Predictive value of fever following arthroplasty in diagnosing an early infection

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SUMMARY

Postoperative fever after orthopaedic surgery is a controversial clinical problem in daily practice because damaged tissue due to surgical intervention can induce the production of proinflammatory cytokines responsible of the systemic inflammatory response syndrome. No current diagnostic marker can differentiate with sufficient accuracy infectious from non-infectious fever in patients undergoing orthopaedic surgery, but early diagnosis of postoperative orthopaedic infections is important in order to rapidly initiate adequate antimicrobial therapy. Review of clinical trials on fever did not establish the parameters reporting sufficient diagnostic accuracy. Blood cultures, white blood-cent count, erythrocyte sedimentation rate and C-reactive protein have low specificity. Procalcitonin and IL-6 can be helpful diagnostic markers supporting clinical findings.
An algorithm for evaluation of fever in orthopaedic surgery may be a helpful tool.

Keywords: post-operative fever, orthopaedic surgery, algorithm.

INTRODUCTION

One of the most intriguing cases an orthopaedic surgeon may be challenged is post-operative fever as its occurrence reports prolonged hospitalization due to the fear of implant lost caused by an infection, increase morbidity and mortality, and high costs [1]. Postoperative fever in patients undergoing arthroplasty is rather common and can be provoked by many factors related to surgical procedure itself such as surgical trauma, haematoma in the surgical site and transfusion of blood or blood products, and by an infection outside surgical site during the post-operative period, such as an urinary tract infection due to urinary catheter or pneumonia [2, 3].

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Patients with febrile episodes generally undergo a complex evaluation where patient's age, comorbidity, geographic area of exposure, and radiologic clinical presentation guide routine laboratory and examinations [4-7]. White blood cell count, erythrocyte sedimentation rate (ERS), C-reactive protein (CRP), culture of urine, culture of blood, and chest X-ray are commonly used to identify the cause of fever, the higher the number of comorbity and the severity of the disease presentation, the higher the number of examinations needing for a rapid diagnosis [8, 9]. Early identification of patients with postoperative infections is of great importance in order to establish an effective antibiotic therapy, reducing disability period and the risk of prosthetic implant failure [10]. Unfortunately, blood markers such as white blood cell count, ERS and CRP, commonly employed in daily practice to investigate infective fever, are elevated for all patients during post-operative surgery and are not helpful in discriminating between early

infection and nonspecific inflammatory response due to surgical trauma [10].

Inflammatory markers and post-operative fever in arthroplasty

New markers such as interleukin-6 (IL-6) have been recently investigated; although these new markers seem to have better accuracy, their diagnostic accuracy has not been clearly established. Kinetic properties of such inflammatory markers are interesting and are considered to be associated to post-operative infection on the basis of preliminary observations, their use could be proposed in clinical practice as a diagnostic marker for prosthetic joint infection. IL-6 is produced by stimulated monocytes and macrophages and induces the production of several acute-phase proteins. Peak of IL-6 is two days after an uncomplicated arthroplasty and it rapidly come back to its normal value. Based on a study considering periprosthetic joint infection associated with revision arthroplasties, an IL-6 cut-off level of 2.55 pg/mL had a sensitivity of 92% and specificity of 59% in diagnosing infection of the implant [11-13].

CRP is an acute phase protein produced by the liver in response to inflammation. Its levels are elevated to their peak values two to three days after surgery and return to normal approximately three or four weeks after surgery. These dynamics make its use of low value in predicting infection during the post-operative period, although a negative value rule out the possibility of an infection following arthroplasty [14, 15].

Serum procalcitonin is a marker supporting clinical and microbiological findings for more reliable differentiation of infectious from non-infectious causes of fever after orthopaedic surgery. The exact mechanisms underlying procalcitonin induction during or after surgery are unknown. Infection and bacterial endotoxins are strong stimuli for the induction of procalcitonin. Unfortunately, surgical procedure can result in an increase of procalcitonin production, although the non-specific induction of procalcitonin production by trauma or tissue injury seems to be lower as compared to a specific induction by bacterial infection. The return of procalcitonin to normal within a few days after an uncomplicated postoperative course can be explained by the physiological half-life of procalcitonin of eighteen to twenty-four hours in the absence of further stimuli inducing procalcitonin production. Only the persistence of an elevated procalcitonin in the post-operative days should be considered suggestive of an infectious complication [12, 16, 17].

