

Chapter 9

Fever

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Fever, which is a regulated elevation in core body temperature, is generally considered to be caused by infection; however, noninfectious causes include inflammatory diseases, neoplasms and immunologically mediated conditions such as some drug fevers.^{1,2} The definition of fever varies; anything above the normal range for body temperature can be defined as fever.^{1,2} Fever in children is most often defined as rectal temperature $>38^{\circ}\text{C}$ if the child is appropriately dressed and resting.³ In adults and children, an individual's body temperature varies with the time of day (normal circadian variation); it is lowest at approximately 6 a.m. and highest between 4 and 6 p.m.¹ The mean amplitude of variability is 0.5°C . Oral temperatures $>37.2^{\circ}\text{C}$ in early morning or $\geq 37.8^{\circ}\text{C}$ any time during the day may also be used to define fever.^{1,4} Outside the neonatal period, children generally have a higher temperature than adults; however, this is poorly documented.^{5,6} Basal core temperatures decrease toward the adult range by 1 year of age and continue to decline until puberty. In children, the height of the temperature elevation has been correlated to the likelihood of serious bacterial infection. Children with temperatures $>41.1^{\circ}\text{C}$ have an increased likelihood of serious bacterial infections.^{3,6} The degree of response to antipyretics does not distinguish serious bacterial infections from viral infections.³

Mild elevations in body temperature occur with exercise, ovulation, pregnancy, excessive clothing (overbundling of infants), ingestion of hot foods or liquids and chewing gum or tobacco.¹

Rectal temperatures are approximately 0.6°C higher and axillary temperatures approximately $0.5\text{--}1^{\circ}\text{C}$ lower than oral temperatures.³ A high fever is usually defined as a temperature $>40.5^{\circ}\text{C}$. Fever is a regulated physiologic response and temperatures $>41^{\circ}\text{C}$ are rare.^{2,7}

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.^{1,2} 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 E_2 , 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, for example, by administering antipyretics or disappearance of pyrogens, the reverse occurs; vasodilation and sweating to dissipate heat, as well as behavioural changes such as removal of clothing.²

Sources of pyrogens, substances that cause fever, are both exogenous and endogenous.^{1,2} The most common exogenous sources are microorganisms, 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 1α and 1β (IL 1α and 1β), tumor necrosis factor alpha (TNF α), IL-6, ciliary neurotropic factor (CNF) and interferon gamma (IFN γ).

Goals of Therapy

- Provide patient comfort
- Reduce parental anxiety
- Reduce metabolic demand caused by fever in patients with cardiovascular or pulmonary disease
- Prevent or alleviate fever-associated mental dysfunction in the elderly (common practice but evidence is unclear)

Patient Assessment (Figure 1)

Fever is a symptom or sign of illness, not a disease, and the reason for fever should be determined.³ Most commonly it is due to infection, often viral. Fever persisting longer than 3 days in those >6 months, recurrent fever or high fever (>40.5°C) should be evaluated by a physician.

Once fever is established, the body initiates processes to permit homeostasis. Peripheral vasodilation causes the skin to feel hot. Sweating may occur. Malaise and fatigue may be seen at higher temperatures. Headache,

backache, myalgia, arthralgia, somnolence, chills and rigors may also be associated with fever.

Drug-induced fever is a symptom of hypersensitivity but can occur with other symptoms such as myalgia, chills and headache. Table 1 lists several medications associated with drug-induced fever.^{9,10,11}

Fever differs from hyperthermia, which is an increase in core temperature without an increase in hypothalamic set point. If hyperthermia is suspected, refer the patient to a physician; antipyretics are not useful (see Chapter 10, Heat-related Disorders).

