Open Access

SCHOLARENA

Journal of Emergency Medical Care

RESEARCH ARTICLE

Approach to the Febrile Patient in the Emergency Setting: Is there anything New?

Karcıoglu O[1*], Topacoglu H[2] and Korkut S[3]

[1]*Professor, University of Health Sciences, Department of Emergency Medicine, Istanbul Education and Research Hospital, Istanbul, Turkey*

[2]*Professors, Duzce University, School of Medicine, Emergency Department, Duzce, Turkey*

[3]*Associate professor, University of Health Sciences, Department of Emergency Medicine, Kartal Dr. Lutfi Kirdar Education and Research Hospital, Istanbul, Turkey*

[*]**Corresponding author:** Karcioglu O, M.D. Professor, University of Health Sciences, Department of Emergency Medicine, Istanbul Education and Research Hospital, Istanbul, Turkey, Tel: +90.505.5252399, E-mail: okarcioglu@gmail.com

Citation: Karcıoglu O, Topacoglu H, Korkut S (2018) Approach to the Febrile Patient in the Emergency Setting: Is there anything New? J Emerg Med Care 1: 102

Abstract

This article reviews the clinical presentation, diagnosis, and treatment of fever following recent advances and new literature findings to update the primary care and emergency physician in the acute setting.

There is ongoing debate on the optimal management of fever in primary care and acute setting. General appearance, vital signs and important clinical findings, comorbid conditions and risk factors would compose an elaborate guide to decide unclarified processes including workup and antibiotic treatment. There is a growing bulk of knowledge supporting that fever is one of the bodily defense mechanisms and therefore should not be aggressively treated except for the patient in extremis and in special circumstances like seizures.

Diagnostic procedures include white blood cell count, lactate, CRP, procalcitonin and blood cultures, when appropriate. Administration of antipyretic agents, antibiotic therapy, seizure control and supportive therapy including fluid resuscitation titrated and individualized for each clinical scenario comprise the ideal treatment in the acute setting.

Keywords: Fever; İnfection; Sepsis; Diagnosis; Treatment; Emergency

Introduction

Fever (pyrexia) is the most common presentation of infection. There is a temperature reading above the normal range (36.5-37.5 °C) due to an increase in the body temperature regulatory set-point. Infectious and/or non-infectious conditions may cause fever as a response to pyrogenic substances forming due to specific triggers (Table 1). It is controlled by certain mechanisms in the hypothalamus. It is a complicated process affected by a myriad causes. In addition, one cannot say that every patients with infection has fever, nor every febrile individual is diagnosed with an infection.

Infectious	Non- Infectious
Sepsis	Seizures
Bacterial infections	Hyperthyroidism
-cellulitis	Neuroleptic malignant syndrome
-cholecystitis/cholangitis	Serotonin syndrome
-pneumonia	Heat stroke
-osteomyelitis	Sympathomimetic use
-urinary tract infections	Anticholinergic overdose
-abscesses	Malignant hyperthermia
-meningitis	Intracranial hemorrhage/hematoma
-otitis/sinusitis	Malignancies
-carditis	Autoimmune
Viral infections	Pulmonary embolism
Parasitic infections	Cerebrovascular accident,
Arthropod infections	thrombosis
Fungal infections	

Table 1: Infectious and/or Non-İnfectious Causes of Fever

There is a dearth of data on the most appropriate management of fever as a symptom. It is very interesting to note that there are only five clinical studies published within the last fifteen years investigating the optimal drug treatment of fever in adults [1-5].

Fever ensues as a reaction to exogeneous and endogenous pyrogens in the body. Superantigens spilled from Gram-positive bacteria, streptococci exemplifyexogeneous pyrogens. Cytokines and prostaglandins triggered by them take part in the inflammatory cascade, which raise the thermostatic point upwards in the hypothalamus. A similar process works in malignancies and some other diseases via cAMP.

Five percent of adult emergency department (ED) admissions and 15% of pediatric referrals are due to fever. Pulmonary embolism, intracranial hemorrhage/cerebrovascular accident, malignancy, autoimmune disorders, seizures, blood transfusion, thyroid diseases, Munchausen's syndromeand drugs are among causes of fever. Table 1 depicts infectious and/or non-infectious conditions triggering febrile episodes.

