Refining the Evaluation of Early Post-Operative Fever

Jessica M. Mayor,,M.D., Stephanie Moreno, B.S., Neal R. Barshes, M.D., M.P.H.

Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Houston,

Abstract:

Fever in the early post-operative setting has never been a specific marker of infection. The mnemonic of the 5Ws, wind, water, wound, walking, and wonder drugs, continues to be used and to prompt potentially unnecessary, nonspecific, and costly evaluations. Similarly, isolated leukocytosis may be even less specific. The approach to patients with fever or leukocytosis in the postoperative period has not been re-evaluated in recent years. Starting with the 5W's, we conducted a review of the literature on the causes of fever in the early post-operative patient and to provide an evidence-based approach to evaluating these patients. Less than one fifth of patients with a fever in the post-operative period have an infectious cause identified. Due to the diversity of post-surgical patients and the advent of minimally invasive techniques, the evaluation of post-operative fever is too varied to be reduced to a simple mnemonic. Instead, we suggest use of a clinically-relevant, tailored beside assessment to guide additional, selective testing. Serum procalcitonin and C-reactive protein may be able to more accurately identify those patients with post-operative fever who have infection. Continued critical assessment of post-operative outcomes is required to develop algorithms to optimize post-operative care.

Keywords: fever; post-operative complications; surgical site infection

Please address correspondence to: Neal R. Barshes, MD, MPH, Associate Professor of Surgery, Michael E. DeBakey Department of Surgery, Baylor College of Medicine.

Introduction

Early post-operative fever (core body temperature of 100.5 degrees Fahrenheit or higher occurring within one week of surgery) may occur in as many as one third of surgical patients and has contributed to extended hospitalizations and costly evaluations. In the past, the 5W acronym has guided surgeons and trainees toward particular salvo of tests which traditionally start with two sets of blood cultures from peripherally sites, a chest x-ray, and urinalysis. Sputum and urine cultures are often added. The fact that the 5W's approach identifies only small number of post-operative infections long been recognized [1], but this has not deterred surgeons and trainees from continuing to use the approach for fever [2], perhaps because no good alternatives have been proposed. Indeed, many clinicians have expanded the application of the 5W's to even evaluate isolated post-operative leukocytosis. The current environment of medical care only highlights the need for a better approach. Cost-containment strategies attempt to stem the excessive growth in U.S. health care costs, including shifts towards reduced hospital length of stays, enhanced recovery protocols, and minimally-invasive approaches to surgery. Laparotomies, central venous catheters, and nasogastric tubes are used much less frequently. Antimicrobial stewardship programs ask surgeons and physicians to be more judicious in their use of antibiotic therapy. Newer laboratory assays have been developed to provide more specific diagnostic data. A critical approach to the evaluation of early post-operative fever may therefore be timely.

We provide here an evidence-based review of the literature pertaining to these topics across surgical specialties. In contrast to the many excellent studies on the incidence of various post-operative complications [3–7] and reviews on the diagnosis and management of specific types of post-operative infections [8–11], this practical review will focus on the on the significance of early post-operative fever and its utility in identifying post-operative infectious complications in the immunocompetent adult surgical patient. Pediatric patients and post-operative infections in the immunosuppressed adult will be beyond the scope of this review. The risk factors, prevention strategies and management of various post-operative infectious complications is also beyond the scope of this review, but fortunately, many outstanding reviews on these topics already exist.[12–17]

Abbreviations:
CRP, C-reactive protein
DVT, deep venous thrombosis
PCT, procalcitonin
SIRS, systemic inflammatory response syndrome

The "Five W's" of Post-Operative Fever

Hyder and colleagues [3] suggest that the 'five W's" of post-operative fever has been used since the 1980s. Although it may have been useful during a time when surgery consisted of fewer but more consistently invasive operations, applying this mnemonic to contemporary surgical practice – including the increasing numbers of patients who have had laparoscopic, endoscopic, robotic, endovascular, or minimally-invasive approaches to "surgery" – has many shortcomings. First is the fact that fever is more a signal of an inflammatory response (in particular, prostaglandin E2 production via complex and redundant physiologic pathways) [18], than it is a sign specific to infection in the post-operative setting. Indeed, six studies of patients with early post-operative fevers report that the number of febrile patients that had an identified infection ranged from 4 to 36% with an pooled proportion of 22% (see Table 1).[1,19–23] This may be supported by the finding that fever is seen in 25% of hip arthroplasty patients receiving conventional post-operative analgesia and only 4% among patients receiving a multimodal pain regimen (despite no difference in the incidence of identified infection in the two cohorts).[24]

