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Clinical approach to fever in the neurosurgical intensive care unit: Focus on drug fever

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Abstract

As fever is one of the cardinal signs of infection, the presence of fever in a patient in the neurosurgical intensive care unit (NSICU) raises the question of whether it is infectious in etiology. Infectious and noninfectious causes of fever in the NSICU may be determined based upon assessment of clinical signs and symptoms, the degree of temperature elevation, the relationship of the pulse to the fever (e.g., an infectious process resulting in hyperpyrexia and bradycardia), and when the fever occurs (e.g., related to the length of stay in the NSICU). There are many noninfectious disorders which contribute to temperatures >102°F in the NSICU; these include drug fevers, deep vein thrombosis, phlebitis/pulmonary embolism, acute myocardial infarction, atelectasis, dehydration, acute gout flare, malignancy, acute pancreatitis, transfusion associated hepatitis, and hemorrhage. Infectious rather than noninfectious disorders, however, are more typically associated with high-grade fevers (>102°F.) in the NSICU, and nosocomial pneumonia, (synonymous with ventilator-associated pneumonia [VAP]), is the leading culprit, followed by nosocomial infections and *Clostridium difficile*.

Keywords: Bradycardia, drug fevers, hyperpyrexia, infection, neurosurgical intensive care unit, noninfectious temperature elevations

INTRODUCTION

Patients in a neurosurgical intensive care unit (NSICU) are often febrile for a variety of reasons. As fever is one of the cardinal signs of infection, it raises the question of whether it is infectious in etiology.[2] Evaluation of infectious vs. noninfectious causes of fever in the NSICU may include: Assessment of clinical signs and symptoms, evaluation of the degree of elevation in temperature, assessment of the relationship of the pulse to the fever, and determination of when the fever occurs (e.g., related to the NSICU length of stay (LOS).

NONINFECTIOUS DISORDERS IN NSICU PATIENTS WITH LOW GRADE FEVERS (<102°F)

In the NSICU, it is not understood why most noninfectious fevers do not exceed 102°F. These temperature elevations are variously attributed to: Deep vein thrombosis/phlebitis, pulmonary embolism, acute myocardial infarction, atelectasis, dehydration, acute gout flare, malignancy, acute

pancreatitis, transfusion associated hepatitis, and hemorrhage.[11,15,18,26,27,30,31,33,34,35] Important infectious diseases associated with fevers <102°F are relatively uncommon in the NSICU, with the exception of *Clostridium difficile* diarrhea, and gas gangrene.[4]

NONINFECTIOUS DRUG FEVERS

The most important noninfectious disorder associated with temperatures >102-104°F in the NSICU are drug fevers that not uncommonly rise to the 102-106.5°F [Table 1].[10,31,37]

INFECTIONS ARE MORE TYPICALLY ASSOCIATED WITH HIGH-GRADE FEVERS (>102°F)

Infectious rather than noninfectious disorders are more typically associated with high-grade fevers (>102°F.) in the NSICU. Nosocomial pneumonia (NP) associated with fevers >102°F is commonly encountered in NSICU patients, and is synonymous with ventilator-associated pneumonia (VAP).[6,8,25,36] Other important causes of high-grade fevers (>102°F) are infections associated with central venous catheters (CVCs) (i.e., intravenous [IV] line infections), *C. difficile* colitis, and nosocomial meningitis (NM).[37] Alternatively, other types of infections that commonly contribute to high-grade fevers in other intensive care unit (ICUs) patients (vs. NSICU) include; intraabdominal sepsis, intrapelvic sepsis, and urosepsis.[6,37]

URINARY TRACT INFECTIONS ARE A RARE CAUSE OF FEVER IN THE NSICU

Urinary tract infections (UTIs) are rarely a cause of fever in the NSICU. Most NSICU patients have an indwelling Foley urinary catheter, and commonly develop catheter-associated bacteriuria (CAB), (e.g., nosocomial UTI). However, CAB is a benign entity that in normal hosts does not aggressively predispose to urosepsis, and most clinicians do not treat CAB. Nosocomial urosepsis is associated almost exclusively with urologic manipulation and consequent fever/bacteremia <24 hours after the invasive urologic procedure.[32] Furthermore, other patients with preexisting renal disease, urological abnormalities (Urological: GU) or with impaired host defenses (e.g., diabetes mellitus, systemic lupus erythematosus (SLE), immunosuppressive therapy, multiple myeloma) may develop urosepsis from CAB.

