Chronic Digoxin Toxicity
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Target Audience: Emergency Medicine Residents (junior and senior level postgraduate learners), Medical Students

Primary Learning Objectives:

1. Recognize signs and symptoms of digoxin toxicity
2. Order appropriate diagnostic studies for evaluation of digoxin toxicity
3. Appropriately interpret ECG
4. Administer digoxin-specific antibody fragments (DSFab)
5. Recognize acute kidney injury as a precipitating factor of toxicity, and treat acute kidney injury appropriately
6. Select an appropriate disposition for patient with digoxin toxicity

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

1. Develop independent differential diagnosis in setting of leading information from the nurse
2. Describe the mechanism of digoxin toxicity and treatment, DSFab
3. Use appropriate dosing strategy for DSFab administration

Critical actions checklist:

1. Order a basic metabolic panel
2. Order a digoxin level
3. Obtain ECG
4. Provide volume resuscitation for acute kidney injury
5. Administer digoxin antibody fragments
6. Consult Poison Center/Toxicologist
7. Admit to the MICU

Environment: Emergency Department treatment area

1. Room Set Up – ED critical care area
    a. Manikin Set Up – Mid or high fidelity simulator
    b. Props – Standard ED equipment
2. Distractors – ED noise, alarming monitor

For Examiner Only

CASE SUMMARY

SYNOPSIS OF HISTORY/ Scenario Background

The setting is an urban emergency department.

The patient is a 63-year-old male with a history of atrial fibrillation, HTN, and CHF brought to the emergency department by EMS for nausea and vomiting for the past four days and confusion that began shortly before arrival.

PMHx: atrial fibrillation, HTN, and CHF

PSHx: None

Medications: ASA 81 mg once daily, Digoxin 250 mcg once daily, Amlodipine 10 mg once daily, Lasix 20 mg twice daily, warfarin 5 mg once daily

Allergies: NKDA

SocHx: smokes ½ ppd for 40 years. Occasional alcohol use. Denies recreational drug use. Sexually active with one female partner, wife of 35 years.

SYNOPSIS OF PHYSICAL

- Obese male, sitting up in bed in no apparent distress.
- Airway patent, BS present bilaterally.
- Bradycardic with irregular rhythm, but otherwise unremarkable cardiac exam.
- Neurologic exam is non-focal. The patient is alert and oriented to himself and location of "hospital," but has some confusion regarding date.

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HISTORY

You are called to see a new patient (63-year-old male) in the general acuity area of the emergency department. You see an obese male in no apparent distress.

Onset of Symptoms: Past 4 days

Background Info: The patient states he has been having nausea and vomiting over the past few days with decreased PO intake. He reports several episodes of non-bloody and non-bilious emesis, but denies abdominal pain and diarrhea. He denies any chest pain, shortness of breath, loss of consciousness, dysuria, hematuria, penile discharge, melena, hematochezia, trauma, headache, changes in vision or hearing.

Additional History

From EMS: Per wife on scene, the patient has been having nausea and vomiting for the past four days. She was concerned because he became confused a couple hours prior to arrival.

Chief Complaint: Nausea, vomiting, and altered mental status

Past Medical Hx: Atrial fibrillation, HTN, and CHF

Past Surgical Hx: None

Habits:
Smoking: ½ ppd
ETOH: Occasional alcohol
Drugs: denies

Family Med Hx: father with CAD, MI, and CHF. Mother with COPD. No siblings.

Social Hx:

Marital Status:	Married to female partner for 35 years
Children:	Two living without medical problems
Education:	College
Employment:	retired high school math teacher

ROS: As per HPI. Otherwise negative.

CASE CONTINUATION

The ex-girlfriend is hysterical and continuously asks if he is going to be ok.

Vital Signs: BP: 110/60 mmHg P: 50/minute R: 18/minute T: 37C (98.6F) POx: 98% (FiO_2=0.21)

Primary Survey
Airway – Patent
Breathing – Breathing comfortably on room air
Circulation – Bradycardia (40-50's), SBP 110's
Disability – Patient is slightly slow to respond to questions but alert and oriented to self and location, confusion regarding time, states it is 1978
Exposure – No trauma, bruising, or rash.

