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Central fever: a challenging clinical entity in neurocritical care

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Review Article

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Fever is probably the most frequent symptom observed in neurointensive care by healthcare providers. It is seen in almost 70% of neurocritically ill patients. Fever of central origin was first described in the journal *Brain* by Erickson in 1939. A significant number of patients develop this fever due to a noninfectious cause, but are often treated as having an infectious fever. Unjustified use of antibiotics adds to the increased cost of treatment and the emergence of resistant strains, contributing to additional morbidity. Since fever has a detrimental impact on the recovery of the acutely injured brain and contributes to an increased stay in the neurointensive care unit (NICU), timely and accurate diagnosis of the cause of fever in the NICU is imperative. Here, we try to understand the underlying mechanism, risk factors, clinical characteristics, diagnosis and management options of the central fever. We also make an attempt to differentiate two noninfectious causes of fever in the NICU: paroxysmal sympathetic hyperactivity and central fever.

Keywords: Humans; Fever; Brain; Intensive care units; Ant-bacterial agents

INTRODUCTION

Fever is probably the most frequent symptom observed in the neurointensive care unit (NICU) by healthcare providers. An oral temperature greater than 37.5℃ is considered a fever [1,2]. Hyperpyrexia is usually a diagnosis of exclusion, with temperatures exceeding 41℃ and nonresponsiveness to antipyretic treatment [3,4]. Fever is seen in almost 70% of neurocritically ill patients [5-10]. Fever of central origin was first described by in the journal *Brain* by Erickson [11] in 1939. A significant number of these patients have fever from noninfectious causes (47% in Kilpatrick et al. [6] and 25% in Commichau et al. [7]), but this is of-ten treated as infectious fever. Unjustified use of antibiotics adds to the increased cost of treatment and the emergence of resistant strains, contributing to additional morbidity. Since fever has a detrimental impact on the recovery of the acutely injured brain [12-15] and contributes to an increase in length of stay in NICU [8]; timely and accurate diagnosis of the cause of fever in the NICU is imperative.

Here, we try to understand the underlying mechanism, risk factors, clinical characteristics, diagnosis and management options of central fever (CF). We also make an attempt to differentiate two noninfectious causes of fever in NICU, paroxysmal sympathetic hyperactivity and CF.

EPIDEMIOLOGY

Overall in the intensive care unit (ICU), at least 50% of fever are reported to be due to noninfectious causes [16]. The incidence of noninfectious fever in the neurology ICU is 23% while in the neurosurgical ICU it is 47% [6]. Of these, the highest rates of febrile episodes occur in patients with subarachnoid hemorrhage (SAH; 50% to 65%), followed by traumatic brain injury (TBI; 4% to 40%) and intracerebral hemorrhage (ICH; 31%), with no cause of fever identified in 28% of patients, suggesting fever of central origin [7,10,17,18]. Hyperthermia is a frequent complication of acute ischemic stroke in 50% of these patients and carries a poor prognosis [19].

PATHOPHYSIOLOGY

An abnormal rise in temperature may be physiological, environmental, or even drug-related, rather than due to infection. The mechanism of CF in the NICU is not well defined but the literature suggests some probable mechanisms. Inflammatory markers causing fever may be triggered by extreme physiologic stress in acute neurologic injury [20,21]. Brain injury may also lead to the disruption of the mesencephalic-diencephalic mechanisms responsible for the inhibition of thermogenesis [22]. Monocytes and macrophages produce the cytokines interleukin 1 (IL-1), IL-6, and tumor necrosis factor α (TNF-α), which act on the organum vasculosum of laminae terminalis. This in turn leads to the release of prostaglandin E2 (PGE2) via activation of the cyclooxygenase-2 (COX-2) enzyme. PGE2 acts on the preoptic area of the hypothalamus leading to an increase in the set point of the hypothalamus, thereby increasing the body temperature [23-34]. Systemic pyrogens, such as IL-1, appear to enter the brain at regions where there is an incomplete blood-brain barrier (circumventricular organs) and act on the preoptic area of the hypothalamus to induce fever [24,35-38]. Various neurological events that take place in febrile patients affect this pathway. Direct hemotoxic damage to thermoregulatory centers in the preoptic region, interference with tonic inhibitory inputs from lower midbrain that ordinarily suppresses thermogenesis, and stimulation of prostaglandin production leading to temperature set point elevation, have all been implicated in the causation of CF [39]. CF is speculated to result from damage to the hypothalamus, midbrain, or pons, and be enhanced by increased sympathetic activity, opening of the ventricles, damage to the frontal lobes, physical distortion, diffuse axonal injury (DAI), or toxic blood metabolites [39]. CF may also be due to the selective loss of warm-sensitive neurons, the osmotic changes detected by the organum vasculosum laminae ter-

minalis, or from hormonal changes (progesterone, prostaglandin) modifying the firing rate of temperature-sensitive neurons in the medial preoptic nucleus [40].

