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

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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

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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

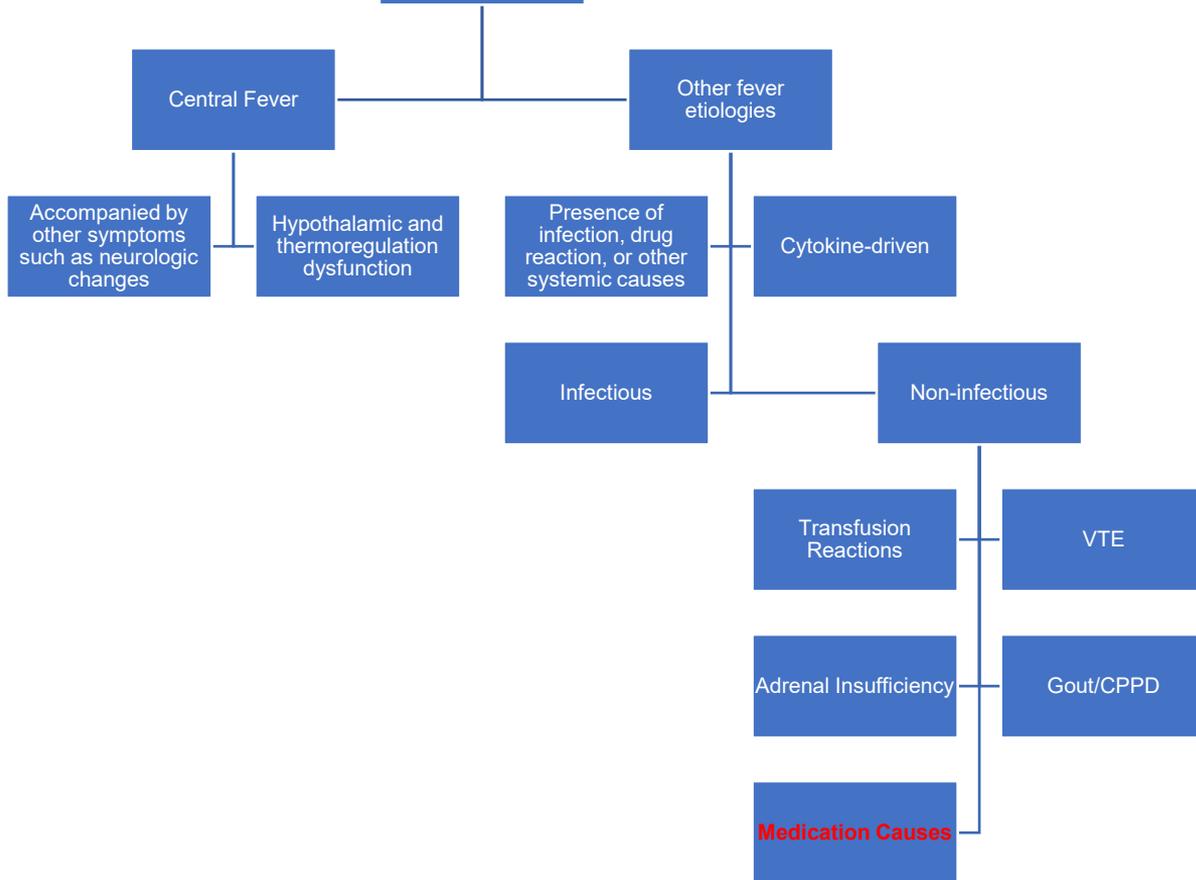SSRI = selective serotonin reuptake inhibitor

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.

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

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

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Mechanisms of Drug Fever

Pyrogen Release

Jarisch-Herxheimer Reaction

Irritant Drugs

Alterations of thermoregulation

Hypersensitivity

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

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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