Required Actions within the First Two Minutes

- Establish safety net (IV, oxygen, cardiac monitor, two large bore IVs, draw blood for labs)
- A/B – Provide supplemental oxygen
- C – Cardiac monitor; NS IV bolus; ECG
- D – Finger stick glucose = 160 mg/dL; diagnostics should be ordered by this time

PHYSICAL EXAM

General Appearance: Obese male, sitting in bed in no apparent distress.

Vital Signs: BP: 110/60 mmHg P: 50/minute R: 18/minute T: 37C (98.6F) POx: 98% (FiO_2=0.21)

Head: Normal

Eyes: PERRLA, pupils 4 to 3 mm bilaterally, extraocular eye movements intact. No nystagmus or gaze deviation.

Ears: TM's normal.

Mouth: Dry mucous membranes and lips

Neck: No tenderness or deformity on exam, full range of motion, no JVD

Skin: Warm and well-perfused, no rash.

Chest: Symmetric chest rise, no TTP

Lungs: Breath sounds present in all anterior and posterior lung fields. Faint rales noted at bases. No wheezes or rhonchi.

Heart: Bradycardic rate with irregular rhythm, normal S1 and S2, no murmurs, rubs

Back: Spine midline, no TTP or deformity.

Abdomen: Soft, slight TTP in epigastric region, no signs of trauma, no rebound/guarding, bowel sounds normal

Extremities: No signs of trauma, slight edema bilaterally to level of mid-shin, pulses are present in all extremities and equal

Genital: Normal

Rectal: Normal tone, guaiac negative

Neurologic: Nonfocal exam, moving all four extremities spontaneously. CN II-XII intact. Slow to respond. Alert and oriented to self and location. Some confusion regarding time, states it is 1978. No dysarthria, ataxia, or focal weakness.

Required Actions within the Next Two Minutes

- Order ECG and laboratory studies
- Begin resuscitation with IV crystalloid
- May order portable CXR
- May order non-contrast head CT

Branch Points

- **IF PATIENT DOES NOT RECEIVE IV FLUIDS,** then he begins to complain of worsening symptoms (nausea, vomiting, chest pain, confusion) and develops worsening hypotension. **BP DECREASES TO 90/60 MMHG.**

CASE CONTINUATION

- ECG shows atrial flutter with slow ventricular response at around 40/minute
- Atropine and external or intravenous pacing, if attempted, are not effective for bradycardia

Required Actions within the Next Several Minutes

- Labs return, notable for elevated creatinine and digoxin level of 3.5 ng/mL
- Digoxin toxicity should be recognized by this time
- Digoxin antibody fragments should be administered by this time
- Poison Center/ToxicologIST may be consulted at this time

Branch Points

- **IF PATIENT DOES NOT RECEIVE IV FLUIDS,** then hypotension continues to worsen (**BP DECREASES TO 80/40 MMHG)** and **MENTAL STATUS WORSENS.**
- **IF EITHER ATROPINE OR TRANSCUTANEOUS PACING IS ATTEMPTED FOR THE BRADYCARDIA, IT IS INEFFECTIVE ININCREASING THE HEART RATE.**
- **IF TRANSVENOUS PACING IS ATTEMPTED FOR THE BRADYCARDIA, IT CAUSES VENTRICULAR FIBRILLATION (UNLESS DIGOXIN ANTIBODY FRAGMENTS HAVE BEEN GIVEN EARLIER).**
- **IF VASOPRESSORS ARE GIVEN FOR HYPOTENSION, THEY ARE INEFFECTIVE.**
- **IF NO DIGOXIN LEVEL ORDERED,** nurse can question physician about the patient's meds
- **IF POISON CENTER/TOXICOLOGIST IS CONSULTED** regarding toxicity and dosage of DSFab:
    - No. of vials = (serum digoxin concentration x patient weight in kg) / 100
    - No. of vials = ((3.5 ng/mL) x 100 kg) / 100 = 3.5, round up to 4