A second limitation is that the 5W's makes absolutely no distinction based on characteristics of the operation – a shortcoming that may be even more apparent since the advent of laparoscopic and other minimally-invasive approaches to intracavitary operations. Across surgical specialties, the association between fever and documented infection varies. Fever may occur in as many as 30% of patients undergoing major gynecologic surgery, yet only 11% are identified as having a serious infection.[22,23] Older literature has estimated that 15-43% of those undergoing abdominal surgery have post-operative fever, and only 27-43% have culture-proven infection.[1,19] In a more recent prospective study of over 1000 elective surgical procedures, while 23.7% of patients had an early post-operative fever, only 18% of febrile patients were diagnosed with an infectious source, half of whom (9%) were able to be diagnosed clinically, leading the authors to conclude that extensive evaluations have little benefit.[20] In a meta-analysis of post-operative fever in orthopedic surgery patients, the prevalence of fever ranged from 8.1% to 87.3%; however, the diagnostic yield of studies performed as part of a fever workup ranged from 0% to 40%.[25] In the trauma setting, 40% of trauma patients admitted to the intensive care unit for at least 48 hours had fever, and 70% of these did not have a source for their fever.[21] Many series reporting a high incidence of post-operative fever are with open operations, but the occurrence of fever is probably nuanced beyond this singular variable, as one third of patients undergoing microscopic subinguinal varicocelectomy under spinal anesthesia compared to 0.4% of patients undergoing microsurgical vasovasostomy under spinal anesthesia.[26] Overall, in most post-operative settings fever seems to have low specificity for the presence of infection (Table 1).

Table 1: A review of studies describing the relationship between early post-operative fever and infection.

Study	population	Incidence of fever	Incidence of infection among those with fever
Schwandt A et al. 2001	laparotomy for gynecologic pathology	28/105 (27%)	4/28 (14%)
de la Torre SH et al. 2003	laparotomy for gynecologic pathology	194/676 (29%)	17% estimated*
Freischlag J et al. 1983	"abdominal surgery"	71/464 (15%)	19/71 (27%)
Jorgensen FS et al. 1988	"major abdominal surgery"	259/608 (43%)	93/259 (36%)
Lesperance R et al. 2011	"general surgical procedures"	245/1,032 (24%)	9/245 (4%)
Benqualid V et al. 2015	major trauma	82/162 (52%)	25/82 (30%)
Composite		879/3,047 (29%)	150/685 (22%)

*reported as number of positive tests among multiple tests, not total number of patients

Thirdly, fever has most often been defined as a core body temperature above a somewhat-arbitrary threshold, often 100.5 degrees Fahrenheit (°F). Approximately half of elderly nursing home patients with infections in one series had maximum temperatures below 101°F, though many (89%) did demonstrate an elevation of 2.4°F or more.[27]

Fourth, in contrast to the systemic inflammatory response syndrome (SIRS) criteria, the 5W approach focuses exclusively on early post-operative fever as an indicator of infection. Hypothermia (core body temperature < 97.7 °F or 36.5 degrees Centigrade), as reflected in the SIRS criteria, is not only as important an indicator of infection as fever, but may also have a higher mortality.[28,29]

Finally, the 5Ws fail to acknowledge that patient characteristics influence the inflammatory response to infection in general and body temperature in particular. Patients who have unexplained fevers tended to be younger, had less severe underlying disease, and may have undergone less extensive operations than those who develop infections.[30] In contrast, infections in the elderly will less often present with elevated body temperature. In one series of cases of intra-abdominal infections, for example, elderly patients presented with fever only about half as often as younger patients. Nausea, vomiting, and diarrhea were also about half as common among the elderly (though hypothermia and a very low polymorphonuclear leukocyte count were more common).[31] While we know the most about advanced age and fever, it is likely that other patient characteristics may also influence the febrile response to infection.

"Wind": Pneumonia and atelectasis

"Wind" represents pneumonia and atelectasis in the "5 W's" paradigm. Pneumonia does occur, but only in 2.0% of cases done with regional anesthesia and in 3.5% of cases done with general anesthesia.[32,33] More than half of post-operative pneumonias that do develop are identified within the first 7 days of an operation. [3]

Ventilator associated pneumonia can be challenging to diagnose accurately despite various respiratory sampling techniques and the existence of diagnostic algorithms.[34] While definitions, classifications systems, and laboratory values are useful, clinicians may also have to rely on clinical signs rather than these adjuncts alone.[35]

Using quantitative bacterial cultures of bronchoalveolar lavage samples, Prekates et al [36] found the sensitivity of broncheoalveolar lavage plus Gram stain for ventilator-associated pneumonia was 77%, the specificity 87%, the positive predictive value 71%, and the negative predictive value 90%. In surgical critical care patients, the Johanson criteria and the clinical pulmonary infection score were both compared to positive respiratory cultures and were both found to have unacceptably low sensitivity, specificity, positive predictive value, negative predictive value, and accuracy.[37]

