Fever in the surgical patient

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INTRODUCTION

Fever is common in the first few days after major surgery and can pose a diagnostic challenge for the care team. While the definition of fever is variable, many use 38°C (100.4°F) as the threshold, although this can be hospital and unit specific [1-3]. Most early postoperative fever is caused by the inflammatory stimulus of tissue damage and exposure to foreign materials that occurs during surgery and resolves spontaneously over a few days. Some call this "physiologic" fever. Therefore, early postoperative fever occurring in the first three days after surgery often requires no further diagnostic workup other than a review of the patient's history and medications and a focused physical examination [4-7].

Starting on postoperative day 4, infections related to the surgical procedure are more common. At this time, the differential diagnosis also includes noninfectious conditions, some of which are life-threatening. A correct diagnosis with early initiation of appropriate therapy can be life-saving. Infections are most commonly of the superficial or deep surgical site, the urinary tract, or the lungs. Noninfectious causes include inflammatory reactions, drug fever, and deep vein thrombosis. It is important to consider a broad differential and not to assume that fever is due to infection. It is also important to highlight that for many conditions, the presence of fever is variable and its absence does not eliminate the possibility of a condition being present.

Fever occurring in the surgical patient, including clinical manifestations, etiologies, evaluation, and diagnosis, is reviewed. Fever as a manifestation of infection may be reduced or absent in immunocompromised patients, including those receiving glucocorticoids, cancer chemotherapy, and post-transplant immunosuppression. Patients who are older, cachectic, frail, or have chronic renal failure may also have a blunted fever response to infection. The evaluation of fever in immunocompromised patients is discussed elsewhere. (See "Fever and rash in immunocompromised patients without HIV infection" and "Approach to the immunocompromised patient with fever and pulmonary infiltrates" and "Overview of neutropenic fever syndromes" and "Diagnostic approach to the adult cancer patient with neutropenic fever".)

TIMING OF POSTOPERATIVE FEVER

The timing of fever after surgery (figure 1 and figure 2) is one of the most important factors to consider in generating a prioritized differential diagnosis (table 1). As such, it is useful to generate the differential diagnoses of infectious and noninfectious causes of fever in the following categories:

- Immediate postoperative (within hours of surgery) (see 'Immediate postoperative' below)
- Early postoperative (postoperative day 0 through day 3) (see 'Early postoperative' below)
- Late postoperative (postoperative days 4 through 30) (see 'Late postoperative' below)
- Delayed (more than 30 days after the procedure) (see 'Delayed postoperative' below)

Immediate postoperative — Perioperative fever has its onset in the operating suite or within hours after surgery. Most fevers that occur in this time period are inflammatory and self-limited. Immediate postoperative fevers can also depend on the type of surgery but tend to be greater in patients with longer and more extensive surgical procedures [8]. Causes of fever that are potentially life-threatening can occur in the immediate postoperative period. A history and physical examination will likely reveal the most common causes and will determine if additional evaluation or treatment is necessary.

The differential diagnosis of immediate postoperative fever includes:

- Inflammation as a direct consequence of surgery
- Trauma- or burn-induced inflammation

- Immune-mediated reactions to medications or blood products
- Malignant hyperthermia
- Infections predating the operation

Surgically induced inflammation — Inflammatory pyrogenic cytokine mediators (such as interleukin [IL]-1, IL-6, tumor necrosis factor, and interferon gamma) occur as a response to surgical stress (figure 3) [9]. In one study of 271 patients who underwent vascular, abdominal, or thoracic surgeries, the median time to maximum temperature elevation over the first 24 hours was 11 hours [10]. Temperature elevations correlated with IL-6 levels in these patients, suggesting that the temperature elevation was surgically mediated. Over half of these patients had a maximum temperature measured that exceeded 38°C (100.4°F).

Immune-mediated reactions — Adverse medication reactions that produce perioperative fever include immune-mediated reactions, such as reactions to antimicrobials and to transfused blood products administered in the operating room. The vasodilation that often accompanies these reactions makes hypotension a common presenting sign; rash may accompany fever in some patients with medication reactions. These reactions often resolve after the transfusion or when the medication is discontinued but should be noted as possible transfusion reaction or medication allergy. (See "Drug fever" and "Approach to the patient with a suspected acute transfusion reaction".)

Malignant hyperthermia — Malignant hyperthermia (MH) typically presents within 30 minutes following the administration of a triggering agent (eg, inhaled anesthetics, succinylcholine) but has been reported later in the operative course and also following cessation of anesthesia. MH is an inherited disorder most commonly manifesting as hypermetabolism associated with general anesthesia. MH-susceptible patients have genetic skeletal muscle receptor abnormalities allowing excessive calcium accumulation in the presence of certain anesthetic triggering agents. Prompt recognition of the initial clinical signs and treatment with dantrolene limits the morbidity and mortality associated with this disorder. (See "Susceptibility to malignant hyperthermia: Evaluation and management" and "Malignant hyperthermia: Diagnosis and management of acute crisis".)

Preexisting infection — Patients who undergo surgery for an infection will often continue to have fevers related to that infection and should be treated accordingly. As an example, a patient with bacterial peritonitis due to a perforated viscus of the abdomen who undergoes surgery may have continued fever and should continue antibiotics beyond the time of infection "source control" depending on clinical trial findings [11].

Early postoperative — Early postoperative fever has an onset within the first three days after surgery. There are many causes of fever in the early postoperative period, and some can be life-threatening. Occasionally, fever is a manifestation of a community-acquired infection that predates surgery, such as a viral upper respiratory tract infection. Nosocomial infections are **not** common during this period. A focused history and physical examination are usually sufficient to rule out nosocomial infection, and cultures or imaging are usually not indicated.

The differential diagnosis of early postoperative fever includes:

- Continued stress-mediated inflammation as a direct consequence of surgery
- Trauma- or burn-mediated inflammation
- Infections predating the operation
- Myocardial infarction
- Urinary tract infection
- Early surgical site infection
- Pneumonia
- Other noninfectious causes

Continued inflammation — Stress-mediated, immune-mediated and infection predating surgery can continue to cause fever within the first three days after surgery.

Fever caused by severe trauma or burns begins in the perioperative period and can persist with gradual resolution over days or even weeks [12]. (See 'Surgically induced inflammation' above and "Overview of inpatient management of the adult trauma patient" and "Hypermetabolic response to moderate-to-severe burn injury and management".)

Myocardial infarction — Myocardial infarction is a known complication of major surgery and is the most common serious postoperative complication that occurs on day 0 [13]. The risk of postoperative myocardial infarction significantly decreases after the first 72 hours from surgery. Fever uncommonly accompanies myocardial infarction, but may occur, especially if there is pericarditis (ie, Dressler syndrome). (See "Perioperative myocardial infarction or injury after noncardiac surgery" and "Post-cardiac injury syndromes".)

Urinary tract infection — Catheter-related infection should be considered for any patient with a catheter in place, especially if insertion was performed under emergency or nonsterile conditions. The risk of urinary tract infection (UTI) increases with the duration of

catheterization [14,15]. UTI is more common in patients who have undergone a genitourinary procedure and in those who have chronic, indwelling catheters prior to surgery. Providers should be aware that positive cultures in patients with indwelling catheters who have no urinary symptoms may be due to chronic colonization or asymptomatic bacteriuria and not the cause of the current fever [16]. (See "Catheter-associated urinary tract infection in adults".)