Posttraumatic hyperthermia, also known as neurogenic fever, is another common cause of fever. Stimulation studies have suggested that the mechanism involves an imbalance between the hypothalamus and the various temperature regulating centers in the brainstem and spinal cord [41]. Won and Lin [42], in their study conducted on rabbits, found that inhibition of five hydroxytryptamine receptors in the anterior hypothalamus increased heat production and decreased heat loss, leading to hyperthermia. Suggested mechanisms for this effect include increased metabolic rate, increased carbon dioxide production, decreased cerebral blood flow, acidosis, brain edema exacerbation, excitotoxic neurotransmitter release, and blood-brain barrier breakdown. Disease-specific mechanisms are also described in Table 1.

Subarachnoid hemorrhage
SAH may cause impairment of hypothalamic thermoregulation due to the presence of clots in the suprasellar cistern. It may also lead to an intense activation of the sympathetic nervous system, leading to peripheral vasoconstriction and thus diminishing the heat-dissipating mechanisms [43].

Intracerebral hemorrhage
Intraventricular hemorrhage (IVH) is thought to elevate the temperature set point in the hypothalamus by direct damage to the thermoregulatory centers in the preoptic region, stimulation of prostaglandin production, or decreased inhibitory feedback from the lower midbrain which suppresses thermogenesis [39].

Tumors
It is hypothesized that a tumor, or its necrotic products, may lead to inflammation of leptomeninges, thus triggering fever [44].

Traumatic brain injury
While TBI can affect all seven pituitary hormones [45], growth hormone (GH) deficiency is most frequently reported [46,47]. Patients with GH deficiency have a reduced sweating capacity which increases the risk of developing hyperthermia [48]. TBI-induced hypothalamic-pituitary damage may be due to direct injury to the hypothalamic-pituitary area, a secondary injury from hypoxia, or increased intracranial pressure [49]. CF in patients with TBI can also be caused by direct injury to the hypothalamus [15,50]. The development of CF is associated with inflammatory changes within the hypothalamus [51].

Table 1. Various neurological diseases and their relation with central fever

Disease	Probable mechanisms	Risk factors	Effects on outcome
TBI	1. GH deficiency	1. Diffuse axonal Injury	1. A negative association between early peak fever greater than 39℃ and hospital mortality
	2. Direct injury to the hypothalamic–pituitary area or secondary injury from hypoxia or increased intracranial pressure.	2. Frontal lobe injuries	2. Possibility of antibiotic overuse, with the associated risk of the emergence of resistant microorganisms
		3. Young age, low GCS on presentation, skull fracture, presence of blood in the parenchyma/ventricles, and acute brain injury.	3. Prolonged coma or unawareness, diabetes insipidus and poor outcomes
		4. Location of the skull fracture in proximity to the hypothalamic region (for example, anterior fossa)	
ICH	1. Direct damage to thermoregulatory centres in the preoptic region, stimulation of prostaglandin production, and decreased inhibitory feedback from the lower midbrain which suppresses thermogenesis	1. ICH with intraventricular extension	1. High mortality and poor functional outcome at 3 months on modified Rankin Scale
		2. Larger hematoma volumes	2. Duration of fever was independently associated with poor outcome in those who survived past 72 hours.
		3. Basal ganglia and thalamic involvement	
		4. Third ventricular shift	
SAH	1. Impair hypothalamic thermoregulation due to presence of clots in suprasellar cistern.	Disease severity, amount of blood in the subarachnoid space and associated IVH	1. Even a single episode of fever after SAH is associated with poorer outcomes even in best-grade patients.
	2. Intense activation of the sympathetic nervous system		2. ↑Vasospasm associated with CF
			3. More severe functional disability and cognitive impairment among survivors
Tumours	Tumour or its necrotic products may lead to inflammation of leptomeninges, thus triggering fever.	More prone with tumours located in the sella, diencephalon, and intraventricular region	Poor outcome
AIS	Hypothalamic dysfunction	It is probable, larger the ischemia more the chances of CF	1. May increase volume of the ischemic zone
			2. ↑ Mortality in stroke patients

TBI, traumatic brain injury; GH, growth hormone; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; IVH, intraventricular hemorrhage; CF, central fever; AIS, acute ischemic stroke.