Pieracci et al [38] evaluated more than 1000 BALs and clinical pulmonary infection scores from 492 surgical critical care patients for ventilator-associated pneumonia. Fever, new infiltrate on chest X-ray, or positive Gram stain were present in every case of ventilator-associated pneumonia in this study. New infiltrate on chest X-ray was the component of clinical pulmonary infection score with the highest sensitivity for ventilator associated pneumonia (91%).[38] For the management of ventilator-associated and hospital-acquired pneumonia, we refer the reader to recent reviews.[35,39,40]

In contrast to pneumonia, early post-operative fever should not be attributed to atelectasis. In a meta-analysis of 998 cardiac, abdominal, and maxillofacial surgery patients, only one of the eight studies included in this analysis found an association between post-operative atelectasis and fever.[41] This study suggests that fever and atelectasis are both associated with an operation, but the association between fever and atelectasis is not causal. In light of these studies, chest x-rays could be selectively obtained only for patients with post-operative fever who have undergone general anesthesia, who remain intubated or have been re-intubated, or who have

additional clinical signs (such as productive cough or history of recent or prior pneumonias) suggesting pneumonia.

"Water": Urinary Tract Infections

"Water" typically refers to urinary tract infections such as cystitis and pyelonephritis in the 5W mnemonic. In contemporary series of surgical outcomes, urinary tract infections have decreased: 0.8% of colorectal surgery patients who had their urinary catheters removed according to recommended timelines vs. 4.1% of those who do not. Rates of urinary tract infections are somewhat higher after rectal surgery (3.5% vs. 9.6%, respectively). Nonetheless, urinary tract infections remain among the three most common infections after surgery [3], and urine cultures may be positive in 14-50% of patients.[22,42] It is also worth noting that the concordance between urinalysis and urine culture results is not perfect, so the clinician should consider obtaining both to increase sensitivity in identifying a urinary tract infections.[22] Considering that bacteriuria occurs in 26% of elderly institutionalized women and 16% of elderly institutionalized men, urinalysis and urine culture should be considered for all elderly patients regardless of whether a catheter was used.[43]

It is worth noting that several groups have reported their experience with avoiding standard bladder catheter placement for at least shorter-duration operations done under either general or spinal anesthesia [44–47], instead selectively catheterizing based on bladder volume. This approach may further reduce the incidence of urinary tract infections after an operation. External catheters (e.g. condom catheters) decrease the incidence of urinary tract infection, but only by about half.[48] Furthermore, when urinary tract infections do occur, external catheters are no less likely to be associated with urinary cultures yielding *Staphylococci*, gram negatives organisms, or *Enterococci*.[45] Considering these factors, a urinalysis with or without urine cultures should be considered for patients with post-operative fever who have had any type of urinary catheter (internal or external) for more than two days or elderly patients without recent catheterization.

"Wound": Surgical Site Infections

SSIs are a potentially preventable cause of morbidity, mortality, and fever after surgery. SSIs complicate 2% to 5% of all surgical procedures and account for 14% to 31% of all healthcare associated infections among hospitalized patients.[50] The incidence of SSIs during the first 30 days after an operation is nearly 5-fold higher than the incidence of UTIs and more than 10-fold higher than the incidence of pneumonia. Early identification is therefore paramount to reduce morbidity and costs.

There is no literature documenting the sensitivity and specificity of fever for predicting SSIs. Traditionally, SSIs have been diagnosed by clinical findings, such as erythema, purulence, or foul odor. As an alternative to clinical exam findings and traditional laboratory tests, newer, rapid diagnostic tests are being developed to detect the presence of bacteria in wounds, including rapid diagnostic testing for host enzymes produced in response to bacterial infection.[51]

"Walking": Venous thromboembolism

"Walking" refers to venous thromboemboli (deep venous thrombosis [DVT] or pulmonary emboli). DVT can cause fever. In a review of 8,615 patients in a venous thromboembolism registry collected during a decade of experience with trauma patients at Singapore General Hospital, 30% of venous thrombi presented with fever alone and no leg swelling.[52] An international multicenter study has found that 4.9% of patients with acute DVT present with fever.[53] Though a study of cancer patients has suggested fever is a risk factor for DVT [54], another series that reports resolution of fever within days of initiating anticoagulation therapy suggests that the DVT may be the cause of fever rather than both entities being a manifestation of an underlying inflammatory state.[55,56] The incidence of DVT may remain elevated for up to a year after surgery.[57,58] However, in most settings, early post-operative rates of DVT are low: 0.2% following colorectal surgery [59], 0.39% in trauma patients [52], and 0.7% after thoracolumbar surgery [60], 1.3% after bariatric surgery [61], and 3.2% after craniotomy for neoplasia.[62] As such, fever should probably only be used as an indication to evaluate for deep venous thrombosis only in two particularly high-risk populations: coronary artery bypass grafting (10-17% incidence) [63–65] or leg amputation (9-28% incidence).[66–69]

"Wonder drugs": Drug-induced fever

There are several well-described, although rare drug-induced hyperthermia syndromes. Serotonin syndrome results from an excess of serotonin at the 5-HT receptor and presents clinically with autonomic hyperactivity, neuromuscular abnormalities, and altered mental status. Medications associated with serotonin syndrome include selective serotonin-reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, tricyclic antidepressants, amphetamines, dextromethorphan, linezolid, sumatriptan, lithium, 3,4-methylenedioxymethamphetamine, and several pain medications, such as tramadol, fentanyl and meperidine.[70–72] Many patients may be taking these classes of medications as an outpatient and are then placed on analgesics post-operatively, putting them at increased risk.

