ACETAMINOPHEN TOXICITY

ALGORITHM 1. ACUTE Acetaminophen Toxicity

ACUTE acetaminophen (APAP) ingestions include:
- All the ingestion taken within a 24 hour time frame

AND
- Presenting less than 24 hours after a known time of ingestion

NONACUTE acetaminophen (APAP) ingestions include:
- Inaccurate timeline (poor history)
- Unknown timeline
- Repeated Supratherapeutic Ingestion (all the ingestion occurs in greater than an 8 hour timeframe)

OR
- Presenting greater than 24 hours after acute ingestion

! All self-harm ingestion attempts require psychiatric evaluation

Consider social work consultation if there are concerns for maltreatment or neglect resulting in APAP ingestion or toxicity.

ACUTE acetaminophen (APAP) ingestion:

- Obtain APAP concentration 4 hours from the earliest time of ingestion
- Complete Metabolic Panel (CMP)
- Obtain a salicylate concentration
- Any other relevant labs

Plot APAP concentration based on earlier time of ingestion, if staggered ingestion (ingestion over time)

Inclusion Criteria:
- Any patient with concern for acetaminophen toxicity

Exclusion Criteria:
- Ingestion of acetaminophen with co-ingestants (i.e. cough and cold preparations) (may contain dextromethorphan, diphenhydramine), sleep/night preparations (PM) (may contain diphenhydramine, chlorpheniramine), opioid combination products)
- Severe ingestions (APAP blood concentrations greater than 300 mcg/ml)
  - Extended release (ER) products
  - IV acetaminophen overdose

Above Treatment Line?

No → Normal Transaminases (AST/ALT)?

No → Consult toxicology through Rocky Mountain Poison & Drug Safety (RMPDS) for further recommendations 1-800-222-1222

Yes → Can medically clear from APAP toxicity

Yes → Normal Transaminases (AST/ALT)?

No →
- Initiate N-acetylcysteine (NAC)
- If AST/ALT abnormal, obtain Prothrombin Time/International Normalized Ratio (PT/INR)

Yes →
- Initiate N-acetylcysteine (NAC)
- Consult toxicology through RMPDS (1-800-222-1222)
- Admit to hospital medicine service

INR greater than 2 OR greater than 1.5 with encephalopathy?

No →
- Consult toxicology through RMPDS (1-800-222-1222)
- Admit to hospital medicine service

Yes →
- Admit to PICU
- Consult Liver Service
  - In Colorado Springs, consult GI
- Consult toxicology through RMPDS (1-800-222-1222) with further questions or co-ingestants
- Other risk factors: pH less than 7.3, acute kidney injury (AKI)

Matthew Rumack Nomogram

ALGORITHM 2. NONACUTE Acetaminophen Toxicity

NONACUTE acetaminophen (APAP) ingestions include:
- Inaccurate timeline (poor history)
- Unknown timeline
- Repeated Supratherapeutic Ingestion (all the ingestion occurs in greater than an 8 hour timeframe)

OR
- Presenting greater than 24 hours after acute ingestion

ACUTE acetaminophen (APAP) ingestions include:
- All the ingestion taken within a 24 hour time frame

AND
- Presenting less than 24 hours after a known time of ingestion

! All self-harm ingestion attempts require psychiatric evaluation

Consider social work consultation if there are concerns for maltreatment or neglect resulting in APAP ingestion or toxicity.

NONACUTE acetaminophen (APAP) ingestion:

Inclusion Criteria:
- Any patient with concern for acetaminophen toxicity

Exclusion Criteria:
- Ingestion of acetaminophen with co-ingestants (i.e. cough and cold preparations) (may contain dextromethorphan, diphenhydramine), sleep/night preparations (PM) (may contain diphenhydramine, chlorpheniramine), opioid combination products)
- Severe ingestions (APAP blood concentrations greater than 300 mcg/ml)
- Extended release (ER) products
- IV acetaminophen overdose

- Obtain APAP concentration immediately
- Complete Metabolic Panel (CMP)
- Any other relevant labs

APAP greater than 20 mcg/ml?

