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The Role of Serum Procalcitonin in Establishing Diagnosis of Bone and Joint Infections

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Abstract

Background: Acute bone and joint infection such as septic arthritis and osteomyelitis diagnostic are still considered as a pitfall especially in the emergency department. Some laboratory markers, such as total Count (TC), Erythrocyte Sedimentation Rate (ESR) and C – Reactive Protein (CRP) assessed regularly whereas those are not specific. Serum PCT has a role as a sensitive and specific marker in supporting the diagnosis of bone and joint infections.

Method: Literature review is done by searching journals with "serum procalcitonin", "bone infections", "diagnosis", and "joint infections" on the search engines. From 37 journals that were reviewed, 34 were found suitable as reference for this paper.

Outcome: High level of serum PCT indicate the activation of immune system, specifically the innate immune system due to microbial infections. One of the most different aspect with CRP is serum PCT infrequently elevates in response to viral infection, which means PCT is useful in differentiating bacterial and viral infections Serum PCT concentration elevates following the endotoxin or cytokines release such as interleukin (IL)- 6, tumor necrosis factor (TNF)-alpha, and IL-1b which usually appears in bone and joint infections. Although its benefits, there are some limitation interfering the usage and levels of serum PCT.

Conclusion: Serum PCT has a role as a sensitive and specific marker in supporting the diagnosis of bone and joint infections due to its sensitivity following endotoxins release. Further researches and studies are required to identify the appropriate usage, interfering factors, and clinical application of serum PCT in establishing the diagnosis of bone and joint infections.

Keywords: Procalcitonin, Bone infections, joint infections, Diagnosis

Introduction

Acute bone and joint infection such as septic arthritis and osteomyelitis diagnostic are still becoming the conundrum in the emergency department. Rapid and proper diagnostic tools are needed in order to know the exact treatment regarding the etiologies. The condition might occur due to some paths; whether it is hematogenous spread, contiguous contamination and infection associate with vascular or neurology insufficiency[1]. A quarter to half of the cases resulting in the loss of functional abilities. These cases may also become life threatening around 5% to 15% of all cases[2,3]. In fact, there are no specific laboratory examinations to diagnose bone and joint infections except the isolation and culture of microorganism which is the gold standard in diagnosing bone and joint infections despite the wide sensitivity range from 30% to 90%[4,5]. Several laboratory markers, such as total Count (TC), Erythrocyte Sedimentation Rate (ESR) and C – Reactive Protein (CRP) are routinely used in the diagnosis of these infections however those are not specific[2].

The annual incidence in a state in United States of America was around 21,8 cases per 100.000 person-years. This annual incidence was higher in men rather than women continuity with the increasing age[6]. Although there are many cases worldwide, the patients often misdiagnosed. Bone and joint infections are orthopedic pitfalls in the emergency department because these may present with nonspecific symptoms, nonspecific laboratory results, and nondiagnostic radiographic studies[7]. The clinical presentation itself may present in various and distinctive appearance that start from chronic wounds and non-specific bone or joint pain to functional debilitation and also neurological disfunction as the spine damaged[8].

Until now, the early diagnostic of both bone and joint infections are really important, thus it may prevent the inclement complications following the diagnosis. Unfortunately, researchers are still developing the exact method or tool to diagnose it, as several regular laboratory examinations are also elevated and not specific in non-pyogenic causes of inflammation[9]. The setbacks in finding the sensitive laboratory markers for diagnosing bacterial infections

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consequent to the overuse and prescribe of antibiotics. This may encompass especially in neonates and elderly patients due to the fact that the clinical signs could be very smidgen[10].

Recent studies showed that serum procalcitonin (PCT) may become a responsive marker in detecting bone and joint infections.11 Serum PCT normally found very low in healthy person whereas it is specifically found elevating in bacterial and fungal infections[11,12]. In addition, serum PCT is unresponsive or only slightly elevated following aseptic inflammation or viral infection. Various studies also reported the ability of serum PCT to differentiate septic arthritis from aseptic inflammation[10,13,14].

As serum PCT extensively studied, there are some important things to be focused further regarding the benefits and shortages. The aim of this paper is to discuss the role of serum PCT as the sensitive predictive marker in diagnosing bone and joint infections.

