

Approach to postoperative fever in pediatric cardiac patients

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ABSTRACT

Fever in the postoperative period in children undergoing surgery for congenital heart disease is fairly common and tends to cause anxiety to both the surgeon and the patient. Such fever is associated with the metabolic response to trauma, systemic response to the cardiopulmonary bypass, hypothermia, presence of drainage tubes, drugs, blood transfusion as well as infections. Establishing the diagnosis requires proper assessment of the patient with focused history, targeted physical examination and judicious use of investigations with the knowledge of the common causes.

Keywords: Cardiac surgery, fever, postoperative

INTRODUCTION

Postoperative fever after cardiac surgery is common and requires a planned approach. Published data about the frequency of postoperative fever in cardiovascular surgery are limited, and the Figure varies from 12% to 73%.^[1-3] Most fevers that develop within the 48 hours after surgery are benign and self limiting. Fever that develops after first 48 hours following surgery is more likely to have an infectious cause,^[3] but noninfectious causes that require further evaluation and treatment must also be considered. It is necessary to have a focused systematic approach towards postoperative fever in the pediatric cardiac surgery patients so that prompt and adequate treatment can be instituted cost-effectively.

In this review, we briefly discuss the common causes of postoperative fever in children undergoing cardiac surgery and the systematic approach to establishing the etiology in a particular patient. We abstracted the most significant published literature on the electronic databases, namely, PubMed and Embase applying specific search terms such as “Postoperative fever”, “Postoperative fever in pediatric cardiac patients”, “Nosocomial infections”, “Nosocomial infections in

pediatric cardiac patients”, etc. We have also assessed abstracts of conference/meetings; consulting authors/experts in the field; and standard text books.

PATHOPHYSIOLOGY AND CAUSES OF POSTOPERATIVE FEVER

In general, the postoperative fever is considered to be associated with the metabolic response to trauma, duration of surgery, the accumulation of blood in closed spaces, presence of drainage tubes, drugs administered during the perioperative period, and infections.^[4-7] In cardiovascular surgery, this postoperative fever has generally been related with the use of cardiopulmonary bypass (CPB), hypothermia, and the post-perfusion syndrome,^[8-11] as well as infection and blood transfusion.^[1-3,12-14] Rectal temperature exceeding 38°C is generally considered to be clinically significant.^[15] While axillary temperature is easy to measure (compared with oral or rectal measurements), it has been found to be an inaccurate estimate of core temperature in children^[16-18] as it is largely influenced by environmental conditions. This is especially important in postoperative cardiac patients who may be having cold extremities with low skin temperature due to low cardiac output state. General causes of fever in the postoperative period can be classified into two broad categories: Infectious and non-infectious [Table 1].

Noninfectious causes

Fever after pediatric cardiac surgery is usually a part of systemic inflammatory response syndrome which can be initiated by a number of processes, including blood contact with foreign surface of the CPB circuit,^[19,20]

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Table 1: Common causes of fever in pediatric postoperative cardiac patients

Infectious	Non-infectious
<ul style="list-style-type: none"> • Pneumonia • Central line associated bloodstream infection • Surgical site infection • Urinary tract infection • Endocarditis • Bed sores • Pharyngitis 	<ul style="list-style-type: none"> • Pump-related fever • Transfusion reaction • Thrombophlebitis • Surgical trauma • Drug fever • Altered function of thermoregulatory center

development of ischemia reperfusion injury secondary to aortic cross-clamping^[20] and presence of endotoxemia. There is a positive correlation between the magnitude of the interleukin-6 response to CPB and duration of CPB.^[4,21] Fever has been found to occur more frequently in the patients undergoing intracardiac surgery and also in patients who had hypothermic CPB.^[22] In its most severe form, this inflammatory reaction, also called “post pump perfusion syndrome”, is characterized by increased capillary permeability, peripheral vasoconstriction, fever, myocardial edema, diffuse cerebral edema, and a diffuse bleeding diathesis.^[23] Although most patients convalesce normally after cardiac surgery, all patients are known to experience these damaging effects albeit to a variable degree.^[23]

The incidence of postpericardiotomy syndrome^[24] following surgery, in which the pericardium has been opened, approaches 30% although patients younger than 2 years of age appear to be less commonly affected. Postpericardiotomy syndrome may cause fever, malaise, chest pain, pleural effusion, raised ESR and on occasion, arthralgias. Treatment is directed at relief of pain with anti-inflammatory agents, diuresis, and drainage of symptomatic effusions. Aspirin has been the mainstay of therapy in children.