White blood cells are considered a valuable marker of infection in the whole population, when they have been investigated following arthroplasty, the average postoperative increase was shown to be about 3×10^6 cells/μL over the first 2 postoperative days with a decline by 4 post-operative days. Due to these dynamics, its accuracy in diagnosing a post-operative infections appears to be low. Moreover, the diagnostic yield of blood cultures in patients with febrile postoperative arthroplasty is low and rarely contributes to clinical management [18-20].

There are currently no evidence-based clinical practice guidelines outlining an approach to the patient with fever following arthroplasty surgery and fever was found to have low accuracy in diagnosing prosthetic joint infection based on current IDSA guidelines [21].

In an era of escalating health care costs, the development of cost-effective, evidence-based practice algorithm for the evaluation of the febrile patient after arthroplasty is needed to minimize practice variation and limit waste without compromising patient care.

Analysis of the literature with critical discussion

To evaluate the presence of fever after orthopaedic surgery and the impact of fever on early prosthetic joint infections, we carried out a systematic search of the English language literature using the MEDLINE database with the search strings 'fever AND arthroplasty' and 'diagnostic markers AND arthroplasty' for reports published from January 2000 to March 2014.

Based on the findings of the studies retrieved, the value of fever and inflammatory markers during the post-operative period was investigated (Table 1).

Altogether, fever was reported in 9 to 37 percent of patients undergoing arthroplasty and disappeared about 7 days after surgery regardless the presence of infection. Fever failed to be a predictive symptom associated to implant infection itself. In the largest study retrieved, only 3% of cases reporting fever during the post-operative period were found to have an infection, instead, about

Table 1 - Main studies investigating the value of fever and biomarkers in patients undergoing arthroplasty

References	*No. cases*	*Parameters investigation*	*Positive infection*	*Follow-up*	*PJI*
Bindelglass et al.	453	Blood culture (22% of cases)	5	6 months	0
Vijaysegaran et al.	101	Blood culture (141 blood cultures)	2	24 months	0
Ghosh et al.	170	Fever 62 cases (36%) No Fever 108 cases	2 12	19 months 19 months	0 2
Czaplicki et al.	426	Fever 64 cases (15%)	ND	24 months	2
Ward et al.	1100	6% positive blood	ND	24 month	ND
Hunziker et al.	103	Procalcitonin	Higher	ND	4
Glehr et al.	84	Procalcitonin, IL-6, CRP	Higher	ND	ND
Bottner et al.	31	Procalcitonin, IL-6, CRP	Higher	ND	ND
Randau et al.	120	Procalcitonin, IL-6 serum IL-6 joint aspirate	Higher	ND	ND

10% of cases without fever reported a post-operative infection [10].

Blood cultures are a valuable tool for diagnosis of infection, but they had a low sensitivity in febrile patients undergoing arthroplasty [22]. Only 2 out of 141 cultures were positive in 101 patients with fever investigated by Vijaysegaran et al. and the source of the retrieved microorganism was not found (of note, both cases did not report prosthetic joint infection after a 6-month follow-up period) [23]. Similar data are reported by Bindelglass et al. investigating 453 cases undergoing arthroplasty [19]. Of 5 cases with a positive culture retrieved in the study, none reported an infection related to the microorganism cultured and none was found to have a prosthetic joint infection during the follow-up.

Data on procalcitonin value were underreported in studies investigating fever and arthroplasty. However, when we checked the value of this inflammatory marker with the key words 'diagnostic markers' and 'arthroplasty', we founded that, when its value was investigated in febrile patients after arthroplasty, there was a significant trend supporting its use in identifying patients with an infection [24].

Unlike CRP and white blood cell count, procalcitonin values were significantly higher in 45 patients with infection compared to 58 uninfected cases on the day of fever onset, day 1 and day 3. Similar data supporting procalcitonin use in association with other biomarkers such as IL-6 and CRP are reported by Glehr et al. and by Bottner et al. in smaller studies investigating febrile patients [11, 12].

