Journal of Acute Medicine 8(3): 77-85, 2018
DOI:10.6705/j.jacme.201809_8(3).0001
Review Article

Acetaminophen Poisoning: A Case Based Approach

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Emergency and critical care physicians commonly evaluate and treat patients poisoned by acetaminophen. While the basics of management were established in the 1970s, over the past 20 years we have recognized subtleties and variations in presentations that alter the approach to evaluation and treatment. In this paper I will present several cases that illustrate some of the most common variations in presentations of acetaminophen poisoning and offer recommendations for modifications of testing and treatment based on several recent studies.

Key words: *acetaminophen, acetylcysteine, overdose*

Acetaminophen (paracetamol) poisoning remains a common cause of hospitalization, liver failure and death in many countries. An emergency physician in a moderately busy hospital can expect to evaluate and treat several cases of acetaminophen poisoning every year. While the basic treatment principles have been well described for over 40 years, recent work has highlighted how variations in presentation can alter the outcomes of patients. The objective of this review is to describe several of the most common presentations of acetaminophen poisoning and suggest how our evaluation and treatment approach should be adjusted based on each presentation.

Case 1: Uncomplicated Acute Ingestion

A 24-year-old non-pregnant female presents 40 minutes after ingestion of 18 g of standard release acetaminophen. She has no complaints and decided to seek care after telling her boyfriend about the ingestion. She has no significant medical history, is on oral contraceptives and denies drug use. Her vital signs are within normal limits and her exam is unremarkable other than she is tearful.

How Should This Patient Be Risk Stratified?

This case represents the most straightforward presentation of acetaminophen poisoning. Patients who ingest more than 15 g of acetaminophen are considered at risk for liver injury and are likely to require treatment with acetylcysteine.[1] Because patients are often unsure of the amount ingested, guidelines recommend measuring a serum acetaminophen concentration at least 4 hrs after the ingestion and plotting that concentration on the Rumack-Matthew Nomogram (Nomogram) to determine if the concentration falls above the treatment line suggesting the patient is "at risk" for liver injury. However, the exact concentration considered "at risk" varies by country. The original manuscript described line starting at 200 mcg/ml 4 hrs decreasing with a half-life of 4 hrs.[2] This line is no longer widely used. While planning the U.S. clinical trial of acetylcysteine, the U.S. Food and Drug Administration required the concentrations used to construct the line be dropped 25% (150 mcg/ml at 4 hrs) and this threshold is currently used in the U.S., Canada and Australia.[3] In the U.K., the threshold of 200 mcg/ml at 4 hrs was used until 2012 when it was lowered to 100 mcg/ml to increase the

Received: July 5, 2018; Revised: July 16, 2018; Accepted: July 24, 2018.
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sensitivity.[4] The current recommendation for Taiwan is 150 mcg/ml. If the history is highly discordant with the measured concentration (e.g., the concentration is low despite a good history of large ingestion) then an inaccurate time of ingestion or delayed absorption should be considered and it is reasonable to repeat the serum concentration in a few hours to assure it has not increased dramatically due to altered absorption.

How Should This Patient Be Treated?

As noted above, the decision to administer N-acetylcysteine (NAC) is based on a 4-hr serum acetaminophen concentration. The 4-hr mark was selected to assure that acetaminophen absorption had occurred. The history of a 16 g ingestion suggests a potential for a "toxic" ingestion (above the treatment line) if the total dose is absorbed. However, her early presentation allows for an intervention to decrease the absorbed dose. While activated charcoal has shown limited benefit in undifferentiated overdose,[5] it has been associated with a decreased need for acetylcysteine treatment in acetaminophen overdose.[6] However, it is not without risks, and given the efficacy of acetylcysteine charcoal is not recommended unless the patient is cooperative and is maintaining their airway.

Case 1 Resolution

The risks and benefits of charcoal were explained to the patient, and she agreed to take the activated charcoal. At 4 hrs, a serum acetaminophen concentration was measured at 110 mcg/ml. As this was below the treatment line she was medically cleared and transferred for evaluation of her depression.

Case 2: Uncomplicated Pediatric Ingestion

A 16-month-old presents to the emergency department (ED) after being found drinking from an open bottle of acetaminophen liquid. The bottle was new and is now empty. The child is healthy, weighs 14 kg and appears well. The bottle contained 120 mL of 160 mg/5 mL acetaminophen suspension.