Figure 1: **Assessment of Patients with Fever**^{1,3,6,8}

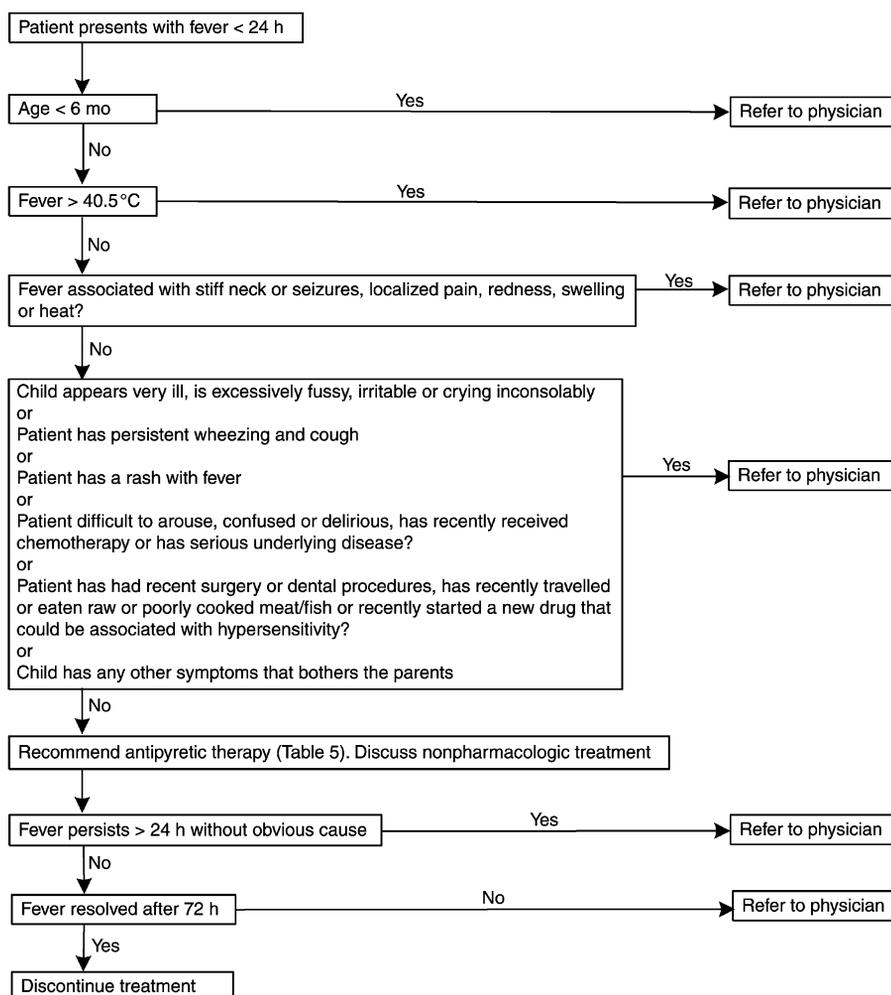


Table 1: Selected Drugs Associated with Fever^{9,10,11}

Allopurinol	Doxepin	NSAIDs (e.g., ibuprofen, naproxen)
Amphotericin B ^a	Epinephrine	Neuroleptics
Antacids	Folic acid	Nifedipine
Antibacterials/antibiotics (e.g., cephalosporins, penicillins, SMX/TMP)	Furosemide	Oral contraceptives
	Griseofulvin	Phenytoin
	Heparin	Procainamide ^a
	Hydralazine	Propylthiouracil
Anticholinergics	Hydrochlorothiazide	Quinidine ^a
Antihistamines	H ₂ -receptor antagonists (e.g., cimetidine)	Quinine ^a
Antineoplastics (e.g., cisplatin, hydroxyurea ^a)	Insulin	Rifampin
Atropine	Interferon	Salicylates
Azathioprine ^a	Iodides	Streptokinase
Barbiturates	Isoniazid	Sulfasalazine
Carbamazepine	Iron dextran	Sulindac
Clofibrate	Metoclopramide	Tacrolimus
Corticosteroids	Methyl dopa ^a	Triamterene
Cyclosporine	MAOIs	Vitamins
Digoxin	Mycophenolate	
Diltiazem		

^a Drugs associated with >5 case reports of drug fever.

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

Measurement of Body Temperature

For available products consult Home Testing Products: Thermometers in *Compendium of Self-Care Products*.

