Systematic review and meta-analysis of the predictive value of C-reactive protein in postoperative infections*

REVISÃO SISTEMÁTICA E METANÁLISE SOBRE O VALOR PREDITIVO DA PROTEÍNA C-REATIVA EM INFECÇÃO PÓS-OPERATÓRIA

REVISIÓN SISTEMÁTICA Y META-ANÁLISIS SOBRE EL VALOR PREDICTIVO DE LA PROTEÍNA C-REACTIVA EN INFECCIÓN POSTOPERATORIAS

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ABSTRACT

This systematic review on C-reactive protein (CRP) was performed with the purpose to identify its predictive value in the prognosis/diagnosis of infection in surgical patients. The sources used in the search were: COCHRANE, EMBASE, LILACS, MEDLINE and OVID, and bibliographic references of the located studies. All studies found increased CRP levels after surgery in cases of postoperative infection (PO), in eight studies a CRP peak between the second and third PO was reported as normal aspect of the CRP curve, reducing in patients without postoperative complications and increasing in patients with complications. The meta-analysis revealed an average of 85% (sensitivity), 86% (specificity), the area under the SROC curve was 0.9060, and the Odds Ratio was 23.56. Along with other clinical interventions, CRP is considerably valuable in the prognosis/diagnosis of postoperative infections.

DESCRIPTORS

C-reactive protein
Postoperative period
Surgical wound infection
Review

RESUMO

Revisão sistemática sobre a proteína C-reativa (PCR) a fim de identificar seu valor preditivo no prognóstico/diagnóstico de infecção em pacientes cirúrgicos. As fontes de busca foram: COCHRANE, EMBASE, LILACS, MEDLINE E OVID, e referências bibliográficas dos estudos encontrados. Em todos os estudos a elevação dos níveis de PCR foi observada após a cirurgia e na presença de infecções pós-operatórias (PO), em oito estudos um pico de PCR entre o segundo e o terceiro PO foi relatado como aspecto normal da curva de PCR, declinando em pacientes sem complicações pós-operatórias, e elevando em pacientes com complicações. A metanálise revelou média de 85% (sensibilidade), 86% (especificidade), a área sob a curva SROC foi de 0,9060, e a Odds Ratio foi de 23,56. A PCR com outras intervenções clínicas apresenta alto valor no prognóstico/ diagnóstico de infecção pós-cirúrgica.

DESCRITORES

Proteína C-reativa
Período pós-operatório
Infecção da ferida operatória
Revisão

RESUMEN

Revisión sistemática sobre la proteína C-reactiva (PCR) para identificar su valor predictivo en pronóstico/diagnóstico de infección en pacientes quirúrgicos. Las fuentes de búsqueda fueron: COCHRANE, EMBASE, LILACS, MEDLINE y OVID, y referencias bibliográficas de los estudios encontrados. En todos los estudios la elevación de los niveles de PCR fue observada después de la cirugía y en presencia de infecciones postoperatorias (PO), en 8 estudios un pico de PCR entre el 2º y el 3º PO fue definida como aspecto normal de la curva de PCR, declinando en pacientes sin complicaciones postoperatorias, y elevándose en pacientes con tales complicaciones. El meta-análisis determinó una media de 85% (sensibilidad), 86% (especificidad), el área bajo la curva SROC fue de 0,9060, y el Odds Ratio fue de 23,56. La PCR junto a otras intervenciones clínicas presenta alto valor en el pronóstico/diagnóstico de infección post quirúrgica.

DESCRIPTORES

Proteína C-reactiva
Periodo postoperatorio
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Revisión

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INTRODUCTION

C-Reactive Protein (CRP), produced by liver cells, is the main plasma protein, with a short circulating half-life (4-6h). It is an acute-phase inflammatory reactant that increases a lot during the inflammatory response triggered by tissue injury or infections, which peaks within 24 to 72 hours, and then rapidly decreases after the resolution of the inflammatory process[1].