No → Normal Transaminases (AST/ALT)?

No → Consult toxicology through Rocky Mountain Poison & Drug Safety (RMPDS) for further recommendations 1-800-222-1222

Yes → Can medically clear from APAP toxicity

Yes → Normal Transaminases (AST/ALT)?

No →
- Initiate N-acetylcysteine (NAC)
- If AST/ALT abnormal, obtain Prothrombin Time/International Normalized Ratio (PT/INR)

Yes →
- Initiate N-acetylcysteine (NAC)
- Consult toxicology through RMPDS (1-800-222-1222)
- Admit to hospital medicine service

INR greater than 2 OR greater than 1.5 with encephalopathy?

No →
- Consult toxicology through RMPDS (1-800-222-1222)
- Admit to hospital medicine service

Yes →
- Admit to PICU
- Consult Liver Service
  - In Colorado Springs, consult GI
- Consult toxicology through RMPDS (1-800-222-1222) with further questions or co-ingestants
- Other risk factors: pH less than 7.3, acute kidney injury (AKI)

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TARGET POPULATION

Inclusion Criteria

Any patient with concern for acetaminophen toxicity.

- Acute supratherapeutic acetaminophen ingestion
- Unknown time of a supratherapeutic acetaminophen ingestion
- Repeated supratherapeutic acetaminophen ingestion

Exclusion Criteria

- Ingestion of acetaminophen with coingestants (ie cough and cold preparations (may contain dextromethorphan, diphenhydramine), PM preparations (may contain diphenhydramine, chlorpheniramine), opioid combination products), or extended release (ER) products. Consult the Medical Toxicology service for recommendations for these patients.
- IV acetaminophen overdose
- Massive or severe ingestions (acetaminophen blood concentrations greater than 300 mcg/ml). Consult the Medical Toxicology service for recommendations for these patients.

BACKGROUND | DEFINITIONS

Acetaminophen is an over-the-counter analgesic and antipyretic that is commonly used in all ages. Therapeutic mechanism of action is via inhibition of the formation of prostaglandins. In overdose or supratherapeutic settings, it can lead to hepatotoxicity. In extreme circumstances, overdose can lead to liver failure, metabolic acidosis, cerebral edema and death. Acetaminophen ingestions are one of the most commonly reported unintentional and intentional ingestions. In the 2017 National Poison Data System annual review, there were almost 110,000 human exposures to acetaminophen single ingredient and combination products. There were 142 deaths attributed to acetaminophen combination exposures, and 140 acetaminophen alone exposures. In pediatrics, acetaminophen ingestions are one of the most common presenting toxicological complaints in the emergency room and a leading toxicological diagnosis requiring admission to both the inpatient ward and ICU.

In normal metabolism, acetaminophen is renally eliminated unchanged (5%) or metabolized via hepatic glucuronidation (40-65%) and sulfation (20-45%). In supratherapeutic ingestion, these metabolic pathways become saturated, and metabolism occurs via CYP 2E1 to NAPQI, which can lead to cellular toxicity (specifically

hepatotoxicity). NAPQI is normally conjugated to glutathione to form nontoxic acetaminophen conjugates which are eliminated in the urine. However, it is overproduced in overdose settings, leading to hepatotoxicity.

DEFINITIONS

- ACUTE ingestion: all of the ingestion of acetaminophen taken within a 24-hour timeframe, and presenting less than 24 hours after initial time of ingestion
- NON-ACUTE ingestion:
  - Inaccurate timeline (poor history)
  - Unknown timeline
  - Repeated Supratherapeutic Ingestion (RSTI): ingestion occurs in greater than a 24-hour timeframe
  - Presenting greater than 24 hours after ingestion

MASSIVE ingestion:

  - Acetaminophen blood concentrations greater than 300 mcg/mL

CLINICAL MANAGEMENT

Obtain thorough history and perform physical exam.