There are a number of ways to measure temperature in an ambulatory setting—oral, rectal, axillary, tympanic membrane, temporal artery and transcutaneous routes (Table 2).⁸ Oral, rectal and axillary temperatures may be taken with an electronic thermometer with a digital display (digital probe). Standard mercury in glass thermometers are no longer recommended due to potential toxicity if they break,⁸ environmental concerns and problems with proper use including long equilibration times, difficulty reading them properly and failure to reset the thermometer. Electronic thermometers are safer and easier to use because they are faster, easier to read and avoid the environmental concerns of mercury. Generally, equilibration times require 30–60 seconds, while up to 10 minutes are required for standard glass thermometers.

Normal temperature ranges associated with various routes and recommended routes based on age are listed in Table 3 and Table 4.

Nonpharmacologic Therapy

Nonpharmacologic interventions include removal of excess clothing and bedding, increased fluid intake to replace increased insensible water loss in fever, maintenance of ambient temperatures around 20–21°C and avoidance of physical exertion.⁸

Sponging increases evaporation to promote heat loss. Tepid water sponging may be useful to reduce body temperature; however, it does not reset the hypothalamic set point.²⁹ Therefore, to maintain the elevated temperature the body actually works harder by shivering (results in increased oxygen consumption). As well, sponging often causes significant patient discomfort.³⁰ Studies show no additional benefit from sponging after antipyretic administration.^{31,32,33} If used, administer antipyretics 30 minutes before sponging to reduce hypothalamic set point.

Tepid sponging, if performed, should be done with water only. Isopropyl alcohol has resulted, rarely, in hypoglycemia, intoxication and coma as a result of absorption through the skin or inhalation of fumes and is not recommended.^{30,34}

Pharmacologic Therapy

There are many arguments against treating a fever.^{1,2,35,36,37}

- 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-limited and the most common consequences of fever are generally harmless—mild dehydration, febrile delirium, febrile seizures and discomfort.

Therefore, the decision to use antipyretics must be individualized. Reduction of fever, not “normal” body temperature, may be the goal. Assessment of the patient should not depend solely on the elevation of temperature (Figure 1).

Acetaminophen, ASA, ibuprofen and naproxen sodium are all currently indicated to reduce fever. These drugs reduce body temperature in febrile patients by decreasing prostaglandin synthesis in the brain and reducing the hypothalamic set point.^{1,35} 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 improve patient discomfort and reduce the risk of increased metabolic demand with shivering.

Acetaminophen is a relatively safe and effective antipyretic with few contraindications, and can be used in any age group.^{38,39} Many years of clinical experience is also an advantage. Using a loading dose of acetaminophen has been studied.⁴⁰ A 30 mg/kg loading dose in children 4 months to 9 years of age resulted in a more rapid and sustained response and a greater reduction in temperature compared to 15 mg/kg. Although this strategy is used in some emergency departments, the safety of this practice has

not been evaluated and the dose is an initial dose only; subsequent doses should be 10–15 mg/kg. Do not recommend a loading dose to parents. Acetaminophen overdose resulting in hepatotoxicity remains a concern. The Food and Drug Administration in the USA is considering a number of warnings and changes regarding acetaminophen⁴¹ while Health Canada has developed a labelling standard which includes warnings regarding hepatotoxicity and maximum package sizes for pediatric products.⁴² It is the preferred agent in those with renal dysfunction or risk factors for GI bleeding.

Standard dosing is provided in Table 5.

