Target Audience: Emergency Medicine Residents, Medical Students

Primary Learning Objectives:

1. Generate a broad differential for hepatitis
2. Detect repeated supratherapeutic acetaminophen overdose in history and physical exam
3. Treat repeated supratherapeutic acetaminophen overdose correctly with N-acetylcysteine

Secondary Learning Objectives: detailed technical/behavioral goals, didactic points

1. Describe the pathophysiology of acetaminophen toxicity
2. Discuss the management priorities for the emergent stabilization of the patient with an acetaminophen overdose
3. Compare acetaminophen toxicity with other diseases and conditions that cause hepatitis, transaminitis, and liver injury, especially with regard to the differences and similarities in presentation, diagnostics, and management priorities
4. Describe the methods used to minimize absorption and enhance elimination of agents in the context of acetaminophen overdose

Critical actions checklist:

1. Order liver function tests
2. Administer supportive therapies for abdominal pain and nausea
3. Order right upper quadrant ultrasound
4. Obtain APAP level
5. Administer N-acetylcysteine
6. Consult Poison Center/Toxicologist
7. Admit to the PICU

Environment:

1. Room Set Up – ED critical care area
    a. Manikin Set Up – Mid or high fidelity simulator
    b. Props – Standard ED equipment

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CASE SUMMARY

SYNOPSIS OF CASE

This is a case of a 38-year-old man with a past medical history of alcoholism/alcohol abuse and biliary colic who now presents with nonspecific symptoms of malaise, nausea, vomiting, and upper abdominal pain. The participant will discover that the patient has recently had his wisdom teeth extracted and has been taking greater than prescribed doses of liquid Lortab® (hydrocodone-acetaminophen), but **this history will be obtained ONLY if the patient is specifically asked about it during the patient interview**.

The patient initially has stable vital signs. Diagnostics reveal that the patient has significant hepatitis and a normal abdominal/hepatic ultrasound (including a normal gallbladder). Diagnostics will also reveal that he has consumed alcohol recently **(AT FACULTY DISCRETION, THIS FEATURE OF THE CASE MAY BE USED TO MAKE THE CASE MORE OR LESS COMPLEX)**. The participant must obtain a thorough history and physical, generate a broad differential diagnosis for hepatitis, suspect repeated supratherapeutic acetaminophen overdose, and treat appropriately with N-acetylcysteine.

SYNOPSIS OF PHYSICAL

This patient presents with

- Abdominal pain in the epigastric and right upper quadrant abdominal areas
- No evidence of recent trauma, alcohol intoxication, or recreational drug use

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CRITICAL ACTIONS

1. **Order liver function tests**

   Order liver function tests. These should, at a minimum, include the AST, ALT, ALP, hepatitis panel, and coagulation studies (PT/INR/PTT).
   Cueing Guideline: The nurse can ask if the doctor wants an IV placed and labs drawn and sent for diagnostic tests.

2. **Administer supportive therapies for abdominal pain and nausea**

   Administer supportive therapies for abdominal pain and nausea. Participant may demonstrate a preference to avoid narcotic analgesics and use non-narcotic agents. This preference and rationales behind it could be explored in the debriefing. Acetaminophen should not be administered (this will obviously complicate the patient's condition). Histamine-2 blockers (e.g., famotidine), proton-pump inhibitors, and antiemetics (e.g., ondansetron) may be considered in the context of this patient's presentation. NSAID administration may be considered.
   Cueing Guideline: The nurse can ask if the doctor would like any medications to relieve the patient's symptoms.

3. **Order a right upper quadrant ultrasound**

   Order a right upper quadrant ultrasound. This study will reveal mild fatty infiltration of the liver. The remainder of the exam, however, will be negative for cholecystitis and cholelithiasis.
   Cueing Guideline: Nurse can ask if the doctor would like any radiographic diagnostics to help diagnose the causes for the patient's symptoms

4. **Obtain APAP level**

   Obtain APAP level. Confirm or exclude acetaminophen as a co-toxicant. The learner fulfills this critical action by ordering the appropriate lab tests.
   Cueing Guideline: The nurse can ask if the doctor would like additional diagnostic tests to help rule-in or rule-out possible etiologies for the patient's symptoms.