Findings on examination

Physical examination takes precedence in the management of the febrile patient, It starts with the vital signs and proceeds with head-to-toe manner. A thorough physical examination can reveal findings not only related to the cause of fever but also complications and consequences of the infective process and fever. Nuchal rigidity suggests meningoencephalitis, although moderately sensitive and specific. Newly emerged rashes can indicate specific infections, while rub or murmurs on auscultation of the heart are of special concern, suggestive of pericarditis and/or endocarditis. Acute cellulitis, including involvement of facial or periorbital soft tissues can be noticed only if examined and sought as necessary because it can be disguised. The physician should have broad knowledge on possible hidden sources of infection causing fever, such that intraabdominal abscesses, perirectal, perianal, perinephritic infection. Similarly, acute otitis, carbuncle and some visceral infections may cause fever and go undetected especially in patients with communication problems, mental retardation, cognitive impairments, etc.

Temperature is measured from axillaryand oral thermometers, although it can give falsly low readings, especially in the elderly. Oral measurements are used widespread, although less reliable than rectal readings. Authors of a meta-analysis including 75 studies reported that the sensitivity of oral temperature measurements with respect to core temperature only around 64% and specificity 96% [6]. This is why we don't need to be too suspicious about a low or high oral temperature reading. On the other hand, it would be better to have a central reading should the oral measurement is normothermic in a moribund patient [7].

Diagnostic tests

Total blood count, urinalysis, chest X-ray are some of the basic tests to order based on the clinical status and history of the patient. In addition, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and procalcitonin (PCT) are among the most widely studied markers to diagnose and prognosticate infections, although they have never reached the desired sensitivity and specificity.

As one of the hallmarks of infection, the discriminatory value of leukocytosis is inferior to those of others, such as CRP and PCT [8]. Although a leukocyte count above 12,000 per mm^3 is one of the criteria for sepsis, leukocytosis per se is a poor predictor of bacteremia and not an indication for obtaining blood cultures (BCs) [9,10]. In a patient with leukocytosis, fever, and system-specific symptoms, some authors recommend to obtain system-specific cultures and imaging (e.g., sputum cultures, chest radiography) emergently [11]. PCT levels increase in bacterial infections rather than viral. Use of antibiotics are shown to be more evidence-based and effective when guided by PCT levels, even if the mortality was unaffected [12].

Another "miraculous molecule", namely CRP starts to rise in 4 to 6 hours and doubles in every 8 hours. The levels reach their peak in 35 to 60 hours [13,14]. As a result, high CRP levels in a patient with fever lasting longer than 12 hours almost invariably indicate bacterial infection [15]. For example, CRP readings above 50 mg/L are 72%-98% sensitive and 66%-75% specific for a diagnosis of sepsis [16].

A well-designed meta-analysis including eight studies disclosed that PCT performs better than leukocyte count and CRP for detecting serious bacterial infection among children with fever without source [8]. The markers had different predictive powers to foresee serious bacterial infection: PCT (odds ratio [OR] 10.6; 95% confidence interval [CI] 6.9 to 16.0), CRP (OR 9.83; 95% CI 7.05 to 13.7), and leukocytosis (OR 4.26; 95% CI 3.22 to 5.63). In brief, the high negative predictive value of PCT for bacteremia renders it to be a safe exclusion marker for serious infective processes such as sepsis or pneumonia.

Srugo, *et al.* published on a novel tool to distinguish bacterial and viral infections in children at 5 pediatric emergency departments and 2 wards from children ≥3 months to ≤18 years [17]. They postulated that the assay was significantly more accurate than CRP, procalcitonin, and routine laboratory parameters. In a systematic review and meta-analysis to investigate the diagnostic accuracy of PCT for bacteraemia, Hoeboer et al. pointed out that PCT had a fair diagnostic accuracy for bacteraemia in adult patients suspected of infection or sepsis [18]. In particular low PCT levels can be used to rule out the presence of bacteraemia (<0.5 ng/mL).