Early surgical site infection — While surgical site infection (SSI) most often presents five days or more after surgery, two organisms, group A streptococcus and *Clostridium perfringens*, can cause fulminant SSI within a few hours after surgery. These infections, although rare, cause brisk inflammatory reactions with fever as well as signs at the surgical site, including erythema and wound drainage. (See "Necrotizing soft tissue infections" and "Surgical management of necrotizing soft tissue infections".)

Pneumonia — Pneumonia associated with surgery most commonly occurs within the first postoperative week, with a peak incidence on day 2 [13]. The risk of pneumonia tapers to a stable, lower rate after the first postoperative week. Aspiration pneumonia should be considered, especially if the patient has vomited when the gag reflex is suppressed by anesthesia or analgesia needed for endotracheal intubation. A nasogastric tube also increases the risk of aspiration [17]. For patients who remain intubated after the initial surgery, the risk of ventilator-associated pneumonia (VAP) increases with the duration of mechanical ventilation [18].

Other noninfectious causes — Early postoperative fever can also be caused by noninfectious conditions, such as pancreatitis, venous thromboembolism, alcohol withdrawal, acute gout, or thyrotoxicosis.

- (See "Clinical manifestations and diagnosis of acute pancreatitis".)
- (See "Phlebitis and thrombosis of the superficial lower extremity veins" and "Clinical presentation and diagnosis of the nonpregnant adult with suspected deep vein thrombosis of the lower extremity" and "Overview of acute pulmonary embolism in adults".)
- (See "Alcohol withdrawal: Epidemiology, clinical manifestations, course, assessment, and diagnosis".)
- (See "Clinical manifestations and diagnosis of gout".)
- (See "Overview of the clinical manifestations of hyperthyroidism in adults" and "Thyroid storm".)

Late postoperative — After postoperative day 3, infection (surgical site, catheter-related, antibiotic-associated) is a common cause of fever. Many patients have been discharged from the hospital by this time. SSI is the most commonly diagnosed cause of fever after day

3 and continues to be the most common cause through postoperative day 30. However, noninfectious causes do continue to occur.

Surgical site infections (SSIs) — SSI most often presents four days or more after surgery. SSIs can be classified as superficial incisional, deep incisional, or organ/space (table 2). The most common causative pathogens depend on the surgery performed. For example, skin flora are most commonly found in infections after clean operations, whereas gastrointestinal flora most commonly cause infections after operations on the gastrointestinal tract [19-22].

Surgery-specific complications — Fever may also be related to specific complications of the surgeries performed. As an example, patients who have gastrointestinal tract surgery may develop anastomotic leaks, which can lead to deep/organ space infections, abscesses, or fistulae. (See 'In specific surgical populations' below.)

Other infections — Patients who require critical care after surgery are at higher risk for developing fever. Nosocomial infections are more common in these patients because of their treatment with invasive medical devices. Device-related infections due to bacteria and fungi include intravascular catheter-related infection with or without bacteremia, ventilator-associated pneumonia, urinary tract infection, acalculous cholecystitis, and sinusitis [23]. Catheter exit site infections and bacteremia associated with intravascular catheters tend to occur in the late postoperative period. Fever from antibiotic-associated diarrhea, typically attributed to *Clostridioides* (formerly *Clostridium*) *difficile*, also occurs more commonly during this period.

- (See "Intravascular non-hemodialysis catheter-related infection: Clinical manifestations and diagnosis".)
- (See "Clinical presentation and diagnostic evaluation of ventilator-associated pneumonia".)
- (See "Catheter-associated urinary tract infection in adults".)
- (See "Acalculous cholecystitis: Clinical manifestations, diagnosis, and management".)
- (See "Clostridioides (formerly Clostridium) difficile infection in adults: Clinical manifestations and diagnosis".)

Noninfectious causes — Noninfectious causes of fever in the late postoperative period include febrile drug reactions, venous thromboembolism, and gout. Febrile drug reactions are a frequent cause of late postoperative fever. Beta-lactam antibiotics and sulfa-containing products are commonly implicated, but other medications, such as H2 blockers, procainamide, phenytoin, and heparin, should be considered. Venous thromboembolism should be considered as a cause of fever in patients with impaired mobility, such as in

patients who are debilitated from chronic medical problems, or due to injury or as a result of the surgical procedure [24]. (See "Drug fever" and "Approach to the patient with a suspected acute transfusion reaction".)

Delayed postoperative — In patients who have recovered from their initial operation, most fevers that occur after four weeks are unrelated to the surgery. Some possible exceptions include delayed infections of implanted devices such as hernia mesh or orthopedic prostheses and development of delayed fistulae. (See "Overview of complications of inguinal and femoral hernia repair", section on 'Deep incisional/mesh infection' and "Prosthetic joint infection: Epidemiology, microbiology, clinical manifestations, and diagnosis" and "Prosthetic joint infection: Treatment".)

CLINICAL EVALUATION

The febrile postoperative patient should be evaluated systematically (table 1).

History — Review the medical record for a history of fever following prior surgeries. Also consider how allergies, medications, and preexisting medical conditions might contribute to the fever. Important considerations in the history of a patient with postoperative fever include:

Recent medical history:

- Was fever present prior to surgery?
- Are there symptoms or signs associated with the fever?
- Have household contacts had fever recently?
- Has the patient traveled to areas where endemic or epidemic infectious diseases occur?
- Has the patient had other recent procedures or initiated new drugs prior to surgery?

Review the patient record for:

- History of fever after previous surgeries
- Preoperative course and presentation

- Details of the operation (date of surgery, emergency or elective, intraoperative complications, anesthesia record)
- Postoperative course
- Allergies
- Medications (in particular, review new medications given for surgery, such as anesthetics, antibiotics, pain medications, medications that suppress the magnitude of fever [eg, nonsteroidal anti-inflammatory drugs, glucocorticoids])
- Transfusions
- Location and type of catheters and timing/verifications of placement

Ask the patient and nurse about:

- Pain
- Sputum production, quality, and volume
- Presence of diarrhea
- Urinary symptoms
- Drainage from surgical site or around drains
- Condition of any intravenous or bladder catheter sites
- Skin changes (areas of skin breakdown, rash, purpura/bruising, erythema, and pallor)

Physical examination — Thorough physical examination is warranted in patients with postoperative fever. In particular, pay special attention to the surgical site. Also, symptomatic nonoperative areas of the body (painful areas, for example) should be examined thoroughly.

Review the record of the patient's vital signs, including temperature, heart rate, and respiratory rate. Determine temperature range in the past day and peak daily temperature values during the hospital stay. Check nurses' notes for fevers not recorded in the vital signs record and other transient patient symptoms and signs.

- Examine the skin for rash, erythema, ecchymosis, hematoma, and pallor.

- Auscultate the lungs for crackles, wheezes, and for the absence of breath sounds in dependent and apical regions.
- Auscultate the heart for murmurs, gallops, and rubs.
- Evaluate the abdomen for tenderness, distention, and hyper- or hypoactive bowel sounds.
- Examine the surgical site for erythema, swelling, tenderness, and drainage.
- Examine catheter, tube, and drain sites for erythema, swelling, tenderness, and drainage.
- Evaluate the extremities for edema, erythema, duskiness, and tenderness.