Table 2: Methods of Measuring Body Temperature

Rectal	Instructions for use in children⁸
<p>Is considered the most accurate and the standard against which other routes of temperature measurement is compared.^{1,7,12}</p> <p>This route is preferred for newborns, in children less than 4–5 years old when an axillary temperature is not sufficient, and when the oral route is not suitable due to mouth breathing. May be less acceptable to toddlers. It is contraindicated in premature infants,¹ the immunocompromised⁷ and in the presence of rectal anomalies, recent anorectal surgery or severe hemorrhoids. A rare complication is perforation of the rectum. This route may also transmit infections.⁷</p>	<ul style="list-style-type: none"> • Place the infant on his back with knees bent or lay infant or young child face down across parent's lap or 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	Instructions for use⁸
<p>This route can be used in children over 5 years old and adults;⁷ younger children may bite the thermometer or have difficulty keeping it in the closed mouth. This may also be a problem for individuals who have difficulty understanding instructions, e.g., the mentally impaired or elderly with dementia.¹</p> <p>Avoid the oral route when nasal breathing is difficult (e.g., due to viral upper respiratory tract infection); mouth breathing will cause spuriously low temperatures. Beverages, either hot or cold, and smoking should be avoided for at least 10 minutes prior to taking an oral temperature.^{1,7}</p>	<ul style="list-style-type: none"> • 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). • Breathe through nose with mouth closed. • Leave thermometer in place until it beeps and temperature is displayed.
Armpit	Instructions for use⁸
<p>Axillary (armpit) temperatures have many disadvantages.⁷ They take a longer time to measure and are affected by a number of factors including hypotension, cutaneous vasodilation and prior cooling of the patient. Axillary temperature may be a poor alternative to rectal temperatures in children aged 3 months to 6 years.^{13,14}</p> <p>Although axillary temperatures are generally considered to be approximately 0.5°C lower than oral temperatures, reliable data are not available to correlate axillary with oral or rectal temperatures. The advantages of axillary temperatures are that this route is very accessible, safe and less frightening to children than rectal temperatures.⁷ The reading should be confirmed via another route if the axillary temperature is >37.2°C.</p>	<ul style="list-style-type: none"> • Place thermometer in apex of axilla. • 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)

Ear	Instructions for use ²⁰
<p>Tympanic thermometers (TT) measure infrared emissions from the tympanic membrane.^{1,15}</p> <p>Because the tympanic membrane and the hypothalamus share the same blood supply, these thermometers are considered to reflect core temperature measurements.¹ The temperature is then converted by the thermometer to reflect oral or rectal temperatures, which may lead to some inaccuracy in the temperature reading. The aiming of the ear probe and proper placement in the ear canal are important for accurate measurements.⁶ Improper placement can result in a lower temperature reading from a lower outer ear canal wall temperature.⁶ There may be a poor correlation of TT with rectal temperatures and this route may not be sensitive enough to screen for fever in pediatric patients^{16,17,18} although performance was good in adults, including the elderly.¹⁹ It is not recommended for children less than 2 years of age by the Canadian Paediatric Society.⁸</p> <p>The advantages of TT include simplicity, speed and patient acceptance.⁷ Less than 2 seconds is needed to obtain a reading. Other advantages include lack of external influences such as hot beverage ingestion, and no mucous membrane contact, therefore minimal risk of disease transmission.⁷ Acute otitis media and nonobstructive cerumen do not appear to affect the accuracy of TT.¹⁵</p> <p>A disadvantage is high cost.</p>	<ul style="list-style-type: none"> • 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 second (or until the device beeps). • Remove from the ear and read temperature.
Plastic colour-changing strips (transcutaneous)	Instructions for use
<p>One transcutaneous route uses a plastic strip that is placed on the forehead for 1 minute and indicates temperature by changing colour.²¹</p> <p>The strip contains 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.^{1,6,7,8,21,22} The strip incorporates a correction factor for this but assumes the factor is the same in all individuals. When studied in emergency departments, they were poor predictors of fever.^{22,23} Their accuracy is affected by ambient temperature (e.g., cold hands holding the strip and nearby heat sources such as a lamp). Because they can register afebrile temperatures in a truly febrile child, possibly delaying medical attention, their use is not recommended.</p>	<ul style="list-style-type: none"> • Place on forehead for 1 minute. • Use not recommended in children.
Temporal artery (Forehead)	Instructions for use ²⁸
<p>Like the tympanic thermometer, the temporal artery thermometer (TAT) uses infrared technology to measure the temperature using a heat balance method.²⁴</p> <p>Infrared sensors compute a temporal artery temperature by rapid, repeated measures to synthesize skin surface and ambient temperature. It has similar advantages as the TT in that it is very quick (3 seconds) and avoids any mucous membrane contact.²⁴</p> <p>It may be prone to less error than the TT²⁵ but is not considered as accurate as rectal temperatures in children.^{25,26,27}</p>	<ul style="list-style-type: none"> • Follow specific manufacturers' directions as they may vary. • Remove dirt, hair or sweat from forehead area. • Turn unit on. • Press button a second 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: TAT = temporal artery thermometer; TT = tympanic thermometer