CASE CONTINUATION

Required Actions within the Next Several Minutes

- Patient should receive DSFab by this time
- MICU should be consulted by this time for definitive disposition

Branch Points

- **IF PATIENT RECEIVES DSFAB, THEN HYPOTENSION AND BRADYCARDIA RESOLVE, AND THE MENTAL STATUS IMPROVES.**
- **IF ORDERED, REPEAT DIGOXIN LEVEL WILL BE ELEVATED (FOLLOWING DSFAB ADMINISTRATION).**
- **IF ORDERED, A REPEAT BMP WILL SHOW A SLIGHTLY IMPROVED CREATININE AND POTASSIUM.**

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CRITICAL ACTIONS

1. **Order a basic metabolic panel**

   Order a basic metabolic panel specifically to assess the serum potassium and creatinine.
   Cueing Guideline: Nurse can ask if the doctor wants blood obtained during IV insertion sent for testing.

2. **Order a digoxin level**

   Order a digoxin level.
   Cueing Guideline: Nurse can ask if the doctor wants blood obtained during IV insertion sent for testing.

3. **Obtain ECG**

   Obtain ECG. Appropriately interpret the rhythm as atrial flutter with slow ventricular response,
   Cueing Guideline: The nurse asks if the doctor has noticed the bradycardia and if an ECG would be needed.

4. **Provide volume resuscitation for acute kidney injury**

   Give 1 to 2 liters of crystalloid for volume resuscitation.
   Cueing Guideline: The nurse may say, “We have a line in place. Would you like any fluids?” or point out the patient’s creatinine level when lab results are available.

5. **Consult Poison Center/Toxicologist**

   The Poison Center or Toxicology Service should be consulted for further management recommendations regarding digoxin toxicity and treatment.
   Cueing Guideline: Once digoxin toxicity suspected or confirmed, the nurse can ask if the doctor has called the Poison Center yet.

6. **Administer digoxin antibody fragments**

   Administer digoxin antibody fragments. A discussion with Poison Center consultant regarding an appropriate dosing strategy may be required and should prompt consultation with the Poison Center/Toxicologist.
   Cueing Guideline: Once digoxin toxicity is confirmed, the nurse can ask if there is an antidote.

7. Admit to the MICU

Admit to the MICU for continued critical care monitoring and reassessment.
Cueing Guideline: Nurse can ask if the doctor has called the critical care team for definitive disposition yet.

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 a basic metabolic panel	
		Order a digoxin level	
		Obtain ECG	
		Provide volume resuscitation for acutekidney injury	
		Consult Poison Center/Toxicologist	
		Administer digoxin antibody fragments	
		Admit to the MICU	

Yes	No	
		Dangerous actions

[1] Modified ABEM Oral Certification Examination checklist and scoresheet

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STIMULUS INVENTORY

#1	Complete blood count
#2	A: Initial basic metabolic panel B: Repeat basic metabolic panel
#3	Urinalysis
#4	Liver function tests
#5	Venous blood gas
#6	Cardiac enzymes
#7	Toxicology
#8	Coagulation studies
#9	A: Initial digoxin level B: Repeat digoxin level
#10	Ammonia
#11	ECG
#12	CXR
#13	AXR

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LAB DATA & IMAGING RESULTS

Stimulus #1	
Complete Blood Count (CBC)	
WBC	11,500/mm^3
Hemoglobin	13.2 g/dL
Hematocrit	40%
Platelets	239,000/mm^3
Differential	
PMNLs	45%
Lymphocytes	55%
Monocytes	2%
Eosinophils	1%

Stimulus #2A and #2B		
Initial/Repeat Basic Metabolic Panel (BMP)		
Sodium	145 mEq/L	146 mEq/L
Potassium	4.5 mEq/L	3.5 mEq/L
Chloride	109 mEq/L	109 mEq/L
Bicarbonate	28 mEq/L	28 mEq/L
Glucose	155 mg/dL	150 mg/dL
BUN	35 mg/dL	26 mg/dL
Creatinine	3.0 mg/dL	2.8 mg/dL