Surgical sites/tubes/drains — The surgical site(s) should be examined. This sometimes requires a surgical team member to be present so that surgical dressings can be removed and inspection can be done together to minimize manipulation of the wound (eg, flap-based reconstruction). The wound drainage should be characterized, specifically if it has changed from serosanguinous to purulent. Tube and drain exit sites must be similarly examined and characterized.

Further testing — Fever in the first day or two after surgery usually resolves spontaneously. Additional investigation in febrile but otherwise clinically unremarkable postoperative patients is probably not indicated for most patients until the third postoperative day [25,26]. The need for further testing should be determined based upon the results of the clinical evaluation. Any further testing should be targeted to the individual patient, based on repeated assessment of symptoms and signs [26-28]. As an example, a chest radiograph may be obtained in the patient with acute respiratory complaints but is not needed in all patients with postoperative fever. Moreover, some studies, such as urine culture in patients with Foley catheters, can provide misleading results and should be reserved for patients with symptoms. (See 'Imaging' below.)

Laboratories — Comprehensive laboratory screening is not indicated for most patients. Specific laboratory or radiographic studies might be indicated by specific history and physical examination findings.

Laboratory testing and cultures may include:

- Complete blood count (CBC) with differential – For most patients who are being evaluated for postoperative fever, we obtain a CBC with differential white blood cell count, unless there is a likely explanation for fever and low suspicion for infection or allergic reaction.

- Urinalysis and culture.
- Sputum gram stain and culture.
- Blood culture (at least two sets from separate "sticks").
- Wound culture – Wound cultures should not be performed as a swab of the surface of the wound. If a wound culture is to be performed, this should be performed in concert with a member of the surgical team.
- Drains, which are potentially colonized, should not be cultured.
- Additional blood tests such as liver function tests, pancreatic enzymes.

The value of serum procalcitonin (PCT) concentration for differentiating bacterial infection from other causes of postoperative fever has been explored in a few studies [29-31]. PCT is produced in C cells of the thyroid and is a more specific marker of bacterial infection than is C-reactive protein. However, postoperative PCT concentrations vary substantially following different types of surgery [31], and from patient to patient following the same type of surgery [32]. Furthermore, PCT has not been found to be a reliable marker for infection in other settings. Thus, PCT is not recommended in the routine evaluation of postoperative fever.

Imaging — Imaging studies may include:

- Lower extremity duplex ultrasound to evaluate for deep vein thrombosis
- Chest radiograph might be indicated by specific findings of pulmonary symptoms
- Thoracic/abdominal computed tomographic (CT) scanning
- Ultrasound or CT scan of the surgical site

EVALUATE FOR COMMON CAUSES

The febrile postoperative patient should be evaluated systematically depending on the timing of fever (table 1), taking into account the timing of the onset of fever and the many possible causes [27,33,34]. Although the list of causes of postoperative fever is extensive, the

initial focus for most patients should be on a limited number of the more common possibilities suggested by the history and physical examination and the timing of fever onset.

A useful initial screen for the more common causes of postoperative fever is represented by the following mnemonic (the 5 Ws), the order of which implies the timing of postoperative fever:

- "Wind" refers to pulmonary causes of fever, including pneumonia, aspiration, and pulmonary embolism (but not atelectasis). (See 'Nosocomial infection' below.)
- "Water" refers to urinary tract infection. (See 'Nosocomial infection' below.)
- "Wound" refers to surgical site infection. (See 'Surgical site infection' below.)
- "Walking" refers to venous thromboembolism. (See 'In the general population' below.)
- "Wonder drugs" refers to drug-related fever. (See 'Medication reaction' below.)

Other Ws have been proposed, including "Waves," "Wonky glands," "Withdrawal," and "What did we do?" [13]. These are reminders to consider cardiac and endocrine causes; alcohol and other substance withdrawal; and other treatments such as medications, blood product transfusions, and intravascular, urethral, nasal, and abdominal catheters as potential causes for a patient's postoperative fever.

Atelectasis has often been used as an explanation for early postoperative fever. Both atelectasis and fever occur frequently after surgery, but their concurrence is probably coincidental rather than causal [35]. Ascribing a postoperative fever to atelectasis probably provides false reassurance and may mislead the clinician from pursuing the true cause of the fever. The incidence of atelectasis peaks within the first couple of days after surgery. In one study of 270 consecutive patients after abdominal surgery, the sensitivity and negative predictive value of fever as a predictor of atelectasis were both less than 50 percent, and the specificity and positive predictive value were 68 and 66 percent, respectively [36]. In another study, there was also no association between fever and the presence, or the degree, of atelectasis [37]. (See "Atelectasis: Types and pathogenesis in adults".)

Self-limited fever is common following most major surgeries [3]. Fever-associated cytokines are released by tissue trauma and do not necessarily signal infection. The magnitude of the trauma is correlated with the degree of the fever response. For example, laparoscopic cholecystectomy is associated with less tissue trauma and fewer episodes of postoperative fever than is open cholecystectomy [8].

Similarly, there is less postoperative fever when coronary artery grafting is performed without the use of a cardiopulmonary bypass pump [38].

Bacterial endotoxins and exotoxins can stimulate cytokine release and cause postoperative fever. Bacteria or fragments of bacteria translocated from the colon (eg, as a consequence of perioperative ileus or hypotension) may be responsible for some episodes of self-limited postoperative fever. Elevated levels of bacterial DNA have been demonstrated with polymerase chain reaction testing of blood from surgical patients, even in patients whose blood cultures are negative [39].

Genetic factors may influence the magnitude of the cytokine release in response to tissue trauma and thus the magnitude of self-limited postoperative fever. For example, children with osteogenesis imperfecta undergoing orthopedic surgery appear to have a greater and more sustained febrile response than matched controls [40].

Fever due to the trauma of surgery usually resolves within two to three days. The severity and duration of these self-limited postoperative fevers depends on the type of surgery [41,42] but tend to be greater in patients with longer and more extensive surgical procedures [8]. Fever caused by severe head trauma can be persistent and may resolve gradually over days or even weeks [12].

Medication reaction — Febrile drug reactions are a frequent cause of postoperative fever and may be accompanied by hypotension or rash.

Antimicrobials and heparin are the medications most commonly associated with postoperative fever, at least in part because they are used so frequently in the postoperative period (table 3). Beta-lactam antibiotics and sulfa-containing products are commonly implicated, but other medications, such as H2-blockers, procainamide, phenytoin, and heparin, should be considered. In addition, antimicrobials and other medications incorporated into implanted materials may cause postoperative fever [43]. (See "Drug fever".)

Several medications commonly used in the postoperative period can interact with selective serotonin reuptake inhibitors or other antidepressants to precipitate fever as one manifestation of the serotonin syndrome. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Drug-drug interactions'.)

Transfusion reaction — Transfusion reactions, such as delayed serologic and hemolytic transfusion reactions, are more common in patients previously sensitized to foreign antigens through prior transfusion or multiple pregnancies [44]. (See "Approach to the patient with a suspected acute transfusion reaction".)

Complement activation due to antibody incompatibilities can also cause acute lung injury in the syndrome of transfusion-related acute lung injury [45]. (See "Transfusion-related acute lung injury (TRALI)".)

Surgical site infection — Surgical site infection (SSI) most often presents in the late postoperative period, one week or more after surgery. Many patients have already been discharged from the hospital by this time [19-22]. In addition, for patients who have new anastomoses, staple lines or ligated ducts may develop a leak that manifests as an SSI. Appropriate imaging should be undertaken with contrast as needed, depending on the surgery performed, to rule out a leak.