5. **Administer N-acetylcysteine**

   Administer N-acetylcysteine for transaminitis and presumed acetaminophen toxicity.
   Cueing Guideline: The nurse can ask the doctor if anything can be given for the patient's symptoms (especially if the learner has identified the transaminitis and exposure to acetaminophen).

6. **Consult Poison Center/Toxicologist**

   Consult Toxicology (either the Poison Center or Toxicologist)
   Cueing Guideline: Nurse can ask the doctor if anyone has called the Toxicologist yet. Nurse may also ask if there is anything more we can do to help improve the patient's condition (once the etiology is known).

7. Admit to the MICU

Admit to the MICU. Patient will not be stable for any other destination.
Cueing Guideline: Nurse can ask the doctor if anyone has called the intensivist to arrange for a definitive disposition decision.

Critical Actions Checklist[1]

Resident Name	
Case Description	

Skills measured **Core competencies: PC** Patient care, **MK** Medical knowledge, **IC** Interpersonal and communication skills **P** Professionalism, **PB** Practice-based learning and improvement **SB** Systems-based practice	**Very Unacceptable**		**Unacceptable**		**Acceptable**		**Very Acceptable**	
Data Acquisition (D) PC MK I	1	2	3	4	5	6	7	8
Problem Solving (S) PC MK PB	1	2	3	4	5	6	7	8
Patient Management (M) PC MK IC P PB SB	1	2	3	4	5	6	7	8
Resource Utilization (R) PC PB SB	1	2	3	4	5	6	7	8
Health Care Provided (H) PC SB	1	2	3	4	5	6	7	8
Interpersonal Relations (I) IC P	1	2	3	4	5	6	7	8
Comprehension of Pathophysiology (P) MK PB	1	2	3	4	5	6	7	8
Clinical Competence (C) PC MK IC P PB SB	1	2	3	4	5	6	7	8

Critical Actions

Yes	No		Comments:
		Order liver function tests	
		Administer supportive therapies for abdominal pain and nausea	
		Order an abdominal and hepatic ultrasound	
		Obtain APAP level	
		Administer N-acetylcysteine	
		Consult Toxicology	
		Admit to the MICU	

Yes	No	
		Dangerous actions

[1] Modified ABEM Oral Certification Examination checklist and scoresheet

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HISTORY

Age: 38

Sex: Male

Name: Jerry Redd

Method of Transportation: Walk in

Person giving information: Patient

Chief Complaint: Malaise, nausea, vomiting, abdominal pain (epigastric and right upper quadrant areas of the abdomen)

HPI: Malaise, nausea, vomiting, and abdominal pain have developed this morning.

If asked: He will admit that he had been well previously until recent dental extraction. The pain in the tooth had been severe, but has been controlled with repeated doses of the liquid hydrocodone/acetaminophen (10mg/325mg)/15mL.

CASE OPTION - If asked: He will admit that he had been out last night with friends and "had a few drinks."

Past Medical Hx: Recent dental extraction, biliary colic, alcoholism/alcohol abuse

Family Med Hx: Unknown (roommate will not be able to contribute data for questions about the family history)

Social Hx:
No tobacco use
Admits recent alcohol use
No observed recreational drug use
Unmarried

Medications "A mouthful/swallow of liquid pain killer every couple of hours for the last few days" (liquid hydrocodone-acetaminophen)

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PLAY OF CASE GUIDELINES

This is a case of a 38-year-old man with a past medical history of alcoholism/alcohol abuse and biliary colic who now presents with nonspecific symptoms of malaise, nausea, vomiting, and right upper abdominal pain.

1. The patient will be stable at the time of presentation.
2. Acetaminophen is the primary toxicant in the case.
3. The patient presents with nausea, vomiting, and abdominal pain indicative of acetaminophen toxicity.
4. If managed correctly, he will require supportive therapy (including analgesics) and N-acetylcysteine.
5. Consultation with the Poison Center/Toxicologist and the Intensivist will also be required.
6. The participant must obtain a thorough history and physical, generate a broad differential diagnosis for hepatitis until the acetaminophen toxicity is suspected or confirmed.
7. The patient requires MICU admission for continued observation and serial reassessments.

