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"Procalcitonine et Protéine C-Réactive comme marqueurs des infections bactériennes: une revue systématique et une méta-analyse"

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Mémoire présenté à la Faculté des études supérieures
en vue de l'obtention du grade de Maître ès Sciences (M.Sc.)
en Science Biomédicales
option Épidémiologie Clinique

Juin 2003

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Faculté des Études Supérieures
Grade octroyé à compter du
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Faculté des Études Supérieures

Ce mémoire intitulé:

"Procalcitonine et Protéine C-Réactive comme marqueurs des infections bactériennes: Une revue systématique et une méta-analyse"

présenté par:

Liliana Simon

a été évalué par un jury composé des personnes suivantes:

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membre du jury

Sommaire

Objectifs: Une méta-analyse comparant la validité des dosages sériques de Procalcitonine (PCT) et de Protéine-C réactive (CRP) pour diagnostiquer une infection d'origine bactérienne chez les patients hopitalisés.

Méthodes: Une recherche de la littérature de 1970 à 2002 permet d'identifier les articles évaluant la PCT et la CRP lors d'infections bactériennes. Les études sont revues par trois experts indépendants et les données sont extraites dans des tables de contingences. Les auteurs des articles sont contactés pour vérifier les données.

Résultats: 351 titres sont identifiés, 110 études prospectives faites chez des patients hospitalisés sont évaluées et 12 articles sont inclus (1497 patients). Les données sont synthétisées en utilisant des méthodes de régressions linéaires et des courbes SROC (Summary Receiver Operating Characteristic) sont générées. La valeur Q, qui réflète la validité du test (correspond au point d'intersection de la courbe SROC avec la ligne où la sensibilité et la spécificité sont égales) est calculée. Pour différencier entre les infections bactériennes et les inflammations non-infectieuses, la PCT est plus sensible que la CRP (0,88 [IC 95% 0,80-0,93] versus 0,75[IC 95% 0,62-0,84]). La PCT est aussi plus spécifique (0,81 [IC 95% 0,67-0,90] versus 0,67 [IC 95% 0,56-0,77]). La valeur Q est meilleure pour la PCT que pour la CRP (0,82 versus 0,73). Pour différencier entre les infections d'origine bactériennes et virales, la PCT est plus sensible que la CRP (0,92 [IC 95% 0,86-0,95] versus 0,86 [IC 95% 0,65-0,95]). Les spécificités sont semblables (0,73 [IC 95% 0,42-0,91] versus 0,70 [IC 95% 0,19-0,96]). La valeur Q de la PCT est meilleure que pour la CRP (0,89 versus 0,83).

Conclusion: La validité de la PCT est plus élevée que celle de la CRP et ce test devrait être favorisé en clinique chez les patients hopitalisés.

Mots-clés: méta-analyse, revue systématique, infections bactériennes, inflammation, sepsis, tests diagnostiques, protéine C-réactive, procalcitonine

Summary

Objective: Meta-analysis comparing the accuracy of serum Procalcitonin (PCT) and C-reactive protein (CRP) for the diagnosis of bacterial infection in hospitalized patients.
Methods: A literature search between 1970 and 2002 for identifying articles evaluating PCT and CRP for the diagnosis of bacterial infections was performed. Each article was independently reviewed by three reviewers and data extracted in 2x2 tables. Authors of articles were contacted to verify data.
Results: 351 titles were identified; 110 prospective studies among hospitalized patients were evaluated and 12 articles (1497 patients) were included. Data were summarized using linear regression methods and summary receiver operating characteristic curves (SROC) were generated. Q values, which reflect accuracy of the test and correspond to the intersection point of the SROC curve with the line where sensitivity and specificity are equal, were calculated. PCT was more sensitive than CRP: 0.88 [95% CI 0.80 – 0.93] versus 0.75 [95% CI 0.62 – 0.84] to differentiate between bacterial and non-infective causes of inflammation. PCT was also more specific: 0.81 [95% CI 0.67 – 0.90] versus 0.67 [95% CI 0.56-0.77]. The Q value for PCT was higher than for CRP: 0.82 and 0.73 respectively. The sensitivity to differentiate between bacterial and viral infections was higher for PCT than for CRP (0.92 [95% CI 0.86 – 0.95] versus 0.86 [95% CI 0.65 – 0.95]). The specificities were comparable (0.73 [95% CI 0.42 – 0.91] versus 0.70 [95% CI 0.19 – 0.96]). The Q value was higher for PCT: 0.89 versus 0.83.
Conclusion: The overall accuracy of PCT is higher than that of CRP and should be favored for use in clinical practice in hospitalized patients.

Key words: meta-analysis, systematic review, bacterial infections, inflammation, sepsis, diagnostic tests, C-reactive protein, procalcitonin

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Chapter II

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List of Acronyms and Abbreviations

APACHE II	Acute physiology and chronic health evaluation II
AminoproCT	Aminoprocalcitonin
CCP	Calcitonin carboxyterminal peptide
CDC	Centers for Disease Control
CI	Confidence Intervals
DP	Dipedtidyl peptidase
CRP	C-reactive protein
D	Differences
DOR	Summary odds ratio
ETT	Endotracheal tube
FN	False Negative
FP	False Positive
FPR	False Positive Rate
ICU	Intensive Care Unit
IFN-γ	Interferon-γ
IL-1β	Interleukin 1β
IL-6	Interleukin 6
iNOS	Nitric oxide synthase
LPS	Lipopolysaccharide
MEDLINE	MELARS Online
MELARS	Medical Literature Analysis and Retrieval System
MeSH	Medical subject headings
MODS	Multiple Organ Dysfunction Syndrome
NK	Natural killer (cells)
NO	Nitric oxide
PCT	Procalcitonin
PELOD	Pediatric Logistic Organ Dysfunction
PICU	Pediatric Intensive Care Unit
PRISM	Pediatric RIsk of Mortality
QUOROM	Quality of Reporting of Meta-analyses

RCT	Randomized controlled trials
S	Sum
Se	Sensitivity
SIRS	Systemic Inflammatory Response Syndrome
SOFA	Sepsis-related organ failure assessment
Sp	Specificity
SROC	Summary Receiver Operating Characteristic
STARD	Standards for Reporting of Diagnostic Accuracy
TN	True Negative
TNFα	Tumor Necrosis Factor α
TP	True Positive
TPR	True Positive Rate
US	United States of America

Dedications

To my parents Gabriella and Imre, brothers Claudio and Nataniel, and grandparents for the support and encouragement throughout all my personal and professional life.

To my caring fiancé David, who has always been understanding and compassionate.

Acknowledgements

For those whose teaching were indispensable for the progress and realization of this project:

Dr. Jacques Lacroix

Dr. France Gauvin

Dr. Devendra Amre

For those who welcomed me at "Hôpital Sainte-Justine":

Dr. Jean Turgeon and all the staff in Pediatrics

Chapter I

Introduction

Definitions of SIRS and sepsis

In 1992, the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference arrived at the current definition of SIRS, sepsis, severe sepsis, septic shock and multiple organ dysfunction syndrome.[1]

Systemic inflammatory response syndrome (SIRS) encompasses the features of systemic inflammation without end-organ damage, identifiable bacteremia, and the need for pharmacological support. The hallmark of SIRS is a proinflammatory state that is marked by tachycardia, tachypnea or hyperpnea, leukocytosis or leukopenia, pyrexia or hypothermia. The key transition from SIRS to sepsis is the presence of an identified pathogen as the cause for SIRS. Most often a bacterial infection will cause a systemic inflammatory response, which can be then characterized as sepsis.

In sepsis, most often bacterial, regulation of the early response to infection may be lost, and a massive detrimental systemic reaction occurs. As result, progressive tissue damage and organ dysfunction may occur. Severe sepsis is the presence of sepsis (SIRS caused by an infection) associated with organ dysfunction, hypoperfusion, or hypotension that usually responds to adequate fluid resuscitation. There is a subset of people with severe sepsis who develop hypotension despite adequate fluid resuscitation and require inotropic or vasopressor agents; these patients have septic shock. Multiple organ dysfunction syndrome (MODS) is defined as the presence of at least two altered organ function in a patient who is acutely ill and in whom homeostasis cannot be maintained without intervention.

Epidemiology of sepsis

Sepsis is a major challenge in medicine. Sepsis is extremely common, has a very high morbidity and mortality and consumes considerable health-care resources. Around 700,000 cases of sepsis are reported annually worldwide and accounting for about $15 billion in health care costs in the U.S. alone.[2] It is the second leading cause of death among patients in non-coronary intensive care units and the 10th leading cause of death overall in the United States.[3] Sepsis is often lethal, killing 20 a 50% of severely affected patients.[4] Bacterial infections are the major cause of sepsis.

Martin et al.[3] recently reviewed the epidemiology of sepsis by assessing discharged data on approximately 750 million hospitalizations in the U.S. over the 22-year period from 1979 through 2000. During this period, there were 10,319,418 reported cases of sepsis, accounting for 1.3 % of all hospitalizations. Even after normalizing for the population census, there was a yearly increase of 8.7 % in the incidence of sepsis, going from about 82.7 cases per 100,000 population to nearly 240.4 per 100,000 population. The average age of patients with sepsis increased consistently over time, from 57.4 years in the first 5-year subperiod (1979 through 1984) to 60.8 years in the last 5-year subperiod (1995 through 2000). Whites had the lowest rates of sepsis during the study period, with both blacks and other nonwhite groups having a similarly elevated risk as compared with whites. Black men had the highest rate of sepsis, the youngest age of onset, and the highest mortality. When considering causative organisms, gram-negative bacteria remain as always, the most important cause of sepsis. The greatest relative changes, however, were observed in the incidence of fungal infections, which increased by 207%. Gram-positive bacteria became the predominant pathogen after 1987; there was an average increase by 26.3% per year in the incidence of gram-positive sepsis. The total in-hospital mortality rate fell from 27.8% during the initial 5-year subperiod (1979 through 1984) to 17.9% during the last 5-year subperiod (1995 through 2000). Yet, because of the increased incidence of sepsis, the total number of deaths continues to increase. Over time, admission days significantly decreased. However, the rate of discharge of surviving

patients to other heath care facilities (i.e., rehabilitation centers or other long-term care facilities) almost doubled, going from 16.8% to 31.8%.

Severe sepsis is also a significant health problem in children. Watson et al.[5] studied the epidemiology of severe sepsis in children using 1995 hospital discharge and population data from seven states (24% of the United States population). They found an incidence of 0.56 cases per 1,000 population per year. The incidence was the highest in infants (5.16 per 1,000) and fell dramatically in older children (0.20 per 1,000 in 10 to 14 years old). It was 15% higher in boys than in girls (0.60 versus 0.52 per 1,000). Hospital mortality was 10.3% (6.2 per 100,000 population). Half of the cases had underlying disease (49.0%), and over one-fifth (22.9%) were low-birth-weight newborns. Respiratory infections (37%) and primary bacteremia (25%) were the most common infections. The mean length of stay and cost were 31 days and $40,600, respectively. Estimated annual total costs were 1.97 billion U.S. dollars nationally.

Severe sepsis is especially common in the elderly and is likely to increase substantially in the coming years as the world population ages.[2] Massive resources have been invested in early diagnosis of sepsis, in developing and evaluating potential therapies, and considerable effort has been undertaken to understand the systemic inflammation and multiple-system organ failure characteristics of severe sepsis.

Diagnosis of Sepsis

Early specific treatment for sepsis is beneficial in trying to prevent the evolution to the more severe forms of the disease, such as severe sepsis, septic shock and MODS. However, treating every SIRS with antibiotics is hazardous. It is estimated that more than 60% of the ICU patients are treated with broad-spectrum antibiotics at any time of their stay. Antibiotics given to a non-infected patient increases the risk of acquiring nosocomial infections caused by multiresistant organisms[6,7] and can double the risk of death.[8-11] Avoiding the use of unnecessary antibiotic use and optimizing the administration of antimicrobial agents help to improve patient outcome, while minimizing resistance.[12] In an European ICU, when a restrictive strategy for the use of antibiotics was adopted, a decrease of 22% in the expenses for antibiotics (saving of 14,400 Euros/year) was noted.[13]

Unfortunately clinical symptoms of sepsis are usually subtle and non-specific and the problem remains the diagnosis of underlying bacterial infection. Presently, diagnosis by using bacterial culture methods remains the standard. However, there is an unavoidable delay in obtaining the results (usually at least 24-48 hours). Besides, only less than one half of the patients with signs and symptoms of sepsis have positive results on blood culture.[14] The demonstration of bacteria in sterile sites is not always evident. Clinically, bacterial infection can be evidenced by finding a collection of purulent material. Significant amount of bacteria can also be recognized by Gram's stain. Rapid immunological detection methods for the identification of bacterial components are available for some pathogens. Hence the identification of suitable markers for the early diagnosis of bacterial infections is paramount.

Presently two markers, procalcitonin (PCT) and C-reactive protein (CRP), are being widely studied to investigate their clinical utility vis-à-vis the diagnosis of bacterial infections.

Procalcitonin

Procalcitonin was described as a precursor for calcitonin in 1975,[15] but it was not until 1992 that it was suggested to be an inflammatory mediator, rising in burned patients.[16] A close correlation between bacterial infections and serum PCT levels was reported in 1993.[17] Thereafter, several studies correlated PCT levels with bacterial infections.

Procalcitonin (PCT) is a 116 amino-acid (13 kDa) protein, derived from the preprocalcitonin. PCT concentrations in the plasma of healthy subjects are negligible, usually within the picogram per milliliter range (10-50 pg/mL).[18] PCT is the pre-hormone of calcitonin and is a member of the "CAPA protein family" (*c*alcitonin gene-related peptide-*a*mylin-(*p*ro)-calcitonin-*a*drenomedullin family). PCT mRNA is synthesized by the *CALC-I* gene on chromosome 11 during normal conditions, sepsis and inflammation. In voluntary healthy subjects, PCT is produced by the C cells of the thyroid, where it is processed into calcitonin and stored in secretory granules. Calcitonin is then released from these granules in response to hormonal or metabolic stimuli. No other genes are known to produce inflammation-induced PCT. The gene is present in various mammals and other species (e.g. salmon), but the DNA sequences and amino acids found in these animals are species-dependent. The large degree of conservation of the gene in various species indicates that it may have biologically important functions,[18] still to be established.

Two types of PCT mRNA are synthesized within PCT-producing cells, resulting in two different proteins, PCT-I and PCT-II. They are very similar in structure, differencing only at eight C-terminal amino acids.[18] The type of protein synthesized or processed depends on the individual circumstances, the type of cells involved, the stimulus for cellular activation, and individual susceptibility of various cell types to these stimuli. Variable quantities of PCT-I and PCT-II mRNA can be detected in different tissues. They are both detected by the commercially available assay.[18]

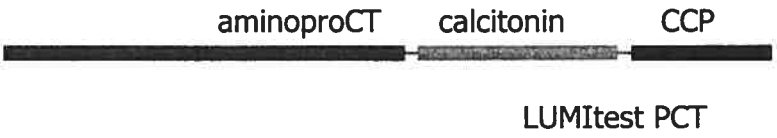

Figure 1 – Cartoon PCT molecule and antibody site binding of the commercially available assay (LUMItest PCT)
aminoproCT, aminoprocalcitonin; CCP, calcitonin carboxyterminal peptide

The stimulus for PCT production during bacterial infection is still under investigation. Some findings suggest that the release of proximal cytokines in sepsis can initiate a greater increase in PCT. High serum PCT concentrations are measured during septic shock and respiratory distress, where massive amounts of TNF are released. The injection of TNF-α into healthy animals is associated with an elevation of serum PCT levels.[19] The intravenous injection of endotoxin into healthy volunteers causes the rapid synthesis of PCT.[20] Increased PCT concentrations were demonstrated after treatment with human recombinant TNF-α and IL-6 in cancer patients.[21]

The site of PCT production during severe generalized infection is still uncertain and controversial. Elevated serum concentrations of PCT were found in patients with sepsis who have undergone prior total thyroidectomy;[17] thus, high PCT plasma levels during systemic inflammation and sepsis are unlikely to be of thyroidal origin. Human peripheral mononuclear cells are another source for PCT production during inflammation and sepsis.[22, 23] However, significant quantities of PCT were induced during leukopenia in a patient on immunosuppressants for chemotherapy, while no leukocytes were detectable in visually and automatically analyzed blood smears.[24] The liver might be a more important source of PCT during inflammation and bacterial infection, as demonstrated by increased PCT production in liver slices after stimulation with recombinant human TNF-α or IL-6.[21]

On the other hand, PCT might have an active functional protective role in patients with sepsis. *In vitro* experiments showed that PCT has influence on cytokine expression. TNF-α induction was significantly reduced in the presence of PCT or its C-terminal 57 amino acid fragment.[25] In cultured smooth muscle cells, low or moderately elevated PCT concentrations significantly suppressed TNF-α and IFN-γ-stimulated production of cDNA of iNOS.[26] However, in animal model of sepsis, increased mortality was observed following intravenous PCT injections. Moreover, neutralization of PCT with antiserum improved the survival of animals following *Escherichia coli* inoculation.[27]

Although still under investigation, it is believed that there is protein modification of the PCT molecule, which most likely occurs by glycosylation or deamination. Two N-terminal amino acids (Ala-Pro) are removed by the enzyme dipedtidyl peptidase IV (DP IV) or CD26. The DP IV enzyme is located on renal, epithelial and endothelial cells, and is induced by proinflammatory mediators and endotoxin. Although the turnover rate of DP IV cleavage is low due to the length of the PCT molecule, a molar excess of the enzyme is present *in vivo*, resulting in high concentrations of truncated PCT in the plasma of patients with severe sepsis. Furthermore, DP IV is known to modify other proteins in which the active form is converted to an inactive form, e.g., chemokines like granulocyte chemotactic protein-2, macrophage-derived chemokine, etc.

The exact function of biologically active PCT is not known; it is possible that it participates in amplifying the inflammatory response during infection. Recombinant procalcitonin and various synthetic proteins have been investigated *in vitro* and in experimental studies. When PCT was applied simultaneously with the inflammatory stimuli TNF-α/IFN-γ, PCT inhibited synthesis of the inflammatory mediator nitric oxide (NO) in vascular smooth muscle culture.[26] However, the time course of PCT during sepsis suggests that it is not a proximal event in the inflammatory cascade, so that PCT is not present initially with TNF-α and IFN-γ in the early stages of inflammation. After the injection of bacterial products *in vivo*, it was found that PCT concentrations increased from the 3rd hour onward, reaching a plateau after 6 hours, whereas TNF-α peaks were detected earlier.[20] Thus, it was investigated whether PCT affects NO synthase (iNOS) by

LPS, TNF-α, and IFN-γ, taking into account the typical 3-hr delay of PCT increase following a bacterial challenge. A further stimulation of inducible nitric oxide synthase transcription rate was found, suggesting that PCT acts as a modulator that augments the inflammatory response triggered by agonists like lipopolysaccharide, tumor necrosis factor-α, and interferon-γ.[28]

There are some studies that show that PCT concentrations are much higher in patients with severe sepsis than in those with sepsis alone.[29, 30] PCT may have a hazardous effect; *in vivo* experiments in hamster endotoxin shock models showed that PCT administered to septic animals increased mortality and that PCT antiserum protected the animals from the lethal effects of sepsis.[27] In the baboon sepsis model, PCT concentrations were significantly different between survivors and nonsurvivors.[31] PCT concentration also seems to correlate with the severity of organ dysfunction, as defined by different scoring systems, such as SOFA (sepsis-related organ failure assessment),[32] or APACHE II (acute physiology and chronic health evaluation II) or survival[33-35] and poorer prognosis.[36, 37] Although initially high PCT concentrations do not necessarily indicate a poor prognosis, serum PCT, could potentially be used to monitor disease activity in patients with sepsis, severe sepsis and septic shock.

C-Reactive Protein

CRP was one of the first "acute phase" markers described. It was originally isolated in 1930 in the serum of patients with pneumonia. With its high affinity for the pneumococcal C polysaccharide, it was later named as C-reactive protein.[38]

CRP belongs to the pentraxin family of proteins, so called because they form a cyclic pentamer composed of five identical non-glycosylated sub-units, non-covalent bound and organized in a very stable discoid-like structure. Another important member of this family is the serum amyloid P component. These proteins are conserved throughout vertebrate evolution, suggesting that CRP has a central role in the immune response.[39, 40]

CRP binds to several polysaccharides and peptido-polysaccharides present in bacteria, fungi and parasites in the presence of calcium. These complexes activate the classical complement pathway, acting as opsonins and promoting phagocytosis. Together with complement components, CRP is the only acute phase protein directly involved in the clearance of micro-organisms. *In vitro*, CRP stimulates cell-mediated cytotoxicity through activation of neutrophils, promoting platelet degranulation and enhancing NK cell activity. Under physiologic conditions, CRP binds to small nuclear ribonucleoproteins, suggesting a direct role in the removal of necrotic tissue.[38, 40]

CRP is detected with low levels in the serum of the normal human population, with a median of 0.8 mg/L and it is below 10 mg/L in 99% of normal samples. Levels above these values are abnormal and indicate the presence of a disease process.

As with other acute phase proteins, CRP is mainly synthesized by the liver, mainly in response to IL-6. TNF-α and IL-1β are also regulatory mediators of CRP synthesis. During acute inflammatory or infectious states, changes in CRP levels are determined by the rate of synthesis and is not modified by any therapy that does not affect the evolution of the disease or interventions such as renal replacement therapy.[40]

Elevations in serum CRP are seen in most invasive infections, including bacterial and fungal infections, even in immunodeficient patients.[40] By contrast, CRP concentrations tend to be lower in most acute viral infections.[40] Nevertheless, this is not absolute and sensitivities and specificities vary among studies. There is limited knowledge of CRP behavior in parasitic infections, but some protozoan parasitic diseases such as malaria, pneumocystosis and toxoplasmosis are also able to cause marked rises in CRP. In chronic infections, such as tuberculosis and leprosy, although abnormal, CRP levels are usually only modestly elevated. In addition to infection, there are several other conditions that are associated with substantial increase in CRP levels, which include trauma, surgery, burns, tissue necrosis, immunologically mediated inflammatory diseases, crystal-induced inflammatory diseases and advanced cancer. However, some inflammatory disease, such as systemic lupus erythematosus, systemic sclerosis, dermatomyositis, Sjögren's disease, ulcerative colitis, leukemia and graft-versus-host disease are associated with only minor elevations of CRP. For reasons unknown, the acute phase response induced by these diseases is unable to raise the CRP, due to failure of synthesis rather than increase in clearance. However, in response to infection these patients are still able to mount a major CRP response. This property is used to distinguish infection from a flare-up of the underlying disease process.[40]

Besides its use in the diagnosis of sepsis, CRP has also been associated to disease severity, with increased levels in patients with septic shock compared to patients with sepsis alone.[34] It has also been evaluated as a prognostic marker. Non-survivors had a median CRP concentration significantly higher than survivors.[41]

Accumulating data pathologically link atherosclerosis and the inflammatory response to vascular injury. Several prospective studies have demonstrated a direct correlation between acute myocardial infarction, rise in CRP, postinfarction adverse events, and subsequent infarct size. Not only that, but a positive association has been found between CRP levels and risk of developing peripheral arterial disease,[38] suggesting that CRP would be a good marker for vascular disease in asymptomatic patients. In these situations, CRP levels are significantly lower (~100 times) than in acute inflammatory processes and is measured with high-sensitive assays.[42] There is no current evidence that lowering CRP

necessarily reduce cardiovascular event rates; however, many interventions known to reduce cardiovascular risk,[42] including the use of anti-cholesterol drugs (statins),[43] have been linked to lower CRP levels.

Meta-analysis technique

Interest in medical applications of meta-analysis has increased significantly in recent years, although meta-analytic procedures have been widely employed in the social sciences since the early 1970s.

The National Library of Medicine defines meta-analysis as "a quantitative method of combining the results of independent studies (usually drawn from the published literature) and synthesizing summaries and conclusions which may be used to evaluate therapeutic effectiveness, plan new studies, etc. It is often an overview of clinical trials." Meta-analysis is a systematic method that uses statistical analysis for extracting, comparing, and combining results from independent studies to get quantifiable outcomes. Meta-analysis should be viewed as an observational study of the evidence; the steps involved are similar to any other research undertaking: formulation of the problem to be addressed, collection and analysis of the data, and reporting of the results.[44] The method consists of a thorough literature review, calculation of an effect size for each study, determination of a composite effect size from the weighted combination of individual effect sizes, and calculation of a fail-safe number (number of unpublished studies with opposing conclusions needed to negate the published literature) to assess the certainty of the composite size.