Etiology

CF can occur following any acute brain injury (Table 2) [38,52-56].

RISK FACTORS

Various predisposing factors have been defined for the occurrence of CF in the NICU. Independent predictors of CF on multivariate analysis include blood transfusion, SAH, IVH, tumor, or onset of fever within 72 hours of hospital admission [57]. Intraventricular catheterization is a risk factor for unexplained fever, which suggests a role for ventricular hemorrhage in the pathogenesis of CF [7]. Risk factors among various acute neurological conditions are re-

ported as follows (Table 1).

Subarachnoid hemorrhage

Disease severity, amount of blood in the subarachnoid space, and IVH are strong risk factors for the development of fever [7,58,59].

Intracerebral hemorrhage

ICH with intraventricular extension and larger hematoma volumes (86.7 ± 66.5 mL CF vs. 33.7 ± 54.4 mL in no fever) are associated with an increased probability of developing CF [18]. There were no significant differences related to the anatomical location of hematoma and presence of CF, but involvement of the basal ganglia and thalamus showed a trend towards an increased chance

Table 2. Causes of central fever

Subarachnoid haemorrhage
Intraventricular haemorrhage
Intracerbral haemorrhage
Tumours: sella, diencephalon, and intraventricular region [52]
Traumatic brain injury
Ischemic stroke
Pontine haemorrhage
Tuberculous meningitis [38]
Following hemispherectomies [53]
Following hemidecortication [54]
Traumatic spine injury [55]
Basilar artery occlusion [56]

of CF [18]. Third ventricular shift in ICH patients is associated with fever within 72 hours of admission and high discharge mortality [59].

Tumors

CF is more frequently associated with tumors located in the sella, diencephalon, and intraventricular regions [52,57].

Traumatic brain injury

Patients with DAI, as shown via imaging, and frontal lobe injuries were independently associated with the presence of CF [60,61]. Other risk factors were young age, low Glasgow Coma Scale on presentation, skull fracture, presence of blood in the parenchyma/ventricles, and acute brain injury [62]. CF is more common in severely ill TBI patients with diffuse white matter damage, brain edema, hyperglycemia, leukocytosis, and hypotension [61]. Frontal lobe injury may serve as an indication of hypothalamic injury, given the nature of mechanical forces within the skull during injury and the proximity of the hypothalamus to the ventricles. Location of the skull fracture in proximity to the hypothalamic region (for example, the anterior fossa) may increase this risk [60].

Ischemic stroke

Magnetic spectroscopy indicates that the temperature of the ischemic zone is higher than in normal areas of the brain. Therefore, larger ischemic infarcts are likely to increase the chance of CF [63].

Traumatic spine injury

CF is also reported after traumatic spine injury, with a mean incidence of 8% [55]. Cervical and thoracic level injuries are more commonly associated with fever, as compared to lumbar injuries. Complete spine injuries have a higher incidence than incomplete injuries [55]. The etiology of fever following spine injury is not thoroughly understood.

Age

CF generally occurs in the younger population, as compared to infectious fever [57].

Level of consciousness

Depressed level of consciousness has also been identified as an independent predisposing factor for noninfectious fever, mainly attributed to immobilization and the increased atelectasis found in these patients [7].

CLINICAL FEATURES OF CENTRAL FEVER

This is a diagnosis of exclusion. CF occurs early, typically within 72 hours of admission after acute brain injury. All the cultures are negative and the chest radiograph is normal. Fever is disproportionately high and persistent. The temperature peak is higher when the fever starts earlier, and will be higher when compared to infectious fever [18]. There is generally less fever-free period and the cumulative fever load is high, accounting for a longer stay in the NICU. Generally, CF is continuous in nature without diurnal variations, plateau-like, and without spikes. Patients with CF have relative bradycardia with a notable absence of perspiration. Sustained fever is another factor in favor of CF [57]. Fever is also resistant to antipyretic medications [62,64-67].