Stimulus #3	
Urinalysis	
Color	Dark Yellow
Specific gravity	1.030
Glucose	Negative
Protein	Negative
Ketones	Trace
LE/Nitrites	Negative
Blood	Negative
WBC/RBC	3/hpf / 2/hpf
Crystals/bacteria	Negative

Stimulus #4	
Liver Function Tests	
AST	49 IU/L
ALT	32 IU/L
ALP	110 IU/L
T. Bilirubin	1.2 mg/dL
D. Bilirubin	0.2 mg/dL
Albumin	4.3 mg/dL

Stimulus #5	
Venous Blood Gas	
pH	7.35
pCO_2	30 mmHg
pO_2	55 mmHg
HCO_3 base deficit	14 mEq/L -1
Lactate	1.6 mmol/L

Stimulus #6	
Cardiac Enzymes	
CPK	80 IU/L
Troponin	< 0.5 ng/mL

Stimulus #7	
Toxicology	
Salicylate	Undetectable
Acetaminophen	Undetectable
Ethanol	Undetectable

Stimulus #8	
Coagulation Studies	
INR	2.2

Stimulus #9A and #9B	
Digoxin level	
Initial	3.5 ng/dL
Repeat	6 ng/dL

Stimulus #10	
Ammonia	
Value	30 mcg/dL

Stimulus #11
ECG Atrial flutter with slow ventricular Response

Stimulus #12-13	
Radiology	
CXR	Normal
AXR	Normal
Head CT (no image)	No heme/mass

Stimulus #1

Complete Blood Count (CBC)

WBC	11,500/mm^3
Hemoglobin	13.2 g/dL
Hematocrit	40%
Platelets	239,000/mm^3
Differential	
PMNLs	45%
Lymphocytes	55%
Monocytes	2%
Eosinophils	1%

Stimulus #2A

Basic Metabolic Panel (BMP)

Sodium	145 mEq/L
Potassium	4.5 mEq/L
Chloride	109 mEq/L
Bicarbonate	28 mEq/L
Glucose	155 mg/dL
BUN	35 mg/dL
Creatinine	3.0 mg/dL

Stimulus #2B

Repeat Basic Metabolic Panel (BMP)

Sodium	146 mEq/L
Potassium	3.5 mEq/L
Chloride	109 mEq/L
Bicarbonate	28 mEq/L
Glucose	150 mg/dL
BUN	26 mg/dL
Creatinine	2.8 mg/dL

Stimulus #3

Urinalysis

Color / pH	Dark Yellow
Specific gravity	1.030
Glucose	Negative
Protein	Negative
Ketones	Trace
LE/Nitrites	Negative
Blood	Negative
WBC/RBC	3/hpf / 2/hpf
Crystals/bacteria	Negative

Stimulus #4

Liver Function Tests

AST	49 IU/L
ALT	32 IU/L
ALP	110 IU/L
T. Bilirubin	1.2 mg/dL
D. Bilirubin	0.2 mg/dL
Albumin	4.3 mg/dL

Stimulus #5

Venous Blood Gas

pH	7.35
pCO_2	30 mmHg
pO_2	55 mmHg
HCO_3 base deficit	14 mEq/L -1
Lactate	1.6 mmol/L