DIAGNOSTIC SIGNIFICANCE OF EXTREME HYPERPYREXIA: NEVER DUE TO INFECTION

An uncommon but important problem in the NSICU is that of extreme hyperpyrexia, [temperatures >106°F], that is almost never due to infection. Extreme hyperpyrexia always implies a noninfectious etiology, like, central fever, malignant hyperthermia, malignant neuroleptic syndrome, relative adrenal insufficiency, or a drug fever.[6,13]

DIAGNOSTIC SIGNIFICANCE OF FEVER AND TIME RELATIONSHIPS

Temporal relationships: Up to 1 week of fever following transfusions of blood and blood products

When the NSICU patient, (acute <7 days vs. delayed >7 days) develops to fevers after receiving blood or blood products helps to determine the etiology of the fevers. Transfusion fevers typically occur within 72 hours, but may, on rare occasion, occur up to 1 week later. Fevers that occur >7 days following transfusions should not typically be ascribed to the transfusions; rather, other viral agents (e.g., such as hepatitis, cytomegalo virus [CMV] may be responsible for these fevers.[1,17]

Timing of other variables contributing to infections in NSICU/hospital patients

Different infections occur at different intervals during the course of a patient's hospitalization. NPs and VAP by definition occur after the patient has been in the hospital for >1 week. CVC-associated fevers (i.e., IV line sepsis) usually occur when the catheter is in place for >1 week, and may result in nosocomial acute bacterial endocarditis (ABE) with bacteremia, resulting in fevers >102°F.[14] Wound infections usually

occur 1-2 weeks postprocedure/postoperatively, and are typically correlated with fevers of <102°F. Transplant associated infections usually occur >2 weeks or more following surgery.

Temporal relationship between invasive procedures and infections in NSICU patients

There is also a temporal relationship between invasive procedures, and procedure-related fevers. External ventricular drainage (EVD) resulting in NM may occur any time after EVD placement. These infections are often attributed to relatively avirulent nosocomial aerobic nonfermentative Gram negative bacilli (GNB), (e.g., *Acinetobacter baumanii*).[20]

CLINICAL SIGNS OF INFECTION

When establishing the etiology of a fever, clinical signs should be carefully analyzed.

Diagnosis of CVC associated infections

In about half of the cases, CVC associated infections are clearly associated with infection at the site of catheter insertion thus the diagnosis of an IV line infection is relatively straight forward. However, in 50% of patients, where there are no signs of skin/wound site infection, the diagnosis must be established by obtaining blood cultures from the noninvolved extremity, and sending the removed CVC tip for semi-quantitative culture. If catheter tip cultures have >15 colonies, and the CVC tip isolate matches the blood isolate, then the diagnosis of CVC associated line infection is confirmed [Table 1].[6,10,14]

Diagnosis of NP or VAP infections requires new infiltrates (>1 week hospitalization)

Establishing the diagnosis of NP or VAP requires that new infiltrates (after >1 week of hospitalization) be identified on chest X-ray (CXR). If NP/VAP are present, new pulmonary infiltrates characteristic of bacterial pneumonia should be apparent on the CXR. Infiltrates on CXR that may have other etiologies common in the NSICU must be excluded; pulmonary hemorrhage, pulmonary drug effects, pulmonary emboli, and congestive heart failure. Since colonization of body fluids, including respiratory secretions, occurs within a week of hospitalization, the physician should not assume that isolates cultured from respiratory secretions of intubated patients have any etiologic relationship to possible NP in the lungs. [10,28,29] For this reason, NP/VAP is treated empirically, and not based on respiratory secretion cultures.

