CHAPTER

28

Febrile Emergencies

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Introduction

Febrile emergencies pose a significant burden in adult as well as pediatric population presenting to the emergency departments. A physician should be well equipped to handle febrile emergencies with promptness, as the patient may deteriorate rapidly unless a quick diagnosis is followed by early treatment. Early treatment may be based on provisional diagnosis, usually dictated by locally prevalent diseases occurring in sporadic as well as epidemic patterns. Uncommon causes in occasional patient should not be overlooked, and a careful search for possible etiology should be accomplished in the emergency department. This may require routine investigations, rapid screening tests, including the bedside ones for infective etiologies, as well as special tests in susceptible cases e.g. toxic screen for suspected neuroleptic malignant syndrome. Febrile emergencies in specific population categories viz. pregnant patients, immunocompromised patients, the elderlys pose a special challenge. The outcome and mortality in febrile emergencies depends on the prompt intervention and treatment in the emergency department in the first 24 hours after presentation.

Definition

Fever is an elevation of body temperature that exceeds the normal daily variation and occurs in conjunction with an increase in the hypothalamic set point.[1] A fever of > 41.5° C (> 106.7° F) is called hyperpyrexia. This extraordinarily high fever can develop in patients with severe infections but most commonly occurs in patients with central nervous system (CNS) hemorrhages. If one considers physiologic basis, in some rare cases, the hypothalamic set point is elevated as a result of local trauma, hemorrhage, tumor, or intrinsic hypothalamic malfunction. It is important to distinguish clinically between fever and hyperthermia since hyperthermia can be rapidly fatal and characteristically does not respond to antipyretics. Hyperthermia is characterized by an unchanged (normothermic) setting of the thermoregulatory center in conjunction with an uncontrolled increase in body temperature that exceeds the body's ability to lose heat. Exogenous heat exposure and endogenous heat production are the two vital mechanisms by which hyperthermia can result in dangerously high internal temperatures.

Grades of fever

- Normal : 36.6° – 37.2° C 98°– 99° F
- Febrile : 37.2° – 41.5° C 99° – 106.7° F
- Hyperpyrexia : > 41.5° C > 106.7° F

Symptoms suggestive of febrile emergencies: These include

- Temperature ≥ 104° F.
- Fever of more than 7 days' duration.
- Worsening of symptoms associated with fever.
- Altered behavior, stiff neck, severe headache, focal neurologic deficit, seizures, photophobia, coma.
- Rash, arthralgia, polyarthritis.
- Chest pain, syncope, dependent edema, orthopnea, cold extremities.
- Breathlessness, wheezing, hemoptysis, cyanosis.
- Severe abdominal pain, repeated vomiting, hematemesis, melena, profuse diarrhea, distension of abdomen.
- Dysuria, oliguria, hematuria, pyuria, facial puffiness, anasarca.
- Bleeding from orifices, skin, mucus membrane, petechiae, rash.
- Deep jaundice, altered sleep, altered mentation.
- Drug ingestion (neuroleptics).
- Environmental exposure (hot climate).
- Known underlying severe disease involving heart, kidneys, lungs, liver or severe systemic disease (sarcoidosis, lupus, malnutrition, diabetes, alcohol or drug abuse).
- Immunocompromised patients with underlying cancer or HIV/AIDS.
- Pregnant females.
- Older people > 75 years old.

Integrated Management of Illnesses in Adults (IMIA)

This concept is proposed as an extrapolation of successful implementation of Integrated Management of Neonatal and Childhood Illnesses (IMNCI) programme, to adults. Fragile physiology akin to infants and children may also be present in adults subgroups viz. alcoholics, immunocompromised status, poor nutrition and poor access to health care. Unattended infections in high risk adults can alter the internal milieu negatively and predispose them to rapidly worsening febrile emergencies. The purpose of IMIA concept is to prioritize recognition and management of serious and critical syndromes rather than specific diagnoses, e.g. treating respiratory failure in febrile Adult Respiratory Distress Syndrome (ARDS) and replacing platelets in febrile thrombocytopenias rather than establishing diagnoses of leptospirosis or dengue fever.

Major categories of febrile emergencies

i. Infections and sepsis.

ii. Oncologic emergencies- febrile neutropenic patients.

iii. Fever in immuno-compromised host.

iv. Fever in elderly.

(Together, the above four conditions comprise majority of the febrile emergencies in routine practice, depending on regional disease profile and settings.)

v. Endocrine-thyroid storm, pheochromocytoma.

vi. Environmental - heat syndromes.

vii. Drug toxicity and poisoning– Neuroleptic malignant syndrome, amphetamine, cocaine, strychnine.

viii. CNS pathology- pontine pathology, cerebral hemorrhage, status epilepticus, hypothalamic injury.

Infections and sepsis

Infections remain the most common cause of fever related emergencies. A comprehensive list of conditions associated with febrile emergencies[2] is given in Table 1.

