Chapter 1

Fever

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Fever is a regulated physiologic response in which a new thermal set-point for body temperature is established by the hypothalamus. In response, the body establishes a new equilibrium of heat loss and production to maintain homeostasis at the higher temperature.[1] Fever is distinguished from disorders of temperature regulation, such as hyperthermia (see Heat-Related Disorders), where heat production exceeds heat loss without an increase in the thermoregulatory set-point. Children <3 months of age and older adults (≥65 years of age) may not mount an elevated temperature in the presence of serious illness but instead remain normothermic or develop hypothermia.

Normal body temperature varies by 0.5°C throughout the day. A common definition of fever is a temperature consistently over 38°C (rectal or rectal equivalent).[2] The febrile response rarely exceeds 41–42°C.[1] The most frequent cause of fever is infection, which is part of a beneficial host response to control and eliminate pathogens.[3] Fever itself is not harmful. Some parents have exaggerated concerns about fever, a concept termed “fever phobia”; this concern should be addressed in the management plan.[4] Health-care professionals may also have misconceptions regarding fever.[5][6]

Malaise and fatigue may be seen at higher temperature or may be due to the underlying illness causing the fever. Discomfort characterized as headache, backache, myalgia, arthralgia, somnolence, chills and rigors may be associated with fever.

There is no evidence that fever aggravates comorbid disease states in patients with heart or pulmonary insufficiency.

Pathophysiology

The thermoregulatory centre in the anterior hypothalamus normally controls core temperature within a narrow range by balancing heat production by muscle and liver tissues with heat dissipation from skin and lungs. With fever, the thermoregulatory set-point is elevated.[7][8] Endothelial cells of the organum vasculosum laminae terminalis, a network of enlarged capillaries surrounding the hypothalamus, release arachidonic acid metabolites when exposed to pyrogens in the circulation. Prostaglandin E₂, released by the hypothalamus, is thought to be the major substance producing an elevation of the thermoregulatory set-point. Initially, with an elevated set-point, there is vasoconstriction of peripheral blood vessels to conserve heat, shivering to increase heat production, and behavioural changes such as seeking warmer environments and clothing. When the set-point is reduced through administration of antipyretics or disappearance of pyrogens, the reverse occurs—vasodilation and sweating to dissipate heat, as well as behavioural changes such as removal of clothing.[8]

Sources of pyrogens (substances that cause fever) are both exogenous and endogenous.[7][8] The most common exogenous sources are microorganisms and their products or toxins (e.g., lipopolysaccharide endotoxin of gram-negative bacteria). Exogenous pyrogens induce formation and release of endogenous pyrogens. Endogenous pyrogens or pyrogenic cytokines are polypeptides produced by host cell macrophages, monocytes and other cells. The most common are interleukin (IL) 1-alpha and...
1-beta, tumor necrosis factor (TNF) alpha, IL-6, ciliary neurotropic factor (CNF) and interferon (IFN) gamma.

**Goals of Therapy**
- Provide patient comfort
- Balance the benefit of symptomatic treatment with possible adverse effects and cost of medication
- In children, relieve parental anxiety
- In pregnant women during the 1st trimester, reduce risk of adverse fetal outcome(s)

**Patient Assessment and Investigations**

Figure 1 presents an algorithm for the assessment of patients with fever.

Fever is a symptom or sign, not a diagnosis. Most commonly, fever is an adaptive response to an infection, often viral. Fever may also occur in malignancy or in rheumatologic or immunologic diseases. Children <6 months of age with a fever should be assessed by an appropriate health-care practitioner.[10]

Fever persisting >3 days in those >6 months of age, recurrent fever or high fever (>40.5°C) should be evaluated by an appropriate health-care practitioner (see Figure 1 for red flags).

Although uncommon, fever may be drug-induced; Table 1 lists medications that may be associated with drug-induced fever.