PHYSICAL EXAM

Vital Signs: BP: 136/86 mmHg P: 90/minute R: 14/minute T: 37C (98.6F) POx: 99%

General Appearance: Awake, alert, coherent, but is uncomfortable.

HEENT: AT/NC. PERRLA. EOMI. No nystagmus. No odor on breath. Supple neck.

Lungs: Clear to auscultation. No wheezes, rales, or rhonchi.

CV: Regular rate and rhythm. No murmurs. Normal perfusion.

Abdomen: Soft but with tenderness in the epigastric and right upper quadrant areas. Non-distended throughout abdomen. Normal bowel sounds.

Extremities: Atraumatic. No edema. Normal strength and gait.

Rectal: Guaiac negative stools.

Back: Normal. No CVA tenderness.

Neurological: Awake. Alert. Interactive. Normal motor function. Normal sensation. Normal mentation and cognition. No ataxia. No asterixis.

Skin: No track marks. No jaundice or rashes.

(NOTE: AT FACULTY DISCRETION, THESE FEATURES – NYSTAGMUS, ODOR ON BREATH, ATAXIA, ETC. – COULD BE ADJUSTED TO ENHANCE THE ALCOHOL-ASSOCIATED ASPECTS OF THIS CASE)

Required Actions within the First Two Minutes

- Perform primary survey (A-B-C-D's) and start patient interview. Perform problem-focused physical exam.
- Peripheral IV access established and diagnostics should be ordered during this period
- Analgesic administration and other supportive therapies should be considered during this period

Branch Points

- **IF ANALGEICS AND OTHER SUPPORTIVE THERAPIES (E.G., HISTAMINE-2 BLOCKERS, PROTON-PUMP INHIBITORS, ETC.) ARE ORDERED AND ADMINISTERED WITHIN THE FIRST TWO MINUTES,** then the patient's pain transiently improves (it will recur later in the case).
- **IF ANTIEMETICS ARE ORDERED AND ADMINISTERED WITHIN THE FIRST TWO MINUTES,** then the patient's nausea transiently improves (it will recur later in the case).
- **IF ACETAMINOPHEN IS ORDERED AND ADMINISTERED WITHIN THE FIRST TWO MINUTES,** it will have no effect on the patient's status during the case (although this is **NOT** a preferred intervention, obviously).
- **ADMINISTRATION OF IV CRYSTALLOID FLUID BOLUSES** will have no effect on the patient's symptoms.
- **AT FACULTY DISCRETION,** the alcohol-associated features of this case may be enhanced or diminished to adjust the complexity of the case.

Required Actions over the Next Four Minutes

- Diagnostics should be returned as ordered
- Transaminitis should be recognized by this time
- Etiologies, including the possibility of drug toxicity (acetaminophen, alcohol-associated), infections (e.g., viral hepatitis - HAV, HBV, HCV, EBV, CMV, etc.), and surgical causes (e.g., cholecystitis, choledocholithiasis, etc.) should be considered at this time

Branch Points

- **IF ACETAMINOPHEN LEVEL HAS NOT BEEN ORDERED BY THIS TIME,** then the patient's nausea, vomiting, and abdominal pain will return.
- **IF N-ACETYLCYSTEINE IS ORDERED AND ADMINISTERED AT THIS TIME,** then this patient's symptoms will coincidently improve.