Considerable amount of money is spent on clinical research. However, findings are not always implemented in routine clinical practice. Systematic reviews of rigorous studies provide the best evidence of the effectiveness of different strategies for promoting behavioral change.[45, 46] Practicing evidence based medicine is one way for clinicians to keep up to date with the exponential growth in medical literature.[47]

Meta-analysis of diagnostic tests versus randomized controlled trials

Systematic reviews of tests are undertaken for the same reasons as systematic reviews of therapeutic interventions: to produce estimates of performance based on all available evidence, to evaluate the quality of published studies, and to account for variation in findings between studies. Reviews of studies of diagnostic accuracy, in common with systematic reviews of randomized controlled trials, involve key stages of question definition, literature searching, evaluation of studies for eligibility and quality, data extraction and data synthesis. However, the details within some of the stages differ.[48]

Systematic reviews of randomized controlled trials are often justified on the grounds that they increase statistical power: by assimilating participants recruited to a series of trials, they increase our ability to detect small but clinically important differences in outcomes between treated and control groups. Statistical power is rarely discussed in studies of diagnostic accuracy as they do not compare two groups, and they do not formally test hypotheses. However, increasing sample sizes by pooling the results of several studies provides an opportunity to improve the precision of these estimates, and to investigate the consistency of test performance and compare results between studies of different designs and from different settings.[48]

Studies of test performance (or accuracy) compare test results between separate groups of patients with and without the target disease, each of whom undergoes the experimental test as well as a second "gold standard" reference test. The relationship between the test results and disease status is described using probabilistic measures, such as sensitivity and specificity. It is important that the results of the reference test are very close to the truth, or else the performance of the experimental test will be poorly estimated. To achieve this, reference tests sometimes involve combining several pieces of information.[48]

There are three major ways in which systematically reviewing studies of diagnostic accuracy differs from reviewing therapeutic interventions: the choice of search terms for

electronic literature searches, the criteria for the assessment of study quality, and the methods for the statistical combination of results.[48]

Electronic database searches for studies of diagnostic accuracy can be more difficult and less productive than those for randomized trials. Occasionally a simple search using just the test name will prove to be sensitive, but many diagnostic technologies (such as ultrasound, x rays, and serology tests) are used across a variety of fields in medicine, so that a mixture of appropriate and inappropriate studies will be retrieved, and the search will not be specific. Including terms for the disease is the search may help.[48] Several *MeSH* terms have been suggested for locating studies of diagnostic accuracy.

Possible bias of meta-analysis of diagnostic tests

The ideal study sample for inclusion in a review is a consecutive (or randomly selected) series of patients recruited from a relevant clinical population. Selection bias may be introduced by selecting patients for inclusion in a non-random manner. This can present as a form of spectrum bias that arises whenever the study population is not representative of the spectrum of disease within which the test will be applied in practice.

In practice, it is easier to include patients with or without the disease as separate groups, as in a case-control study. This can lead to bias, however, as detection rates vary according to the severity of the disease, and the chances of falsely positive diagnosis will vary between patients according to the alternative disease that they do have. Choosing cases that have already been identified as having the disease will introduce bias into the estimates of test sensitivity, choosing controls that are completely healthy will introduce bias into the estimates of test specificity.[48]

As well as being selected in a correct manner, it is also important that the study samples are selected from similar healthcare settings. This is more a matter of the applicability of a study rather than study quality. Importantly, it is possible that the spectrum of disease and alternative diagnoses varies between different points in the health care referral process, such as primary and secondary care. As the sensitivity and specificity might not be constant across the spectrum of the disease or across the alternative conditions, the observed values of test sensitivity and specificity in the two samples might differ. This variation has nothing directly to do with disease prevalence within the study group: although it is likely that the prevalence of the disease will also differ between points in a referral process, the observed sensitivity and specificity will only change if the proportionate mix of the spectrum of diseased and non-diseased patients varies as well. Variation in prevalence may be a hint of the presence of spectrum bias, but it is not its cause.[48]

The selection of a good reference standard is crucial. Typically the reference standard is considered a "gold standard", and the comparison is one-sided: if there are any disagreements between the reference standard and the experimental test it is always assumed that the experimental test is incorrect. It is important that the two tests are based on independent measurements. In some circumstances the reference diagnosis may be made on the basis of a battery of clinical tests and other available clinical evidence. If this is the case, the battery of results should not include the experimental test result, or else the diagnostic accuracy will most likely be overestimated. Such an effect is known as incorporation bias.[48]

Verification bias is a problem when the decision to undertake the reference investigation is influenced by the result of the experimental test or other factors which indicate that the disease is unlikely. There are two levels of incomplete verification: partial verification where not all participants undergo the reference investigation, and differential verification where different reference tests are used according to the results of the experimental test. Partial verification bias usually leads to the numbers of true negative and false negative participants being reduced, so that sensitivity is biased upward and specificity biased downwards. In contrast, differential verification bias may lead to both estimates being biased upwards.[48]

Blinding involves each test being undertaken and interpreted without knowledge of the results of the other. This is especially important for tests that involve subjective judgements, such as those that rely on human perceptions in interpreting images and sounds.[48]

Another important aspect of quality is whether both diagnostic tests were undertaken before any treatment was started. Where this does not occur, a treatment paradox can be introduced: patients who are diagnosed with the disease at the first test can be treated and cured before the second test, and misclassified as false positives or false negatives depending on which tests was used first.[48]

Inclusion of the test results of all participants in the analysis is important. Many tests report some results as being in a *grey-zone*, or occasionally as *test failures*. Although including these outcomes in an analysis is not always straightforward, ignoring them will present a test more favourably than is justified.[48]

Ideally, a study report should include clear descriptions of the reference and the experimental tests, with definitions of positive and negative outcomes for both, and descriptions of demographic characteristics, co-morbidities, the source and referral history of the patients. Lijmer et al.[49] provided evidence that case control study designs rather than clinical cohort overestimated diagnostic accuracy by a relative diagnostic odds ratio of 3.0 (95% CI 2.0 - 4.5), being the greatest potential source of bias. Studies using differential reference standards were also found to overestimate diagnostic performance compared to those using the same reference standard for both, whilst partial verification did not introduce a consistent effect. Unblinded studies were on average more likely to overestimate diagnostic accuracy. They also noted that the omission on reporting specific details of a study was associated with systematic differences in results.[48]

The problem of publication bias are more difficult: there are no studies in the literature which estimate rates of publication bias for diagnostic accuracy studies, and such investigations are difficult to undertake, as studies cannot easily be identified before they are undertaken. Also, there is no way to investigate whether or not the studies identified are a biased sample. Some authors have suggested that publication bias may in fact be a greater problem for studies of diagnostic accuracy than for randomized controlled trials.[50]

Heterogeneity of studies in a meta-analysis

Another important source of variation to consider in meta-analyses of diagnostic accuracy is the variation introduced by changes in diagnostic threshold. The studies included in a systematic review may have used different thresholds to define positive and negative test results. Some may have done this explicitly, for example by varying numerical cut-points used to classify a biochemical measurement as positive or negative. For others there may be naturally occurring variations in diagnostic thresholds between observers or between laboratories. The choice of a threshold may also have been determined according to the prevalence of the disease – when the disease is rare, a low threshold may have been used to avoid large numbers of false positive diagnoses being made. Unlike random variability and other sources of heterogeneity, varying the diagnostic threshold between studies introduces a particular pattern into the ROC plot of study results. If such variation is present, the points will demonstrate curvature that parallels to the underlying ROC curve for that test. The approach to combining studies in these situations involves deriving the best-fitting ROC curve rather than summarising the results as a single point.[48]

The simplest method of combining studies of diagnostic accuracy is to compute weighted averages of the sensitivity, specificities or likelihood ratios. This method should only be applied in the absence of variability of the diagnostic threshold. The possibility of a threshold effect can be investigated before this method is used, both graphically by plotting the study results on an ROC plot, and statistically, by undertaking tests of heterogeneity of sensitivities and specificities and investigating whether there is a relationship between them. The homogeneity of the sensitivities and specificities from the studies can be tested using standard chi-squared tests as both measures are simple proportions. Calculation of the correlation coefficient between sensitivities and specificities will test whether they are related, as would be the case if there was variation in the diagnostic threshold. If an association between the sensitivities and specificities is detected, use of weighted averages will lead to underestimation of diagnostic performance, as the point corresponding to the average of the sensitivities and the average of the specificities always falls below the ROC curve. Note that when the studies

in the systematic reviews have small sample sizes, tests for heterogeneity and correlation have low statistical power, and therefore a threshold related effect may exist but remain undetected by the statistical tests.[48]

If there is any evidence that the diagnostic threshold varies between the studies, the best summary of the results of the studies will be an ROC curve rather than a single point. Diagnostic tests where the diagnostic odds ratio is constant regardless of the diagnostic threshold have symmetrical ROC curves. In these situations, it is possible to use standard meta-analysis methods for combining odds rations to estimate the common diagnostic odds ratio, and hence to determine the best-fitting ROC curve. Once the summary odds ratio, DOR, has been calculated the equation of the corresponding ROC curve is given by: sensitivity = $1/\{1+(1/(DOR \times [(1-specificity)/specificity])\}$.[48]

Moses and Shapiro methods for estimation of summary ROC curves

Difference between studies in patient groups, test execution and study design can introduce variability in diagnostic odds ratios. Both methods of pooling odds ratios can be extended to investigate the possible importance of these features. If it can be assumed that the summary ROC curves are symmetrical, the impact of other factors can be investigated using standard methods of meta-regression for odds ratios. Alternatively, Litternberg-Moses regression method can be extended by adding a covariate to the regression equation for each potential effect modifier. The exponential of each of these terms estimates multiplicative increases in diagnostic odds ratios for each factors.[48]

When the diagnostic odds ratio changes with diagnostic threshold, asymmetrical ROC curves occur. Litternberg, Moses and Shapiro proposed a method for fitting a whole family of summary ROC curves which allow for variation in DOR (summary odds ratio) with threshold.[51, 52]

The method considers the relationship between the DOR and a summary measure of diagnostic threshold, given by the product of the odds of true positive and the odds of false positive results. As a diagnostic threshold decreases, the numbers of positive diagnosis (both correct and incorrect) increases, and the measure of threshold increases.

The diagnostic odds ratio is denoted by D, and the logarithm of the measure of threshold by S. D and S can be calculated from the true positive rate (TPR) and false positive rate (FPR) using the following equations:

$S = \ln \{[TPR/(1-TPR)] \times [FPR/(1-FPR)]\} = \text{logit}(TPR) + \text{logit}(FPR)$

$D = \ln(DOR) = \ln \{[TPR/(1-TPR)] \times [(1-FPR)/FPR]\} = \ln [(LR + \text{ve})/(LR - \text{ve})]$ $= \text{logit}(TPR) - \text{logit}(FPR)$, where *logit* indicates the *log of the odds*, as used in logistic regression.

Littenberg and Moses' method first consders a plot of the log of the diagnostic odds ratio (D) against the measure of threshold (S) calculated for each of the studies. They

propose computing the best fitting straight line through the points of the graph. If the equation of the fitted line is given by: $D = a + bS$ testing the significance of the estimate of the slope parameter b testes whether there is significant variation in diagnostic performance with threshold. If the line can be assumed horizontal, the diagnostic odds ratio does not change with threshold, and the method yields symmetrical ROC curves, similar to those obtained from directly pooling odds ratios. However, if there is a significant trend in the diagnostic odds ratio with diagnostic threshold then ROC curves are asymmetrical, the summary ROC curve being calculated as:

$$\text{sensitivity} = 1/[1 + (1/e^{a/(1-b)} \times (1 - \text{specificity}/\text{specificity})^{(1+b)/(1-b)}].$$ [48]

Once S and D have been calculated for each study in the meta-analysis, a simple least-squares regression is used to fit a straight line to the points. The regression line is then back-transformed into sensitivity and specificity. A confidence interval (CI) on the summary ROC curve can be obtained by back-transforming the CI form the linear regression.[53]

The present study

Previous studies have suggested that both PCT and CRP could be promising diagnostic markers for bacterial infections.[17, 19, 29, 30, 33, 34, 37, 38, 40, 54-134] However the accuracy of these markers has varied across studies, especially as a result of limitations in sample size and differences in study designs. In order to adequately summarize the utility of these markers in clinical practice, we carried out a meta-analysis and systematically reviewed studies that simultaneously investigated these tests as markers for bacterial infection.

Chapter II

Article

Procalcitonin and C-Reactive Protein as Markers of Bacterial Infection: A Systematic Review and Meta-Analysis

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RUNNING TITLE: PCT & CRP, meta-analysis

WORD count (text only): 3746

ABSTRACT

Context: Procalcitonin and C-reactive protein have been advocated to diagnose bacterial infection. Their accuracy remains uncertain.

Objective: Meta-analysis of published studies to compare the accuracy of procalcitonin and C-reactive protein as diagnostic markers of bacterial infection.

Data Sources: Studies published in MEDLINE (1970 – 2002) that evaluated procalcitonin and C-reactive protein for the diagnosis of bacterial infections were identified. Cross-references were reviewed.

Data Selection: 351 titles were identified; 110 prospective studies among hospitalized patients were evaluated. Articles were selected by three reviewers.

Data Extraction: Data were extracted in 2 by 2 tables. Authors of articles were contacted to verify data.

Data Synthesis: 12 articles were included (1497 patients). Data were summarized using linear regression methods and summary receiver operating characteristic curves were generated. Procalcitonin was more sensitive than C-reactive protein: 0.88 [95% CI 0.80 – 0.93] versus 0.75 [95% CI 0.62 – 0.84] for differentiating between bacterial and non-infective causes of inflammation; difference 0.13 [95% CI 0.08 – 0.17], $p < 0.05$. Procalcitonin was also more specific: 0.81 [95% CI 0.67 – 0.90] versus 0.67 [95% CI 0.56 – 0.77]; difference 0.14 [95% CI 0.08 – 0.20], $p < 0.05$. The Q value for procalcitonin was higher than for C-reactive protein: 0.82 and 0.73 respectively. The sensitivity for differentiating between bacterial and viral infections was higher for procalcitonin than for C-reactive protein (0.92 [95% CI 0.86 – 0.95] versus 0.86 [95% CI 0.65 – 0.95]); difference 0.06 [95% CI 0.005 –

0.11], $p < 0.05$. The specificities were comparable (0.73 [95% CI 0.42 – 0.91] versus 0.70 [95% CI 0.19 – 0.96]); difference 0.03 [95% CI 0.04 – 0.1], $p > 0.05$. The Q value was higher for procalcitonin: 0.89 versus 0.83 for C-reactive protein.

Conclusions: The diagnostic value of procalcitonin was higher than the one for C-reactive protein in hospitalized patients. Procalcitonin should be favored for use in clinical practice.

KEY WORDS

meta-analysis, systematic review, bacterial infections, inflammation, sepsis, diagnostic tests, C-reactive protein, procalcitonin

INTRODUCTION

Bacterial infections are a major cause of hospitalization, intensive care unit admission and mortality. Bacterial infections often activate the systemic inflammatory network, causing systemic inflammatory response syndrome (SIRS). This acute activation as a result of bacterial, fungal, viral and/or parasitic infections is referred to as sepsis.[1] Bacterial infections are the leading cause of systemic inflammation and sepsis.[2] Because the presentations may be similar, a major challenge in clinical practice is to accurately distinguish between SIRS and sepsis. Around 700,000 cases of sepsis are reported annually worldwide and account for about US$ 15 billion in health care costs in the U.S. alone.[3] Recent data from the Centers for Disease Control (CDC) indicate that the incidence of sepsis is increasing by an average of 16% a year in the U.S.. During the 20-year period from 1979 to 1999, the incidence of sepsis increased by more than 329%. It went from 78 to 259 cases per 100,000 people. The associated mortality rate is decreasing, though, dropping from 29% in 1979 to 17.4% in 1999. However, because of the increased incidence of sepsis, the total number of people who die from sepsis continues to increase each year.[2]

Recognizing sepsis and bacterial infections is important in order to initiate timely and appropriate treatment. The increase in antibiotic resistance due to inappropriate use of broad-spectrum antibiotics makes the identification of the cause increasingly critical. However the early diagnosis of bacterial infections is difficult and sometimes challenging. It requires demonstration of bacteria in sterile sites, either by finding pus or a significant amount of bacteria by Gram's stain or culture, or by showing the presence of bacterial

genome by PCR. Presently, diagnosis by using bacterial culture methods is the reference standard. However, its utility is often hampered by delays in obtaining the results (usually at least 24 - 48 hours). Hence the identification of suitable markers for the early diagnosis of bacterial infections is paramount.

Two potential markers, procalcitonin (PCT) and C-reactive protein (CRP), are presently being widely studied to investigate their accuracy vis-à-vis the diagnosis of bacterial infections. PCT is the pre-hormone of calcitonin. Under physiologic conditions, serum concentration of PCT is negligible or undetectable.[4] CRP is an acute phase reactant that rises whenever an inflammatory process is present. Previous studies have suggested that both PCT and CRP could be promising diagnostic markers for bacterial infections. However the reported diagnostic accuracy of these markers has varied across studies. This is probably due to differences in study designs and/or limitations in sample size. In order to adequately summarize the accuracy of these markers, we carried out a meta-analysis and systematically review of studies that simultaneously investigated PCT and CRP as markers for bacterial infection.

METHODS

Retrieving the Literature. All studies published in MEDLINE from January 1, 1970 through May 30, 2002 that evaluated PCT and/or CRP for the diagnosis of bacterial infections were identified using pre-established search strategies. Referring to at least one keyword per category, cross-searching of the following five categories were done using a Boolean strategy: (1) type of study (descriptive study or diagnosis or epidemiological study or meta-analysis or multicenter study or prospective or review-literature or reproducibility or test or validation); (2) site of the study (critical care or hospital or intensive care); (3) subjects (human); (4) test (C-reactive protein or interferon or interleukin or procalcitonin or white blood cell count or sedimentation) and (5) disease (infection or cross infection or hospital acquired infection or meningitis or multiple organ dysfunction syndrome or MODS or pneumonia or sepsis or septicemia or septic shock or systemic inflammatory response syndrome or SIRS). The bibliography of the relevant articles were further cross-checked to search for articles not referenced in MEDLINE.

Selection of Studies, Inclusion and Exclusion Criteria, and Data Extraction. Studies that prospectively and simultaneously evaluated both PCT and CRP as diagnostic markers for bacterial infection in hospitalized patients were evaluated. Studies examining all age groups were included. Retrospective studies, reviews, animal studies and studies with incomplete data were excluded. The titles and abstracts of all pertinent articles were reviewed by three independent reviewers (LS, FG, JL) to identify potentially relevant studies. Discrepancies or disagreements, if any, on the inclusion or exclusion of studies were resolved by consensus. Whenever possible, the raw data from the articles were used to construct 2 by 2 tables.

When raw data was unavailable, the tables were constructed using given measures of sensitivity and specificity. Some studies reported the sensitivity and specificity at many cutoff points. In such instances, we chose the cutoff point with the best efficiency value, which is found by dividing the sum of cases classified as true positives and true negatives by the total number of cases.[5] Authors of individual articles were contacted and asked to complete or correct any missing or incorrect information.

Quality Assessment. We evaluated the methodological quality of the included studies by applying the criteria for assessing randomized clinical trials design-related bias described by Chalmers et al.[6] Four aspects of each study were evaluated for the assessment of the quality of the research: (1) basic descriptive material; (2) study protocol; (3) analysis of the data and (4) data potentially useful for combination of several randomized clinical trials results. The latter three aspects were graded and a score was awarded to each item under each aspect. Subsequently, an overall quality index for each study was obtained by adding up the item scores and dividing by the total possible score. Rate of agreement among the three independent reviewers was calculated for each item and expressed as a percentage.

Meta-analysis. The meta-analysis approach that uses linear regression techniques to combine data from independent studies evaluating similar diagnostic test/criteria as described by Moses and Shapiro was utilized.[7] To create the summary receiver operating characteristic (SROC) curve, we first calculated the true-positive rate (TPR) and false-positive rate (FPR) from each individual study from the reconstructed 2 by 2 tables. These rates were then converted to their logistic transform (log [TPR/1-TPR] and log [FPR/1-FPR]). The sum (S) and the difference (D) of these logistic transforms were calculated for each study as well as a

regression line fitted to these points, with D as the dependent variable and S as the independent variable (D = a + bS). Based on this equation, the values of sensitivity and specificity required to construct the SROC curve were then calculated as: sensitivity = $1/(1 + 1/e^{a/(1-b)}) \times (1 - \text{specificity}/\text{specificity})^{(1+b)/(1-b)}$. The resulting values were then plotted in the SROC space to obtain the SROC curve. We took into account the differences in sample sizes among the studies by weighting each observation by the reciprocal of the variance of D and performing weighted regression. To further compare the accuracy between PCT and CRP, we calculated the Q values from the SROC curves obtained for each of these criteria. This value represents the intersection point of the SROC curve with a diagonal line from the left upper corner to the right lower corner of the ROC space, where sensitivity and specificity are equal. A higher Q value indicates higher accuracy.

RESULTS

From the initial search of the MEDLINE database (January 1, 1970 to May 30, 2002), a total of 351 publications were retrieved. Of these, 110 studies that suggested that PCT and/or CRP were performed in hospitalized patients with bacterial infection were selected.[8-117] On reviewing these abstracts, 21 articles[97-117] that prospectively and simultaneously evaluated PCT and CRP were identified. Another article[118] was found after searching the bibliographies and other related information sources, including textbooks. On detailed review of these 22 articles, 12 of them were deemed appropriate for the meta-analysis.[106-117] Four of the 22 studies were excluded [100, 102-104] because study design was not geared towards the evaluation of the role of PCT and CRP as diagnostic markers of infection, and other outcomes such as prognosis, mortality or PCT kinetics was evaluated. Six other studies were excluded because the study population and data extraction was not clear,[105, 118] the study population was an extension of another published study,[97, 98, 101] or because no control group was evaluated.[99] Whenever possible, authors were contacted and asked to verify the data extracted from the original article. They were also asked to provide any available supplementary information pertaining to the criteria used for diagnosing infection. Results of each individual study included in the present meta-analysis derived from their 2 by 2 tables are presented in Tables 1 through 4.

The methodological evaluation of study quality is presented in Table 5. The average quality index was 62/101. When evaluating the study protocols, patient selection was always well described and half of the studies included consecutive patients. Test definition, description

and value were adequately described in most of the studies. Assays were blindly performed, but there was no blinding when samples were drawn from the patients. The accuracy of the tests was calculated in all studies, largely by constructing a ROC curve. No description was available on whether the statistician who performed the analyses was blinded to the diagnosis. Results were presented in a non-uniform way among the included studies. There were a total of 324 items rated to evaluate the quality of the studies. Complete agreement between reviewer scores was seen in 86.4% of the items (280/324); in 12.7% (41/324) there was agreement between two reviewers, and complete disagreement was observed in less than 1% (3/324).

In all included studies PCT was measured by an immuno-luminometric assay (ILMA) with the commercially available LUMItest PCT (distributed by BRAHMS Diagnostica GmbH, Berlin, Germany). However, CRP concentrations were determined using several different techniques and assays. They were: a laser nephelometric technique[101] (BN 100, Medgenix Diagnostics, Fleurius, Belgium),[106, 111] Image analyser, Beckman,[107] immunonephelometric method (BNA analyser, Behring Werke AG, Marburg, Germany),[112] enzymatic heterogeneous sandwich immunoassay (Vitros 950 analyser; Johnson and Johnson, Rochester, New York, USA),[108] EMIT C-reactive protein assay (E. Merck Diagnostica, Zürich, Switzerland),[110] Vitor 9501 RC System, Ortho-Clincal-Diagnostics GmbH, Neckargemünd, Germany[114] or direct immunotrubidimetry (Tina-Quant™, Boehringer Mannnheim, Germany).[116]

Bacterial infections were mainly determined by isolation of pathogen from blood and/or other sterile sites, although characteristic clinical and/or radiological presentation was also

used for the diagnosis. Viral culture and anti-viral or anti-bacterial antibody titers were used in some studies to confirm an infectious diagnosis. Biopsy and autopsy were rarely performed. Estimates of sensitivity and specificity of the different tests evaluated are shown in Tables 1 through 4. One study[108] had three groups of patients (bacterial infections, viral infections and non-infective causes of inflammation) and was analyzed in both groups presented below.

The SROC curves for PCT and CRP are plotted over the domain of TPR and FPR in Figure 1 for 10 studies (905 patients) included in the meta-analysis that evaluated PCT and CRP as diagnostic markers for bacterial infections compared with non-infective causes of inflammation. The SROC curve provides evidence on the individual contribution of each study to the regression analysis. PCT has significantly higher accuracy as compared to CRP in the discrimination between bacterial infections and non-infective causes of inflammation. Pooled sensitivity for PCT was 0.88 [95% CI 0.80 – 0.93] versus 0.75 [95% CI 0.62 – 0.84] for CRP. The difference in sensitivities was 0.13 (i.e. 13%) [95% CI 0.08 – 0.17], $p < 0.05$, therefore significant. Pooled specificity for PCT was also higher than the one for CRP: 0.81 [95% CI 0.67 – 0.90] versus 0.67 [95% CI 0.56 – 0.77], respectively. The difference in specificities was 0.14 (i.e. 14%) [95% CI 0.08 – 0.20], $p < 0.05$, therefore significant. This was confirmed on calculation of the Q values, which was higher for PCT (Q = 0. 82 [95% CI 0.64 – 0.99]) than that for CRP (Q = 0. 73 [95% CI 0.64 – 0.82]).

In Figure 2, the SROC curves for PCT and CRP are plotted over the domain of TPR and FPR for 3 studies (592 patients) included in the meta-analysis that evaluated PCT and CRP as diagnostic markers for bacterial infections compared with viral infections. PCT was also

significantly better than CRP for differentiating between bacterial and viral infections. Pooled sensitivity for PCT was 0.92 [95% CI 0.86 – 0.95], compared to 0.86 [95% CI 0.65 – 0.95] for CRP. The difference in sensitivities was 0.06 (i.e. 6%) [95% CI 0.005 – 0.11], $p < 0.05$, therefore significant. Pooled specificities were however comparable: PCT 0.73 [95% CI 0.42 – 0.91] versus CRP 0.70 [95% CI 0.19 – 0.96]. The difference in specificities was 0.03 (i.e. 3%) [95% CI -0.04 – 0.1], $p > 0.05$, therefore not significant. The Q values calculated from the curves were higher for PCT (Q = 0. 89 [95% CI 0.82 – 0.96]) than that for CRP (Q = 0. 83 [95% CI 0.81 – 0.85]), suggesting that in terms of overall accuracy, PCT is better than CRP when differentiating between bacterial and viral infections.