Trauma, including the trauma associated with surgery, induces the production of pyrogenic cytokines in the absence of infection. Fever may be a marker of cerebral injury with altered function of the thermoregulatory centre in hypothalamus.^[25,26] It has been found that postoperative hyperthermia is related to cognitive dysfunction after cardiac surgery. It is possible that either hyperthermia induced the worsened cognitive outcome or processes that resulted in worsened cognitive outcome also induced hyperthermia.^[26]

Nosocomial infections

Nosocomial infections in children after heart surgery occur in 12.9 to 30.8%.^[27-31] Bloodstream infections (BSI) are one of the commonest nosocomial infections^[29,30,32] seen in children undergoing cardiac surgery with studies reporting an incidence as high as 65% of total nosocomial infections.^[31] Infants with sepsis can have fever (>38°C rectal), hypothermia (<37°C rectal), apnea,

or bradycardia or tachycardia with no other recognized cause.^[33] Central line associated blood stream infections are laboratory-confirmed BSIs that are not secondary to an infection at another body site in patients with central line in place at the time of or within 48 hours before onset (of event BSI).

Lower respiratory tract is another common site for nosocomial infection in the postoperative period.^[31,32] The diagnosis of pneumonia is based on a combination of clinical, radiological, and laboratory findings. Patient on ventilator can present with temperature instability, worsening gas exchange on ventilator, increased respiratory secretions and suctioning requirements and/or new chest findings with two or more serial chest radiographs revealing at least one of the findings in the form of new or progressive and persistent infiltrate, consolidation, cavitation, or pneumatoceles.

Surgical site infections (SSI) contribute a significant percentage of nosocomial infections in children who have undergone cardiac surgery.^[30] SSI can be superficial incisional, deep incisional or organ/space SSI. Urinary tract infections (UTIs) also constitute about 7% of all postoperative infections in children following cardiac surgery.^[29] Presence of pyuria (urine specimen with ≥ 10 WBC/mm³ or ≥ 3 WBC/high-power field of unspun urine), positive dipstick for leucocyte esterase or nitrite and microorganism present on gram stain of unspun urine are diagnostic clue for UTI. Patients with UTI or SSI may present with systemic manifestations of fever/hypothermia, apnea, bradycardia, lethargy, cough, nausea, and vomiting.

The incidence of infective endocarditis (IE) in the first postoperative month is low for most defects and increases with time after surgery. However, when prosthetic valves or conduits are used in surgical repairs and hemodynamic problems persist, the risk for IE is high even in the immediate postoperative period (first 2 weeks after surgery).^[33] Morris *et al.*,^[34] have found highest risk in children who have had repair or palliation of cyanotic CHD or prosthetic aortic valve replacement.

APPROACH TO A CHILD WITH FEVER AFTER CARDIAC SURGERY

There are few studies assessing evaluation of fever in congenital heart disease. Almost half of the normally convalescing patients develop fever in first 24 h of surgery.^[22,35] This early onset pyrexia usually resolves by 48–72 hours in most of the patients.^[2,22] During this period, those unfamiliar with cardiac surgical patients frequently order numerous blood, respiratory secretions and urine cultures, white blood cell counts and other special studies without any indication other than fever. The expense of such studies is rarely justified, as fever

is due to an inflammatory response to CPB. A statistical difference has been found in the incidence of fever after the third postoperative day between patients without infection and patients with bacteremia, wound infection or pneumonia. The presence of fever 48 hours after surgery should prompt a diligent search for deep-seated infection.^[36] Appropriate evaluation of postoperative fever includes a careful history, targeted physical examination, and additional studies if indicated.

History

Age of the patient has a bearing on importance of fever in postoperative period.^[37] Young infants with fever are more likely to have an infectious etiology.^[31] Patients with poor nutritional status^[38] and immunosuppressed state are more likely to develop nosocomial infection. Attention should be directed to prior known drug hypersensitivity.