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STIMULUS INVENTORY

#1	Complete blood count
#2	Basic metabolic panel
#3	Urinalysis
#4	Liver function tests
#5	Arterial blood gas
#6	Creatinine phosphokinase
#7	Toxicology / Urine drug screen
#8	Coagulation studies
#9	Point-of-care serum glucose
#10	Abdominal/Hepatic US
#11	Lactate

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LAB DATA & IMAGING RESULTS

Stimulus #1	
Complete Blood Count (CBC)	
WBC	14,000/mm^3
Hemoglobin	13 g/dL
Hematocrit	36%
Platelets	286,000/mm^3
Differential	
PMNLs	80%
Lymphocytes	9%
Monocytes	7%
Eosinophils	4%

Stimulus #2	
Basic Metabolic Profile (BMP)	
Sodium	140 mEq/L
Potassium	3.8 mEq/L
Chloride	98 mEq/L
Bicarbonate	22 mEq/L
Glucose	90 mg/dL
BUN	23 mg/dL
Creatinine	0.7 mg/dL

Stimulus #3	
Urinalysis	
Color	Yellow
Specific gravity	1.030
Glucose / Protein	Negative
Urobilinogen	Trace
Ketones	Trace
Leuk. Esterase	Negative
Nitrites	Negative
WBC	0/hpf
RBC	0/hpf

Stimulus #4	
Liver Function Tests	
AST	3340 U/L
ALT	2800 U/L
Alk Phos	120 U/L
T. Bilirubin	2.3 mg/dL
Albumin	3.5 mg/dL
Protein	7 mg/dL

Stimulus #5	
Arterial Blood Gas	
pH	7.36
pCO_2	38 mm Hg
pO_2	100 mm Hg
HCO_3	22 mEq/L
SaO_2	99% (FiO_2=0.21)

Stimulus #6	
Creatine phosphokinase	
CPK	80 U/L

Stimulus #7	
Toxicology	
Salicylate	< 4 mg/dL
Acetaminophen	150 mcg/mL
Ethanol	180 mg/dL
Urine drug screen	
Amphetamines	Negative
Benzodiazepines	Negative
Cocaine	Negative
Opiates	Negative
TCAs	Negative
THC	Negative

Stimulus #8	
Coagulation Studies	
INR	1.5
PTT	38 seconds

Stimulus #9
Point-of-care serum glucose
90 mg/dL

Stimulus #10	
Abdominal/ Hepatic US	No cholelithiasis. No stone-in-neck. No pericholecystic fluid or gallbladder wall thickening. Fatty infiltration.

Stimulus #11	
Lactate	2.8 mmol/L

Stimulus #1

Complete Blood Count (CBC)

WBC	14,000/mm^3
Hemoglobin	13 g/dL
Hematocrit	36%
Platelets	286,000/mm^3
Differential	
PMNLs	80%
Lymphocytes	9%
Monocytes	7%
Eosinophils	4%

Stimulus #2

Basic Metabolic Profile (BMP)

Sodium	140 mEq/L
Potassium	3.8 mEq/L
Chloride	98 mEq/L
Bicarbonate	24 mEq/L
Glucose	90 mg/dL
BUN	23 mg/dL
Creatinine	0.7 mg/dL

Stimulus #3

Urinalysis

Color	Yellow
Specific gravity	1.030
Glucose	Negative
Protein	Trace
Ketones	Trace
Leuk. Esterase	Negative
Nitrites	Negative
WBC	0/hpf
RBC	0/hpf

Stimulus #4

Liver Function Tests

AST	3340 U/L
ALT	2800 U/L
Alk Phos	120 U/L
T. Bilirubin	2.3 mg/dL
Albumin	3.5 mg/dL
Protein	7 mg/dL

Stimulus #5

Arterial Blood Gas

pH	7.36
pCO_2	38 mm Hg
pO_2	100 mm Hg
HCO_3	22 mEq/L
SaO_2	99% (FiO_2=0.21)

Stimulus #6

Creatine phosphokinase

CPK	80 U/L

Stimulus #7

Toxicology

Salicylate	< 4 mg/dL
Acetaminophen	150 mcg/mL
Ethanol	180 mg/dL

Urine drug screen

Amphetamines	Negative
Benzodiazepines	Negative
Cocaine	Negative
Opiates	Negative
TCAs	Negative
THC	Negative

Stimulus #8

Coagulation Studies

INR	1.5
PTT	38 seconds

Stimulus #9

Serum glucose

90 mg/dL

Stimulus #10

Abdominal/Hepatic US	No cholelithiasis. No stone-in-neck. No pericholecystic fluid or gallbladder wall thickening. Fatty infiltration.