THE ONE-TIME "<102° F SPIKE RULE" IS NEVER DUE TO INFECTION

The one-time <102°F fever spike is classical for noninfectious disorders and is never due to infection. [6,10] Establishing the correct clinical diagnosis requires taking into account the degree and duration of the temperature elevation vs. the duration of the NSICU stay. Fevers associated with blood transfusions are usually transient, that is, presenting as a single fever spike within <1 week. Fevers from transient bacteremias of 102-106°F may occur as a consequence of manipulation of a colonized or an infected mucosal surface (e.g., insertion/removal of a Foley catheter, suctioning of an endotracheal or tracheostomy tube, removal of a peripheral IV line or CVC).

THE RELATION OF PULSE TO TEMPERATURE: NONINFECTIOUS ETIOLOGIES OF RELATIVE BRADYCARDIA IN NSICU PATIENTS

The relationship of pulse to temperature provides an important clue to establishing the diagnosis for a variety of infectious diseases [Table 2]. Normally, the pulse rises in concert with the temperature, (e.g., for every degree Fahrenheit temperature is increased, the pulse should rise 10 beats/min). If the pulse rate is lower than predicted from a given temperature (>102°F), then relative bradycardia is present, unless the patient is on a beta blocker, receiving Verapamil or Diltiazem, or has a pacemaker-induced rhythm. Given these exclusion criteria, relative bradycardia in NSICU patients with fever strongly suggests a central or drug fever. Alternatively, only rarely do other ICU patients develop relative

bradycardia secondary to NP/VAP due to nosocomial legionnaire's disease (cluster or outbreak) [Table 2].[7,13]

DIAGNOSIS OF DRUG FEVERS THAT OCCUR IN APPROXIMATELY 10% OF NSICU PATIENTS

Drug fevers occur in approximately 10% of ICU and NSICU patients in the United States, and, therefore, present common diagnostic problems [Table 1]. Drug fevers may occur in patients with infectious diseases and multiple comorbidities, with superimposed drug fevers. Classically, patients with drug fevers look "relatively well" for the degree of fever, allowing for the manifestations of other diseases.[3,5,19] Regardless of the degree of fever, patients with drug fevers invariably exhibit relative bradycardia if the temperature is elevated >102°F; below this level (<102°F) the pulse/temperature deficit cannot be fully appreciated [Table 2].

Laboratory findings for patients with drug fevers

Excluding other conditions, patients with drug fevers will demonstrate an otherwise unexplained leukocytosis with a shift to the left (mimicking infection). They may also exhibit elevated erythrocyte sedimentation rate (ESR) (over the patient's normal baseline). However, their blood cultures will be negative (excluding contaminants). In addition, since the liver typically mediates drug fevers, there are usually mild increases in serum transaminase, and immunoglobulin E (IgE) levels [Table 2].[21,22,23,24,38]

Evaluation of past medical history in patients with drug fevers

The past medical history of a patient with a drug fever frequently includes an atopic history (e.g., if they are allergic to one or more medications). A common misconception is that the patient cannot have a drug fever because the patient has been on a particular medication for years without prior incident. While drug fevers may occur hours or days after beginning a new medication, most drug fevers occur due to chronic medications that the patient has been on for months or years. Clinically, "the longer the patient has been on a sensitizing medication, the more likely the drug fever is due to that medication."[10,19]

Hematological abnormalities (high eosinophil and low atypical lymphocyte counts) may signal drug fevers

There are certain hematological findings that should be evaluated to determine whether patients have a drug fever[10,16,19]. Eosinophils (on peripheral smear) in a patient with an otherwise unexplained obscure fever in the NSICU should suggest a drug fever.[10,19] Low numbers of atypical lymphocytes are often also present with drug fevers.