Preoperative course

Normally, if the clinical condition of the patient allows, one of the selection criteria for elective cardiovascular surgery is the absence of any infectious process. But occasionally if patients with any clinical manifestation of infection (e.g. rhinorrhea, cough, etc) preoperatively, undergo surgery, they may present with early postoperative fever due to infection. Presence of previous infection and longer preoperative stay are known risks factors associated with postoperative infection.^[29,32,39]

Details of procedure (intraoperative course)

The duration of surgery, type of surgery (intracardiac or extracardiac), institution and duration of CPB and aortic clamping, and induction of hypothermia are important perioperative variables that influence occurrence of early postoperative fever, which is mostly due to procedure-related systemic inflammatory response syndrome. Few studies have corroborated prolonged CPB time and duration of the surgery as risk factors for nosocomial infections after cardiac surgery in children.^[29,32,37] Also, details of blood products administered are important in evaluating postoperative fever. The quality of prosthetic material and/or implanted devices should be ascertained especially in cases of suspected IE.

Postoperative course

Open sternum after the surgery^[32] as well as postoperative reopening of sternum increase the risk for postoperative infections.^[29] Intensity and duration of inotropic support have been related to the risk of developing infections correlating with prolonged central line usage.^[39,37] Nursing information, such as if the patient has diarrhea, respiratory symptoms or has developed skin sores is relevant. Information regarding change in character of sputum or respiratory secretions in ventilated patients or increased suctioning requirements should be sought.

Physical examination

A meticulous physical examination should be done on regular basis. Assessment of all vital signs is relevant. A careful search for infectious cause should be made especially in patients with fever persisting after 48 hours postoperatively, high grade fever, hemodynamic instability, presence of metabolic acidosis or lactatemia, or altered glucose homeostasis.

- Surgical site should be examined for pain and tenderness, purulent discharge, localized swelling, redness, and wound dehiscence.
- Chest should be examined for signs of pneumonia, effusion, and empyema.
- Patient with catheter-associated UTI may have associated tenderness in lumbar region or hypogastrum.
- A careful search for skin sores should be made.
- Central and peripheral catheter sites should be assessed for thrombophlebitis or cellulitis.

Hematological tests

Cardiac surgery is associated with an elevated leucocyte count mainly attributable to an increase in the percentage of neutrophils.^[40] This increase in the leucocyte count is seen during the first three days after which it normalizes.^[13] In the presence of sepsis, leucocyte count may be elevated or depressed for age or there may be >10% immature neutrophils.

After CPB, the platelet count falls, primarily due to platelet damage and destruction in the bypass circuit and hemodilution.^[41] The platelet count falls by approximately 30% by the conclusion of surgery, reaching a nadir of 40 to 60% on the second or third postoperative day but >10% of patients continue to have a platelet count of <50% of baseline on the fourth postoperative day.^[42] Although heparin-induced thrombocytopenia (HIT) has been recognized in adults, there are a few reported cases of HIT in children.^[43,44] Thrombocytopenia per se is associated with gram negative or fungal sepsis. Peripheral platelet destruction is the mechanism for the thrombocytopenia in sepsis, with the evidence that endotoxin causes morphologic changes, platelet aggregation, and release of thromboplastic phosphatides (platelet factor III) *in vitro*. It is markedly reduced if the patient progresses to disseminated intravascular coagulation.

Inflammatory Markers-C-reactive protein procalcitonin

Quantitative C-reactive protein (CRP) estimation is a valuable laboratory test in the evaluation of febrile young children who are at risk for occult bacteremia and systemic bacterial infection, with a better predictive value than the total leucocyte count or absolute neutrophil count.^[38] Procalcitonin seems to have an advantage

over CRP because of its earlier increase upon infection and a better negative predictive value, as for example evident in children with fever of unknown origin.^[38] An increment of both PCT and CRP is observed just after CPB. PCT values usually peak at 24 hours after surgery (median value 0.77 to 0.79 ng/ml)^[45,46] or immediately after CPB (median value 0.58 ng/ml),^[45] which correlates with the standard range for a low probability of systemic bacterial infection. CRP values usually remain elevated on first 48 hours after CPB (median values 36.6 to 58.82 mg/L on day 1 and median values 13 to 38.3 mg/L on day 2),^[45,46] which overlap with the standard range of high probability of systemic infection. Also the procalcitonin increase in sepsis often correlates with the severity of the condition and with subsequent mortality.^[47] PCT values reported in infected patients are generally higher than in non-infected patients after cardiac surgery and the cutoff point for discriminating infection ranges from 1 to 5 ng/ml, and the dynamics of PCT levels on serial monitoring may be more important than absolute values. Thus PCT scores over CRP in early prediction of sepsis in postoperative cardiac patients after CPB especially those having fever within first 48 hours after cardiac surgery.