Malignant hyperthermia is an autosomal dominant disorder caused by a mutation in the RYR-1 receptor of skeletal muscle that results is a hypermetabolic crisis after exposure to inhalational anesthetics, succinylcholine, or in very rare cases, stress. Malignant hyperthermia has a low incidence (1 in 100,000-250,000 anesthetic procedures) and is treated with dantrolene.[70,73] Neuroleptic malignant syndrome presents similarly to malignant hyperthermia with high fever, muscle rigidity, delirium, and dysautonomia; it is caused by medications that act on dopamine receptors – most commonly antipsychotics.[70,74] In addition, fevers can be caused by toxicity secondary to anticholinergics, such as antispasmodics, antihistamines, TCAs, anti-Parkinsonian drugs, neuroleptics, atropine, and belladonna alkaloids, or sympathomimetics, such as methylenedioxymethamphetamine, monoamine oxidase inhibitors, amphetamines, and cocaine. As in the other drug-induced hyperthermia syndromes, stopping the offending agent and supportive care with external cooling and volume resuscitation are mainstays of treatment.[70] Similarly, drugs, such as clopidogrel, can also rarely cause fever, likely secondary to a hypersensitivity reaction.[75]

Other infectious causes of fever

Other infectious etiologies responsible for early post-operative fever are rare but worth reviewing because of the high associated mortality or morbidity. First, Clostridium difficile colitis is seen in a small overall number of post-operative patients, with incidence ranging from 0.1% in hip and knee arthroplasty patients to 1.6% in patients undergoing colectomy.[76,77] Mortality has been estimated at 9%.[78]

Necrotizing myofascial infections, including those associated with *Clostridium perfingens* but also *Eschericia coli*, *Klebsiella pneumoniae*, and *Bacteroides* species, may present with severe pain at an incision site (including port sites), high fever and tachycardia 12-36 hours after surgery. Delays in treatment are common, and mortality is high.[79] Phlebitis associated with peripheral intravenous catheters can occur in 7-15% of hospitalized patients.[80,81] Bacteremia from catheter-related phlebitis or suppurative thrombophlebitis are less common but can be a source of early post-operative infection.[82,83] Infection of orthopedic hardware, pacemakers, and other prosthetic materials may also be a source of post-operative fever, both early after implantation as well as late after implantation but soon after other invasive procedures.[84–87] Decubitus ulcers at the sacrum or other pressure points for patients can also be a source of fever. Typically associated with long duration hospitalizations in immobile patients, decubitus ulcers can occasionally be seen in patients who have had prolonged operative times.[88,89] Meningitis and cerebral or epidural abscesses have been reported following epidural or spinal anesthesia. Though rare, it can be fatal.[90]

When initially described in 1982, nosocomial sinusitis (sinus infection associated with nasotracheal tubes or other instrumentation) was estimated to account for 5% of nosocomial fevers.[91] More recently, the incidence has been estimated at 0.15% of hospitalized patients, occurring mainly in patients with an indwelling nasogastric or endotracheal tube.[92] Acute suppurative parotitis is probably even rarer still, but it should be considered in dehydrated patients with no oral input who have tenderness of the cheek or jaw with leukocytosis and/or fever.[93–95]

Additional non-infectious causes of fever

In addition to infectious causes of fever, there are many non-infectious causes of fever which could potentially occur in the early post-operative period.[96] As mentioned previously, MI can cause fever in the post-operative period. Fever has been noted to occur in about 15% of patients with ST-elevation myocardial infarcts and appears to correlate with infarct size. [97,98] It is not known how often fever is seen in non-ST elevation myocardial infarcts. Given that post-operative myocardial infarcts are diagnosed in the first 48-72 hours after an operation [3], it may therefore be reasonable to obtain a 12-lead EKG for evaluation of myocardial infarction in patients who have fever within the first 72 hours of an operation but no other clinical signs or symptoms of myocardial infarction.

Post-operative hematoma is frequently mentioned as a cause of fever despite little data existing to corroborate this.[99,100] Some series noted that most patients with hematomas present with fever [26,101], while others suggest no association.[102] It seems reasonable to think that hematoma can be a cause of fever, though it is unclear *how often* it is the source.