Drug fever correlated with drug rash and hematological abnormalities

Typically, a drug fever is correlated with a drug rash and hematological abnormalities, which do not correlate with any significant pathological physical findings.[9,12] Establishing the diagnosis is relatively straightforward. Typical clinical features include: Leukocytosis with a shift to the left, eosinophils in the peripheral smear, mildly elevated serum transaminases, a rising ESR, and negative blood cultures (excluding skin contaminants).

Sulfonamides: A sensitizing medication associated with drug fevers

The patient may be on "sensitizing medications" related to sulfonamides, either acutely or chronically, that are likely to contribute to drug fevers. These include; Colace, Lasix, Thiazide diuretics, sleep medications, antiarrhythmics, opiates, sedatives, and antiseizure medications (e.g., Dilantin) [Table 3].

Misconception that antibiotics are the most common cause of drug fevers

It is a misconception that antibiotics are the most common cause of drug fevers [Table 1]. While some antibiotics, particularly trimethoprim/sulfamethoxazole (TMP-SMX) and Beta Lactam (ß lactam) are frequent causes of drug fevers, most other antibiotics rarely cause drug fevers.[19,22,38] The clinician should always look first at nonantibiotic medications for the cause of drug fevers [Table 3].[7,10] Clinically, the diagnosis of a drug fever may be confirmed by discontinuing the offending "sensitizing medication." If the drug fever is due to the discontinued "sensitizing medication," the fever will decrease within <72 hours. However, fevers associated with drug rashes may last for days or weeks.[9,12]

Difficulties establishing the diagnosis of a drug fever

Establishing the diagnosis of a drug fever may be difficult as it depends on laboratory findings that may prove confusing to the clinician. For example, most complete blood counts (CBC) are done by autoanalyzers that are insensitive to atypical lymphocytes (<5%) and eosinophils.[7,10,19]

Summary of drug fevers in NSICU patients

In summary, drug fevers should always be kept in mind in NSICU patients since they are a common occurrence. Patients may have drug fevers alone, or drug fevers superimposed upon an infection (e.g., NP/VAP). While drug fever is a diagnosis of exclusion, there are usually sufficient clinical findings to establish a clinical diagnosis of a drug-related fever. This diagnosis is also proven by discontinuing the "sensitizing medication" with resultant rapid resolution of the fever and their accompanying laboratory abnormalities.

Footnotes

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REFERENCES

1. Barton JC. Non-hemolytic, noninfectious transfusion reactions. Semin Hematol. 1981;18:95–121. [PubMed: 6164098]

2. Boulant JA. The preoptic-anterior hypothalamus in thermoregulation and fever. Clin Infect Dis. 2000;31:S157–61. [PubMed: 11113018]

3. Bystryn JC. Drug fever. Am J Med Sci. 1972;264:473–4. [PubMed: 4650804]

4. Caines C, Gill MV, Cunha BA. Non-Clostridium difficile nosocomial diarrhea in the intensive care unit. Heart Lung. 1997;26:83–4. [PubMed: 9013225]

5. Cluff LE, Johnson JE. Drug fever. Progr Allergy. 1964;8:149.

6. Cunha BA. Clinical approach to fever in the CCU. Crit Care Clin. 1998;8:1–14. [PubMed: 9448975]

7. Cunha BA. Diagnostic significance of relative bradycardia. Clin Microbiol Infect Dis. 2000;6:633–4.

8. Cunha BA. Fever in the Intensive Care Unit. Intensive Care Med. 1999;25:648–51. [PubMed: 10470566]

9. Cunha BA. Rash and fever in the intensive care unit. In: Abraham E, Vincent JL, Kochanek P, editors. Textbook of Critical Care Medicine. 5th ed. Philadelphia: Elsevier; 2005. pp. 113–9.

10. Cunha BA. Clinical Approach to Fever in the ICU. In: Cunha BA, editor. Infectious diseases in Critical Care Medicine. 3rd ed. New York: Informa; 2010. pp. 1–18.