CRP can connect with the cell membrane components, constituting complexes that activate the complement system, releasing opsonins and possibly phagocytosis and removing these structures from the circulation. Its connection with the cell membranes only occurs after their rupture. This property suggests that CRP plays an important role in the host's non-specific defense, through the removal of cell remnants deriving from necrotic or damaged cells in the inflammation process, permitting tissue repair[2].

It is known that, on the first day after the surgical procedure, CRP increases due to clinical phenomena like leukocytosis, fever and arrhythmias and rapidly drops at the end of the inflammatory response[3].

CRP is a test that has been used for the early identification of surgical site infection (SSI). Various studies demonstrate that preoperative CRP levels remained high in patients who developed a postoperative infection[3]. It is non-specific though, and can be mixed up with many diseases causing an inflammatory response. Other factors that can change CRP levels are obesity, smoking, degenerative osteoarthrosis, change in the acute phase and response to age, burns, post-traumatic stress, emotional disorders and menstrual cycle[4].

This review sought evidence regarding the predictive value of changes in CRP serum levels in patients' development of postoperative infection. If positive, CRP can turn into an effective marker to predict infection development.

METHOD

This systematic review was developed according to the recommendations of the Cochrane Collaboration[5]. The search was accomplished between December 2008 and January 2009 in the electronic databases COCHRANE, EMBASE, LILACS, PubMed/MEDLINE and OVID, besides the bibliographic references cited in the identified publications. To select the descriptors, the tools PubMed/MEDLINE MeSH (Medical Subject Headings Section), and the BVS Portal DeCS (Health Sciences Descriptors) were used. To define the descriptors, the PICO[6] strategy was chosen, in which: Participants = patients submitted to surgeries; Intervention = CRP serum level dosage; Comparison = CRP concentration between preoperative and postoperative periods or during the postoperative period only; Outcome = postoperative infections, related with CRP alterations (Table 1).

Table 1 – Indexed descriptors used in searches based on the PICO strategy – São Paulo – 2009

	Descriptors
Participants **and**	Surgery OR Surgery patients OR adult OR aged
Intervention **and**	c-reactive protein or PCR or protein, c reactive or serum c- reactive protein or protein, c reactive
Comparison **and**	Preoperative period or postoperative period or postoperative care or postoperative complications
Outcome	Infection(s) or surgical wound infection or wound infection or surgical complications or urinary tract infections or infection, urinary tract or pneumonia

Only full versions of original research were considered, without any restriction as to age, gender and surgery type, besides publication language and year. The studies were analyzed regarding the type of research, focus, population, results and strength of evidence or recommendation level, according to the classification of the Center for Evidence-Based Medicine, Oxford, adapted for use in the Portuguese language[7]. In addition, the studies were analyzed for internal validity, in line with the following criteria[8]: similarity of the population and surgical procedure or risk factor adjustments for CRP alterations, monitoring over time for the observation of outcomes, evaluator blinding.

The meta-analysis involved 11 studies with sensitivity and specificity test results. To analyze these data, Meta – Disc software was used, version beta 1.1.1 (freeware)[9]. The true positive (sensitivity) and false positive (1 – specificity) levels were summarized in the SROC – Summary Receiver Operating Characteristic curve (Figure 1) where, to demonstrate the performance of the diagnostic test as a whole, the area under the curve was calculated and, to evidence the studies' accuracy, the Q value was calculated, which represents the highest common sensitivity and specificity rate. Also, the Odds Ratio was calculated, an indicator that also assesses diagnostic performance through the combination of sensitivity, specificity, true–negative and false-negative.