DISCUSSION

Early identification of bacterial infections is still a challenge for clinicians. It usually requires bacterial culture results for the definitive diagnosis, which may take up to at least 48 hours to be available. Identification of an early marker would therefore be extremely useful. Based on our systematic review and meta-analysis, we observed that PCT was, in general, a more accurate marker for bacterial infection than CRP. This was observed both when differentiating between bacterial infections and non-infective causes of inflammation and for differentiating between bacterial and viral infections.

PCT appears to be a promising marker. Under physiologic conditions, PCT is derived from the preprocalcitonin, secreted by the C-cells of the thyroid in response to hypercalcemia.[4] The mechanism proposed for PCT production following inflammation and its role are still not completely known. It is believed that PCT is produced by the liver[119] and by peripheral blood mononuclear cells,[120] modulated by lipopolysaccharides and sepsis-related cytokines. Following stimulation, PCT secretion begins within 4 h, peaks at 8 h, remains elevated at 24 h[119, 121, 122] and clears when the insult appears to be under control.[123] In addition, the kinetics of PCT are very stable. The assay is relatively easy to perform and the test result is available within two hours, permitting inclusion of the results in short-term clinical decision making. The cost of the test is moderate (approximately US$ 10).[107]

PCT concentration seems to correlate with severity of disease, with levels higher in patients with severe sepsis than in those with sepsis alone.[49, 124] PCT concentration also seems to

correlate with severity of organ dysfunction, as defined by different scoring systems, such as SOFA (sepsis-related organ failure assessment),[125] and APACHE II (acute physiology and chronic health evaluation II) or survival.[110, 116, 126] In a baboon sepsis model, PCT concentrations were significantly lower in survivors than in non-survivors.[127] These data suggest that serum PCT could therefore be used not only to diagnose, but also to monitor disease activity in patients with sepsis, severe sepsis and septic shock. Continuously increasing plasma PCT levels usually indicate that the systemic inflammation has not subsided, the infection is not under control and/or the therapeutic measures are not effective. These patients are more likely to have a poorer prognosis.[45, 128] Interestingly, PCT may also have a non-beneficial effect; *in vivo* experiments in hamster endotoxin shock models showed that PCT administered to septic animals increased mortality and that PCT antiserum protected the animals from the lethal effects of sepsis.[129] The reasons for this are unclear.

CRP is frequently used to diagnose bacterial infections, especially in European countries.[37] CRP is synthesized by the liver, mainly in response to IL-6, but also in response to TNF-α and IL-1b. IL-6 and IL-1 are cytokines produced not only during infection, but also in many types of inflammation such as vasculitis, rheumatoid arthritis, nephritis, etc.[130] It is thought that CRP rises nonspecifically whenever an inflammatory process is present, and often will not or cannot further increase if the condition becomes more severe.[107] Following stimulation, secretion starts within 4 - 6 h, doubling every 8 h but peaking only after 36 h. It functions by binding to polysaccharides in bacteria, fungi and parasites and activating the classical complement pathway. Recently, CRP has been shown to predict incidents of myocardial infarction, stroke, peripheral arterial disease, and sudden cardiac death.[130] The

assay for CRP is easy to perform, often automated and has a relatively low cost (approximately US$ 5).[107]

We must underline some strengths of this systematic review. Decisions on inclusion or exclusion were based on consensus of three independent reviewers, giving more credibility to the results. There was a high agreement rate among reviewers in every step of this meta-analysis. Authors from individual papers were contacted and asked to confirm or correct the information retained from the original paper. The response rate from the contacting authors was notably high (66.7%), giving additional strength to the data analyzed.

The validity of a clinical trial depends on appropriate allocation, interpretation and application of the results, handling of withdrawals, blinding and statistical analysis.[6] As would be expected, none of the studies included in this review were completely free from all potential biases and limitations. Nevertheless, most of them were of good quality. All the studies selected involved prospective data collection, good description of diagnosis of infection and statistical analysis. Half of the studies recruited their patients consecutively, with minimal withdrawal from the study, thereby minimizing selection bias. Few studies reported information on blinding, which could potentially have altered the trustworthiness of the data.

In the studies included in this meta-analysis, PCT and CRP samples were drawn at admission or at the moment infection was suspected, together with cultures or other tests deemed appropriate to diagnose infection. Therefore, there was no verification bias, which could exist when the decision to perform the reference test (in this case cultures) is based on the

result of the test under examination (PCT and CRP). Description of diagnostic criteria were identified in the papers and confirmed by contacting the authors. In all studies, patients were allocated to the infected or non-infected group without prior knowledge of PCT and CRP results, minimizing investigator bias that could occur when investigators are not blinded to the results of the study and reference tests. Spectrum bias was also insignificant because of the nature of this analysis. This bias occurs when diagnostic accuracy is examined by comparing test results among patients known to have disease (bacterial infection) and among a group of normal subjects (case control study) as opposed to a clinical population covering the spectrum of causal agents (viral infections or non-infective causes of inflammation). In most cases, these biases could lead to an inflation of the accuracy of the test or criteria under study.

A large spectrum of the population was covered in the meta-analysis, which spanned 30 years of data and allowed the generalization of the results. Studies included 46 neonates, 638 children and 702 adults in different areas of the hospital; about half of them were in intensive care units, both pediatric and adult units. 905 patients were included in the analysis that compared patients with bacterial infections and non-infective causes of inflammation, and 592 patients were included in the comparison of bacterial and viral infections.

The purpose of conducting a statistical analysis of the extracted data is to determine a summary estimate of effect. In the meta-analysis technique, pooling of results across studies or averaging sensitivity and specificity causes underestimation of test performance because the relationship between sensitivity and specificity is not linear. However, the underestimation is no more than 2% for each parameter.[131] We selected a random effects

model which assumes that the studies included in the meta-analysis belong to a random sample of a universe of such studies, since both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis.

This systematic review has some limitations. The lag time between the beginning of symptoms and study entry was not provided in most of the studies. It is thus possible that patients were in different stages of the disease. However, considering that the patients were not previously treated for bacterial infection, this time difference should not modify the diagnostic accuracy of the tests. This meta-analysis does not evaluate serial measurements of PCT or CRP for the diagnosis of bacterial infection; it evaluates a one-time measurement at the time infection was suspected. Some classification bias was possible when allocating patients to the infected (bacterial or viral) or non-infected groups. Even in the face of positive culture results, there is not always enough evidence to discriminate between infection and colonization.

The accuracy of diagnostic markers can depend on the specific methods used for their measurement. Invariably, PCT measurements were performed using the commercially available antibody system (BRAHMS, Hennigsdorf, Germany). This assay is specific and uses two antibodies that bind to two sites (calcitonin and katacalcin) of the procalcitonin molecule thus ruling out cross-reactivity. The reported detection limit of the assay is 0.1 ng/ml while procalcitonin levels of healthy subjects are usually undetectable.[132] However, methods of measurement of CRP largely varied among the 12 included studies; 8 different methods were used for the CRP quantification. The implications of this variability are

unknown to the final result of this meta-analysis. However, each study was included using its own best cutoff value and the linear regression methods used in the analysis account for possible threshold differences between studies.

When performing a literature review, one must consider some degree of publication bias. It is realistic to speculate that studies have a higher likelihood of being published when they are either of good quality or when they show encouraging results.[133] Such a selective publication policy, particularly that based on encouraging results, could lead to an inflation of the associations that were found, but there is no method to control for this bias when a systematic review is comparing the predictive value of two tests.

This meta-analysis does provide a reasonable comparison between PCT and CRP and allows the investigator or clinician to decide on the choice of the most appropriate test suitable for his or her clinical setting. With this study, we can conclude that the overall accuracy of PCT is higher than that of CRP both for differentiating between bacterial and viral infections and between bacterial infections and other non-infective causes of systemic inflammation. We therefore think that PCT is a good marker for bacterial infection and could be considered for widespread use in clinical practice. However, the usefulness of these tests remains to be determined.

ACKNOWLEDGEMENTS

We gratefully thank Chantal Roy for expert technical assistance. This work was financed by the Canadian Institutes of Health Research, Grant # MSP-13278.

REFERENCES

1. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest.* Jun 1992;101(6):1644-1655.
2. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med.* Apr 17 2003;348(16):1546-1554.
3. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med.* Jul 2001;29(7):1303-1310.
4. Whicher J, Bienvenu J, Monneret G. Procalcitonin as an acute phase marker. *Ann Clin Biochem.* 2001;38(Pt 5):483-493.
5. Gottfried EL, Wagar EA. Laboratory testing: a practical guide. *Dis Mon.* Aug 1983;29(11):1-41.
6. Chalmers TC, Smith H, Jr., Blackburn B, et al. A method for assessing the quality of a randomized control trial. *Control Clin Trials.* May 1981;2(1):31-49.
7. Moses LE, Shapiro D, Littenberg B. Combining independent studies of a diagnostic test into a summary ROC curve: data-analytic approaches and some additional considerations. *Stat Med.* Jul 30 1993;12(14):1293-1316.
8. Benitz WE, Han MY, Madan A, Ramachandra P. Serial serum C-reactive protein levels in the diagnosis of neonatal infection. *Pediatrics.* 1998;102(4):E41.

9. Berland M, Mein-Bottini M, Charvet PY, Revol A, Drai J, Pic JC. [The significance of the level of C-reactive protein in gynecologic infections]. *Rev Fr Gynecol Obstet.* 1990;85(10):539-544.

10. Borschsenius F, Bruun JN, Michaelsen TE, Tonjun T. Serum C-reactive protein in systemic infections due to Neisseria meningitidis. *NIPH Ann.* 1986;9(1):15-21.

11. Cadwgan AM, Watson WA, Laing RB, MacKenzie AR, Smith CC, Douglas JG. Presenting clinical features and C-reactive protein in the prediction of a positive stool culture in patients with diarrhoea. *J Infect.* 2000;41(2):159-161.

12. Chiu CH, Lin TY, Bullard MJ. Identification of febrile neonates unlikely to have bacterial infections. *Pediatr Infect Dis J.* 1997;16(1):59-63.

13. Cobben JM, Cornelissen PJ, Haverkorn M, Waelkens JJ. [CRP versus BSE in pediatrics. How good is a diagnostic test?]. *Tijdschr Kindergeneeskd.* 1990;58(5):169-174.

14. Cox ML, Rudd AG, Gallimore R, Hodkinson HM, Pepys MB. Real-time measurement of serum C-reactive protein in the management of infection in the elderly. *Age Ageing.* 1986;15(5):257-266.

15. Dev D, Wallace E, Sankaran R, et al. Value of C-reactive protein measurements in exacerbations of chronic obstructive pulmonary disease. *Respir Med.* 1998;92(4):664-667.

16. Diculencu D, Miftode E, Turcu T, Buiuc D. [The value of C-reactive protein for the differentiation of bacterial meningitis from viral meningitis]. *Rev Med Chir Soc Med Nat Iasi.* 1995;99(1-2):144-150.

17. Dofferhoff AS, Bom VJ, de Vries-Hospers HG, et al. Patterns of cytokines, plasma endotoxin, plasminogen activator inhibitor, and acute-phase proteins during the treatment of severe sepsis in humans. *Crit Care Med.* 1992;20(2):185-192.

18. Fassbender K, Pargger H, Muller W, Zimmerli W. Interleukin-6 and acute-phase protein concentrations in surgical intensive care unit patients: diagnostic signs in nosocomial infection. *Crit Care Med.* 1993;21(8):1175-1180.

19. Flores JM, Jimenez PI, Rincon D, et al. [C reactive protein as marker of infection among patients with severe closed trauma]. *Enferm Infecc Microbiol Clin.* 2001;19(2):61-65.

20. Gustafsson R, Johnsson P, Algotsson L, Blomquist S, Ingemansson R. Vacuum-assisted closure therapy guided by C-reactive protein level in patients with deep sternal wound infection. *J Thorac Cardiovasc Surg.* May 2002;123(5):895-900.

21. Hogarth MB, Gallimore R, Savage P, et al. Acute phase proteins, C-reactive protein and serum amyloid A protein, as prognostic markers in the elderly inpatient. *Age Ageing.* 1997;26(2):153-158.

22. Hogevik H, Olaison L, Andersson R, Alestig K. C-reactive protein is more sensitive than erythrocyte sedimentation rate for diagnosis of infective endocarditis. *Infection.* 1997;25(2):82-85.

23. Icard P, Fleury JP, Regnard JF, et al. Utility of C-reactive protein measurements for empyema diagnosis after pneumonectomy. *Ann Thorac Surg.* 1994;57(4):933-936.

24. Katz JA, Mustafa MM, Bash RO, Cash JV, Buchanan GR. Value of C-reactive protein determination in the initial diagnostic evaluation of the febrile, neutropenic child with cancer. *Pediatr Infect Dis J.* 1992;11(9):708-712.

25. Korppi M, Kroger L. C-reactive protein in viral and bacterial respiratory infection in children. *Scand J Infect Dis.* 1993;25(2):207-213.

26. Korppi M, Heiskanen-Kosma T, Leinonen M. White blood cells, C-reactive protein and erythrocyte sedimentation rate in pneumococcal pneumonia in children. *Eur Respir J.* 1997;10(5):1125-1129.

27. Krediet T, Gerards L, Fleer A, van Stekelenburg G. The predictive value of CRP and I/T-ratio in neonatal infection. *J Perinat Med.* 1992;20(6):479-485.

28. Ksssler A, Grunert C, Wood WG. The limitations and usefulness of C-reactive protein and elastase-alpha 1-proteinase inhibitor complexes as analytes in the diagnosis and follow-up of sepsis in newborns and adults. *Eur J Clin Chem Clin Biochem.* 1994;32(5):365-368.

29. Kunzig HJ, Schmidt-Rohde P, Kramer M, Prinz H. [Acute phase proteins (C-reactive protein, orosomucoid, haptoglobin)-- specific markers in the diagnosis of inflammatory adnexal diseases]. *Geburtshilfe Frauenheilkd.* 1985;45(12):881-886.

30. Marchand A, Van Lente F, Galen RS. The assessment of laboratory tests in the diagnosis of acute appendicitis. *Am J Clin Pathol.* 1983;80(3):369-374.

31. Matson A, Soni N, Sheldon J. C-reactive protein as a diagnostic test of sepsis in the critically ill. *Anaesth Intensive Care.* 1991;19(2):182-186.

32. Miller PR, Munn DD, Meredith JW, Chang MC. Systemic inflammatory response syndrome in the trauma intensive care unit: who is infected? *J Trauma.* 1999;47(6):1004-1008.

33. Mustard RA, Jr., Bohnen JM, Haseeb S, Kasina R. C-reactive protein levels predict postoperative septic complications. *Arch Surg.* 1987;122(1):69-73.

34. Ortqvist A, Hedlund J, Wretlind B, Carlstrom A, Kalin M. Diagnostic and prognostic value of interleukin-6 and C-reactive protein in community-acquired pneumonia. *Scand J Infect Dis.* 1995;27(5):457-462.

35. Parnaby RM, Eaton SE, Shafi MS, Bell D. The value of serum C-reactive protein levels as a marker of sepsis in intensive care unit patients. *Clin Intensive Care.* 1994;5(3):106-113.

36. Peltola HO. C-reactive protein for rapid monitoring of infections of the central nervous system. *Lancet.* 1982;1(8279):980-982.

37. Povoa P. C-reactive protein: a valuable marker of sepsis. *Intensive Care Med.* Mar 2002;28(3):235-243.

38. Pulliam PN, Attia MW, Cronan KM. C-reactive protein in febrile children 1 to 36 months of age with clinically undetectable serious bacterial infection. *Pediatrics.* 2001;108(6):1275-1279.

39. Ruiz-Laiglesia FJ, Torrubia-Perez C, Amiguet-Garcia JA, Fiteni-Mera I. [Value of C-reactive protein for detecting bacteremia in febrile patients]. *Presse Med.* 1996;25(24):1105-1108.

40. Sheldon J, Riches P, Gooding R, Soni N, Hobbs JR. C-reactive protein and its cytokine mediators in intensive-care patients. *Clin Chem.* 1993;39(1):147-150.

41. Shortland DB, MacFadyen U, Elston A, Harrison G. Evaluation of C. reactive protein values in neonatal sepsis. *J Perinat Med.* 1990;18(3):157-163.

42. van den Broek PJ, Radder AM, Hermans J. [The significance of body temperature, sedimentation, C-reactive protein, leukocyte count and differential for the diagnosis of infections in an internal medicine emergency department]. *Ned Tijdschr Geneesk.* 1990;134(52):2536-2540.

43. Vanlieferinghen P, Peigue-Lafeuille H, Gaulme J, Amram S, Gentou C, Raynaud EJ. [C-reactive protein and orosomucoid determinations in a neonatal pathology unit]. *Pediatrie.* 1986;41(2):121-125.

44. Virkki R, Juven T, Rikalainen H, Svedstrom E, Mertsola J, Ruuskanen O. Differentiation of bacterial and viral pneumonia in children. *Thorax.* 2002;57(5):438-441.

45. Adamik B, Kubler-Kielb J, Golebiowska B, Gamian A, Kubler A. Effect of sepsis and cardiac surgery with cardiopulmonary bypass on plasma level of nitric oxide metabolites, neopterin, and procalcitonin: correlation with mortality and postoperative complications. *Intensive Care Med.* 2000;26(9):1259-1267.

46. Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infection. *Lancet.* 1993;341(8844):515-518.

47. Boeken U, Feindt P, Micek M, Petzold T, Schulte HD, Gams E. Procalcitonin (PCT) in cardiac surgery: diagnostic value in systemic inflammatory response syndrome (SIRS), sepsis and after heart transplantation (HTX). *Cardiovasc Surg.* 2000;8(7):550-554.

48. Chiesa C, Panero A, Rossi N, et al. Reliability of procalcitonin concentrations for the diagnosis of sepsis in critically ill neonates. *Clin Infect Dis.* 1998;26(3):664-672.

49. de Werra I, Jaccard C, Corradin SB, et al. Cytokines, nitrite/nitrate, soluble tumor necrosis factor receptors, and procalcitonin concentrations: comparisons in patients with septic shock, cardiogenic shock, and bacterial pneumonia. *Crit Care Med.* 1997;25(4):607-613.

50. Harbarth S, Holeckova K, Froidevaux C, et al. Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis. *Am J Respir Crit Care Med.* 2001;164(3):396-402.

51. Kuse ER, Langefeld I, Jaeger K, Kulpmann WR. Procalcitonin in fever of unknown origin after liver transplantation: a variable to differentiate acute rejection from infection. *Crit Care Med.* 2000;28(2):555-559.

52. Marc E, Menager C, Moulin F, et al. [Procalcitonin and viral meningitis: reduction of unnecessary antibiotics by measurement during an outbreak]. *Arch Pediatr.* 2002;9(4):358-364.

53. Ruokonen E, Ilkka L, Niskanen M, Takala J. Procalcitonin and neopterin as indicators of infection in critically ill patients. *Acta Anaesthesiol Scand.* 2002;46(4):398-404.

54. Whang KT, Steinwald PM, White JC, et al. Serum calcitonin precursors in sepsis and systemic inflammation. *J Clin Endocrinol Metab.* 1998;83(9):3296-3301.

55. Arber C, Passweg JR, Fluckiger U, et al. C-reactive protein and fever in neutropenic patients. *Scand J Infect Dis.* 2000;32(5):515-520.

56. Boeken U, Feindt P, Zimmermann N, Kalweit G, Petzold T, Gams E. Increased preoperative C-reactive protein (CRP)-values without signs of an infection and complicated course after cardiopulmonary bypass (CPB)- operations. *Eur J Cardiothorac Surg.* 1998;13(5):541-545.

57. Bohuon C, Assicot M, Raymond J, Gendrel D. [Procalcitonin, a marker of bacterial meningitis in children]. *Bull Acad Natl Med.* 1998;182(7):1469-1475.

58. Chiba Y, Muraoka R, Ihaya A, et al. Postoperative inflammatory reactions of impregnated Dacron grafts. *Surg Today.* 1999;29(11):1225-1228.

59. Claeys R, Vinken S, Spapen H, et al. Plasma procalcitonin and C-reactive protein in acute septic shock: clinical and biological correlates. *Crit Care Med.* 2002;30(4):757-762.

60. Del Beccaro MA, Mendelman PM, Inglis AF, Richardson MA, Duncan NO, Shugerman RP. Acute-phase reactants and acute bacterial otitis media. *Am J Dis Child.* 1992;146(9):1037-1039.

61. Dinant GJ, de Kock CA, van Wersch JW. Diagnostic value of C-reactive protein measurement does not justify replacement of the erythrocyte sedimentation rate in daily general practice. *Eur J Clin Invest.* 1995;25(5):353-359.

62. Eriksson S, Olander B, Pira U, Granstrom L. White blood cell count, leucocyte elastase activity, and serum concentrations of interleukin-6 and C-reactive protein after open appendicectomy. *Eur J Surg.* 1997;163(2):123-127.

63. Fransen EJ, Maessen JG, Elenbaas TW, van Aarnhem EE, van Dieijen-Visser MP. Enhanced preoperative C-reactive protein plasma levels as a risk factor for postoperative infections after cardiac surgery. *Ann Thorac Surg.* 1999;67(1):134-138.

64. Gervaix A, Galetto-Lacour A, Gueron T, et al. Usefulness of procalcitonin and C-reactive protein rapid tests for the management of children with urinary tract infection. *Pediatr Infect Dis J.* 2001;20(5):507-511.

65. Hatherill M, Tibby SM, Turner C, Ratnavel N, Murdoch IA. Procalcitonin and cytokine levels: relationship to organ failure and mortality in pediatric septic shock. *Crit Care Med.* 2000;28(7):2591-2594.

66. Heiskanen-Kosma T, Korppi M. Serum C-reactive protein cannot differentiate bacterial and viral aetiology of community-acquired pneumonia in children in primary healthcare settings. *Scand J Infect Dis.* 2000;32(4):399-402.

67. Herrmann W, Ecker D, Quast S, Klieden M, Rose S, Marzi I. Comparison of procalcitonin, sCD14 and interleukin-6 values in septic patients. *Clin Chem Lab Med.* 2000;38(1):41-46.

68. Hjortdahl P, Landaas S, Urdal P, Steinbakk M, Fuglerud P, Nygaard B. C-reactive protein: a new rapid assay for managing infectious disease in primary health care. *Scand J Prim Health Care.* 1991;9(1):3-10.

69. Huber-Spitzy V, Arocker-Mettinger E, Herkner K, et al. Diagnosis and therapy of bacterial endophthalmitis, and serum levels of inflammation markers. *Infection.* 1992;20(3):122-127.

70. Juffrie M, Meer GM, Hack CE, et al. Inflammatory mediators in dengue virus infection in children: interleukin-6 and its relation to C-reactive protein and secretory phospholipase A2. *Am J Trop Med Hyg.* 2001;65(1):70-75.

71. Kornman L, Jacobs V, Hodgson RP, et al. Chorioamnionitis: how useful is the determination of C-reactive protein? *Aust N Z J Obstet Gynaecol.* 1988;28(1):45-48.

72. Kragsbjerg P, Holmberg H, Vikerfors T. Serum concentrations of interleukin-6, tumour necrosis factor-alpha, and C-reactive protein in patients undergoing major operations. *Eur J Surg.* 1995;161(1):17-22.

73. Lembo RM, Marchant CD. Acute phase reactants and risk of bacterial meningitis among febrile infants and children. *Ann Emerg Med.* 1991;20(1):36-40.

74. Matsuo S, Tsumori M, Yamamoto Y, Takahashi H. [Clinical and laboratory correspondence to outpatients with the extreme value of C-reactive protein]. *Rinsho Byori.* 1992;40(12):1307-1311.

75. Mercer LJ, Block BS, Hajj SN. Measurement of C-reactive protein to compare ceftizoxime versus cefoxitin/doxycycline therapy for septic pelvis: a preliminary report. *Clin Ther.* 1987;10(Suppl A):59-65.

76. Mercer LJ, Hajj SN, Ismail MA, Block BS. Use of C-reactive protein to predict the outcome of medical management of tuboovarian abscesses. *J Reprod Med.* 1988;33(1 Suppl):164-167.

77. Mimoz O, Benoist JF, Edouard AR, Assicot M, Bohuon C, Samii K. Procalcitonin and C-reactive protein during the early posttraumatic systemic inflammatory response syndrome. *Intensive Care Med.* 1998;24(2):185-188.

78. Molnar Z, Szakmany T, Koszegi T, Tekeres M. Microalbuminuria and serum procalcitonin levels following oesophagectomy. *Eur J Anaesthesiol.* Jul 2000;17(7):464-465.

79. Nylen ES, Snider RH, Jr., Thompson KA, Rohatgi P, Becker KL. Pneumonitis-associated hyperprocalcitoninemia. *Am J Med Sci.* 1996;312(1):12-18.

80. Oberhoffer M, Karzai W, Meier-Hellmann A, Bogel D, Fassbinder J, Reinhart K. Sensitivity and specificity of various markers of inflammation for the prediction of tumor necrosis factor-alpha and interleukin-6 in patients with sepsis. *Crit Care Med.* 1999;27(9):1814-1818.

81. Panichi V, Migliori M, De Pietro S, et al. Plasma C-reactive protein in hemodialysis patients: a cross-sectional, longitudinal clinical survey. *Blood Purif.* 2000;18(1):30-36.

82. Pettila V, Pentti J, Pettila M, Takkunen O, Jousela I. Predictive value of antithrombin III and serum C-reactive protein concentration in critically ill patients with suspected sepsis. *Crit Care Med.* 2002;30(2):271-275.

83. Philip AG, Mills PC. Use of C-reactive protein in minimizing antibiotic exposure: experience with infants initially admitted to a well-baby nursery. *Pediatrics.* 2000;106(1):E4.

84. Pinilla JC, Hayes P, Laverty W, Arnold C, Laxdal V. The C-reactive protein to prealbumin ratio correlates with the severity of multiple organ dysfunction. *Surgery.* 1998;124(4):799-805; discussion 805-796.