### Table 1: Selected Drugs Associated with Fever[12][13][14]

<table>
<thead>
<tr>
<th>Allopurinol</th>
<th>Diltiazem</th>
<th>Methyldopa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>Doxepin</td>
<td>Metoclopramide</td>
</tr>
<tr>
<td>Antacid</td>
<td>Epinephrine</td>
<td>Mycophenolate</td>
</tr>
<tr>
<td>Antibacterials/antibiotics, e.g., cephalosporins, penicillins, SMX/TMP</td>
<td>Folic acid</td>
<td>Nifedipine</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Furosemide</td>
<td>NSAIDs, e.g., ibuprofen, naproxen</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Griseofulvin</td>
<td>Oral contraceptives</td>
</tr>
<tr>
<td>Antineoplastics, e.g., cisplatin, hydroxyurea</td>
<td>Heparin</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Hydralazine</td>
<td>Procainamide</td>
</tr>
<tr>
<td>Atropine</td>
<td>Hydrochlorothiazide</td>
<td>Propylthiouracil</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>H2-receptor antagonists (e.g., cimetidine)</td>
<td>Quinidine</td>
</tr>
<tr>
<td>Barbitaltes</td>
<td>Insulin</td>
<td>Quinine</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Interferon</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Clofibrate</td>
<td>Iodides</td>
<td>Salicylates</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Iron dextran</td>
<td>Sulfasalazine</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Isoniazid</td>
<td>Tacrolimus</td>
</tr>
<tr>
<td>Digoxin</td>
<td>MAOIs</td>
<td>Triamterene</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vitamins</td>
</tr>
</tbody>
</table>

**Abbreviations**
- MAOIs = monoamine oxidase inhibitors; NSAIDs = nonsteroidal anti-inflammatory drugs; SMX/TMP = sulfamethoxazole/trimethoprim

**Measurement of Body Temperature**

Measurement of “core” body temperature (e.g., viscera, major arteries) is invasive and impractical except in ICU settings; therefore the oral, rectal, axillary, temporal artery, tympanic membrane and transcutaneous routes are used to approximate core temperature. Different anatomic sites have different temperatures, so all are approximations of “body” temperature.[7] Although measurement
error can occur with any method, in children ≤5 years of age, *rectal* thermometry is the gold standard in Canada for definitive measurement of temperature.[2] Other temperature measurement methods can be used as a screening tool for low-risk children; these include *tympanic* temperature measurement in children ≥2 years of age and *axillary* temperature measurement in children of all ages.[2] In children >5 years of age and adults, *oral* thermometry is recommended for confirmation of fever.[2] Invasive measurement of temperature in critically ill adults and children, and temperature control in this population, is beyond the scope of this chapter.

The non-invasive methods of measuring temperature in the ambulatory setting (rectal, oral, axillary, ear/tympanic membrane, transcutaneous and temporal artery) are listed in Table 2.[10] Oral, rectal and axillary temperatures may be taken with an electronic thermometer with a digital display (digital probe). Normal, route-specific temperature ranges and preferred routes based on age are listed in Table 3.

**Table 2: Methods of Measuring Body Temperature**

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
<th>Instructions For Use</th>
</tr>
</thead>
</table>
| Rectal  | Recommended for definitive temperature measurement in children <2 y. Axillary temperatures are acceptable for screening low-risk children. It is contraindicated in premature infants, the immunocompromised and in the presence of rectal anomalies, recent anorectal surgery or severe hemorrhoids. A rare complication is perforation of the rectum. | - For children: place the infant on his or her back with knees bent or lay infant or young child face down across parent's lap or in fetal position on flat surface. For adults: lay patient in fetal position on flat surface.  
  - Lubricate anus and thermometer with petroleum jelly (pea-size quantity).  
  - With one hand, gently insert thermometer 2–3 cm into rectum.  
  - Hold buttocks closed against thermometer with other hand.  
  - Leave thermometer in place until it beeps and temperature is displayed. |
| Oral    | Can be used in children >5 y and adults. Not routinely recommended in children <2 y. Using this method may not be possible in individuals who have difficulty understanding instructions, e.g., the mentally impaired or elderly with dementia. Avoid the oral route when nasal breathing is difficult, e.g., due to viral upper respiratory tract infection; mouth breathing may cause spuriously low temperatures. Beverages, either hot or cold, and smoking should be avoided for at least 10 min prior to taking an oral temperature. | - Place thermometer on either side of mouth (between gum and cheek) or under the tongue.  
  - Hold in place with lips or fingers (not the teeth).  
  - Have patient breathe through nose with mouth closed.  
  - Leave thermometer in place until it beeps and temperature is displayed. |
| Axilla  | Axillary (armpit) temperatures are recommended for screening temperature assessment of low-risk children <5 y. Disadvantages of this route are the length of time needed to obtain a temperature and variation due to a number of factors including hypotension, cutaneous vasodilation and prior cooling of the patient. Although axillary temperatures are generally considered to be approximately 0.5°C lower than oral temperatures, reliable data are not available to support this correlation. The advantages of axillary temperatures are that this route is very accessible, safe and may be less frightening to children than rectal temperatures. The reading should be confirmed via another route if the axillary temperature is >37.2°C. | - Place thermometer in apex of axilla.  
  - Have patient hold elbow against chest to stabilize the thermometer.  
  - Leave thermometer in place until it beeps and temperature is displayed. |

