# Drug Fever in the Critically Ill: Recognition and Management Pearls

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# Disclosures

The planner(s) and speaker(s) have indicated that there are no relevant financial relationships with any ineligible companies to disclose.

# Learning Objectives

At the end of this session, learners should be able to:

- Outline the definition and mechanism of drug fever in the critically ill patient
- Differentiate drug fever from other fever etiologies
- Identify the common medications associated with drug fever in the critically ill patient
- Formulate a diagnosis and management plan for a critically ill patient with drug fever

# Outline

- Background knowledge
- Review the mechanisms of drug fever
- Review fever of unknown origin (FUO)
- Evaluate common medication causes
- Diagnostic approach
- Management approach to drug fever

# Abbreviation Key

ADR = adverse drug reactions

BP = blood pressure

CDC = Centers for disease control

CPPD = Calcium pyrophosphate deposition disease

CK = creatinine kinase

COPD = chronic obstructive pulmonary disease

CRP = C-Reactive protein

CT = Computed tomography

CXR = chest x-ray

DF = Drug fever

DRESS = Delayed reaction with eosinophilia and systemic symptoms

FNDP = Foundation for New Drug Pharmacovigilance

FUO = Fever of unknown origin

HR = heart rate

ICU = Intensive care unit

IDSA = Infectious disease society of America

IM = intramuscular

MAOI = monoamine oxidase inhibitor

NICU = neonatal intensive care unit

PICU = pediatric intensive care unit

RR = respiratory rate

SCCM = Society for critical care medicine

SSRI = selective serotonin reuptake inhibitor

VTE = Venous thromboembolism

WBC = White blood cell count

# What Defines “Fever”?

| | |
|---|---|
| Healthy Individuals | 37°C (98°F) |
| **Fever** | |
| CDC Guidelines | 38°C (100.4°F) |
| SCCM and IDSA Guidelines for ICU patients | 38.3°C (101°F) |
| Hyperpyrexia/Hyperthermia | >41°C (105.8°F) |

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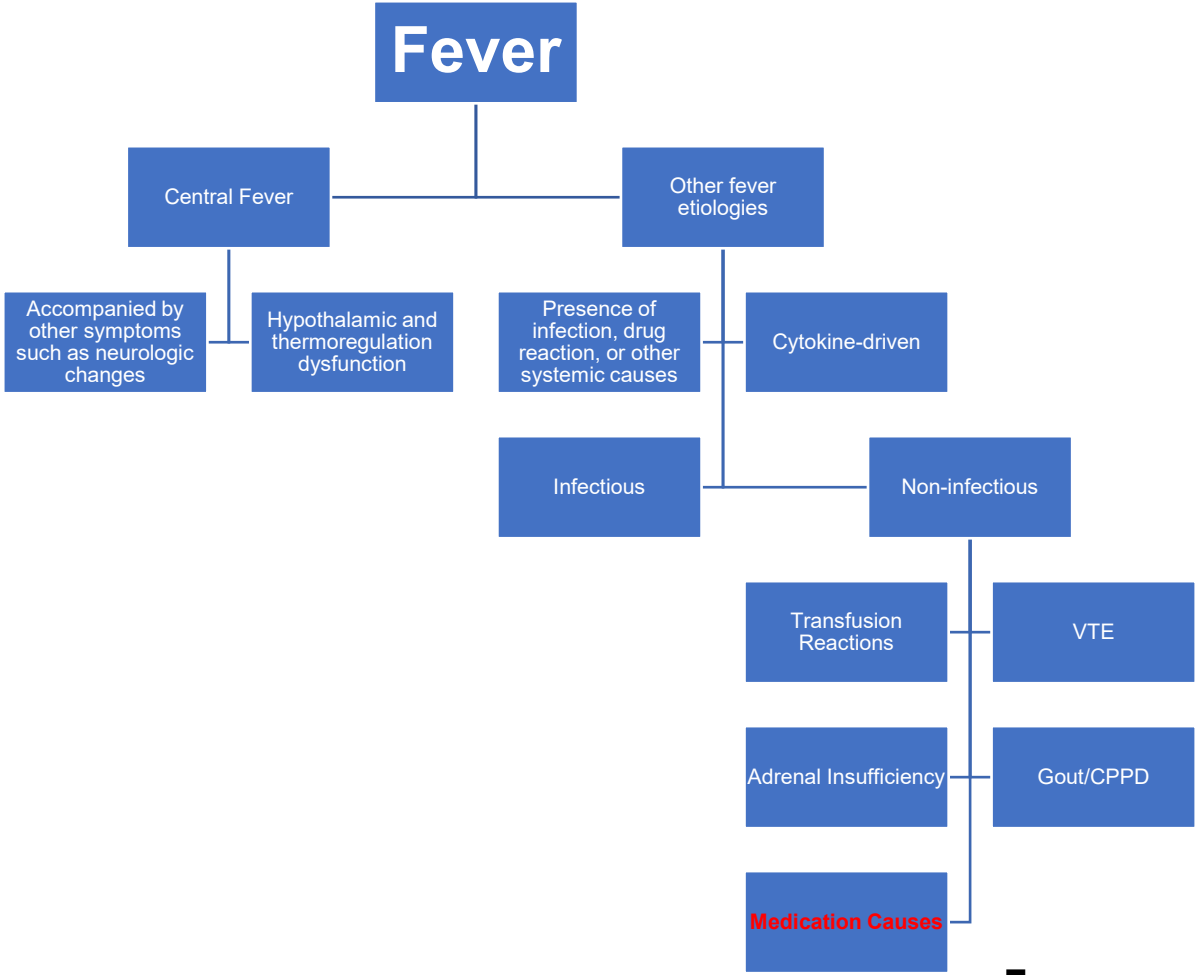
Balli S, Shumway KR, Sharan S. StatPearls; 2025.

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Balli S, Shumway KR, Sharan S. StatPearls; 2025.

# Epidemiology of Drug Fever

**3-5%** of febrile episodes in the ICU

**Approximately 33%** due to antibiotics

Diagnosis of **exclusion**

Diagnosis made by the temporal relation between fever and medications

Fever onset within **7-10 days** of medication initiation

Resolution within **72 hours** of drug discontinuation

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Achaiah NC, Bhutta BS, AK AK. StatPearls; 2025.