Bacteriological assessment

Diagnosis of laboratory-confirmed BSI is made by at least 1 blood culture positive for recognized pathogen or at least 2 blood cultures positive for common skin contaminant.^[33] Ideally, blood specimens for culture should be obtained from two to four blood draws from separate venipuncture sites, and not through a vascular catheter.^[33] But, for a pediatric blood draw blood culture may consist of a single bottle because of volume constraints.^[33] The ability to exclude bacteremia on the basis of a negative blood culture result depends on the sensitivity and negative predictive value of this test. Many factors influence the yield from blood cultures but the single most important factor is blood volume. When the volume of blood submitted for culture is inadequate, a negative blood culture result is potentially misleading in falsely excluding significant bacteremia.^[48] Also, lack of aseptic procedure may lead to the contamination of blood samples, and a high false-positive rate.

Pleural fluid, bronchoalveolar lavage (BAL), protected specimen brushing or lung parenchyma culture are minimally contaminated specimens and can be used for etiologic diagnosis of pneumonia. Quantitatively cultured tracheal aspirate has demonstrated performance characteristics (sensitivity, specificity, predictive value) similar to bronchoscopically collected specimens in several studies.^[49-51] Bronchoscopic sampling also entails risks and costs that are greater than that associated with tracheal aspirate or non-bronchoscopic BAL. The ultimate choice of strategy used to diagnose ventilator-associated pneumonia will be dependent on consideration of local

expertise and availability of personnel to perform the procedure, perceived risk to the patient, experience, and cost.

In presence of local signs of SSI or open sternum, aseptically obtained fluid or tissue from incision site or drain should be cultured. Laboratory diagnosis of UTI requires presence of 10^5 CFU/ml with no more than two species of microorganisms in urine culture of a symptomatic patient. If patient is on effective antimicrobial therapy, presence of $<10^5$ colonies/ml of a single uropathogen species is sufficient for confirming UTI.^[35]

Radiological assessment

Chest X-ray should be done for evaluating developing infiltrates, cavitations, and pneumatoceles, especially in patients with clinical signs of pneumonia. It is important to differentiate between effusions due to various causes as infective, heart failure, postpericardiotomy syndrome or simply collected blood utilizing ultrasound-guided aspiration of pleural fluid and analysis.

Echocardiography

Echocardiography is indicated especially in patients with prolonged fever (>7 days), those who have undergone repair or palliation of cyanotic congenital heart disease, cases with prosthesis/implant, poor nutritional status and no response to antibiotics for clinching the diagnosis of IE. Typical echocardiographic findings include vegetations, abscesses, new valvular insufficiency, and other acute changes in intracardiac flow patterns. It is observed that transthoracic echocardiography (TTE) is more likely to identify vegetations in children with normal anatomy or isolated valvular pathology than in those with complex cyanotic CHD, as a result of interference in the latter group by artificial grafts, conduits, and valves.^[42,52] Although standard TTE is sufficient in most clinical circumstances, especially in younger infants or children, it may not be adequate when imaging is inhibited by poor ultrasound penetration as can occur in post-cardiac surgery patients. In these circumstances, transesophageal echocardiography may be an important adjunct to TTE.^[53]

MANAGEMENT

Early postoperative fever with onset within 48 h of surgery is most likely due to the effect of CPB, surgical trauma or transfusion related requiring only symptomatic treatment. Patients having hemodynamic instability, persistent tachycardia, bradycardia, high fever, hypoglycemia or hyperglycemia, metabolic acidosis, persistently elevated lactate levels, preoperative viral illness or partially treated bacterial sepsis should be evaluated for systemic sepsis with blood counts, inflammatory markers (PCT and CRP), blood cultures, and chest X-ray (if chest signs), and appropriate broad

spectrum antibiotics should be started pending the culture reports.

Patients with high index of suspicion for infection should be started on empirical broad spectrum antibiotics after sending appropriate cultures. The possibility of postpericardiotomy syndrome should be kept in mind in case of onset of fever after 4–5 days of surgery especially if the trends of inflammatory markers and cultures suggest absence of infective pathology.