History:

- Inquire about past medical history (hospitalizations, recent illness, psychiatric history including past suicidal ideation or attempts)
- Take a medication history. This includes regular medications or recently taken medications. Potential other medications that the patient could have access to is also important in ruling out other ingestions.
- Obtain details of events including timeline of events (when ingestion occurred), the maximum amount suspected (tablet strength, size of bottle, estimate of number of tabs remaining), and subsequent timeline of events (any therapies, interventions, symptoms that have developed prior to arrival).

Clinical Symptoms of acetaminophen toxicity:

- Most patients will develop nausea/vomiting after supratherapeutic ingestion of acetaminophen.
- Some patients may be asymptomatic.
- In a large overdose, somnolence or CNS depression may develop.
- Acetaminophen is common in combination preparations. Thus, initial symptoms may be due to coingestants such as antitussive agents (dextromethorphan), antihistamines (diphenhydramine, chlorpheniramine), and opioids (codeine, oxycodone, hydrocodone). These coingestants, specifically antihistamines, can lead to irregular kinetics, erratic absorption, and unpredictable toxicity.

Clinical Progression of acetaminophen toxicity:

- Nausea/vomiting can last 24-36 hours after ingestion. In large overdose, metabolic acidosis and cardiovascular collapse can occur within hours of ingestion.
- Without treatment, elevated liver tests will begin approximately 20-24 hours after time of ingestion (as early as 12 hours in the most severe of ingestions). The aspartate aminotransferase (AST) will be the first to rise, followed by alanine aminotransferase (ALT). Level of transaminase elevation can range from 2-3 times normal, to greater than 10-20,000 IU/L in severe toxicity. Maximum liver toxicity occurs between 72-96 hours after ingestion. Elevated liver enzymes do not universally indicate liver synthetic dysfunction, including coagulopathy.

- Liver synthetic dysfunction (if occurs) can occur approximately 2-3 days after ingestion. Signs may include coagulopathy, and encephalopathy.
- Acute kidney injury (if occurs) can occur 2-5 days after ingestion, often peaking at 7 days after ingestion.
- Without treatment, fatalities can occur 3-5 days after acute overdose.
- In recovery phase after ingestion, the AST typically will decline prior to ALT, followed by improvements in liver and kidney function.

Prognosis of acetaminophen toxicity:

- Ingestions that present and receive N-acetylcysteine within 8-10 hours from time of ingestion universally do well and expect a full recovery.
- Even those who present after the 8-10 hour time frame and receive N-acetylcysteine typically do well
- Patients who present after the setting of a chronic repeated supratherapeutic ingestion (RSTI), late presenting acute ingestion, and/or already with signs of liver synthetic dysfunction, have a guarded and potentially poor prognosis.
- Lactate greater than 3.0 mmol/l after fluid resuscitation or 3.5 mmol/l at 55 hours after ingestion has been an indicator of increased mortality without transplantation.
- The most commonly used indicator for the need for immediate transplantation in adults with acetaminophen toxicity is the King's College Criteria (KCC). Survival rate of adult patients who meet KCC and do not receive organ transplant is less than 20%. KCC includes:
  - pH less than 7.30 after adequate fluid resuscitation

    OR Combination of:
  - Creatinine (Cr) greater than 3.4 mg/ml
  - Prothrombin (PT) greater than 100 s (INR greater than 6.5)
  - Grade 3 or 4 hepatic encephalopathy (grading does not apply when coingestants or other substances may influence mental status)
    - Grade 1: difficulties with concentration or attention, mild confusion sleep disturbances, slurred speech
    - Grade 2: drowsy/lethargic, disoriented or moderate confusion, inappropriate behavior
    - Grade 3: marked confusion (stupor), incoherent, somnolent but arousable
    - Grade 4: coma, unresponsive to pain
- Other scores used to assess adult patients for need for transplantation after acetaminophen ingestion include APACHE 2 score greater than 15, APACHE 3 score greater than 60, or combination of hypoglycemia, coagulopathy, and lactic acidosis.