RESULTS

MEDLINE displayed the largest number of studies (244), followed by OVID (80), EMBASE (70), COCHRANE (10) and LILACS (2). In total, 27 studies were pre-selected, that is, which seemed to answer the research question, after excluding repeated papers and adding two bibliographic references. After an analysis with a second evaluator, 7 others were excluded, totaling 20 included studies. The reasons for

exclusion were: not monitoring the infection variable in the postoperative period (3); consideration of the therapeutic focus on CRP only (2); retrospective design without prognostic focus (1); monitoring time of postoperative complications (until 3rd PO day) far below recommendations (1). All included studies were published as from the end of the 1990's and almost all were prospective cohort studies, except for E7 (case-control) and E19 (retrospective cohort). Although E8 describes the research as a case series, during the analysis of its methodological design, it was detected that this was actually a prospective cohort study, and it was included as such in this review.

Table 2 – Distribution of studies included in the systematic review according to a general synthesis of their main aspects – São Paulo – 2009

E	Design	Evid level	CRP analysis	Pop.	Surgery types	Other analyses	Control or exclusion criteria	Postoperative CRP assessment	CRP predictive of infection	Sensitivity and Specificityidade
1	Prospective Cohort	1B	Post-operative	48	Orthopedic	-	-	4th till 21st day	Yes	Sensitivity: 60% Specificity: 100%
2	Prospective Cohort	1B	Pre-operative	220	Orthopedic	Erythrocyte Sed. White cell	Antibiotics therapy	-	Yes	Sensitivity: 94% Specificity: 71%
3	Prospective Cohort	1B	Pre- and post-operative	66	Orthopedic	Erythrocyte Sed. Plasma Visc.	Tumor Arthritis Immunosuppressive agents	0 till 21st day	Yes	-
4	Prospective Cohort	1B	Pre- and post-operative	149	Orthopedic	Erythrocyte Sed.	Tumor Infection Autoimmune disease Liver dysfunction	-	Yes	Sensitivity: 53% Specificity: 76%
5	Prospective Cohort	1B	Pre- and post-operative	383	Gastroint	White cell	-	0 till 12th day	Yes	Sensitivity: 68,9% Specificity: 84,6%
6	Prospective Cohort	1B	Pre- and post-operative	80	Orthopedic	Erythrocyte White cell Transferrin	-	0 till 23rd day	Yes	Sensitivity: 67% Specificityi: 89%
7	Case-control	2B	Pre- and post-operative	100	Cardiac		Tumor Arthritis	-	Yes	-
8	Prospective Cohort	1B	Pre- and post-operative	32	Gastroint	IL-6 Transferrin	-	0 till 5th day	Yes	Sensitivity: 87,5% Specificity:83,3%
9	Prospective Cohort	1B	Pre-operative	144	Orthopedic	Biopsy	-	-	Yes	Sensitivity: 72,5% Specificity: 80,9%
10	Prospective Cohort	1B	Pre- and post-operative	200	Cardiac		-	0 till 10th day	Yes	Sensitivity: 92% Specificity: 86%
11	Prospective Cohort	1B	Pre- and post-operative	597	Cardiac		Tumor Infection Autoimmune disease Immunosuppressive agents	0 till 4th day	Yes	-
12	Prospective Cohort	1B	Pre- and post-operative	349	Orthopedic		Tumor CRP>5mg/dl Infection Recent surgery	0 till 30th day	Yes	Sensitivity: 100% Specificity: 98,4%
13	Prospective Cohort	1B	Pre- and post-operative	593	Cardiac		-	0 till 6th day	Yes	-
14	Prospective Cohort	1B	Pre- and post-operative	32	Orthopedic	Erythrocyte Sed.	Infection Autoimmune disease Immunosuppressive agents Chronic kidney failure	0 till 30th day	Yes	Sensitivity: 93% Specificity: 65%
15	Prospective Cohort	1B	Pre- and post-operative	100	Orthopedic		Tumor Obesity CRP>5mg/dl Infection Recent surgery Immunosuppressive agents Liver dysfunction	0 till 15th day	Yes	-
16	Prospective Cohort	1B	Pre- and post-operative	1418	Orthopedic		Tumor CRP>5mg/dl Infection Recent surgery	0 till 6th day	Yes	Sensitivity: 92% Specificity: 93%
17	Prospective Cohort	1B	Pre- and post-operative	112	Gastroint	White cell	Liver dysfunction Chronic kidney failure	0 till 7th day	Yes	Sensitivity: 74,4% Specificity: 75,3%
18	Prospective Cohort	1B	Pre- and post-operative	179	Orthopedic	White cell	Infection	0 till 30th day	Yes	Sensitivity: 100% Specificity: 83,6%
19	Retrospective Cohort	2B	Post-operative	230	Orthopedic	Erythrocyte Sed.	-	-	Yes	Sensitivity: 97% Specificityidade: 81%
20	Prospective Cohort	1B	Pre- and post-operative	688	Gastroint	White cell	-	0 till 12th day	Yes	Sensitivity: 69,3% Specificity: 87,1%