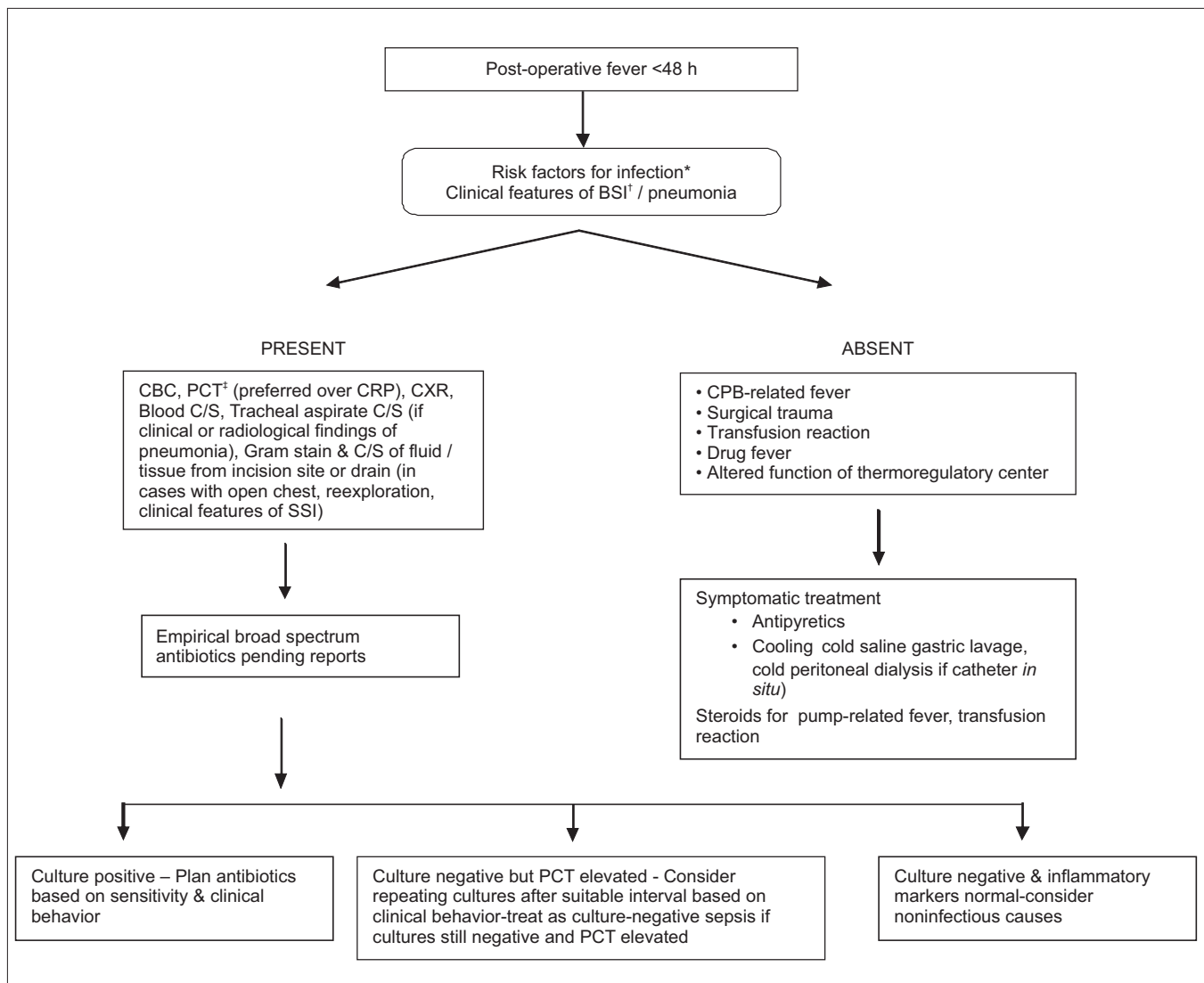
The choice of antibiotics should be guided by the individual unit's infection profile and susceptibility patterns. In our unit we are using combination of second generation cephalosporin and aminoglycoside as first line of antibiotic. For febrile patients with suspected infection who are not toxic and hemodynamically stable, we use a combination of piperacillin–tazobactam

or cefoperazone–sulbactam with aminoglycoside. Carbapenems are reserved for patients who are sick and hemodynamically unstable. Gram positive coverage with vancomycin is used for patients with prolonged period of open sternum, ECMO or reexploration of chest.