How Should This Case Be Risk Stratified?

The generally accepted toxic dose of acetaminophen in adults in a single ingestion is 150 mg/kg.[7] However, children are felt to be somewhat protected from acetaminophen toxicity and most guidelines support a toxic dose of 200 mg/kg for children younger than.[7,8] In this case, the ingested dose was approximately 3,840 mg or 274 mg/kg. Therefore this child is at risk for acetaminophen toxicity. A serum acetaminophen concentration measured at 4 hrs was 170 mcg/ml which is above the treatment line when plotted on the Rumack-Mathew Nomogram (Nomogram).

How Should This Patient Be Treated?

While activated charcoal may decrease the absorption of acetaminophen, there are few studies showing a therapeutic benefit in pediatrics and it is very difficult to administer to children. As the vast majority of pediatric acetaminophen ingestions are not clinically significant,[9] routine charcoal administration is not recommended.

The high 4-hr serum acetaminophen concentration in this case is an indication for acetylcysteine therapy. For more than 40 years, the standard treatment protocol for acetylcysteine has involved the administration of three different infusions; a 150 mg/kg dose administered over 15–60 minutes, a 50 mg/kg dose administered over 4 hrs (12.5 mg/kg/hr) and a 100 mg/kg dose administered over 16 hrs (6.25 mg/kg/hr). While this protocol is safe and effective, it often led to dosing errors and delays in therapy[10] while the intravenous therapy (iv) bags were prepared and many patients suffered uncomfortable side effects.[11] Recently, several authors have suggested alternative dosing protocols that use one or two iv bags and often combine the first two infusions over 4 hrs.[12-14] These protocols are associated with fewer adverse effects and medication errors.

Case 2 Resolution

The child is started on acetylcysteine using a two bag protocol with a loading dose of 50 mg/kg/hr for 4 hrs and second infusion of 6.25 mg/kg/hr for 16 hrs. The child does well and the serum transaminase activity remained within normal limits.

Case 3: Large Acute Ingestion

A 17-year-old female presents after a reported ingestion of 40 g of acetaminophen 4 hrs prior to admission as a self-harm attempt. The patient had several episodes of vomiting and is now sleepy but will wake up and answer questions. This is her fourth self harm attempt in the last 18 months. Her only medical

history is depression and anxiety. Her vital signs are within normal limits and her exam is unremarkable other than her somnolence. Her blood chemistry and transaminase are within normal limits, but her acetaminophen concentration is 430 mcg/ml.

How Should This Patient Be Risk Stratified?

On first examination, this case shares many characteristics with Case 1. It is an acute ingestion with a (relatively) early presentation and the patient has no liver damage. However, the one major difference is the history of a very large (> 30 g) ingestion and a very high serum acetaminophen concentration (above the "high risk line" which starts at 300 mcg/ml 4 hrs-Nomogram).[15] In the past 10 years, multiple reports have identified large ingestions where patients have developed hepatic failure despite receiving acetylcysteine within 8 hrs.[16-18] These findings are supported by two recent observational studies showing that patients with very large ingestions (> 30 g) may not be completely protected with standard acetylcysteine dosing.[15,19,20]

How Should This Patient Be Treated?

The original studies of acetylcysteine suggested that all patients who received early treatment would do well.[1,21] The exceptions identified in the studies mentioned in the previous paragraph suggest that a massive overdose may produce a mismatch between N-acetyl-p-benzoquinone imine (NAPQI) (the toxic metabolite of acetaminophen) formation and the detoxification by conjugation to glutathione. Computer models and large observational studies have suggested that higher doses of acetylcysteine increase the detoxification of NAPQI and attenuate some liver injury.[22] There are several approaches used to increase the dose including doubling the final infusion rate to 12.5 an hr, repeating the entire protocol every 20 hrs or using the oral dosing protocol (140 mg/kg load over 1 hr followed by 17.5 mg/kg/hr for 48 hrs).[23]

In addition to higher doses of acetylcysteine, one study also found an association of between activated charcoal administration (within 4 hrs) with decreased serum acetaminophen concentrations and with an 88% decrease in the rate of hepatotoxicity.[20] Therefore activated charcoal should be very strongly considered in cases where the history or serum concentrations suggest a large (> 30 g) ingestion.