(cont’d)
Table 2: Methods of Measuring Body Temperature (cont’d)

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
<th>Instructions For Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ear</strong>&lt;sup&gt;[16]&lt;/sup&gt;</td>
<td>The tympanic membrane and the hypothalamus share the same blood supply. The TT may better reflect core temperature measurements.&lt;sup&gt;[7]&lt;/sup&gt; The temperature is then converted by the thermometer to reflect oral or rectal temperatures, which may lead to some inaccuracy in the temperature reading. Proper placement in the ear canal is important.&lt;sup&gt;[11]&lt;/sup&gt; Improper placement can result in a lower reading that reflects the outer ear canal wall temperature.&lt;sup&gt;[11]&lt;/sup&gt; There may be a poor correlation between tympanic and rectal temperatures and a TT may not be sensitive enough to screen for fever in pediatric patients.&lt;sup&gt;[17][18][19]&lt;/sup&gt; Performance was good in adults, including the elderly.&lt;sup&gt;[20]&lt;/sup&gt; The Canadian Paediatric Society does not recommend a TT for children &lt;2 y.&lt;sup&gt;[10]&lt;/sup&gt; Advantages of a TT include simplicity, speed and patient acceptance.&lt;sup&gt;[15]&lt;/sup&gt; Less than 2 s is needed to obtain a reading. Other advantages include lack of external influences such as hot beverage ingestion and no mucous membrane contact; therefore, there is a decreased risk of disease transmission.&lt;sup&gt;[15]&lt;/sup&gt; Acute otitis media and nonobstructive cerumen do not appear to affect the accuracy of a TT.&lt;sup&gt;[21]&lt;/sup&gt; A disadvantage is the high cost of the thermometer.</td>
<td></td>
</tr>
</tbody>
</table>
| Transcutaneous | “Fever strips” contain encapsulated thermophototropic esters of cholesterol (called liquid crystals) that change colour in response to temperature changes. They are easier to read and require less time than a standard thermometer, but are less reliable because skin temperature is not a reliable indicator of core temperature.<sup>[7][11][19][22][23]</sup> When studied in emergency departments, fever strips were poor predictors of fever.<sup>[23][24]</sup> Accuracy is affected by ambient temperatures such as cold hands holding the strip or nearby heat sources such as a lamp. A truly febrile child may register as afebrile, possibly delaying medical attention. | • Follow specific manufacturers' directions as they may vary.  
• Apply a clean probe tip.  
• Gently tug on ear, pulling it back. This helps to straighten the ear canal so an accurate reading can be obtained.  
• Gently insert the thermometer into the ear until the ear canal is fully sealed off.  
• Squeeze and hold down the button for 1 s (or until the device beeps).  
• Remove from the ear and read temperature. |
| **Temporal artery (forehead)**<sup>[25]</sup> | Like the TT, the TA thermometer uses infrared technology to measure the temperature using a heat balance method.<sup>[26]</sup> Infrared sensors compute a temporal artery temperature by rapid, repeated measures to synthesize skin surface and ambient temperature. It is similar to a TT in that it is very quick (< 3 s) and avoids any mucous membrane contact.<sup>[26]</sup> It may be prone to less error than a TT<sup>[27]</sup> but is not considered as accurate as rectal temperatures in children.<sup>[27][28][29]</sup> A meta-analysis showed insufficient accuracy to substitute a TA thermometer for currently available temperature measurement methods.<sup>[30]</sup> | • Based on poor performance in studies, use cannot be recommended for children or adults.  
• Follow specific manufacturers' directions as they may vary.  
• Remove dirt, hair or sweat from forehead area.  
• Turn unit on.  
• Press button a 2nd time.  
• Place thermometer probe gently and flush onto the area approximately 1.25 cm above the centre of the eyebrow.  
• Sweep the skin from above eyebrow to temple until you hear a beep.  
• Read the temperature display. |

Abbreviations: TA = temporal artery; TT = tympanic thermometer
Table 3: **Normal Pediatric Temperature Ranges Associated with Measurement Technique**[10]