Sepsis syndrome

Sepsis is caused by the systemic response to a severe infection. When sepsis is associated with dysfunction of organs distant from the site of infection, the patient has severe sepsis. Severe sepsis may be accompanied

Table I : Common infection related febrile emergencies

Clinical Syndrome	Possible Etiologies	Treatment
Bacterial Infections		
Gram-negative sepsis	Pseudomonas spp., gram-negative enteric bacilli	Piperacillin/tazobactam (3.75 gm, 4 hourly) or Ceftazidime (2 gm, 8 hourly)
Gram-positive sepsis	Staphylococcus spp., Streptococcus spp.	Vancomycin (1 gm, 12 hourly) + Gentamicin (5 mg/kg per day)
Post-splenectomy sepsis	Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis	Ceftriaxone (2 gm, 12 hourly)
Meningococcemia	N. meningitidis	Penicillin G (4 million Units 4 hourly) or Ceftriaxone (2 gm 12 hourly)
Purpura fulminans	S. pneumoniae, H. influenzae, N. meningitidis	Ceftriaxone (2 gm 12 hourly)
Erythroderma: toxic shock syndrome	Group A Streptococcus, Staphylococcus aureus	Penicillin G (2 million Units 4 hourly) or Vancomycin (1 gm 12 hourly) + Clindamycin (600 mg 8 hourly)
Necrotizing fasciitis	Group A Streptococcus, mixed aerobic/anaerobic flora	Penicillin G (2 million Units 4 hourly) + Clindamycin (600 mg 8 hourly) + Gentamicin (5 mg/kg per day)
Clostridial myonecrosis	Clostridium perfringens	Penicillin G (2 million Units 4 hourly) + Clindamycin (600 mg 8 hourly)
Tetanus	Clostridium tetani	Tetanus immune globulin 5000 units IM Metronidazole 1 gm 12 hourly
Bacterial meningitis	S. pneumoniae, N. meningitidis	Ceftriaxone (2 gm 12 hourly)
Suppurative intracranial infections	Staphylococcus spp., Streptococcus spp., anaerobes, gram-negative bacilli	Vancomycin (1 gm 12 hourly) + Metronidazole (500 mg 8 hrly) + Ceftriaxone (2 gm 12 hourly)
Brain abscess	Streptococcus spp., anaerobes, Staphylococcus spp.	Penicillin G (4 million Units 4 hourly) or Vancomycin (1 gm 12 hourly) + Metronidazole (500 mg 8 hourly)
Acute bacterial endocarditis	S. aureus, β-hemolytic streptococci, HACEK group (Haemophilus aphrophilus, H. paraphrophilus, H. parainfluenzae, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae); Neisseria spp., S. pneumoniae	Ceftriaxone (2 gm 12 hourly) + Vancomycin (1 gm 12 hourly)
Bacterial Pneumonia	*Streptococcus pneumoniae, Haemophilus influenzae*; *Klebsiella*, *Staphylococcus aureus*, *Legionella pneumophila*, *Escherichia coli* and *Pseudomonas*, *Enterobacter*, and *Serratia* species.	Penicillin G (2 million Units 4 hourly), or Azithromycin 500 mg OD, or Levofloxacin 750 mg OD, or Amoxicillin and clavulanate 1.2 gm BID, or Vancomycin 1 gm BID, or Ceftriaxone 1-2 gm BID, or Linezolid 400-600 mg BID. Combinations: A macrolide plus a third-generation cephalosporin, (as single agents) amoxicillin and sulbactam, piperacillin and tazobactam, or ticarcillin and clavulanate.

Clinical Syndrome	Possible Etiologies	Treatment
Aspiration Pneumonia	*Pseudomonas aeruginosa, Moraxella catarrhalis*, *Bacteroides*, *Peptostreptococcus*, *Fusobacterium* species.	Ceftriaxone 1-2 gm BID, or Amoxicillin and clavulanate 1.2 gm BID, or Piperacillin and tazobactam 3.375 g (piperacillin 3 g and tazobactam 0.375 g) TID, or Imipenem and cilastatin 1 gm BID, or Amikacin 5 mg/kg/day, or Vancomycin 1gm BID as single drugs or in combination.
PCP pneumonia	*Pneumocystis carinii*	Trimethoprim-sulfamethoxazole 2 double-strength tab TID, or Pentamidine 4 mg/kg/day, or Atovaquone 750 mg BID, or Clindamycin 600-900 mg TID + Primaquine 15 mg OD, or Dapsone 100 mg OD + trimethoprim 5 mg/kg TID.
Viral Infections		
Viral Pneumonia	Influenza virus types A and B, respiratory syncytial virus (RSV), adenovirus, parainfluenza virus 1,2,& 3, rhinovirus, Hantavirus, cytomegalovirus (CMV), paramyxovirus species (measles), varicella-zoster virus, Epstein-Barr virus, CMV, herpes simplex virus, avian influenza virus A/H5N1 (SARS)	Acyclovir 10 mg/kg 8 hourly; Ganciclovir 2.5 mg/kg 8 hourly; Oseltamivir 75 mg BID.
Viral Encephalitis	Herpes simplex virus (herpesvirus), Japanese B encephalitis (flavivirus),	Acyclovir 10 mg/kg 8 hourly Foscarnet 40 mg/kg/dose IV TID for 14-21 days, followed by maintenance dose of 90-120 mg/kg/d Ganciclovir 5 mg/kg IV BID for 14 days followed by maintenance dose of 5 mg/kg IV OD.
Rabies	Rhabdovirus	No specific treatment
Dengue fever	Flavivirus	No specific treatment
Fungal Infections		
Fungal Pneumonia	*Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatitidis, Cryptococcus neoformans, Paracoccidioides brasiliensis, Candida* species, *Aspergillus* species, *Mucor* species	Amphotericin B 0.25-1.5 mg/kg/d IV; not to exceed 1.5 mg/kg/d; Amphotericin B, liposomal 3-5 mg/kg/day; Amphotericin B lipid complex 5 mg/kg/day; Caspofungin 70 mg IV over 1 h on day 1; then 50 mg IV OD; Anidulafungin 200 mg IV on day 1; then 100 mg/d IV; Fluconazole 400 mg OD; Itraconazole 200-400 mg/ day.
Rhinocerebral mucormycosis	*Fungus of the group* Mucorales: *Rhizopus, Rhizomucor, Cunninghamella, Apophysomyces, Saksenaea, Absidia, Mucor, Syncephalastrum, Cokeromyces, Mortierella*	Amphotericin B 1-1.5 mg/kg IV OD; Liposomal Amphotericin B 5 mg/kg/day; Amphotericin B lipid complex 5 mg/kg/day; Posaconazole 200 mg TID.
Parasitic Infections		
Malaria	*Plasmodium falciparum,* *Plasmodium vivax*	Artemesinin based combination therapy [3]