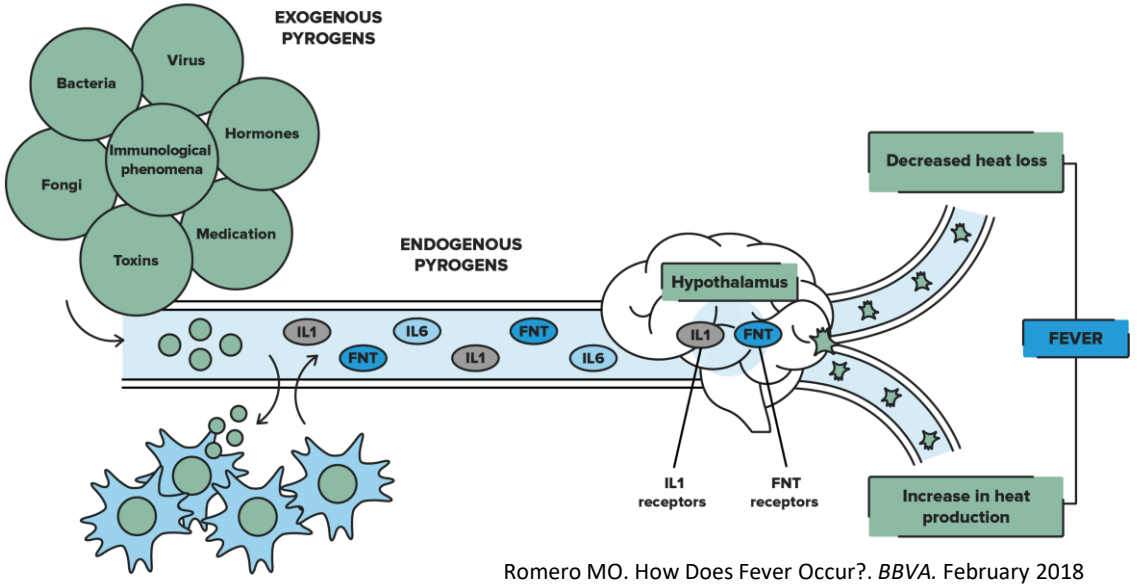
# Mechanisms of Drug Fever

- Pyrogen Release
- Jarisch-Herxheimer Reaction
- Irritant Drugs
- Alterations of thermoregulation
- Hypersensitivity

Jenkins RD, Woodhouse KW. Adverse Drug Reaction Bull; 1999.

# Pyrogen Release

- Medications implicated in drug fever act as exogenous pyrogens
- Stimulate host immune cells to release endogenous pyrogens
- Endogenous pyrogens act on the hypothalamic thermoregulatory center to raise the set-point for body temperature




Romero MO. How Does Fever Occur?. *BBVA.* February 2018

**<u>Drug Causes:</u>** interferons, amphotericin B

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Jenkins RD, Woodhouse KW. Adverse Drug Reaction Bull; 1999.

# Jarisch-Herxheimer Reaction

- Acute, transient inflammatory response during treatment of spirochetal infections
- Endotoxin-like materials released by bacteria increase cytokines
- Symptoms: **fever**, myalgias, and rash
- NOT an adverse drug reaction
- Onset: 2-8 hours after antibiotic administration

**Drug causes:** antibiotics for treatment of spirochetal infections

Jenkins RD, Woodhouse KW. Adverse Drug Reaction Bull; 1999.
Butler T. Am J Trop Med Hyg; 2017.

# Irritant Drugs

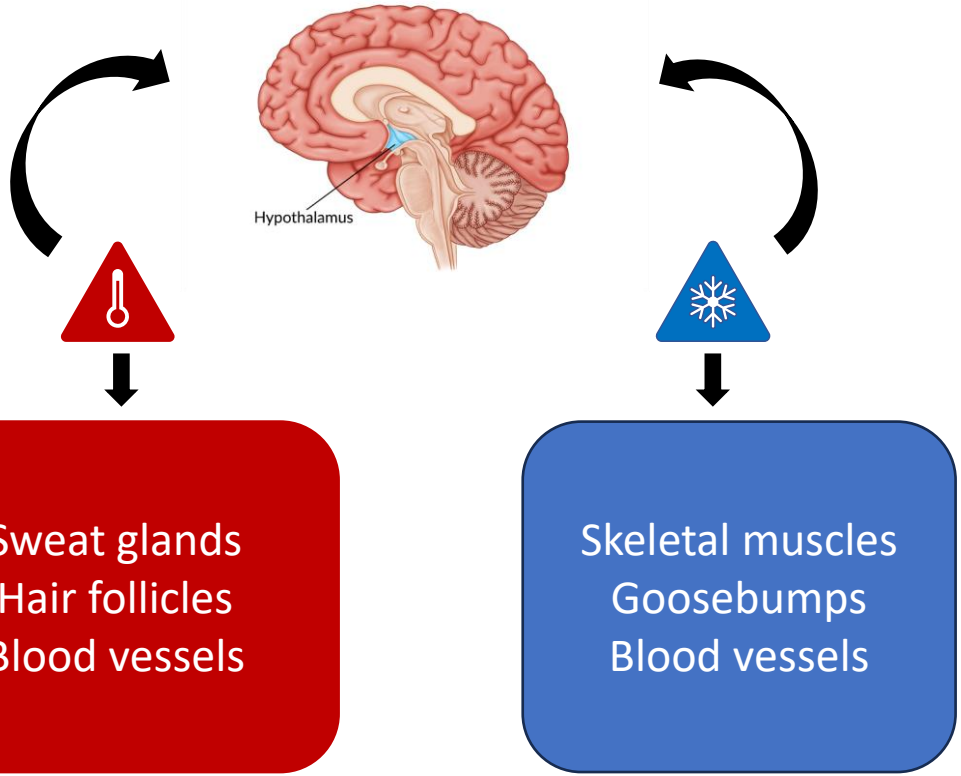
- Cause inflammation or tissue damage
- Secondary infections
  - Chemical phlebitis
  - Sterile abscess formation (with IM injections such as diclofenac)

- **Drug causes:** vancomycin, erythromycin, cephalosporins



Jenkins RD, Woodhouse KW. Adverse Drug Reaction Bull; 1999.

# Alterations of Thermoregulation

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Jenkins RD, Woodhouse KW. Adverse Drug Reaction Bull; 1999.

# Alterations of Thermoregulation

- Centrally: alter the set body temperature to high temperatures by impairing hypothalamic function
  - **Drug causes:** anticholinergics, and tricyclic antidepressants

- Peripherally: reduce the ability to lose heat by vasodilation and sweating. Metabolism can be altered leading to an increase in heat production
  - **Drug causes:** amphetamines

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Jenkins RD, Woodhouse KW. Adverse Drug Reaction Bull; 1999.

# Hypersensitivity

- Low-grade fever with other features of hypersensitivity
- Onset: 7-10 days
- Leads to diagnostic difficulty

- **Drug causes:** beta-lactams, vancomycin, sulfa antibiotics, ACEIs, and anti-seizure drugs

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Jenkins RD, Woodhouse KW. Adverse Drug Reaction Bull; 1999.

