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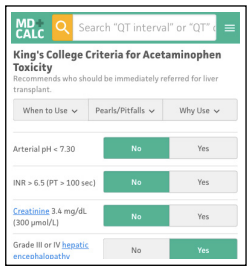

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King's College Criteria for Acetaminophen Toxicity

Introduction: The King's College Criteria for Acetaminophen Toxicity recommend which patients should be immediately referred for liver transplant.

Points & Pearls

- The King's College Criteria (KCC) were developed to determine which patients with fulminant hepatic failure (FHF) should be referred for liver transplant.
- The KCC can be applied to all acetaminophen ingestions (acute or chronic) with signs of severe acute liver injury.
- There are no worldwide standard criteria for transplantation, but the KCC are the most widely applied.
- The KCC indicators predict a poor prognosis, and select the patients most likely to benefit from an immediate liver transplant referral.
- The etiology of the acute liver failure is important in determining indicators of poor prognosis (acetaminophen ingestion vs other causes).
- Metabolic acidosis alone OR a combination of Grade III or IV hepatic encephalopathy (HE), prothrombin time (PT) > 100 sec, and creatinine level > 3.4 mg/dL predicted 77% of total deaths (O'Grady 1989).

Points to keep in mind:

- The KCC are criticized for predicting mortality often when patients are too sick for a transplant.
- The use of prolonged *N*-acetylcysteine therapy, which was not standard when the KCC were created, has significantly lowered the complication rate and need for transplants.
- PT values are often not comparable across laboratories, due to the use of different reagents.
- Serum lactate (a marker of liver injury) and phosphate (a marker of liver regeneration) have been used as alternative early prognostic indicators or adjuncts to the KCC.
- The KCC is specific but not sensitive; that is, while fulfillment of the criteria carries a poor prognosis, lack of fulfillment may still carry an unfavorable outlook.

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Critical Actions

Patients with acute liver failure should be managed in centers with expertise in caring for these patients. This includes patients who do not yet appear to be gravely ill, since it can be hazardous to transfer patients later in the disease course.

Evidence Appraisal

The KCC were derived from a retrospective review of 588 patients with FHF over 13 years (O'Grady 1989). The predictors are slightly different based on the etiology of the FHF (acetaminophen vs other causes). The arterial pH, HE, PT, and creatinine predictors were derived from 310 patients with acetaminophen-induced FHF, and were retrospectively validated on a separate group of 121 patients with acetaminophen-induced FHF (O'Grady 1989).

The criteria are well validated and reflect the degree of multiorgan dysfunction. In addition, the criteria are specific but not sensitive; fulfillment of the criteria suggests a poor prognosis, but patients who do not fulfill the criteria may also still have a poor prognosis.

In the study, patients were transferred to King's College Hospital at a relatively late stage (median time of 51 hours after acetaminophen ingestion) and

Why to Use

Acetaminophen poisoning is the most common cause of acute liver failure in the United States, the United Kingdom, and many other countries. The only treatment option that radically improves the outcome of acute liver failure is emergency liver transplantation. Therefore, proper identification of which patients to refer and transfer is critically important. In addition, appropriate transplant candidates must be identified as early as possible to provide a realistic window for a graft to become available.

When to Use

- The KCC are used for patients with acetaminophen-induced liver failure, to show the degree of multiorgan dysfunction.
- The criteria can be used alone or with serum lactate and phosphate to predict which patients will have a poor prognosis without a liver transplant.

Next Steps

- All patients with acetaminophen-induced hepatotoxicity should receive *N*-acetylcysteine.
- Frequent monitoring should be performed for coagulation parameters, complete blood counts, metabolic panels, blood gases, and blood glucose.
- Serum aminotransferases and bilirubin should be monitored daily.
- Patients should be monitored and treated for hypoglycemia, hypokalemia, and hypophosphatemia.
- Administration of fresh frozen plasma is indicated only in the setting of active hemorrhage or prior to invasive procedures in coagulopathic patients. Prophylactic administration of fresh frozen plasma is not recommended, as it does not improve mortality and can interfere with assessments of liver function.

were the most severely ill (the majority of patients were admitted with HE stages III or IV). This may have affected the predictive values of the test criteria.