Certain neoplasms can cause fever. While hematologic malignancies are the most common cancers associated with fever, renal cell carcinoma is the most common solid tumor associated with fever of unknown origin.[103] Fever is found in 20-30% of renal cell carcinoma patients, and is the presenting symptom in approximately 2% of patients.[104] Very rarely, hepatocellular carcinoma can present with fever, and this tends to occur in advanced cases with poor survival.[105] Thirty-four percent of patients with atrial myxomas present with fever and constitutional symptoms due to IL-6 secretion.[106] Other tumors rarely associated with fever of unknown origin include colon carcinoma, pancreatic carcinoma, and metastases to the liver and central nervous system.[103]

Adverse reactions to transfusions of blood products can produce fever. Febrile non-hemolytic transfusion reactions most commonly present with fever and shaking chills, occur during the transfusion or within a few hours of its completion, are likely caused by interactions between donor HLA or leukocyte specific antigens and recipient cytotoxic antibodies, and can be minimized by pretreatment with acetaminophen. The incidence of febrile non-

hemolytic transfusion reactions is higher after platelet transfusion (4-30%) than after red blood cell transfusion (0.5%).[107] Allergic transfusion reactions, transfusion-associated sepsis, and transfusion-related acute lung injury can also cause fevers immediately during transfusion, after 4-6 hours post-transfusion, and within 6 hours of transfusion, respectively.[107]

The three most prevalent endocrine causes of fever are thyrotoxicosis, adrenal insufficiency, and pheochromocytoma. Hyperthyroid states cause temperature control deregulation, leading to hyperthermia.[108] In patients with adrenal insufficiency, whether primary (Addison disease) or secondary, fever can be triggered by an infection or present as a fever of unknown origin. Here, fever is caused by unregulated cytokine release due to lack of inhibition by cortisol; treatment is with intravenous hydrocortisone.[108,109] With pheochromocytomas, the mechanism of hyperthermia is not well understood but is thought to be related to the hypermetabolic state and decreased ability to dissipate heat due to impaired vasodilation generated by excess catecholamine production.[108]

When alcohol withdrawal progresses to delirium tremens, which usually occurs 48-72 hours after consumption of the last drink, the associated autonomic instability can produce fevers.[110,111] This timing would generally lend to these fevers occurring in the early post-operative period. Finally, Sweet's syndrome (febrile neutrophilic dermatosis) manifests as fever and erythematous papules. It is usually a cutaneous presentation of systemic illness, such as leukemia or inflammatory bowel disease.[112]

Dehydration is sometimes listed as a cause of fever. Severe dehydration may result in loss of the ability to regulate body temperature. With reduced hydration and blood flow to the skin, the ability to sweat and dissipate heat is diminished, possibly causing fever.[113] There is empirical data demonstrating a relationship between fever and dehydration in the pediatric population.[114] As no data supports the relationship in adults, it is probably best to not ascribe the primary cause of early post-operative fever in the adult surgical patient to dehydration as the primary cause.

Laboratory Testing to Identify Infection among Patients with Fever

Leukocytosis is often considered marker of infection, but – like fever – it is probably reflective of some inflammatory response. Leukocytosis is defined

Table 2: Studies evaluating the diagnostic accuracy of serum procalcitonin levels of detecting various types of infections in the post-operative setting.

Study	Study population & prevalence of event of interest (percentage)	Procalcitonin threshold (ng/mL)	Sensitivity estimate	Specificity estimate	Negative predictive value estimate	Positive predictive value estimate
Aouifi A, et al 2000	97 cardiac surgery patients; any infection in 54 (56%)	0.50	93%	70%	86%	79%
		1.0	85%	95%	84%	96%
		5.0	44%	100%	59%	100%
		10.0	28%	100%	59%	100%
Giaccaglia V, et al. 2016	504 colorectal surgery patients; anastomotic leaks in 28 (6%)	2.3 on POD3	59%	92%	97%	34%
		2.7 on POD5	70%	93%	96%	32%
Hayati F, et al. 2017	3 colorectal surgery patients; anastomotic leak in 3 (4%)	5.27 on POD3	100	85%	100%	23%
Takakura Y et al 2013	118 elective colorectal surgery patients; surgical site infections in 18 (16%)	0.77 on POD1	83%	64%	95%	30%
		1.5 on POD3	50%	95%	91%	64%
Abu Elyazed MM, et al 2017	100 patients undergoing abdominal surgery; hospital acquired pneumonia in 14 (14%)	1.44 on POD3	88%	75%		
Munoz JL, et al 2016	115 patients undergoing laparoscopic sleeve gastrectomy; septic complications in 13 (11%)	0.95 on POD2	100%	100%	100%	100%
Varetto G, et al 2016	80 men undergoing open aortic surgery; any early infection in 24 (29%)	0.20	93%	46%		
		0.41	79%	62%		
		0.60	57%	77%		
		0.98	43%	85%		
Oberhofer D, et al. 2012	79 patients undergoing elective colorectal surgery; infectious complications in 29 (37%)	1.34	76%	68%		

