et al. [20], diuresis was performed in patients with poisoning doses > 0.5 mg/kg. Furthermore, maintaining an abundant diuresis would increase colchicine elimination [10]. However, diuresis was not mentioned in the case series as shown in Table 2. Herein, diuresis remains uncertain for the treatment of acute colchicine poisoning. Much more experimental or clinical data is needed to evaluate its therapeutic efficacy in the future.

Blood purification

Colchicine can be rapidly absorbed by the jejunum and ileum, and peak plasma concentrations would reach the first peak level at time 0.5–1.5 h after oral ingestion [37], Colchicine would be widely distributed throughout the body. Unfortunately, there are no expert recommendations on blood purification for colchicine poisoning. Considering the apparent volume of distribution and mild-moderate plasma protein-binding rate, hemoperfusion and hemodialysis have no therapeutic effect [9, 26, 38].

The therapeutic effects of plasma exchange (PE) [39, 40] and continuous veno-venous hemofiltration (CVVHDF) [38] were uncertain and need further clinical verification. Matthias et al. reported that plasma exchange did not significantly remove colchicine from the whole body of the poisoned patient [40]. The probable reason for the failure of plasma exchange is the redistribution of colchicine from plasma to tissue compartments [40]. Notably, PE could not only remove metabolic wastes but also improve the coagulation function by replenishing coagulation factors and fibrinolytic proteins. Therefore, early plasma exchange was used to treat adults or children with high doses of colchicine [39, 41]. PE is beneficial to the recovery of the colchicine-poisoned patient to some extent.

CVVHDF did not show satisfactory efficacy, since only a small amount of colchicine was removed from the body [20]. Viewed from another perspective, CVVHDF can not only remove inflammatory mediators and excessive fluid load but also regulate electrolyte and acid–base disorders. It exerts a beneficial effect on cardiac and renal function. Although PE and CVVHDF only eliminated a small amount of colchicine, early PE combined with CVVHDF improved the prognosis [20]. Hence, more clinical studies are needed to determine whether the two therapeutic methods can be used to treat patients with colchicine overdose.

Extracorporeal life support (ECLS)

Colchicine toxicity can result in multiple organs failure including acute respiratory failure and cardiogenic shock with a high mortality rate [42]. Acute respiratory failure accounted for about one-third of complications [43]. Acute respiratory distress syndrome (ARDS) may develop as a severe complication of hypovolemic shock or sepsis due to the direct injury to the pulmonary vasculature. As shown in Table 2, mechanical ventilation was performed in about 60% of patients with respiratory failure. Mechanical ventilation is essential for improving respiratory function and maintaining oxygenation, especially for patients with an overdose colchicine. Moreover, colchicine can impair myocardial function characterized by cardiogenic shock and malignant arrhythmia including complete atrioventricular block, asystole, and ventricular tachycardia [44]. Colchicine results in histological changes in myocytes and affects cardiac impulse generation and conduction [44]. Extracorporeal life support (ECLS) is a major supportive treatment against refractory cardiogenic shock caused by any stimulus. ECLS, also known as extracorporeal membrane oxygenation (ECMO), can be used as a "bridge to recovery". ECLS can not only maintain oxygenation of the organs but also overcome the refractory cardiogenic shock phase. Much evidence indicates that ECLS can be recommended as a routine supportive treatment for fatal colchicine poisoning [42, 45, 46].

Improvement of hematopoiesis

Bone marrow hematopoiesis suppression is an extremely serious complication of acute colchicine poisoning. Prophylactic platelet transfusion is beneficial for the prevention of

spontaneous bleeding in acute colchicine-poisoned patients. In addition, elective central venous catheter placement is essential for these patients with acute colchicine poisoning who need fluid resuscitation or blood perfusion. Hence, if platelet counts in the peripheral blood $< 20 \times 10^9$/L, platelet transfusion is recommended [20, 47]. Likewise, if hemoglobin levels < 60 g/L, red blood cells should be transfused. If plasma fibrinogen concentration dropped to < 1.5 g/L, human fibrinogen may be given [20]. Fresh frozen plasma can be transfused to supplement clotting factors with the aim of improving coagulation function [20]. Blood transfusion is beneficial for recovery.