<table>
<thead>
<tr>
<th>Measurement Technique</th>
<th>Normal Temperature Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axilla</td>
<td>34.7–37.3°C (94.5–99.1°F)</td>
</tr>
<tr>
<td>Ear</td>
<td>35.8–38°C (96.4–100.4°F)</td>
</tr>
<tr>
<td>Oral</td>
<td>35.5–37.5°C (95.9–99.5°F)</td>
</tr>
<tr>
<td>Rectal</td>
<td>36.6–38°C (97.9–100.4°F)</td>
</tr>
</tbody>
</table>

**Therapeutic Choices**

**Nonpharmacologic Choices**

Nonpharmacologic interventions include removal of excess clothing and bedding, increased fluid intake to replace insensible water loss during fever, maintenance of ambient temperatures around 20–21°C, and avoidance of physical exertion.[10]

Physical methods for heat reduction use convection, evaporation or conduction to counteract the body's attempt to maintain a higher temperature set-point (fever). The body opposes physical cooling by attempting to re-establish a high temperature through shivering and vasoconstriction,[31] which are uncomfortable and theoretically could increase metabolic work. There are few studies comparing physical methods to antipyretics in children. Pharmacologic methods are preferred because they lower the hypothalamic set-point.[31]

In the rare instance where core temperatures exceed 41–42°C, physical methods may be used in addition to pharmacologic methods.

- Sponging with tepid or cold water uses evaporation to dissipate body heat. Sponging with alcohol is *not recommended* as it may be absorbed through the skin, inhaled or accidentally ingested by the patient. Sponging with alcohol has been associated with hypoglycemia, intoxication and coma.[32][33]

- Ice packs or cooling (hypothermia) blankets may be applied to the skin to lower body temperature by conduction.

- Circulating fans, sometimes directed over ice before reaching the patient, use convection to transfer heat away from the skin surface.

**Pharmacologic Choices**

There are many arguments against treating a fever:[7][8][34][35][36]

- Fever is an important defence mechanism; it enhances the immune response.

- Use of antipyretics may impair the use of temperature as an important clinical tool for monitoring the progress of an infection or response to antibiotics.

- Fever is usually self-limiting and, though sometimes distressing, the associated symptoms of fever (mild dehydration, discomfort, febrile delirium and febrile seizures) are usually not harmful.

Therefore, the decision to use antipyretics must be individualized. The goal should be reduction of fever rather than “normal” body temperature. Assessment of the patient should not depend solely on the elevation of temperature (see Figure 1).
Acetaminophen, ASA, ibuprofen and naproxen sodium are all currently indicated to reduce fever; however, naproxen and ASA should not be used in children. Antipyretics reduce body temperature in febrile patients by decreasing prostaglandin synthesis in the brain and reducing the thermoregulatory set-point. They do not lower normal body temperature. Short-term treatment with these drugs is associated with few side effects. Intermittent administration of antipyretics may result in drug-induced fluctuations in temperature and concomitant shivering, which may make the individual feel worse. Use at regular intervals may reduce patient discomfort and the risk of increased metabolic demand caused by shivering.

There is no evidence that reduction of temperature via antipyretic therapy is beneficial; thus, the main goal of antipyretic therapy in non-pregnant patients is patient comfort. In a pregnant patient who is in her 1st trimester, the goal of antipyresis is protection of the fetus.

In theory, antipyretic therapy may be justified if the metabolic demands of fever (increased metabolic rate, norepinephrine-mediated peripheral vasoconstriction, increased oxygen consumption) are greater than the clinical benefits. As a result, textbooks still recommend aggressive antipyretic therapy in patients with underlying pulmonary or cardiovascular disease despite the lack of evidence to support this practice. Similarly, antipyretics are recommended by some experts to reverse fever-induced mental dysfunction in the elderly, but benefits of this practice have not been studied clinically.

Available antipyretics also have analgesic effects, which can decrease discomfort if present. Most guidelines for children recommend consideration of antipyretics only for febrile children who appear distressed or unwell. Evidence indicates that antipyretic therapy does not prevent febrile seizures, a phenomenon that may occur in children about 6 months to 6 years of age.

A response to antipyretic therapy does not exclude the possibility that serious underlying illness is present. Clinical decision-making should not be based on response to fever treatment.