Stimulus #11

Lactate	2.8 mmol/L

Debriefing Notes: Repeated Supratherapeutic Acetaminophen Toxicity

Educational Goals: Review the key principles of the diagnosis and management of the management of acetaminophen toxicity from repeated supratherapeutic dosing

Acetaminophen (Tylenol) is a nonopioid analgesic and antipyretic medication found in many over-the-counter and prescription products such as Tylenol PM, Vicodin, Percocet, Nyquil, Tylox, Vicks Formula 44-D. The recommended maximum daily dose of acetaminophen for adults is 4g/day, and 75-90mg/kg/day for children. Alcoholics may safely take Tylenol in therapeutic doses, but they are at increased risk for hepatotoxicity in overdose.

A *repeated supratherapeutic ingestion* (RSTI) is defined as more than one ingestion of acetaminophen during a period exceeding 8 hours that resulted in a cumulative dose greater than 4g per 24 hours. By comparison, a *therapeutic dose* is 4g per 24-hour period or less, and an *acute overdose* is a dose greater than 4g that occurred in an 8-hour period. RSTI may occur in patients taking analgesics for pain who are not aware they are ingesting multiple medications containing acetaminophen (e.g., taking both Tylenol and Vicodin which contains Tylenol) or who are taking extra doses in an attempt to control their pain, or in dosing errors in the pediatric patient.

III. **Mechanism of Toxicity. Acetaminophen is largely metabolized by the liver. In therapeutic doses, about 90% of acetaminophen is conjugated to nontoxic metabolites (glucuronides and sulfates). A small portion (<5%) is conjugated by the cytochrome P450 enzyme subunit CYP2E1 to a toxic metabolite, N-acetyl-p-benzoquinoneimine (NAPQI). Under normal conditions, NAPQI is further conjugated by glutathione, to nontoxic metabolites and renally eliminated.**

Liver Injury In toxic doses, the usual metabolic pathways are overwhelmed, and acetaminophen is shunted to the cytochrome P450 pathway creating NAPQI. Glutathione stores are depleted, and NAPQI is produced. Cellular injury and hepatic necrosis may occur as NAPQI accumulates.

Renal Injury Cytochrome P450 activity in the kidneys is thought to cause direct renal damage. Renal insufficiency may also develop during fulminant hepatic failure due to hepatorenal syndrome. Renal toxicity is usually associated with liver injury.

Pharmacokinetics Acetaminophen is rapidly absorbed. Peak levels occur within 30-120 minutes with normal doses. Delayed absorption may occur with sustained release products or with co-ingestions that slow the GI tract (opioids, anticholinergics). The elimination half-life is 1-3 hours after therapeutic doses and may extend to 12 hours after overdose.

Toxic Dose Toxicity in adults may occur with acute ingestions of 7g, or 200mg/kg in children. Hepatic injury following a repeated supratherapeutic ingestion may occur at any dose above 4g for more than a 24-hour period.

Clinical Presentation Due to a subacute course in the setting of RSI, patients may present anywhere along a spectrum – normal LFTs to asymptomatic elevation of enzymes to hepatic failure.

Diagnosis With RSTI, an acetaminophen level **CANNOT** be plotted on the Rumack-Matthew nomogram that is used in the setting of acute ingestions. Draw an APAP level and AST/ALT at the time of presentation. Any patient with an APAP level> 10mcg/mL **OR** elevated AST/ALT should start N-acetylcysteine (NAC).

Emergency and Supportive Care Treat nausea and vomiting to protect airway and support safe administration of charcoal and NAC when indicated (see below). Provide standard supportive care for liver and renal failure. Contact liver transplant team early if fulminant hepatic failure appears imminent or occurs.

Decontamination Administer activated charcoal within 2 hours of ingestion (consider later if extended release preparations). Use antiemetics for nausea. Activated charcoal does bind to NAC, but the effect is not thought to be clinically significant. Gastric emptying is not recommended unless there is a suspicion for concomitant serious coingestants (e.g., calcium channel blockers, tricyclic antidepressants).