Case 3 Resolution

The patient is given 50 g activated charcoal and started on acetylcysteine. The patient is administered 50 mg/kg/hr over the first 4 hrs then started on an infusion of 12.5 mg/kg/hr (double the normal rate). Over the next 24 hrs her serum alanine aminotransferase (ALT) rises to 350 IU/L while her serum acetaminophen falls to 160 mcg/ml and her acetylcysteine is continued and the final infusion rate is continual to 12.5 mg/kg/hr. On hospital day 2 the serum ALT peaks and 1,350 IU/L and her acetaminophen is non-detectable. On hospital day 3 the ALT is down to 350 IU/L and acetylcysteine is stopped and she is medically cleared.

Case 4: Unknown Time of Ingestion

A 40-year-old female presents somnolent and confused. She was last seen 14 hrs prior to presentation when she was intoxicated and had an argument with her husband. Emergency medical services were called and found her sleeping in her bed with multiple non-prescription medications as well as empty alcohol bottles in the room. Her vital signs were normal, she appears sleepy and is not cooperating with the examination. Standard testing was unremarkable and a pregnancy test was negative. The serum acetaminophen was 110 mcg/ml, the serum ALT activity was 35 IU/L. Her serum ethanol concentration was 85 mg/dL.

How Should This Patient Be Risk Stratified?

The main characteristic of useful screening tests is that they provide early identification of a treatable condition. Ideally the condition should also be common; otherwise the cost of the test may exceed the therapeutic benefit. Occult acetaminophen ingestion in the setting of self-harm attempts has these characteristics. However, without a clear time of ingestion, it is not possible to use the Nomogram to risk stratify the patient. As the risk of hepatic injury for this patient cannot be accurately determined, the most prudent course is to initiate treatment.

Ethanol use may affect the risk of liver injury from acetaminophen poisoning. The relationship between ethanol and risk of liver injury is complex. Ethanol is a substrate and an inducer of cytochrome P450 2E1 (CYP2E1), the enzyme responsible for the formation of the toxic metabolite of acetaminophen. When ethanol is co-ingested with acetaminophen,

the ethanol will compete with acetaminophen for CYP2E1 and decrease the formation of the toxic metabolite.[24] However, ethanol also increases the amount of CYP2E1 in the liver and this effect lasts for several hours after ethanol consumption. Therefore, patients who drink ethanol regularly but who have no ethanol in their system when they ingest the acetaminophen will have increased formation of the toxic metabolite.[25] This biphasic response has been documented in experimental conditions and the findings are supported by observational studies.

Treatment

While it is reasonable to initiate treatment for this case, the patient is presenting before the onset of ALT elevation and the acetaminophen concentration is not that large. This patient is an excellent candidate for shorter course of therapy. Truncated or "patient tailored" protocols have been suggested for many years, and one of the first descriptions of this approach was from Taiwan.[26] There are several theoretical arguments to support their efficacy, and a small clinical trial found the rates of ALT elevation were similar for the standard 21-hr, 300 mg/kg protocol and an accelerated protocol where a 250 mg/kg dose is administered over 12 hrs.[27] Recently, a larger cohort of patients treated with this protocol had excellent outcomes.[28] The importance of these protocols is that they allow low risk patients to be treated in an ED observation unit. By completing the medical treatment in a shorter time, we can facilitate prompt psychiatric evaluation and treatment.

Case 4 Resolution

The physician initiates acetylcysteine and treats for 12 hrs. At this time, the serum acetaminophen concentration is undetectable and the serum transaminase activities are stable. The patient is medically cleared and transferred to a psychiatric facility.

Case 5: Repeated Supratherapuetic Ingestion

A 38-year-old male presents with a toothache for the past 3 days. He has poor dentition and has not been to a dentist in several years. He states he is here to obtain pain relief and a referral to have the tooth removed. He reports taking "handfuls" of a non-prescription pain reliever over the past 3 days with no relief. His vital signs are within normal limits, and with the exception of grossly decayed teeth his exam is unremarkable.

How Should this Patient Be Risk Stratified?

There are no large studies that have compared approaches to evaluating patients who have staggered excessive acetaminophen ingestion occurring over more than 8 hrs. Interestingly, cases like this are among the most common causes of liver failure in the U.S.[29] The first systematic description of repeated supratherapeutic acetaminophen ingestion was published in 2002 and the authors noted that no cases developed liver failure when treatment was started while the serum transaminase activity lower than 50 IU/L.[30] This led to a treatment recommendation for all patients with a supratherapeutic acetaminophen concentration (> 20 mcg/ml) or serum transaminase > 50 IU/L. While this protocol is widely accepted, there have been no systematic studies evaluating this approach.

