Evidence-Base for Fever Interventions Following Stroke

Hilaire J. Thompson, PhD, RN, CNRN, ACNP-BC

The febrile response is an important and adaptive host defense. In the context of brain injury, however, fever is thought to induce secondary brain injury and be associated with worse outcomes and higher mortality rates. For many years, researchers and clinicians have identified fever as a critical concern in the management of patients after stroke. Recent work has focused on care processes in fever management of the stroke patient. Most studies have focused solely on frequency of temperature measurement or antipyretic administration rather than examining the full scope of possible intervention.

Background and Significance
Fever is an adaptive response of the host to a perceived threat and is frequently encountered by healthcare professionals. Instead of being an adaptive response, in the presence of an acute neurological insult such as stroke, fever has been associated with worsened outcomes, such as larger infarct volume, higher rates of mortality, and greater disability and dependence. The underlying mechanism for the secondary injury related to fever is the heightened inflammatory response induced by the elevation in temperature. This makes the blood–brain barrier more permeable to immune cells, leading to cerebral edema and neuronal death. Additionally, fever increases the production of free radicals, promoting glutamate release and resulting in excitotoxicity.

Fever is seen in between 40% and 60% of patients after stroke. The American Heart Association (AHA) stroke guidelines state that maintenance of normothermia (T<99.6°F; 37.6°C) should be the standard of care. This point is echoed in the AHA Scientific Overview of Nursing and Interdisciplinary Care of the Ischemic Stroke Patient, which states that “Temperatures of >99.6°F should be managed aggressively” as a Class I recommendation (p. 2926). Similarly, the European Stroke Initiative recommends treating temperature >37.5°C. Nurses frequently must manage fever, and their decision-making is relevant to clinical outcomes. A comprehensive review of the literature was conducted with the aim to identify the evidence-base for fever monitoring and management in persons after acute ischemic stroke. Search terms included stroke, ischemic stroke, fever, hyperthermia, measurement, and nursing intervention. From the literature review, guidance was developed for monitoring for and managing fever in adult ischemic stroke patients and identify areas needing further research.

Temperature Measurement: Site and Frequency
The monitoring of body temperature is considered a standard of care for stroke patients. The AHA/American Stroke Association (ASA) guidelines specify frequency of monitoring to be not less than every 30 minutes while in the emergency department and every 4 hours (or as required) in the acute care setting (Table 1). A recent study of current practices in the United States reported that the oral route was the primary method of monitoring temperature in the neuroscience patient, including those with stroke. Although recent studies in stroke patients have reported using the axilla as a site for temperature measurement, this is not a recommended location for monitoring temperature in acutely ill adults and should be avoided. When choosing a temperature monitoring site, nurses must be aware that oral, bladder, and rectal (T_μ) temperatures are generally lower than brain (T_br) temperatures (eg, T_μ-T_br, 0.1–2.0°C) and that this gradient is larger during fever (see also Table 1).

Protocols for Fever Management
Recently, US nurses were surveyed to assess if their institution has a fever/hyperthermia management protocol specific to stroke and other neuroscience patients. Although 27% of survey respondents indicated that their institution had such a protocol for neuroscience patients as a whole, only 8% reported having a specific protocol for stroke patients. The most common first line intervention in these protocols was acetaminophen at a dose of 650 mg (see Table 2). Other first-line interventions common to these protocols were physical cooling measures, such as ice packs and fans.

Limited research has attempted to bundle fever management within clinical treatment protocols for stroke with promising success. The quality in acute stroke care study examined use of an evidence-based clinical bundle (fever, sugar, swallowing) for the first 72 hours postadmission to improve patient outcomes after stroke. The bundle included monitoring temperature regularly, as well as paracetamol for temperature >37.5°C. The authors found that those patients treated in acute stroke units utilizing the fever, sugar, swallowing bundle had significantly lower mean temperatures, fewer temperatures >37.5°C, as well as improved modified Rankin Scale scores.
at 90 days postdischarge, indicating both improved care and patient outcomes. Because of the bundled approach of care, it is not clear to what extent reduction in fever burden directly impacted patient outcomes.

### Administration of Antipyretics

Administration of antipyretics for fever in patients after stroke is standard per AHA/ASA guidelines, and primary stroke centers in the United States most often use oral acetaminophen at dose of 650 mg every 4 hours. It is important for nurses to note that hypotension is a recognized side effect of intravenous administration of paracetamol/acetaminophen and requires close monitoring in acute stroke patients. High-dose paracetamol/acetaminophen (6 g daily for 3 days) was not found to improve stroke outcome at 3 months compared with control, but was found to improve outcome in subgroup analyses of persons presenting with an elevated temperature. The Paracetamol (Acetaminophen) in Stroke 2 (PAIS II) trial is now underway to examine the effect of high dose paracetamol on function in persons presenting with elevated temperature. The use of ibuprofen in the treatment of fever in patients after stroke is controversial. In the Paracetamol and Ibuprofen in Acute Stroke (PISA) trial, ibuprofen was found to be no more beneficial than placebo or acetaminophen in maintaining normothermia and has increased concerns of bleeding risk.