Continuous fever, lasting longer than 6 hours for 2 or more consecutive days, has been considered persistent [57]. The combination of negative cultures; absence of infiltrate on chest radiographs; diagnosis of SAH, IVH, or tumor; and onset of fever within 72 hours of admission, predict CF with a probability of 0.90 [57]. In a study conducted by Thompson et al. [15], fever persisted for weeks to months in 4% to 37% of patients with TBI. Vasospasm with SAH is also predictive of CF [22].

The criteria for systemic inflammatory response syndrome and leukocytosis are similar to central and infectious fever. This underscores the difficulty in differentiating central and infectious fever prospectively in the critically ill population. The extreme physiologic stress provoked by acute neurologic injury can cause a rise in inflammatory markers and increased sympathetic response [21,22]. The percentage of neutrophils is higher in patients with infectious fever, suggesting that while leukocytosis may not be a reliable clinical variable to decide whether to use empirical antibiotics or discontinue antibiotics early, the presence of a left shift remains useful [57].

Extreme hyperpyrexia, defined as fever ≥41.1℃ (106°F), is usually noninfectious. Examples include CF, drug fever, malignant hyperthermia, transfusion reactions, adrenal insufficiency, thyroid storm, neuroleptic malignant syndrome, heat stroke, acalculous cholecystitis, mesenteric ischemia, acute pancreatitis, deep vein thrombosis, and pulmonary embolism [68,69]. A single fever spike of 102°F is classical for noninfectious disorders and is never due to infection. Fever associated with blood transfusions are usually transient, that is, they present as a single fever spike within < 1 week [68,70].

TEMPERATURE PULSE RELATIONSHIP

Relative bradycardia is a feature of CF. The following applies to adult patients with temperatures > 102°F and when pulse is taken simultaneously with temperature. 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, verapamil or diltiazem, or has a pacemaker-induced rhythm or heart block. In absence of these exclusion criteria, relative bradycardia in neurosurgical ICU patients with fever strongly suggests a central or drug fever (Table 3) [71].

Diagnosis

A high index of suspicion is needed for the diagnosis of CF. Diagnosis of CF is a diagnosis of exclusion in predisposed patients with neurological injury. The practice guidelines from the task force of the Society for Critical Care Medicine suggest a "careful clinical assessment" and "cost-conscious approach" for obtaining a diagnosis through laboratory and radiological tests [72]. The clinical signs of pneumonia, bacteremia, sinusitis, urinary tract infection, catheter site infection, meningitis, or ventriculitis should be investigated. A chest radiograph, culture of blood, urine and trachea are the baseline tests done in all cases. Any long-standing venous line or catheter should also be removed.

Certain biomarkers have been developed to differentiate infectious from noninfectious causes, including serum procalcitonin (PCT) assays, endotoxin detection systems, triggering receptor expressed on myeloid cells-S (TREM-1), C-reactive protein, TNF-α, and IL-6. PCT of 0.5 ng/mL or greater was useful in differentiating infectious fever from CF in SAH and ICH patients [73]. This test is shown to have high specificity and a reasonably high negative predictive value. A decision tree has been suggested by Hocker et al. [57], but no specific diagnostic paradigm has been suggested for universal usage.

DIFFERENTIAL DIAGNOSIS

Some common differential diagnoses are important to be distinguished before making a diagnosis of CF, since it a diagnosis of exclusion. Nonresponse to antibiotics in CF may lead to misdiagnosis of antibiotic failure or resistance in CF (Table 4).

Bacteremia

Bacteremia should be investigated by sending at least three blood cultures within 24 hours of suspected infection. Each culture should be sent from a separate venepuncture site or intravascular device. Intravascular catheters should be suspected as an infection risk in young nonimmune compromised patients with abrupt onset of septicemia. These patients may have inflammation at the site of insertion that can provide a clue to the diagnosis, though this is absent in 60% of patients. Difficulty in drawing a sample from the line may be another indicator of intravenous catheter-related infection.