Drug Causes: interferons, amphotericin B
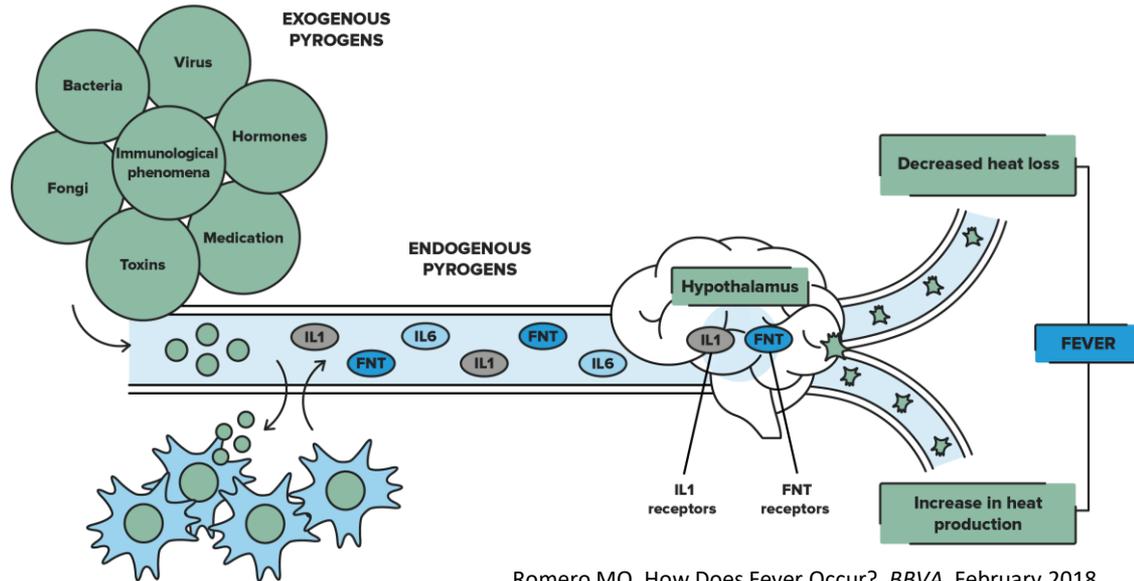
Romero MO. How Does Fever Occur?. *BBVA.* February 2018

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

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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.

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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.

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Alterations of Thermoregulation

Hypothalamus

Sweat glands
Hair follicles
Blood vessels

Skeletal muscles
Goosebumps
Blood vessels

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

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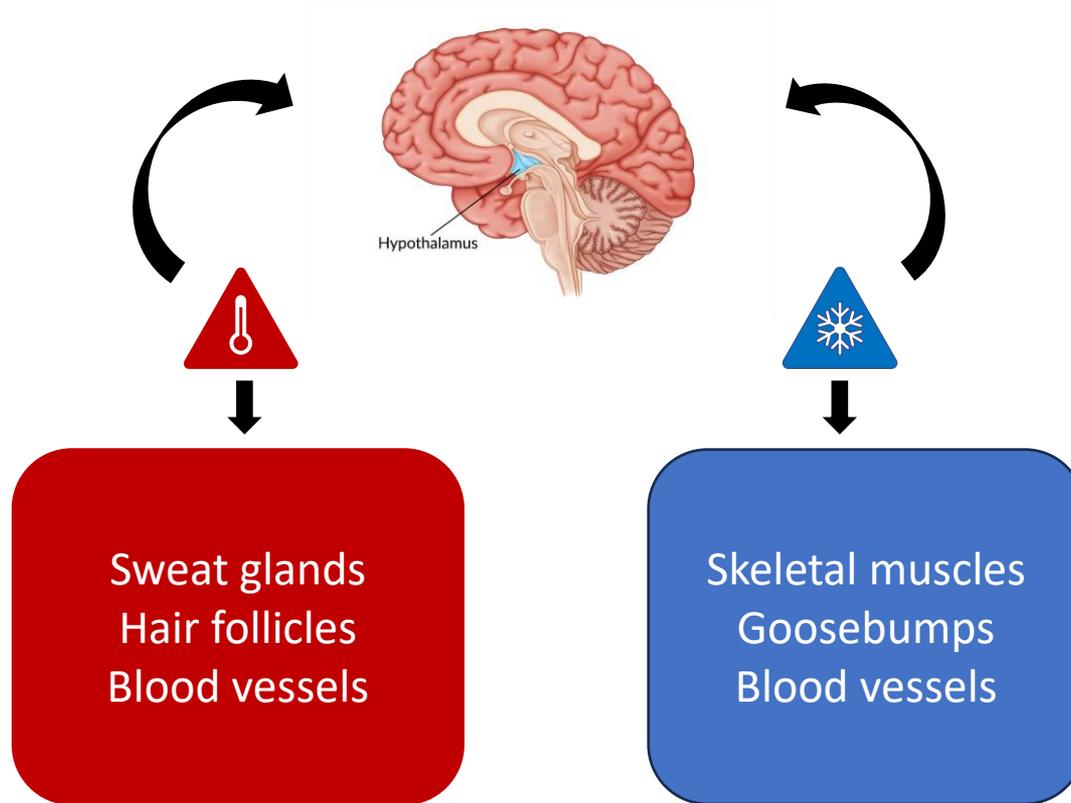
Alterations of Thermoregulation