# Drug Induced Hyperthermia

- Malignant Hyperthermia
- Neuroleptic Malignant Syndrome
- Serotonin Syndrome
- DRESS

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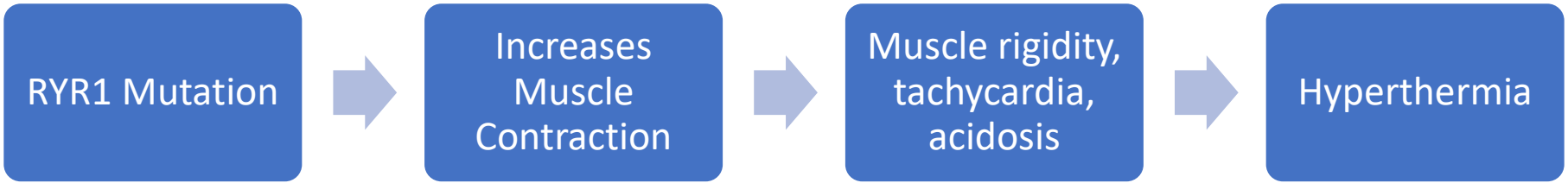
Walter E, et. al. *J intensive care society.* 2015

# Malignant Hyperthermia




**Common triggers:** volatile anesthetics and succinylcholine

**Clinical Features:** Rapid Rise in CO2, Hyperthermia, Muscle rigidity, Rhabdomyolysis, Hyperkalemia, Acidosis

**Diagnosis:** Caffeine-halothane contracture test, CK elevation, myoglobinuria

**Treatment:** Dantrolene, discontinue triggering agent, cooling, treat hyperkalemia

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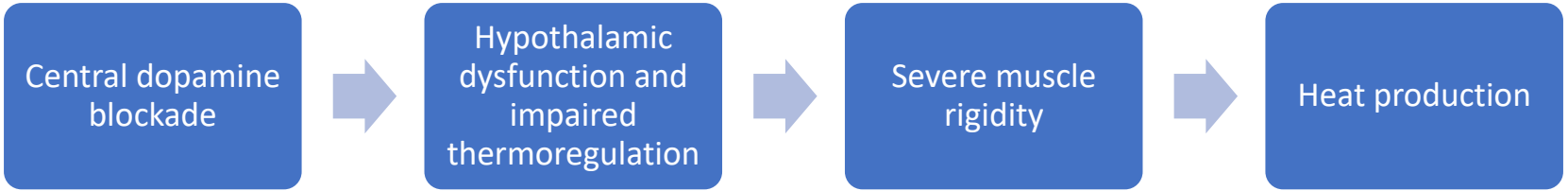
Walter E, et. al. *J intensive care society.* 2015

# Neuroleptic Malignant Syndrome




**Common Triggers:** Antipsychotics and dopamine withdrawal

**Presentation:** Hyperthermia, rigidity, altered mental status, autonomic instability

**Diagnosis:** elevated CK, leukocytosis, onset of 1-3 days

**Treatment:** Stop offending agent, supportive care, bromocriptine or dantrolene

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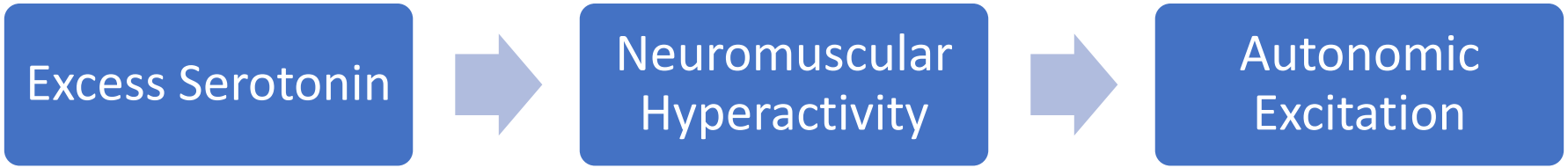
Walter E, et. al. *J intensive care society.* 2015

# Serotonin Syndrome




**Common triggers:** SSRIs, MAOIs, drug-drug reactions

**Presentation:** hyperthermia, hyperreflexia, tremor, agitation

**Diagnosis:** Hunter criteria

**Treatment:** Stop offending agent, benzodiazepines, cyproheptadine

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Walter E, et. al. *J intensive care society.* 2015

# DRESS


**Common Triggers:** antiepileptics, sulfonamides, vancomycin

**Presentation:** Fever, rash, edema, eosinophilia, organ involvement

**Diagnosis:** RegiSCAR criteria, eosinophilia

**Treatment:** stop offending agent, systemic corticosteroids

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Walter E, et. al. *J intensive care society.* 2015

# Fever of Unknown Origin

- **FUO criteria:** a temperature of 38.3°C or higher for a period of 3 inpatient days or at least 3 outpatient visits
- **Classifications:**
  - Classic
  - Nosocomial ICU vs non-ICU patients
  - Immunodeficiency-related
  - Travel-associated



Haider G, Singh N. *N Engl J Med*. 2022.

# Nosocomial FUO (ICU)

- Increased incidence of prolonged and unexplained fevers in hospitalized patients due to medical advances
- 31% of febrile critically ill patients had non-infectious fevers
- **Initial Assessment**
  - Nosocomial infections (catheter-associated infections)
  - Urinary tract infections
  - Pneumonias
  - Intraabdominal infections
  - Sinusitis
  - *Clostridium difficile* infections

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Haider G, Singh N. *N Engl J Med*. 2022.

# Assessment Question #1

Which feature is most suggestive of drug fever rather than infectious fever in a critically ill patient?

A. Fever associated with leukocytosis and hypotension
B. Fever that persists despite appropriate antimicrobial therapy
C. Fever occurring within 24 hours of central line placement
D. Fever accompanied by purulent respiratory secretions

# Naranjo Adverse Drug Reaction Probability Scale

- Validated, standardized questionnaire
- Reduces subjectivity in adverse event assessment
- Commonly used in clinical practice, case reports, and research
- Aids in differentiating drug-related reactions from disease progression or other causes

Naranjo CA, et al. Clin Pharmacol Ther. 1981_x000B_Edwards IR, Aronson JK. Lancet; 2000.

# Naranjo Adverse Drug Reaction Probability Scale

- Consists of 10 weighted questions
- Questions assess temporal relationship, de-challenge and rechallenge, alternative causes and dose-response
- Total score categorizes adverse event probability

| Score | Interpretation |
|---|---|
| ≥9 | Definite ADR |
| 5-8 | Probable ADR |
| 1-4 | Possible ADR |
| 0 | Doubtful ADR |

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Naranjo CA, et al. Clin Pharmacol Ther. 1981_x000B_Edwards IR, Aronson JK. Lancet; 2000.