Blood cultures (BC)

As the most sensitive tool to detect bacteremia, BCs are ordered in most patients with fever, chills, leukocytosis, focal infection, and/or sepsis. In fact, BCs should not be obtained in every febrile patient seen in the clinical practice. False-positive results of BC may cause unnecessarily lengthened stay in hospital, unjustified use of antibiotics, which result in boosting healthcare costs. Patients suspected to succumb to septic shock are good candidates for obtaining BC, especially if a change in the management is

contemplated. At least 7 ml of blood sample should be drawn from two different body sites to analyze in BC.

Immune supressed patients have a high risk to harbor a serious source of infection. BC is mostly obsolete in hemodynamically stablepatients suspected to have community-acquired pneumonia (CAP), simple cellulitis, urinary tract infections, etc. On the other hand, false-positive results of BC are as high as 8% in patients with CAP [19].

BCs are warranted in patients suspected to have sepsis, meningitis, complicated pyelonephritis, endocarditis and nosocomial pneumonia, while it is not justified in those with cellulitis (except for periorbital and facial) simple pyelonephritisand CAP [20] (Table 2). Many reports indicated that clinical status, general appearance play the pivotal role in decisionmaking for BCs. A study from United States cited that only 0.4% (n=12) out of 31% (BC ordered) of 2705 previously healthy children admitted with a diagnosis of CAP turned out to be positive [21]. None of those positive BCs led to an important change in the treatment strategy or mortality. Again, data from recent publications emphasize that they do not favor obtaining BCs in patients with CAP without comorbid diseases definitely [22].

	Blood Cultures Warranted	Blood Cultures Unnecessary
Conditions/Empyrical Diagnoses	Sepsis meningitis Complicated pyelonephritis endocarditis nosocomial pneumonia Facial/periorbital cellulitis	cellulitis (except facial) simple pyelonephritis and urinary tract infections Community-acquired pneumonia Upper respiratory tract infections Simple wound infections

Table 2: Conditions that Necessitate and do not Necessitate Blood Cultures

Independent risk factors for true bacteremia in patients with pneumonia are a history of chronic liver failure, CURB-65 (Confusion, Urea, Respiratory Rate, Blood Pressure, Age) score of 4 or 5, and PneumoniaSeverity Index (PSI) Class V.

Does fever need to be treated?

There are reports that treatment of fever with paracetamol did not improve outcome in ICU patients and shorten length of stay [23]. In addition, fever is postulated to augment the efficacy of antibiotics and inhibits bacterial proliferation. Early steep rise in the temperature is shown to be associated with lowered mortality in some studies [24,25].

Basically, treatment of fever encompasses physical measures including light dressing, tepid sponging and fanning. Fluid requirements are boosted in case of protracted fever and thus rehydration is a major part of the management. The modes of treatment of the febrile patient is summarized and explained in Table 3.

Treatment	Explanatory notes
Tepid sponging, wetting	The efficiency increases with the body surface area wetted. Repeat wetting can be necessary to augment effect. Warm showers will boost reduction in the temperature.
Fanning	The effect resembles wetting, albeit milder.
Hydration	The fluid losses (both insensible and those resulted from poor intake) should be replaced. Overhydration is not proved beneficial.
Drug treatment	Ideally, should be considered after the abovementioned treatments have been proved ineffective.
-Paracetamol	1 gr paracetamol can be infused to alleviate fever acutely, though the daily dose is 2 gr for adults (around 1-1.5 gr in school-age children). Beware of using in neonates till 3 months old.
-Other non-steroidal anti-inflammatory drugs (NSAID)	Ibuprofen is one of the most commonly used NSAID, and sometimes in association with paracetamol. Do not exceed 1.2 gr. These group of drugs may increase risk of serious cardiovascular thrombotic events, Diclofenac has comparable antipyretic efficacy with other NSAIDS in rectal, inramuscular or oral use (1 mg/kg by rectal)[36].

Table 3: The arsenal of treatment of the febrile patient in the acute setting

Very recent research pointed out that 1 gr paracetamol infusion can acutely and effectively alleviate fever. Febrile symptoms were recovered in 38.5% of those treated with placebo and 80% of those receiving, paracetamol in the first 6 hours [5]. Paracetamol normalizes fever in around 3 hours. The compound crosses the blood-brain barrier and thus combines analgesic and antipyretic effect via central mechanisms [26]. Treatment with paracetamol in its usual dosesis almost free of risks, except for allergy, patients with liver failure and measures to be taken against Reye's syndrome.