In a systematic review of 14 eligible studies (Bailey 2003), the estimated overall sensitivity and specificity of the KCC for predicting mortality were 58% and 95%, respectively. The search for earlier prognostic indicators with a higher sensitivity for poor prognosis led to investigations of alpha-fetoprotein, coagulation factor V, ketone body ratio, lactate, and phosphate. Lactate and phosphate concentrations were initially found to have improved predictive ability compared to the KCC, but subsequent studies have shown slightly inferior predictive ability. The addition of lactate or phosphate to the KCC may improve sensitivity and negative predictive value.

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Calculator Creator

John O'Grady, MD
Click here to read more about Dr. O'Grady.

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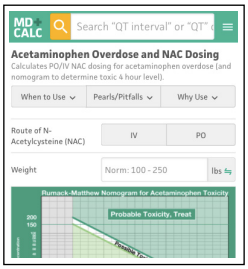

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Acetaminophen Overdose and *N*-Acetylcysteine (NAC) Dosing

Introduction: Acetaminophen Overdose and *N*-Acetylcysteine Dosing calculates oral and intravenous *N*-acetylcysteine dosing for acetaminophen overdose, and determines the toxic 4-hour level using the Rumack-Matthew nomogram.

Points & Pearls

- An acetaminophen concentration obtained prior to 4 hours post-ingestion cannot be plotted on the Rumack-Matthew nomogram, and only confirms acetaminophen exposure, not toxicity.
- It is important to get an accurate time of ingestion, as the Rumack-Matthew nomogram is entirely dependent on knowing time of ingestion.
- Start *N*-acetylcysteine (NAC) treatment within 8 hours post-ingestion to decrease the risk of hepatotoxicity (aspartate transaminase [AST] or alanine transaminase [ALT] > 1000 IU/L).
- For patients presenting 8 to 24 hours post-ingestion, start NAC while awaiting the acetaminophen concentration; NAC can be continued or discontinued depending on the level when the result is available.

Advice

- Early administration of NAC (< 8 hours post-ingestion) is vital to decreasing the risk of hepatotoxicity; acetaminophen is a leading cause of drug-induced liver injury.
- Acetaminophen is widely available in prescription and over-the-counter medications, either as a single agent or in combination products (eg, dextromethorphan, opioids, diphenhydramine).
- Maintain a strong index of suspicion for acetaminophen toxicity in all patients with an intentional drug overdose and those with therapeutic misadventures (eg, taking excessive amounts of a single product, or using recommended doses of several different products that contain acetaminophen).

Critical Actions

Serum acetaminophen concentration should be obtained for all patients who present with an intentional overdose, or those who have used excessive amounts of acetaminophen-containing products. NAC treatment should be initiated within 8 hours post-ingestion to decrease risk of hepatotoxicity.

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Evidence Appraisal

In 1981, Rumack et al published the results of their nationwide, multiclinic open study, which was started in 1976 at the Rocky Mountain Poison Center in Denver. The study was conducted to assess the effectiveness of oral acetylcysteine in preventing hepatotoxicity in patients with acetaminophen overdose presenting within 24 hours of ingestion. The cohort included 662 consecutive patients with an acetaminophen overdose. Incidence of hepatotoxicity and time to treatment for patients with acetaminophen concentration in the probable toxic range (a line intersecting 200 µg/mL [1324 µmol/L] at 4 hours and 50 µg/mL [331 µmol/L] at 12 hours) were 7% when treated within 10 hours of ingestion, 29% when treated within 10 to 16 hours of ingestion, and 62% when treated within 16 to 24 hours of ingestion.