Material and Methods

This paper writing methodology was literature review. The making of this paper included correlating literatures from several journals from the search engines, such as www.pubmed.com, nature.com and scholar.google.com. Authors searched with keywords "serum procalcitonin", "bone infections", "diagnosis", and "joint infections" on the search engines. The references that were included are papers which discussing about the ability and role of serum PCT in supporting the diagnosis bone and joint infections. From 37 journals that were reviewed, 34 were found fit as reference for this paper. The collected information noted, and analyzed for validity and reliability, interpreted and compiled into one scientific literature review.

Result and Discussion

Diagnosing bone and joint infections

Detail survey regarding the medical history is really important by identifying the predisposition factor to support the joint infection such as septic arthritis. Not only does it help establish the diagnosis but also making sure of the causative microorganisms. The causative microorganism may also be indicated by the duration, a virulent Staphylococcus aureus as acute onset of severe pain, swelling, erythema, and stiffness of the joint are the symptoms that mainly appear. There are several risk factors that should be asked in the anamnesis including pre-existing joint diseases such as rheumatoid arthritis, gout, pseudogout, osteoarthritis, lupus erythematosus, trauma and recent surgery[15].

There are several important things should be considered in ensuring the diagnosis of joint infections, apart from clinical examination, serum analysis, imaging, and microbiological culture are often assessed[15]. Histopathology examination of the synovial tissue sample may complete the diagnosis of septic arthritis. In the gram-negative bacteria, the histopathology may confirm bacterial infection following the presentation of acute or chronic inflammatory cells[15,16]. Various markers that usually be tested are TC, ESR, and CRP. Although these markers routinely be checked, they are not the specific marker in detecting and diagnosis septic arthritis as there is still no gold standard in establishing the diagnosis[17]. Imaging such as ultrasound may also be valuable sometimes, it may confirm the existence of a joint effusion and synovial inflammation, particularly in the hip and shoulder[18]. Radiographs examinations including MRI, scintigraphy, and CT are useful in evaluating the inflammation and destruction condition of the joint, thus it may not demarcate the difference between septic arthritis and other form of acute arthritis[19].

Along the lines of septic arthritis, osteomyelitis is also one of orthopedic pitfall in emergency department because of the deadlock in establishing the diagnosis[7]. In osteomyelitis, the cortex and the medulla of bone are in inflammatory condition. Basically, there are two type of mechanism which strongly correlated with osteomyelitis, starting from blood-borne or through bone, the accurate diagnosis should be established as osteomyelitis may lead to the chronic refractory stage[7,8]. To diagnose bone infection, there are several aspects which should be considered starting from patient's history, clinical signs, serum analysis, imaging, and microbiological culture. Signs that commonly occur are diffuse or non-specific pain, minimal swelling, local tenderness or a small area of increased temperature[7,8,20].

C-reactive protein, erythrocyte sedimentation rate or white blood cell count are the conventional serum that analyzed in the case of suspected osteomyelitis[21]. Unfortunately, those serums are not specific in diagnosing osteomyelitis[2]. As commonly used, these markers will be elevated in

Table 1: Sensitivity

Modality	Sensitivity (%)	Specificity (%)
Plain radiographs	43-75	75-83
Computed tomography	65-75	65-75
Magnetic resonance imaging	82-100	75-96
Three-phase bone scan	73-100	73-79
White blood cell scan	80-90	80-90

response of acute infection or even chronic infections[7]. Further investigation is needed, to support the diagnosis, blood serology test may be needed. A suggestive information might be achieved through imaging although the specificity and sensitivity are quite distinctive[20]. Plain x-ray is a common radiograph examination ordered. X-ray may detect the sequestration of the bone, bone lone progressivity, infection callus, fractured gap, and bone lysis. MRI or CT may also be considered in the radiograph examination to know further detailed information about the extent of bone and soft tissue infection[20,22].

Microbiological culture can be done by doing biopsy of fluid or abscess guided by CT.20 However, the best result of microbiological culture will be achieved if the patients have not consumed any antimicrobials for the past 14 days[22]. Histopathological analyzes support the microbiological examination by taking samples in the open surgery process[15].

Overview of serum procalcitonin (PCT)

Serum PCT is the precursor of calcitonin in the 116-amino acid and also the 32-amino acid hormone that adjusts serum calcium. 1 ng/ml is the normative concentration of serum PCT in healthy patients. The French author offered the first presentation of serum PCT back in 1993, which addressed to differ bacterial infections and non-bacterial inflammatory condition[23]. Serum PCT increases betimes due to inflammatory responses or systemic bacterial infections, for example are bacterial meningitis, septic shock, bacteremia, and pyelonephritis[23,24]. Inflammation associated with bacterial endotoxins may increase the serum PCT levels. PCT as a 116-amino acid peptide encounters posttranslational proteolysis into calcitonin. PCT is formed in C cells which can be found in thyroid gland and secreted from leukocytes of the blood in peripheral. The presence of bacterial lipopolysaccharides and cytokines elevate the level of serum PCT[25].