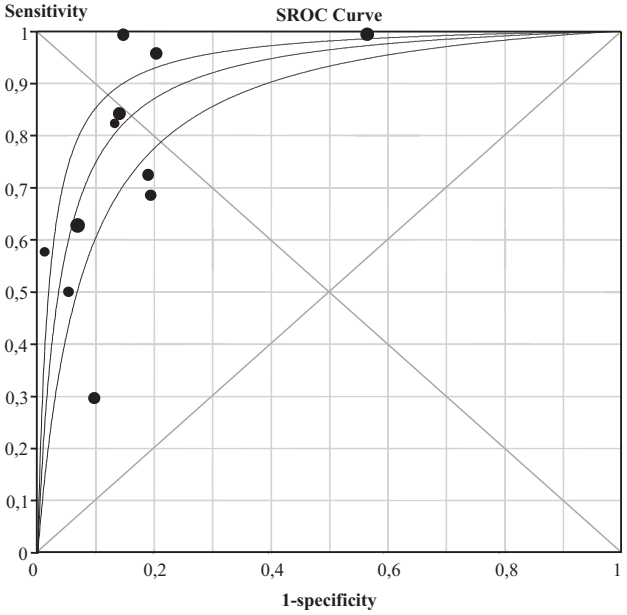
The number of participants ranged from 32 (E8) till 1418 (E16), but the majority only considered clean surgeries (orthopedic-12 and cardiac-04), while one included different surgeries (orthopedic with and without prosthesis placement). The remainder included gastrointestinal surgeries (04) (Table 2). Most studies (15) verified CRP levels in the pre- and postoperative period, E1 and E19 in the postoperative period only and E2 and E9 in the preoperative period only. Great variation was found though, in the postoperative verification period, which varied a lot: until 4th (E11), 5th (E8), 6th (E13, E16), 7th (E17), 10th (E10), 12th (E5, E20), 15th (E15), 21st (E1, E3), 23rd (E6) and 30th (E14, E12, E18) day. E2, E4, E7, E9, E19 did not mention the period. CRP samples in all studies were obtained through venipuncture.

Only 12 studies cited intervening variables for control or patient exclusion, mainly E15 (7), followed by E4, E12, E16 (4 each). The most mentioned variables were: neoplasm (7), previous infection (7) and use of immunosuppressive drugs (4) (Table 2). Similarly, 12 studies defined postoperative infection diagnosis criteria. Surgical site infections were the most mentioned (E2; E4; E5; E6; E8; E10; E12; E18; E19), followed by septicemia (E7; E8; E11; E17), pneumonia (E5; E17) and urinary tract infection (E5; E8).

When assessing the evidence level for prognostic studies[7], the large majority (18) fit into category A, evidence level 1B (prospective cohort). Recommendation level B, evidence level 2B, referred to the classification of E7 and E19, as these were a case-control and a retrospective or historical cohort study, respectively.

All studies reached favorable conclusions concerning CRP as a prognostic marker for infection in surgical patients and the majority (15) performed sensitivity and specificity analysis, but with a wide range of levels. Sensitivity ranged from 53.0% to 100.0% and the mean sum of all studies corresponded to 81.3%. Specificity ranged from 65.0% to 100% and the mean was 83.6%. The study with the highest sensitivity and specificity levels was E12 (100.0% and 98.4%, respectively), while E4 showed the lowest levels (53.0% and 76.0%) (Table 2).