Table 3: **Normal Pediatric Temperature Ranges Associated with Measurement Technique⁸**

Measurement Technique	Normal Temperature Range
Rectum	36.6°C–38°C (97.9°F–100.4°F)
Mouth	35.5°C–37.5°C (95.9°F–99.5°F)
Armpit	34.7°C–37.3°C (94.5°F–99.1°F)
Ear	35.8°C–38°C (96.4°F–100.4°F)

Source: Canadian Paediatric Society, 2008. "Fever and Temperature Taking". For more information, visit www.caringforkids.cps.ca.

Table 4: **Recommendations for Temperature Measuring Techniques⁸**

Age	Recommended Technique	
Birth to 2 y	First choice:	Rectum (for an exact reading)
	Second choice:	Armpit (to check for fever)
	Not recommended:	Tympanic membrane thermometers
Between 2 and 5 y	First choice:	Rectum
	Second choice:	Ear, armpit
Older than 5 y	First choice:	Mouth
	Second choice:	Ear, armpit

Source: Canadian Paediatric Society, 2008. "Fever and Temperature Taking". For more information, visit www.caringforkids.cps.ca.

Ibuprofen is an alternative to acetaminophen when there are no contraindications to its use. There is less experience with it and it is more expensive, but with short-term use in children there appears to be no difference in adverse event rates compared to acetaminophen.^{44,45,46,47} However, renal failure in children has been reported, particularly when the child is dehydrated, therefore avoid in children with diarrhea and vomiting.^{8,48} In one study, time without fever in the first 4 hours after administration was greater with ibuprofen than acetaminophen and time to fever clearance was shorter with ibuprofen.⁴⁹ A meta-analysis showed that ibuprofen (5–10 mg/kg) as compared to acetaminophen (10–15 mg/kg) was a better antipyretic producing greater temperature reductions at 2, 4 and 6 hours after dosing.⁵⁰ Ibuprofen may also have a longer duration of action⁵⁰ than acetaminophen and is less toxic in overdose.^{51,52}

ASA should be avoided in children less than 18 years old who have a viral illness because of its associa-

tion with Reye's syndrome in influenza and varicella. Reye's syndrome consists of acute encephalopathy with cerebral edema, fatty infiltration of the liver and metabolic derangements such as hypoglycemia. It occurs in otherwise previously healthy children. Since the cause of fever is unknown initially in many circumstances, avoid ASA in children.^{53,54,55}

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.

Alternating Antipyretics

In the past, alternating acetaminophen with ASA for management of fever unresponsive to a single agent was recommended. Since ASA is no longer recommended in children and adolescents because of an association with Reye's syndrome, this practice has been abandoned. However, recommendations to alternate acetaminophen with ibuprofen have emerged.^{56,57} Alternating or combining acetaminophen and ibuprofen has not been shown to be either safe or more effective than a single antipyretic.^{49,58,59,60,61} This recommendation is often confusing to caregivers and could result in increased dosing errors.^{62,63}

Table 5 outlines dosing, side effects, contraindications, precautions and toxicity in overdose of ASA, acetaminophen, ibuprofen and naproxen sodium.

Fever in Specific Patient Groups

Children

Young children have an immature central nervous system thermoregulatory system, and in the first 2 months of life may have minimal or no fever during an infectious illness. Since neonates and infants are less able to mount a febrile response, when they do become febrile, it is more likely to indicate a major illness. After 3 months of age, the degree of fever more closely approximates that seen in older children.⁶⁴

Fever is common in children and is usually due to bacterial or viral infection. Because children have had less exposure than adults to infectious agents, they are more susceptible upon initial contact. Reactions to vaccinations may also be a cause of fever. Compared to adults, children are more sensitive to ambient temperature (due to a greater body surface area for heat exchange) and at higher risk for dehydration.⁶⁴

Table 5: Drug Therapy for Fever

For available products consult Analgesic Products: Internal Analgesics and Antipyretics; Baby Care Products: Antipyretics in *Compendium of Self-Care Products*.