Ventilator-associated pneumonia

Ventilator-associated pneumonia is the second most common cause of infectious fever in any ICU. It is distinguished by a culture of respiratory secretion which can be obtained by various techniques, including expectoration, nasopharyngeal washing, saline induction, deep tracheal suctioning, bronchoscopic specimen/brush samples, aspiration, and bronchoscopic or nonbronchoscopic lavage (mini-BAL). Chest radiography for abscess, atelectasis, effusion, and consolidation should also be done.

Urinary tract infection

Urinary tract infection is the next leading cause of fever. Diagnosis is excluded by sending urine for direct microscopic examination, staining, and culture.

Diarrhea

Diarrhea is another important cause of fever in the ICU. It should be suspected in any patient with diarrhea and who has been given

Table 3. Temperature pulse relationship

Temperature (°F)	Appropriate pulse response (/min)	Relative bradycardia
106	150	<140
105	140	<130
104	130	<120
103	120	<110
102	110	<100

Table 4. Differential diagnosis of fever in neurointensive care unit

Infectious causes
    Ventilator-associated pneumonia
    Sinusitis
    Meningitis
    Encephalitis
    Catheter-related sepsis
    Sepsis
    Clostridium difficile diarrhea
    Abdominal sepsis
    Complicated wound infections
    Urinary tract infection
    Acute respiratory distress syndrome, both late and fibro-proliferative stage
    Systemic inflammatory response syndrome
Noninfectious causes
    Alcohol/drug withdrawal
    Postoperative fever (48 hours postoperative)
    Post-transfusion fever
    Drug fever
    Connective tissue disease
    Myocardial infarction
    Pancreatitis
    Acalculous cholecystitis
    Ischemic bowel (without primary peritonitis)
    Gastrointestinal bleed
    Aspiration pneumonitis
    Fat emboli
    Gout/pseudo gout
    Transplant rejection
    Hematoma
    Cirrhosis
    Decubitus ulcer
    Phlebitis/thrombophlebitis
    Intravenous contrast reaction
    Neoplastic fever
    Deep venous thrombosis
    Pulmonary emboli
Neurological diseases
    Increased intracranial pressure
    Nonconvulsive status epilepticus
    Autonomic dysreflexia
    Cushing response
    Agitation
    Dystonia
    Malignant catatonia
    Stiffman syndrome
    Paroxysmal sympathetic hyperactivity
    Mixed autonomic hyperactivity syndrome
Drugs/Toxins
    Delirium
    Serotonin syndrome
    Acute drug withdrawal (intrathecal baclofen, dopamine agents)
    Narcotic withdrawal
    Neuroleptic syndrome
    Malignant hyperthermia
    Scorpion envenomation
    Gamma hydroxybutyrate intoxication
    Fenfluramine-phentirmine overdose
    Drug overdoses (e.g., aspirin, anticholinergic drugs)
Endocrine diseases
    Pheochromocytoma
    Thyroid storm
    Adrenal insufficiency
Other diseases
    Carotid sinus injury
    Baroreceptor failure
    Renal artery stenosis
    Irukandji syndrome

antibiotic treatment or chemotherapy in the past 60 days. The most common organism implicated is *Clostridium difficile* [74,75]. It can be excluded by enzyme immunosorbent assay (EIA) for detecting toxins A and B, or by culture (though it is more time consuming).

Sinusitis

Sinusitis is an uncommon cause of fever in the ICU, but may have a grave impact on patient outcomes. Risk factors include obstruction of the ostia draining the sinuses, nasal intubation of trachea, or the passage of a nasogastric tube. Though occult, it can spread to the brain, lungs, and blood, leading to serious consequences [76]. It can be ruled out by a radiograph, ultrasound, magnetic resonance imaging or computed tomography scan transnasal puncture.

Surgical site infection

Surgical site infection accounts for 3% of fever in the ICU, which can easily be diagnosed by local inspection and cultures from the wound site [77,78]. Abscess in the lung, abdomen or any other region may also be a cause of fever.