How Should This Patient Be Treated?

There have been no studies evaluating treatment protocols for staggered ingestions. Initially, these patients were treated using the same protocol as acute ingestion. However, once it was recognized that most patients who present without liver injury (normal transaminase activity) do well while those with elevated transaminase activity have a much more guarded prognosis, treatment protocols were targeted toward these two groups. Serum transaminase activity reflects hepatocyte necrosis that has already occurred. Therefore the elevation of transaminase activity lags behind hepatocyte injury and substantial portion of patients who present with transaminase elevation will go on to have additional injury over the next 12–24 hrs.[30]

Case 5 Resolution

A serum acetaminophen concentration was 35 mcg/ml and his serum ALT and aspartate aminotransferase (AST) were 25 and 28 respectively. The patient was treated with acetylcysteine for 12 hrs at which time his serum acetaminophen was not detectable and his AST and ALT were unchanged. Had the patient developed an ALT above 50 IU/L the treatment would have been continued until the ALT was clearly declining. The patient was counseled about appropriate use of non-prescription pain medications and discharged.

Case 6: Late Presentation With Acute Liver Failure

A 26-year-old male presents with vomiting, abdominal pain and confusion. The family states that the patient had the flu for the past week and had been taking several non-prescription products to treat his fever and body aches. They note that he has used "a few" bottles of acetaminophen containing products. On exam the patient is somnolent and mildly confused. His vital signs are not remarkable. He has dry mucous membranes, slightly icteric sclera and moderate right upper quadrant tenderness. His blood count is normal; he has mild renal impairment with a creatinine of 1.8 mg/dL. He has a marked elevation of the serum transaminase with an ALT of 8,500 IU/L a total bilirubin of 2.5 mg/dL and coagulopathy with an international normalized ratio (INR) of 3.2 and his arterial pH is 7.28 and his serum lactate is 2.8 mmol/L.

How Should This Patient Be Risk Stratified?

This patient has evidence of encephalopathy in the setting of acute liver injury and therefore meets the criteria for acute liver failure. This diagnosis is further supported by his elevated INR which demonstrates hepatic synthetic dysfunction, his elevated bilirubin reflecting impaired hepatic clearance and his renal injury. This degree of illness requires liver transplant evaluation. The most commonly used guidelines are the King's College Criteria which were developed in 1989,[31] but some have suggested that other criteria may be more effective.[32] Recently, the King's College Criteria were updated and the new guidelines have a high sensitivity and specificity when applied in our current intensive care unit (ICU) setting.[33] The new criteria are applied at day 1 and day 2 and can be calculated at kingsalfpredictor.org.

How Should This Patient Be Treated?

Patients with acute liver failure should be treated in an intensive care setting and have early consultation with a liver transplant service. Patients will often require close monitoring of glucose, fluid and electrolyte status, vasopressors for cardiac support and airway management. Common complications include infection, cerebral edema, bleeding from coagulopathy and renal failure. In a large single center trial, acetylcysteine was found to decrease mortality and therefore it is often used in combination with supportive care.[34] The utility of other interventions such as hypothermia and routine intracranial pressure monitoring are of uncertain value.

Case 6 Resolution

The patient was fluid resuscitated, started on acetylcysteine and admitted to the ICU. He was evaluated by the transplant team and felt to be a poor candidate due to ongoing substance abuse and his estimated survival using kingsalfpredictor.org was > 90% without transplant. Twelve hrs after admission, he developed more somnolence and was intubated. On hospital day 1, his creatinine continued to rise and he was started on renal replacement therapy. On hospital day 3, his serum ALT peaked and started to decline, and his INR also began to fall. By hospital day 5 he was extubated, and the acetylcysteine and renal replacement therapy were stopped. On hospital day 7 he was transferred out of the ICU and began treatment for alcohol abuse and depression.