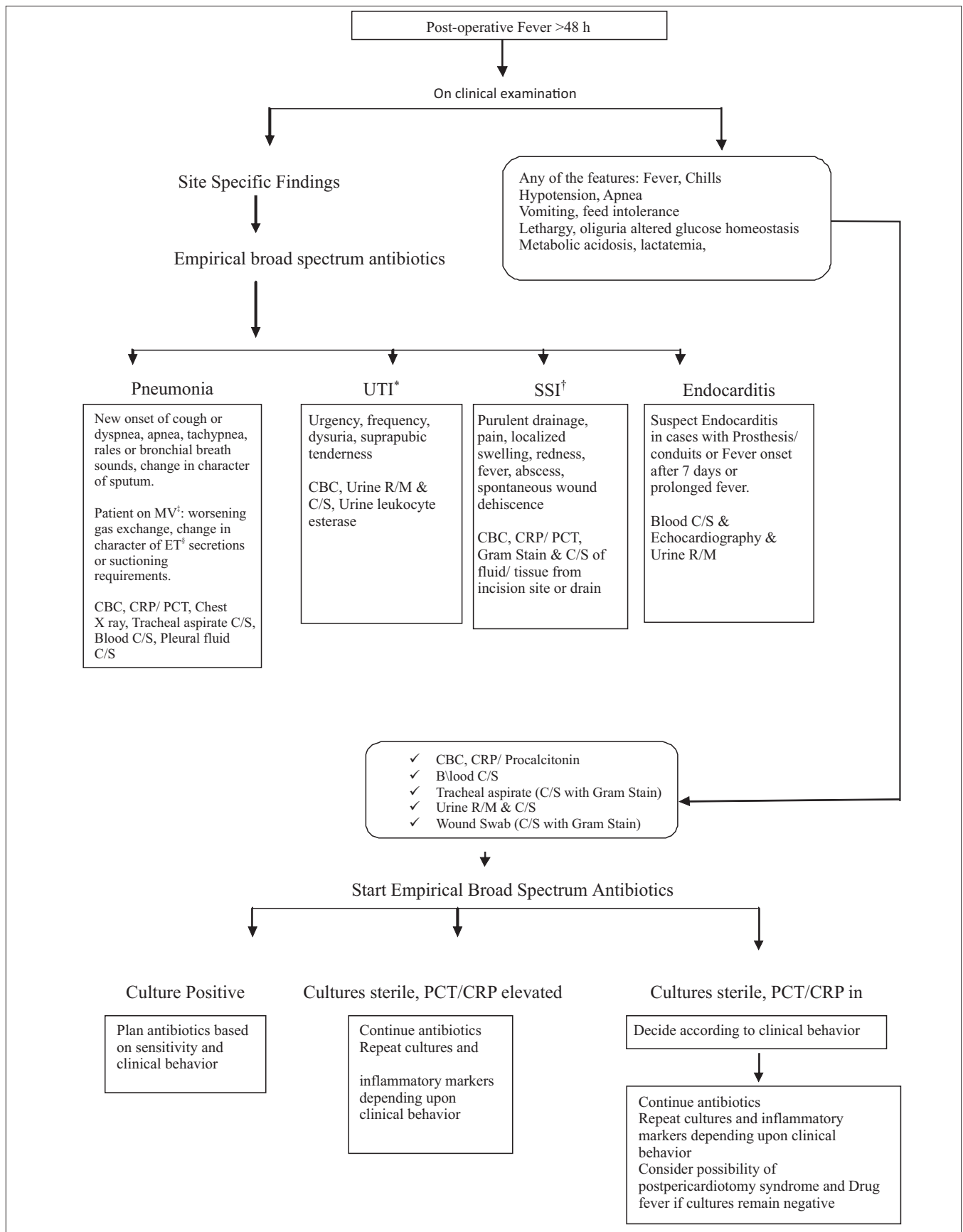
An approach to postoperative fever in pediatric cardiac patients has been summarized in Flowchart 1 (fever onset <48 hours) and Flowchart 2 (fever onset >48 hours).

CONCLUSIONS

Postoperative fever in pediatric cardiac patients while fairly common can be an exasperating and expensive entity. The approach needs to be judicious in choosing the timing of when to intervene and also establish a well-defined process to investigate fever. However, nothing



Flowchart 1: Approach to postoperative fever with onset <48 h. *young infants, immunosuppressed (e.g. absent thymus, severe malnutrition), prolonged preoperative hospitalization, preoperative infection, prolonged CPB time, open sternum in PICU, postoperative reexploration of chest, †Bloodstream infection, ‡Procalcitonin



Flowchart 2: Approach to postoperative fever onset > 48 hrs. *UTI - Urinary Tract Infection, †SSI- Surgical Site Infection, ‡mechanical ventilation, §Endotracheal tube

can supplant good clinical acumen and a heightened index of suspicion.

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