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

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

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

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

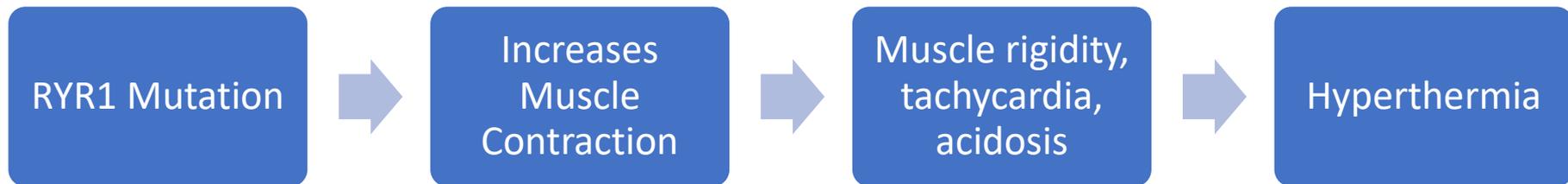Jenkins RD, Woodhouse KW. Adverse Drug Reaction Bull; 1999.

Drug Induced Hyperthermia

Malignant Hyperthermia

Neuroleptic Malignant Syndrome

Serotonin Syndrome

DRESS

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

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Malignant Hyperthermia

RYR1 Mutation → Increases Muscle Contraction → Muscle rigidity, tachycardia, acidosis → Hyperthermia

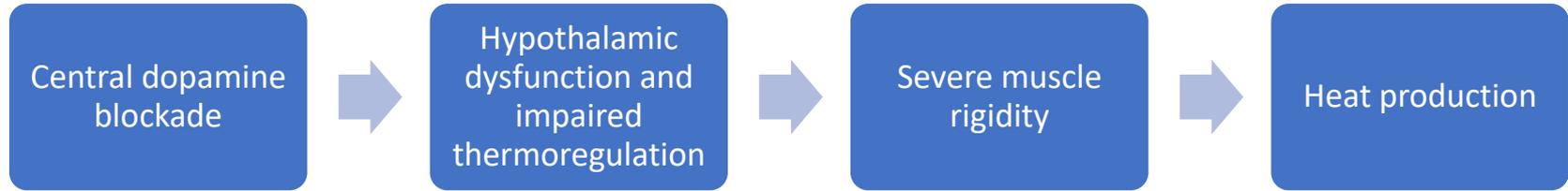**Common triggers:** volatile anesthetics and succinylcholine

Clinical Features: Rapid Rise in CO_2, 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

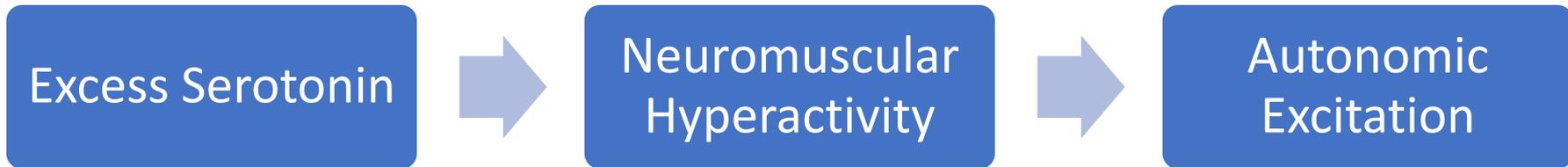| Central dopamine blockade	→	Hypothalamic dysfunction and impaired thermoregulation	→	Severe muscle rigidity	→	Heat production

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

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

Serotonin Syndrome

Excess Serotonin → Neuromuscular Hyperactivity → Autonomic Excitation

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

T-Cell mediated delayed hypersensitivity	→	Possible viral reactivation	→	Immune dysregulation

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

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

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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