POD = post-operative day

as white blood cell count of over 10-12.0 cells x 10^6/ uL. White blood cell count count has a low sensitivity (60%) but good specificity (90%) for infection.[115] In a study investigating leukocytosis following total hip and knee arthroplasty, the authors concluded that leukocytosis was a benign finding in 38% of patients.[116] Other surgical subspecialties have documented similar results. For example, after gynecologic robotic surgery, Goel et al [117] found that 29% (59/204) of cases developed post-operative leukocytosis, and there was no correlation between leukocytosis on post-operative day 1 and infectious complications. Occasionally very high degrees of leukocytosis – including a leukemoid reaction (white blood cell count exceeding 50,000/mm3) – can occasionally be seen with post-operative *Clostridium difficile* diarrhea and is typically associated with a high mortality.[118–121] Overall, though, the presence of a post-operative leukocytosis common and seems to provide even less specific information than the presence of an early post-operative fever.

Using clinical data to diagnose infections may not always be reliable and the importance of the time of laboratory collection may vary. Diagnostic yield of blood cultures seems especially low.[42] Blood cultures representing 108 febrile events were taken from 72 patients on adult surgical services. Nine grew pathogens; of these, four were contaminants. The cost for each of the five patients with positive cultures was $2798 (in 1991 United States dollars). Blood culture vials were more likely to be positive if blood was drawn on post-operative days 4 through 10; white blood cell count and temperature at the time of phlebotomy were not predictive of positive culture.[122]

Procalcitonin (PCT) is an intracellular precursor of calcitonin.[123] Circulating levels of PCT in healthy subjects are below the detection limit, but was discovered to be elevated in patients with bacterial infection.[124] The production of PCT during inflammation is regulated by TNF in response to an endotoxin. After exposure to an endotoxin, serum TNF rises first, followed by interleukin-6 (IL-6), and then PCT before CRP is able to be detected in serum. The reason that un-cleaved PCT is secreted during infection has not been elucidated.[125] An operation will elevate PCT levels, but levels diverge quickly afterwards with levels approaching normal within about a week in patients without infection versus remaining elevated in patients with infection.[126] PCT seems to have excellent diagnostic accuracy in identifying various post-operative infections (Table 2).

A threshold of 1 ng/mL had a sensitivity of 85%, a specificity of 95%, a positive predictive value of 96%, and a negative predictive value of 84% in a cardiac surgery cohort.[127] In a meta-analysis of eight studies evaluating PCT in identifying intra-abdominal infections, anastomotic leaks, and surgical site infections after colorectal surgery, a cutoff of 1.26 ng/mL on post-operative day 5 had a sensitivity of 78% and a specificity of 88%. Similarly-high estimates of diagnostic accuracy were obtained for PCT on post-operative day one (>0.77 ng/mL) and day three

Table 3: Studies evaluating the diagnostic accuracy of serum C-reactive protein (CRP) levels of detecting various types of infections in the post-operative setting.

Study	Study sample	CRP threshold, mg/mL	Sensitivity estimate	Specificity estimate	Negative predictive value estimate	Positive predictive value estimate
Aouifi A, et al 2000	97 cardiac surgery patients; any infection in 54 (56%)	10	98%	10%	75%	75%
		25	92%	24%	69%	69%
		50	84%	40%	65%	65%
		150	64%	84%	65%	64%
Giaccaglia V, et al. 2016	504 colorectal surgery patients; anastomotic leaks in 28 (6%)	16.9 on POD3	59%	82%	96%	20%
Hayati F, et al. 2017		12.5 on POD5	74%	86%	98%	22%
Takakura Y, et al 2013	118 elective colorectal surgery patients; surgical site infections in 18 (16%)	9.5 on POD3	78%	58%	93%	26%
Munoz JL, et al 2016	115 patients undergoing laparoscopic sleeve gastrectomy; septic complications in 13 (11%)	150 mg/L	100%	100%		
Oberhofer D, et al. 2012	79 patients undergoing elective colorectal surgery; infectious complications in 29 (37%)					

POD = post-operative day

(>1.5ng/mL).[128] High levels of diagnostic accuracy have also been reported following laparoscopic sleeve gastrectomy in morbidly obese patients [115], open aortic operations [129], and also useful in identifying hospital-acquired pneumonia after abdominal surgery.[126]