Case 7: Massive Acute Ingestion

A 15-year-old female presents is found unresponsive. She is transported to the ED. Upon arrival her vital signs are within normal limits other than a mild tachypnea, but she is unresponsive (Glasgow Coma Scale, GCS = 5) and is therefore intubated. There are no signs of trauma on her physical exam and a head computed tomography (CT) is negative. Her initial laboratory studies are remarkable for normal electrolytes and renal function but an anion gap metabolic acidosis (pH = 7.18, anion gap = 25), elevated blood glucose and a high serum lactate. Her family states that she has a history of behavioral disturbances and self-harm attempts. She was last seen 6 hrs prior after having a fight with her mother. A serum acetaminophen is measured at greater than 800 mcg/ml and her serum transaminase activity is normal. A urine pregnancy test and drug screen are negative.

How Should This Patient Be Risk Stratified?

Obviously this patient has a very high serum acetaminophen concentration and while the exact time of ingestion is unknown, it is clear she will require acetylcysteine. However, she also has other metabolic abnormalities including a lactic acidosis and hyperglycemia. These findings strongly suggest massive acetaminophen ingestion. These metabolic effects that occur within a few hours of a massive ingestion were first described in 1986.[35] The mechanism behind these effects is thought to

be inhibition of cellular respiration by the high acetaminophen concentration. These effects are generally present before the onset of liver injury and are not thought to be due to the oxidative metabolites.

How Should This Patient Be Treated?

These patients often require airway management and intense supportive care from presentation. Acetylcysteine can prevent hepatic injury, but as noted in case 3 above, the dose should be increased to provide additional protection. There is some controversy regarding the optimal treatment for the metabolic effects. There are several reports describing recovery with supportive care and acetylcysteine alone. However, the Extracorporeal Treatment in Poisoning (EXTRIP) consensus guidelines recommend consideration of hemodialysis for patients with altered mental status, metabolic acidosis, an elevated lactate, and an acetaminophen concentration is greater than 700 mcg/ml even if NAC is administered.[36] Case reports suggest that hemodialysis can clear the acidosis and the lactate, remove the acetaminophen and improve the patient's mental status. However, since acetylcysteine is cleared by dialysis, the rate of infusion should be increased (generally it is doubled) during the hemodialysis session.

Case 7 Resolution

The patient was admitted to the ICU and started on acetylcysteine. She was treated with one six hour session of hemodialysis and her metabolic abnormalities were normalized. During dialysis the acetylcysteine rate was doubled. At the end of dialysis her serum acetaminophen concentration was 110 mcg/ml. Acetylcysteine was continued for another 24 hrs at which time the acetaminophen was undetectable and the serum transaminase were normal. She was medically cleared and transferred to a psychiatric unit.

Conclusions

The first 6 cases all represent acetaminophen-related presentations that are commonly encountered in the ED. Emergency physicians should feel comfortable assessing and treating these patients. The seventh case represents a very rare presentation, however it is important that emergency physicians are aware that extremely large ingestions may present very early with the metabolic derangements and that dialysis is a treatment option.

While I have outlined my preferred approach to each case, it is important to note that many other approaches are reasonable. I have provided a flow chart (Fig. 1) that provides a reasonable approach to the vast majority of cases encountered in the ED as well as some suggestions on decontamination (Table 1). In the end, I suggest there are two simple rules of thumb: (1) Start treatment if the acetaminophen concentration or the transaminase are elevated and (2) stop treatment when the serum acetaminophen is non-detectable and the transaminase are normal. These rules of thumb along with excellent supportive care are the cornerstones of successful treatment and will get you through all but the most severe acetaminophen cases.

Acknowledgements

I appreciate the comments of Dr. Yen-Chia Chen as well as the manuscript reviewers.

Disclosures

Dr. Heard has investigator-initiated research grants for an acetaminophen biomarker from McNeil Consumer Healthcare and royalties from UpToDate for chapters on acetaminophen poisoning.

References

1. Smilkstein MJ, Knapp GL, Kulig KW, Rumack BH. Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose. Analysis of the national multicenter study (1976 to 1985). *N Engl J Med* 1988;319:1557-1562. doi:10.1056/NEJM198812153192401
2. Rumack BH, Peterson RC, Koch GG, Amara IA. Acetaminophen overdose. 662 cases with evaluation of oral acetylcysteine treatment. *Arch Intern Med* 1981;141:380-385. doi:10.1001/archinte.141.3.380
3. Rumack BH. Acetaminophen hepatotoxicity: the first 35 years. *J Toxicol Clin Toxicol* 2002;40:3-20. doi:10.1081/CLT-120002882
4. Medicines and Healthcare products Regulatory Agency. Treating paracetamol overdose with intravenous acetylcysteine: new guidance. Available at: https://www.gov.uk/drug-safety-update/treating-paracetamol-overdose-with-intravenous-acetylcysteine-new-guidance. Accessed August 14, 2018.
5. Cooper GM, Le Couteur DG, Richardson D, Buckley NA. A randomized clinical trial of activated charcoal for the routine management of oral drug overdose. *QJM* 2005;98:655-660. doi:10.1093/qjmed/hci102