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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

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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'

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

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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

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

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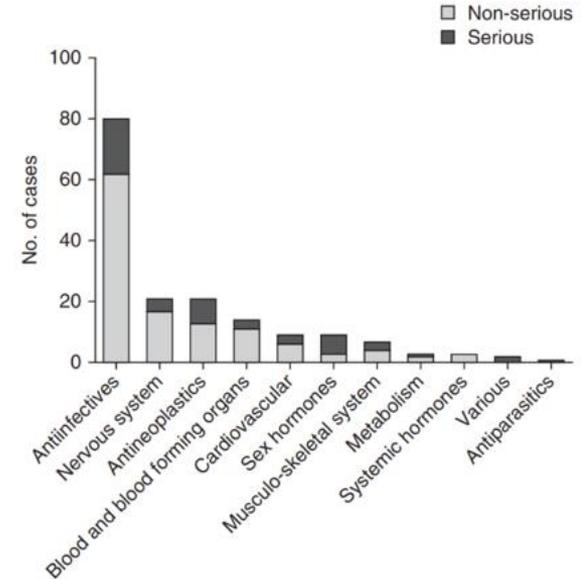
Vodovar, D. *et al.* 2012

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

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

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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)

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

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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

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

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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

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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

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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 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

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Clinical Presentation

Time between initiation of drug and fever onset

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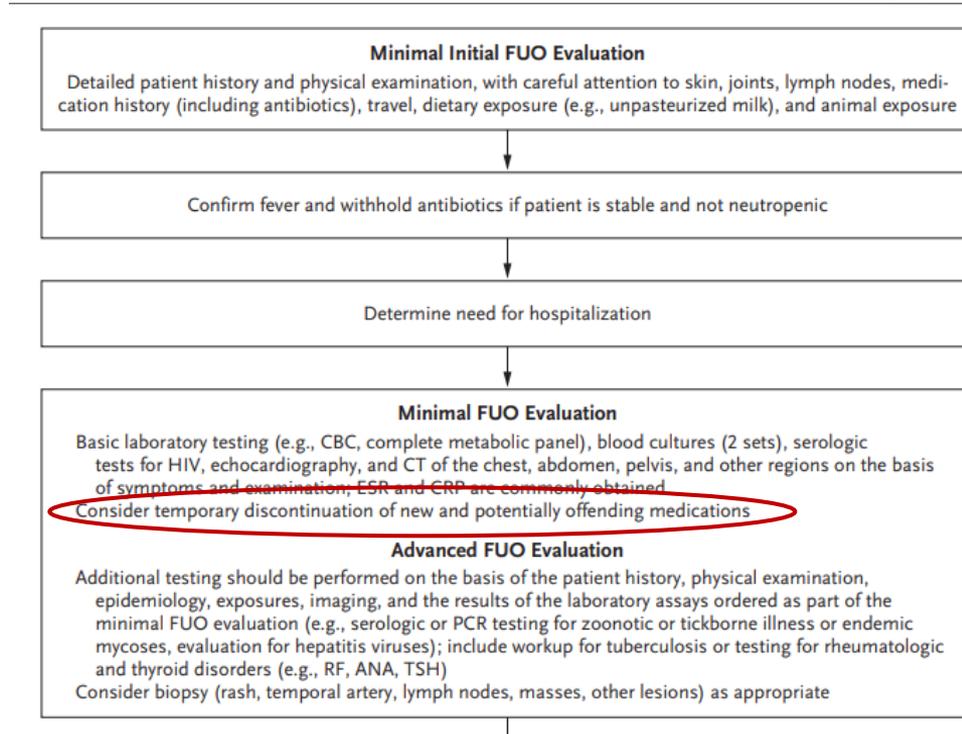- Quicker onset if the patient had previous exposure