Acetaminophen and ibuprofen are the therapeutic agents most commonly used for reducing fever. Naproxen sodium and ASA are antipyretic options available for adults. Acetaminophen and ibuprofen have been studied in large populations and are considered safe in therapeutic doses. National guidelines for children in the United States and the United Kingdom recommend use of antipyretics only for the treatment goal of patient comfort. The dose, frequency of administration and adverse effects associated with acetaminophen and ibuprofen differ (see Table 4). With regard to efficacy in temperature reduction in children, a systematic review of randomized trials showed comparable efficacy of a single dose of either acetaminophen or ibuprofen in terms of pain relief, with about 15% more children in the ibuprofen group having temperature reduction at 4 and 6 hours. The clinical significance of these marginal benefits is unclear.

ASA is not recommended in children or adolescents because of the potentially increased risk of Reye syndrome. Naproxen sodium is the most recent nonprescription NSAID available for fever. It has a longer half-life with a corresponding less frequent administration schedule. There are no data on the use of naproxen sodium for treatment of fever in children.

Some clinicians recommend alternating acetaminophen and ibuprofen administration to reduce fever; however, there is insufficient evidence to support this as a routine practice and it is not recommended. While alternating or combining acetaminophen and ibuprofen may result in a greater period of time without fever, the clinical benefit of this difference is uncertain. It is important to note that no difference was found in patient discomfort in the only 2 trials that assessed it. This practice has not been shown to be either safe or more effective in improving discomfort than a single antipyretic. In addition, potential risks of prescribing 2 antipyretics may include parental confusion and dosing errors with associated toxicity.
Acetaminophen is safer than NSAIDs in older individuals who have risk factors predisposing to gastrointestinal and renal toxicity.

**Optimizing Antipyretic Dosing and Administration in Children**

Review the following points with all parents when recommending an antipyretic preparation for a child:

- Ensure parents/caregivers understand that fever is rarely harmful and does not have to be treated.
- Explain that comfort is the goal and not achievement of an arbitrary “normal” temperature.
- Assist parents in calculating the correct weight-based dose (mg/kg) of the drug and ensure they know the maximum number of doses that can be administered in a 24-hour period.
  - In a study of 100 caregivers given a mock dosing scenario that required them to determine and measure a correct dose of acetaminophen for their child, only 40% stated an appropriate dose for their child.[49]
  - Of 118 children given an antipyretic at home and subsequently brought to the emergency department, only 47% had been given a proper dose.[50] Underdosing may be a cause of unnecessary emergency department visits.[51] This also leads to added stress for both the parent and sick child.[52]
- Ensure the parent has and will use an appropriate measuring device.
  - In the mock dosing study reported above, only 67% of caregivers accurately measured the amount they intended to give. Forty-three percent measured out a correct amount of acetaminophen; however, 30% of these did so by accident by inaccurately measuring an improper dose.[49]
  - Consider demonstrating the correct use of the dosing device. Ask the caregiver to repeat instructions back to you. It may be helpful to mark the dosing device with the correct dose.[53]
- Ask what form of product they have at home and calculate the appropriate volume of liquid or number of tablets for the child. Explain the differences in concentration between drops and syrup and that tablets come in different strengths for children.[53]
  - Multiple miscalculated overdoses of acetaminophen given by parents represent an important cause of acetaminophen toxicity.[54][55][56]
  - Use of incorrect measuring devices, differences in medication concentrations (e.g., pediatric drops vs. suspensions), use of adult formulations for pediatric patients and unrecognized acetaminophen content in multiple-ingredient cough and cold products contribute to this problem.[55]
- Ask about other preparations parents may be coadministering and ensure they are aware of the antipyretic content of these products. The coadministration of these products should be carefully monitored to ensure the cumulative dose is within the recommended range.

**Choices during Pregnancy and Breastfeeding**

Studies in humans suggest that exposure to fever and other heat sources during the 1st trimester of pregnancy is associated with increased risk of neural tube defects and multiple congenital abnormalities[57][58] and therefore temperature reduction may be considered in these patients. Although 1 study indicated a possible benefit of antipyretic therapy,[59] others have not[60] and a recent meta-analysis suggests additional research is required.[61]

*Acetaminophen* crosses the placenta and is relatively safe for short-term use in pregnancy when therapeutic doses are used.[62]
Use of ASA and NSAIDs can result in a number of problems during pregnancy such as interference of labour and premature closure of the ductus arteriosus resulting in many effects including persistent pulmonary hypertension in the infant. Platelet aggregation is inhibited in the newborn if ASA is ingested by the mother within 7 days of delivery and salicylates displace bilirubin from protein binding sites. Increased bleeding has been reported in both mothers and infants if ASA is ingested close to the time of delivery.\[63\] ASA and NSAIDs should be avoided in the 1st and 3rd trimesters of pregnancy; however, low-dose ASA (81 mg) is considered compatible with pregnancy.\[62\]

Both acetaminophen and ibuprofen are considered safe to take while breastfeeding.\[62\]

For more information, see Pregnancy and Breastfeeding: Self-care Therapy for Common Conditions.