# Vodovar, D. *et al.* 2012

**Objective**

- Investigate drugs associated with drug fever and report outcomes

**Methods**

- Utilized the Foundation for New Drug Pharmacovigilance (FNDP) to collect adverse drug reactions
- Diagnostic criteria:
  - Body temperature > 38°C
  - Absence of other causes, conditions, and skin reactions causing fever
  - Timing of fever onset with drug administration and the disappearance of the fever within 72 hours following discontinuation
  - No recurrence of fever within 72 hours after fever resolution
  - Exclusion of other differential diagnoses: antipsychotic malignant syndrome, serum sickness, serotonin syndrome and malignant hyperthermia

**Outcomes analyzed**

- Naranjo scoring tool: A total score corresponding to the likelihood of drug fever as 'doubtful', 'possible', 'probable', or 'definite'

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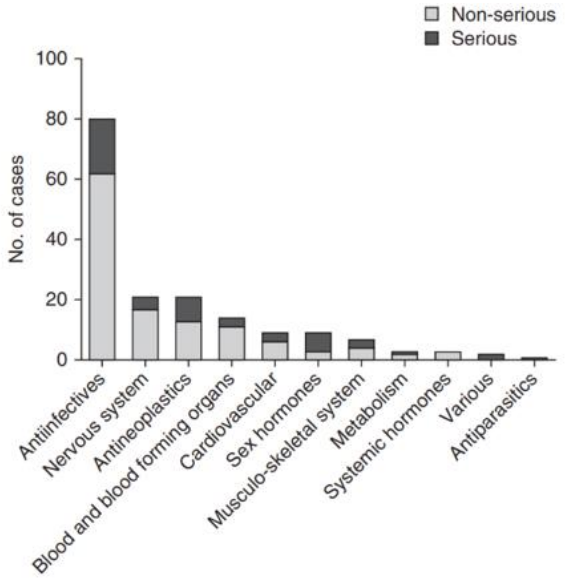
Vodovar, D., LeBeller, C., Mégarbane, B. et al. *Drug Saf* 2012.

# Vodovar, D. *et al.* 2012

## Results

- 167 cases enrolled
- Drug fever represented 0.05% of all adverse drug reactions reported (167/323,340)
- 33% of the cases were ‘possible’, 47% were ‘probable’ and 20% were ‘definite’
- DF pattern was continuous (71/137; 52%) or intermittent (66/137; 48%)
- Time from drug administration to fever average onset was 2 days.
  - DF appeared <12 hours after first exposure to the drug in 11% of patients (14/137) and within 10 days in 74% of patients (101/137)
- 115 drugs were shown to be responsible for DF
  - **Antimicrobial** agents most frequently associated

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Vodovar, D., LeBeller, C., Mégarbane, B. et al. *Drug Saf* 2012.

# Vodovar, D. *et al.* 2012

**Conclusion**

- Drug fever remains underdiagnosed and underreported
- Many drug classes associated with DF:
  - **Antimicrobials**, antiseizure, antineoplastics, immunomodulating and musculoskeletal agents

**Discussion**

- Diagnosis of drug fever remains difficult
- Rarely associated with severe symptoms and blood abnormalities
- Potential for initial hospitalization or prolonged hospitalization (25% of cases in the series)
- Contributes to additional health care costs

**Limitations**

- Cases were based on spontaneous reporting
- Likely underreporting

ADVOCATE HEALTH

Vodovar, D., LeBeller, C., Mégarbane, B. et al. *Drug Saf* 2012.

# Yaita K, et. al. 2016

**Objective**

- Retrospective analysis of drug fever in patients undergoing infectious disease consultations

**Methods**

- 388 patient records with infectious disease consults
- Chart reviewed and summarized drug fever characteristics

**Outcomes analyzed**

- Clinical signs (bradycardia, onset of drug fever and alleviation of fever once discontinued)
- Laboratory tests (WBC, CRP, procalcitonin, and transaminases)

ADVOCATE HEALTH

Yaita K, Sakai Y, Masunaga K, Watanabe H. *Intern Med.* 2016.

# Yaita K, et. al. 2016

## Results

- 16 patients met inclusion criteria
- Duration of drug administration prior to become febrile = 8.6±5.3
- Interval between the discontinuation of the drug and alleviation of fever = 3.4 ±3.3
- Clinical signs and laboratory tests were compatible with previous reports
- Five cases involved the use of glycopeptides (vancomycin and teicoplanin)
- Five cases involved the use of beta-lactams
- Procalcitonin levels were negative, CRP was low, and mild elevation in transaminases

| | (n=16) |
|---|---|
| Peak WBC, mean ± SD (/μL) | 7,519 ± 3,551 |
| (Eosinophils, mean ± SD) (/μL) | (420 ± 575) |
| Peak AST level, mean ± SD (IU/L) | 47.7 ± 46.0 |
| Peak ALT level, mean ± SD (IU/L) | 48.9 ± 59.5 |
| Peak CRP level, mean ± SD (mg/dL) | 5.1 ± 3.9 |
| Peak PCT level [a] | |
| ≤ 0.1 (ng/dL) | 8 |
| 0.1 - 0.25 (ng/dL) | 2 |
| > 0.25 (ng/dL) | 1 |
| Neutropenia | 4 |
| Eosinophilia | 4 |

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Yaita K, Sakai Y, Masunaga K, Watanabe H. *Intern Med.* 2016.

# Yaita K, et. al. 2016

**Conclusion**

- Demonstrated glycopeptides and beta-lactams may be an origin of drug fever
- A negative or low procalcitonin level with other clinical findings may be helpful in diagnosis

**Discussion**

- Characteristics including the onset, time to improvement after discontinuation, bradycardia, moderate to slightly elevated WBC, low CRP, and mild elevation in transaminases were compatible with results shown in previous reports
- Prevalence of relative bradycardia and glycopeptides was higher than expected (14/16 patients)

**Limitations**

- Retrospective study
- Commonly, more than one antibiotic was simultaneously administered
- Other antibiotics had been administered after previous drug was stopped

ADVOCATE HEALTH

Yaita K, Sakai Y, Masunaga K, Watanabe H. *Intern Med.* 2016.

# Naden M, et. al. 2023

**Objective**

Evaluated incidence of fever in critically ill pediatric patients receiving continuous infusion dexmedetomidine

**Methods**

- Retrospective study
- Admitted to the pediatric or neonatal intensive care units (PICU or NICU) between November 2017 and December 2021
- Continuous infusion of dexmedetomidine

**Outcomes analyzed**

- Fever of ≥38°C
- Patient and drug characteristics in the febrile and afebrile groups compared

ADVOCATE HEALTH

Naden MP, et. al. J Pediatr Pharmacol Ther. 2025

# Naden M, et. al. 2023

## Results

- 151 patients evaluated
- 13/151 experienced fever ≥38°C (8.6%)
- Statistically significant differences in age, weight, and maximum rate of dexmedetomidine infusion between the fever and non-fever groups
- Febrile patients were younger than those in afebrile group (p=0.0006)
- Febrile group received higher median maximum infusion rate (0.8 mcg/kg/h) for a longer duration (p=0.0001)
- Median temperature of febrile group: 38.2°C
- Median time to fever onset 9.7 hours at median dexmedetomidine rate of 0.4 mcg/kg/h

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Naden MP, et. al. J Pediatr Pharmacol Ther. 2025

# Naden M, et. al. 2023

**Conclusion**

- First study to evaluate the relationship between dexmedetomidine and fever development in pediatric population
- Significant correlations between fever and decreased age, higher doses and longer durations of infusion

**Discussion**

- Incidence of fever in this study higher than that reported in drug monograph
- The findings related to maximum dose unsurprising given dose-dependent effects

**Limitations**

- Retrospective study
- Small number of patients meeting the primary objective
- Inconsistency of temperature collection methods which included oral, axillary, rectal, and bladder

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Naden MP, et. al. J Pediatr Pharmacol Ther. 2025

# Assessment Question #2

Which medication class is most commonly associated with hypersensitivity-mediated drug fever in the ICU?