	<i>Acetaminophen</i>	<i>Ibuprofen</i>	<i>ASA</i>	<i>Naproxen Sodium</i>
Dose				
Adults	325–650 mg Q4-6H po/pr PRN (maximum 4 g/day)	200–400 mg Q4-6H po PRN (maximum 1.2 g/day)	325–650 mg Q4-6H po PRN (maximum 4 g/day)	220 mg Q8-12H po PRN (maximum 440 mg/day) Age >65: 220 mg Q12H po
Children	10–15 mg/kg Q4-6H po/pr PRN (no greater than 5 doses per day or 65 mg/kg/day)	5–10 mg/kg Q6-8H po (maximum 4 doses per day or 40 mg/kg/day)	Use not recommended	≥12 y: adult dose
Dosing in renal dysfunction	ClCr 10–50 mL/min: extend interval from Q4 to Q6H ClCr <10 mL/min: Q8H	No adjustment in renal dysfunction required ^a	ClCr 10–50 mL/min: extend interval from Q4 to Q6H Avoid if ClCr <10 mL/min ^a	Avoid if ClCr <30 mL/min ^a
Onset of effect	30 min	Within 1 h	Within 1 h	20 min (pain relief; no data for fever)
Time to peak effect	3 h	2–4 h	3 h	No data
Duration	4–6 h	6–8 h	4–6 h	No data
Adverse effects	Repeated dosing at or slightly above upper limit of recommended doses may result in severe hepatic toxicity	Dyspepsia, heartburn, abdominal pain, diarrhea GI bleeding Dizziness, headache, nervousness, fatigue, irritability Skin rash Allergic reactions Reduced renal function, acute renal failure Sodium and water retention Platelet dysfunction	Dyspepsia, heartburn, abdominal pain, diarrhea, rectal irritation (suppositories) GI bleeding Skin rash Allergic reactions Sodium and water retention Platelet dysfunction	Dyspepsia, heartburn, abdominal pain, diarrhea GI bleeding Dizziness, headache, lightheadedness, drowsiness, insomnia Skin rash Allergic reactions Reduced renal function, acute renal failure Sodium and water retention Platelet dysfunction

For available products consult Analgesic Products: Internal Analgesics and Antipyretics; Baby Care Products: Antipyretics in *Compendium of Self-Care Products*.

	Acetaminophen	Ibuprofen	ASA	Naproxen Sodium
Contraindications/ Precautions	Hypersensitivity Chronic alcohol consumption Malnutrition/fasting	Peptic ulcer disease, GI perforation or bleeding Hypersensitivity Bleeding disorders Concomitant alcohol use Individuals who rely on vasodilatory renal prostaglandins for renal function (HF, hepatic cirrhosis with ascites, chronic renal failure, hypovolemia)	Children <18 y Active GI lesions History of recurrent GI lesions Bleeding disorders Thrombocytopenia ASA hypersensitivity Concomitant alcohol use Individuals who rely on vasodilatory renal prostaglandins for renal function (HF, hepatic cirrhosis with ascites, chronic renal failure, hypovolemia)	Peptic ulcer disease, GI perforation or bleeding, IBD History of asthma, urticaria or allergic-type reactions after taking ASA or other NSAIDs Severe liver impairment or active liver disease Severe renal impairment (<30 mL/min) Severe cardiac impairment and a history of hypertension Coagulation disorders Individuals who rely on vasodilatory renal prostaglandins for renal function (HF, hepatic cirrhosis with ascites, chronic renal failure, hypovolemia)
Drug interactions	Alcohol: increased risk of hepatotoxicity Enzyme inducers (e.g., phenytoin, barbiturates, carbamazepine, isoniazid) decrease acetaminophen levels	Alcohol and corticosteroids: increased risk of GI pain/ulceration Antagonism of hypotensive effects of ACEI, diuretics, beta-blockers Anticoagulants: increased risk of bleeding Increased levels of cyclosporine and risk of nephrotoxicity Increased levels of lithium, methotrexate ^b Reduction of ASA's antiplatelet effects ⁴³	Alcohol and corticosteroids: increased risk of GI pain/ulceration Antagonism of hypotensive effects of ACEI, diuretics, beta-blockers Anticoagulants: increased risk of bleeding Increased levels of methotrexate ^b ASA may decrease therapeutic effect of uricosuric agents (probenecid, sulfinpyrazone)	Alcohol and corticosteroids: increased risk of GI pain/ulceration Antagonism of hypotensive effects of ACEI, diuretics, beta-blockers Anticoagulants: increased risk of bleeding Increased levels of cyclosporine and risk of nephrotoxicity Increased levels of lithium, methotrexate ^b Reduction of ASA's antiplatelet effects ⁴³