Other non-steroidal anti-inflammatory drugs (NSAIDs), e.g., ibuprofen, are also used extensively to treat fever in both children and adults worldwide. Administration of ibuprofen has been found superior to paracetamol, and is as efficacious as the ibuprofen-paracetamol combination [27].

How to justify use of antibiotics in the febrile patient?

Unjustified prescription and use of antibiotics is a world-wide plague which is debated extensively, not only by medical professionals but also the patients. Subheadings of the huge problem include the cost, resistance due to unnecessary use, and side effects.

The decision making process for use of antibiotics in the ED is usually an empyrical one. A recent Cochrane review reported that handing patient a prescription in case of upper respiratory infections while telling him/her to delay starting the treatment (Delayed antibiotic prescriptions) is a reasonable way for the management, which also augments patient satisfaction [28].

A detailed physical examination and history would guide a decision to immediate commencement of antibiotics or withholding them. In this context, pre-test probability is of utmost importance for this process. Of note, a history of chemotherapy, use of corticosteroids and other drugs that may interfere with the immune system, diabetes, pulmonary diseases would serve valuable guides in the decision. Although many physicians order tests such as total blood count, urinalysis and chest x-ray "automatically" for every febrile patient, cost-effectiveness and usefulness of the tests with high pre-test probability are much better. Furthermore, serological tests for viral antigens, urine and blood cultures can be of help in selected cases.

Circumstances in which expedient administration of antibiotics can be life-saving include septicshock, acute bacterial meningitis, certain infections in the immune supressed hosts, endocarditis and febrile neutropenia. For instance, antibiotics should be injected without waiting for the results of lumbar puncture or computed tomographyin patients suspected to have meningitis [29]. Sepsis originating from unidentified source is one of the most common serious conditions in the ED. These patients may be administered Piperacillin/tazobactam 4.5 gr IV±Vancomycin (should there be substantial risk for methicillin-resistant Staphylococcus aureus-MRSA) ± Gentamycin after necesary cultures are obtained. MRSA risk is considered to be significant in patients with indwelling catheters and other instrumentation, staying in hospital longer than two weeks in the last three months, in those under institutional care, IV drug use etc.

Treatments other than antibiotics

In case of anaerobic infections (suspected with smell and appearance of the wound or site)surgical debridement is of utmost importance to get rid of the devitalized tissue.

Treatment with corticosteroids in patients with sepsis and/or septic shock are advocated more commonly in the recent years. A new study demonstrated that children with septic shock recovered more quickly following an early-phase use of corticosteroids [30].

Fever in sepsis

Absence of fever in patients with acute bacterial meningitis and/or sepsis is associated with increased mortality, which is a reflection of the protective role of fever forthe organism in infections [31,32]. SIRS criteria encompass both hyperthermia and hypothermia as suggestive of sepsis, although in some septic patients neither do exist. Literature data pointed out that one fourth of the elderly with sepsis have blunted febrile response to sepsis [33].

Reports indicated that lack of fever and low bicarbonate levels are independent predictors of deterioration in the 48 hours after admission in the ED. On the other hand, q-SOFA scoring system is thought to have disregarded the presence of fever. Although the scale was devised to use in the emergency setting, it should be known that it predicts mortality but does not diagnose sepsis.

Fever in non-infectious conditions

Hyperthermia differ from fever in many aspects.The pathophysiology of hyperthermia does not involve a response to the pyrogens and therefore, there will be no improvement with antipyretic agents.

Around one-sixth of the patients with pulmonary embolism and fever, investigations did not reveal any proven cause of febrile response other than the main diagnosis [34]. Chest tomography and CT-angiogram can be ordered in a patient with fever if pulmonary embolism and sepsis are hard to discern, since chest x-ray would not be dagnostic in most cases.

Chow *et al.* conducted a systematic review on children with fever and cited that about half of patients with "fever of unknown origin" (FUO) in published case series are ultimately shown to be due to infections with collagen vascular disease and malignancy also being common diagnoses [35].