Drug fever

Drug fever is caused by some commonly used drugs in the NICU, such as phenytoin, salicylates, barbiturates, methyldopa, furosemide, penicillin, cephalosporin, sulfonamide, amphotericin B, rarely corticosteroids, clindamycin, tetracycline, macrolide. Onset of fever is usually within 1 to 2 weeks of drug initiation, and it can easily be diagnosed by stopping the drug. Suspicion of drug fever can also arise from relative bradycardia and the patient being inappropriately well for the degree of fever. Fever usually disappears within 3 days of stopping drugs or antibiotics in such cases

Table 5. Paroxysmal sympathetic hyperactivity vs. central fever

Feature	PSH	CF
Onset	Usually after a week of ABI and may last up to 1 year. Generally seen after cessation of ICU sedation	Occurs within 72 hours of ABI
Associated signs and symptoms	Tachycardia, hypertension, tachypnoea, dystonia, diaphoresis	No such association
Fever	At least one episode per day for 3 consecutive days (2–3 cycles/day)	Unusually high fever remains for most of the time (plateau-like with no diurnal variation)
Trigger	Essential diagnostic criteria (mostly nonnoxious stimuli)	No such trigger defined
Mechanism	Excitatory-inhibitory model: most commonly accepted	Inflammatory cytokines increase the set point of hypothalamus
Leukocytosis	Generally absent	Present
Heart rate	Tachycardia	Relative bradycardia
Sweating	Generally present	Absent
Posturing/Dystonia	Generally present (one of the diagnostic criteria)	Absent
Pupil size	Usually increased	Normal
Paroxysmal nature	Yes	No
Most common pathology	TBI	SAH
Diagnostic criteria	Defined by multidisciplinary international committee (diagnostic likelihood tool)	No such diagnostic criteria
Core clinical features	Six core sympathetic and motor clinical features	No such clinical features

PSH, paroxysmal sympathetic hyperactivity; CF, central fever; ABI, acute brain injury; ICU, intensive care unit; TBI, traumatic brain injury; SAH, subarachnoid hemorrhage.

[71,79].

Other differential diagnoses are listed in Table 4.

PAROXYSMAL SYMPATHETIC HYPERACTIVITY VS. CENTRAL FEVER

Both are diagnoses of exclusion in patients with neurological injuries during their stay in neurocritical care. They both occur in the NICU in acute brain-injury patients. Differentiating one from the other is very crucial in proper care and appropriate management, and thus ultimately affects patient outcomes. Differentiating features are listed in Table 5.

Impact on outcome

Fever predisposes the brain to harmful effects by disrupting the blood-brain barrier, an increasing excitatory amino acid release, and increasing the production of free radicals [80]. There is an exacerbation of neuronal injury in fever. The permeability of the blood-brain barrier is related to body temperature and higher temperatures increase the extravasation of proteins [81,82]. There is a lack of literature for a definitive association between the duration of fever and increased mortality. Studies conducted by Circiumaru et al. [83] and Peres Bota et al. [84] found that fever lasting longer than 5 days was associated with increased mortality. These results are in contrast to a study conducted by Schulman et al.

[85], who found increased patient mortality when fever was aggressively controlled, although it should be noted that these were nonneurological trauma patients. Fever is also found to increase the length of ICU stay [8,9].

The brain injury patient is at risk of secondary injury from fever, as for every 1°C rise in body temperature there is a 13% increase in the metabolic rate [86]. Increased body temperature causes permanent neuronal damage and worsens prognosis in animal models of ischemic brain injury [40,87-91]. Fever is also known to increase delirium and agitation [92,93]. However, fever is not found to increase intracranial pressure [94]. Fever also increases cardiac output, oxygen consumption, and heart rate [95]. This increased demand on the heart is poorly compensated in patients with previously compromised cardiac function and in sepsis [96]. Fever has also been associated with increased multiorgan dysfunction and mortality [97]. Higher temperature is further associated with cell protein denaturation, susceptibility to acid-base and electrolyte disturbances, and impaired oxygen release [98].

Subarachnoid hemorrhage

Even a single episode of fever after SAH is associated with poorer outcomes, even in good-grade patients [99]. Vasospasm in SAH patients is associated with CF, independent of hemorrhage severity or the presence of infection [7,12,22,57,100-102]. Treatment-refractory fever during the first 10 days after SAH is associ-

ated with increased mortality, more severe functional disability, and cognitive impairment among survivors [58]. Cumulative fever burden, defined as the sum of time with temperatures > 38.3℃ in the first 13 days, is associated with worse outcomes, including incomplete recovery in good-grade SAH patients and potentially late recovery in poor-grade patients [102].