The meta-analysis revealed a mean sensitivity level of 85%, and a mean specificity level of 86%. The SROC curve (Figure 1) summarizes the sensitivity levels and false-positives (1- specificity), resulting in 0.9060 for the area under the curve (AUC), and 0.8377 (Q) as the highest common sensitivity and specificity level. The global Odds Ratio of these studies was 23.56 (CI: 11.50 – 48.25).



The area under the curve (AUC) = 0.9060 (the closer to 1 the better). The highest common sensitivity and specificity level was Q* = 0.8377.

Figure 1 – SROC – Summary Receiver Operating Characteristic Curve – São Paulo – 2009

DISCUSSION

Hospital infections are considered a public health problem in Brazil and around the world. Surgical site infection is the second most important infection in hospitalized patients, leading to a rise in treatment costs, increasing the probability of surgical re-interventions and increasing mortality rates[10]. Although risk factors for infection development in surgical patients can be estimated, its prediction, with high probability levels, still represents a challenge. Various markers have been studied in recent years, searching for their predictive value with regard to inflammatory and infectious processes[11-14]. This is the first systematic review on studies that investigated CRP.

The fact that almost all studies (18) used the prospective cohort design not only entailed better quality for prognostic foci, but also permitted a practically homogeneous systematic review in terms of the research type. Thus, it complied with the first quality criterion, regarding the study design.

Despite the varying number of participants (between 32 and 1418) in the studies, internal validity criteria concerning the surgery type and CRP analysis in the pre- and postoperative periods were homogeneous. In the first case, all studies included the same types of surgeries (orthopedic-12, cardiac-04, gastrointestinal-04) (Table 2). Although E18 considered orthopedic surgeries with and without prosthesis, the use of the same surgery type in almost all studies, and mainly of clean surgeries (16), homogenizes a relevant risk factor for surgical site infection, regarding the surgery's contamination potential. In the second case, similarly, most studies (15) verified the CRP in the pre- and postoperative periods (Table 2). This criterion is obviously important to compare and conclude on the CRP as a prognostic factor or not.

This comparative analysis between preoperative CRP level and postoperative infection, present in 4 of the studies included (E4; E7; E11 and E13), observed that patients with increased CRP in the preoperative period (higher than 5mg/dl) revealed higher incidence levels of postoperative complications. Study E9, on the other hand, which compared the relation between CRP concentration in the preoperative period and the presence of an infectious focus in the postoperative period, resulted in a positive predictive value of 59.2% and a negative predictive value of 88.5%.

Some studies also report a CRP serum concentration peak between the second and third postoperative day (E1; E3; E5; E10; E15; E16; E17 and E20) as a normal characteristics of the CRP curve. Patients without infectious complications presented a decline in CRP serum levels after this peak; while patients with postoperative infection showed no important CRP decline after its peak and continued with CRP levels higher than 10mg/dl. Studies E4 and E12 related the appearance of a second CRP peak after the decline of its normal peak with a greater chance of postoperative infection development.

Another pre- and postoperative analysis, developed in studies E5, E12, E13 and E20, appoint a cohort level of 140mg/dl of CRP on the 4th postoperative day, that is, patients with 140mg/dl or more of serum PCR on the 4th PO are at a greater change of developing post-surgical infections.

The CRP samples in all studies were collected through venipuncture, but great variation was found in the postoperative analysis period, cited in 15 studies included and ranging from the 4th until the 30th day (Table 2). This fact is concerning, as monitoring time was in accordance with the recommendations of the *Center for Disease Control and Prevention* (CDC) for the development of postoperative infection (30 days) in only three of these studies; this period would have to be up to one year[15].