(cont'd)

Table 5: Drug Therapy for Fever (cont'd)

For available products consult Analgesic Products: Internal Analgesics and Antipyretics; Baby Care Products: Antipyretics in *Compendium of Self-Care Products*.

	<i>Acetaminophen</i>	<i>Ibuprofen</i>	<i>ASA</i>	<i>Naproxen Sodium</i>
Overdose	Nausea, vomiting, hepatotoxicity, death	GI disturbances, bleeding, CNS depression, metabolic acidosis, hypotension, bradycardia, seizures, drowsiness, diaphoresis, liver dysfunction, death. Serious toxicity from overdose is unusual	Tinnitus, hyperpyrexia, hyperventilation, acid-base disturbances, nausea, vomiting, dehydration, coma, seizures, bleeding, hepatotoxicity, renal failure, hyper- or hypoglycemia, death	Drowsiness, dizziness, disorientation, heartburn, indigestion, epigastric pain, abdominal discomfort, nausea, vomiting, transient alterations in liver function, hypoprothrombinemia, renal dysfunction, metabolic acidosis, apnea and seizures
Other comments	Rectal products slowly and incompletely absorbed Preferred agent in pregnancy and breastfeeding	Take with food Avoid in 3rd trimester of pregnancy May be used while breastfeeding In patients on long-term ASA for cardioprotection take ibuprofen at least 30 minutes after ASA ingestion or at least 8 hours before ASA ingestion to avoid a potential interaction ⁴³ Only give to children if they are drinking reasonably well ⁸	Take with food Rectal products slowly and incompletely absorbed Avoid in 3rd trimester of pregnancy and while breastfeeding	Drink a full glass of water with each dose Take with food Food slightly delays absorption Avoid in 3rd trimester of pregnancy May be used while breastfeeding although shorter acting NSAIDs (ibuprofen) may be preferred

^a NSAIDs are generally avoided in the presence of renal dysfunction because of the risk of renal toxicity. Dosing is provided if acetaminophen is contraindicated and benefit is seen to outweigh risk.

^b More likely to occur with antineoplastic doses of methotrexate.

Abbreviations: ACEI = angiotensin converting enzyme inhibitor; CNS = central nervous system; GI = gastrointestinal; HF = heart failure; IBD = inflammatory bowel disease; NSAIDs = nonsteroidal anti-inflammatory drugs

In children ages 3 months to 5 years, seizures occur with 2–5% of febrile episodes.⁶⁵ Although simple febrile seizures are rarely associated with neurologic damage or permanent seizure disorders, they concern and frighten parents. For this reason, antipyretics are often recommended for children in this age group, particularly those with previous febrile seizures or neurologic problems. Recommending antipyretics at the first sign of fever is not effective in preventing recurrent febrile seizures even though this practice is frequently recommended.^{65,66,67}

Patients with Cardiovascular or Pulmonary Disorders

Increased metabolic demands which occur during the chill phase (increased metabolic rate, norepinephrine-mediated peripheral vasoconstriction, increased arterial blood pressure) may aggravate comorbid disease states in patients with heart failure, coronary, pulmonary or cerebral insufficiency. Fever may result in deterioration in cognitive function and delirium.¹

The Elderly

Older individuals exhibit less intense fevers in response to infection compared to younger individuals.⁶⁸ They also become hypothermic more often when infected and have greater morbidity and mortality from infections.⁶⁸ Fever in individuals older than 60 is less likely to be a benign febrile illness than it is in younger individuals;⁶⁹ therefore, it is important to carefully assess fever in the elderly. The elderly are more likely to have the cardiovascular and pulmonary conditions described above. **Acetaminophen** is safer in older individuals with risk factors predisposing to GI and renal toxicity of **NSAIDs**.