85. Pinkola K, Darvas K. [Procalcitonin rapid test in surgical patients treated in the intensive care unit]. *Magy Seb.* 2001;54(6):368-370.

86. Putto A, Ruuskanen O, Meurman O, et al. C reactive protein in the evaluation of febrile illness. *Arch Dis Child.* 1986;61(1):24-29.

87. Racine A, Abribat D, Ensergueix G, Lucas Y, Poux JB. [The value of the C-reactive protein assay for the early diagnosis of neonatal infection at the maternity ward and pediatric service of a general hospital center]. *Ann Pediatr (Paris).* 1989;36(4):253-257.

88. Sabat R, Hoflich C, Docke WD, et al. Massive elevation of procalcitonin plasma levels in the absence of infection in kidney transplant patients treated with pan-T-cell antibodies. *Intensive Care Med.* 2001;27(6):987-991.

89. Singh UK, Sinha RK, Suman S, Singh VK. C-reactive protein as an indicator of complications in bacterial meningitis. *Indian Pediatr.* 1996;33(5):373-376.

90. Smith RP, Lipworth BJ, Cree IA, Spiers EM, Winter JH. C-reactive protein. A clinical marker in community-acquired pneumonia. *Chest.* 1995;108(5):1288-1291.

91. Soderquist B, Sundqvist KG, Jones I, Holmberg H, Vikerfors T. Interleukin-6, C-reactive protein, lactoferrin and white blood cell count in patients with S. aureus septicemia. *Scand J Infect Dis.* 1995;27(4):375-380.

92. Torre D, Zeroli C, Giola M, et al. Acute-phase proteins and levels of interleukin 1B, interleukin 6, tumor necrosis factor alpha, and interleukin 8 in children with pertussis. *Am J Dis Child.* 1993;147(1):27-29.

93. Unkila-Kallio L, Kallio MJ, Peltola H. The usefulness of C-reactive protein levels in the identification of concurrent septic arthritis in children who have acute hematogenous osteomyelitis. A comparison with the usefulness of the erythrocyte sedimentation rate and the white blood-cell count. *J Bone Joint Surg Am.* 1994;76(6):848-853.

94. van Langevelde P, Joop K, van Loon J, et al. Endotoxin, cytokines, and procalcitonin in febrile patients admitted to the hospital: identification of subjects at high risk of mortality. *Clin Infect Dis.* 2000;31(6):1343-1348.

95. Wanner GA, Keel M, Steckholzer U, Beier W, Stocker R, Ertel W. Relationship between procalcitonin plasma levels and severity of injury, sepsis, organ failure, and mortality in injured patients. *Crit Care Med.* 2000;28(4):950-957.

96. Yentis SM, Soni N, Sheldon J. C-reactive protein as an indicator of resolution of sepsis in the intensive care unit. *Intensive Care Med.* 1995;21(7):602-605.

97. Gendrel D, Raymond J, Assicot M, et al. Measurement of procalcitonin levels in children with bacterial or viral meningitis. *Clin Infect Dis.* 1997;24(6):1240-1242.

98. Gendrel D, Raymond J, Coste J, et al. Comparison of procalcitonin with C-reactive protein, interleukin 6 and interferon-alpha for differentiation of bacterial vs. viral infections. *Pediatr Infect Dis J.* 1999;18(10):875-881.

99. Hedlund J, Hansson LO. Procalcitonin and C-reactive protein levels in community-acquired pneumonia: correlation with etiology and prognosis. *Infection.* 2000;28(2):68-73.

100. Meisner M, Tschaikowsky K, Hutzler A, Schick C, Schuttler J. Postoperative plasma concentrations of procalcitonin after different types of surgery. *Intensive Care Med.* 1998;24(7):680-684.

101. Moulin F, Raymond J, Lorrot M, et al. Procalcitonin in children admitted to hospital with community acquired pneumonia. *Arch Dis Child.* 2001;84(4):332-336.

102. Oberhoffer M, Vogelsang H, Russwurm S, Hartung T, Reinhart K. Outcome prediction by traditional and new markers of inflammation in patients with sepsis. *Clin Chem Lab Med.* 1999;37(3):363-368.

103. Somech R, Zakuth V, Assia A, Jurgenson U, Spirer Z. Procalcitonin correlates with C-reactive protein as an acute-phase reactant in pediatric patients. *Isr Med Assoc J.* 2000;2(2):147-150.

104. Tschaikowsky K, Hedwig-Geissing M, Schiele A, Bremer F, Schywalsky M, Schuttler J. Coincidence of pro- and anti-inflammatory responses in the early phase of severe sepsis: Longitudinal study of mononuclear histocompatibility leukocyte antigen-DR expression, procalcitonin, C-reactive protein, and changes in T-cell subsets in septic and postoperative patients. *Crit Care Med.* 2002;30(5):1015-1023.

105. von Heimburg D, Stieghorst W, Khorram-Sefat R, Pallua N. Procalcitonin--a sepsis parameter in severe burn injuries. *Burns.* 1998;24(8):745-750.

106. Aouifi A, Piriou V, Bastien O, et al. Usefulness of procalcitonin for diagnosis of infection in cardiac surgical patients. *Crit Care Med.* 2000;28(9):3171-3176.

107. Enguix A, Rey C, Concha A, Medina A, Coto D, Dieguez MA. Comparison of procalcitonin with C-reactive protein and serum amyloid for the early diagnosis of bacterial sepsis in critically ill neonates and children. *Intensive Care Med.* 2001;27(1):211-215.

108. Hatherill M, Tibby SM, Sykes K, Turner C, Murdoch IA. Diagnostic markers of infection: comparison of procalcitonin with C reactive protein and leucocyte count. *Arch Dis Child.* 1999;81(5):417-421.

109. Lorrot M, Moulin F, Coste J, et al. [Procalcitonin in pediatric emergencies: comparison with C-reactive protein, interleukin-6 and interferon alpha in the differentiation between bacterial and viral infections]. *Presse Med.* 2000;29(3):128-134.

110. Muller B, Becker KL, Schachinger H, et al. Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit. *Crit Care Med.* 2000;28(4):977-983.

111. Penel N, Fournier C, Degardin M, Kouto H, N'Guyen M. [Fever and solid tumor: diagnostic value of procalcitonin and C- reactive protein]. *Rev Med Interne.* 2001;22(8):706-714.

112. Rothenburger M, Markewitz A, Lenz T, et al. Detection of acute phase response and infection. The role of procalcitonin and C-reactive protein. *Clin Chem Lab Med.* 1999;37(3):275-279.

113. Schwarz S, Bertram M, Schwab S, Andrassy K, Hacke W. Serum procalcitonin levels in bacterial and abacterial meningitis. *Crit Care Med.* 2000;28(6):1828-1832.

114. Selberg O, Hecker H, Martin M, Klos A, Bautsch W, Kohl J. Discrimination of sepsis and systemic inflammatory response syndrome by determination of circulating plasma concentrations of procalcitonin, protein complement 3a, and interleukin-6. *Crit Care Med.* 2000;28(8):2793-2798.

115. Suprin E, Camus C, Gacouin A, et al. Procalcitonin: a valuable indicator of infection in a medical ICU? *Intensive Care Med.* 2000;26(9):1232-1238.

116. Ugarte H, Silva E, Mercan D, De Mendonca A, Vincent JL. Procalcitonin used as a marker of infection in the intensive care unit. *Crit Care Med.* 1999;27(3):498-504.

117. Viallon A, Zeni F, Pouzet V, et al. Serum and ascitic procalcitonin levels in cirrhotic patients with spontaneous bacterial peritonitis: diagnostic value and relationship to pro-inflammatory cytokines. *Intensive Care Med.* 2000;26(8):1082-1088.

118. Brunkhorst FM, Wegscheider K, Forycki ZF, Brunkhorst R. Procalcitonin for early diagnosis and differentiation of SIRS, sepsis, severe sepsis, and septic shock. *Intensive Care Med.* 2000;26:S148-S152.

119. Nijsten MW, Olinga P, The TH, et al. Procalcitonin behaves as a fast responding acute phase protein in vivo and in vitro. *Crit Care Med.* 2000;28(2):458-461.

120. Oberhoffer M, Stonans I, Russwurm S, et al. Procalcitonin expression in human peripheral blood mononuclear cells and its modulation by lipopolysaccharides and sepsis-related cytokines in vitro. *J Lab Clin Med.* 1999;134(1):49-55.

121. Dandona P, Nix D, Wilson MF, et al. Procalcitonin increase after endotoxin injection in normal subjects. *J Clin Endocrinol Metab.* 1994;79(6):1605-1608.

122. Brunkhorst FM, Heinz U, Forycki ZF. Kinetics of procalcitonin in iatrogenic sepsis. *Intensive Care Med.* 1998;24(8):888-889.

123. Meisner M, Lohs T, Huettemann E, Schmidt J, Hueller M, Reinhart K. The plasma elimination rate and urinary secretion of procalcitonin in patients with normal and impaired renal function. *Eur J Anaesthesiol.* Feb 2001;18(2):79-87.

124. Al-Nawas B, Krammer I, Shah PM. Procalcitonin in diagnosis of severe infections. *Eur J Med Res.* 1996;1(7):331-333.

125. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med.* Jul 1996;22(7):707-710.

126. Lind L, Bucht E, Ljunghall S. Pronounced elevation in circulating calcitonin in critical care patients is related to the severity of illness and survival. *Intensive Care Med.* Jan 1995;21(1):63-66.

127. Redl H, Schlag G, Togel E, Assicot M, Bohuon C. Procalcitonin release patterns in a baboon model of trauma and sepsis: relationship to cytokines and neopterin. *Crit Care Med.* Nov 2000;28(11):3659-3663.

128. Meisner M, Tschaikowsky K, Palmaers T, Schmidt J. Comparison of procalcitonin (PCT) and C-reactive protein (CRP) plasma concentrations at different SOFA scores during the course of sepsis and MODS. *Crit Care (Lond).* 1999;3(1):45-50.

129. Nylen ES, Whang KT, Snider RH, Jr., Steinwald PM, White JC, Becker KL. Mortality is increased by procalcitonin and decreased by an antiserum reactive to procalcitonin in experimental sepsis. *Crit Care Med.* 1998;26(6):1001-1006.

130. Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. *Circulation.* Jan 28 2003;107(3):363-369.

131. Mitchell MD. Validation of the summary ROC for diagnostic test meta-analysis: a Monte Carlo simulation. *Acad Radiol.* Jan 2003;10(1):25-31.

132. Karzai W, Oberhoffer M, Meier-Hellmann A, Reinhart K. Procalcitonin--a new indicator of the systemic response to severe infections. *Infection.* 1997;25(6):329-334.

133. Lijmer JG, Mol BW, Heisterkamp S, et al. Empirical evidence of design-related bias in studies of diagnostic tests. *Jama.* Sep 15 1999;282(11):1061-1066.

TABLES and FIGURES

Table 1. Results derived from the 2 by 2 tables of individual studies for PCT – bacterial infections vs. non-infective causes of inflammation

	TP/FN	FP/TN	Se	95% CI	Sp	95% CI
Aouifi et al. [106]	46/2	8/41	0.96	0.85 - 0.99	0.84	0.70 - 0.92
*Enguix et al. [107]	19/3	1/23	0.86	0.64 - 0.96	0.96	0.77 - 1.00
*Hatherill et al. [108]	103/3	9/40	0.97	0.91 - 0.99	0.82	0.68 - 0.91
*Muller et al. [110]	52/3	6/40	0.95	0.84 - 0.99	0.87	0.73 - 0.95
*Penel et al. [111]	43/14	0/5	0.75	0.62 - 0.85	1.00	0.48 - 1.00
*Rothenburger et al. [112]	12/2	3/42	0.86	0.56 - 0.97	0.93	0.81 - 0.98
Selberg et al. [114]	19/5	3/6	0.79	0.57 - 0.92	0.67	0.31 - 0.91
*Suprin et al. [115]	49/6	26/14	0.89	0.77 - 0.95	0.35	0.21 - 0.52
*Ugarte et al. [116]	75/31	36/48	0.71	0.61 - 0.79	0.57	0.46 - 0.68
*Viallon et al. [117]	19/2	2/38	0.90	0.68 - 0.98	0.95	0.82 - 0.99
Total (REM Pooled)[h]			0.88	0.80 - 0.93	0.81	0.67 - 0.90

Table 2. Results derived from the 2 by 2 tables of individual studies for CRP – bacterial infections vs. non-infective causes of inflammation

	TP/FN	FP/TN	Se	95% CI	Sp	95% CI
Aouifi et al. [106]	50/33	4/10	0.60	0.49 - 0.71	0.71	0.42 - 0.90
*Enguix et al. [107]	19/4	1/22	0.83	0.61 - 0.94	0.96	0.76 - 1.00
*Hatherill et al. [108]	73/0	37/43	1.00	0.95 - 1.00	0.54	0.42 - 0.65
*Muller et al. [110]	41/9	17/34	0.82	0.68 - 0.91	0.67	0.52 - 0.79
*Penel et al. [111]	43/24	0/1	0.64	0.52 - 0.75	1.00	0.03 - 1.00
*Rothenburger et al. [112]	14/30	1/14	0.32	0.19 - 0.48	0.93	0.66 - 1.00
Selberg et al. [114]	19/9	3/2	0.68	0.48 - 0.83	0.40	0.07 - 0.83
*Suprin et al. [115]	55/5	19/14	0.92	0.81 - 0.97	0.42	0.26 - 0.61
*Ugarte et al. [116]	80/26	3/53	0.75	0.66 - 0.83	0.63	0.52 - 0.73
*Viallon et al. [117]	13/3	8/37	0.81	0.54 - 0.95	0.82	0.67 - 0.91
Total (REM Pooled)[h]			0.75	0.62 - 0.84	0.67	0.56 - 0.77

Table 3. Results derived from the 2 by 2 tables of individual studies for PCT – bacterial infections vs. viral infections

	TP/FN	FP/TN	Se	95% CI	Sp	95% CI
*Hatherill et al. [108]	103/6	9/8	0.94	0.88 - 0.98	0.47	0.24 - 0.71
Lorrot et al. [109]	126/16	36/258	0.89	0.82 - 0.93	0.88	0.83 - 0.91
*Schwarz et al. [113]	11/0	5/14	1.00	0.72 - 1.00	0.74	0.49 - 0.90
Total (REM Pooled)[h]			0.92	0.86 - 0.95	0.73	0.42 - 0.91

Table 4. Results derived from the 2 by 2 tables of individual studies for CRP – bacterial infections vs. viral infections

	TP/FN	FP/TN	Se	95% CI	Sp	95% CI
*Hatherill et al. [108]	73/2	36/12	0.97	0.90 - 1.00	0.25	0.14 - 0.40
Lorrot et al. [109]	122/30	40/244	0.80	0.73 - 0.86	0.86	0.81 - 0.90
*Schwarz et al. [113]	14/6	1/8	0.70	0.46 - 0.87	0.89	0.51 - 0.99
Total (REM Pooled)[h]			0.86	0.65 - 0.95	0.7	0.19 - 0.96

Table 5. Quality assessment of the 12 included studies

Papers [b]		Aouifi [106]	Enguix [107]	Hatherill [108]	Lorrot [109]	Muller [110]	Penel [111]	Rothenburger [112]	Schwarz [113]	Selberg [114]	Suprin [115]	Ugarte [116]	Viallon [117]
Criteria[a]	Max												
The study protocol													
Patient selection description	3	3	2	3	3	3	3	3	3	2.5	2	3	3
Number of patients seen and reject log	3	1	0	1.5	3	1.5	3	2	2	1.5	1.5	3	2.5
Withdrawals	3	0	0	3	3	0	3	0	0	0	3	3	3
Test definition	3	3	3	3	3	3	3	3	3	3	3	3	3
Gold standard used - description	3	3	3	3	3	2.5	3	1	3	2.5	3	2.5	3
Gold standard used - value	10	8.3	8.3	10	10	10	8.3	5	10	8.3	10	6.7	10
Consecutive cases	3	3	0	0	0	3	3	0	3	0	0	3	3
All test done in all patients	3	3	3	3	3	3	3	3	1.5	3	3	3	3
Blinded samples withdrawal	3	0	0	0	0	0	0	0	0	0	0	0	0
Blinded samples assays	8	8	8	8	8	8	8	8	8	8	8	8	8
Prior estimate of numbers: endpoints, difference of clinical interest α and β	3	0	0	0	0	0	0	0	0	0	0	0	0
Statistical analysis													
Evaluation on major endpoints	4	4	4	4	3	4	3	3	4	4	4	4	4
Confidence interval	3	0	3	3	3	0	0	0	3	3	0	0	0
Regression or correlation between tests	2	2	0	0	0	0	0	2	0	2	0	2	2
Rate of concordance	2	0	0	0	0	0	0	0	0	0	0	0	0
Kappa score	2	0	0	0	0	0	0	0	0	0	0	0	0
Accuracy of the test	4	4	4	4	4	4	4	4	4	4	4	4	4
SROC curve	4	4	4	4	4	4	0	4	0	4	0	4	4
Appropriate statistical tests	4	4	4	4	2.7	4	2	3.3	3.3	4	4	4	4
Statistical analysis well done	4	3.3	3.3	4	2.7	4	1.7	2.7	3.3	4	3.3	4	4
Description of withdrawals	4	0	0	4	4	0	4	0	0	0	4	4	4

Handling of withdrawals	4	0	0	4	1	0	1	0	0	0	1	1	1
Side effect discussion	3	0	3	0	0	0	0	0	0	1	0	0	1.5
Blinding of statistician or analyst	8	0	0	0	0	0	0	0	0	0	0	0	0
Presentation of results													
Dates of starting and stopping accession	2	2	0	0	2	2	2	2	2	0	2	2	2
Results of prerandomization	2	2	0	1	2	1.7	2	1	2	2	2	2	2
Timing of events	4	3.3	4	0	2	3.3	2.7	2.7	3.3	3.3	3.3	2.7	4
Total	101	60.9	56.6	66.5	66.4	61	59.7	49.7	58.4	60.1	61.1	68.9	75

Table 5. Quality assessment of the 12 included studies (cont)

Figure 1. SROC curves comparing serum PCT and CRP – bacterial infections vs. non-infective causes of inflammation

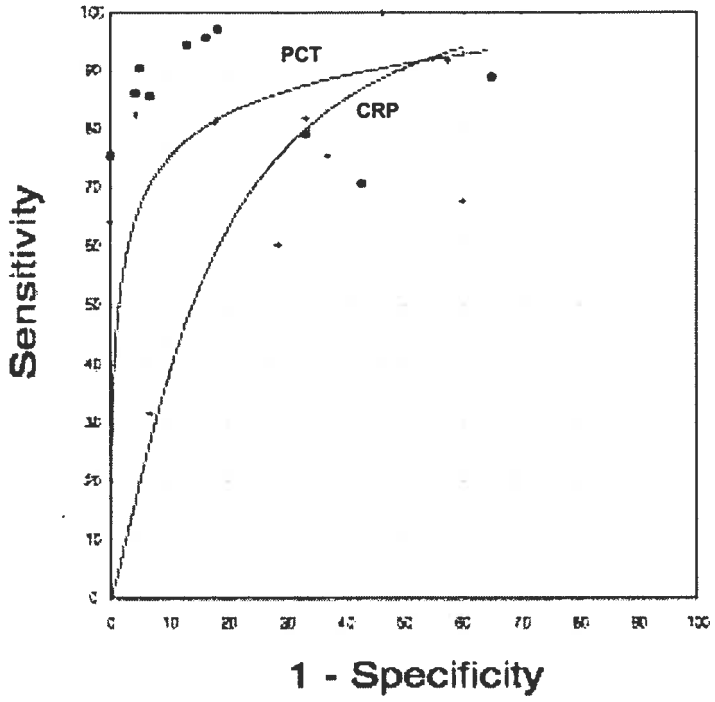
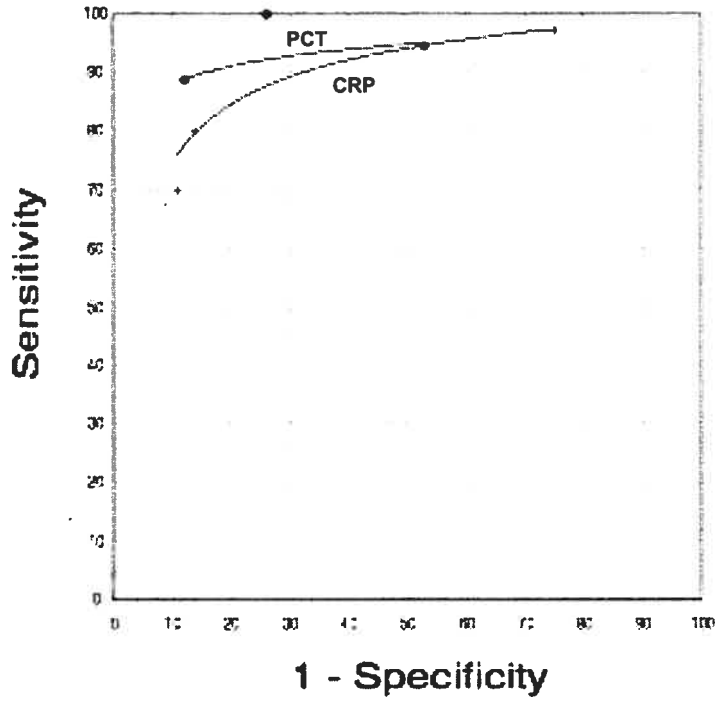


Figure 2. SROC curves comparing serum PCT and CRP – bacterial infections vs. viral infections



LEGENDS Tables

- Table 1.

TP, number of true positive patients; FN, number of false negative patients; FP number of false positive patients; TN, number of true negative patients; Se, sensitivity (Se = TP/(TP + FN)); Sp, specificity (Sp = TN (TN + FP)); 95% CI, 95% confidence interval; REM, random effects model; *data confirmed by original author

- Table 2.

See legend in Table 1

- Table 3.

See legend in Table 1

- Table 4.

See legend in Table 1

- Table 5.

[a] Questionnaire adapted from Chalmers et al.[6] For each item, results are expressed as average score of 3 reviewers.

[b] papers included in the meta-analysis

Max, maximal score; SROC, summary receiver operating characteristic

LEGENDS Figures

- Figure 1.

Each point contributing to the SROC curve represents one study: *circles*, PCT; $^{+}$, CRP

- Figure 2.

Each point contributing to the SROC curve represents one study: *circles*, PCT; $^{+}$, CRP

Chapter III

Discussion and Conclusion

Study identification, selection and inclusion in this meta-analysis

Study identification. Two online searches of the National Library of Medicine MEDLINE database were performed using the PubMed search engine. The searches covered from January 1, 1970 through May 30, 2002. The search was completed on June, 2001. The search combined medical subject headings (MeSH) in five different categories: (1) type of study, (2) site of the study, (3) subjects, (4) test and (5) disease, linked by AND terms. Within each category, medical subject headings were linked by OR terms. The MeSH terms used were (1) type of study (descriptive study or diagnosis or epidemiological study or meta-analysis or multicenter study or prospective or review-literature or reproducibility or test or validation); (2) site of the study (critical care or hospital or intensive care); (3) subjects (human); (4) test (C-reactive protein or interferon or interleukin or procalcitonin or white blood cell count or sedimentation) and (5) disease (infection or cross infection or hospital acquired infection or meningitis or multiple organ dysfunction syndrome or MODS or pneumonia or sepsis or septicemia or septic shock or systemic inflammatory response syndrome or SIRS).

The titles of the resulting citations (351) were scanned. The resulting set was further limited by excluding reviews, editorials, or letters. Abstracts of potentially relevant articles were then retrieved (110[17, 19, 29, 33, 34, 37, 40, 41, 54-59, 61, 64-71, 73-87, 89-104, 106-111, 113-117, 119-132, 134-162]). Additional articles were sought by scanning bibliographies in the reference sections of selected articles or review articles on diagnosis of infection, sepsis, procalcitonin and C-reactive protein. The authors of primary studies identified through literature searches were contacted by letter, or by email or both, seeking verification of the data extracted, or additional data not presented in the published study, and to enquire about knowledge of

unpublished or additional studies. Additional articles suggested by experts on the field were also reviewed (1 article[63]).

Selection of Studies, Inclusion and Exclusion Criteria, and Data Extraction. Studies that prospectively and simultaneously evaluated both PCT and CRP as diagnostic markers for bacterial infection in hospitalized patients were evaluated. Studies examining all age groups were included. Retrospective studies, reviews, animal studies and studies with incomplete data were excluded. The titles and abstracts of all pertinent articles were reviewed by three independent reviewers (LS, FG, JL) to identify potentially relevant studies. Discrepancies or disagreements, if any, on the inclusion or exclusion of studies were resolved by consensus. Whenever possible, the raw data from the articles were used to construct 2 by 2 tables. When raw data was unavailable, the tables were constructed using given measures of sensitivity and specificity. Some studies reported the sensitivity and specificity at many cutoff points. In such instances, we chose the cutoff point with the best efficiency value, which is found by dividing the sum of cases classified as true positives and true negatives by the total number of cases.[163]

Details on studies included in the meta-analysis

Aouifi et al.[54] measured PCT and CRP in 97 consecutive adults with suspected infection in the postoperative course of cardiac surgery. Fifty-four (54) were proven to have bacterial infection (17 pneumonia, 16 bacteremia, 9 mediastinitis, 12 septic shock). Serum PCT was markedly higher in patients with septic shock (96.98 ng/mL) compared with a moderate increase in patients with pneumonia (4.85 ng/mL) and bacteremia (3.57 ng/mL). There was a low level increase in patients without infection (0.41 ng/mL). Surprisingly, patients with mediastinitis had low PCT (0.80 ng/mL). They found a threshold of 1 ng/mL for prediction of infection, with a sensitivity of 85% and specificity of 95%; positive predictive value of 96% and negative predictive value of 84%. Serum CRP was high in all patients, without intergroup difference. For prediction of infection with CRP, a value of 50 mg/L was sensitive (84%) but poorly specific (40%). They concluded that PCT is highly sensitive and specific for the diagnosis of septic shock in postoperative patients that are not receiving antibiotics.