A. Fluoroquinolones
B. Beta-lactam antibiotics
C. Vasopressors
D. Proton pump inhibitors

# Clinical Presentation

## Time between initiation of drug and fever onset

- Development of fever is 2-8 days
- Varies widely depending on the medication
- Quicker onset if the patient had previous exposure

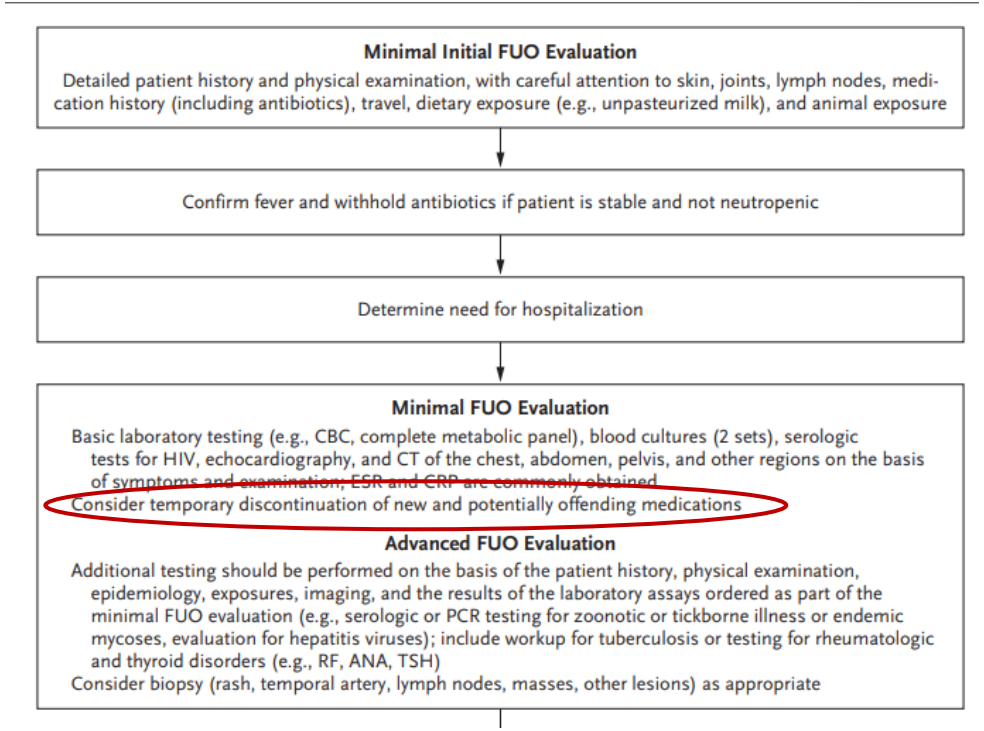
## Fever Pattern

- No specific fever pattern was observed for drug fever
- Not used as a diagnostic indicator

## Associated Symptoms

- Bradycardia (pulse-temperature dissociation, Faget's sign)
- Skin manifestations
- Shaking/chills/rigors occur

# Fever of Unknown Origin (FUO) Algorithm

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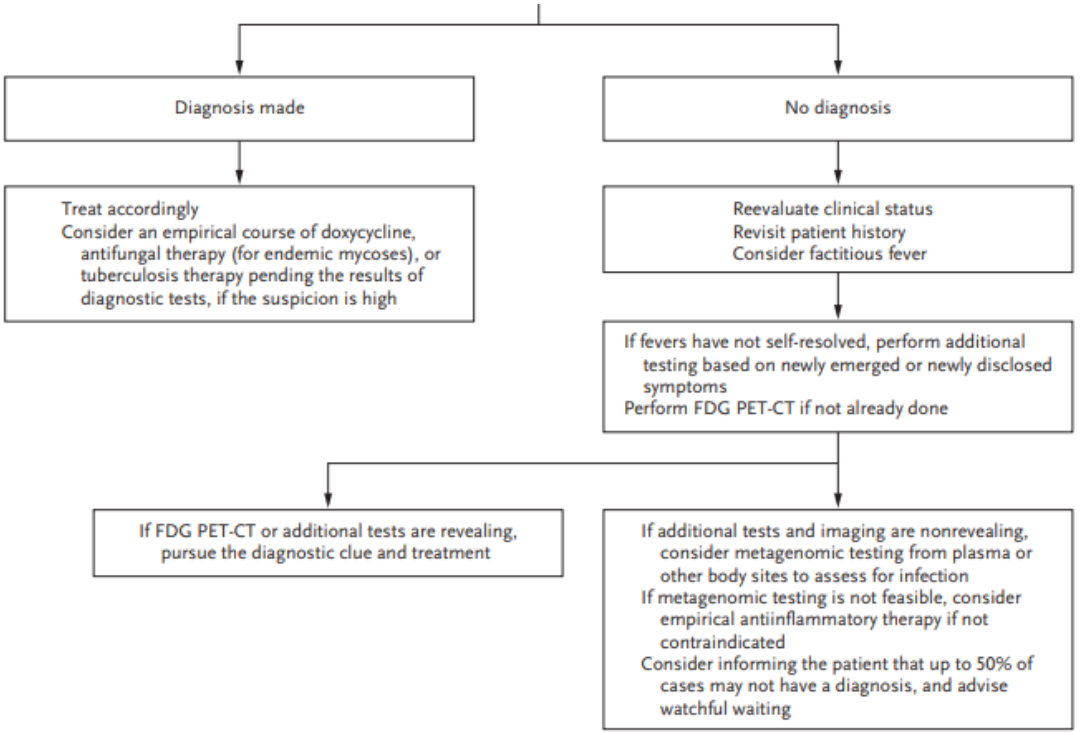
Haider G, Singh N. *N Engl J Med*. 2022.

# FUO Algorithm




Haider G, Singh N. *N Engl J Med*. 2022.

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# Diagnosis

Negative blood cultures, excluding contaminants, and look “relatively well” for the degree of fever

Considered in the differential diagnosis with a new-onset fever in patients previously afebrile for more than 48h or prolonged fever for more than 72 hours despite appropriate treatment

Difficult diagnosis with no localizing signs, may present as an FUO

Tentative diagnosis of drug fever should be established after excluding other diseases. Include detailed history and physical exam

Clinical clue: relative bradycardia

- In such patients, pulse-temperature deficits have no diagnostic significance.

Someko H, Okazaki Y, Kuniyoshi Y. et. al. *Internal Med.* 2024.
Burke AC. *Infectious Disease Clinics of North America.* 2007.