11. Cunha BA. Fever in malignant disorders. Infect Dis Pract. 2004;28:335–6.

12. Cunha BA. The Diagnostic approach to rash and fever in the CCU. Crit Care Clin. 1998;8:35–54.

13. Cunha BA. The diagnostic significance of fever curves. Infect Dis Clin North Am. 1996;10:33–44. [PubMed: 8698993]

14. Cunha BA, Gill MV, Lazar J. Acute infective endocarditis. Infect Dis Clin North Am. 1996;10:811–34. [PubMed: 8958170]

15. Engoren M. Lack of association between atelectasis and fever. Chest. 1995;107:81–4. [PubMed: 7813318]

16. Ferrara JL. The febrile platelet transfusion reaction: A cytokine shower. Transfusion. 1995;35:89–90. [PubMed: 7825217]

17. Fenwick JC, Cameron M, Naiman SC, Haley LP, Ronco JJ, Wiggs BR, et al. Blood transfusion as a cause of leucocytosis in critically ill patients. Lancet. 1994;344:855–6. [PubMed: 7916402]

18. Garibaldi RA, Brodine S, Matsumiya S, Coleman M. Evidence for the non-infectious etiology of early postoperative fever. Infect Control. 1985;6:273–7. [PubMed: 3847403]

19. Johnson DH, Cunha BA. Drug Fever. Infect Dis Clin North Am. 1996;10:85–91. [PubMed: 8698996]

20. Krol V, Hamid NS, Cunha BA. Neurosurgically related nosocomial Acinetobacter baumannii meningitis: Report of two cases and literature review. J Hosp Infect. 2009;71:176–80. [PubMed: 19084290]

21. Kumar KL, Reuler JB. Drug fever. West J Med. 1986;144:753–5. [PMCID: PMC1306783] [PubMed: 3487884]

22. Lipsky BA, Hirschmann JV. Drug fever. JAMA. 1981;245:851–4. [PubMed: 7463680]

23. Mackowiak PA. Drug fever: Mechanism, maxims and misconceptions. Am J Med Sci. 1987;294:275–86. [PubMed: 3310641]

24. Mackowiak PA, Le Maistre CF. Drug fever: A critical appraisal of conventional concepts. Ann Intern Med. 1987;106:728–33. [PubMed: 3565971]

25. Marik PE. Fever in the ICU. Chest. 2000;117:855–69. [PubMed: 10713016]

26. Marik PE, Andrews L, Maini B. The incidence of deep venous thrombosis in ICU patients. Chest. 1997;111:661–4. [PubMed: 9118705]

27. Marx N, Neumann FJ, Ott I, Gawaz M, Koch W, Pinkau T, et al. Induction of cytokine expression in leukocytes in acute myocardial infarction. J Am Coll Cardiol. 1997;26:83–4.

28. Meduri GU, Mauldin GI, Wunderink RG, Leeper KV, Jr, Jones CB, Tolley E, et al. Causes of fever and pulmonary densities in patients with clinical manifestations of ventilator-associated pneumonia. Chest. 1994;106:221–35. [PubMed: 8020275]

29. Meduri GU. Diagnosis and differential diagnosis of ventilator-associated pneumonia. Clin Chest Med. 1995;16:61–93. [PubMed: 7768095]

30. Murray HW, Ellis GC, Blumenthal DS, Sos TA. Fever and pulmonary thromboembolism. Am J Med. 1979;67:232–5. [PubMed: 463928]

31. Niven DJ, Leger C, Stelfox HT, Laupland KB. Fever in the critically ill: A review of epidemiology, immunology, and management. Intensive Care Med. 2012;27:290–7.