Enguix et al.[73] evaluated PCT and CRP as diagnostic markers of bacterial sepsis in 46 critically ill neonates. Twenty-six (26) were confirmed to have sepsis. With a PCT cutoff value of 6.1 ng/mL, they found 98.6% of sensitivity and 88.9% of specificity, while with a CRP cutoff of 23 mg/L, they found 95.8% of sensitivity and 83.6% of specificity. They concluded that in critically ill neonates, PCT concentration is a better diagnostic marker of sepsis than CRP. They also evaluated the value of SAA (serum amyloid), which was not found to be as good of a marker as PCT.

Hatherill et al.[80] evaluated PCT and CRP compared to leukocyte count as diagnostic markers for bacterial infection in 175 critically ill children. Forty-three (43) were non-infected controls with signs of inflammation, 14 had viral infections and 112 had bacterial infection. They found that admission PCT was significantly higher in children with septic shock (94.6 ng/mL), compared with localized bacterial infection (2.9 ng/mL), viral infection (0.8 ng/mL) and non-infected controls (0). Area under the ROC curve was 0.96 for PCT, 0.83 for CRP and 0.51 for leukocyte count. A cutoff concentration for

optimal prediction of septic shock was > 20 ng/mL for PCT and > 50 mg/L for CRP. They suggested a procalcitonin concentration of > 2 ng/mL to be useful in differentiating severe bacterial diseases in infants and children.

Lorrot et al.[97] evaluated 436 infants and children hospitalized for bacterial (162 patients) or viral infections (274 patients) and compared PCT, CRP, interleukine-6 and interferon-alpha as markers for bacterial infection. A threshold for PCT of > 1 ng/mL had a sensitivity of 78% and a specificity of 94%, while a cutoff value of > 20 mg/L for CRP had a sensitivity of 85% and a specificity of 73%. They concluded that a PCT value of 1 ng/mL or greater had better specificity, sensitivity and predictive value than CRP, IL-6 or interferon-alpha in children for distinguishing between bacterial and viral infections.

Muller et al.[33] studied 101 consecutive critically ill adults with SIRS. Bacterial sepsis was found in 58% of the cases versus 42% of non-infected controls. Serum PCT concentrations were significantly elevated only in patients with bacterial infection (sepsis, severe sepsis or septic shock). With a cutoff value of 1 ng/mL, PCT was found to be the most discriminatory laboratory variable as compared with CRP, interleukin-6, and lactate values, with an overall sensitivity of 89% and specificity of 94%. They also found that high serum PCT concentrations were associated with poor prognosis.

Penel et al.[109] evaluated PCT and CRP as diagnostic markers in 68 consecutive non-neutropenic febrile patients with solid tumors and suspected infection. Forty-three (43) patients were confirmed to have bacterial infection. There was no significant difference in the CRP levels of both groups (infected 134 mg/L vs. non-infected 154 mg/L). However, PCT was significantly higher in the infected patients (0.44 ng/mL vs. 0.26 ng/mL). With a threshold of 1 ng/mL for PCT, sensitivity was 37.2% and specificity 94.7% and with a threshold of 2 ng/mL, specificity was 100% for the diagnosis of infection.

Rothenburger et al.[162] evaluated PCT and CRP as diagnostic markers for bacterial infection following cardiopulmonary bypass in a non-infected group (43 patients) and in a bacteria-infected group (15 patients). They found PCT to be useful to differentiate

between acute phase response following cardiopulmonary bypass or local infections from systemic infections. They found a PCT threshold of 4 ng/mL combined with a CRP value of 180 mg/L to represent the best cutoff points which distinguish between acute phase response and infection. PCT sensitivity was 86% and specificity 98%, while CRP sensitivity was 100% and specificity 75%.

Schwarz et al.[119] compared PCT and CRP levels at admission of 30 adult patients with meningitis (16 bacterial and 14 non-bacterial). They also evaluated white blood count, cerebrospinal fluid leukocyte count, cerebrospinal fluid protein and lactate levels in these two populations. They found PCT (cutoff level of 0.5 ng/mL) to be the variable with the highest specificity for the diagnosis of bacterial infection (100%), despite a low sensitivity (79%). Using a CRP cutoff value of 8 mg/L, the sensitivity was 94%, but the specificity was only 57%. They concluded that PCT was a useful additional variable for distinguishing bacterial from non-bacterial meningitis.

Selberg et al.[120] prospectively evaluated PCT and CRP, together with interleukin-6, protein complement 3a and leukocyte elastase in 22 adult patients with sepsis and 11 with SIRS. They found that plasma concentrations of PCT, C3a, and IL-6 were significantly higher in patients with sepsis. With a threshold for PCT of 3.3 ng/mL, sensitivity was 86% and specificity 54%, while for a threshold of 60 mg/L for CRP sensitivity was 86%, but specificity was only 18%. They concluded that PCT, IL-6 and C3a were more reliable to differentiate between sepsis and SIRS than the other markers. They recommended an early assessment of patients with SIRS and suspected sepsis with PCT and C3a.

Suprin et al.[125] prospectively assessed the use of PCT and CRP for the diagnosis of bacterial infection in 77 patients with bacterial infection and 20 patients with SIRS in a medical ICU. Initial PCT and CRP levels were higher in infected patients compared to patients with SIRS, regardless of the severity of sepsis. For a PCT cutoff value of 2 ng/mL, sensitivity was 65% and specificity 70%. For a CRP cutoff value of 100 mg/L, both sensitivity and specificity were 74%. Both serum levels of PCT and CRP were significantly higher in patients with septic shock, than in those with SIRS, sepsis and severe sepsis. CRP levels, but not PCT, were higher in severe sepsis than SIRS. They

concluded that PCT and CRP had poor sensitivity and specificity for the diagnosis of infection.

Ugarte et al.[34] evaluated PCT and CRP as markers of infection in critically ill patients of a medical ICU; 111 patients with bacterial infections were compared to 79 non-infected patients. They found the best cutoff value for PCT 0.6 ng/mL and for CRP 79 mg/L. Compared with CRP, PCT had lower sensitivity (67.6% vs. 71.8%), specificity (61.3% vs. 66.6%), and area under the receiver operating characteristic curve (0.66 vs. 0.78) respectively. They concluded that neither PCT nor CRP was a good marker of infection in critically ill patients. However, they could represent a useful adjunctive parameter to identify bacterial infection and correlated well with severity of infection.

Viallon et al.[129] assessed the role of PCT and proinflammatory cytokines (TNF-α and IL-6) in the diagnosis of spontaneous bacterial peritonitis. They evaluated 21 patients with spontaneous bacterial peritonitis and 40 patients with sterile ascitic fluid in the emergency room. For the diagnosis of spontaneous bacterial peritonitis, the best markers were serum levels of PCT, with a cutoff value of 0.75 ng/mL (sensitivity 95% and specificity 98%) and ascitic fluid levels of IL-6. CRP had low sensitivity (62%) and specificity (57%). They concluded that serum PCT might become a useful marker for the diagnosis of spontaneous bacterial peritonitis in cirrhotic patients.

Details on studies excluded in this meta-analysis

Brunkhorst et al.[63] evaluated PCT, CRP, white blood count and APACHE-II score in 185 patients with suspected infection (all etiologies). They found PCT to be a good marker to differentiate patients with sepsis and severe sepsis, with sensibility of 96% and specificity of 86% (cutoff value of 2 ng/mL). Data to construct the 2 by 2 tables could not be extracted from the paper and we were unable to complete them with the original author.

Gendrel et al.[77, 78] evaluated PCT and CRP as markers for bacterial versus viral meningitis in children. They found PCT to be a better marker than CRP for the diagnosis of bacterial meningitis. One study[77] was excluded from the meta-analysis because the population evaluated was a part of the populations in another study already included[47] and no complete data was available. The other study[78] was excluded because it was a part of another study already included[47], with repeat data.

Hedlund et al.[82] prospectively evaluated PCT and CRP as indicators of etiology and prognosis in patients admitted for community-acquired pneumonia. They found that all patients had elevated CRP levels at admission (> 10 mg/L), but only 54% had elevated PCT levels (> 0.1 ng/mL). The severity of disease measured by APACHE II score was strongly associated with admission levels of PCT, but not CRP. This study was excluded because there was not a control group without bacterial infection and data extraction was not possible.

Meisner et al.[160] looked at the kinetics of PCT and CRP in the postoperative course of different types of surgery and compared normal with abnormal postoperative course, including infectious and other complications. This study was excluded because study design was not geared towards the evaluation of the role of PCT and CRP as diagnostic markers of infection.

Moulin et al.[102] evaluated PCT and CRP as markers for bacterial versus viral pneumonia in hospitalized children. They found PCT (cut-off value of 1 ng/mL) to have a better

sensitivity, specificity and greater positive and negative predictive values when compared to CRP, IL-6 or white blood count. This study was excluded from the meta-analysis because it evaluated a subgroup of patients and an extension of another study already included[47], with repeated data.

Oberhoffer et al.[41] evaluated inflammatory markers in septic patients as a prognostic indicator. They found that PCT was the better marker associated with outcome when compared with CRP, leukocyte count, and body temperature. This study was excluded because study design was not geared towards the evaluation of the role of PCT and CRP as diagnostic markers of infection, and prognosis was evaluated as outcome.

Somech et al.[124] evaluated PCT and CRP as acute markers in febrile children, but could not separate those patients into groups according to different etiologies of their illness. They found a parallel rise in PCT and CRP. The study was probably a retrospective analysis of data and study design was not geared towards the evaluation of the role of PCT and CRP as diagnostic markers of infection.

Von Heimburg et al.[131] evaluated the correlation between admission levels of PCT with CRP, sepsis, burn size, inhalation injury and mortality in severely burned patients. They found PCT levels to correlate with severity of injury and septic complications. This study was excluded because data extraction was not possible.

Tschaikowsky et al.[161] determined the time course of histocompatibility leukocyte antigen (HLA)-DR expression in peripheral blood mononuclear cells and their relationship to markers of inflammation, organ function, and outcome during severe sepsis. This study was excluded because study design was not geared towards the evaluation of the role of PCT and CRP as diagnostic markers of infection.

Evaluating quality of the studies

The methodology for designing and conducting studies of diagnostic accuracy is still maturing and there is an understanding that the sources of variability and the potential bias is growing. We evaluated the methodological quality of the included studies by applying the criteria for assessing randomized clinical trials design-related bias described by Chalmers et al.[164] Four aspects of each study were evaluated for the assessment of the quality of the research: (1) basic descriptive material; (2) study protocol; (3) analysis of the data and (4) data potentially useful for combination of several randomized clinical trials results. The latter three aspects were graded and a score was awarded to each item under each aspect. Subsequently, an overall quality index for each study was obtained by adding up the item scores and dividing by the total possible score. Rate of agreement among the three independent reviewers was calculated for each item and expressed as a percentage.

In 1996 the Cochrane diagnostic and screening test methods working group updated the "Cochrane Methods Group On Systematic Review Of Screening And Diagnostic Tests: Recommended Methods.[165] In 1999 the Quality of Reporting of Meta-analyses (QUOROM) conference was convened to address standards for improving the quality of reporting of meta-analyses of clinical randomised controlled trials (RCTs).[166] In the same year, at the Cochrane colloquium meeting, the Cochrane diagnostic and screening test methods working group discussed the low methodological quality and substandard reporting of diagnostic test evaluations. The working group felt that the first step towards correcting these problems was to improve the quality of reporting of diagnostic studies. The working group aimed to develop a checklist of items that should be included in the reported of a study of diagnostic accuracy, proposing the STARD (*Standards for Reporting of Diagnostic Accuracy*) statement to improve the quality of reporting of studies of diagnostic accuracy.[167]

The STARD statement consists of a checklist of 25 items and flow diagram that authors can use to ensure that all relevant information is present. The proposed items in the checklist are:[168]

1) identify the article as study of diagnostic accuracy (recommended MeSH heading "sensitivity and specificity")
2) state the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups
3) describe the study population: the inclusion and exclusion criteria, setting and location where data were collected
4) describe participant recruitment: was recruitment based on presenting symptoms, results from previous tests, or the fact that the participants had received the index tests or the reference standard
5) describe participant sampling: was the study population a consecutive series of participants defined by the selection criteria in items 3 and 4? If not, specify how participants were further selected
6) describe data collection: was data collection planned before the index test and reference standard were performed (prospective study) or after (retrospective study)
7) describe the reference standard and its rationale
8) describe technical specifications of material and methods involved including how and when measurements were taken, and/or cite references for index tests and reference standard
9) describe definition of and rationale for the units, cutoffs and/or categories of the results of the index tests and the reference standard
10) describe the number, training and expertise of the persons executing and reading the index tests and the reference standard
11) describe whether of not the readers of the index tests and reference standard were blind (masked) to the results of the other test and describe any other clinical information available to the readers
12) describe methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g., 95% confidence interval)
13) describe methods for calculating test reproducibility, if done
14) report when study was done, including beginning and ending dates of recruitment

15) report clinical and demographic characteristics of the study population (e.g., age, sex, spectrum of presenting symptoms, co-morbidity, current treatments, recruitment centers)
16) report the number of participants satisfying the criteria for inclusion that did or did not undergo the index tests and/or the reference standard; describe why participants failed to receive either test (a flow diagram is strongly recommended)
17) report time interval from the index tests to the reference standard, and any treatment administered between them
18) report distribution of severity of disease (define criteria) in those with the target condition; other diagnoses in participants without the target condition
19) report a cross tabulation of the results of the index tests (including indeterminate and missing results) by the results of the reference standard; for continuous results report the distribution of the test results by the results of the reference standard
20) report any adverse events from performing the index tests or the reference standard
21) report estimates of diagnostic accuracy and measures of statistical uncertainty (e.g, 95% confidence interval)
22) report how indeterminate results, missing responses and outliers of the index tests were handled
23) report estimates of variability of diagnostic accuracy between subgroups of participants, readers or centers, if done
24) report estimates of test reproducibility, if done
25) discuss the clinical applicability of the study findings

Possible bias and validity of this meta-analysis

The present study employed a comprehensive search strategy. Formal criteria for study inclusion were defined prior to analysis of the search results. We were unable to find previous attempts to summarize the accuracy of simultaneous PCT and CRP for diagnosis of bacterial infection in the medical literature. Our results spanned three decades of diagnostic test evaluation. It is possible that there is an effect of time which results and accuracy change according to publication time. However, all included studies date from 1999 to 2001.

The present study attempted to summarize data from primary sources in the published medical literature on the diagnostic accuracy of procalcitonin and c-reactive protein for the diagnosis of bacterial infection. The studies identified represent a rather large population, including neonates, children and adults. The underlying population varied, including neonates with late sepsis, children hospitalized with febrile illnesses, critically ill children with medical illnesses, adults hospitalized with meningitis, spontaneous bacterial peritonitis, neutropenic febrile episodes in patients with solid tumors, critically ill adults with medical diseases or post operatory of cardiac heart surgery. This heterogeneity was not controlled for, since we evaluated the use of these tests as markers for bacterial infection in general. Because few studies had the same group population, a subgroup analysis was not performed since the small number of studies available conferred low power to detect such differences in accuracy.

Data were insufficient to examine other study characteristics that may have influenced study outcome, such as age of participants (pediatric vs. adult), baseline disease (medical vs. surgical or acute vs. chronic), hospital setting (wards vs. intensive care), or symptom duration. Lag-time between initiation of symptoms and diagnostic strategies were not reported in the studies. Bacterial infection, though, is usually a progressive disease that evolves with time, depending on the immune status of the patient. Therefore, unless there is a known event that might have initiated the infection (a certain procedure), this is not a variability that can be accounted for in clinical studies. Increases in duration of

illness may bias studies towards higher prevalence of proved bacterial infection. Previous treatments may also induce a bias, since they might change the spectrum of the disease. There might have been some variation in the time of diagnositc tests (PCT and CRP) and reference tests (cultures) performance in the studies included in this meta-analysis that could affect results, since not all studies reported the exact time interval between performance of these tests.

We must underline some strengths of this systematic review. Decisions on every step, from inclusion or exclusion to data extraction were based on consensus of three independent reviewers, giving more credibility to the results. There was a high agreement rate among reviewers in every step of this meta-analysis. Authors from individual papers were contacted and asked to confirm or correct the information retained from the original paper. The response rate from the contacting authors was notably high (66.7%), giving additional strength to the data analyzed.

This study has several limitations. Firstly, a question remains on the choice of diagnostic reference standard. Diagnosis of bacterial infection is not always evident; cultures are the main reference test, but they are not always positive. Methods to overcome this limitation include examining multiple data for the diagnosis of infection, such as presence of pus or bacteria per gram stain, and combining clinical and laboratorial diagnosis of bacterial infections, such as meningitis or osteomielitis. This remains an area for improvement in future studies, and consensus on standardization. Most of the studies had what were considered adequate diagnostic assessment for the reference disease status. Misclassification of classification by an imperfect reference test will lead to bias in the assessment of a diagnostic test. In general, an imperfect reference test will underestimate the performance of a diagnostic test. Meta-analytic methods have been described to adjust for imperfections in the reference standard, although those techniques were not applied to the data presented here.[169]

It is likely that other types of bias were present in some of these studies. Empirical observation of the quantitative effects of study design flaws on the findings of diagnostic studies has shown that case-control designs, studies that use different reference tests for

positive and negative results of the diagnostic test under study, and lack of blinding led to overestimation of diagnostic test accuracy.[49] All included studies were case-control, prospectively designed. Half of the studies recruited their patients consecutively, with minimal withdrawal from the study, thereby minimizing selection bias. Few studies reported information on blinding, which could potentially have altered the trustworthiness of the data.

Quality assessment of the studies was performed, but not included in the analysis. It is possible that difference in accuracy would have been observed it this was accounted for.

Several other forms of bias have not been shown to be important predictors of variation in assessment of diagnostic accuracy.[49] Verification bias refers to the bias that may occur if the reference test is applied based on the results of the diagnostic test being studied. None of the studies included the PCT of CRP for the diagnosis of bacterial infection or evaluated their results for the decision of performing the reference tests (cultures). Consequently, no evaluation of verification bias was used in this meta-analysis.

The accuracy of diagnostic markers can depend on the specific methods used for their measurement. Invariably, PCT measurements were performed using the commercially available antibody system (BRAHMS, Hennigsdorf, Germany). This assay is specific and uses two antibodies that bind to two sites (calcitonin and katacalcin) of the procalcitonin molecule thus ruling out cross-reactivity. The reported detection limit of the assay is 0.1 ng/ml while procalcitonin levels of healthy subjects are usually undetectable.[88] However, methods of measurement of CRP largely varied among the 12 included studies; 8 different methods were used for the CRP quantification. The implications of this variability are unknown to the final result of this meta-analysis. However, each study was included using its own best cutoff value and the linear regression methods used in the analysis account for possible threshold differences between studies.
It should also be noted that an apparent threshold effect can arise through variation in other factors which simultaneously increase (or decrease) both true positive and false positive diagnosis rate.[48]

This meta-analysis does not evaluate serial measurements of PCT or CRP for the diagnosis of bacterial infection; it evaluates a one-time measurement at the time infection was suspected.

Tests for heterogeneity and correlation were not performed in this meta-analysis, since they have low statistical power when the studies in the systematic reviews have small sample sizes,[48] and therefore a threshold related effect may exist but remain undetected by the statistical tests.

The main problems of meta-analysis actually arise before the analysis of the data is begun, in the searching for studies. There is an inevitable publication bias, which is the phenomenon by which significant and positive results are more likely to be reported, and reported more prominently, than non-significant and negative ones. Another important step is the selection of the studies to be included in the meta-analysis, so that they evaluate the same outcome measurement. Despite extensive and rigorous techniques applied during the preparation of this meta-analysis, it is not completely free of biases.

In the meta-analysis technique, pooling of results across studies or averaging sensitivity and specificity (which are in effect the same method) causes underestimation of test performance, because the relationship between sensitivity and specificity is not linear. This is most easily understood by considering a ROC graph with two points: one at 50% sensitivity and 90% specificity and the other with 90% sensitivity and 50% specificity. Averaging these results (or pooling if one assumes both studies have equal numbers of positive findings) would yield a sensitivity of 70% and a specificity of 70%. Assuming a constant diagnostic odds ratio, the true sensitivity and specificity at the point where the two are equal should be 75%. Meta-analysis of diagnostic odds ratios fails to capture the interdependence of sensitivity and specificity.[53]

The logistic regression method (Littenberg-Moses method) used in this meta-analysis systematically underestimates the sensitivity and specificity for very high levels of test performance, but the underestimation is no more than 2% for each parameter. An increase in the size of the clinical trials being meta-analyzed virtually eliminates this bias.

Back-transforming the CI from the linear regression of the logistic gives a reasonably conservative CI on the summary ROC curve. This too is subject to the systematic underestimation at very high levels of sensitivity and specificity in the meta-analysis of small studies.[53]

The results of this meta-analysis suggest that the accuracy for PCT is higher than that of CRP for differentiating between bacterial and both viral infections and other non-infective causes of inflammation. We tried to evaluate if antibiotic administration influenced the results, but there was not enough data descriptions in the original studies to allow such analysis.

We selected a random effects model, that assumes that the studies included in the meta-analysis belong to a random sample of a universe of such studies, since both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis. If there is significant heterogeneity among the results of the included studies, random effects models will give wider confidence intervals than fixed effect models. We believe that the results of this meta-analysis could be generalized to different patient populations (external validity).

This meta-analysis does not address the question of the best threshold of the tests studied. Raw data from each individual patient would be required, which unfortunately was not available. Moreover, the sensitivity and specificity for combined tests, PCT and CRP, could also not be evaluated without individual raw data for PCT and CRP for every patient included in this meta-analysis.

This study may have implications for how clinicians perform their clinical evaluation for bacterial infections. These data show that PCT, rather than CRP, is a promising marker for bacterial infection in hospitalized patients, with high sensitivity and specificity for differentiating between bacterial and viral infections and between bacterial infections and non-infective causes of inflammation. It is however important to consider that these

markers do not allow a final diagnosis of infection, but are should rather view as screening tool in clinical practice.

This study has implications for clinical research. This study has highlighted the selected nature of existing data on diagnostic accuracy of simultaneous PCT and CRP for the diagnosis of bacterial infections. A potentially useful consideration would be the gain in sensitivity and specificity that might result from using a combination of CRP and PCT. Further attention should be devoted to evaluating the usefulness of these tests in the clinical practice.

Future directions

The evaluation of the diagnostic accuracy of a test is also only one component of assessing whether it is of clinical value. Therapeutic interventions can only be recommended for use in health care only if they are shown on average to be of benefit to patients: the same criteria apply for the use of a diagnostic test, and even the most accurate of tests can be clinically useless and do more harm than good. Studies of diagnostic accuracy cannot prove that a diagnostic investigation is effective, but can discern whether the performance of a test is satisfactory for it to have the potential to be effective.[48]

In order to answer some of these questions, we designed a prospective pilot-study of consecutive cases of SIRS in the Pediatric Critical Care Unit of Sainte-Justine Hospital. The objectives were to determine the feasibility of a multicenter study in order to determine the predictive value of PCT as a diagnostic marker for bacterial infections in critically ill children with SIRS. Secondary objectives would be to determine the predictive value of PCT combined with CRP as diagnostic markers for bacterial infections; to determine the influence of prior use of antibiotics on the predictive value of these tests; to estimate the accrual of information provided by PCT with respect to the diagnosis of bacterial infection in critically ill children with SIRS in comparison to the value of other tests (clinical data, Gram coloration, CRP, etc); to compare the a priori probability (pre-test odds) of infection, as estimated by clinician at the bedside, to the a posteriori probability (revised probability, or post-test odds), as estimated by the same clinician, given the new information provided by PCT, clinical data, Gram coloration, CRP, etc.; to estimate and to compare the cost-usefulness of these tests: PCT and CRP in terms of changes in the clinical practice, decreasing antibiotic days, decreasing admission time in the PICU and/or mortality.

We screened 259 patients with SIRS over a 7-month period and included 66 patients, collecting baseline data, PCT, CRP, and diagnostic tests for infection (blood and urine

cultures and ETT and/or other cultures deemed relevant). This study is currently in the phase of data analysis.

Conclusion and Recommendation

With this meta-analysis, we can conclude that the overall accuracy of PCT is higher than that of CRP for differentiating between bacterial and both viral infections and other non-infective causes of inflammation in hospitalized patients.

At this point, PCT should be favored over CRP for the use in clinical practice as an early diagnostic marker for bacterial infection in hospitalized patients. The remaining questions are the combined accuracy of PCT and CRP and the clinical utility of these tests. These answers should be provided with the planned multicenter study.