Conclusion

There is ongoing debate on the optimal management of fever in primary care and acute setting. General appearance, vital sgns and important clinical findings, comorbid conditions and risk factors would compose an elaborate guide to decide unclarified processes including workup and antibiotic treatment. Needless to say, the decision would be an extremely individualized one. There is a growing bulk of knowledge advocating that fever is one of the bodily defense mechanisms and therefore should not be

aggressively treated except for the patient in extremis and in special circumstances like seizures. Thus no recipés are good for all situations in the context of fever.

References

1. Morris PE, Promes JT, Guntupalli KK, Wright PE, Arons MM (2010) A multi-center, randomized, double-blind, parallel, placebo controlled trial to evaluate the efficacy, safety, and pharmacokinetics of intravenous ibuprofen for the treatment of fever in critically ill and non-critically ill adults. Crit Care 14: R125.

2. Azuma A, Kudoh S, Nakashima M, Nagatake T (2011) Antipyretic and analgesic effects of zaltoprofen for the treatment of acute upper respiratory tract infection: verification of a noninferiority hypothesis using loxoprofen sodium. Pharmacology 87: 204-13.

3. Bachert C, Chuchalin AG, Eisebitt R, Netayzhenko VZ, Voelker M (2005) Aspirin compared with acetaminophen in the treatment of fever and other symptoms of upper respiratory tract infection in adults: a multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group, single-dose, 6-hour doseranging study. Clin Ther 27: 993-1003.

4. Krudsood S, Tangpukdee N, Wilairatana P, Pothipak N, Duangdee C, et al. (2010) Intravenous ibuprofen (IV-ibuprofen) controls fever effectively in adults with acute uncomplicated Plasmodium falciparum malaria but prolongs parasitemia. Am J Trop Med Hyg 83: 51-5.

5. Tsaganos T, Tseti IK, Tziolos N, Soumelas GS, Koupetori M, et al. (2017) Randomized, controlled, multicentre clinical trial of the antipyretic effect of intravenous paracetamol in patients admitted to hospital with infection. Br J Clin Pharmacol 83: 742-50.

6. Niven DJ, Gaudet JE, Laupland KB, Mrklas KJ, Roberts DJ, et al. (2015) Accuracy of peripheral thermometers for estimating temperature: a systematic review and meta-analysis. Ann Intern Med 163: 768-77.

7. DeWitt S, Chavez SA, Perkins J, Long B, Koyfman A (2017) Evaluation of fever in the emergency department. Am J Emerg Med 35: 1755-8.

8. Yo CH, Hsieh PS, Lee SH, Wu JY, Chang SS, et al. (2012) Comparison of the test characteristics of procalcitonin to C-reactive protein and leukocytosis for the detection of serious bacterial infections in children presenting with fever without source: a systematic review and meta-analysis. Ann Emerg Med 60: 591-600.

9. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, et al. (2013) Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 41: 580-637.

10. Coburn B, Morris AM, Tomlinson G, Detsky AS (2012) Does this adult patient with suspected bacteremia require blood cultures? JAMA 308: 502-11.

11. Riley LK, Rupert J (2015) Evaluation of Patients with Leukocytosis. Am Fam Physician 92: 1004-11.

12. Schuetz P, Muller B, Christ-Cran M, Stolz D, et al. (2012) Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. Cochrane Dafigase Syst Rev 10: CD007498.

13. Pepys MB, Hirschfeld GM (2003) C-reactive protein: a critical update. J Clin Invest 111: 1805-12.

14. Povoa P, Salluh JI (2012) Biomarker-guided antibiotic therapy in adult critically ill patients:a critical review. Ann Intensive Care 2: 32.

15. Lee CC, Hong MY, Lee NY, Chen PL, Chang CM, et al. (2012) Pitfalls in using serum C-reactive protein to predict bacteremia in febrile adults in the ED. Am J Emerg Med 30: 562-9.

16. Povoa P (2002) C-reactive protein: a valuable marker of sepsis. Intensive Care Med 28: 235-43.

17. Srugo I, Klein A, Stein M, Golan-Shany O, Kerem N, et al. (2017) Validation of a Novel Assay to Distinguish Bacterial and Viral Infections.Pediatrics 140.