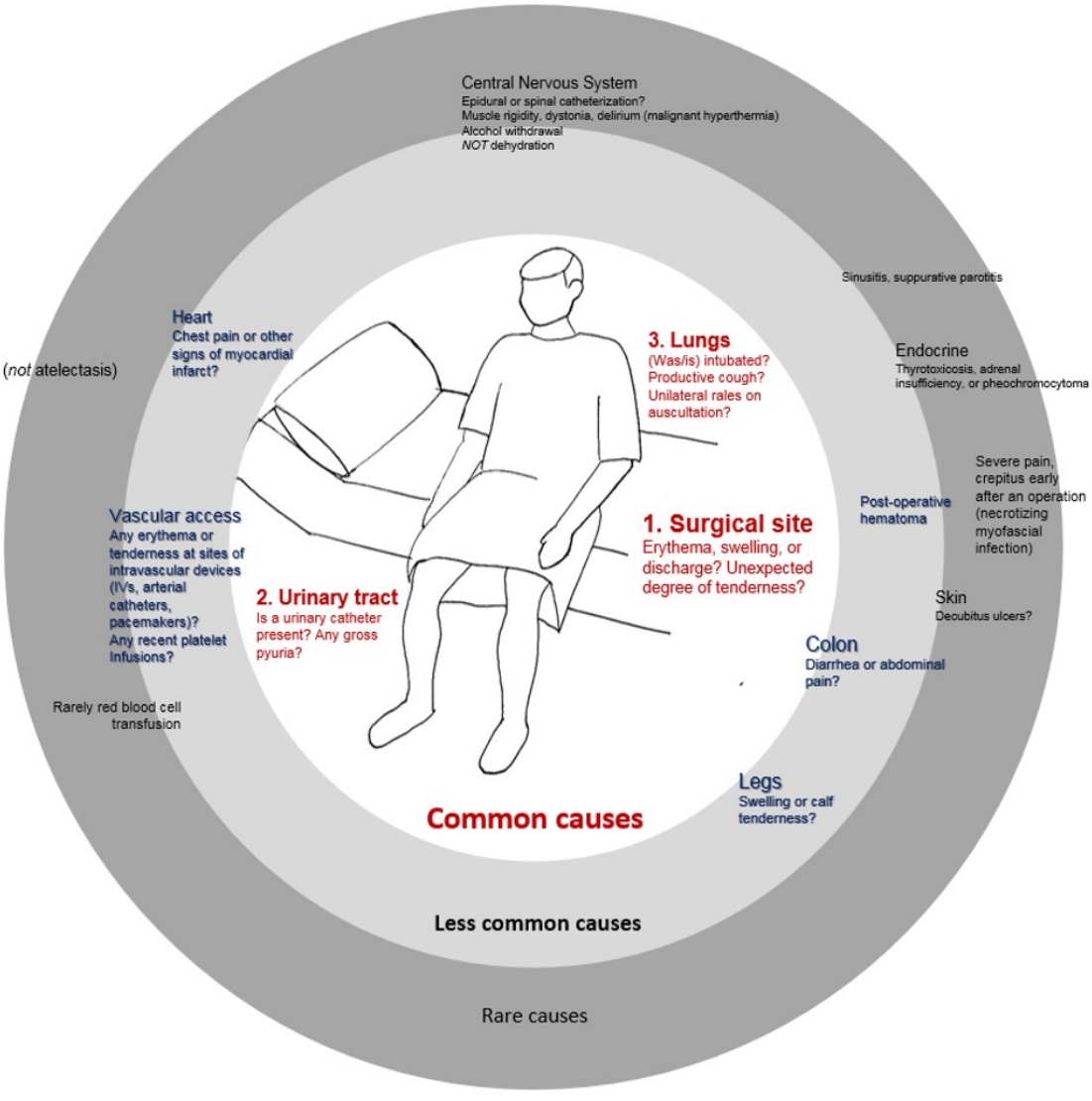
C-reactive protein (CRP) is a plasma protein that is synthesized in the liver in response to circulating levels of IL-6, and possibly IL-1 and TNF-α. It also binds to a variety of other ligands, including damaged cell membranes [130], small nuclear ribonucleoprotein particles, apoptotic cells, as well as glycans, phospholipids, and other components of microorganisms.[131] Ligand-bound CRP activates the classical complement pathway.[131]. Studies that have assessed the utility of CRP in identifying post-operative infections suggest that the diagnostic accuracy is comparable to that of PCT, making it a reasonable alternative to use in centers that do not perform PCT testing (Table 3). It is worthwhile noting that CRP also has utility in identifying many of the aforementioned complications, but it seems to have slightly lower diagnostic accuracy than PCT.[126,128,132,133] In most studies, a level of 100 mg/L was tested.[132]

Unless new evidence demonstrates some utility, we suggest against using an isolated leukocytosis to initiate any further evaluation for post-operative infection. PCT or CRP may be the best lab assays to stratify patients who do or do not have infection.