# Society of Critical Care Medicine and the Infectious Diseases Society of America Guidelines for Evaluating New Fever in Adult Patients in the ICU

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O'Grady NP, Alexander E, Alhazzani W, et al. Crit Care Med; 2023.

# IDSA/SCCM recommendations

Central temperature monitoring methods are preferred. May also include oral or rectal temperature monitoring

Avoid antipyretic medications for the specific purpose of reducing temperature

Imaging

- Chest radiograph is recommended
- If recently underwent intraabdominal surgery, recommend a CT and/or abdominal ultrasound
- When other diagnostic tests failed to establish an etiology, recommend a CT

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O'Grady NP, Alexander E, Alhazzani W, et al. Crit Care Med; 2023.

# IDSA/SCCM recommendations

## Laboratory testing

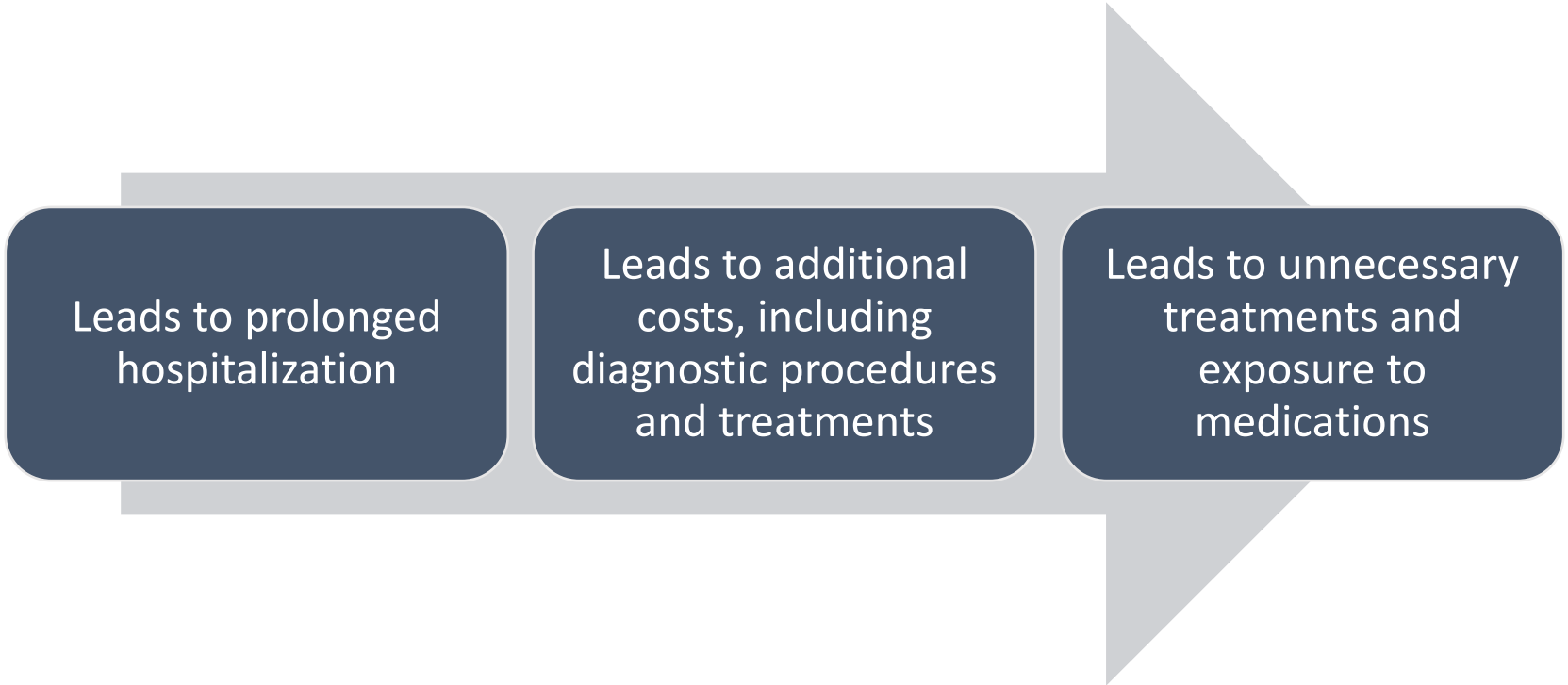
- With central venous catheters, recommend collection from catheter and peripherally for blood cultures
  - Collect two sets of blood cultures from different sites at the same time
- When urinary tract infection is suspected, replace urinary catheter and obtain cultures from the new catheter
- With suspected pneumonia or upper respiratory tract infections, recommend testing for viral pathogens
- **Specific for drug fever**
  - Eosinophilia (eosinophils >300)
  - Leukopenia (incidence 0.9-90%)
  - Normal procalcitonin

## Bacterial infection probability

- Low to intermediate → recommend CRP and procalcitonin
- High → recommend NOT using CRP or procalcitonin

Abhilash V et al, Sch. J. App. Med. Sci., 2014
Someko H, Okazaki Y, Kuniyoshi Y. et. al. *Internal Med.* 2024.
O'Grady NP, Alexander E, Alhazzani W, et al. Crit Care Med; 2023.