18. Hoeboer SH, van der Geest PJ, Nieboer D, Groeneveld AB (2015) The diagnostic accuracy of procalcitonin for bacteraemia: a systematic review and meta-analysis. Clin Microbiol Infect 21: 474-81.

19. Benenson RS, Kepner AM, Pyle 2nd DN, Cavanaugh S (2007) Selective use of blood cultures in emergency department pneumonia patients. J Emerg Med 33: 1-8.

20. Long B, Koyfman A (2016) Best Clinical Practice: Blood Culture Utility in the Emergency Department. J Emerg Med 51: 529-39.

21. Kwon JH, Kim JH, Lee JY, Kim YJ, Sohn CH, et al. (2017) Low utility of blood culture in pediatric community-acquired pneumonia: An observational study on 2705 patients admitted to the emergency department. Medicine (Baltimore) 96.

22. Neuman MI, Hall M, Lipsett SC, Hersh AL, Williams DJ, et al. (2017) Pediatric Research in Inpatient Settings Network. Utility of Blood Culture Among Children Hospitalized With Community-Acquired Pneumonia. Pediatrics 140.

23. Young P, Saxena M, Bellomo R (2015) Acetaminophen for fever in critically ill patients with suspected infection. N Engl J Med 373: 2215-24.

24. Saxena M, Young P, Pilcher D, Bailey M, Harrison D, et al. (2015) Early temperature and mortality in critically ill patients with acute neurological diseases: trauma and stroke differ from infection. Intensive Care Med 41: 823-32.

25. Young PJ, Saxena M, Beasley R, Bellomo R, Bailey M, et al. (2012) Early peak temperature and mortality in critically ill patients with or without infection. Intensive Care Med 38: 437-44

26. Koh W, Nguyen KP, Jahr JS (2015) Intravenous non-opioid analgesia for peri- and postoperative pain management: a scientific review of intravenous acetaminophen and ibuprofen. Korean J Anesthesiol 68: 3-12.

27. Vyas FI, Rana DA, Patel PM, Patel VJ, Bhavsar RH (2014) Randomized comparative trial of efficacy of paracetamol,ibuprofen and paracetamol-ibuprofen combination for treatment of febrile children.Perspect Clin Res 5: 25-31.

28. Spurling GK, Del Mar CB, Dooley L, Foxlee R, Farley R (2017) Delayed antibiotic prescriptions for respiratory infections. Cochrane Database Syst Rev 9.

29. The Johns Hopkins Hospital. Antibiotic Guidelines 2015-2016. Copyright 2015 by The Johns Hopkins Hospital Antimicrobial Stewardship Program.

30. El-Nawawy A, Khater D, Omar H, Wali Y (2017) Evaluation of Early Corticosteroid Therapy in Management of Pediatric Septic Shock in Pediatric Intensive Care Patients. Pediatr Infect Dis J 36: 155-9.

31. Hernández C, Fehér C, Soriano A, Marco F, Almela M, et al. (2015) Clinical characteristics and outcome ofelderly patients with community-onset bacteremia. J Infect 70: 135-43.

32. Fernandes D, Gonçalves-Pereira J, Janeiro S, Silvestre J, Bento L, et al. (2014) Acute bacterial meningitis in the intensive care unit and risk factors for adverse clinical outcomes: retrospective study. J Crit Care 29: 347-50.

33. Wester AL, Dunlop O, Melby KK, Dahle UR, Wyller TB (2013) Age-related differences in symptoms, diagnosis and prognosis of bacteremia. BMC Infect Dis 13: 346.

34. Stein PD, Afzal A, Henry JW, Villareal CG (2000) Fever in acute pulmonary embolism. Chest 117: 39-42.

35. Chow A, Robinson JL (2011) Fever of unknown origin in children: a systematic review. World J Pediatr 7: 5-10.

36. Sharif MR, Rezaei MH, Aalinezhad M, Sarami G, Rangraz M (2016) Rectal Diclofenac Versus Rectal Paracetamol: Comparison of Antipyretic Effectiveness in Children. Iran Red Crescent Med J 18.