Differential Diagnosis:

- Although toxicity is quite different, other over-the-counter analgesics are often mistaken for each other, including aspirin, and NSAIDs.
- Other etiologies for hepatotoxicity and liver failure, both toxicological and non-toxicological in nature, should be explored.

Monitoring:

- Continuous cardiac/pulse oximetry monitoring is recommended for unstable and critically ill patients.

LABORATORY STUDIES | IMAGING

- For ACUTE ingestions: acetaminophen concentration and complete metabolic panel should be obtained at 4 hours after the earliest known time of ingestion (or upon presentation if after 4 hours). This concentration can be plotted on the Matthew-Rumack Nomogram to determine treatment plan.
- For NON-ACUTE ingestions: acetaminophen concentration and complete metabolic panel should be obtained upon presentation. The Matthew-Rumack Nomogram is not applicable.
- Obtain coagulation panel if elevated liver tests are noted.
- Obtain a venous blood gas for patients with metabolic acidosis noted on their electrolytes, altered mental status, or liver synthetic dysfunction.
- A salicylate concentration should be obtained to rule out erroneous reporting of analgesic ingested.
- Other studies include labs or electrocardiogram to investigate coingestants as clinically indicated.

THERAPEUTICS

Routinely Indicated: N-acetylcysteine

- There are no changes in morbidity or mortality between the 2 routes of administration of N-acetylcysteine. IV is more often used due to the ease of use, shorter duration/course of treatment, and difficulties with PO administration with significant nausea/vomiting.
- There may be circumstances in severe overdose when the rate and/or amount of N-acetylcysteine is increased. This should be done in consultation with the Medical Toxicology Service.

Intravenous (IV) N-acetylcysteine

- 2-Bag regimen
- FIRST dose: 200 mg/kg/dose (max: 20 grams) infused over 4 hours
- SECOND dose (standard): 100 mg/kg/dose (max: 10 grams) infused over 16 hours
- ALTERNATIVE SECOND dose (massive ingestion): 200 mg/kg/dose (max: 20 grams) infused over 16 hours
- Continuation of treatment beyond the second dose may be needed if liver tests continue to be elevated, or acetaminophen concentration continues to be detectable: 100 mg/kg/dose (max: 10 grams) infused over 16 hours. Begin subsequent bags immediately after prior bag finishes.
- If patient is started on a 3-bag regimen at an outside facility (150mg/kg loading dose over 1 hour followed by 50mg/kg over 4 hours) – may switch patient over to 16 hour 'second' dose on arrival.
- Common adverse events:
  - Non-allergic anaphylactic reactions (NAARs) – rash, hives, flushing, throat tightness, angioedema
  - Gastrointestinal – dyspepsia, nausea, vomiting
  - Can administer diphenhydramine, decrease the rate of IV administration, or transition to PO formulation with significant adverse events.
  - Can also cause a slight bump in INR, though should still be less than 2. An INR greater than 2 should not be attributed to IV N-acetylcysteine.

Oral (PO) N-acetylcysteine

- N-acetylcysteine 20% (200 mg/ml):

  There is no data for use of the OTC supplement tablets for acetaminophen poisoning. Dosing below is based on effervescent tablet (Cetylev) or a solution for oral administration that is prepared from the solution for oral inhalation:

  - 72-hour regimen: Consists of 18 doses; total dose delivered: 1,330 mg/kg
    - Loading dose: 140 mg/kg; maximum dose: 15 g/dose
    - Maintenance dose: 70 mg/kg every 4 hours for 17 doses; maximum dose: 7.5 g/dose
      - Repeat dose if emesis occurs within 1 hour of administration.
      - Note: 72-hour regimen may be shortened, but this should be done in consultation with the medical toxicology service.
- Common adverse events (or difficulties with compliance):
  - Similar to IV, although less NAARs and more GI related ADEs
  - Number of doses and volume may be hard for patient to tolerate
  - Has sulfur (rotten-egg) smell/taste -- may be mixed in juices, soda, or other vehicles to aid in palatability.