by hypotension or evidence of hypoperfusion. When hypotension cannot be corrected by infusing fluids, the diagnosis is *septic shock*. The incidence of severe sepsis and septic shock has increased over the past 20 years; this is attributable to various factors including aging population; increasing longevity of patients with chronic diseases; increase in incidence of HIV / AIDS, widespread use of antimicrobial agents, glucocorticoids, indwelling catheters and mechanical devices, and mechanical ventilation. Infections of the lung, abdomen, or urinary tract are most common, and approximately half of the patients have bacteremia. Gram-positive and -negative bacteria, viruses, fungi, rickettsiae, and protozoa have all been reported to produce the clinical picture of septic shock, and the overall response is generally independent of the specific type of invading organism. Hemodynamic changes in septic shock occur in two characteristic patterns: early, or hyperdynamic, and late, or hypodynamic, septic shock. The toxicity of the infectious agents and their byproducts and the subsequent metabolic dysfunction drive the progressive deterioration of cellular and organ function. ARDS, thrombocytopenia, and neutropenia are common complications. Treatment comprises liberal volume expansion with a crystalloid solution to a PCWP of 15 mmHg and the restoration of arterial oxygenation with inspired oxygen and frequently with mechanical ventilation are the highest priorities. In the presence of sepsis, augmentation of cardiac output may require inotropic support with dopamine, norepinephrine, or vasopressin in the presence of hypotension or with dobutamine if arterial pressure is normal. Antimicrobial chemotherapy should be initiated as soon as samples of blood and other relevant sites have been cultured. Maximal recommended doses of antimicrobial drugs should be given intravenously, with adjustment for impaired renal function when necessary. High-dose activated protein C (aPC) provides a survival benefit in patients with severe sepsis and septic shock. aPC is approved in adults with APACHE II score ≥ 25 and a low risk of hemorrhage-related side effects. It is administered as a constant intravenous infusion of 24 μg/kg/ hour for 96 h. Other agents for sepsis under clinical trials include vasopressin, monoclonal antibodies to endotoxin, bactericidal permeability-increasing (BPI) protein, nontoxic lipid A analogs, PAF antagonists, recombinant IL-1Ra, genetically engineered soluble receptors for TNF-α, and monoclonal antibodies to TNF-α.[1] Surgical debridement or drainage may also be necessary to control the infection.

Febrile neutropenia

Fever in a neutropenic patient should be considered a medical emergency. Febrile neutropenia is one of the most common complications related to cancer treatment, particularly chemotherapy. The condition contributes to 50 per cent of deaths associated with leukemia, lymphomas, and solid tumors. Bacterial infections are common in patients with febrile neutropenia, but fungal sources are increasingly prevalent. Symptoms include a temperature of 101° F (38.3° C) or more and an absolute neutrophil count (ANC) less than 500 per mm^3 (0.5×10^9 per L). Patients with cancer presenting with fever soon after chemotherapy should receive inpatient treatment with empiric antibiotics until the ANC is more than 500 per mm^3 for 72 hours. Generally, multi-drug regimens are used when gram-positive and gram negative organisms are suspected. Empiric vancomycin therapy is added in hospitals where methicillin-resistant, gram-positive organisms are common or if specific clinical findings are present. Antifungals e.g. amphotericin B, are recommended if there is no improvement within the first three days of treatment. Routine use of antivirals, granulocyte transfusions, and colony-stimulating factors is not recommended.

Fever in immunocompromised host

Causes of a weakened immune system include cancer, cancer treatment medication, organ transplant medication, prolonged steroid therapy, HIV/ AIDS, age older than 65, asplenic status, sarcoidosis, lupus, malnutrition, diabetes, heavy alcohol or drug use. Fever due to focal or systemic infections is treated in the same way as in patients with febrile neutropenia.