Stimulus #6

Cardiac Enzymes

CPK	80 IU/L
Troponin	< 0.5 ng/mL

Stimulus #7

Toxicology

Salicylate	Undetectable
Acetaminophen	Undetectable
Ethanol	Undetectable

Stimulus #8

Coagulation Studies

INR	2.2

Stimulus #9A

Digoxin level

Initial	3.5 ng/dL

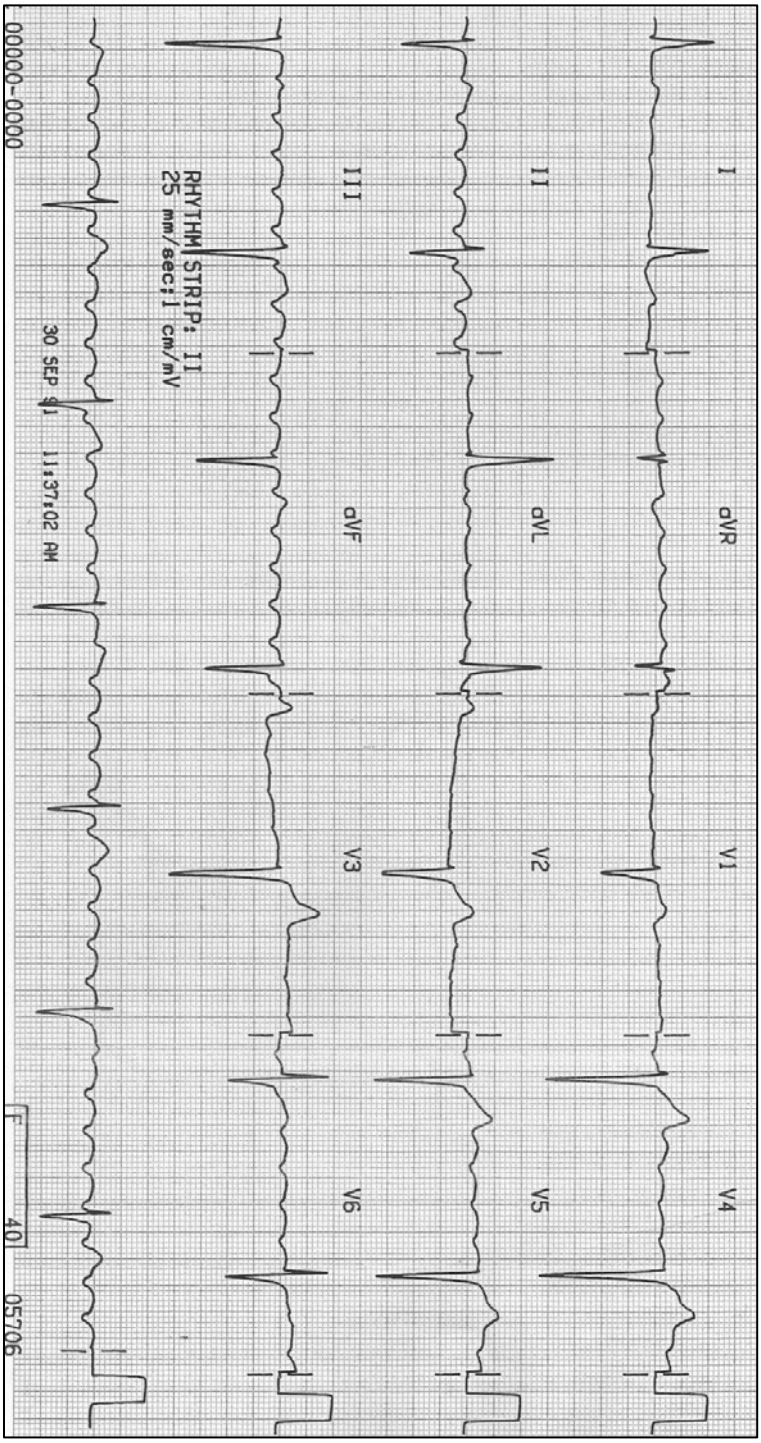
Stimulus #9B

Digoxin level	6 ng/dL

Stimulus #10

Ammonia	
Value	30 mcg/dL

Stimulus #11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Stimulus #12

Stimulus #13

Debriefing Materials – <u>Digoxin Toxicity</u>

Sources of Exposure: Digoxin is a cardioactive steroid (CAS) used in the treatment of congestive heart failure and atrial fibrillation/flutter. Digitoxin is another CAS. Numerous plants contain cardioactive steroids including foxglove, oleander, red squill, and lily of the valley.