# Consequences of Not Diagnosing Drug Fever

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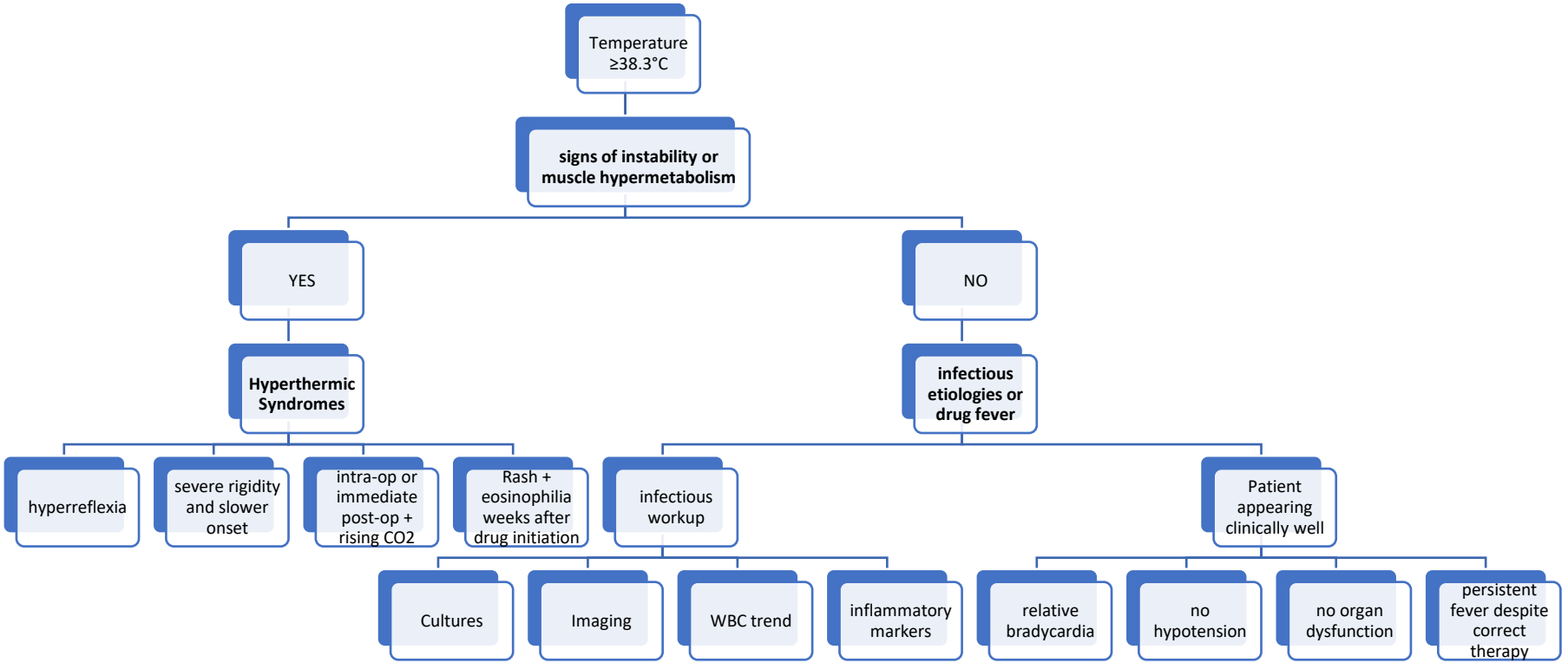
Vodovar, D., LeBeller, C., Mégarbane, B. et al. *Drug Saf* 2012.

# Assessment Question #3

According to IDSA/SCCM guidance, which action is MOST appropriate when evaluating persistent fever of unknown origin in a critically ill patient?

A. Escalate antimicrobial therapy empirically
B. Discontinue all antipyretics
C. Perform a structured reassessment including medication review
D. Delay further workup until fever persists for ≥7 days

# Drug Fever Differentials

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# Management

Discontinue the suspected culprit drug to confirm the diagnosis

Drug discontinuation is both diagnostic and treatment

The prognosis is usually favorable

- A study on drug fever reported that 97% of patients recovered without complication

Someko H, Okazaki Y, Kuniyoshi Y. et. al. *Internal Med.* 2024.

# Management

Specific medication causes have been identified through case reports

- Beta-lactam antibiotics
- Sedatives
- Antiseizure medications
- Antipsychotics
- H2 Receptor Antagonist

# Beta-lactam Antibiotics

## Patient Presentation

- 36-year-old female
- Admitted for scoliosis correction surgery
- At post-operation day 6, the incision site was slightly red.
- Wound was debrided

## Intervention

- Intravenous vancomycin and piperacillin/tazobactam was initiated
- The patient had developed fevers at day 3 of antibiotic therapy

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Li, Z, Shen, Jianxiong, et. al. *Medicine*. 2015

# Beta-lactam Antibiotics

## Workup

- A thorough history was completed
- Imaging included a chest radiography
- Physical examination
- Blood cultures and urinalysis
- The infectious workup came back negative

## Conclusion

- All systemic antibiotics were discontinued
- The fever lasted for a total of 2 weeks
- The patient's temperature returned to normal 4 days after piperacillin/tazobactam was discontinued

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Li, Z, Shen, Jianxiong, et. al. *Medicine*. 2015

# Sedation

## Patient Presentation

- 34-year-old male
- Admitted for COVID-19 pneumonia
- Clinical course complicated by severe hypoxia and cardiac arrest requiring ICU admission

## Intervention

- On day 7 of admission, respiratory status improved and being prepared for extubation
- The patient's sedation was transitioned to dexmedetomidine
- Developed a fever 12 hours after the start of infusion

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Fadel R, et al. *chest*. 2021;160(4):a895

# Sedation

## Workup

Fevers prompted empiric sepsis management with intravenous fluids and broad-spectrum antibiotics

Blood, fungal, and respiratory cultures were unremarkable

## Conclusion

With no clear fever etiology, the dexmedetomidine was weaned

After the dexmedetomidine was discontinued, temperature returned to normal

Dexmedetomidine corresponded to a ‘probable’ associated on the Naranjo Adverse Drug Reaction Scale

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Fadel R, et al. *chest*. 2021;160(4):a895

# Antiseizure medication

## Patient Presentation

- 24-year-old male admitted to the ICU with seizures
- Experienced a tonic-clonic seizure 4 days prior to admission
- Has a history of prior seizures 7 years prior, not on antiseizure medication prior to admission

## Intervention

- Patient received a loading dose of levetiracetam and continued scheduled dosing
- On day 2 of admission, patient became febrile, and continued to be persistently febrile

ADVOCATE HEALTH

Flannery AH, et al. Pharmacotherapy; 2015.

# Antiseizure medication

## Workup

- Broad-spectrum antibiotics were initiated and escalated on day 8
- The infectious disease team was consulted on day 4 due to continued fever of unknown origin
- Blood cultures and viral cultures were repeated and negative
- Bilateral upper and lower venous duplex was negative for thrombosis

## Conclusion

- On day 11 of persistent fever, all antibiotics were discontinued
- On day 14, patient remained febrile and medication profile was reviewed. Levetiracetam was identified as a causative agent
- Levetiracetam was discontinued and changed to phenytoin
- The following day patient was afebrile until discharge
- Levetiracetam was scored ‘probable’ on the Naranjo Adverse Drug Reaction Scale

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Flannery AH, et al. Pharmacotherapy; 2015.

# Antipsychotics

## Patient Presentation

- 40-year-old female
- History of schizophrenia, non-compliant with medication

## Intervention

- Olanzapine 10 mg daily was initiated
- On day 17; patient developed a fever

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Yang CH, Chen YY. Psychopharmacol Bull; 2017.

# Antipsychotics

## Workup

- Physical exam unremarkable
- Laboratory data: cell counts, creatinine phosphokinase unremarkable
- Urine cultures and blood cultures negative
- autoimmune antibodies, cancer antigens, cerebrospinal fluid analysis, chest films, abdominal ultrasonography, were unremarkable

## Conclusion

- Treatment with multiple antibiotic courses and antipyretics failed to improve fever
- On day 47; drug fever was suspected and olanzapine dose was decreased to 5 mg
- On day 52; the patient's temperature had normalized

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Yang CH, Chen YY. Psychopharmacol Bull; 2017.