Chapter IV

Bibliography

1. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest.* Jun 1992;101(6):1644-1655.
2. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med.* Jul 2001;29(7):1303-1310.
3. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med.* Apr 17 2003;348(16):1546-1554.
4. Wheeler AP, Bernard GR. Treating patients with severe sepsis. *N Engl J Med.* Jan 21 1999;340(3):207-214.
5. Watson RS, Carcillo JA, Linde-Zwirble WT, Clermont G, Lidicker J, Angus DC. The epidemiology of severe sepsis in children in the United States. *Am J Respir Crit Care Med.* Mar 1 2003;167(5):695-701.
6. Fagon JY, Chastre J, Hance AJ, Montravers P, Novara A, Gibert C. Nosocomial pneumonia in ventilated patients: A cohort study evaluating attributable mortality and hospital stay. *Am J Med.* 1993;94:281-288.
7. Kollef MH, Ward S, Sherman G, et al. Inadequate treatment of nosocomial infections is associated with certain empiric antibiotic choices. *Crit Care Med.* 2000;28:3456-3464.
8. Ewig S, Torres A, El-Ebiary M, et al. Bacterial colonization patterns in mechanically ventilated patients with traumatic and medical head injury. *Am J Respir Crit Care Med.* 1999;159:188-198.
9. Brun-Buisson C. Could invasive diagnostic techniques for ventilator-associated pneumonia be associated with reduced antibiotic usage inthe ICU? *New Horizons.* 1996;4:345-352.
10. Kollef MH, Silver P, Murphy DM, Trovillion E. The effect of late-onset ventilator-associated pneumonia in determining patients mortality. *Chest.* 1995;108:1655-1662.
11. Singh-Naz N, Sprague BM, Patel KM, Pollack MM. Risk factors for nosocomial infection in critically ill children: A prospective cohort study. *Crit Care Med.* 1996;24:857-858.
12. Kollef MH. Optimizing antibiotic therapy in the intensive care unit setting. *Crit Care.* Aug 2001;5(4):189-195.
13. Blanc P, Von Elm BE, Geissler A, Granier I, Boussuges A, Durand Gasselin J. Economic impact of a rational use of antibiotics in intensive care. *Intensive Care Med.* Dec 1999;25(12):1407-1412.

14. Fischer J, Fanconi S. Systemic inflammatory response syndrome (SIRS) in pediatric patients. In: Tibboel D, van der Voort E, eds. *Update in Intensive Care and Emergency Medicine 25. Intensive Care in Childhood. A challenge to the future.* Berlin: Springer-Verlag; 1996:239-254.
15. Moya F, Nieto A, JL RC. Calcitonin biosynthesis: evidence for a precursor. *Eur J Biochem.* Jul 1 1975;55(2):407-413.
16. Nylen ES, O'Neill W, Jordan MH, et al. Serum procalcitonin as an index of inhalation injury in burns. *Horm Metab Res.* Sep 1992;24(9):439-443.
17. Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infection. *Lancet.* 1993;341(8844):515-518.
18. Meisner M. Pathobiochemistry and clinical use of procalcitonin. *Clin Chim Acta.* Sep 2002;323(1-2):17-29.
19. Whang KT, Steinwald PM, White JC, et al. Serum calcitonin precursors in sepsis and systemic inflammation. *J Clin Endocrinol Metab.* 1998;83(9):3296-3301.
20. Dandona P, Nix D, Wilson MF, et al. Procalcitonin increase after endotoxin injection in normal subjects. *J Clin Endocrinol Metab.* 1994;79(6):1605-1608.
21. Nijsten MW, Olinga P, The TH, et al. Procalcitonin behaves as a fast responding acute phase protein in vivo and in vitro. *Crit Care Med.* 2000;28(2):458-461.
22. Oberhoffer M, Stonans I, Russwurm S, et al. Procalcitonin expression in human peripheral blood mononuclear cells and its modulation by lipopolysaccharides and sepsis-related cytokines in vitro. *J Lab Clin Med.* 1999;134(1):49-55.
23. Balog A, Ocsovszki I, Mandi Y. Flow cytometric analysis of procalcitonin expression in human monocytes and granulocytes. *Immunol Lett.* Dec 3 2002;84(3):199-203.
24. Monneret G, Laroche B, Bienvenu J. Procalcitonin is not produced by circulating blood cells. *Infection.* Jan-Feb 1999;27(1):34-35.
25. Monneret G, Pachot A, Laroche B, Picollet J, Bienvenu J. Procalcitonin and calcitonin gene-related peptide decrease LPS-induced tnf production by human circulating blood cells. *Cytokine.* Jun 2000;12(6):762-764.
26. Hoffmann G, Totzke G, Seibel M, Smolny M, Wiedermann FJ, Schobersberger W. In vitro modulation of inducible nitric oxide synthase gene expression and nitric oxide synthesis by procalcitonin. *Crit Care Med.* 2001;29(1):112-116.
27. Nylen ES, Whang KT, Snider RH, Jr., Steinwald PM, White JC, Becker KL. Mortality is increased by procalcitonin and decreased by an antiserum reactive to procalcitonin in experimental sepsis. *Crit Care Med.* 1998;26(6):1001-1006.
28. Hoffmann G, Czechowski M, Schloesser M, Schobersberger W. Procalcitonin amplifies inducible nitric oxide synthase gene expression and nitric oxide production in vascular smooth muscle cells. *Crit Care Med.* Sep 2002;30(9):2091-2095.
29. de Werra I, Jaccard C, Corradin SB, et al. Cytokines, nitrite/nitrate, soluble tumor necrosis factor receptors, and procalcitonin concentrations: comparisons

in patients with septic shock, cardiogenic shock, and bacterial pneumonia. *Crit Care Med.* 1997;25(4):607-613.

30. Al-Nawas B, Krammer I, Shah PM. Procalcitonin in diagnosis of severe infections. *Eur J Med Res.* 1996;1(7):331-333.
31. Redl H, Schlag G, Togel E, Assicot M, Bohuon C. Procalcitonin release patterns in a baboon model of trauma and sepsis: relationship to cytokines and neopterin. *Crit Care Med.* Nov 2000;28(11):3659-3663.
32. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med.* Jul 1996;22(7):707-710.
33. Muller B, Becker KL, Schachinger H, et al. Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit. *Crit Care Med.* 2000;28(4):977-983.
34. Ugarte H, Silva E, Mercan D, De Mendonca A, Vincent JL. Procalcitonin used as a marker of infection in the intensive care unit. *Crit Care Med.* 1999;27(3):498-504.
35. Lind L, Bucht E, Ljunghall S. Pronounced elevation in circulating calcitonin in critical care patients is related to the severity of illness and survival. *Intensive Care Med.* Jan 1995;21(1):63-66.
36. Meisner M, Tschaikowsky K, Palmaers T, Schmidt J. Comparison of procalcitonin (PCT) and C-reactive protein (CRP) plasma concentrations at different SOFA scores during the course of sepsis and MODS. *Crit Care (Lond).* 1999;3(1):45-50.
37. Adamik B, Kubler-Kielb J, Golebiowska B, Gamian A, Kubler A. Effect of sepsis and cardiac surgery with cardiopulmonary bypass on plasma level of nitric oxide metabolites, neopterin, and procalcitonin: correlation with mortality and postoperative complications. *Intensive Care Med.* 2000;26(9):1259-1267.
38. Zimmerman MA, Selzman CH, Cothren C, Sorensen AC, Raeburn CD, Harken AH. Diagnostic implications of C-reactive protein. *Arch Surg.* Feb 2003;138(2):220-224.
39. Szalai AJ, McCrory MA. Varied biologic functions of C-reactive protein: lessons learned from transgenic mice. *Immunol Res.* 2002;26(1-3):279-287.
40. Povoa P. C-reactive protein: a valuable marker of sepsis. *Intensive Care Med.* Mar 2002;28(3):235-243.
41. Oberhoffer M, Vogelsang H, Russwurm S, Hartung T, Reinhart K. Outcome prediction by traditional and new markers of inflammation in patients with sepsis. *Clin Chem Lab Med.* 1999;37(3):363-368.
42. Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. *Circulation.* Jan 28 2003;107(3):363-369.
43. Ridker PM. Connecting the role of C-reactive protein and statins in cardiovascular disease. *Clin Cardiol.* Apr 2003;26(4 Suppl 3):III39-44.
44. Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. *Bmj.* Dec 6 1997;315(7121):1533-1537.

45. Mulrow CD. Rationale for systematic reviews. *Bmj.* Sep 3 1994;309(6954):597-599.

46. Bero LA, Grilli R, Grimshaw JM, Harvey E, Oxman AD, Thomson MA. Closing the gap between research and practice: an overview of systematic reviews of interventions to promote the implementation of research findings. The Cochrane Effective Practice and Organization of Care Review Group. *Bmj.* Aug 15 1998;317(7156):465-468.

47. Straus SE, Sackett DL. Using research findings in clinical practice. *Bmj.* Aug 1 1998;317(7154):339-342.

48. Dekks JJ. *Systematic reviews of evaluation of diagnositc and screening tests*; 2001.

49. Lijmer JG, Mol BW, Heisterkamp S, et al. Empirical evidence of design-related bias in studies of diagnostic tests. *Jama.* Sep 15 1999;282(11):1061-1066.

50. Irwig L, Tosteson AN, Gatsonis C, et al. Guidelines for meta-analyses evaluating diagnostic tests. *Ann Intern Med.* Apr 15 1994;120(8):667-676.

51. Moses LE, Shapiro D, Littenberg B. Combining independent studies of a diagnostic test into a summary ROC curve: data-analytic approaches and some additional considerations. *Stat Med.* Jul 30 1993;12(14):1293-1316.

52. Littenberg B, Moses LE. Estimating diagnostic accuracy from multiple conflicting reports: a new meta-analytic method. *Med Decis Making.* Oct-Dec 1993;13(4):313-321.

53. Mitchell MD. Validation of the summary ROC for diagnostic test meta-analysis: a Monte Carlo simulation. *Acad Radiol.* Jan 2003;10(1):25-31.

54. Aouifi A, Piriou V, Bastien O, et al. Usefulness of procalcitonin for diagnosis of infection in cardiac surgical patients. *Crit Care Med.* 2000;28(9):3171-3176.

55. Arber C, Passweg JR, Fluckiger U, et al. C-reactive protein and fever in neutropenic patients. *Scand J Infect Dis.* 2000;32(5):515-520.

56. Benitz WE, Han MY, Madan A, Ramachandra P. Serial serum C-reactive protein levels in the diagnosis of neonatal infection. *Pediatrics.* 1998;102(4):E41.

57. Berland M, Mein-Bottini M, Charvet PY, Revol A, Drai J, Pic JC. [The significance of the level of C-reactive protein in gynecologic infections]. *Rev Fr Gynecol Obstet.* 1990;85(10):539-544.

58. Boeken U, Feindt P, Micek M, Petzold T, Schulte HD, Gams E. Procalcitonin (PCT) in cardiac surgery: diagnostic value in systemic inflammatory response syndrome (SIRS), sepsis and after heart transplantation (HTX). *Cardiovasc Surg.* 2000;8(7):550-554.

59. Boeken U, Feindt P, Zimmermann N, Kalweit G, Petzold T, Gams E. Increased preoperative C-reactive protein (CRP)-values without signs of an infection and complicated course after cardiopulmonary bypass (CPB)-operations. *Eur J Cardiothorac Surg.* 1998;13(5):541-545.

60. Bohuon C, Assicot M, Raymond J, Gendrel D. [Procalcitonin, a marker of bacterial meningitis in children]. *Bull Acad Natl Med.* 1998;182(7):1469-1475.

61. Borschsenius F, Bruun JN, Michaelsen TE, Tonjun T. Serum C-reactive protein in systemic infections due to Neisseria meningitidis. *NIPH Ann.* 1986;9(1):15-21.

62. Bossink AW, Groeneveld AB, Thijs LG. Prediction of microbial infection and mortality in medical patients with fever: plasma procalcitonin, neutrophilic elastase-alpha1- antitrypsin, and lactoferrin compared with clinical variables. *Clin Infect Dis.* 1999;29(2):398-407.

63. Brunkhorst FM, Wegscheider K, Forycki ZF, Brunkhorst R. Procalcitonin for early diagnosis and differentiation of SIRS, sepsis, severe sepsis, and septic shock. *Intensive Care Med.* 2000;26:S148-S152.

64. Cadwgan AM, Watson WA, Laing RB, MacKenzie AR, Smith CC, Douglas JG. Presenting clinical features and C-reactive protein in the prediction of a positive stool culture in patients with diarrhoea. *J Infect.* 2000;41(2):159-161.

65. Chiesa C, Panero A, Rossi N, et al. Reliability of procalcitonin concentrations for the diagnosis of sepsis in critically ill neonates. *Clin Infect Dis.* 1998;26(3):664-672.

66. Chiu CH, Lin TY, Bullard MJ. Identification of febrile neonates unlikely to have bacterial infections. *Pediatr Infect Dis J.* 1997;16(1):59-63.

67. Claeys R, Vinken S, Spapen H, et al. Plasma procalcitonin and C-reactive protein in acute septic shock: clinical and biological correlates. *Crit Care Med.* 2002;30(4):757-762.

68. Cobben JM, Cornelissen PJ, Haverkorn M, Waelkens JJ. [CRP versus BSE in pediatrics. How good is a diagnostic test?]. *Tijdschr Kindergeneeskd.* 1990;58(5):169-174.

69. Del Beccaro MA, Mendelman PM, Inglis AF, Richardson MA, Duncan NO, Shugerman RP. Acute-phase reactants and acute bacterial otitis media. *Am J Dis Child.* 1992;146(9):1037-1039.

70. Dev D, Wallace E, Sankaran R, et al. Value of C-reactive protein measurements in exacerbations of chronic obstructive pulmonary disease. *Respir Med.* 1998;92(4):664-667.

71. Diculencu D, Miftode E, Turcu T, Buiuc D. [The value of C-reactive protein for the differentiation of bacterial meningitis from viral meningitis]. *Rev Med Chir Soc Med Nat Iasi.* 1995;99(1-2):144-150.

72. Du Clos TW, Mold C. The role of C-reactive protein in the resolution of bacterial infection. *Curr Opin Infect Dis.* Jun 2001;14(3):289-293.

73. Enguix A, Rey C, Concha A, Medina A, Coto D, Dieguez MA. Comparison of procalcitonin with C-reactive protein and serum amyloid for the early diagnosis of bacterial sepsis in critically ill neonates and children. *Intensive Care Med.* 2001;27(1):211-215.

74. Eriksson S, Olander B, Pira U, Granstrom L. White blood cell count, leucocyte elastase activity, and serum concentrations of interleukin-6 and C-reactive protein after open appendicectomy. *Eur J Surg.* 1997;163(2):123-127.

75. Fassbender K, Pargger H, Muller W, Zimmerli W. Interleukin-6 and acute-phase protein concentrations in surgical intensive care unit patients: diagnostic signs in nosocomial infection. *Crit Care Med.* 1993;21(8):1175-1180.

76. Flores JM, Jimenez PI, Rincon D, et al. [C reactive protein as marker of infection among patients with severe closed trauma]. *Enferm Infecc Microbiol Clin.* 2001;19(2):61-65.

77. Gendrel D, Raymond J, Assicot M, et al. Measurement of procalcitonin levels in children with bacterial or viral meningitis. *Clin Infect Dis.* 1997;24(6):1240-1242.

78. Gendrel D, Raymond J, Coste J, et al. Comparison of procalcitonin with C-reactive protein, interleukin 6 and interferon-alpha for differentiation of bacterial vs. viral infections. *Pediatr Infect Dis J.* 1999;18(10):875-881.

79. Gervaix A, Galetto-Lacour A, Gueron T, et al. Usefulness of procalcitonin and C-reactive protein rapid tests for the management of children with urinary tract infection. *Pediatr Infect Dis J.* 2001;20(5):507-511.

80. Hatherill M, Tibby SM, Sykes K, Turner C, Murdoch IA. Diagnostic markers of infection: comparison of procalcitonin with C reactive protein and leucocyte count. *Arch Dis Child.* 1999;81(5):417-421.

81. Harbarth S, Holeckova K, Froidevaux C, et al. Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis. *Am J Respir Crit Care Med.* 2001;164(3):396-402.

82. Hedlund J, Hansson LO. Procalcitonin and C-reactive protein levels in community-acquired pneumonia: correlation with etiology and prognosis. *Infection.* 2000;28(2):68-73.

83. Heiskanen-Kosma T, Korppi M. Serum C-reactive protein cannot differentiate bacterial and viral aetiology of community-acquired pneumonia in children in primary healthcare settings. *Scand J Infect Dis.* 2000;32(4):399-402.

84. Herrmann W, Ecker D, Quast S, Klieden M, Rose S, Marzi I. Comparison of procalcitonin, sCD14 and interleukin-6 values in septic patients. *Clin Chem Lab Med.* 2000;38(1):41-46.

85. Hogevik H, Olaison L, Andersson R, Alestig K. C-reactive protein is more sensitive than erythrocyte sedimentation rate for diagnosis of infective endocarditis. *Infection.* 1997;25(2):82-85.

86. Huber-Spitzy V, Arocker-Mettinger E, Herkner K, et al. Diagnosis and therapy of bacterial endophthalmitis, and serum levels of inflammation markers. *Infection.* 1992;20(3):122-127.

87. Juffrie M, Meer GM, Hack CE, et al. Inflammatory mediators in dengue virus infection in children: interleukin-6 and its relation to C-reactive protein and secretory phospholipase A2. *Am J Trop Med Hyg.* 2001;65(1):70-75.

88. Karzai W, Oberhoffer M, Meier-Hellmann A, Reinhart K. Procalcitonin--a new indicator of the systemic response to severe infections. *Infection.* 1997;25(6):329-334.

89. Katz JA, Mustafa MM, Bash RO, Cash JV, Buchanan GR. Value of C-reactive protein determination in the initial diagnostic evaluation of the febrile, neutropenic child with cancer. *Pediatr Infect Dis J.* 1992;11(9):708-712.

90. Kornman L, Jacobs V, Hodgson RP, et al. Chorioamnionitis: how useful is the determination of C-reactive protein? *Aust N Z J Obstet Gynaecol.* 1988;28(1):45-48.

91. Korppi M, Heiskanen-Kosma T, Leinonen M. White blood cells, C-reactive protein and erythrocyte sedimentation rate in pneumococcal pneumonia in children. *Eur Respir J.* 1997;10(5):1125-1129.

92. Korppi M, Kroger L. C-reactive protein in viral and bacterial respiratory infection in children. *Scand J Infect Dis.* 1993;25(2):207-213.

93. Krediet T, Gerards L, Fleer A, van Stekelenburg G. The predictive value of CRP and I/T-ratio in neonatal infection. *J Perinat Med.* 1992;20(6):479-485.

94. Ksssler A, Grunert C, Wood WG. The limitations and usefulness of C-reactive protein and elastase-alpha 1-proteinase inhibitor complexes as analytes in the diagnosis and follow-up of sepsis in newborns and adults. *Eur J Clin Chem Clin Biochem.* 1994;32(5):365-368.

95. Kuse ER, Langefeld I, Jaeger K, Kulpmann WR. Procalcitonin in fever of unknown origin after liver transplantation: a variable to differentiate acute rejection from infection. *Crit Care Med.* 2000;28(2):555-559.

96. Kunzig HJ, Schmidt-Rohde P, Kramer M, Prinz H. [Acute phase proteins (C-reactive protein, orosomucoid, haptoglobin)-- specific markers in the diagnosis of inflammatory adnexal diseases]. *Geburtshilfe Frauenheilkd.* 1985;45(12):881-886.

97. Lorrot M, Moulin F, Coste J, et al. [Procalcitonin in pediatric emergencies: comparison with C-reactive protein, interleukin-6 and interferon alpha in the differentiation between bacterial and viral infections]. *Presse Med.* 2000;29(3):128-134.

98. Marchand A, Van Lente F, Galen RS. The assessment of laboratory tests in the diagnosis of acute appendicitis. *Am J Clin Pathol.* 1983;80(3):369-374.

99. Matson A, Soni N, Sheldon J. C-reactive protein as a diagnostic test of sepsis in the critically ill. *Anaesth Intensive Care.* 1991;19(2):182-186.

100. Mercer LJ, Block BS, Hajj SN. Measurement of C-reactive protein to compare ceftizoxime versus cefoxitin/doxycycline therapy for septic pelvis: a preliminary report. *Clin Ther.* 1987;10(Suppl A):59-65.

101. Miller PR, Munn DD, Meredith JW, Chang MC. Systemic inflammatory response syndrome in the trauma intensive care unit: who is infected? *J Trauma.* 1999;47(6):1004-1008.

102. Moulin F, Raymond J, Lorrot M, et al. Procalcitonin in children admitted to hospital with community acquired pneumonia. *Arch Dis Child.* 2001;84(4):332-336.

103. Mustard RA, Jr., Bohnen JM, Haseeb S, Kasina R. C-reactive protein levels predict postoperative septic complications. *Arch Surg.* 1987;122(1):69-73.

104. Nylen ES, Snider RH, Jr., Thompson KA, Rohatgi P, Becker KL. Pneumonitis-associated hyperprocalcitoninemia. *Am J Med Sci.* 1996;312(1):12-18.

105. Oberhoffer M, Karzai W, Meier-Hellmann A, Bogel D, Fassbinder J, Reinhart K. Sensitivity and specificity of various markers of inflammation for the prediction of tumor necrosis factor-alpha and interleukin-6 in patients with sepsis. *Crit Care Med.* 1999;27(9):1814-1818.

106. Ortqvist A, Hedlund J, Wretlind B, Carlstrom A, Kalin M. Diagnostic and prognostic value of interleukin-6 and C-reactive protein in community-acquired pneumonia. *Scand J Infect Dis.* 1995;27(5):457-462.

107. Parnaby RM, Eaton SE, Shafi MS, Bell D. The value of serum C-reactive protein levels as a marker of sepsis in intensive care unit patients. *Clin Intensive Care.* 1994;5(3):106-113.

108. Peltola HO. C-reactive protein for rapid monitoring of infections of the central nervous system. *Lancet.* 1982;1(8279):980-982.

109. Penel N, Fournier C, Degardin M, Kouto H, N'Guyen M. [Fever and solid tumor: diagnostic value of procalcitonin and C- reactive protein]. *Rev Med Interne.* 2001;22(8):706-714.

110. Pettila V, Pentti J, Pettila M, Takkunen O, Jousela I. Predictive value of antithrombin III and serum C-reactive protein concentration in critically ill patients with suspected sepsis. *Crit Care Med.* 2002;30(2):271-275.

111. Pinkola K, Darvas K. [Procalcitonin rapid test in surgical patients treated in the intensive care unit]. *Magy Seb.* 2001;54(6):368-370.

112. Povoa P, Almeida E, Moreira P, et al. C-reactive protein as an indicator of sepsis. *Intensive Care Med.* 1998;24(10):1052-1056.

113. Pulliam PN, Attia MW, Cronan KM. C-reactive protein in febrile children 1 to 36 months of age with clinically undetectable serious bacterial infection. *Pediatrics.* 2001;108(6):1275-1279.

114. Putto A, Ruuskanen O, Meurman O, et al. C reactive protein in the evaluation of febrile illness. *Arch Dis Child.* 1986;61(1):24-29.

115. Racine A, Abribat D, Ensergueix G, Lucas Y, Poux JB. [The value of the C-reactive protein assay for the early diagnosis of neonatal infection at the maternity ward and pediatric service of a general hospital center]. *Ann Pediatr (Paris).* 1989;36(4):253-257.

116. Ruiz-Laiglesia FJ, Torrubia-Perez C, Amiguet-Garcia JA, Fiteni-Mera I. [Value of C-reactive protein for detecting bacteremia in febrile patients]. *Presse Med.* 1996;25(24):1105-1108.

117. Ruokonen E, Ilkka L, Niskanen M, Takala J. Procalcitonin and neopterin as indicators of infection in critically ill patients. *Acta Anaesthesiol Scand.* 2002;46(4):398-404.

118. Ruokonen E, Nousiainen T, Pulkki K, Takala J. Procalcitonin concentrations in patients with neutropenic fever. *Eur J Clin Microbiol Infect Dis.* 1999;18(4):283-285.

119. Schwarz S, Bertram M, Schwab S, Andrassy K, Hacke W. Serum procalcitonin levels in bacterial and abacterial meningitis. *Crit Care Med.* 2000;28(6):1828-1832.

120. Selberg O, Hecker H, Martin M, Klos A, Bautsch W, Kohl J. Discrimination of sepsis and systemic inflammatory response syndrome by determination of circulating plasma concentrations of procalcitonin, protein complement 3a, and interleukin-6. *Crit Care Med.* 2000;28(8):2793-2798.

121. Sheldon J, Riches P, Gooding R, Soni N, Hobbs JR. C-reactive protein and its cytokine mediators in intensive-care patients. *Clin Chem.* 1993;39(1):147-150.

122. Shortland DB, MacFadyen U, Elston A, Harrison G. Evaluation of C. reactive protein values in neonatal sepsis. *J Perinat Med.* 1990;18(3):157-163.

123. Smith RP, Lipworth BJ, Cree IA, Spiers EM, Winter JH. C-reactive protein. A clinical marker in community-acquired pneumonia. *Chest.* 1995;108(5):1288-1291.

124. Somech R, Zakuth V, Assia A, Jurgenson U, Spirer Z. Procalcitonin correlates with C-reactive protein as an acute-phase reactant in pediatric patients. *Isr Med Assoc J.* 2000;2(2):147-150.

125. Suprin E, Camus C, Gacouin A, et al. Procalcitonin: a valuable indicator of infection in a medical ICU? *Intensive Care Med.* 2000;26(9):1232-1238.

126. Torre D, Zeroli C, Giola M, et al. Acute-phase proteins and levels of interleukin 1B, interleukin 6, tumor necrosis factor alpha, and interleukin 8 in children with pertussis. *Am J Dis Child.* 1993;147(1):27-29.

127. Unkila-Kallio L, Kallio MJ, Peltola H. The usefulness of C-reactive protein levels in the identification of concurrent septic arthritis in children who have acute hematogenous osteomyelitis. A comparison with the usefulness of the erythrocyte sedimentation rate and the white blood-cell count. *J Bone Joint Surg Am.* 1994;76(6):848-853.

128. van den Broek PJ, Radder AM, Hermans J. [The significance of body temperature, sedimentation, C-reactive protein, leukocyte count and differential for the diagnosis of infections in an internal medicine emergency department]. *Ned Tijdschr Geneeskd.* 1990;134(52):2536-2540.