Febrile emergencies in elderly

Febrile emergencies result in significant morbidity and mortality in older adults. Pneumonia and influenza, diabetes mellitus with its infectious sequelae, and complications from bacteremia, represent leading causes of death in the elderly. Underlying illnesses, such as diabetes, cerebrovascular accidents (CVA), and malignancies, and altered immune function with aging, compounded by factors like malnutrition, alcoholism, immobility, institutionalization, and urinary incontinence, further enhance this risk for severe infections. Classic clinical evidence of serious infections may be masked by co-morbid conditions; delay in diagnosis and treatment may unfortunately result as a consequence.

Pneumonia in the elderly can cause serious and life-threatening illness. Debilitating conditions, such as cigarette smoking, chronic obstructive pulmonary disease, congestive heart failure, CVA, dementia, and higher bacteremic complications, such as empyema, contribute to poor outcome in this age group. Streptococcus pneumoniae is the most common cause of community-acquired and nursing home-acquired pneumonia in the elderly, but in 35 to 58% of cases, no pathogen is identified. The incidence of Staphylococcus aureus pneumonia in the elderly increases 10 to 20 times during influenza epidemics. Klebsiella pneumoniae is the most common gram-negative bacterial agent associated with pneumonia acquired in nursing homes. Among other common bacterial pathogens associated with severe pneumonia in the elderly, non-typable Hemophilus influenzae, Escherichia coli, Acinetobacter species, Moraxella catarrhalis, Legionella species, and Pseudomonas species have been implicated. Hospitalization for treatment of pneumonia in the elderly is recommended, because associated factors, including respiratory compromise, dehydration, delirium, electrolyte abnormalities, bacteremic complications (empyema, meningitis, and endocarditis), and septic shock may be present.

Urinary tract infection (UTI) is the most common bacterial infection in the elderly. In men, the incidence of UTI increases dramatically with age, from 2 - 4% for those 65 to 70 years of age, to more than 22% for those over the age of 81. The reason for this increase includes decreased prostatic secretions and impaired bladder emptying from outlet obstruction. The increased incidence in elderly women is a consequence of ineffective micturition, previous instrumentation, or underlying disease. The most frequent complication of UTI in the elderly is bacteremia, 26% of which develop into generalized sepsis. UTI can lead to sepsis in approximately 22% of older women with pyelonephritis. Common bacterial pathogens implicated in such cases include Proteus mirabilis, K. pneumoniae, Pseudomonas, enterococcus, and coagulase-negative staphylococci. Empiric therapy initiated in such patients should thus be directed toward these organisms. Trimethoprim-sulfamethoxazole is a good and inexpensive initial choice. In severe systemic infections, ceftazidime or other third-generation cephalosporins and an aminoglycoside or quinolone can be started.

Meningitis in the elderly remains a formidable disease with mortality rates ranging from 40 to 80%. Meningitis can be caused by a variety of organisms, including bacteria, viruses, and fungi, or mycobacteria. The classic features of fever, headache, and neck stiffness may be absent, and confusion, coma, anorexia, nausea, or vomiting may be the only presenting symptom. Common etiologic agents for elderly include S. Pneumoniae, H.Influenzae, E. coli, K. pneumoniae, P. aeruginosa, Proteus, and Enterobacter, Listeria monocytogenes. The empiric antibiotic regimen for acute bacterial meningitis in the elderly should include bactericidal agents, that is a third-generation cephalosporin (to cover S. pneumoniae, H. influenzae, and other rare gram-negative bacteria) and ampicillin (for Listeria) pending results of the definitive bacteriologic etiology. When high-level S. pneumoniae resistance to penicillin is suspected, vancomycin should be included in the initial empiric regimen.

Sepsis and septic shock cause death in a significant number of elderly persons. Elderly persons presenting with altered mental status

hypothermia or hyperthermia, dyspnea, oliguria, thrombocytopenia, and DIC should arouse clinical suspicion for sepsis and septic shock. Sepsis and its sequelae are generally caused by bacteremic infections; with aging, pneumonia, UTIs, cellulitis, and gastrointestinal pathological conditions are frequently implicated. Septic shock is most often associated with gram-negative bacteremic infections, including Klebsiella, E. coli, and Serratia. Shock can also be secondary to gram-positive infections or associated with toxemia from localized infections, for example, toxic shock syndrome. Septic shock is an increasingly common infectious disease emergency in the elderly. Extended-spectrum antibiotic combination agents that provide adequate gram-negative coverage are often required.

Thyroid storm

The clinical syndrome of thyroid storm is characterized by fever, central nervous system changes (agitation, delirium, or a deteriorating mental status), and cardiovascular dysfunction (disproportionate tachycardia or tachyarrhythmia with or without congestive cardiac failure), and symptoms of marked hyper-metabolism.[4] Therapy is directed at supportive care, dehydration, hyperthermia, and treatment of the precipitating event.[5] Drugs to reduce fever (antipyretics) are indicated, but aspirin should be avoided, as it is known to increase thyroid hormone levels. Anti-thyroid medication blocks the synthesis of new hormone, and inorganic iodine solution (Lugol's solution) blocks the release of pre-formed hormone. Lugol's iodine is given after oral antithyroid drugs to avoid exacerbation of hyperthyroidism. Betablockers control the systemic effects of thyroid hormone excess. Ultra short-acting beta-blockers like esmolol have been used with success. A 'relative' steroid deficiency occurs and steroid administration is always recommended which also decreases the peripheral conversion of T4 to T3. Peritoneal dialysis and plasmapheresis are used to reduce the high level of circulating T4 and T3 in a thyroid storm. Cholestyramine is also used to bind T4 and T3 within the gastrointestinal tract.