Pregnancy

Studies in humans suggest that exposure to fever and other heat sources during the first trimester of pregnancy is associated with increased risk of neural tube defects and multiple congenital abnormalities.^{70,71} Although one study indicated a possible benefit⁷² of antipyretic therapy others have not.⁷³

Acetaminophen crosses the placenta and is relatively safe for short-term use in pregnancy when therapeutic doses are used. Use of **ASA** and **NSAIDs** can result in a number of problems. Since these drugs inhibit prostaglandin synthesis, they may interfere with labor and cause premature closure of the ductus arteriosus resulting in 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.⁵¹ See Appendix V, *Pregnancy and Breastfeeding: Nonprescription Therapy for Common Conditions*.

Fever Phobia

The term “fever phobia” describes unrealistic concerns and misconceptions parents and health professionals have regarding fever in children.^{74,75,76,77,78} Health care professionals should undertake educational interventions to ensure appropriate management of fever and rational use of antipyretics.

Optimizing Dosing and Administration

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

- 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 the parent in calculating the correct mg/kg dose 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 the caregiver to determine and measure a correct dose of acetaminophen for their child, only 40% stated an appropriate dose for their child.⁷⁹
 - Of 118 children given an antipyretic at home and subsequently brought to the emergency department, only 47% had been given a proper dose.⁸⁰ Underdosing may be a cause of unnecessary emergency department visits.⁸¹ This also leads to added stress for both the parent and sick child.⁸²
- Ask what form of product they have at home and calculate the appropriate number of millilitres or tablets for the child.
 - Multiple miscalculated overdoses of acetaminophen given by parents account for an important cause of acetaminophen toxicity.^{83,84,85}
 - 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.⁸⁴

- 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.⁷⁹
- Ask about *other preparations*, particularly cough and cold products, they 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.

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. 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 other allergic reactions.
- Patients with pre-existing comorbid illness for edema and decreased urine output.
- For other common side effects, such as GI intolerance and tinnitus (Table 5).
- To ensure appropriate doses, products and measuring devices are being used, and the patient is not receiving excessive amounts of antipyretics through use of cough and cold or analgesic products.
- To ensure the patient is not receiving interacting medications (Table 5). Recommend avoiding alcohol.

Suggested Readings

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Fever — What You Need to Know

Hints to help you manage a fever:

- Treat the person, not the fever. By itself, fever is rarely dangerous. It is not always necessary to use drugs to lower a fever.
- **Do not** wake a sleeping child to give drugs for fever.
- **Do not** use fever medication for more than 3 days without consulting a doctor.
- Use acetaminophen or ibuprofen for fever in children and adolescents. **Do not** use ASA—it can cause Reye’s syndrome, a serious liver disorder.
- Use one drug only. **Do not** alternate acetaminophen and ibuprofen.
- Read the labels carefully. Make sure you use the right form of medicine for your child (liquid or pills). Determine the dosage based on your child’s weight. Use the proper measuring device to be sure the amount is accurate.
- Check other medications, especially medications for cough and cold, to see if they contain

acetaminophen, ibuprofen or ASA. Be sure you are not giving your child too much of these medicines.

- Keep all medications out of reach of children.
- Encourage the person with fever to drink lots of fluids.
- Keep the person cool by removing excess clothing and bedding.

When should you contact your doctor?

- Contact the doctor for:
 - fever over 40.5°C
 - children less than 2 months old who have fever
 - a child who appears very ill, has a stiff neck, has a seizure, is confused or delirious, or is crying without stopping
- Contact the doctor if the person with a fever has recently had chemotherapy.