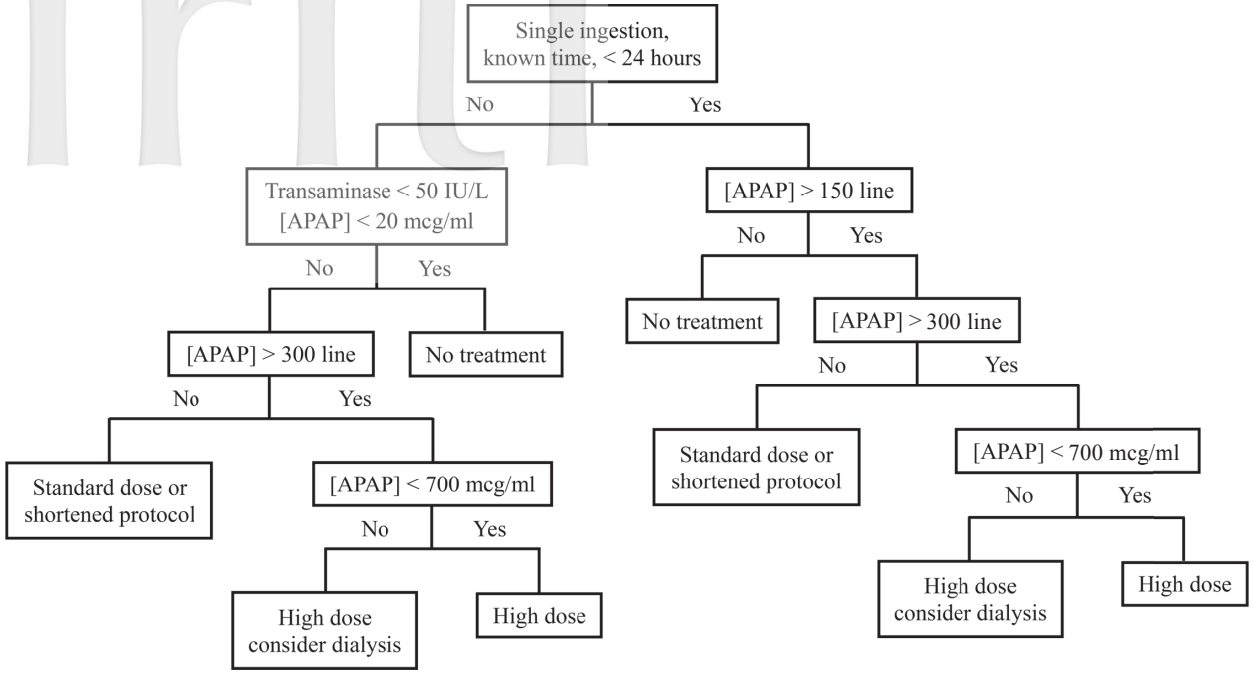

Fig. 1. Evaluation of acetaminophen ingestion. For patients on acetylcysteine: (1) measure acetaminophen concentration [APAP] every 12 hrs until < 10 mcg/ml; (2) measure transaminase, creatinine, electrolytes and international normalized ratio (INR) every 12 hrs. Risk stratify for transplant if patient has (1) hepatic encephalopathy, (2) acute kidney injury (creatinine > 2.0 mg/dL), (3) coagulopathy (INR > 2.5), (4) aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 1,000 IU/L, and (5) acidemia (pH < 7.3). It is reasonable to stop treatment when (1) [APAP] < 10 mcg/ml and (2) downtrending or normal transaminase.