Pheochromocytoma

Pheochromocytoma produce, store, and secrete catecholamines. Fever has been reported in association with the production of interleukin-6. Elevated temperature more commonly reflects catecholamine-mediated increases in metabolic rate and diminished heat dissipation secondary to vasoconstriction. The associated hypertension may be sustained or episodic and often severe. The paroxysms or cries associated with pheochromocytoma usually have a sudden onset and may last from a few minutes to several hours or longer. Headache, profuse sweating, palpitations, and apprehension, often with a sense of impending doom, are common. Pain in the chest or abdomen may be associated with nausea and vomiting. Either pallor or flushing may occur during the attack. The blood pressure is elevated, often to alarming levels, and the elevation is usually accompanied by tachycardia. Such paroxysms may be treated with oral prazosin, intravenous phentolamine or nitroprusside. The long term treatment comprises α-blockers (phenoxybenzamine), followed by addition of a β-blocker, if required.

Heat stroke

Heatstroke is common in tropical climates. It is the most severe form of the heat-related illnesses and is defined as a body temperature higher than 41.1° C (106° F) associated with anhydrosis and neurologic dysfunction. Two forms of heatstroke exist. Exertional heatstroke (EHS) generally occurs in young individuals who engage in strenuous physical activity for a prolonged period of time in a hot environment. EHS is characterized by hyperthermia, diaphoresis, and an altered sensorium, which may manifest suddenly during extreme physical exertion in a hot environment.[6] Non-exertional heatstroke (NEHS) more commonly affects sedentary elderly individuals, persons who are chronically ill, and very young persons. Classic NEHS occurs during environmental heat waves and is more common in areas that have not experienced a heat wave in many years. Classic NEHS is characterized by hyperthermia, anhidrosis, and an altered sensorium, which develop suddenly after a period of prolonged elevations in ambient temperatures (heat waves).

Core body temperatures greater than 41° C are diagnostic, although heatstroke may occur with lower core body temperatures. CNS symptoms, ranging from minor irritability to delusions, irrational behavior, hallucinations, and coma have been described.

Morbidity and mortality from heatstroke are related to the duration of the temperature elevation. When therapy is delayed, the mortality rate may be as high as 80%; however, with early diagnosis and immediate cooling, the mortality rate can be reduced to 10%. Mortality is highest among the elderly population, patients with preexisting disease, those confined to a bed, and those who are socially isolated.

Rapid reduction of the core body temperature is the cornerstone of treatment because the duration of hyperthermia is the primary determinant of outcome. The basic premise of rapidly lowering the core temperature to about 39° C (avoid overshooting and rebound hyperthermia) remains the primary goal. Aggressive fluid resuscitation generally is not recommended because it may lead to pulmonary edema. Antipyretics (e.g., acetaminophen, aspirin, other nonsteroidal anti-inflammatory agents) have no role in the treatment of heatstroke. Benzodiazepines are used to treat agitation and shivering, and seizures. Treatment of rhabdomyolysis involves infusion of large amounts of intravenous fluids (fluid requirements may be as high as 10 L), alkalinization of the urine, and infusion of mannitol. ARDS should be treated aggressively, with early mechanical ventilation and positive end-expiratory pressure (PEEP).

Drug-induced hyperthermia

This has become increasingly common as a result of the increased use of prescription psychotropic drugs and illicit drugs. Drug-induced hyperthermia may be caused by Amphetamines, cocaine, phencyclidine (PCP), methylenedioxymethamphetamine (MDMA; "ecstasy"), lysergic acid diethylamide (LSD), salicylates, lithium, anticholinergics, sympathomimetics.[1]

Malignant hyperthermia

It occurs in individuals with an inherited abnormality of skeletal-muscle sarcoplasmic reticulum that causes a rapid increase in intracellular calcium levels in response to halothane and other inhalational anesthetics or to succinylcholine. Elevated temperature, increased muscle metabolism, muscle rigidity, rhabdomyolysis, acidosis, and cardiovascular instability develop rapidly. This condition is often fatal.

The serotonin syndrome

This is seen with selective serotonin uptake inhibitors (SSRIs), MAOIs, and other serotonergic medications, has many overlapping features, including hyperthermia, but may be distinguished by the presence of diarrhea, tremor, and myoclonus rather than the leadpipe rigidity of neuroleptic malignant syndrome.

Neuroleptic Malignant Syndrome (NMS)

It has been reported to occur with all drugs that effect the central dopaminergic system (including dopamine agonists and levodopa).[7] These include phenothiazines; butyrophenones, including haloperidol and bromperidol; fluoxetine; loxapine; tricyclic dibenzodiazepines; metoclopramide; domperidone; thiothixene; molindone; as well as withdrawal of dopaminergic agents. The classic triad involves the autonomic nervous system (fever in 100%), the extrapyramidal system (rigidity), and cognitive changes. The two characteristic laboratory findings reported in 75% of cases are a high CPK and leukocytosis. 95% of patients are iron deficient.