Nosocomial infection — Urinary tract infection (UTI), pneumonia, especially ventilator-associated pneumonia (VAP), and intravascular catheter-related infection are the most common infectious causes of postoperative fever. Nosocomial bacterial and fungal pathogens are usually implicated. The infecting microorganisms generally are found as endogenous flora of the skin or bowel, but the flora change as patients are hospitalized for longer periods and receive antimicrobial therapy. When patients are readmitted to the hospital, organisms acquired in the community may also be involved. As an example, *Pasteurella multocida* SSIs have been caused by pet cats and dogs licking a surgical site [46]. Patients who require critical care after surgery are at higher risk for nosocomial infection [24]. (See "Infections and antimicrobial resistance in the intensive care unit: Epidemiology and prevention".)

- Patients receiving mechanical ventilation during surgery are at increased risk for VAP, which correlates with the duration of mechanical ventilation [18]. The risk of pneumonia tapers to a stable, lower rate over the first postoperative week and with the discontinuation of mechanical ventilation. Pneumonia is a common cause of fever after cardiac surgery and may occur in more than 5 percent of patients [47]. Pneumonia is associated with reintubation, hypotension, neurologic dysfunction, and transfusion of more than three units of blood components [47]. (See "Clinical presentation and diagnostic evaluation of ventilator-associated pneumonia".)

- Patients with depressed mental status or gag reflex due to anesthesia and analgesia are more susceptible to aspiration if they vomit after surgery. A nasogastric tube also increases gastroesophageal reflux and the risk for aspiration [17]. (See "Aspiration pneumonia in adults".)

- UTI is a frequent cause of postoperative fever in patients with indwelling urethral catheters. The risk of UTI increases with the duration of catheterization [14,15]. UTI is more common in patients who have undergone a genitourinary procedure and in those who have chronic, indwelling catheters prior to surgery. Infection of the urinary tract at any level is the major consideration in

evaluating patients with fever after urologic surgery. Although bacteriuria due to a urethral catheter is common, culture alone is not as revealing as the combination of urine culture findings and urine analysis for pyuria and bacteriuria. Deep infections, such as prostatic and perinephric abscess, may present with fever and pain but relatively benign urine findings. Infection can also spread from the lower urinary tract through Batson's venous plexus to the lumbar spine and present after the UTI is resolved. (See "Catheter-associated urinary tract infection in adults".)

- Catheter exit site infections and bacteremia associated with intravascular catheters also tend to occur in the late postoperative period but should be considered as sources of fever in any patient with a catheter in place, especially if insertion was performed under emergent or nonsterile conditions. (See "Intravascular catheter-related infection: Epidemiology, pathogenesis, and microbiology".)

- Antibiotic-associated diarrhea – Fever from antibiotic-associated diarrhea, typically attributed to *Clostridioides* (formerly *Clostridium*) *difficile*, occurs more commonly in the late postoperative period. (See "Clostridioides (formerly Clostridium) difficile infection in adults: Epidemiology, microbiology, and pathophysiology".)

- Viral infection – Viral infections in the postoperative patient, usually associated with the transfusion of blood products, can arise late in postoperative patients [38]. These include cytomegalovirus (CMV), hepatitis viruses, and human immunodeficiency virus (HIV). Parasitic infections (eg, toxoplasmosis, babesiosis, *Plasmodium malariae* infection) can also rarely be transmitted via transfusion [48-51]. Donated blood is screened by immunoassay techniques for a number of viruses (table 4). Other infective agents may be transmitted (eg, *Babesia* is screened for only by questioning potential blood donors) [52]. Other viral infections can also be transmitted nosocomially, such as has occurred with severe acute respiratory syndrome [53]. Postoperative viral infections such as VAP can occasionally be caused by the reactivation of latent viruses, such as CMV or herpes simplex virus, especially in immunosuppressed patients [54-56].

CONSIDER LESS COMMON CAUSES

Other less common causes of fever in postoperative patients, in general or limited to specific surgical populations, include [57]:

In the general population

- Sinusitis – Sinusitis and, less commonly, otitis media, can occur particularly in patients with nasotracheal or nasogastric tubes. Mild sinusitis in a critically ill patient may not be clinically apparent [58,59].

- Acalculous cholecystitis – Acalculous cholecystitis can occur, particularly in critically ill patients (eg, severe trauma) [60].

- Pancreatitis – Pancreatitis can be due to an adverse reaction to perioperative medications, a consequence of endoscopic retrograde cholangiopancreatography, or alcohol use disorder. Pancreatitis can also be related to the surgery performed. (See 'In specific surgical populations' below.)

- Endocarditis – Infective endocarditis due to perioperative bacteremia is more likely to present late (weeks or months) after surgery.

- Parotitis – Parotitis, usually due to *Staphylococcus aureus*, occurs in patients who have undergone manipulation of the oral cavity or who are significantly dehydrated postoperatively, but is far less common with contemporary anesthesia and perioperative care techniques than in the past [61].

- Gout/pseudogout – Gout and pseudogout in association with joint inflammation and effusion can cause fever [62,63]. Oncologic surgery or concomitant cancer may be additional risk factors for postoperative gout. Joint manipulation and hyperparathyroidism are risk factors for pseudogout. (See "Clinical manifestations and diagnosis of gout" and "Clinical manifestations and diagnosis of calcium pyrophosphate crystal deposition (CPPD) disease".)

- Dermatologic conditions – Various cutaneous drug reactions (eg, acute generalized exanthematous pustulosis, the DRESS [drug reaction with eosinophilia and systemic symptoms] syndrome, cutaneous small vessel vasculitis) cause inflammatory changes in the skin and may be associated with fever [64]. (See "Drug eruptions".)

  Pyoderma gangrenosum, although rare in the postoperative period, is an ulcerative inflammatory skin disorder that can mimic wound infection [65]. It is important to make the distinction, as treatment for pyoderma is glucocorticoid therapy, not antibiotics.

In specific surgical populations

- Intra-abdominal sepsis – The primary cause of postoperative fever that is unique to abdominal surgery is deep abdominal abscess. Distinguishing between abscess, hematoma, and a benign peritoneal fluid collection can be difficult. Imaging studies and needle

aspiration may be helpful, but exploration is sometimes necessary. Empiric antimicrobial treatment should be directed at the combination of aerobic gram-negative enteric bacilli and anaerobes.

- Pancreatitis/splenoportal thrombosis – Pancreatitis more frequently causes postoperative fever after upper abdominal surgeries than after other surgeries [66]. Pancreatitis could be caused by direct mechanical trauma or obstruction to pancreatic drainage and is therefore more common in procedures involving the pancreas and nearby structures. The diagnosis can be made by elevated serum amylase and lipase concentrations with the considerations that salivary glands also produce amylase, and macro variants of amylase can produce elevated serum concentrations. (See "Clinical manifestations and diagnosis of acute pancreatitis".)

  Splenoportal thrombosis may cause fever following splenectomy and is recognized with increased frequency since the availability of computed tomographic (CT) scanning [67]. Risk factors include massive splenomegaly and myeloproliferative and hemolytic disorders. (See "Mesenteric venous thrombosis in adults".)