Recommended in some patients:

Activated Charcoal

- For *acute* ingestions who present less than 2 hours post ingestion with normal mentation, consider dose of activated charcoal (0.5-1 g/kg), ONLY if the patient can voluntarily self-administer.

Intravenous Fluids

- Patients with severe toxicity and illness, nausea/vomiting, or inability to have oral intake should receive intravenous fluid resuscitation and maintenance fluids with appropriate dextrose and electrolytes.

Extracorporeal Removal

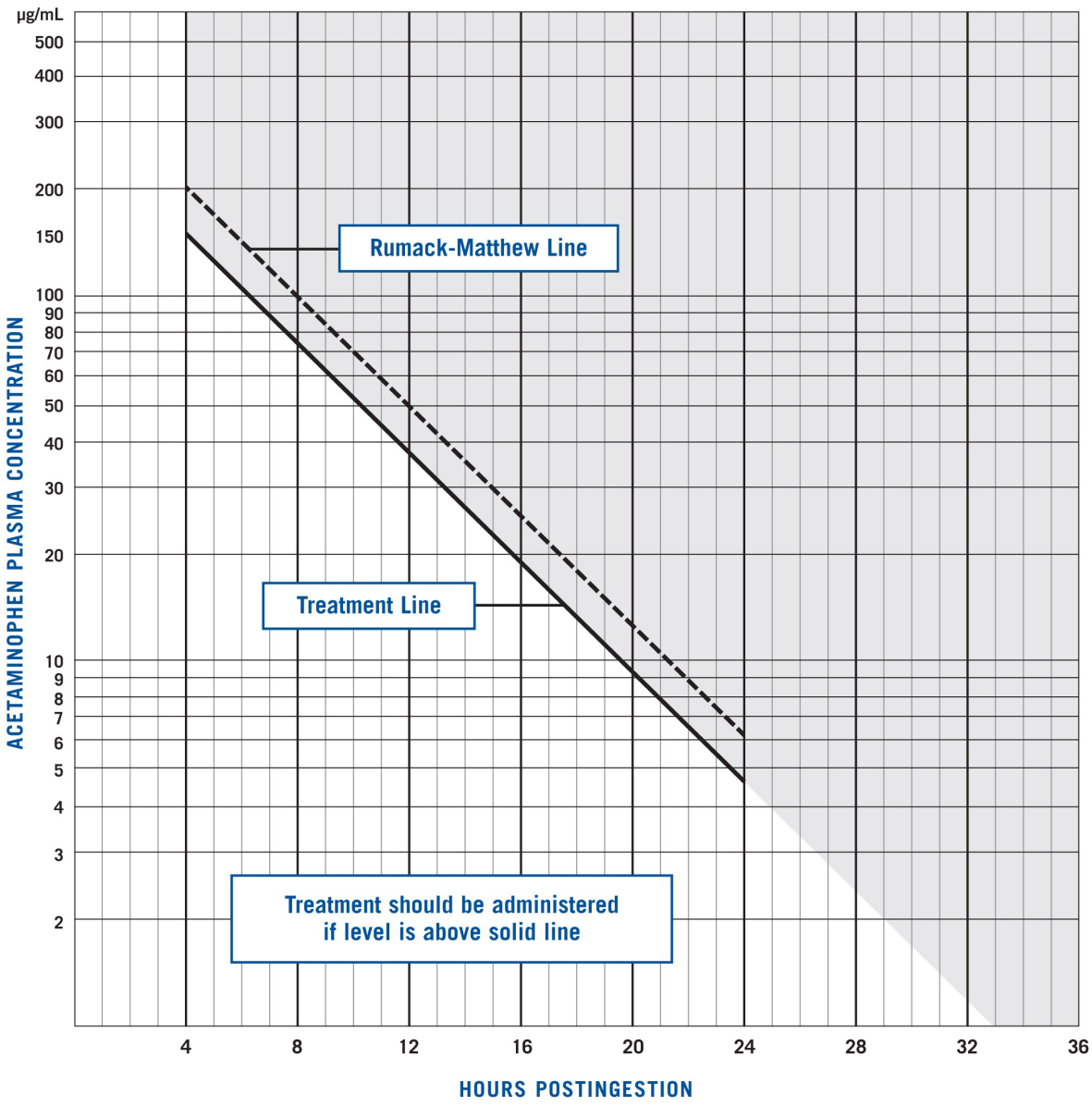
- In severe overdose, where toxicity has led to CNS symptoms, metabolic acidosis (which is typically acetaminophen blood concentrations greater than 800 mcg/ml), hemodialysis or continuous renal replacement therapy have been used to correct the metabolic derangements in addition to extracting acetaminophen. This modality is used sparingly and should be used in consultation with Medical Toxicology Service and renal service.