Table 1. Critical points in managing acetaminophen overdose

Concern	Action
History of ingestion of > 15 g and presentation within 4 hrs.	Consider offering activated charcoal to cooperative patients to decrease the probability of requiring acetylcysteine.
Pediatric accidental ingestion.	Toxicity unlikely and charcoal rarely should be used.
History of ingestion of > 30 g or serum concentration > 300 mcg/ml at 4 hrs.	Increase acetylcysteine dose (such as doubling final infusion to 12.5 mg/kg/hr).
Time of ingestion is not known or repeated supratherapeutic ingestion.	Treat patients with an unknown time of ingestion and a detectable acetaminophen concentration or history of exposure and elevated transaminase activity.
Acute liver failure (hepatic encephalopathy) or serum pH < 7.2 after resuscitation.	Contact transplant center. Risk stratify using kingsalfpredictor.org. Administer acetylcysteine even if no delectable acetaminophen.
Serum acetaminophen concentration > 700 mcg/ml with acidosis, altered mental status and elevated lactate.	Consider hemodialysis in addition to acetylcysteine.

6. Buckley NA, Whyte IM, O'Connell DL, Dawson AH. Activated charcoal reduces the need for N-acetylcysteine treatment after acetaminophen (paracetamol) overdose. *J Toxicol Clin Toxicol* 1999;37:753-757. doi:10.1081/CLT-100102452
7. Dart RC, Erdman AR, Olson KR, et al. Acetaminophen poisoning: an evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol (Phila)* 2006;44:1-18. doi:10.1080/15563650500394571
8. Mohler CR, Nordt SP, Williams SR, Manoguerra AS, Clark RF. Prospective evaluation of mild to moderate pediatric acetaminophen exposures. *Ann Emerg Med* 2000;35:239-244. doi:10.1016/S0196-0644(00)70074-6
9. Brass EP, Reynolds KM, Burnham RI, Green JL. Frequency of poison center exposures for pediatric accidental unsupervised ingestions of acetaminophen after the introduction of flow restrictors. *J Pediatr* 2018;198:254-259. doi:10.1016/j.jpeds.2018.02.033
10. Bailey GP, Najafi J, Elamin ME, et al. Delays during the administration of acetylcysteine for the treatment of paracetamol overdose. *Br J Clin Pharmacol* 2016;82:1358-1363. doi:10.1111/bcp.13063
11. Sandilands EA, Bateman DN. Adverse reactions associated with acetylcysteine. *Clin Toxicol (Phila)* 2009;47:81-88. doi:10.1080/15563650802665587
12. Isbister GK, Downes MA, McNamara K, Berling I, Whyte IM, Page CB. A prospective observational study of a novel 2-phase infusion protocol for the administration of acetylcysteine in paracetamol poisoning. *Clin Toxicol (Phila)* 2016;54:120-126. doi:10.3109/15563650.2015.1115057
13. Johnson MT, McCammon CA, Mullins ME, Halcomb SE. Evaluation of a simplified N-acetylcysteine dosing regimen for the treatment of acetaminophen toxicity. *Ann Pharmacother* 2011;45:713-720. doi:10.1345/aph.1P613
14. Wong A, Graudins A. Simplification of the standard three-bag intravenous acetylcysteine regimen for paracetamol poisoning results in a lower incidence of adverse drug reactions. *Clin Toxicol (Phila)* 2016;54:115-119. doi:10.3109/15563650.2015.1115055
15. Marks DJB, Dargan PI, Archer JRH, et al. Outcomes from massive paracetamol overdose: a retrospective observational study. *Br J Clin Pharmacol* 2017;83:1263-1272. doi:10.1111/bcp.13214
16. Schwartz EA, Hayes BD, Sarmiento KF. Development of hepatic failure despite use of intravenous acetylcysteine after a massive ingestion of acetaminophen and diphenhydramine. *Ann Emerg Med* 2008;54:421-423. doi:10.1016/j.annemergmed.2008.10.001
17. Wang GS, Monte A, Bagdure D, Heard K. Hepatic failure despite early acetylcysteine following large acetaminophen-diphenhydramine overdose. *Pediatrics* 2011;127:e1077-e1080. doi:10.1542/peds.2010-2521
18. Doyon S, Klein-Schwartz W. Hepatotoxicity despite early administration of intravenous N-acetylcysteine for acute acetaminophen overdose. *Acad Emerg Med* 2009;16:34-39. doi:10.1111/j.1553-2712.2008.00296.x
19. Cairney DG, Beckwith HK, Al-Hourani K, Eddleston M, Bateman DN, Dear JW. Plasma paracetamol concentration at hospital presentation has a dose-dependent relationship with liver injury despite prompt treatment with intravenous acetylcysteine. *Clin Toxicol (Phila)* 2016;54:405-410. doi:10.3109/15563650.2016.1159309
20. Chiew AL, Isbister GK, Kirby KA, Page CB, Chan BSH, Buckley NA. Massive paracetamol overdose: an observational study of the effect of activated charcoal and increased acetylcysteine dose (ATOM-2). *Clin Toxicol (Phila)* 2017;55:1055-1065. doi:10.1080/15563650.2017.1334915
21. Smilkstein MJ, Bronstein AC, Linden C, Augenstein WL, Kulig KW, Rumack BH. Acetaminophen overdose: a 48-hour intravenous N-acetylcysteine treatment protocol. *Ann Emerg Med* 1991;20:1058-1063. doi:10.1016/S0196-0644(05)81352-6
22. Woodhead JL, Howell BA, Yang Y, et al. An analysis of N-acetylcysteine treatment for acetaminophen overdose using a systems model of drug-induced liver injury. *J Pharmacol Exp Ther* 2012;342:529-540. doi:10.1124/jpet.112.192930
23. Heard K, Rumack BH, Green JL, et al. A single-arm clinical trial of a 48-hour intravenous N-acetylcysteine protocol for treatment of acetaminophen poisoning. *Clin Toxicol (Phila)* 2014;52:512-518. doi:10.3109/15563650.2014.902955
24. Prescott LF. Paracetamol, alcohol and the liver. *Br J Clin Pharmacol* 2000;49:291-301. doi:10.1046/j.1365-2125.2000.00167.x
25. Thummel KE, Slattery JT, Ro H, et al. Ethanol and production of the hepatotoxic metabolite of acetaminophen in healthy adults. *Clin pharmacol Ther* 2000;67:591-599. doi:10.1067/mcp.2000.106574
26. Tsai CL, Chang WT, Weng TI, Fang CC, Walson PD. A patient-tailored N-acetylcysteine protocol for acute acetaminophen intoxication. *Clin Ther* 2005;27:336-341. doi:10.1016/j.clinthera.2005.03.002
27. Bateman DN, Dear JW, Thanacoody HK, et al. Reduction of adverse effects from intravenous acetylcysteine treatment for paracetamol poisoning: a randomised controlled trial. *Lancet* 2014;383:697-704. doi:10.1016/S0140-6736(13)62062-0
28. Pettie J, Sandilands EA, Dow MA, et al. NACCT Abstracts 2016: treatment of acetaminophen overdose with a 12 h acetylcysteine regimen: the first report of safety and efficacy in routine clinical practice. *Clin Toxicol* 2016;54:666. doi:10.1080/15563650.2016.1197486