Fever Pattern

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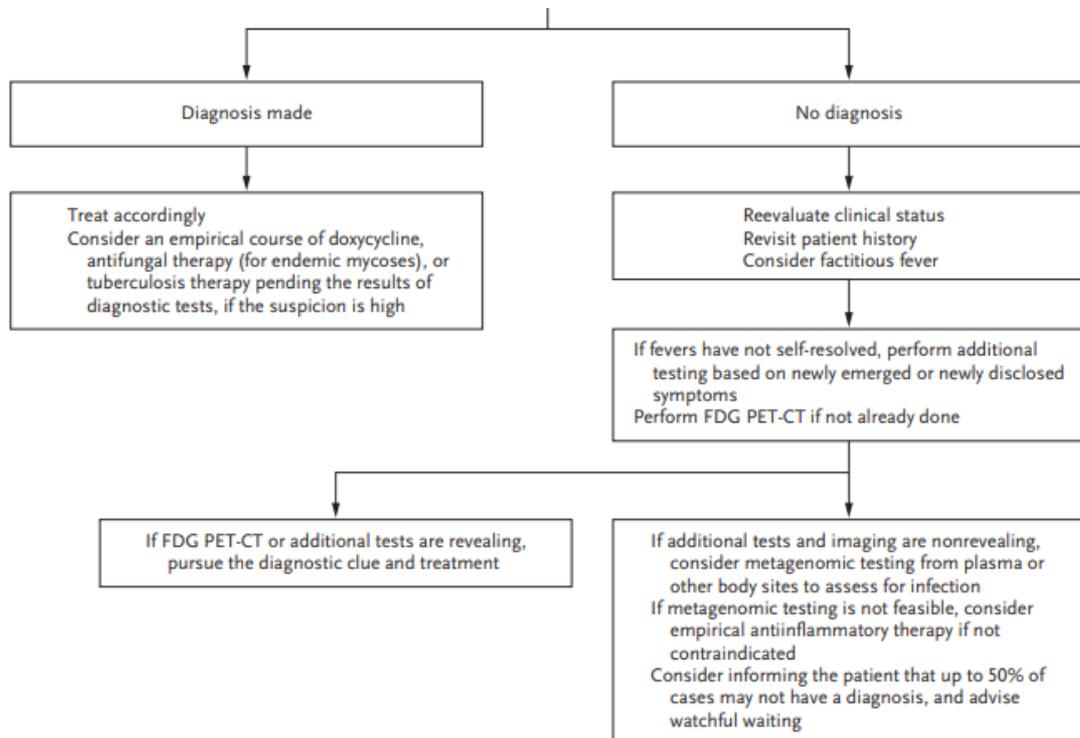- Not used as a diagnostic indicator

Associated Symptoms

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

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Fever of Unknown Origin (FUO) Algorithm

Minimal Initial FUO Evaluation
Detailed patient history and physical examination, with careful attention to skin, joints, lymph nodes, medication history (including antibiotics), travel, dietary exposure (e.g., unpasteurized milk), and animal exposure

Confirm fever and withhold antibiotics if patient is stable and not neutropenic

Determine need for hospitalization

Minimal FUO Evaluation
Basic laboratory testing (e.g., CBC, complete metabolic panel), blood cultures (2 sets), serologic tests for HIV, echocardiography, and CT of the chest, abdomen, pelvis, and other regions on the basis of symptoms and examination; ESR and CRP are commonly obtained
Consider temporary discontinuation of new and potentially offending medications

Advanced FUO Evaluation
Additional testing should be performed on the basis of the patient history, physical examination, epidemiology, exposures, imaging, and the results of the laboratory assays ordered as part of the minimal FUO evaluation (e.g., serologic or PCR testing for zoonotic or tickborne illness or endemic mycoses, evaluation for hepatitis viruses); include workup for tuberculosis or testing for rheumatologic and thyroid disorders (e.g., RF, ANA, TSH)
Consider biopsy (rash, temporal artery, lymph nodes, masses, other lesions) as appropriate

FUO Algorithm

Diagnosis made

> Treat accordingly
> Consider an empirical course of doxycycline, antifungal therapy (for endemic mycoses), or tuberculosis therapy pending the results of diagnostic tests, if the suspicion is high

No diagnosis

> Reevaluate clinical status
> Revisit patient history
> Consider factitious fever

> If fevers have not self-resolved, perform additional testing based on newly emerged or newly disclosed symptoms
> Perform FDG PET-CT if not already done

> If FDG PET-CT or additional tests are revealing, pursue the diagnostic clue and treatment

> If additional tests and imaging are nonrevealing, consider metagenomic testing from plasma or other body sites to assess for infection
> If metagenomic testing is not feasible, consider empirical antiinflammatory therapy if not contraindicated
> Consider informing the patient that up to 50% of cases may not have a diagnosis, and advise watchful waiting

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

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.