Although surgical site infection (SSI) was the most used infection for outcome analysis (E2; E4; E5; E6; E8; E10; E12; E18; E19), others were also taken into account: septicemia (E7; E8; E11; E17), pneumonia (E5; E17) and urinary tract (E5; E8). Thus, it is concluded that, although this was not expressed in most studies, the CRP analysis period considered the variation periods in its levels, between normal and altered, instead of the infection development periods.

Other criteria, related to extrinsic risk factors for infection, were also homogeneous, like the surgical technique and environment. Although not described, it seemed that the same teams performed each study.

The greatest variation in criteria, and hence the main factor of non-homogeneity among the studies, referred to patients' intrinsic risk factors. Only 12 studies cited control or exclusion of patients based on these factors. Nevertheless, the number of these factors varied a lot and did not always coincide among the studies. The largest number of control factors was found in E15 (7), followed by E4, E12, E16 (4 each). The most mentioned factors were: tumor (7), previous infection (7) and use of immunosuppressive agents (4) (Table 2), which interfere in CRP levels.

Risk factors for surgical site infection, however, widely ranked with the best evidence level[14], were not mentioned, like the duration of the surgery. Only E2 mentioned antibiotics use.

Thus, the best research design (prospective cohort) and CRP variation analyses before and after the surgery and specificity and sensitivity analysis constituted the main homogeneity criteria in most studies. Although the latter resulted in great variation (between 53.0% and 100.0% for sensitivity and between 65.0% and 100% for specificity), all of them exceeded 50% and the mean sums of the studies that performed these analyses were high (81.3%-sensitivity and 83.6%-specificity) (Table 2).

The meta-analysis proves the effectiveness of C-reactive protein as an immunological marker of inflammatory and/or infectious processes, as the calculation result of the area under the curve was 0.9060 and, the closer this result approaches 1, the better the diagnostic test. The mean sensitivity level reveals that 85% of the CRP tests result in true-positives, while the remaining 15% are false negatives. The mean specificity level of 86% results in true-negatives, while the other 14% are false positives. These sensitivity and specificity data, together with the Odds Ratio of 23.56 (the closer to 100 the better the diagnostic test), decrease the reliability of applying the CRP to test for the development of postoperative infection.

As this is a considerably homogeneous systematic review in terms of the best research evidence for the intended focus and other criteria used (type of surgery, pre- and postoperative CRP, analysis and achievement of high mean sensitivity and specificity levels), it seems that the CRP possesses predictive value for the development of surgical infection. Before recommending the CRP as a risk marker for surgical infection, it is prudent to develop further research with stricter internal validity criteria, tak-

ing into account the control for variables for which homogeneity could not be obtained yet, mainly acknowledged risk factors for surgical infection.

Some of the studies analyzed even weigh these issues, as C-reactive protein is a non-specific inflammatory marker, which can be high in inflammatory (but not necessarily infectious) processes. As a result, many studies affirm the prognostic/diagnostic value of CRP as a tool that should be used together with clinical assessment and other possible laboratory tests[16-19].

CONCLUSION

As this is a homogeneous systematic review in terms of the research design, providing the best evidence for the intended focus, and in view of some internal validity criteria in the studies analyzed, it is concluded that CRP alterations are of value to predict postoperative infection development in patients. This predictive value is more reliable, however, when CRP levels are analyzed together with clinical assessment or, also, when the CRP curve is analyzed across the postoperative period, comparing it with the normal curve. This fact is evidenced through the meta-analysis, which confirms CRP as an immunological marker (SROC curve), but limits its use as a diagnostic test. That is the case because this is a non-specific protein, which hence should not be analyzed punctually in post-surgical infections, but by comparing its previous levels.

Further research is needed though, with homogeneous internal validity criteria, before recommending CRP as a risk marker for these infections.