Not Routinely Indicated:

Gastric Lavage, whole bowel irrigation, or cathartics to promote defecation

Disposition

- Acute ingestion: patients with an acetaminophen above the Matthew-Rumack Nomogram Treatment Line will require course of N-acetylcysteine.



Nomogram: acetaminophen plasma concentration vs time after acetaminophen ingestion (adapted with permission from Rumack and Matthew. *Pediatrics*. 1975;55:871-876). The nomogram has been developed to estimate the probability of whether a plasma acetaminophen concentration in relation to the interval postingestion will result in hepatotoxicity and, therefore, whether acetylcysteine therapy should be administered.

CAUTIONS FOR USE OF THIS CHART:

1. Time coordinates refer to time postingestion.
2. Graph relates only to plasma concentrations following a single, acute overdose ingestion.
3. The Treatment Line is plotted 25% below the Rumack-Matthew Line to allow for potential errors in plasma acetaminophen assays and estimated time from ingestion of an overdose (Rumack et al. *Arch Intern Med*. 1981;141(suppl):380-385).

- Unknown or RSTI: patients with a supratherapeutic concentration (acetaminophen greater than 20 mcg/ml) or elevated transaminases will require course of N-acetylcysteine

ADMISSION to inpatient/observation

- Consult toxicology via the Rocky Mountain Poison and Drug Safety (RMPDS) at 1-800-222-1222
- Patients without significant liver dysfunction (INR greater than 2) can be observed in the ED or admitted to the inpatient hospitalist service for course of N-acetylcysteine

ADMISSION to ICU

- If INR greater than 2 OR INR greater than 1.5 WITH encephalopathy:
  - Other significant risk factors: pH less than 7.3, acute kidney injury (AKI), metabolic acidosis
- Consult Liver Service who will be primary consultation
    - In Colorado Springs, consult GI
- Consult toxicology via the Rocky Mountain Poison and Drug Safety (RMPDS) at 1-800-222-1222 for further questions or if there are coingestants
- Patients admitted to ICU with involvement of Liver Service (GI in Colorado Springs), can be transferred to the Liver Inpatient Service once clinically stable.

STOPPING CRITERIA FOR N-acetylcysteine

- For an acute acetaminophen ingestion, repeat LFTs and acetaminophen concentration and INR, if applicable, 1-2 hours prior to completing each 16-hour bag or prior to last PO dose.
- For a *nonacute* acetaminophen toxicity, repeat labs q12 hours (LFTs, acetaminophen concentration, and INR, if applicable).
- Duration of N-acetylcysteine may be shortened per toxicology recommendations. In patients with an elevated INR, N-acetylcysteine should not be stopped without discussion with Liver Service (GI in Colorado Springs).
- Recommended stopping criteria for *any* acetaminophen toxicity:
  - Acetaminophen level undetectable
  - LFTs (AST/ALT) remain normal (if elevated liver tests occurred) OR declining and approximately 50% of peak levels.
  - Cr less than 2 mg/dl and declining (if applicable)
  - INR less than 2 and declining (if applicable)
  - Clinically well (without encephalopathy)