It is an idiosyncratic, life-threatening complication of treatment with neuroleptic drugs that is characterized by fever, severe muscle rigidity, and autonomic and mental status changes. Antipsychotic-induced dopamine blockade likely plays a pivotal triggering role in the condition. In the first theory, the dopaminergic receptor antagonism by neuroleptics may interfere with dopamine's normal role in central thermoregulation. In the second theory, NMS is believed to share

a pathophysiology with malignant hyperthermia. Sympathetic nervous system activation or dysfunction may play a significant role in the pathogenesis of NMS. Patients with NMS may have rhabdomyolysis, resulting in significant increases in serum creatine kinase, aldolase, transaminases, and lactic acid dehydrogenase concentrations, with the risk of subsequent myoglobinuric renal failure. Patients may also have metabolic acidosis, hypoxia, decreased serum iron concentrations, elevated serum catecholamines, and leukocytosis. Rating scale for diagnosis of NMS are available.[8]

The offending agent must be withdrawn immediately, after which supportive medical therapy is the mainstay of management of NMS. Volume resuscitation should be aggressive, especially given that most patients with NMS are dehydrated in the acute phase of the illness. Serial monitoring and correction of electrolyte abnormalities is critical. Recent reports suggest that alkalinized fluids or even bicarbonate loading may be of particular benefit in preventing renal failure. In extreme hyperthermia, physical cooling measures are important. Benzodiazepines, administered orally or parenterally, may ameliorate symptoms and hasten recovery in NMS. Several dopaminergic drugs, including bromocriptine and amantadine, may reverse parkinsonism in NMS and have been reported in case reports and meta-analyses to reduce time to recovery and halve mortality rates when used alone or in combination with other treatments. The starting dose of bromocriptine is 2.5 mg orally two or three times a day, increased to a total daily dose of 45 mg if necessary. Dantrolene may be useful only in cases of NMS with extreme temperature elevations, rigidity, and true hypermetabolism. The dose is 1–2.5 mg/kg body weight administered initially, followed by 1 mg/kg every 6 hours, if rapid resolution of the fever and rigidity is observed, with tapering or switching to oral dantrolene after the first few days.

Cocaine toxicity

Cocaine toxicity can lead to hyperthermia, dysrhythmias, acute coronary syndromes, neurologic effects due to CNS stimulation, agitated delirium, rhabdomyolysis, acidosis. Hyperthermia may result from extensive muscular activity in the setting of warm ambient temperature and, perhaps, humidity in combination with aberrant thermoregulation in the hypothalamus and mesolimbic system. Cocaine-induced agitation and seizures can also contribute to hyperthermia. Patients with cocaine poisoning may exhibit severe CNS and cardiovascular dysfunction, leading to a loss of airway protective reflexes, cardiovascular collapse, and mortality. Patients presenting with cocaine toxicity initially receive interventions directed at all patients in potentially unstable condition, including attention ABCs, oxygen, IV, and monitoring (cardiac monitoring and pulse oximetry). Unfortunately, there is no antidote for cocaine. The initial management includes infusion of dextrose 50% in water (D50W) and thiamine, followed by activated charcoal to patients with oral ingestions of cocaine. Psychomotor agitation and convulsions are managed with diazepam or lorazepam. Neuromuscular blockade with vecuronium is indicated to control muscle activity and the subsequent development of acidosis. Nitroprusside, nitroglycerin, phentolamine are effective in controlling the blood pressure. Hyperthermia is treated with convection cooling, which involves spraying the patient's exposed body with tepid water as fans circulate air. Tepid water prevents maladaptive shivering that may be induced by conduction cooling methods, although such methods as ice packs, ice water gastric lavage, or cooling blankets may be employed to reduce body temperature to 101° F in 30-45 minutes. The effects of cocaine are generally short lived.

Strychnine poisoning

The primary natural source of strychnine is the plant Strychnos nux vomica. This plant is found in southern Asia (India, Sri Lanka, and East Indies) and Australia. Strychnine is used primarily as a pesticide, particularly to kill rats. Following the

ingestion (swallowing) of strychnine, symptoms of poisoning usually appear within 15 to 60 minutes. Strychnine acts as a blocker or antagonist at the inhibitory or strychnine-sensitive glycine receptor (GlyR), a ligand-gated chloride channel in the spinal cord and the brain. Strychnine causes muscular convulsions and eventually death through asphyxia or sheer exhaustion. The subject will die within 2–3 hours after exposure.

People exposed to low or moderate doses of strychnine by any route will have the following signs or symptoms: Agitation, apprehension or fear, restlessness, painful muscle spasms possibly leading to fever and to kidney and liver injury, uncontrollable arching of the neck and back, rigid arms and legs, jaw tightness, difficulty in breathing, dark urine. People exposed to high doses of strychnine may have respiratory failure and brain death within the first 15 to 30 minutes of exposure. There is no specific antidote for strychnine. Treatment of strychnine poisoning involves an oral application of an activated charcoal infusion which serves to absorb any poison within the digestive tract that has not yet been absorbed into the blood. Anticonvulsants such as phenobarbital or diazepam are administered to control convulsions, along with muscle relaxants such as dantrolene to combat muscle rigidity.