Specific Drugs and Antidotes The Rumack-Matthew nomogram CANNOT be used to estimate the risk of hepatotoxicity in RSTI. At presentation check a serum APAP level and AST/ALT. If the APAP level is above 10 mcg/mL **or** the AST**/**ALT are elevated, start NAC treatment for 12 hours. If abnormalities persist, continue NAC treatment and call the Poison Center. If the APAP level is undetectable **and** AST and ALT are normal at the end of 12 hours, treatment may be stopped.

NAC may be administered IV or orally.

1. Intravenous (Acetadote)
    A. Loading dose: 150mg/kg infused over 15-60 minutes
    B. Maintenance Infusion #1: 50mg/kg (12.5mg/kg/hr) over 4 hours
    C. Maintenance Infusion #2: 100mg/kg (6.25 mg/kg/hr) until treatment endpoint (12 hours or more).
    D. NAC should be continued for the full course of 21 hours total. If LFTs are abnormal, or serum APAP is detectable at the end of the course, continue the third bag of NAC [100mg/kg (6.25 mg/kg/hr)] until both LFTs are normal (or trending toward the patient's baseline) and serum APAP is undetectable (<10-20 mcg/mL). Consult a medical toxicologist / poison center before changing the duration of therapy (based on AST/ALT, coagulation [INR] function, and acetaminophen concentration).
    E. Adverse events include anaphylactoid reactions. See attached protocol for more information.
2. Oral (Mucomyst)
    A. Loading dose: 140 mg/kg diluted to a 5% solution
    B. Maintenance dose: 70mg/kg diluted to a 5% solution every 4 hours x3 or more based on criteria below.
    C. Treatment course: 12 hours or more
    D. NAC should be continued for the full course. If LFTs are abnormal or serum acetaminophen is detectable at the end of the course, continue NAC until both LFTs are normal (or trending toward the patient's baseline) and serum APAP is undetectable (<10-20 mcg/mL). Consult a medical toxicologist / poison center before changing the duration of therapy (based on liver AST/ALT, coagulation [INR] function, and acetaminophen concentration).

Prognosis In a prospective case series of 249 patients with repeated supratherapeutic ingestions of acetaminophen, 126 patients had an AST <50 IU/L, 47 patients had levels 50-1000 IU/L, and 37 patients had an AST>1000 IU/L. No patient with a normal AST (<50 IU/L) at presentation developed hepatotoxicity. Seven patients with AST of 50-1000 IU/L on presentation developed hepatotoxicity, and one died of hepatic failure. Five patients with AST>1000 IU/L on presentation died, and one required liver transplantation. In summary, only patients with abnormal AST at presentation developed hepatotoxicity. (Daly FS, et al. Ann Emerg Med. 2004;44:393-398)

AST on presentation	# Patients	Developed Hepatotoxicity	Died/Liver Transplant
<50 IU/L	126	0	0
50-1000	47	7	1
>1000	37	37	5

The risk of hepatotoxicity in patients exposed to repeated supratherapeutic ingestions of acetaminophen appears to be related to the amount of APAP ingested and the duration of time of the exposure. NAC therapy is beneficial in these patients. It should be started if the APAP level is above 10 mcg/mL **or** the AST ***/***ALT are elevated.

Repeated Supratherapeutic Acetaminophen Toxicity Do's and Don'ts

DO ask patients with pain complaints (toothaches, back pain, cancer) about the amount of acetaminophen they use.

DO NOT use the Rumack-Matthew nomogram to determine if the APAP level is toxic.

DO NOT stop NAC therapy until the full 12-hour course is finished or truncated therapy is recommended by the Poison Center.

References

Daly FS, et al. Prospective Evaluation of Repeated Supratherapeutic Acetaminophen (Paracetamol) Ingestion. Ann Emerg Med. 2004;44:393-398.

Dart RC Acetaminophen. In Dart RC, Caravati EM, McGuigan M et al eds. *Medical Toxicology* 3rd edition. Philadelphia PA: Lippencott Williams & Wilkins, 2004: pp.723-737.

Olson KR. Acetaminophen. In Olson KR, ed. *Poisoning & Drug Overdose* New York NY: McGraw-Hill, 2004: pp. 66-69.