129. Viallon A, Zeni F, Pouzet V, et al. Serum and ascitic procalcitonin levels in cirrhotic patients with spontaneous bacterial peritonitis: diagnostic value and relationship to pro-inflammatory cytokines. *Intensive Care Med.* 2000;26(8):1082-1088.

130. Virkki R, Juven T, Rikalainen H, Svedstrom E, Mertsola J, Ruuskanen O. Differentiation of bacterial and viral pneumonia in children. *Thorax.* 2002;57(5):438-441.

131. von Heimburg D, Stieghorst W, Khorram-Sefat R, Pallua N. Procalcitonin--a sepsis parameter in severe burn injuries. *Burns.* 1998;24(8):745-750.

132. Wanner GA, Keel M, Steckholzer U, Beier W, Stocker R, Ertel W. Relationship between procalcitonin plasma levels and severity of injury, sepsis, organ failure, and mortality in injured patients. *Crit Care Med.* 2000;28(4):950-957.

133. Whicher J, Bienvenu J, Monneret G. Procalcitonin as an acute phase marker. *Ann Clin Biochem.* 2001;38(Pt 5):483-493.

134. Yentis SM, Soni N, Sheldon J. C-reactive protein as an indicator of resolution of sepsis in the intensive care unit. *Intensive Care Med.* 1995;21(7):602-605.

135. Cox ML, Rudd AG, Gallimore R, Hodkinson HM, Pepys MB. Real-time measurement of serum C-reactive protein in the management of infection in the elderly. *Age Ageing.* 1986;15(5):257-266.

136. Dofferhoff AS, Bom VJ, de Vries-Hospers HG, et al. Patterns of cytokines, plasma endotoxin, plasminogen activator inhibitor, and acute-phase proteins during the treatment of severe sepsis in humans. *Crit Care Med.* 1992;20(2):185-192.

137. Gustafsson R, Johnsson P, Algotsson L, Blomquist S, Ingemansson R. Vacuum-assisted closure therapy guided by C-reactive protein level in patients

with deep sternal wound infection. *J Thorac Cardiovasc Surg.* May 2002;123(5):895-900.

138. Hogarth MB, Gallimore R, Savage P, et al. Acute phase proteins, C-reactive protein and serum amyloid A protein, as prognostic markers in the elderly inpatient. *Age Ageing.* 1997;26(2):153-158.

139. Icard P, Fleury JP, Regnard JF, et al. Utility of C-reactive protein measurements for empyema diagnosis after pneumonectomy. *Ann Thorac Surg.* 1994;57(4):933-936.

140. Vanlieferinghen P, Peigue-Lafeuille H, Gaulme J, Amram S, Gentou C, Raynaud EJ. [C-reactive protein and orosomucoid determinations in a neonatal pathology unit]. *Pediatrie.* 1986;41(2):121-125.

141. Marc E, Menager C, Moulin F, et al. [Procalcitonin and viral meningitis: reduction of unnecessary antibiotics by measurement during an outbreak]. *Arch Pediatr.* 2002;9(4):358-364.

142. Chiba Y, Muraoka R, Ihaya A, et al. Postoperative inflammatory reactions of impregnated Dacron grafts. *Surg Today.* 1999;29(11):1225-1228.

143. Dinant GJ, de Kock CA, van Wersch JW. Diagnostic value of C-reactive protein measurement does not justify replacement of the erythrocyte sedimentation rate in daily general practice. *Eur J Clin Invest.* 1995;25(5):353-359.

144. Fransen EJ, Maessen JG, Elenbaas TW, van Aarnhem EE, van Dieijen-Visser MP. Enhanced preoperative C-reactive protein plasma levels as a risk factor for postoperative infections after cardiac surgery. *Ann Thorac Surg.* 1999;67(1):134-138.

145. Hatherill M, Tibby SM, Turner C, Ratnavel N, Murdoch IA. Procalcitonin and cytokine levels: relationship to organ failure and mortality in pediatric septic shock. *Crit Care Med.* 2000;28(7):2591-2594.

146. Hjortdahl P, Landaas S, Urdal P, Steinbakk M, Fuglerud P, Nygaard B. C-reactive protein: a new rapid assay for managing infectious disease in primary health care. *Scand J Prim Health Care.* 1991;9(1):3-10.

147. Kragsbjerg P, Holmberg H, Vikerfors T. Serum concentrations of interleukin-6, tumour necrosis factor-alpha, and C-reactive protein in patients undergoing major operations. *Eur J Surg.* 1995;161(1):17-22.

148. Lembo RM, Marchant CD. Acute phase reactants and risk of bacterial meningitis among febrile infants and children. *Ann Emerg Med.* 1991;20(1):36-40.

149. Matsuo S, Tsumori M, Yamamoto Y, Takahashi H. [Clinical and laboratory correspondence to outpatients with the extreme value of C-reactive protein]. *Rinsho Byori.* 1992;40(12):1307-1311.

150. Mercer LJ, Hajj SN, Ismail MA, Block BS. Use of C-reactive protein to predict the outcome of medical management of tuboovarian abscesses. *J Reprod Med.* 1988;33(1 Suppl):164-167.

151. Mimoz O, Benoist JF, Edouard AR, Assicot M, Bohuon C, Samii K. Procalcitonin and C-reactive protein during the early posttraumatic systemic inflammatory response syndrome. *Intensive Care Med.* 1998;24(2):185-188.

152. Molnar Z, Szakmany T, Koszegi T, Tekeres M. Microalbuminuria and serum procalcitonin levels following oesophagectomy. *Eur J Anaesthesiol.* Jul 2000;17(7):464-465.

153. Panichi V, Migliori M, De Pietro S, et al. Plasma C-reactive protein in hemodialysis patients: a cross-sectional, longitudinal clinical survey. *Blood Purif.* 2000;18(1):30-36.

154. Philip AG, Mills PC. Use of C-reactive protein in minimizing antibiotic exposure: experience with infants initially admitted to a well-baby nursery. *Pediatrics.* 2000;106(1):E4.

155. Pinilla JC, Hayes P, Laverty W, Arnold C, Laxdal V. The C-reactive protein to prealbumin ratio correlates with the severity of multiple organ dysfunction. *Surgery.* 1998;124(4):799-805; discussion 805-796.

156. Sabat R, Hoflich C, Docke WD, et al. Massive elevation of procalcitonin plasma levels in the absence of infection in kidney transplant patients treated with pan-T-cell antibodies. *Intensive Care Med.* 2001;27(6):987-991.

157. Singh UK, Sinha RK, Suman S, Singh VK. C-reactive protein as an indicator of complications in bacterial meningitis. *Indian Pediatr.* 1996;33(5):373-376.

158. Soderquist B, Sundqvist KG, Jones I, Holmberg H, Vikerfors T. Interleukin-6, C-reactive protein, lactoferrin and white blood cell count in patients with S. aureus septicemia. *Scand J Infect Dis.* 1995;27(4):375-380.

159. van Langevelde P, Joop K, van Loon J, et al. Endotoxin, cytokines, and procalcitonin in febrile patients admitted to the hospital: identification of subjects at high risk of mortality. *Clin Infect Dis.* 2000;31(6):1343-1348.

160. Meisner M, Tschaikowsky K, Hutzler A, Schick C, Schuttler J. Postoperative plasma concentrations of procalcitonin after different types of surgery. *Intensive Care Med.* 1998;24(7):680-684.

161. Tschaikowsky K, Hedwig-Geissing M, Schiele A, Bremer F, Schywalsky M, Schuttler J. Coincidence of pro- and anti-inflammatory responses in the early phase of severe sepsis: Longitudinal study of mononuclear histocompatibility leukocyte antigen-DR expression, procalcitonin, C-reactive protein, and changes in T-cell subsets in septic and postoperative patients. *Crit Care Med.* 2002;30(5):1015-1023.

162. Rothenburger M, Markewitz A, Lenz T, et al. Detection of acute phase response and infection. The role of procalcitonin and C-reactive protein. *Clin Chem Lab Med.* 1999;37(3):275-279.

163. Gottfried EL, Wagar EA. Laboratory testing: a practical guide. *Dis Mon.* Aug 1983;29(11):1-41.

164. Chalmers TC, Smith H, Jr., Blackburn B, et al. A method for assessing the quality of a randomized control trial. *Control Clin Trials.* May 1981;2(1):31-49.

165. Cochrane. Cochrane Methods Group on Systematic Review of Screening and Diagnostic Tests: Recommended Methods. *The Cochrane Group*. updated 6 June 1996. Available at: http://www.cochrane.org/cochrane/sadtdoc1.htm.

166. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the

QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet.* Nov 27 1999;354(9193):1896-1900.

167. Bossuyt PM, Reitsma JB, Bruns DE, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. *Bmj.* Jan 4 2003;326(7379):41-44.

168. Bossuyt PM, Reitsma JB, Bruns DE, et al. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. *Clin Chem.* Jan 2003;49(1):7-18.

169. Walter SD, Irwig L, Glasziou PP. Meta-analysis of diagnostic tests with imperfect reference standards. *J Clin Epidemiol.* Oct 1999;52(10):943-951.

Chapter V

Annexes

Annex I: abstract for presentation at the "Congrès des Résidents du Département de Pédiatrie", November 2002, Hôpital Sainte-Justine, University of Montreal, QC, Canada

Procalcitonin and C-Reactive Protein as markers of bacterial infection: a meta-analysis

Liliana Simon, France Gauvin, Devendra Amre, Chantal Roy, Patrick Saint-Louis, Jacques Lacroix, Hôpital Sainte-Justine, Université of Montréal, Quebec, Canada

Introduction: Bacterial infections are a major cause for SIRS (Systemic Inflammatory Response Syndrome) that is frequently associated with hospitalization, death, and substantially increases costs related to health care. Differentiation of bacterial infection (sepsis) as a cause for SIRS from viral and other non-infective causes is important for the appropriate use of antibiotics. However, on many occasions, presently used culture methods delay diagnosis and result in over usage of antibiotics. The latter is primarily responsible for the development of multi-resistant bacteria hampering effective management. Serum biomarkers such as Procalcitonin (PCT) and C-reactive protein (CRP) have been suggested as early diagnostic markers of bacterial infection. However, their accuracy and clinical utility remains unknown.

Objective: We conducted a meta-analysis of published studies to compare the accuracy of serum PCT and CRP as diagnostic markers of bacterial infection.

Data Sources: All studies published in Medline from January 1, 1970 through May 30, 2002 that evaluated PCT and/or CRP for the diagnosis of bacterial infections were identified using pre-established search strategies and considered for analysis. Cross-references, computer databases and published books were also reviewed to identify relevant studies.

Study Selection: Prospective studies carried out among hospitalized patients were evaluated. No restriction was placed on the age group of the population studied. Retrospective studies, reviews and studies with incomplete data were excluded. Relevant articles were selected by three independent reviewers. Discrepancies or disagreements, if any, on the inclusion or exclusion of studies were resolved by consensus.

Data Extraction: The data was extracted in 2 by 2 tables. Authors of individual articles were contacted to complete/correct any missing/incorrect information.

Data Analysis: 22 articles were selected for revision and 14 were included (1355 patients) in the meta-analysis. Data were summarized using linear regression methods that account for possible threshold differences between studies and SROC (Summary Receiver Operating Characteristic) curves were generated to compare the accuracy of the

diagnostic tests. For differentiating between bacterial and non-infective causes of inflammation, PCT was more sensitive (Se) than CRP: 0.86 [95% CI 0.75 – 0.91] versus 0.71 [95% CI 0.63 – 0.79]. PCT also had a higher Specificity (Sp) than CRP: 0.80 [95% CI 0.65 – 0.90] versus 0.71 (95% CI 0.62-0.79). This was also reflected in the higher Q value observed for PCT: 0.81 and 0.73 respectively. When differentiating between bacterial and viral infections, the Se for PCT was better than CRP (0.91 [95% CI 0.85 – 0.95] versus 0.82 [95% CI 0.74 – 0.88]), the Sp were however comparable (0.82 [95% CI 0.74 – 0.88] versus 0.86 [95% CI 0.76 – 0.93]). The overall accuracy was also higher for PCT: Q values 0.88 and 0.78 respectively.

Conclusion: The overall accuracy of PCT is higher than that of CRP both for differentiating between bacterial and viral infections and bacterial and other non-infective causes of inflammation. The clinical utility and the cost-benefit aspects of this test need to further evaluated.

Annex II: abstract for oral presentation at the "4th World Congress on Pediatric Intensive Care", June 8 - 12, 2002 - Boston, MA, USA

Serum Procalcitonin (PCT) and C-Reactive Protein (CRP) as markers of bacterial infection: a meta-analysis

Liliana Simon, France Gauvin, Devendra Amre, Chantal Roy, Patrick Saint-Louis, Jacques Lacroix

Objective: Differentiation between bacterial, viral and non-infective causes of inflammation is important for the appropriate management of affected patients. A meta-analysis comparing the accuracy of serum PCT and CRP for the diagnosis bacterial infection was performed.
Methods: A Medline search between January 1, 1970 and May 30, 2002 for identifying articles evaluating PCT and/or CRP for the diagnosis of bacterial infections was performed. Prospective studies among hospitalized patients were selected. Each article was independently reviewed by three reviewers and data extracted in 2x2 tables. Discrepancies/disagreements were resolved by consensus. Authors of individual articles were contacted to complete/correct any missing/incorrect information.
Results: A total of 12 articles were retained in the final analysis (1499 patients). Data were summarized by estimating pooled accuracy measures and SROC (Summary Receiver Operating Characteristic) curves were generated. For differentiating between bacterial and non-infective causes of inflammation, PCT was more sensitive (Se) than CRP: 0.87 [95% CI 0.79 – 0.92] versus 0.72 [95% CI 0.62 – 0.80] and more specific (Sp) 0.83 [95% CI 0.68 – 0.92] versus 0.76 [95% CI 0.63-0.85] respectively. Overall accuracy, measured by the Q-value, was also higher for PCT: 0.83 versus 0.75 respectively. When differentiating between bacterial and viral infections, the Se for PCT was higher than CRP (0.90 [95% CI 0.86 – 0.93] versus 0.62 [95% CI 0.51 – 0.72]), but the Sp was lower (0.76 [95% CI 0.52 – 0.90] versus 0.94 [95% CI 0.78 – 0.98]). Q values were higher for PCT: 0.88 and 0.73 respectively.
Conclusion: The overall accuracy of PCT is higher than that of CRP both for differentiating between bacterial and viral or non-infective causes of inflammation. PCT could be recommended for widespread use in clinical practice.

Annex III: Booklet for data extraction

DIAGNOSTIC DES INFECTIONS PAR LA PROCALCITONINE (PCT) OU LA C-REACTIVE PROTEIN (CRP) CHEZ DES PATIENTS TRAITÉS EN SOINS INTENSIFS: MÉTA-ANALYSE.

Livret d'annotation

Last update: March 22, 2002 vv.

A) Données générales

1. Nom de l'examinateur .....
   - 1.1. Liliana Simon (noter le chiffre 1)
   - 1.2. Lars Desmets (noter le chiffre 2)
   - 1.3. Guillaume Émeriaud (noter le chiffre 3)
   - 1.4. Soraya Cinthia Mendes Xavier (noter le chiffre 4)

2. Description bibliographique de l'article évalué:
   - 2.1. Nom du premier auteur .....
   - 2.2. Nom de la revue .....
   - 2.3. Année de publication 19..... ou 200.....
   - 2.4. Volume de la revue .....
   - 2.5. Pages de l'article .....

3. Critères d'inclusion (tous les critères doivent être présents)	oui	non
3.1. Article ou abstract publié après revue par des pairs	O	O
3.2. Étude prospective	O	O
3.3. Étude portant sur des patients hospitalisés ou vus en salle d'urgence...	O	O
3.4. Étude portant sur la procalcitonine (PCT)	O	O
3.5. Étude portant sur la protéine C réactive (CRP)	O	O
3.6. Étude cherchant à identifier une infection	O	O

4. Causes d'exclusion a priori de la méta-analyse valables pour toutes les études (NB: un seul critère suffit pour exclure une étude, mais nous vous demandons de cocher tous les raisons d'exclusion de cet article):	oui	non
4.1. Étude confondant les infections avec d'autres pathologies	O	O
4.2. Étude sans groupe-contrôle	O	O
4.3. Étude incluant des patients non-hospitalisés	O	O
4.4. Étude ne portant ni sur la PCT ni sur la CRP	O	O
4.5. Étude ne comportant pas au moins l'un des tests de la question 8 ...	O	O
4.6. Étude ininterprétable	O	O
4.7. Étude faite chez l'animal	O	O
4.8. Étude rétrospective	O	O
4.9. Étude non publiée	O	O
4.10. Étude publiée après le premier avril 2002	O	O
4.11. Étude publiée avant le premier janvier 1970	O	O
4.12. Étude introuvable	O	O

4.13. Étude répétant des données publiées ailleurs ..... O O
4.14. Éditorial, revue, mise à jour, chapitre de livre ..... O O
4.15. Thèse non publiée dans une revue avec comité de lecture ..... O O
4.16. Autre (préciser.....) ..... O O

5. Cause d'exclusion a posteriori de la méta-analyse d'une étude, c'est-à-dire exclusion après analyse des résultats par les 3 experts (N.B.: cette question sera répondue par Jacques Lacroix): oui non
5.1. Données non fournies ni par l'article ni par l'auteur ..... O O
5.2. Impossibilité d'obtenir un consensus des experts ..... O O
5.3. Autre (préciser.....) ..... O O

6. Causes d'exclusion a priori de la partie de la méta-analyse portant sur les données stratifiées selon que le patient recevait ou non des antibiotiques au moment du prélèvement des tests (PCT, CRP, etc.) (NB: un seul critère suffit pour exclure l'étude de cette partie de la méta-analyse, mais nous vous demandons de cocher tous les raisons d'exclusion de cet article): oui non
6.1. Données non fournies ni par l'article ni par l'auteur ..... O O
6.2. Autre (préciser.....) ..... O O

7. Étude publiée sous la forme... oui non
7.1. d'un résumé (abstract) ..... O O
7.2. d'un article ..... O O
7.3. autre type de publication (ex. thèse) ..... O O

8. Description de l'étalon de référence (gold standard) de l'étude. – Les auteurs ont diagnostiqué les infections en se basant sur le ou les critères suivants (cocher toutes les bonnes réponses) : oui non
8.1. On clinical data ..... O O
8.2. On radiological data ..... O O
8.3. On sample of upper respiratory secretions (trachea) ..... O O
8.4. On sample of lower respiratory secretions (brush, BAL, etc) ..... O O
8.5. On blood culture ..... O O
8.6. On urine culture ..... O O
8.7. On culture of spinal fluid ..... O O
8.8. On culture of skin ..... O O
8.9. On a biopsy ..... O O
8.10. On an autopsy ..... O O
8.11. On culture for bacteria ..... O O
8.12. On culture for fungi ..... O O
8.13. On culture for virus ..... O O
8.14. On an increase of antibody titer ..... O O
8.15. On serological identification of germ(s) (i.e. ELISA) ..... O O
8.16. On biochemical identification of germ(s) (i.e. PCR) ..... O O
8.17. On other criteria ..... O O

B) Évaluation des études cliniques [1]

B.1 Données de bases (basic descriptive material): dans cette section, il faut cocher une seule bonne réponse par question.

	oui
1. Biostatisticien:	
1.1. Un biostatisticien fait partie des auteurs	O
1.2. L'aide d'un biostatisticien est signalée dans les remerciements ...	O
1.3. Ni l'un, ni l'autre	O
1.4. Donnée inconnue	O
2. Pays d'origine du projet de recherche (country):	oui
2.1. États-Unis	O
2.2. Royaumes-Unis	O
2.3. Pays scandinaves	O
2.4. Autre pays (spécifier.....)	O
2.5. Donnée inconnue	O
3. Centre(s) hospitalier(s) (center status):	oui
3.1. Un seul centre hospitalier	O
3.2. Multicentrique, mais moins de 5 centres	O
3.3. Multicentrique, et ≥ 5 centres	O
4. Sources de financement; cocher toutes les réponses positives (sources of financial support; multiple items possible):	oui
4.1. N.I.H. ou C.I.H.R.	O
4.2. Autre organisme subventionnaire pourvu d'un comité de révision ...	O
4.3. Autre organisme subventionnaire sans comité de révision	O
4.4. Compagnie pharmaceutique	O
4.5. Autre source (spécifier.....)	O
4.6. Aucune source de financement précisée	O
5. Provenance des patients; cocher toutes les réponses positives (sources of patients; multiple items possible):	oui
5.1. Hôpital universitaire	O
5.2. Hôpital public	O
5.3. Hôpital privé	O
5.4. Clinique non hospitalière	O
5.5. Industrie	O
5.6. Autre source (spécifier.....)	O
5.7. Aucune source précisée	O
6. Signification des résultats (significance of findings; cocher un choix):	oui
6.1. Résultat statistiquement significatif et en faveur du groupe étudié (++; statistically significant treatment or result)	O
6.2. Tendance positive (positive trend in favor of treatment or test) ...	O

[1] La liste de questions inclues dans la section B est inspirée fortement de l'article suivant: Chalmers TC, Smith H, Blackburn B, et al. A method of assessing the quality of a randomized control trial. Controlled Clin Trials 1981;2:31-49.

6.3. Pas de différence (no difference) ..... O
6.4. Tendance négative (trend in favor of control) ..... O
6.5. Résultat statistiquement significatif, mais en faveur du groupe contrôle (statistically significant control) ..... O
6.6. Opininion de l'auteur très en faveur ou très en défaveur du traitement ou du test étudié, mais aucune statistique proposée ..... O
6.7. Statistique non faite ..... O

7. Effet secondaire du traitement ou du test (side effect; ex. pneumothorax): oui
7.1. Incidence statistiquement significative (statistically significant treatment or result) ..... O
7.2. Tendance positive (positive trend in favor of treatment or test) ... O
7.3. Pas d'effets secondaires (no side effects) ..... O
7.4. Données manquantes ..... O

8. Type d'étude; cocher toutes les réponses positives (type of trial; multiple items possible):

	oui	non
8.1. Comparaison simple (simple comparative)	O	O
8.2. Avec blocs (restricted; blocking)	O	O
8.3. Stratifiée (stratified)	O	O
8.4. En chassé-croisé (cross-over)	O	O
8.5. Factorielle (factorial)	O	O
8.6. Autre type (spécifier.....)	O	O
8.7. Type inconnu ou imprécisable	O	O

B.2 Évaluation du plan de l'étude d'un test (evaluation of the design in the study protocol): dans cette section, il faut annoter le pointage approprié pour chaque question.

9. Description de la méthode de collectage des patients (description of the method used to collect patients): ..... points
   - Description adéquate (adequate) : 3 points
   - Description acceptable (fair) : 1.5 points
   - Description inadéquate (inadequate)) : 0 point
10. Description du nombre de patients vus et exclus (number of patients seen and reject log): ..... points
   - Description détaillée: 3 points
   - Description partielle : 1.5 points
   - Aucune description, donnée manquante (unknown)) : 0 point
11. Attrition, c'est-à-dire retrait en cours d'étude (withdrawals): ..... points
   - Description détaillée (list given) : 3 points
   - Pas d'attrition: 1.5 points
   - Aucune liste, donnée manquante (unknown) ou taux de retraits > 15 % pour une étude à long terme ou > 10 % pour une étude ayant duré moins de 3 mois: 0 point
12. Description du test étudié (test definition): ..... points

- Description adéquate (adequate) : 3 points
- Description acceptable (fair) : 1.5 points
- Description inadéquate (inadequate) : 0 point

13. Test servant d'étalon de référence (gold standard used):
    13.1. Description de l'étalon de référence: ..... points
    - L'étalon de référence est précisée de façon adéquate: 3 points
    - L'étalon de référence est précisée de façon acceptable: 1.5 points
    - L'étalon de référence est précisée de façon inadéquate ou il n'est pas précisée (unstated) : 0 point

    13.2. Valeur de l'étalon de référence choisi: ..... points
    - L'étalon de référence est adéquat : 10 points
    - L'étalon de référence est acceptable : 5 points
    - L'étalon de référence est inadéquat : 0 point
14. L'échantillon a été collecté chez des cas consécutifs: ..... points
    - Oui: 3 points
    - Non: 0 point
    - Donnée manquante (unknown) : 0 point
15. Tous les tests ont été faits chez tous les patients inclus dans l'étude: ..... points
    - Oui: 3 points
    - Non: 1.5 points
    - Donnée manquante (unknown) : 0 point
16. Les tests ont été prélevés sans que la condition du patient ne soit connue par la personne faisant le prélèvement: ..... points
    - Oui: 3 points
    - Partiellement: 1.5 points
    - Non ou donnée manquante (unknown) : 0 point
17. Les analyses paracliniques des prélèvements ont été réalisées sans que la condition du patient ne soit connue par la personne faisant l'analyse en laboratoire: ..... points
    - Oui: 8 points
    - Partiellement: 4 points
    - Non ou donnée manquante (unknown) : 0 point
18. Le nombre de patients nécessaires pour réaliser l'étude a été évalué avant que l'étude ne soit commencée (prior estimate of numbers: endpoints selected, difference of clinical interest α and ß estimated): ..... points
    - Oui: 3 points
    - Non ou donnée manquante (unknown) : 0 point

a) Total du pointage pour la section B.2:	..... points
b) Total maximum possible du pointage pour la section B.2:	45 points
Proportion a / b (%):	..... %

B.3 Analyse statistique : dans cette section, il faut annoter le chiffre de la bonne réponse pour chaque question.