- Postpartum endometritis – Postpartum endometritis, manifested by fever, pelvic pain, and purulent vaginal discharge, is more common in postpartum patients with preexisting medical problems, after premature rupture of membranes, difficult deliveries, and after the use of internal fetal monitoring. (See "Postpartum endometritis".)

- Lymphangitis/cellulitis – In patients who have undergone surgery that has disrupted venous or lymphatic drainage, delayed cellulitis/lymphangitis can develop; this type of cellulitis can be recurrent [68,69]. (See "Cellulitis following pelvic lymph node dissection" and "Breast cancer-associated lymphedema".)

- Post-implantation syndrome – In patients who undergo endovascular repair of aortic aneurysm with an endoluminal stent-graft, a syndrome has been described that can include fever, leukocytosis, elevated C-reactive protein levels, and perigraft gas seen radiographically. Fever above 101.4ºF (38.6ºC) has been reported in up to two thirds of patients in some series. Blood cultures are negative, and the fevers resolve without antimicrobial therapy [70,71]. This is sometimes referred to as "postimplantation syndrome"; its cause is uncertain [72,73]. (See "Complications of endovascular abdominal aortic repair", section on 'Postimplantation syndrome'.)

- Ischemia – Another noninfectious cause of fever after vascular surgery is arterial embolization, or "blue toe" syndrome. A similar syndrome can be caused by emboli from an infected graft. (See "Embolism to the lower extremities".)

- Implant/mesh/graft infection – Infection due to more indolent microorganisms (eg, coagulase-negative staphylococci) can cause delayed fever, especially in patients with implanted medical devices or grafts.

  Prosthetic implant infections include:

  - Orthopedic hardware infection. (See "Prosthetic joint infection: Epidemiology, microbiology, clinical manifestations, and diagnosis" and "Prosthetic joint infection: Treatment".)

  - Mesh infection. (See "Overview of complications of inguinal and femoral hernia repair", section on 'Deep incisional/mesh infection'.)

  - Vascular graft infection – Vascular graft infections may occur by direct inoculation of the surgical site or, less frequently, by hematogenous spread. Vascular graft infections most commonly present soon after surgery but can occur months to years later. Determining that a graft has become infected can be difficult. Vascular imaging can be helpful, but negative findings do not rule out a graft infection.

- Meningitis – Meningitis is a frequent and serious cause of fever after neurosurgery [74]. Bacterial meningitis can also occur after head and neck invasive diagnostic or surgical procedures or spinal anesthesia that inadvertently violates the subarachnoid space, causing a "CSF (cerebrospinal fluid) leak." Classic symptoms and signs of meningeal inflammation (eg, headache, photophobia, nuchal rigidity), are not usually helpful following neurosurgery because they can be caused by hemolyzed blood from the surgery irritating the meninges. Microscopic and analytical examination of the CSF is indicated in patients with fever because, combined with specific clinical findings, characteristics of the CSF can help to distinguish patients with infections from those with chemical meningitis. Patients with all of the following criteria can probably be safely observed without administration of antimicrobials: fever less than 39.4ºC (102.9ºF); CSF white blood count less than 7,500/microL; CSF glucose above 10 mg/dL; no delirium, seizure, or surgical site inflammation [75]. Measurement of CSF lactate might be useful in distinguishing bacterial meningitis from those with chemical meningitis in neurosurgery patients [76,77].

- Sternal wound infection/mediastinitis – Sternal wound infection occurs in approximately 1 percent of patients after median sternotomy with a median time to infection of 20 days in one multi-institutional cohort study [78]. Sternal wound infection more than one month after surgery is unusual (only 9 percent in another study [79]). A positive blood culture in a persistently febrile patient can be the first manifestation of a sternal wound infection, occurring before apparent wound inflammation [80]. A high index of

suspicion is needed because mediastinitis causes protracted hospitalization and an increased need for reoperation and rehospitalization, and is associated with significant mortality (14 to 47 percent [81-85]). The risk factors associated with sternal wound infection and mediastinitis, microbiology and treatment are reviewed separately. (See "Postoperative mediastinitis after cardiac surgery" and "Surgical management of sternal wound complications".)

INITIAL TREATMENT

General measures — Any unnecessary treatments, including medications and catheters, should be discontinued in patients with postoperative fever. It is probably appropriate to suppress the fever in most patients with one or two days of scheduled acetaminophen to minimize patient discomfort and the physiologic stress and metabolic demands of fever and shivering [86]. This approach is unlikely to mask a significant pathologic condition. Acetaminophen should be avoided in patients with malnutrition, hepatic insufficiency, and alcohol use disorder. Additional treatment depends upon the cause of the fever. An alternative treatment of fever in a patient without contraindication is nonsteroidal anti-inflammatory agents (eg, ibuprofen).

Antimicrobial therapy — It is important to highlight that most cases of postoperative fever are due to noninfectious causes. A decision to administer antibiotics to a patient with postoperative fever depends upon careful clinical assessment, including an appraisal of the patient's stability. Empiric antimicrobial therapy is reasonable in patients who likely have infection as a cause of postoperative fever. In these cases, selected treatment should provide coverage for the most likely pathogen(s) based on the site of suspected infection. As an example, a patient with a suspected intra-abdominal or pelvic infection should be treated with a regimen effective against aerobic gram-negative enteric bacilli and anaerobes. Empiric antifungal therapy should not be included unless the patient is at high risk for fungal infection.

If a site of infection is identified and/or cultures are positive, the broad-spectrum regimen should be focused to cover the probable or known causative organism(s). Gram stain findings and hospital antibiograms can be used to guide empiric antimicrobial selection, but definitive treatment should be based upon antimicrobial susceptibility results from cultured organisms. Nosocomial pathogens are often resistant to many antimicrobials. Careful selection of antimicrobial treatment can help to avoid adverse medication reactions and can help to minimize the prevalence of resistant organisms in the hospital. Antimicrobial treatment beyond the empiric period of 48 hours should be reserved for patients in whom an infection has been identified. If a source of fever is not apparent and blood cultures show no growth, then discontinuation of antimicrobials should be seriously considered.

Surgical management — Surgical management is required to treat postoperative fever due to an infectious complication related to the surgical site or conduct of the operation. (See 'Early surgical site infection' above and 'Surgical site infections (SSIs)' above and 'Surgery-specific complications' above and 'In specific surgical populations' above.)

SUMMARY AND RECOMMENDATIONS

- Fever (>38°C [100.4°F]) is common in immediate and early postoperative period. This febrile response may be due to tissue trauma with cytokine release, circulating bacterial endotoxins from endogenous gut flora, or other causes. Inpatients with perioperative fever should be evaluated with a history and a physical exam to ensure that there is no preexisting cause of infection or a rapidly progressive surgical site infection. Other sources, such as medication reactions, should be ruled out. In most other patients, no further diagnostic testing is required. (See 'Introduction' above.)

- Atelectasis and fever can both occur after surgery; however, they do not correlate well with each other. Although atelectasis is often cited as a cause of fever in the surgical patient, the association is probably coincidental and not causal. Chest radiography is not indicated in most febrile patients in the immediate postoperative period. Further evaluation and laboratory studies (urinalysis, blood cultures) should be tailored to the individual patient based on history, symptoms, and physical findings. (See 'Clinical evaluation' above and 'Further testing' above.)