**Monitoring of Therapy**

Recommendations for frequent monitoring of temperature likely contribute to parental concern and fever phobia. The temperature should be taken if the patient feels warm or looks ill, to determine the initial temperature. Subsequently, temperatures need not be taken more than 2–4 times daily unless the patient has recently received chemotherapy, for which referral to the emergency department is of utmost importance (see Figure 1 for “red flags”). In adults, if the fever persists for 24 hours without an apparent cause, or for more than 3 days, medical attention should be sought. The degree of illness and not the temperature should guide therapy and referral.

Monitor:

- All patients given antipyretics for development of rash or allergic reactions
- Patients with pre-existing comorbid illness for edema and decreased urine output
- For signs and symptoms of dehydration; if NSAIDs are used, discontinue the drug immediately if dehydration occurs
- For common side effects, such as GI intolerance and tinnitus (see Table 4)
- To ensure appropriate doses, products and measuring devices are being used
- To ensure the patient is not receiving more than the maximum recommended dose of any antipyretic, e.g., through use of coadministered cough and cold or analgesic products
- To ensure the patient is not receiving interacting medications (see Table 4); recommend avoiding alcohol

**Therapeutic Tips**

- Ask about other concomitant preparations (particularly cough and cold products) and ensure patients/caregivers are aware of the antipyretic content of these products. The coadministration of these products should be carefully monitored to ensure the cumulative dose is within the recommended range.
- In children, use doses of acetaminophen or ibuprofen based on the child's weight, not on age. Maximum dose per day should be specified.
- Concentrations of liquid acetaminophen and ibuprofen preparations vary according to product. Remind caregivers to check the concentration of a product each time medication is given.
- Acetaminophen is the drug most frequently involved in analgesic overdose in children <6 years of age. Store antipyretics in locked cabinets to prevent inappropriate access. Instruct parents to use a calibrated measuring device, and educate them about the many formulations available and the potential for error with substitution or the combination of products.
Figure 1: **Assessment of Patients with Fever[^7][^9][^10][^11]**

In a patient presenting with fever, if any of the following are true, refer patient to the emergency department immediately:
- Age <3 months
- Presence of stiff neck, seizure, localized pain, redness, swelling or heat
- New wheeze/cough
- Recent cancer therapy, e.g., chemotherapy
- In children: appearing very ill, excessively fussy, irritable, crying inconsolably or other symptom(s) worrying the parents

If none of the above are true, assess for any additional red flags:
- Age <6 months
- Fever >40.5°C
- Persistent wheeze/cough
- New onset rash and fever
- Difficult to rouse, confused or delirious
- Presence of serious underlying illness
- Recent surgery or dental procedure
- Recent travel
- Recent consumption of raw or undercooked meat or fish
- Recent initiation of new medication

If the patient is requesting advice on how to manage fever, consider recommending self-care comfort measures:
- Antipyretic therapy (see Table 4) is generally *not* recommended but can be used to improve comfort (see Pharmacologic Choices)
- Additional comfort measures, e.g., removal of excess clothing and bedding, increased fluid intake, ambient temperature set at 20–21°C, avoidance of physical exertion. On a case-by-case basis, consider other comfort measures such as a heating pad if earache is present, a cold drink/treat (e.g., Popsicle) in the case of sore throat

Fever persists >24 h without obvious cause and/or new, concerning symptoms have arisen?

- Yes
- No

Fever resolved after 72 h?