### Physical Cooling Measures

Physical cooling measures (eg, ice packs, air and water circulating blankets, water circulating pads, iced saline administration) have been reported to have mixed effectiveness in patients after stroke. Use of an indwelling catheter to measure temperature control has also been used to manage fever in persons after stroke, but these systems are not viewed as first-line therapies for management. It is important to note that during the chill phase of fever (when temperature is rising), it is critical to administer an antipyretic before use of physical cooling measures to avoid shivering, which increases oxygen use and metabolic demand. During chill phase, the body will attempt to resist physical cooling measures and use heat generating mechanisms to reach and defend a higher set point temperature. As a result, it is important to monitor for shivering using a validated assessment measure in any patient in whom physical cooling measures are used. The proper use of cooling blankets with neuroscience patients is important in this context as blanket temperatures are often set at the lowest setting, which may induce shivering and increase cerebral oxygen metabolism as a result of the increased temperature gradient. In the only study to date that has examined multiple blanket temperatures, a warmer temperature (24 versus 7°C) was as effective in reducing temperature during fever while promoting optimal comfort, but many protocols do not reflect this finding. Finally, the use of protective wraps or surface counterwarming measures on the hands, feet, and groin to prevent shivering when using physical cooling measures is an important element of any protocol.

### Implications for Future Research

There is a dearth of evidence available from both nursing and biomedical research regarding the optimal management approach to fever in the stroke patient. This is particularly true in relation to the evaluation of stepwise protocols to fever management and comparative effectiveness studies. As much of this management is multidisciplinary, the research should be as well. The guidance regarding monitoring and management of fever in the stroke patient is based on best available

### Table 1. Guidance Regarding Monitoring Fever in the Stroke Patient

<table>
<thead>
<tr>
<th>Monitoring Goal: Assess for Presence of Fever</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency</strong></td>
</tr>
<tr>
<td>Emergency Department: monitored along with other vital signs q30 minutes</td>
</tr>
<tr>
<td>Critical Care or Acute Stroke Unit: temperature minimally q 4 h; q 1 h if intervening for fever to assess intervention effectiveness until return to normothermia</td>
</tr>
<tr>
<td><strong>Site (in order of accuracy)</strong></td>
</tr>
<tr>
<td>Core* (bladder, rectal most common)</td>
</tr>
<tr>
<td>Oral</td>
</tr>
<tr>
<td>Tympanic</td>
</tr>
<tr>
<td>Temporal artery and Axilla not recommended for detection of fever*</td>
</tr>
</tbody>
</table>

*Core sites also include pulmonary artery, brain, esophageal; however, these are not frequently available in acute stroke patients.

### Table 2. Guidance Regarding Management of Fever in the Stroke Patient

<table>
<thead>
<tr>
<th>Management Goal: Keep Normothermic</th>
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</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
</tr>
<tr>
<td>Acetaminophen/paracetamol 650-1000 mg</td>
</tr>
<tr>
<td>Physical cooling measures</td>
</tr>
<tr>
<td><strong>Considerations</strong></td>
</tr>
<tr>
<td>Assess response; monitor for hypotension if administered IV; total dose not to exceed 4 g/day</td>
</tr>
<tr>
<td>Use only in combination with or following antipyretic administration</td>
</tr>
<tr>
<td>Monitor for shivering using validated scale</td>
</tr>
<tr>
<td>Consider use of protective wraps or counterwarming measures for greater effectiveness</td>
</tr>
</tbody>
</table>

*The only study to date that has examined multiple blanket temperatures, a warmer temperature (24 versus 7°C) was as effective in reducing temperature during fever while promoting optimal comfort, but many protocols do not reflect this finding. Finally, the use of protective wraps or surface counterwarming measures on the hands, feet, and groin to prevent shivering when using physical cooling measures is an important element of any protocol (Table 2).
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Evidence, yet not all of the recommendations are supported by Class I evidence and further randomized and pragmatic trials are needed. Development of a stronger evidence base for physical cooling measures for fever management is particularly needed. Bundling monitoring for and management of fever in stroke patients with other evidence-based care measures seems to have promise, but more replication is needed across other entities. Additionally, it is not clear if reduction of fever burden changes either immediate (neurological assessment) or later functional outcomes, and work in this area is necessary. Quality monitoring and improvement activities could be particularly useful in these assessments.

**Take-Home Points**

- Temperature should be monitored every 30 minutes while in the Emergency Department and minimally every 4 hours in the hospital. Recommended sites for monitoring in order of accuracy include core, oral, tympanic.
- There is a lack of specificity in guidelines for stroke for fever management; only antipyretics (acetaminophen/paracetamol) are endorsed and have strong evidence to support.
- Physical cooling should only be done in conjunction with antipyretics because of the potential to induce shivering. Development of a stronger evidence base for physical cooling measures for fever management in stroke patients is needed.
- The bundled approach to fever management shows promise for improving compliance with quality measures.

**Disclosures** None.

**References**


**Key Words:** ischemic stroke ■ outcome and process assessment ■ nursing
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