# H2 Receptor Antagonist

## Patient Presentation

- 59-year-old female
- Admitted for management of Guillain-Barre syndrome
- Long-term admission in the neurocritical ICU

## Intervention

- Famotidine was initiated early in hospitalization for gastrointestinal prophylaxis
- Throughout appropriate treatment, patient has suffered from a mild persistent fever

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Gonter A, et. al. *CHEST*. 2025

# H2 Receptor Antagonist

## Workup

- Imaging negative for acute pathology
- Extensive infectious workup was initiated twice in the span of 2 weeks and unremarkable
- Additional differentials were examined

## Conclusion

- Common offending drugs were eliminated in a stepwise fashion
- On day 25 of persistent fever, famotidine was discontinued and the fever resolved within 12 hours

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Gonter A, et. al. *CHEST*. 2025

# Real-World Management of Drug-Induced Fever

- Iatrogenic causes of fevers are commonly overlooked
- Important to exclude all other etiologies of fever
- Drug induced fever is a diagnosis of exclusion
- Diagnosis confirmed by withdrawal of offending agent

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# Assessment Question #4

Which management strategy is most appropriate once drug fever is suspected?

A. Continue the offending agent and add scheduled antipyretics
B. Substitute the suspected drug with an agent from the same class
C. Discontinue the suspected agent and monitor for fever resolution
D. Initiate corticosteroids empirically

# Case: BL – Persistently Febrile

BL is a 72-year-old male admitted for septic shock secondary to pneumonia

**PMH:** COPD, hypertension

**Initial resuscitation:** intravenous fluids, vasopressor support, and empiric antibiotics: Vancomycin and piperacillin/tazobactam

**Prior to admission medications**

- Amlodipine 10 mg daily
- Omeprazole 20 mg daily
- Tiotropium inhaler 2 puff daily

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# BL Initial Workup

## Vital Signs

- **T39°C**
- HR 122 bpm
- BP 82/46 mmHg
- RR 28
- SpO2 86% RA

## Imaging

- CXR: Right lower lobe consolidations

## Initial Labs

- WBC: 19.8
- Lactate 4.6
- Procalcitonin 14.2 ng/L
- CRP 28 mg/dL

## Cultures

- Respiratory culture +*Streptococci pneumoniae*
- Blood cultures negative

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# Hospital Course: Day 6

## Vital Signs

- **T38.6-39°C**
- HR 72 bpm
- BP 124/72 mmHg
- RR 16
- SpO2 96% RA

## Imaging

- CXR: improving right lower lobe opacity
- Ultrasound of extremities negative for thrombosis

## Initial Labs

- WBC: 7.8
- Lactate 1
- Procalcitonin 0.10 ng/L
- CRP 0 mg/dL

## Cultures

- Repeat blood cultures negative
- Respiratory viral panel negative

# Assessment

## Clinical Presentation

- **Timing:** continued fever after 6 days of appropriate treatment
- Relative bradycardia

## Diagnosis

- Repeat infectious and non-infectious workups negative
- Looks “well” for temperature

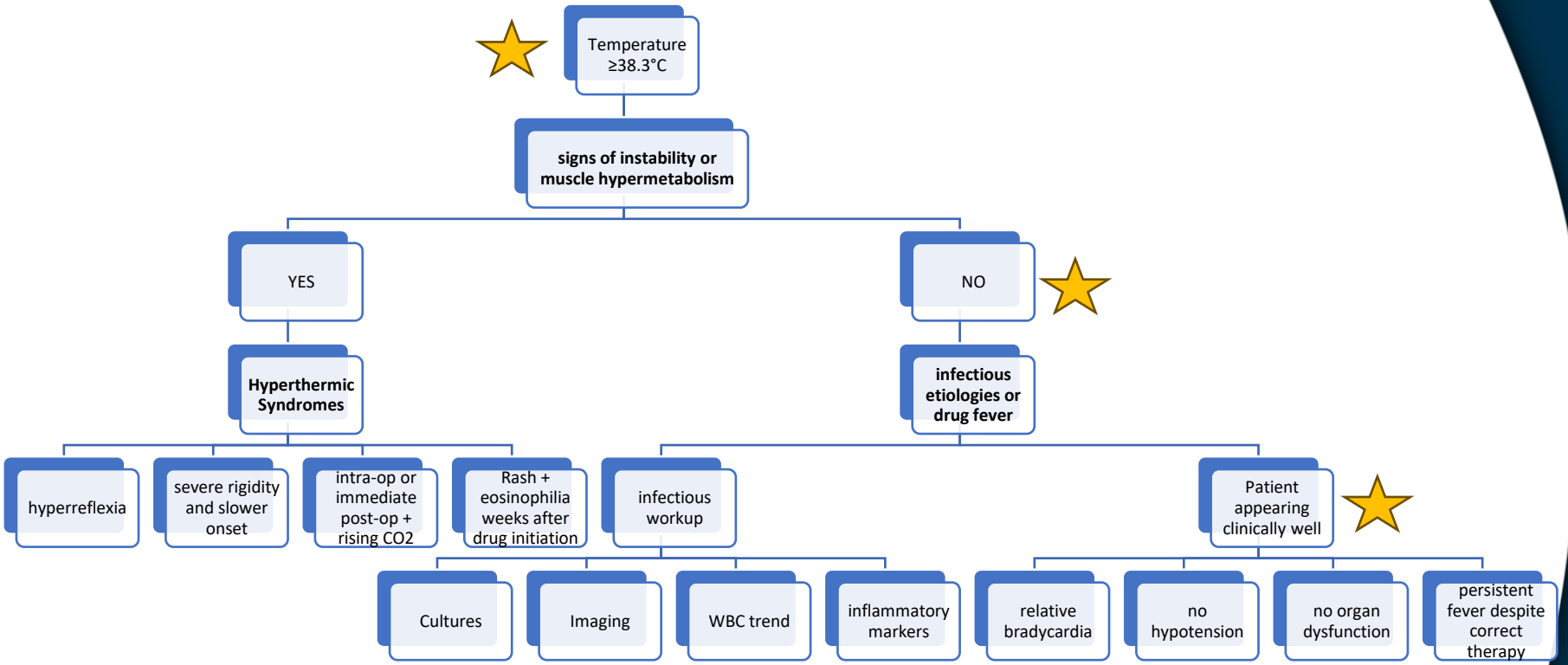
Is this drug fever?

# Case: BL – Persistently Febrile

**Inpatient Medications**

- Vancomycin 1,250 mg IV daily
- Piperacillin/tazobactam 3.375 mg IV every 8 hours
- Amlodipine 10 mg by mouth daily
- Tiotropium inhaler 2 puffs daily
- Omeprazole 20 mg by mouth daily

# Assessment

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# Case: BL – Plan

All other etiologies of fever were ruled out

Both antibiotics were discontinued

The team monitored for resolution of fever

Within 48 hours the patient became afebrile

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# Summary/Conclusion

Drug fever is underreported and underdiagnosed

Primary literature is sparce regarding drug fever and there are specific medications that can be potential causes

Drug fever is a diagnosis of exclusion; rule out all other causes of fever first

Consider drug fever in the differential diagnosis when treating patients with a fever of unknown origin

Opportunity to optimize patient care, decrease hospital length of stay and healthcare costs

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# Questions?

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