- Starting with postoperative day 4, the differential diagnosis of fever in the surgical patient evolves to include infectious and noninfectious etiologies (table 1). Surgical site infection, pneumonia, urinary tract infection, and intravascular catheter infection are the predominant infectious causes of fever following surgery and are often due to nosocomial multidrug-resistant organisms. The most common noninfectious cause of fever in the surgical patient is a medication reaction (table 3); antimicrobial agents or heparin are the drugs most frequently implicated. (See 'Late postoperative' above.)

- Considerations following specific surgeries are discussed above. (See 'In specific surgical populations' above.)

- All unnecessary treatments, including medications, nasogastric tubes, and intravascular and urinary catheters, should be discontinued. Treating the fever with acetaminophen is often appropriate. Antibiotics are not routinely indicated for most patients with fever in the early postoperative period, but hemodynamically unstable patients should be treated empirically with broad-

spectrum antibiotics, which should be discontinued after 48 hours if no source of infection has been identified. (See 'Initial treatment' above.)

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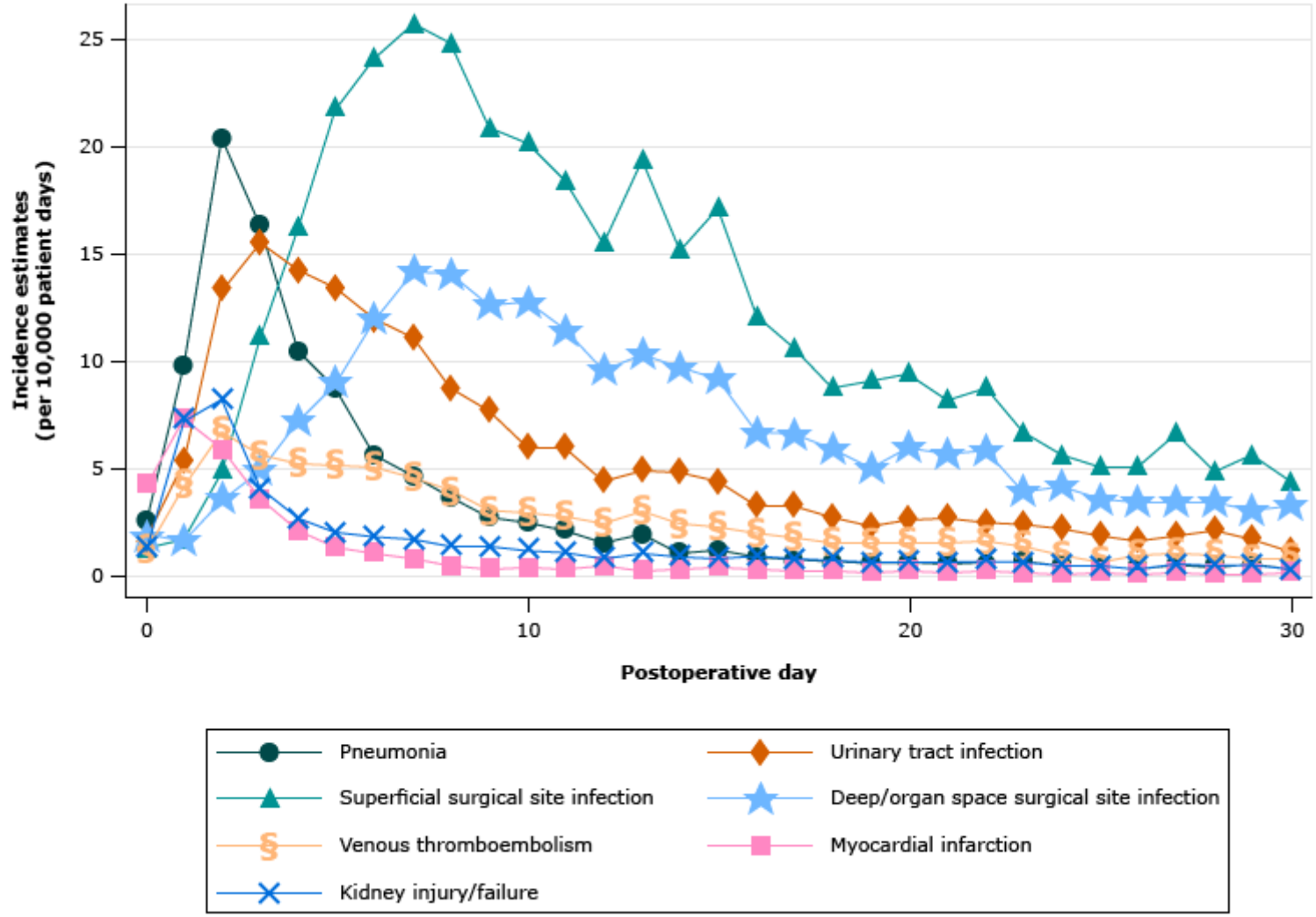
Topic 2886 Version 17.0