Intracerebral hemorrhage

The presence of CF leads to poor outcomes and is an independent risk factor for mortality in ICH patients [18]. This results in high mortality and poor functional outcomes at 3 months on the modified Rankin Scale. In one study, the presence of CF led to unfavorable outcomes in 100% cases at 90 days postictus, while the absence of fever was associated with unfavorable outcomes in only 46.9% of patients [18]. In a retrospective study of 251 patients with spontaneous ICH, the duration of fever was independently associated with poor outcomes in those who survived past 72 hours [14].

Acute ischemic stroke

Pyrexia in experimental animals may increase the volume of the ischemic zone [40,84-87]. Also, fever greater than 39℃ increases mortality in stroke patients [103].

Traumatic brain injury

In a cohort of more than 100,000 patients, a negative association was observed between early peak fever greater than 39℃ and hospital mortality in patients with TBI [103]. Further, this correlation was not seen in patients with central nervous system infection. Because CF starts earlier and lasts longer than infectious fever, there is a high risk of antibiotic overuse and the associated risk of the emergence of resistant microorganisms [57]. CF may be associated with prolonged coma or unawareness, diabetes insipidus, and overall poor outcomes [50,64,65,67,104].

TREATMENT

Although many treatment regimens have been suggested, none have been identified as superior to others in the treatment of fever [65,105]. However, controlling fever is an important part of management in CF, owing to its detrimental effects on the brain. Pharmacologic methods include acetaminophen, acetylsalicylic acid, and other nonsteroidal antiinflammatory medications and corticosteroids [106,107].

Other methods to decrease temperature include rotary fans, sponging, and surface cooling devices. However, these have had limited efficacy and are uncomfortable for the patient. Surface cooling devices have also been reported to increase the incidence of shivering, increase oxygen consumption and even cause thermal burns [107,108]. Hypothermia blankets can lead to large temperature fluctuations [109,110]. Air blankets have been increasingly used and are found to have better efficacy and produce better patient comfort [110]. Some authors have suggested the use of sand body-conformed wraps, intravascular cooling devices, head-only cooling caps, or inhaled perfluorocarbon cooling systems [111].

Several studies have tried intravenous infusion of cold saline, showing promising results and no increase in complications [112]. A few studies have tried local (brain) cooling. This may prevent the side effects of global hypothermia, such as impaired coagulation, arrhythmias and deep vein thrombosis [113-116]. However, no large multicentre trial is available, leading to no definitive conclusions on the use of selective brain cooling.

IL-1 antagonists have been shown to produce significant improvements in rat models of TBI [117], although no human trials have been conducted. However, it has been shown that even a small temperature decrease in febrile patients can improve neurologic outcomes [118].

Morphine

Remission of CF is reported with morphine post-TBI [119].

Chlorpromazine

Sometimes, when traditional management fails, chlorpromazine has been tried with variable success. Chlorpromazine produces antipyretic actions because of its ability to render the patient thermolabile and its effect on thermoregulation [120,121]. Hyperpyrexia following hemispherectomy has been reported to respond to chlorpromazine [121].

Baclofen

Baclofen successfully abolished prolonged central hyperthermia in a patient with basilar artery occlusion leading to brain stem infarction [56].

Bromocriptine

There are anecdotal case reports of the successful use of bromocriptine for treatment of CF [122,123].

Growth hormone therapy

Successful treatment of CF by GH therapy has been reported, with the mechanism related to the improvement of sweat production [124].

FUTURE DIRECTIONS

There are no guidelines or directions to help differentiate CF from other noninfectious causes of fever in the NICU. The literature is sparse and unclear. The diagnostic criteria are not well defined and not standardized. Treatment modalities for this clinical entity have been symptomatic only and mostly rely on over the counter drugs. No standard therapy has been defined in the literature. Multicentre large studies are required to better define CF, understand its pathophysiology, and guide standard management protocols in neurocritical care settings.

CONCLUSION

CF is an important diagnosis in neurocritical care. It not only prevents unnecessary antibiotic use, but its early recognition would also help improve patient management and prevent delayed discharge from the hospital. The current key to diagnosis in a predisposed patient is a high index of suspicion, along with thorough clinical examination, radiological, microbiological, and biochemical tests. Immediate attainment of normothermia is the current recommendation, as fever worsens the brain insult. Treatment includes various pharmacological agents and surface cooling methods to decrease body temperature. Studies are lacking on the best methods for diagnosis, treatment, and prevention of CF. Thus, more human trials are needed in this field to make any definitive recommendations.

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