Cerebral Hemorrhage

Intra-cerebral hemorrhage and sub-arachnoid hemorrhage can develop fever due to inflammation of meninges. In pontine hemorrhage, deep coma with quadriplegia, pin-point pupils, hyperpyrexia, hyperpnea, severe hypertension, and hyperhidrosis are common. Although high fever may be an obvious symptom, underlying CNS pathology should be located and treated.

Hypothalamic fever

The term hypothalamic fever is sometimes used to describe elevated temperature caused by abnormal hypothalamic function. This may be seen in some cases when the hypothalamic set point is elevated as a result of local trauma, hemorrhage, tumor, or intrinsic hypothalamic malfunction.[1] However, most patients with hypothalamic damage have hypothermia rather than hyperthermia.

Regional and seasonal febrile emergencies

Febrile emergencies can vary depending on different regions and changing seasons, against the epidemiologic background. Certain infections leading to febrile emergencies are seen in different parts of the country following heavy rains and floods. Outbreaks of malaria, leptospirosis, dengue, gastroenteritis have been reported from Orissa, Maharashtra, Gujarat and Delhi. The most recent serious outbreak of Dengue Fever in India was in 2006. In total around 3400 cases of dengue fever were reported across 11 states. Approximately 10% of the patients have severe disease and require admission; as significant proportion of patients will have multi-organ failure, requiring treatment in critical care units. Clinical features suggestive of complications in these diseases include breathlessness, hemoptysis, crepts in lungs, cyanosis, petechiae, external bleeding, oliguria/ anuria, systolic BP < 90 mmHg, pulse pressure < 20 mmHg, anemia, deep icterus, meningism, altered sensorium, convulsions. Investigations suggestive of complications in febrile patients include Hb <8 gm%, S.Bilirubin > 5 mg%, S.Creatinine > 2 mg%, platelets < 80,000/cu mm, hematocrit > 50% in females and > 55% in males, peripheral smear showing malarial parasites' index ≥ 2%, diffuse shadows on chest X-ray. Certain high-risk patients e.g. pregnant females, patients with liver disease, HIV/AIDS, alcoholism tend to have a severe course and warrant caution. Hantavirus pulmonary syndrome begins with fever and myalgia, and progressive pulmonary edema and respiratory failure can occur in 80-90% of patients within 2 days of hospitalization. An overview of common seasonal febrile emergencies is given in Table 2.

Conclusion

Patients with fever usually have underlying infections. Though not common, but other causes of febrile emergencies have to be considered in appropriate patients viz. endocrine febrile

Table 2 : Common seasonal febrile emergencies

	Malaria	Leptospirosis	Dengue	Typhoid	AGE, Cholera
Salient clinical features	Intermittent fever with chills & rigors (Cold stage → Hot stage → Cold stage), anemia, mild jaundice, s/s of complications	Fever, headache, myalgias (thigh and calf muscles), sub-conjunctival suffusion, petechiae, mild jaundice, s/s of complications	Fever, headache, retro-orbital pain, bodyache, backache, rash (sparing palms & soles), petechiae, leucopenia, s/s of complications	Remittent → continuous fever, relative bradycardia, headache, abdominal pain, diarrhea, anorexia, nausea, vomiting, dry cough , s/s of complications	Loose motions, vomitings, abdominal pain, fever, profuse watery diarrhea in cholera, S/S of dehydration, s/s of complications
Laboratory diagnosis	Malarial parasites in peripheral blood smear Falciparum/ Vivax antigen	1st week: PCR 2nd week: IgM antibodies (Elisa or Rapid tests)	1st week: PCR 2nd week: IgM & IgG antibodies (Elisa or Rapid tests)	1st week: Blood culture 2nd week: Widal test, rapid serology tests (TyphiRapid, Typhidot, Tubex)	Routine stool examination Stool culture & sensitivity Hanging drop preparation for darting motility (for cholera)
Treatment	In chloroquine sensitive area: Tab. Chloroquine available as 250 mg which contains 150 mg of chloroquine base. Dose:- 4 Tab stat, 4 Tab. on Day 2, 2 Tab. on Day 3. Total dose 25 mg base / kg = 1500 mg base for 60 kg adult (10 Tabs.) *PLUS* Falciparum Malaria: Tab.Primaquine 45 mg (6 tabs of 7.5 mg) as single dose Vivax Malaria: Tab. Primaquine 15 mg (2 Tabs. of 7.5 mg) OD x 14 days In chloroquine resistant area: Tab. Sulfadoxine (500 mg) + Pyrimethamine (25 mg) 3 Tabs on day 1, *PLUS* Tab.Artesunate (50 mg) 4 tabs OD x 3 days Other Artemesinin based combination therapies[3]	Cap. Doxycycline (100 mg) 1 BID x 7 days OR Cap Amoxycillin (500 mg) 1 QID x 7 days OR Tab. Erythromycin (500 mg) 1 QID x 7 days *In severe cases:* Inj. Crystalline Penicillin 20 lac units (after test dose) I.V. in 100 ml NS over 1 hr - 6 hourly x 7-10 days, (renal correction if S. Creatinine more than 1.5 mg %) OR Inj. Ampicillin 500 mg I.V. QID for 7-10 days.	No specific antimicrobial treatment. I.V. fluids (RL, DNS) for hemodynamic stabilization.	Tab.Ciprofloxacin (750 mg)- 1 PO BID x 14 days (not in pregnancy) OR Tab. Cefixime (200 mg)- 2 PO BID x 14 days (safe in pregnancy) OR Inj. Ciprofloxacin 200 mg (100 ml) I.V. BID x 14 days *Severe typhoid (altered mentation, shock):* Inj. Ceftriaxone 2 gm I.V. in 100 ml NS over 1 hr, BID on days 1-3, then 1 gm I.V. bid x 14 days (once the fever comes down, Tab. Cefixime can be substituted) + Inj. Amikacin 750 mg I.M. OD x 10 days	Inj. Ciprofloxacin (200 mg) 100 ml I.V. BID Inj. Metrogyl 500 mg (100 ml) I.V. TID Cap. Doxycycline (100 mg)- 1 BID *Fluid replacement:* Severe Dehydration- I.V. Ringers Lactate 500 ml over 15 mins. x 3; then 500 ml RL every 20-30 mins till dehydration is corrected. Moderate Dehydration- I.V. RL 500 ml every hour till dehydration is corrected; ORS 2-4 litres in first 4 hrs.