GRAPHICS

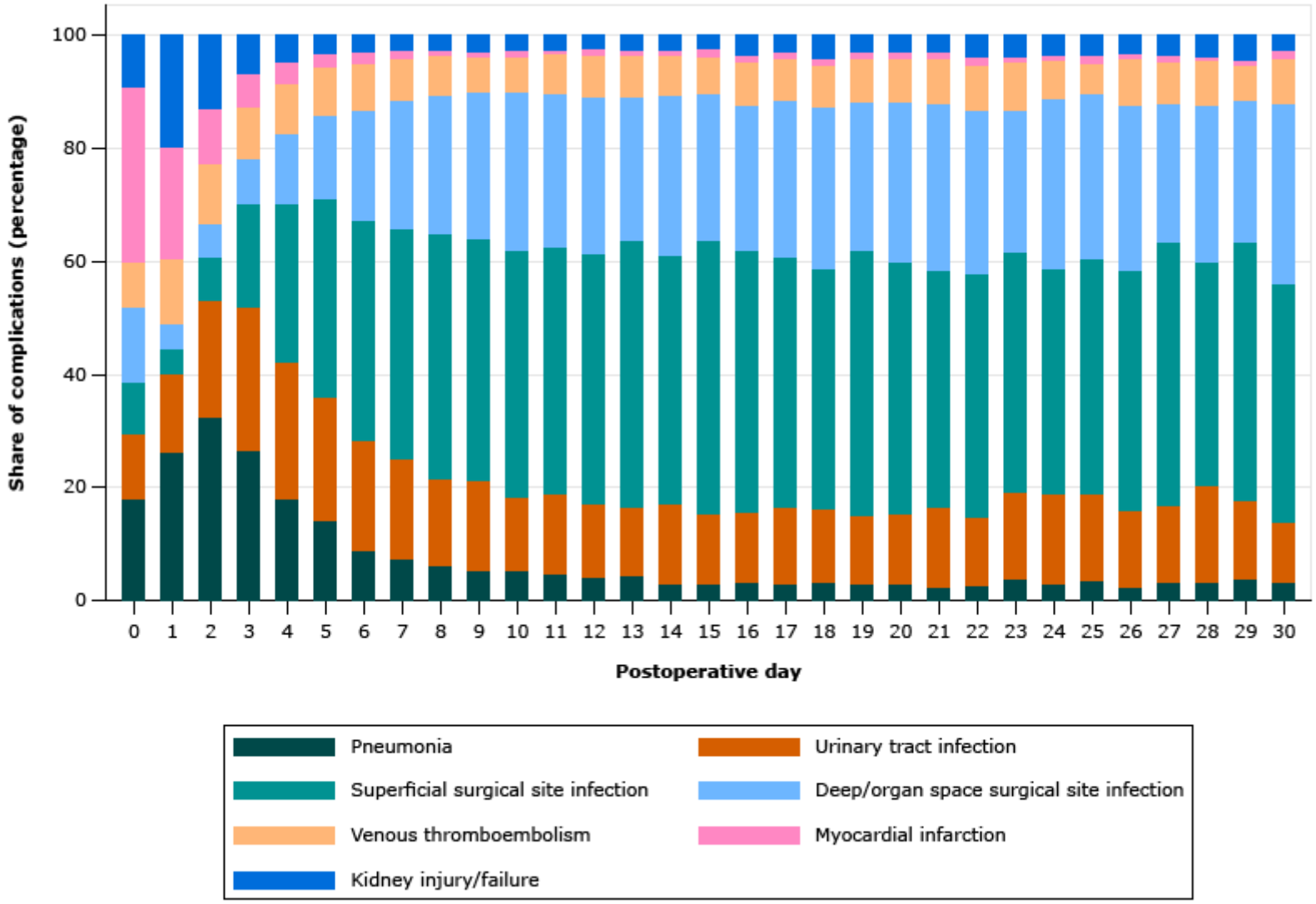
Timing of postoperative fever



Daily incidence of index postoperative complications.

Graphic 120992 Version 1.0

Postoperative fever complications



Share of daily complications over 30 postoperative days among surgical patients.

Graphic 122773 Version 1.0

Rapid overview: Approach to fever in a postoperative patient

Postoperative fever definition and causes

Temperature >38°C (100.4°F)

- Immediate: Within hours of surgery
- Early: Postoperative days 0 through 3
- Late: Postoperative days 4 through 30
- Delayed: More than 30 days after the procedure

Fever can be a normal response to surgery or be due to another cause.

Infection is only one of the other possible causes.

Most early postoperative fevers are due to surgical trauma.

Most patients with fever after the third postoperative day have an infection.

Noninfectious causes of fever that are potentially life-threatening can occur in the immediate and early postoperative periods.

Evaluation

Patient characteristics

Review medical record for allergies, medications, preexisting medical conditions.

Review medical record for fever complicating prior surgeries.

Recent medical history

When was the surgery? What was the nature of the surgery?

Was the surgery under emergency circumstances or elective? Were there intraoperative complications?

What types of catheters/devices/drains were placed, and when were they placed?

Ask the patient and nurse about pain; cough; sputum production, quality, and volume; skin changes; and diarrhea.

Physical examination

Review record for vital signs, including peak and trough values since surgery.

Examine the skin for rash, erythema, ecchymosis, hematoma, and pallor.

Auscultate the lungs for crackles, wheezes, and for the absence of breath sounds in dependent and apical regions.

Auscultate the heart for murmurs, gallops, and rubs.

Evaluate the abdomen for tenderness, distention, and hyperactive or hypoactive bowel sounds.

Examine the surgical site for erythema, swelling, tenderness, and drainage.

Examine catheter, tube, and drain sites for erythema, swelling, tenderness, and drainage.

Evaluate the extremities for edema, erythema, duskiness, and tenderness.

Laboratory

Comprehensive laboratory screening is not indicated for most patients. Specific laboratory or radiographic studies may be indicated by specific history and physical examination findings.

- CBC with differential
- Chest radiograph
- Blood cultures (at least 2 sets from separate "sticks")
- Sputum and gram stain
- Wound culture
- Urinalysis and culture

Others based on specific findings: Abdominal CT scan for abdominal pain, hepatic and pancreatic enzymes following upper gastrointestinal surgery, extremity ultrasound for suspected deep vein thrombosis.

Consider less common causes of fever

Myocardial infarction

Pericarditis (Dressler syndrome)

Pulmonary embolism

Anastomotic leak

Necrotizing soft tissue infection

Alcohol withdrawal

Thyrotoxicosis

Adrenal crisis

Endocarditis

Malignant hyperthermia

Cerebral infarction/hemorrhage

Evaluate for more common causes of fever

Infectious

Surgical procedure associated (eg, surgical site infection, intra-abdominal abscess, cholangitis, osteomyelitis, meningitis)

Nosocomial infection (eg, pneumonia, urinary tract infection, intravascular device-related bloodstream infection, antibiotic-associated diarrhea, infusion-related infection)

Others (eg, acalculous cholecystitis, sinusitis, otitis media, prostatitis, endocarditis)

Transfusion-associated viral infections

Noninfectious

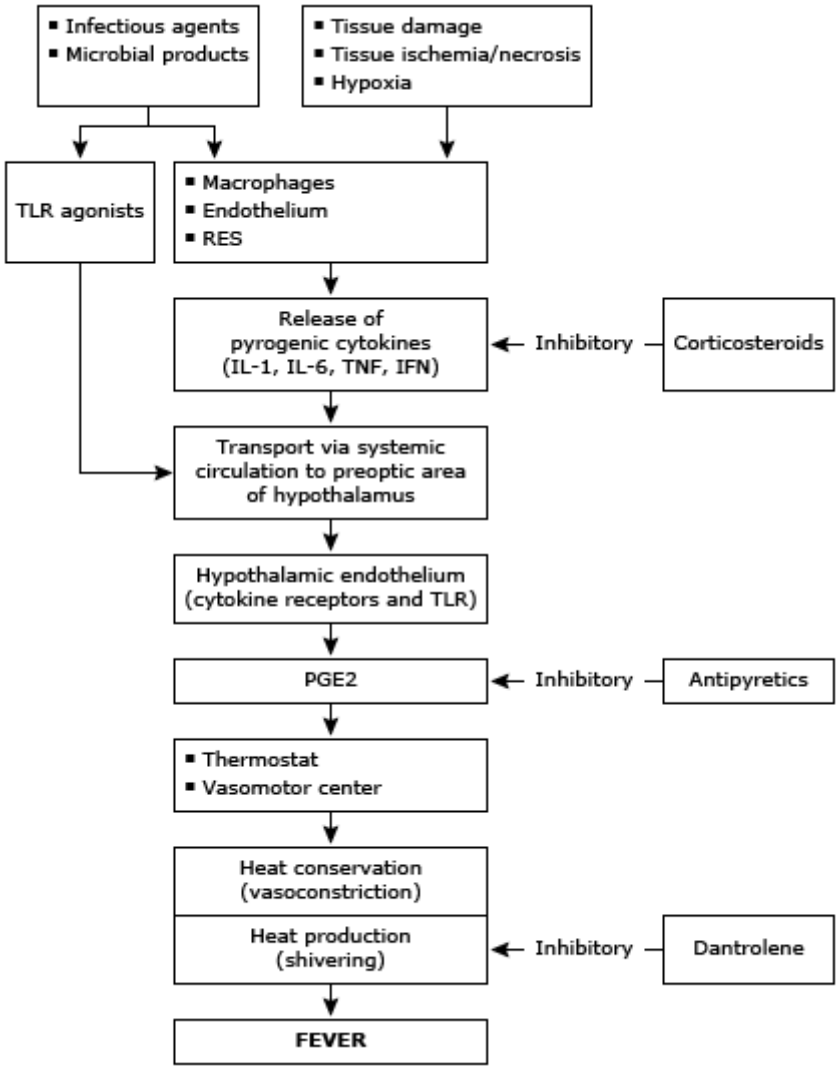
Surgical procedure associated (eg, bowel ischemia, pancreatitis, transplant rejection)

Surgical site inflammation without infection (eg, hematoma, seroma, foreign body reaction [eg, suture, prosthetic mesh, vascular graft material])
Deep vein thrombosis/superficial vein thrombosis
Transfusion reaction
Gout/pseudogout
Neoplasia
Medications
Treatment
General measures
Resuscitation, as needed.
Control pain.
Antipyretics – Acetaminophen is often appropriate to reduce fever but should be avoided in patients with alcohol use disorder, starvation, or hepatic impairment.
Empiric antimicrobial therapy is reasonable in patients who likely have infection as a cause of postoperative fever. In these cases, treatment should provide coverage for the most likely pathogen(s) based on the site of suspected infection and be administered after cultures are sent, if possible. Continuation or cessation of antimicrobial therapy should be tailored to culture results.
Specific treatment
Source control of infection (eg, abscess drainage, removal of catheters).