29. Larson AM, Polson J, Fontana RJ, et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. *Hepatology* 2005;42:1364-1372. doi:10.1002/hep.20948
30. Daly FF, O'Malley GF, Heard K, Bogdan GM, Dart RC. Prospective evaluation of repeated supratherapeutic acetaminophen (paracetamol) ingestion. *Ann Emerg Med* 2004;44:393-398. doi:10.1016/j.annemergmed.2004.05.005
31. O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology* 1989;97:439-445. doi:10.1016/0016-5085(89)90081-4
32. Craig DG, Ford AC, Hayes PC, Simpson KJ. Systematic review: prognostic tests of paracetamol-induced acute liver failure. *Aliment Pharmacol Ther* 2010;31:1064-1076. doi:10.1111/j.1365-2036.2010.04279.x
33. Bernal W, Wang Y, Maggs J, et al. Development and validation of a dynamic outcome prediction model for paracetamol-induced acute liver failure: a cohort study. *Lancet Gastroenterol Hepatol* 2016;1:217-225. doi:10.1016/S2468-1253(16)30007-3
34. Keays R, Harrison PM, Wendon JA, et al. Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial. *BMJ* 1991;303:1026-1029. doi:10.1136/bmj.303.6809.1026
35. Flanagan RJ, Mant TG. Coma and metabolic acidosis early in severe acute paracetamol poisoning. *Hum Toxicol* 1986;5:179-82. doi:10.1177/096032718600500305
36. Gosselin S, Juurlink DN, Kielstein JT, et al. Extracorporeal treatment for acetaminophen poisoning: recommendations from the EXTRIP workgroup. *Clin Toxicol (Phila)* 2014;52:856-867. doi:10.3109/15563650.2014.946994