	Malaria	Leptospirosis	Dengue	Typhoid	AGE, Cholera
Complications	Cerebral malaria, black water fever, algid malaria, ARDS, hepatitis, renal failure, thrombocytopenia, DIC, anemia, hypoglycemia, lactic acidosis, shock	ARDS, hepatitis, renal failure, anemia, thrombocytopenia, meningoencephalitis, myocarditis, shock	Dengue hemorrhagic fever (DHF): thrombocytopenia, petechiae, spontaneous bleeding Dengue Shock Syndrome (DSS): hypotension, narrow pulse pressure, elevated hematocrit, circulatory failure	Meningoencephalitis, thrombocytopenia, DIC, intestinal bleeding, gut perforation, shock, pneumonia	Dehydration, shock, renal failure, metabolic acidosis, hypokalemia with paralytic ileus
Treatment of complications	• Hypotension- I.V. DNS, RL; I.V. Dextran, Hemaccel with caution; Inj. Dopamine infusion @ 5-20 ug/kg/min after CVP is restored to normal. • Anemia- If hemoglobin falls below 7 g/dl- transfusion of fresh blood or packed cells. • Thrombocytopenia- (a)If hemorrhage present, Platelets < 40,000/cumm- Transfuse 6 bags of Platelets, Grouping not essential in emergency; (b) Platelets < 20,000/cumm, even if no hemorrhage-consider transfusion of 3-4 bags of platelets. • Liver dysfunction- If encephalopathy present: Tab. Metronidazole 500 mg TID, Cap.Neomycin 1 gm QID, Syp.Lactulose 30 ml TID, oral lactobacilli preparation, high bowel wash BID. • Renal dysfunction- (a) Insert CVP line (Basilic only); (b) Maintain CVP between 8-10 cm H_2O with I.V. NS,DNS, RL; (c) I.V. Lasix 40 mg once CVP is > 6 cm, repeat 100 mg at 2 hrs if no response; (d) I.V. Dopamine 2.5-5 µg/kg/min if no response to Lasix; (e) Manage/prevent Hyperkalemia, acidosis, fluid overload; (f) Hemo-dialysis, if indicated. • ARDS – High flow nasal oxygen, Non-invasive ventilation, Invasive mechanical ventilation. • Convulsions- Inj. Phenytoin 15 mg/kg (800 mg) loading dose I.V. slowly over 10 mins; maintenance dose- 100 mg I.V./ P.O. TID . • Indication for Steroids (1-3 mg/kg/day of Dexamethasone I.V. for 3-5 days, OR Inj. Methylprednisolone 1gm I.V. OD for 3 days): ARDS, Thrombocytopenia, Pulmonary hemorrhage. • Dehydration- Severe: I.V. Ringers Lactate 500 ml over 15 mins. x 3, then 500 ml RL every 20-30 mins. till dehydration is corrected. Moderate Dehydration- I.V. RL 500 ml every hour till dehydration is corrected. ORS 2-4 litres in first 4 hrs.				

emergencies, drug toxicity and poisoning. Heat syndromes should be strongly considered in hot climates when environmental temperatures reach unusually high limits. Monsoon and flooding predisposes to mosquito breeding and spread of diseases like malaria and dengue. Leptospirosis outbreaks have been recorded after floods in coastal areas of India. Management of febrile emergencies involves treatment of fever as well as of the underlying pathology. Prompt recognition and treatment of febrile emergencies is prudent to minimize associated mortality. The concept of IMIA is proposed to prioritize recognition and management of serious and critical syndromes rather than specific diagnoses, e.g. prompt treating respiratory failure in febrile ARDS and replacing platelets in febrile thrombocytopenia rather than establishing diagnoses of leptospirosis or dengue fever.

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