CBC: complete blood count; CT: computed tomography.

Graphic 79357 Version 5.0

Fever stimulators and inhibitors



Starting from the top left, infectious agents and/or microbial products, as well as cytokines and other inflammatory processes, induce macrophages, endothelial cells, and the reticuloendothelial system to produce and secrete pyrogenic cytokines into the circulation. These pyrogenic cytokines induce the synthesis of PGE2 in the hypothalamus. In addition, microbial toxins, acting as ligands to the TLRs in the hypothalamus, stimulate the synthesis of PGE2 by the hypothalamus. PGE2 raises the thermostatic set point in the hypothalamus to febrile levels. The vasomotor center sends signals for heat conservation

(vasoconstriction) and heat production (shivering). Corticosteroids reduce the peripheral synthesis of pyrogenic cytokines, whereas antipyretics reduce PGE2 levels in the brain. Dantrolene directly inhibits heat production.

TLR: toll-like receptor; RES: reticuloendothelial system; IL-1: interleukin-1; IL-6: interleukin-6; TNF: tumor necrosis factor; IFN: interferon; PGE2: prostaglandin E2.

Courtesy of Reuven Porat, MD, and Charles A Dinarello, MD.

Graphic 80455 Version 5.0

Criteria for defining a surgical site infection (SSI)

Superficial incisional SSI

Infection occurs within 30 days after the operation

AND

Infection involves only skin or subcutaneous tissue of the incision

AND at least **ONE** of the following:

1. Purulent drainage, with or without laboratory confirmation, from the superficial incision.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.
3. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat **AND** superficial incision is deliberately opened by surgeon, **UNLESS** incision is culture-negative.
4. Diagnosis of superficial incisional SSI by the surgeon or attending physician.

Do **NOT** report the following conditions as SSI:

1. Stitch abscess (minimal inflammation and discharge confined to the points of suture penetration).
2. Infection of an episiotomy or newborn circumcision site.
3. Infected burn wound.
4. Incisional SSI that extends into the fascial and muscle layers (see deep incisional SSI).

NOTE: Specific criteria are used for identifying infected episiotomy and circumcision sites and burn wounds.

Deep incisional SSI

Infection occurs within 30 days after the operation if no implant* is left in place or within 1 year if implant is in place and the infection appears to be related to the operation

AND

Infection involves deep soft tissues (eg, fascial and muscle layers) of the incision

AND at least **ONE** of the following:

1. Purulent drainage from the deep incision but not from the organ/space component of the surgical site.
2. A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38°C), localized pain, or tenderness, unless site is culture-negative.
3. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
4. Diagnosis of a deep incisional SSI by a surgeon or attending physician.

NOTES:

1. Report infection that involves both superficial and deep incision sites as deep incisional SSI.
2. Report an organ/space SSI that drains through the incision as a deep incisional SSI.

Organ/space SSI

Infection occurs within 30 days after the operation if no implant* is left in place or within 1 year if implant is in place and the infection appears to be related to the operation

AND
Infection involves any part of the anatomy (eg, organs or spaces), other than the incision, which was opened or manipulated during an operation and at least one of the following:
1. Purulent drainage from a drain that is placed through a stab wound¶. If the area around a stab wound becomes infected, it is not an SSI. It is considered a skin or soft tissue infection, depending on its depth into the organ/space.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space.
3. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
4. Diagnosis of an organ/space SSI by a surgeon or attending physician.

* National Nosocomial Infection Surveillance definition: a nonhuman-derived implantable foreign body (eg, prosthetic heart valve, nonhuman vascular graft, mechanical heart, or hip prosthesis) that is permanently placed in a patient during surgery.
¶ If the area around a stab wound becomes infected, it is not an SSI. It is considered a skin or soft tissue infection, depending on its depth.

Data from: Mangram AJ, Horan TC, Pearson ML, et al. Guideline for prevention of surgical site infection. In: Infection Control and Hospital Epidemiology, CDC 1999; 20:247.

Graphic 79765 Version 7.0

Medications associated with fever

Antimicrobials
Penicillins
Cephalosporins
Fluoroquinolones
Vancomycin
Sulfonamides
Nitrofurantoin
Rifampin
Amphotericin B
Cardiovascular medications
Thiazide diuretics
Furosemide
Spironolactone
Hydralazine
Quinidine
Procainamide
Alpha methyldopa
Anticonvulsants
Phenytoin
Other
Heparin (especially unfractionated)
Salicylates
Nonsteroidal antiinflammatory drugs
Allopurinol
Immunoglobulins
Iodides
Propylthiouracil
Hydroxyurea
Mycophenolate mofetil

Graphic 82602 Version 2.0

Infectious agents for which donated blood is screened in the United States

Infectious agent	Comments on testing
Babesia microti (babesiosis)	Many units in high-risk regions of the United States; either with an antibody assay alone or with an antibody assay and a PCR assay
Cytomegalovirus	Selected units to establish a CMV-negative inventory for at-risk recipients; immunoassay for antibody
Hepatitis B virus	All units; immunoassay for HBsAg and HBc antibody and nucleic acid minipool testing for viral DNA
Hepatitis C virus	All units; immunoassay for antibody (with further confirmation testing if reactive) and nucleic acid minipool testing for viral RNA
HIV-1 and 2	All units; immunoassay for antibody (with further confirmation testing if reactive) and nucleic acid minipool testing for viral RNA
HTLV-I and II	All units; immunoassay for antibody
Treponema pallidum (syphilis)	All units; immunoassay
Trypanosoma cruzi (Chagas disease)	Initial donation from all donors; immunoassay for antibody (with further confirmation testing if reactive)
West Nile virus	All units; nucleic acid minipool or individual donation testing for viral RNA
Zika virus	All units; nucleic acid minipool or individual donation testing for viral RNA

Refer to UpToDate for a discussion of the laboratory testing of donated blood. In addition to this testing, platelets, which are stored at room temperature, also undergo bacterial testing, the details of which vary by institution. Additional donor screening, self-deferral, and in some cases pathogen inactivation processes are used to address other infectious risks.

PCR: polymerase chain reaction; CMV: cytomegalovirus; HBsAg: hepatitis B surface antigen; HBc: hepatitis B core antigen; HIV: human immunodeficiency virus; HTLV: human T-lymphotropic virus.

Graphic 106595 Version 5.0

Contributor Disclosures

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