32. Paradisi F, Corti G, Mangani V. Urosepsis in the critical care unit. Crit Care Clin. 1998;114:165–80. [PubMed: 9561812]

33. Petersen SR, Sheldon GF. Acute acalculous cholecystitis: A complication of hyperalimentation. Am J Surg. 1979;138:814–7. [PubMed: 116561]

34. Ryan M, Levy MM. Clinical review: Fever in intensive care unit patients. Crit Care. 2003;7:221–5. [PMCID: PMC270667] [PubMed: 12793871]

35. Shea KW, Cunha BA. Fever in the Intensive Care Unit. Infect Dis Clin North Am. 1996;10:185–210. [PubMed: 8698990]

36. Stumacher RJ. Fever in the ICU. Infect Dis Pract. 1996;20:89–92.

37. Tu RP, Cunha BA. Significance of fever in the Neurosurgical Intensive Care Unit. Heart Lung. 1998;17:608–11. [PubMed: 3056881]

38. Young EJ, Fainstein V, Musher DM. Drug-induced fever: Cases seen in the evaluation of unexplained fever in a general hospital. Rev Infect Dis. 1982;4:69–77. [PubMed: 7071457]

Figures and Tables

Table 1

Variable	Clinical features of drug fever
History	• Individuals often atopic to one or more medications • Patients on a "sensitizing medication" for days or more commonly, months/years
Physical examination	• Fevers usually >102°F (102-106.5°F not uncommon) • Relative bradycardia (with temperature >102°F) • Patients appear "inappropriately well" for degree of fever • Excluding septic patients who also have drug fever • No rash • Rash, if present, represents drug rash (not drug fever), which is usually accompanied by fever • Drug rashes usually maculopapular (occasionally with a petechial component), central, and may involve palms/soles (See Table 2)
Laboratory tests	• Leukocytosis (with left shift) • Eosinophils are usually present (eosinophilia is uncommon) • Elevated ESR (may reach>100 mm/h) • Mildly elevated serum transaminases

Clinical Features of Drug Fever

Table 2

Infectious causes	Noninfectious causes
Legionella	Drugs
Psittacosis	ß-blockers
Q fever	Verapamil
Typhus	Diltiazem
Babesiosis	CNS lesions
Malaria	Lymphomas
Typhoid fever	Factitious fevers
Leptospirosis	Drug fever
Yellow fever	
Dengue fever	
Viral hemorrhagic fevers	
RMSF	

Determination of Relative Bradycardia
Criteria
Inclusive
Patient must be an adult
Temperature > 102°F
Pulse must be taken simultaneously with the temperature
Exclusive
Patient has no arrhythmia, second-/third-degree heart block or pacemaker-induced rhythm
Patient not on ß blocker, Verapamil, or Diltiazem

Temperature-Pulse Relationships

Temperature	Appropriate pulse response	Pulse rate with relative bradycardia
106°F (41.1°C)	150/min	<140/min
105°F (40.6°C)	140/min	<130/min
104°F (40.7°C)	130/min	<120/min
103°F (39.4°C)	120/min	<110/min
102°F (39.8°C)	110/min	<100/min

CNS: Central nervous system; RMSF: Rocky mountain spotted fever

Infectious and Noninfectious Causes of Relative Bradycardia

Table 3

Common causes	Uncommon causes	Rare causes
Antibiotics	Any other medication	Antibiotics
ß-lactams		Aminoglycosides
Sulfonamides (TMP-SMX)		Tetracyclines
Nonantibiotics		Macrolides
Sulfa-containing drugs		Clindamycin
Stool softeners (Colace)		Chloramphenicol
Diuretics (Lasix)		Vancomycin
Sleep medications		Aztreonam
Antiseizure medications		Quinolones
Antidepressants/ tranquilizers		Carbapenems
Antiarrhythmics		Tigecycline
NSAIDS		Daptomycin
(Nonsteroidal)		Quinupristin/ dalfopristin
Antiinflammatory drugs)		Linezolid
Opiates		Nonantibiotics
		Digoxin
		Steroids
		Diphenhydramine
		Aspirin
		Vitamins

Drug Fever: Sensitizing Medications