Prescott et al (1979) studied 100 patients with acetaminophen poisoning who were treated with intravenous NAC. Serum acetaminophen concentrations above a line intersecting 200 µg/mL (1323 µmol/L) at 4 hours and 30 µg/mL (199 µmol/L) at 15 hours were measured, and the incidence of hepatotoxicity was as follows: 0 of 40 patients treated within 8 hours of ingestion, 1 of 62 patients (1.6%) treated within 10 hours of ingestion, and 20 of 38 patients (53%) treated within 10 to 24 hours of ingestion. A retrospective analysis of 57 patients treated with supportive care alone (no intravenous NAC) showed a 58% incidence of hepatotoxicity (33 of 57 patients).

Another study of 11,195 cases of suspected acetaminophen overdose (Smilkstein 1988) described the outcomes of 2540 patients who were treated with 72-hour oral NAC. Among patients at probable risk for hepatotoxicity (acetaminophen concentration above a line intersecting 200 µg/mL [1323 µmol/L] at 4 hours and 50 µg/mL [331 µmol/L] at 12 hours, and below a line intersecting 300 µg/mL [1985 µmol/L] at 4 hours and 75 µg/mL [496 µmol/L] at 12 hours), 6.1% developed hepatotoxicity when NAC was initi-

Why to Use

NAC is the antidote to acetaminophen toxicity. The Rumack-Matthew nomogram is the most sensitive risk prediction tool in medical toxicology. It identifies patients who are at very low risk of developing hepatotoxicity after an acetaminophen overdose and who do not require NAC. All patients whose plots fall above the treatment line on the nomogram should be treated with NAC to decrease the risk of developing hepatotoxicity.

When to Use

Use the Acetaminophen Overdose and *N*-Acetylcysteine Dosing tool to calculate for acute, single ingestions of acetaminophen (where entire ingestion occurs within an 8-hour period), with:

- A known time of ingestion.
- Immediate release formulation.
- Absence of formulations or co-ingestants that alter absorption and bowel motility (eg, anticholinergics, opioids).

See the **Next Steps** section if the time of ingestion is unknown, if an extended release formulation was ingested, or if co-ingestion has occurred.

Next Steps

If time of ingestion is known:

- Obtain an acetaminophen concentration at 4 hours post-ingestion or as soon as possible thereafter.
- Plot the acetaminophen concentration on the Rumack-Matthew nomogram.
- If the plot is above the "treatment line" (the line connecting 150 µg/mL [993 µmol/L] at 4 hours and 4.7 µg/mL [31 µmol/L] at 24 hours), administration of NAC is indicated.

If time of ingestion is unknown:

- Determine the earliest possible time of ingestion.
- If < 24 hours post-ingestion, plot on Rumack-Matthew nomogram and initiate administration of NAC if plotted above treatment line.
- If the earliest time of ingestion cannot be estimated, treatment with NAC is indicated if:
  - There is a detectable acetaminophen concentration.
  - There are abnormal aminotransferase (AST or ALT) levels.

If the patient ingested extended release formulations or co-ingested opioids, anticholinergics, or other medications that slow gut motility:

- Obtain an initial 4-hour post-ingestion acetaminophen concentration.
  - If the concentration plots above the Rumack-Matthew nomogram treatment line, treatment with NAC is indicated, and should be initiated within 8 hours post-ingestion.
  - If the concentration plots above the Rumack-Matthew nomogram treatment line, repeat the acetaminophen concentration testing at 6 to 7 hours post-ingestion.

In cases of chronic acetaminophen ingestion:

- For patients taking repeated, supratherapeutic acetaminophen ingestions (> 4 grams per day), treatment with NAC is indicated if:
  - There is a detectable acetaminophen concentration.
  - There are abnormal aminotransferase (AST or ALT) levels.

ated within 10 hours of ingestion, and 26.4% developed hepatotoxicity when NAC was initiated within 10 to 24 hours of ingestion.

Use the Calculator Now

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Calculator Creator

Barry H. Rumack, MD
Click here to read more about Dr. Rumack.

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