REFERENCES

1. Volanakis JE. Human C-reactive protein: expression, structure, and function. Mol Immunol. 2001;38(2-3):189-97.
2. Santos MG, Pegoraro M, Sandrini F, Macuco EC. Fatores de risco no desenvolvimento da aterosclerose na infância e adolescência. Arq Bras Cardiol. 2008; 90(4):301-8.
3. Fransen EJ, Maessen JG, Elenbaas TWO, van Aarnhem EE, van Dieijen-Visser MP. Increased preoperative C-reactive protein plasma levels as a risk factor for postoperative infections after cardiac surgery. Ann Thorac Surg. 1999;67 (1):134-8.
4. Carvalho Junior LH, Santos L, Mendonça CJA, Campos CT, Andrade MAP. Evaluation of skin temperature, reactive C protein, and hemosedimentation speed variation in uncomplicated primary knee total arthroplasty. Acta Ortop Bras. 2006;14(3):161-4.
5. Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Review of Interventions: version 5.1.0 [Internet]. Oxford: The Cochrane Library; 2011 [cited 2011 May 15]. Available from: http://www.cochrane-handbook.org/
6. Nobre M, Bernardo W. Prática clínica baseada em evidências. Rio de Janeiro: Elsevier; 2006. Cenários clínicos: questões bem formuladas; p. 25-34.
7. Nobre M, Bernardo W. Prática clínica baseada em evidências. Rio de Janeiro: Elsevier; 2006. Diretrizes clínicas baseadas em evidências; p. 171-93.
8. Nobre M, Bernardo W. Prática clínica baseada em evidências. Rio de Janeiro: Elsevier; 2006. Avaliação crítica da pesquisa clínica; p.157-70.
9. Zamora J, Abraira V, Muriel A, Khan K, Coomarasamy A. Meta-DiSc: a software for meta-analysis of test accuracy data. BMC Med Res Methodol. 2006;6:31.
10. Oliveira AC, Ciosak SI. Infecção de sítio cirúrgico no seguimento pós-alta: impacto na incidência e avaliação dos métodos utilizados. Rev Esc Enferm USP. 2004;38(4): 379-85.
11. Schinsky ME, Della Valle CJ, Sporer SM, Paprosky WG. Perioperative testing for joint infection in patients undergoing revision total hip arthroplasty. J Bone Joint Surg Am. 2008;90(9):1869-75.
12. Okafor B, MacLellan G. Postoperative changes of erythrocyte sedimentation rate, plasma viscosity and C-reactive protein levels after hip surgery. Acta Orthop Belg. 1998;64(1):52-6.
13. Bourquignat A, Férard G, Jenny JY, Gaudias J, Kempf I. Diagnostic value of C-reactive protein and transthyretin in bone infections of the lower limb. Clin Chim Acta. 1996;255(1):27-8.
14. Aguilar-Nascimento JE, Marra JG, Slhessarenko N, Fontes CJF. Efficacy of National Nosocomial Infection Surveillance score, acute-phase proteins, and interleukin-6 for predicting postoperative infections following major gastrointestinal surgery. São Paulo Med J. 2007;125(1):34-41.
15. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR; Hospital Infection Control Practices Advisory Committee. Guideline for Prevention of Surgical Site Infection, 1999. Infect Control Hosp Epidemiol. 1999;20(4):247-78.
16. Dupont C, Rodenbach J, Flachaire E. The value of C-reactive protein for postoperative monitoring of lower limb arthroplasty. Ann Readapt Med Phys. 2008;51(5):348-57.
17. Fink B, Makowiak C, Fuerst M, Berger I, Schäfer P, Frommelt L. The Value of synovial biopsy, joint aspiration and C-reactive protein in the diagnosis of late peri- prosthectic infection of total knee replacements. J Bone Joint Surg Br. 2008;90(7):874-8.
18. Neumaier M, Scherer MA. C-reactive protein levels for early detection of postoperative infection after fracture surgery in 787 patients. Acta Orthop. 2008;79 (3):428-32.
19. Welsch T, Frommhold K, Hinz U, Weigand M, Kleeff J, Friess H, et al. Persisting elevations of C-reactive protein after pancreatic resections can indicate developing inflammatory complications. Surgery. 2008;143(1):20-8.

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