The value of IL-6 in patients with prosthetic joint infection was highlighted by the findings of several studies, but its value in respect to the fever itself remained unclear (we must consider that the relative dosage is not routinely performed in daily practice). In fact, Randau investigated the biomarkers in 120 patients with prosthetic joint infection and founded that high serum IL-6 was a valuable and even more accurate marker than either ERS or CRP, but they did not investigate the value of IL-6 in respect to the presence of fever during the peri-operative period [13].

New perspectives

Based on the data retrieved by literature search, we constructed a diagnostic algorithm useful to examine the patients with post-operative fever after arthroplasty and able to distinguish infectious from non-infectious fever (Figure 1).

We suggest that the presence of fever prompts an accurate clinical examination and laboratory investigation.

In our diagnostic algorithm, continuous fever persisting during the second day after arthroplasty can represent indication to dosage of serum procalcitonin and IL-6 (if the dosage is available). If procalcitonin dosage is elevated, blood culture and other microbiological investigations can be performed on the basis of clinical findings. In fact,

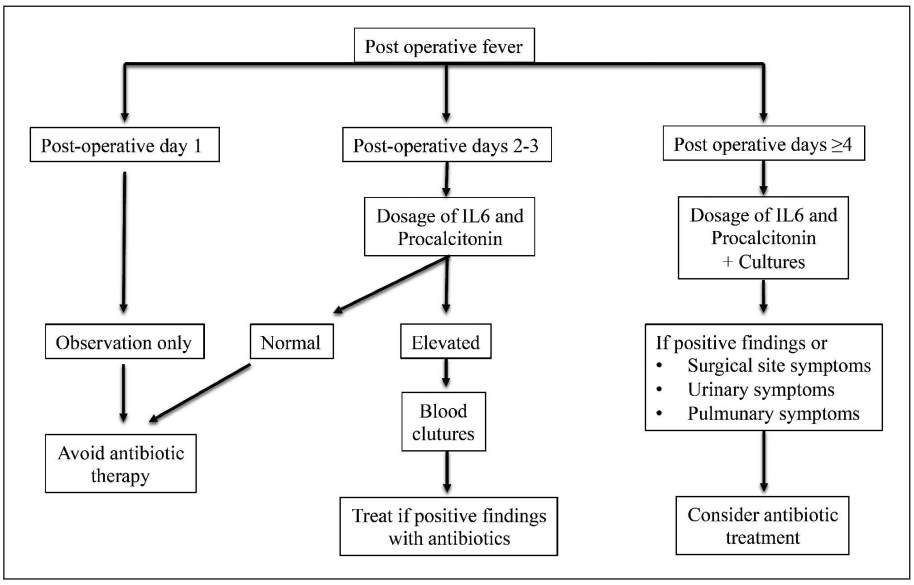

Figure 1 - Diagnostic algorithm of post-operative fever.

the presence of associated symptoms should guide the choice of subsequent investigation, such as chest X-ray in presence of pulmonary symptoms or culture of urine in presence of urinary tract symptoms. Also surgical site has to be object of an accurate clinical evaluation for the presence of swelling, warmth and drainage. Culture from an infected surgical site should be immediately attempted.
Timely administration of adequate antibiotic therapy is an important factor to reduce morbidity and mortality in patients with postoperative infections and thus a thorough clinical examination and diagnostic algorithm is mandatory [25]. Antibiotic therapy must be started only in presence of an established bacterial infection.

CONCLUSION

The development of fever during the first few days following arthroplasty is a relatively common finding. However, its relation with perioperative factors remains largely unclear.
Fever in the first few days following surgery is known to be a normal physiological response and there is no specific test indicating the presence of infection at this early stage of operation.
Serum procalcitonin has moderate diagnostic accuracy in predicting infection in patients with a new onset of fever during the early period after orthopaedic surgery. The course of procalcitonin levels is different in a fever of infectious origin compared with fever of non-infectious origin and thus should be investigated. On the basis of the findings retrieved, when fever is present, procalcitonin is a reliable marker for infection and is more relevant than CRP for the diagnosis of postoperative infection.
IL-6 is considered a valuable early marker of prosthetic joint infection but its use in diagnosing postoperative infectious fever should receive further investigation. Furthermore, its routine use in the clinical practice may be limited in many surgical settings.
Adherence to pre-established algorithm in presence of fever can reduce cost and ameliorate effectiveness of diagnostic and therapeutic choice [26].

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