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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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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

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

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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.

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Consequences of Not Diagnosing Drug Fever

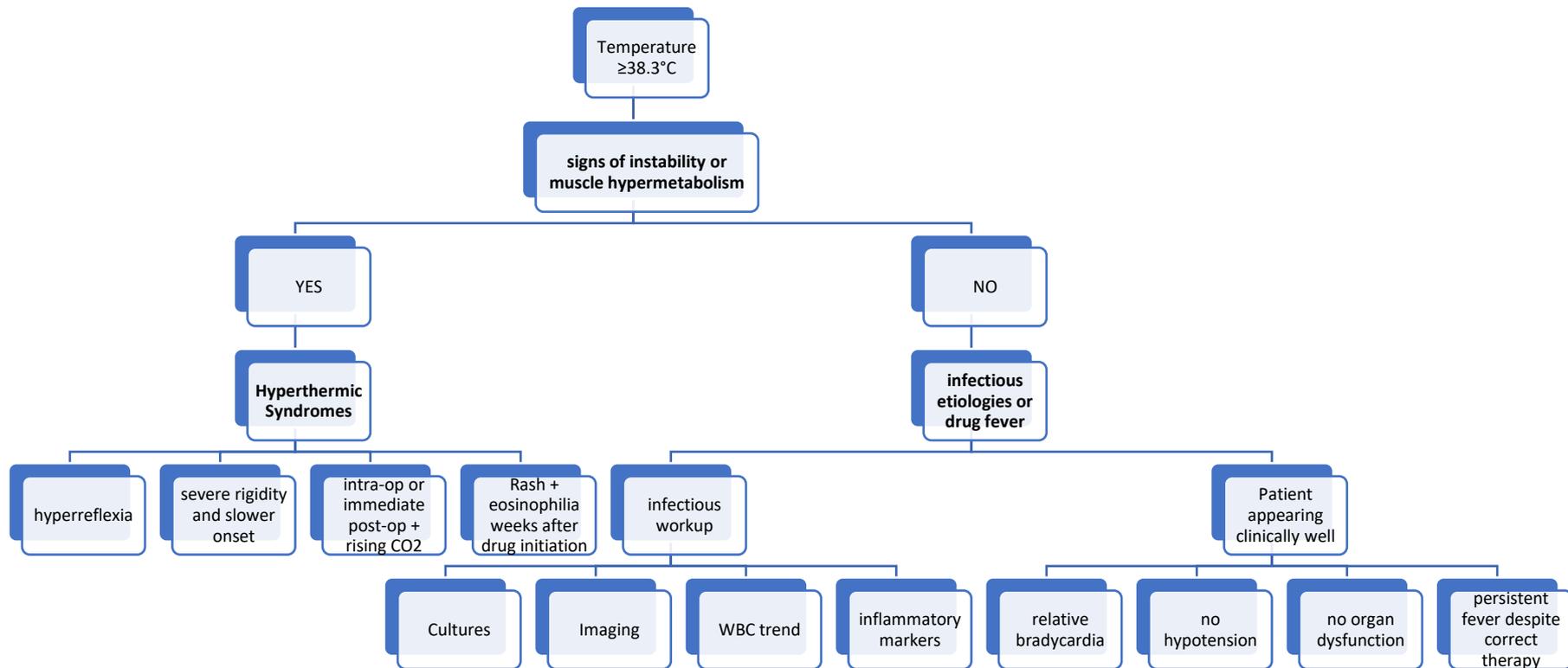| Leads to prolonged hospitalization | Leads to additional costs, including diagnostic procedures and treatments | Leads to unnecessary treatments and exposure to medications |

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

Temperature ≥38.3°C

signs of instability or muscle hypermetabolism

YES → **Hyperthermic Syndromes**
- hyperreflexia
- severe rigidity and slower onset
- intra-op or immediate post-op + rising CO_2
- Rash + eosinophilia weeks after drug initiation

NO → **infectious etiologies or drug fever**
- infectious workup
  - Cultures
  - Imaging
  - WBC trend
  - inflammatory markers
- Patient appearing clinically well
  - relative bradycardia
  - no hypotension
  - no organ dysfunction
  - persistent fever despite correct therapy

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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.

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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

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

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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

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

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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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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

Flannery AH, et al. Pharmacotherapy; 2015.