Pathophysiology:

- Cardioactive steroids are direct inhibitors of the sodium-potassium ATPase found in myocardiocytes
- This increases intracellular sodium, which prevents the antiporter from exchanging sodium for calcium
- The overall effect is increased intracellular calcium
- This results in enhanced inotropy at therapeutic levels
- In toxicity, excessive elevation of calcium elevates the resting membrane potential, producing myocardial sensitization and predisposing to dysrhythmias

Severity of Ingestion:

- Overall, digoxin use has been decreasing over time
- There are about 3,500 exposures to CAS medications per year, resulting in about 20 deaths. There are around 2000 exposures to CAS-containing plants per year with no reported attributable deaths during one study period.
- Severity of digoxin toxicity correlates with serum level.
- Severity of acute CAS toxicity correlates with elevation in potassium.

Organ System Effects:

- Ophthalmologic: photophobia, blurring, scotomata, decreased visual acuity, yellow halos around lights
- Cardiovascular: alterations in rate and rhythm resulting in nearly any dysrhythmia
- Neurologic: lethargy, confusion, and weakness
- Gastrointestinal: nausea, vomiting, and abdominal pain

Diagnostic Testing:

- Toxicity should be suspected by history and physical
- ECG findings suggestive of digoxin toxicity include paroxysmal atrial tachycardia with high-degree AV block, bidirectional ventricular tachycardia
- Serum digoxin level
    - Most accurate 6 hours after time of ingestion in acute overdose
    - Levels drawn earlier in acute overdose can be falsely elevated
    - Levels drawn after administration of DSFab will also be falsely elevated
    - In general, a toxic digoxin level is considered to be above 2 ng/mL
- Chemistry panel: Repeat as needed, especially when monitoring potassium

Treatment:

- Definitive treatment: digoxin-specific antibody fragments (DSfab)
- Indications for treatment
    - Any digoxin-related life-threatening dysrhythmias
    - K+ concentration > 5 mEq/L in acute overdose
    - Chronic elevation in serum digoxin concentration (SDC) with associated dysrhythmias, significant GI symptoms, or altered mental status

    - SDC ≥ 15 ng/mL at any time, or ≥ 10 ng/mL 6 h post ingestion
    - Ingestion of 10 mg in adults or 4 mg in children
    - Poisoning with non-digoxin cardioactive steroid
- Hyperkalemia: marker for severity of toxicity, especially in acute overdose
    - Debate regarding the treatment of hyperkalemia with calcium in CAS toxicity
    - Some animal studies and case reports suggest an increased risk for dysrhythmia and death
    - However, there are numerous case reports of successful treatment of hyperkalemia associated with CAS toxicity with calcium without harm
    - Treatment with DSFab is preferred and will resolve hyperkalemia
    - Insulin/glucose can also be an effective temporizing measure
- Cardiac dysrhythmias:
    - Symptomatic bradycardia generally resistant to pacing
    - Dysrhythmias resolve after treatment with DSFab
    - Treat hemodynamically unstable V-tach and V-fib with cardioversion and defibrillation, respectively

Consultations:

- Consult the regional poison center or a local medical toxicologist for additional information and patient care recommendations

Disposition:

- Admit patients with major signs and symptoms to an ICU (cardiovascular ICU or medical ICU)

Take-Home Points:

- Cardioactive steroid toxicity can occur from exposure to medications (digoxin, digitoxin) as well as naturally occurring sources, such as foxglove
- CAS inhibit the cardiac myocyte sodium-potassium ATP-ase, causing an increase in intracellular calcium and increased inotropy
- In addition to cardiac effects, symptoms of toxicity can include nausea, vomiting, abdominal pain, fatigue, visual disturbances, and altered mental status
- In overdose, CAS can produce nearly any dysrhythmia on ECG, but A-fib, A-flutter, or PAT with AV block and bidirectional ventricular tachycardia are highly suggestive of toxicity
- Definitive treatment is with digoxin-specific antibody fragments, which can also be effective in non-digoxin CAS toxicity

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