In systemic inflammation, especially in the bacterial infection, the serum PCT level may increase up to 1000 times, this is conducted by many numbers of tissues organ (lung, liver, kidney, adipose tissue) which also involves in the circulation.26 To measure PCT concentration, the first measurable amount are detected after 2 – 4 hours stimulation with the highest value within 6 – 24 hours[26,27]. Compare to CRP, the value of this marker begin to elevate 12-24 hours after stimulation, it will achieve a maximum concentration after 48 hours[27]. CRP concentration is affected by neutropenia, immunodeficiency conditions and the use of non-steroid and steroid anti-inflammatory drugs on the other hand, PCT is a stable marker which is not affected[28]. The intensity of the inflammatory response and the severity of infection predispose the level of serum PCT, addressing the higher level of serum PCT the more severe form of the infections occurred[27,28]. Serum PCT is important in supporting the diagnosis of some symptoms such as febrile illness which is still not clearly defined, meningitis, respiratory infections, urinary tract infections, burn trauma, and also bloodstream infections[30].

Role of PCT in diagnosing bone and joint infections

Early and proper identification of acute bone and joint infections are really important in order to choose the accurate choice of treatment. However, this is still a challenging case for surgeons especially in the emergency department. The right diagnosis is important in early management for the better outcome. The main issues are related to the difficulties in establishing diagnosis leading to remiss administration of antibiotics. In addition, pus culture has low positivity rates and sensitivity followed by none of good laboratory examination with appropriate sensitivity and specificity[23]. Serum PCT is reported to have a good capability in detecting acute phase of bacterial infections. PCT rises promptly due to bacterial infections and also becoming the prognostic parameter in several infections such as pneumonia and meningitis[30].

High level of serum PCT indicate the activation of immune system, specifically the innate immune system due to microbial infections. 22 – 26 hours is the biological half-life activity of PCT which means superior compare to CRP and other acute-phase reactants[31]. One of the most different aspect with CRP is serum PCT infrequently elevates in response to viral infection, which means PCT is useful in differentiating bacterial and viral infections[32]. Serum PCT concentration elevates following the endotoxin or cytokines release such as interleukin (IL)- 6, tumor necrosis factor (TNF)-alpha, and IL-1b. On the other hand, the secretion of interferon (INF)-gamma after viral infection causing down-regulation of PCT which can be taken as an advantage in distinguishing viral and bacterial infections[28,30]. Viral infections also stimulate α-interferon by macrophages which inhibits the production of TNF [32].

There are several studies conducted in order to know whether PCT is capable in detecting acute bone and joint infections. A prospective two-year study was conducted by Koratmula in 2018, showed that from 238 patients subjects PCT is more promising than CRP in diagnosing bone and joint infections.33 A paper published by Shen also stated that PCT may be useful as a predictor of osteomyelitis or septic arthritis. Serum PCT is recommended to become the rule-in test at the cut-off value of 0.5 ng/mL and can be used as a rule-out test at the cut-off value of 0.3 ng/ml.9

There area advantageous and disadvantageous in using serum PCT. As have been stated before some benefits in assessing serum PCT are including the specific result to differ the etiologic of

infection between bacterial or non-bacterial infections. Serum PCT is also widely available in many laboratories, so it can be easily tested in many cases. However, some limitations may also be found in the use of this serum. Distinctive price point should be considered as some other serum assessments are cheaper. Nonspecific elevation of serum PCT can exist because of stress, such as following trauma and surgery or even in a patient with cardiac shock. Elevated PCT levels are also associated with Kawasaki disease or different types of vasculitis and paraneoplastic syndromes[34].

Conclusion

The current studies about the usage of serum PCT has increased rapidly. Serum PCT has a role as a sensitive and specific marker in supporting the diagnosis of bone and joint infections. It seems serum PCT is a reliable marker that can be use in the emergency department regarding suspected septic arthritis or osteomyelitis case. Further studies need to be done to ensure the detailed role of serum PCT.

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