- Yes
- No

No further treatment required. Discontinue antipyretic, if one has been used

[^7]: Reference 7
[^9]: Reference 9
[^10]: Reference 10
[^11]: Reference 11
Table 4: **Drug Therapy for Fever**

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Dosage</th>
<th>Adverse Effects</th>
<th>Drug Interactions</th>
<th>Comments</th>
<th>Cost[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td><em>ibuprofen</em></td>
<td>Children &lt;6 months: 5 mg/kg Q8H PO PRN; maximum 40 mg/kg/day; do not exceed the adult dose</td>
<td>Uncommon with infrequent use and recommended dose. GI intolerance and bleeding, allergic reactions, tinnitus, visual disturbances, nephropathy. Sodium and water retention. Dehydration enhances risk of renal toxicity. Platelet dysfunction can result in increased bleeding risk.</td>
<td>Increased risk of GI pain/ulceration with alcohol, corticosteroids. Antagonism of hypotensive effects of ACE inhibitor, beta-blockers, diuretics. Increased risk of bleeding with anticoagulants, SSRIs. Increased levels of cyclosporine (and risk of nephrotoxicity) with methotrexate [b], lithium. Reduction of ASA antiplatelet effects.</td>
<td>Renal dysfunction: no adjustment required; however, should be avoided in renal dysfunction due to effects of prostaglandin inhibition on renal function. Do not give if dehydration is present; ensure patient has adequate intake of fluids. NSAIDs have been associated with an increased risk of severe skin and soft tissue infections in children with chicken pox and to a lesser extent in adults with shingles. Limited data exist for the use of ibuprofen in children &lt;2 months of age. Some nonprescription products contain ibuprofen in combination with other drugs; advise parents/caregivers to check labels carefully to avoid inadvertent administration of excessive doses.</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td><em>naproxen sodium</em></td>
<td>Children &lt;12 y: not recommended</td>
<td>See ibuprofen.</td>
<td>See ibuprofen.</td>
<td>See ibuprofen.</td>
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</tr>
<tr>
<td>Class</td>
<td>Drug</td>
<td>Dosage</td>
<td>Adverse Effects</td>
<td>Drug Interactions</td>
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<td>---------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Para-aminophenol Derivatives</td>
<td>acetylsalicylic acid</td>
<td>Children: 10–15 mg/kg Q4–6H PO PRN for symptom management; maximum 75 mg/kg/day; do not exceed the adult dose Adults: 325–650 mg Q4-6H PO/PRN; maximum 4000 mg/day</td>
<td>Uncommon with infrequent use and recommended dose. Hypersensitivity, agranulocytosis, anemia (rare). Chronic use and overdose associated with hepatotoxicity, nephropathy. Potential for toxicity enhanced if concurrent dehydration, prolonged fasting, diabetes mellitus, obesity, concomitant viral infection or family history of hepatotoxic reaction.</td>
<td>Increased risk of hepatotoxicity with alcohol and isoniazid. Decreased acetaminophen levels with enzyme inducers, e.g., barbiturates, carbamazepine, phenytoin. Acetaminophen has been reported to increase INR in warfarin-treated patients. Check INR if acetaminophen ≥2 g/day is used for ≥3 consecutive days. Adjust warfarin dosage as required.</td>
<td>Use with caution in patients with liver dysfunction or active liver disease. Rectal administration results in erratic absorption and should be used under HCP supervision. Available as oral drops, tablets, chewable tablets, suppositories and suspension. Acetaminophen may be associated with exacerbation of wheezing in febrile children. Many nonprescription products contain acetaminophen in combination with other drugs. Advise patients/caregivers to check labels carefully to avoid inadvertent administration of excessive doses.</td>
<td>$</td>
</tr>
<tr>
<td>Salicylates</td>
<td>ASA</td>
<td>Children &lt;18 y: not recommended; avoid use Adults: 325–650 mg Q4–6H PO PRN; maximum 4000 mg/day</td>
<td>GI upset. Avoid in patients with renal failure, peptic ulcer disease, heart failure and ASA-sensitive asthma. See ibuprofen. ASA may decrease therapeutic effect of uricosuric agents, e.g., probenecid, sulfinpyrazone.</td>
<td>Avoid if ClCr &lt;10 mL/min. Enteric-coated products will have delayed onset of action.</td>
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</tr>
</tbody>
</table>

[a] Cost per day; includes drug cost only.
[b] More likely to occur with antineoplastic doses of methotrexate.

Abbreviations
ACE = angiotensin-converting enzyme; ClCr = creatinine clearance; GI = gastrointestinal; HCP = health-care provider; INR = international normalized ratio; NSAID = nonsteroidal anti-inflammatory drug; SSRI = selective serotonin-reuptake inhibitor

Legend:  $ < $1
Suggested Readings


References