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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

Yang CH, Chen YY. Psychopharmacol Bull; 2017.

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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

Yang CH, Chen YY. Psychopharmacol Bull; 2017.

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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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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

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

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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

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

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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

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

Hospital Course: <u>Day 6</u>

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
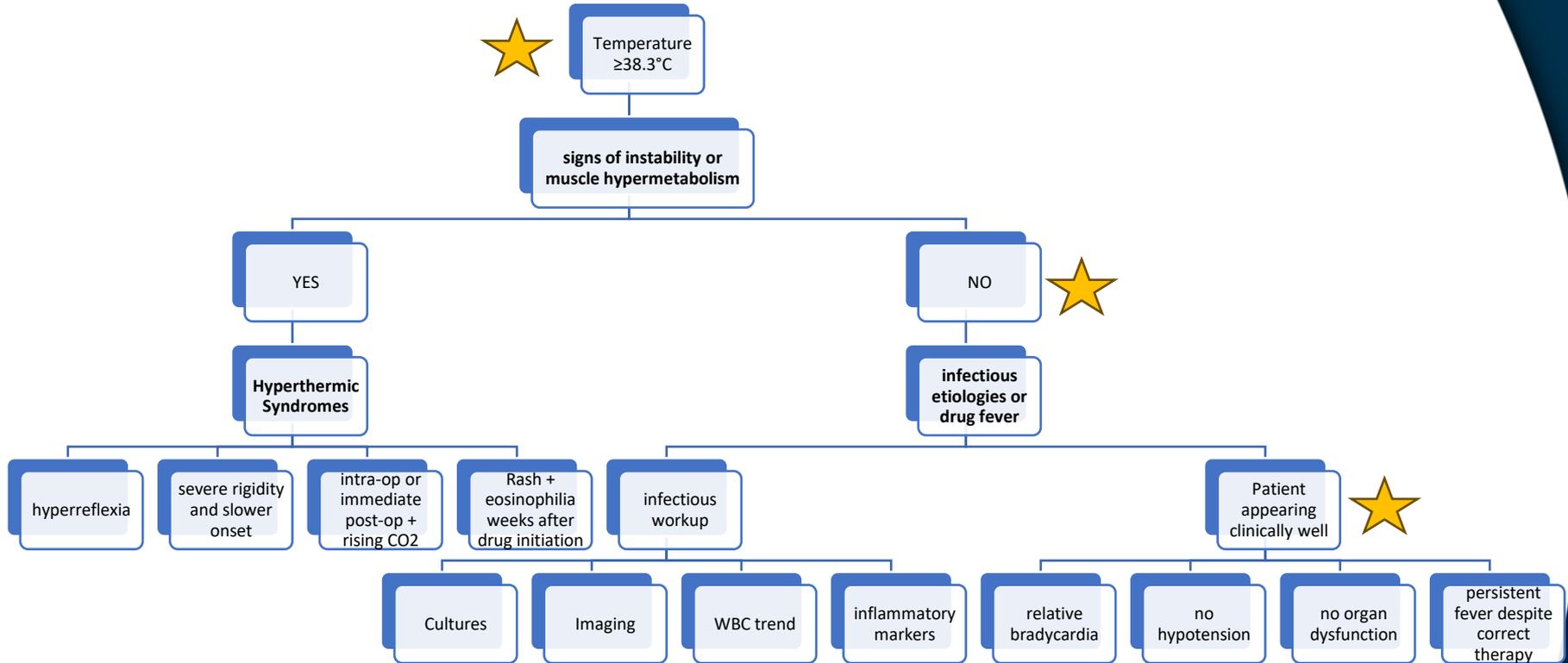- Looks "well" for temperature

Is this drug fever?

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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

Temperature ≥38.3°C

signs of instability or muscle hypermetabolism

YES → **Hyperthermic Syndromes**
- hyperreflexia
- severe rigidity and slower onset
- intra-op or immediate post-op + rising CO_2
- Rash + eosinophilia weeks after drug initiation

NO → **infectious etiologies or drug fever**
- infectious workup
  - Cultures
  - Imaging
  - WBC trend
  - inflammatory markers
- Patient appearing clinically well
  - relative bradycardia
  - no hypotension
  - no organ dysfunction
  - persistent fever despite correct therapy

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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