SUGGESTIONS FOR AN UPDATED ALGORITHM

Based on the findings of this review, we would suggest a bedside assessment for all patients with post-operative fever that identify common or noteworthy sources and help direct further testing. If unfamiliar with the patient, the clinician should

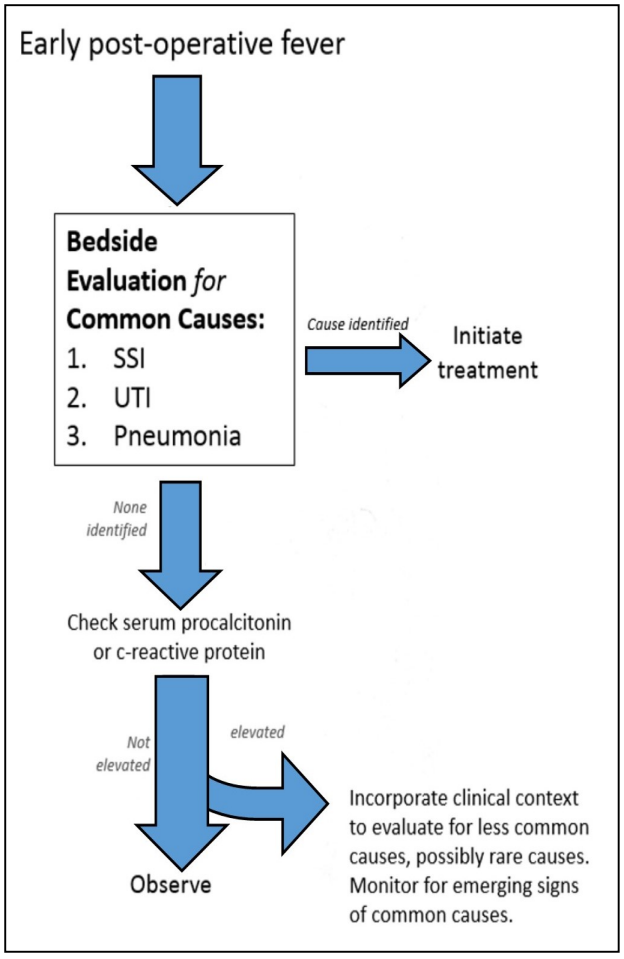
Figure 1: Causes of early post-operative fever in the surgical patient, organized by frequency and location.



obtain details on the operation performed (including indication for the operation, anesthesia given, whether platelets were transfused, etc.). The patient should be questioned about clinical symptoms that might suggest common causes of post-operative fever, including surgical site infection (pain, discharge), pneumonia (cough, dyspnea), and urinary tract infection (dysuria, urinary frequency, or urinary urgency). Additional questions should elicit symptoms associated with rarer but clinically-important infections: diarrhea, chest pain, dyspnea, pain at vascular access sites, and .

A "primary survey" of sorts should focus the exam on identifying either common or readily-identifiable causes of infection (Figure 1). This should start with inspecting the surgical incision for erythema or drainage. The wound should be palpated for an unexpected degree of tenderness, for fluctuance, or for crepitus. Next, the surgeon should see whether a urinary catheter (indwelling or external) is present. It should be noted whether the patient remains intubated or has had prolonged post-operative intubation. The patient should be asked about any productive cough, and the lungs should be auscultated for unilateral rales.[134] The site of all vascular access devices, including intravenous catheters, central venous catheters, and pacemakers, should be examined for erythema, swelling, drainage, and tenderness. The patient should be examined for calf swelling or tenderness in the posterior calf. Laboratory testing and imaging should be obtained based on abnormal findings on this primary survey (ex. chest x-ray, urinalysis and urine cultures, stool for *Clostridium difficile* testing). It is worth emphasizing that a bedside assessment – rather than ordering an incentive spirometer and salvo of laboratory and imaging tests – should be the first (and possibly only, in some cases) step in evaluating the patient with an early post-operative fever.

Figure 2: *Suggested algorithm for evaluation and management of early post-operative fever.*



If this primary survey identifies no clinical signs or symptoms that would point toward a source, a serum PCT or a CRP level should be obtained (Figure 2). If within normal, the fever should be observed. If elevated, the surgeon should evaluate other potential context-specific sources. For example, as DVT is relatively common after cardiac surgery and lower extremity amputations, it would be appropriate to order a lower extremity ultrasound in these patients.[63–69] Similarly, urinalysis and urine cultures should be considered for elderly women with indwelling bladder catheters.[43]

Finally, surgeons should not feel compelled to treat early post-operative fever with acetaminophen or other aggressive measures. Several trials, including the recent "HEAT" trial [135,136], demonstrate no benefit, while findings from one small trial [137] and another large observational study [138] suggest a higher rate of death among patients receiving antipyretic therapy (acetaminophen and/or non-steroidal anti-inflammatory medications).

Conclusions

Early post-operative fever has never been a very specific indicator of infection in the surgical patient, and fewer than one fifth of patients with fever have an infectious cause identified. An isolated leukocytosis may be even less specific still. Unfortunately, a contemporary, evidence-based approach to the evaluation of post-operative fever is too contextual to be summed up in a mnemonic or proverb. The best approach may be a bedside assessment that incorporates the clinical context can guide the selective use of testing. Surgical site infection is overall the most common infectious cause and should be considered in all post-operative patients with fever. Serum PCT or CRP levels may help more specifically identify the subset of patients with fever who have infection. Surgeons should continue to critically assess outcomes in their specialty and individual clinical practice to develop algorithms best for their patients.

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