MEDICAL CLEARANCE

- All self-harm ingestion attempts will need psychiatric evaluation.
- Consider social work consultation if there are concerns for maltreatment or neglect resulting in acetaminophen ingestion or toxicity.
- All discharged patients who have LFTs that have not completely normalized upon medical clearance will need outpatient follow up with repeat LFTs every 1-2 weeks until normalized. If liver tests remain elevated after 1 month, they will need follow up with Liver Team as outpatient. In addition, all patients who develop acute liver failure and recover will require Liver Team follow up.

PARENT | CAREGIVER EDUCATION

- Most patients who receive N-acetylcysteine within 8-10 hours within the time of ingestion will fully recover.
- Once recovered, long-term liver injury or dysfunction is not expected.
- Poison prevention counseling
- Mental health resources

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APPROVED BY

Clinical Pathways and Measures Committee – October 23, 2023
Pharmacy & Therapeutics Committee – November 2, 2023

MANUAL/DEPARTMENT	Clinical Pathways/Quality
ORIGINATION DATE	August 1, 2019
LAST DATE OF REVIEW OR REVISION	October 23, 2023
COLORADO SPRINGS REVIEW BY	 Michael DiStefano, MD Chief Medical Officer, Children's Hospital Colorado – Colorado Springs
APPROVED BY	 Lalit Bajaj, MD, MPH Chief Quality and Outcomes Officer

REVIEW | REVISION SCHEDULE

Scheduled for full review on October 23, 2027

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ATENCIÓN: si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al 1-720-777-9800.

CHÚ Ý: Nếu bạn nói Tiếng Việt, có các dịch vụ hỗ trợ ngôn ngữ miễn phí dành cho bạn. Gọi số 1-720-777-9800.

주의: 한국어를 사용하시는 경우, 언어 지원 서비스를 무료로 이용하실 수 있습니다. 1-720-777-9800 번으로 전화해 주십시오

注意：如果您使用繁體中文，您可以免費獲得語言援助服務。請致電1-720-777-9800。

ВНИМАНИЕ: Если вы говорите на русском языке, то вам доступны бесплатные услуги перевода. Звоните 1-720-777-9800.

ማስታወሻ: የሚናገሩት ቋንቋ አማርኛ ከሆነ የትርጉም እርዳታ ድርጅቶች፣ በነጻ ሊያግዝዎት ተዘጋጀተዋል፡ ወደ ሚከተለው ቁጥር ይደውሉ 1-720-777-9800 (መስማት ለተሳናቸው.

ملحوظة: إذا كنت تتحدث اذكر اللغة، فإن خدمات المساعدة اللغوية تتوافر لك بالمجان. اتصل برقم 1-720-777-9800 (رقم

ACHTUNG: Wenn Sie Deutsch sprechen, stehen Ihnen kostenlos sprachliche Hilfsdienstleistungen zur Verfügung. Rufnummer: 1-720-777-9800.

ATTENTION : Si vous parlez français, des services d'aide linguistique vous sont proposés gratuitement. Appelez le 1-720-777-9800.

ध्यान दनु होस्तपाइले नेपाल बोल्नहन्छ भन तपाइको निम्त भाषा सहायता सवाहरू नःशल्क रूपमा उपलब्ध छ । फोन गनु होसर् 1-720-777-9800 ।

PAUNAWA: Kung nagsasalita ka ng Tagalog, maaari kang gumamit ng mga serbisyo ng tulong sa wika nang walang bayad. Tumawag sa 1-720-777-9800.

注意事項：日本語を話される場合、無料の言語支援をご利用いただけます。1-720-777-9800 まで、お電話にてご連絡ください。

Ntị: Ọ bụrụ na asụ Ibo, asụsụ aka ọasụ n'efu, defu, aka. Call 1-720-777-9800.