In addition, granulocytogenesis is remarkably suppressed by colchicine overdose. Recombinant human granulocyte-colony stimulating factor (G-CSF) can stimulate the proliferation and differentiation of granulocytes, further enhancing the function of mature granulocytes [48]. It can effectively reduce the risk of sepsis in patients with colchicine overdose [23, 48]. Recombinant human thrombopoietin (TPO) has been demonstrated to increase platelet count in patients with immune thrombocytopenia [49]. TPO should be administrated to the colchicine-poisoned patients, if platelet counts in the peripheral blood $< 50 \times 10^9$/L [20]. The application of G-CSF and TPO can attenuate the severity and shorten the duration of neutropenia and thrombocytopenia [20].

Antimicrobial therapy

Severe colchicine poisoning can lead to myelosuppression followed by leukopenia and immune dysfunction with an increased risk of infection. Many previous studies illustrated that patients with colchicine intoxication were susceptible to infections due to the change in granulocyte counts and inhibition of leukocyte functions [50–52]. Antimicrobial therapy is essential for patients with colchicine poisoning at an appropriate time. Regrettably, this point is not described in detail according to the published studies. As shown in Tables 2 and 3, only five patients (25%) of the patients with colchicine poisoning had positive blood cultures. Thirteen patients (65%) received antibiotics and three patients (15%) received antifungal therapy. β-lactam antibiotics were prescribed in 62% of patients with antibiotherapy. Ideally, the selection of antimicrobial agents should be based on the microbial culture followed by antimicrobial susceptibility testing results. However, microbial culture would take three to five days to furnish a definitive result. It would contribute to a delay in medical treatment. Therefore, antimicrobial agents are selected empirically at the right time based on the clinical manifestations and inflammatory biomarkers [e.g., C-reactive protein (CRP) and procalcitonin] in the absence of positive cultures [20, 52]. Particularly, it should also be noted that inappropriate antibiotics might select microbial/fungal resistance. Future investigations in this area are needed.

N-acetylcysteine

It is well known that colchicine can induce endothelial and mucosal damage due to oxidative stress [53]. *N*-Acetylcysteine (NAC) exhibits its antioxidant ability by reducing oxidant-induced cell damage and apoptosis [54]. NAC was previously used in the treatment of acetaminophen poisoning, pulmonary fibrosis, and cystic fibrosis [55]. Likewise, treatment with NAC significantly improved oxidative stress-induced cellular damage by colchicine [53]. NAC was used to treat 25% of patients with colchicine poisoning (Tables 2 and 3). Much more evidence is needed to certify the efficacy of NAC in the future.

Potential antidotes

Currently, there are no clinically available antidotes for colchicine toxicity. Colchicine-specific antigen-binding fragments (Fabs) were previously demonstrated to bind to colchicine with a high affinity and enable redistribution and elimination of colchicine [2]. A recent study demonstrated early administration of colchicine-specific Fab was highly effective in preventing severe toxicity in a porcine model [56]. The colchicine-specific Fab fragments were successfully to treat a patient who attempted suicide with 60 mg colchicine [2]. Nevertheless, colchicine-specific Fab is not commercially available as yet. In addition, another new discovery showed that an engineered lipocalin (Lcn2) that tightly complexes colchicine can be used as an effective antidote to scavenge colchicine and reverse its toxic effects [57]. Much more clinical studies are needed to determine whether the two methods can be applied to human poisoning.

Conclusions

In summary, colchicine poisoning with a high mortality rate is a rare but life-threatening event. Patients with overdose of colchicine may present with gastrointestinal disorders followed by multiple organ failure, myelosuppression, shock, and acid–base imbalance. Early gastric lavage and catharsis with multiple doses of activated charcoal can be repeated and used to remove colchicine in the gastrointestinal tract. Fluid supplementation can promote the elimination of colchicine through the kidneys. Early PE combined with CVVHDF may improve the prognosis. ECLS can be recommended as a vital supportive treatment for fatal colchicine poisoning. Both G-CSF and TPO can attenuate the severity

and shorten the duration of neutropenia and thrombocytopenia. NAC can improve oxidative stress-induced cellular damage by colchicine. Colchicine-specific Fabs and engineered lipocalin (Lcn2) may be potential antidotes to reverse the toxic effects of colchicine. Much more studies are needed to certify the efficacy of these methods mentioned above.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Human and animal rights This article does not contain any studies with human participants or animals performed by any of authors.

Informed consent For this type of study, formal consent is not required.

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