19. Évaluation de l'objectif primaire, soit le diagnostic d'infection: ..... points
    - ➢ Le test statistique employé est décrit et les résultats du calcul statistique (p, odds ratio avec son intervalle de confiance à 95 %...) sont précisés: 4 points
    - ➢ Le test statistique fait n'est pas précisé, mais les résultats obtenus le sont: 1 point
    - ➢ Le test statistique fait est précisé, mais pas les résultats obtenus: 1 point
    - ➢ Ni le test statistique, ni les résultats obtenus ne sont précisés: 0 point
20. Inférence statistique
    - 20.1. Intervalle de confiance: ..... points
      - ➢ Oui: 3 points
      - ➢ Non: 0 point
      - ➢ Donnée inappropriée ou donnée manquante (not available) : 0 point
    - 20.2. Régression ou corrélation entre les tests calculée: ..... points
      - ➢ Oui: 2 points
      - ➢ Non: 0 point
      - ➢ Donnée inappropriée ou donnée manquante (not available) : 0 point
    - 20.3. Taux de concordance évalué et rapporté: ..... points
      - ➢ Oui: 2 points
      - ➢ Non: 0 point
      - ➢ Donnée inappropriée ou donnée manquante (not available) : 0 point
    - 20.4. Score de kappa évalué et rapporté: ..... points
      - ➢ Oui: 2 points
      - ➢ Non: 0 point
      - ➢ Donnée inappropriée ou donnée manquante (not available) : 0 point
21. Reproductibilité du test (reproducibility of the test) [2] ..... points
    - ➢ Reproductibilité évaluée: 4 points
    - ➢ Reproductibilité non évaluée: 0 point
22. Validité du test (accuracy of the test) [3]
    - 22.1. Sensibilité, spécificité: ..... points
      - ➢ Sensibilité et spécificité du test évaluées: 4 points
      - ➢ Sensibilité ou spécificité du test évaluée: 2 points
      - ➢ Ni sensibilité ni spécificité évaluée: 0 point
    - 22.2. Courbe receiver oparating characteristic (ROC): ..... points
      - ➢ Courbe ROC construite: 4 points
      - ➢ Pas de courbe ROC: 0 point
23. Les tests statistiques choisis sont-ils appropriés?
    - 23.1. Les tests statistiques choisis sont-ils appropriés? ..... points
      - ➢ Tout à fait (excellent) : 4 points
      - ➢ Plus ou moins (good) : 2 points

---

[2] Cette question est inspirée de l'article suivant: Cook DJ, Fitzgerald JM, Guyatt GH, Walter S. Evaluation of the protected brush catheter and bronchoalveolar lavage in the diagnosis of nosocomial pneumonia. J Intensive Care Med 1991;6:196-205.

[3] Cette question est de notre propre cru.

- Pas tellement (fair) : 1 point
- Pas du tout (poor) : 0 point

23.2. L'analyse statistique est-elle bien faite? ..... points
- Tout à fait (excellent) : 4 points
- Bonne (good) : 2 points
- Assez bonne (fair) : 1 point
- Pas du tout (poor) : 0 point

24. Retraits pendant l'étude (withdrawals).

24.1. Description des retraits dans l'article (description of withdrawals)..... points
- Pertes décrites d'une façon ou l'autre (listed) : 4 points
- Aucun retrait (none) : 4 points
- Pas de description des retraits ou donnée inconnue (no list/unknown) : 0 point
- Taux de retraits > 15 %: 0 point

24.2. Conduite face aux retraits (handling of withdrawals). ..... points
- Pertes analysées d'une façon ou l'autre (analyzed several ways) : 4 points
- Inclus dans la randomization (included in original randomization) : 4 points
- Cas exclus (discarded) : 1 point
- Le cas est changé de groupe (changed groups) : 0 point
- Conduite inconnue (unknown), pas d'attrition ou donnée non disponible (no withdrawal/N.A.) : 0 point

25. Discussion concernant les complications ou les coûts associées au test étudié (side effects discussion). ..... points
- Adéquate: 3 points
- Correcte (fair) : 1.5 points
- Insatisfaisante (poor) ou non disponible (N.A.) : 0 point

26. L'analyste ou le statisticien ont calculé les statistiques sans connaître les résultats attendus (blinding of statistician or analyst to expected results) ..... points
- Oui: 8 points
- Partiellement: 4 points
- Non ou donnée manquante (unknown) : 0 point

a) Total du pointage pour la section B.3:	..... points
b) Total maximum possible du pointage pour la section B.3:	44 points
Proportion a / b (%):	..... %

B.4 Présentation des résultats (presentation of results): dans cette section, il faut annoter le chiffre de la bonne réponse.

27. Les dates du début et de la fin de l'étude sont précisées (dates of starting and stopping accession): ..... points
- Oui : 2 points
- Non: 0 point

28. Résultats avant la randomisation (results of prerandomization); c'est-à-dire analyse des données de base obtenues (baseline data): ..... points

- ➢ Analyse des résultats (data analysis) adéquate: 2 points
- ➢ Analyse des résultats (data analysis) acceptable (fair) : 1 point
- ➢ Analyse des résultats (data analysis) inadéquate ou donnée manquante: 0 point

29. Le temps d'apparition des événements est précisé (timing of events): ..... points
    - ➢ De façon adéquate (adequate) : 4 points
    - ➢ De façon acceptable (fair) : 2 points
    - ➢ De façon inadéquate (inadequate) : 0 point

a) Total du pointage pour la section B.4:	..... points
b) Total maximum possible du pointage pour la section B.4:	8 points
Proportion a / b (%):	..... %

a) Total du pointage des sections B.2, B.3 et B.4 :	..... points
b) Total maximum possible du pointage des sections B.2, B.3 et B.4 :	97 points
Proportion a / b (%):	..... %

C) Extraction des données (annotation des résultats de l'étude)

C.1 Procalcitonine (PCT)

30. Cette étude évaluait la valeur de la PCT pour le diagnostic d'une infection :
    - ❑ Oui
    - ❑ Non

    N.B.: ne pas remplir le reste de la section C.1 si vous avez répondu par la négative à la question précédente.

31. Dans cette étude, la PCT était mesurée par laquelle ou lesquelles des méthodes suivantes (cocher toutes les bonnes réponses)?
    - ❑ Immuno-luminometric assay (LUMItest®PCT, BRAHMS Diagnostica (Berlin, Germany).
    - ❑ Semi-quantitative test (PCT-Q, BRAHMS Diagnostica, Berlin, Germany).
    - ❑ Autre méthode:

32. Dans cette étude, quel était le seuil de PCT considéré comme limite supérieure de la norme? Procalcitonine (PCT): _____ ng/mL.

33. En vous fiant à votre lecture de l'article, les données relatives au diagnostic d'une infection par la PCT étaient les suivantes pour l'ensemble des patients (s'il-vous-plaît, n'écrivez rien dans la table de contingence à droite):

	GOLD STANDARD Infection	GOLD STANDARD No infection
PCT +	TP: ___	FP: ___
PCT –	FN: ___	TN: ___

DATA IN PAPER

	GOLD STANDARD Sepsis	GOLD STANDARD No infection
PCT +	___	___
PCT –	___	___

CORRECTION

34. En vous fiant à votre lecture de l'article, les données relatives au diagnostic d'une infection par la PCT étaient les suivantes pour les ***patients ayant reçu au moins une***

dose d'antibiotique au cours des 24 heures précédant le prélèvement sanguin pour la mesure de la PCT (s'il-vous-plaît, n'écrivez rien dans la table de contingence à droite):

	GOLD STANDARD Infection	No infection	GOLD STANDARD Sepsis	No infection
PCT +	TP: ___	FP: ___	___	___
Test				
PCT –	FN: ___	TN: ___	___	___
	DATA IN PAPER		***CORRECTION***	

35. En vous fiant à votre lecture de l'article, les données relatives au diagnostic d'une infection par la PCT étaient les suivantes pour les ***patients n'ayant pas reçu au moins une dose d'antibiotique*** au cours des 24 heures précédant le prélèvement sanguin pour la mesure de la PCT (s'il-vous-plaît, n'écrivez rien dans la table de contingence à droite):

	GOLD STANDARD Infection	No infection	GOLD STANDARD Sepsis	No infection
PCT +	TP: ___	FP: ___	___	___
Test				
PCT –	FN: ___	TN: ___	___	___
	DATA IN PAPER		***CORRECTION***	

C.2 Protéine C réactive (CRP)

36. Cette étude évaluait la valeur de la CRP pour le diagnostic d'une infection :
    - ☐ Oui
    - ☐ Non

    N.B.: ne pas remplir le reste de la section C.2 si vous avez répondu par la négative à la question précédente.

37. Dans cette étude, quel était le seuil de CRP considéré comme limite supérieure de la norme? C reactive protein (CRP): _____ ng/mL or_____ µg/L

38. En vous fiant à votre lecture de l'article, les données relatives au diagnostic d'une infection par la CRP étaient les suivantes pour l'ensemble des patients (s'il-vous-plaît, n'écrivez rien dans la table de contingence à droite):

	GOLD STANDARD		GOLD STANDARD	
	Infection	No infection	Sepsis	No infection
CRP +	TP: ___	FP: ___	___	___
CRP –	FN: ___	TN: ___	___	___
Test	***DATA IN PAPER***		***CORRECTION***	

39. En vous fiant à votre lecture de l'article, les données relatives au diagnostic d'une infection par la CRP étaient les suivantes pour les ***patients ayant reçu au moins une dose d'antibiotique*** au cours des 24 heures précédant le prélèvement sanguin pour la mesure de la CRP (s'il-vous-plaît, n'écrivez rien dans la table de contingence à droite):

	GOLD STANDARD Infection	GOLD STANDARD No infection
CRP +	TP: ___	FP: ___
CRP –	FN: ___	TN: ___

DATA IN PAPER

	GOLD STANDARD Sepsis	GOLD STANDARD No infection
CRP +	___	___
CRP –	___	___

CORRECTION

40. En vous fiant à votre lecture de l'article, les données relatives au diagnostic d'une infection par la ..... étaient les suivantes pour les ***patients n'ayant pas reçu au moins une dose d'antibiotique*** au cours des 24 heures précédant le prélèvement sanguin pour la mesure de la ..... (s'il-vous-plaît, n'écrivez rien dans la table de contingence à droite):

	GOLD STANDARD Infection	GOLD STANDARD No infection
CRP +	TP: ___	FP: ___
CRP –	FN: ___	TN: ___

DATA IN PAPER

	GOLD STANDARD Sepsis	GOLD STANDARD No infection
CRP +	___	___
CRP –	___	___

CORRECTION

C.3 Autre test

41. Cette étude évaluait la valeur de ..... pour le diagnostic d'une infection :
    - ☐ Oui
    - ☐ Non

    N.B.: ne pas remplir le reste de la section C.3 si vous avez répondu par la négative à la question précédente.

42. Dans cette étude, quel était le seuil de ..... considéré comme limite supérieure de la norme? _____

43. En vous fiant à votre lecture de l'article, les données relatives au diagnostic d'une infection par la ..... étaient les suivantes pour l'ensemble des patients (s'il-vous-plaît, n'écrivez rien dans la table de contingence à droite):

		GOLD STANDARD		GOLD STANDARD	
		Infection	No infection	Sepsis	No infection
_____	Test	TP: ___	FP: ___	___	___
_____		FN: ___	TN: ___	___	___
		DATA IN PAPER		***CORRECTION***	

44. En vous fiant à votre lecture de l'article, les données relatives au diagnostic d'une infection par la ..... étaient les suivantes pour les ***patients ayant reçu au moins une dose d'antibiotique*** au cours des 24 heures précédant le prélèvement sanguin pour la mesure de la ..... (s'il-vous-plaît, n'écrivez rien dans la table de contingence à droite):

	GOLD STANDARD Infection	GOLD STANDARD No infection
_____	TP: ___	FP: ___
Test		
_____	FN: ___	TN: ___

DATA IN PAPER

	GOLD STANDARD Sepsis	GOLD STANDARD No infection
	___	___
	___	___

CORRECTION

45. En vous fiant à votre lecture de l'article, les données relatives au diagnostic d'une infection par la ..... étaient les suivantes pour les ***patients n'ayant pas reçu au moins une dose d'antibiotique*** au cours des 24 heures précédant le prélèvement sanguin pour la mesure de la CRP (s'il-vous-plaît, n'écrivez rien dans la table de contingence à droite):

	GOLD STANDARD Infection	GOLD STANDARD No infection
_____	TP: ___	FP: ___
Test		
_____	FN: ___	TN: ___

DATA IN PAPER

	GOLD STANDARD Sepsis	GOLD STANDARD No infection
	___	___
	___	___

CORRECTION

Annex IV: Layout of the letter to the authors

Date

Address

Re: meta-analysis PCT and CRP

Dear Dr.:

We are performing a meta-analysis on the validity of PCT and CRP as diagnostic markers of infection in hospitalized patients. This meta-analysis will include this paper that you have written:

Since this meta-analysis should include your paper, we would like you to verify the following data and to answer to the following questions:

In this study, the test evaluated was/were:

- ❑ Procalcitonin (PCT)
- ❑ C-reactive protein (CRP)

In this study, the diagnosis of infection was based on (please, check all positive answers)

- ❑ clinical data
- ❑ radiological data
- ❑ sample of tracheal respiratory secretions
- ❑ sample of lower respiratory secretions (brush specimen, bronchoalveolar lavage, etc)
- ❑ blood culture
- ❑ catheter tip culture
- ❑ culture of spinal fluid
- ❑ stool culture
- ❑ urine culture
- ❑ culture of skin
- ❑ a biopsy
- ❑ an autopsy
- ❑ culture for bacteria
- ❑ culture for fungi
- ❑ culture for virus
- ❑ increase of antibody titer
- ❑ serological identification of germ(s) (i.e. ELISA)
- ❑ biochemical identification of germ(s) (i.e. PCR)
  Please, specify: _____
- ❑ other criteria:
  Please, specify: _____

Data on procalcitonin (PCT)

From your paper we extracted the number of patients in each category (infection vs no infection) according to PCT results (contingency table on the left). Please, complete the contingency table on the right if the data is incorrect.

GOLD STANDARD

Threshold ng/mL	Infection	No Infection
PCT +	TP:	FP:
PCT -	FN:	TN:
	N =	N =

DATA IN THE PAPER

GOLD STANDARD

Threshold _____	Infection	No Infection
PCT +	TP:	FP:
PCT -	FN:	TN:
	N = ____	N = ____

CORRECTION

Data on C-reactive protein (CRP)

From your paper we extracted the number of patients in each category (infection vs no infection) according to CRP results (contingency table on the left). Please, complete the contingency table on the right if the data is incorrect.

GOLD STANDARD

Threshold mg/dL	Infection	No Infection
CRP +	TP:	FP:
CRP -	FN:	TN:
	N =	N =

DATA IN THE PAPER

GOLD STANDARD

Threshold _____	Infection	No Infection
CRP +	TP:	FP:
CRP -	FN:	TN:
	N = ____	N = ____

CORECTION

Attached to this letter is a list of papers we found that evaluated the validation of PCT or CRP for diagnosis of infection in hospitalized patients. If you are aware of any other paper or study — published or not — on the subject, please write these references or indicate the address of the principal authors.

Please, return this questionnaire with the label enclosed.
I thank you for your kind attention to this matter.
Sincerely,

Jacques Lacroix, M.D.
Division of Pediatric Intensive Care
Department of Pediatrics
Sainte-Justine Hospital
3175 Côte Sainte-Catherine
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FAX: (514)-345-4822
E-mail: [redacted]

List of references on the validation of PCT or CRP for the diagnosis of infection in hospitalized patients

1. Adamik, B., et al., *Effect of sepsis and cardiac surgery with cardiopulmonary bypass on plasma level of nitric oxide metabolites, neopterin, and procalcitonin: correlation with mortality and postoperative complications.* Intensive Care Med, 2000. **26**(9): p. 1259-67.
2. Aouifi, A., et al., *Usefulness of procalcitonin for diagnosis of infection in cardiac surgical patients.* Crit Care Med, 2000. **28**(9): p. 3171-6.
3. Arber, C., et al., *C-reactive protein and fever in neutropenic patients.* Scand J Infect Dis, 2000. **32**(5): p. 515-20.
4. Assicot, M., et al., *High serum procalcitonin concentrations in patients with sepsis and infection.* Lancet, 1993. **341**(8844): p. 515-8.
5. Benitz, W.E., et al., *Serial serum C-reactive protein levels in the diagnosis of neonatal infection.* Pediatrics, 1998. **102**(4): p. E41.
6. Berland, M., et al., *[The significance of the level of C-reactive protein in gynecologic infections].* Rev Fr Gynecol Obstet, 1990. **85**(10): p. 539-44.
7. Boeken, U., et al., *Increased preoperative C-reactive protein (CRP)-values without signs of an infection and complicated course after cardiopulmonary bypass (CPB)- operations.* Eur J Cardiothorac Surg, 1998. **13**(5): p. 541-5.
8. Boeken, U., et al., *Procalcitonin (PCT) in cardiac surgery: diagnostic value in systemic inflammatory response syndrome (SIRS), sepsis and after heart transplantation (HTX).* Cardiovasc Surg, 2000. **8**(7): p. 550-4.
9. Bohuon, C., et al., *[Procalcitonin, a marker of bacterial meningitis in children].* Bull Acad Natl Med, 1998. **182**(7): p. 1469-75.
10. Borschsenius, F., et al., *Serum C-reactive protein in systemic infections due to Neisseria meningitidis.* NIPH Ann, 1986. **9**(1): p. 15-21.
11. Cadwgan, A.M., et al., *Presenting clinical features and C-reactive protein in the prediction of a positive stool culture in patients with diarrhoea.* J Infect, 2000. **41**(2): p. 159-61.
12. Chiba, Y., et al., *Postoperative inflammatory reactions of impregnated Dacron grafts.* Surg Today, 1999. **29**(11): p. 1225-8.
13. Chiesa, C., et al., *Reliability of procalcitonin concentrations for the diagnosis of sepsis in critically ill neonates.* Clin Infect Dis, 1998. **26**(3): p. 664-72.
14. Chiu, C.H., T.Y. Lin, and M.J. Bullard, *Identification of febrile neonates unlikely to have bacterial infections.* Pediatr Infect Dis J, 1997. **16**(1): p. 59-63.
15. Claeys, R., et al., *Plasma procalcitonin and C-reactive protein in acute septic shock: clinical and biological correlates.* Crit Care Med, 2002. **30**(4): p. 757-62.
16. Cobben, J.M., et al., *[CRP versus BSE in pediatrics. How good is a diagnostic test?].* Tijdschr Kindergeneeskd, 1990. **58**(5): p. 169-74.
17. Cox, M.L., et al., *Real-time measurement of serum C-reactive protein in the management of infection in the elderly.* Age Ageing, 1986. **15**(5): p. 257-66.
18. de Werra, I., et al., *Cytokines, nitrite/nitrate, soluble tumor necrosis factor receptors, and procalcitonin concentrations: comparisons in patients with septic shock, cardiogenic shock, and bacterial pneumonia.* Crit Care Med, 1997. **25**(4): p. 607-13.

19. Del Beccaro, M.A., et al., *Acute-phase reactants and acute bacterial otitis media.* Am J Dis Child, 1992. **146**(9): p. 1037-9.
20. Dev, D., et al., *Value of C-reactive protein measurements in exacerbations of chronic obstructive pulmonary disease.* Respir Med, 1998. **92**(4): p. 664-7.
21. Diculencu, D., et al., *[The value of C-reactive protein for the differentiation of bacterial meningitis from viral meningitis].* Rev Med Chir Soc Med Nat Iasi, 1995. **99**(1-2): p. 144-50.
22. Dinant, G.J., C.A. de Kock, and J.W. van Wersch, *Diagnostic value of C-reactive protein measurement does not justify replacement of the erythrocyte sedimentation rate in daily general practice.* Eur J Clin Invest, 1995. **25**(5): p. 353-9.
23. Dofferhoff, A.S., et al., *Patterns of cytokines, plasma endotoxin, plasminogen activator inhibitor, and acute-phase proteins during the treatment of severe sepsis in humans.* Crit Care Med, 1992. **20**(2): p. 185-92.
24. Enguix, A., et al., *Comparison of procalcitonin with C-reactive protein and serum amyloid for the early diagnosis of bacterial sepsis in critically ill neonates and children.* Intensive Care Med, 2001. **27**(1): p. 211-5.
25. Eriksson, S., et al., *White blood cell count, leucocyte elastase activity, and serum concentrations of interleukin-6 and C-reactive protein after open appendicectomy.* Eur J Surg, 1997. **163**(2): p. 123-7.
26. Fassbender, K., et al., *Interleukin-6 and acute-phase protein concentrations in surgical intensive care unit patients: diagnostic signs in nosocomial infection.* Crit Care Med, 1993. **21**(8): p. 1175-80.
27. Flores, J.M., et al., *[C reactive protein as marker of infection among patients with severe closed trauma].* Enferm Infecc Microbiol Clin, 2001. **19**(2): p. 61-5.
28. Fransen, E.J., et al., *Enhanced preoperative C-reactive protein plasma levels as a risk factor for postoperative infections after cardiac surgery.* Ann Thorac Surg, 1999. **67**(1): p. 134-8.
29. Gendrel, D., et al., *Measurement of procalcitonin levels in children with bacterial or viral meningitis.* Clin Infect Dis, 1997. **24**(6): p. 1240-2.
30. Gendrel, D., et al., *Comparison of procalcitonin with C-reactive protein, interleukin 6 and interferon-alpha for differentiation of bacterial vs. viral infections.* Pediatr Infect Dis J, 1999. **18**(10): p. 875-81.
31. Gervaix, A., et al., *Usefulness of procalcitonin and C-reactive protein rapid tests for the management of children with urinary tract infection.* Pediatr Infect Dis J, 2001. **20**(5): p. 507-11.
32. Harbarth, S., et al., *Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis.* Am J Respir Crit Care Med, 2001. **164**(3): p. 396-402.
33. Hatherill, M., et al., *Diagnostic markers of infection: comparison of procalcitonin with C reactive protein and leucocyte count.* Arch Dis Child, 1999. **81**(5): p. 417-21.
34. Hatherill, M., et al., *Procalcitonin and cytokine levels: relationship to organ failure and mortality in pediatric septic shock.* Crit Care Med, 2000. **28**(7): p. 2591-4.

35. Hedlund, J. and L.O. Hansson, *Procalcitonin and C-reactive protein levels in community-acquired pneumonia: correlation with etiology and prognosis.* Infection, 2000. **28**(2): p. 68-73.
36. Heiskanen-Kosma, T. and M. Korppi, *Serum C-reactive protein cannot differentiate bacterial and viral aetiology of community-acquired pneumonia in children in primary healthcare settings.* Scand J Infect Dis, 2000. **32**(4): p. 399-402.
37. Herrmann, W., et al., *Comparison of procalcitonin, sCD14 and interleukin-6 values in septic patients.* Clin Chem Lab Med, 2000. **38**(1): p. 41-6.
38. Hjortdahl, P., et al., *C-reactive protein: a new rapid assay for managing infectious disease in primary health care.* Scand J Prim Health Care, 1991. **9**(1): p. 3-10.
39. Hogarth, M.B., et al., *Acute phase proteins, C-reactive protein and serum amyloid A protein, as prognostic markers in the elderly inpatient.* Age Ageing, 1997. **26**(2): p. 153-8.
40. Hogevik, H., et al., *C-reactive protein is more sensitive than erythrocyte sedimentation rate for diagnosis of infective endocarditis.* Infection, 1997. **25**(2): p. 82-5.
41. Huber-Spitzy, V., et al., *Diagnosis and therapy of bacterial endophthalmitis, and serum levels of inflammation markers.* Infection, 1992. **20**(3): p. 122-7.
42. Icard, P., et al., *Utility of C-reactive protein measurements for empyema diagnosis after pneumonectomy.* Ann Thorac Surg, 1994. **57**(4): p. 933-6.
43. Juffrie, M., et al., *Inflammatory mediators in dengue virus infection in children: interleukin-6 and its relation to C-reactive protein and secretory phospholipase A2.* Am J Trop Med Hyg, 2001. **65**(1): p. 70-5.
44. Katz, J.A., et al., *Value of C-reactive protein determination in the initial diagnostic evaluation of the febrile, neutropenic child with cancer.* Pediatr Infect Dis J, 1992. **11**(9): p. 708-12.
45. Kornman, L., et al., *Chorioamnionitis: how useful is the determination of C-reactive protein?* Aust N Z J Obstet Gynaecol, 1988. **28**(1): p. 45-8.
46. Korppi, M. and L. Kroger, *C-reactive protein in viral and bacterial respiratory infection in children.* Scand J Infect Dis, 1993. **25**(2): p. 207-13.
47. Korppi, M., T. Heiskanen-Kosma, and M. Leinonen, *White blood cells, C-reactive protein and erythrocyte sedimentation rate in pneumococcal pneumonia in children.* Eur Respir J, 1997. **10**(5): p. 1125-9.
48. Kragsbjerg, P., H. Holmberg, and T. Vikerfors, *Serum concentrations of interleukin-6, tumour necrosis factor-alpha, and C-reactive protein in patients undergoing major operations.* Eur J Surg, 1995. **161**(1): p. 17-22.
49. Krediet, T., et al., *The predictive value of CRP and I/T-ratio in neonatal infection.* J Perinat Med, 1992. **20**(6): p. 479-85.
50. Ksssler, A., C. Grunert, and W.G. Wood, *The limitations and usefulness of C-reactive protein and elastase-alpha 1-proteinase inhibitor complexes as analytes in the diagnosis and follow-up of sepsis in newborns and adults.* Eur J Clin Chem Clin Biochem, 1994. **32**(5): p. 365-8.

51. Kunzig, H.J., et al., *[Acute phase proteins (C-reactive protein, orosomucoid, haptoglobin)-- specific markers in the diagnosis of inflammatory adnexal diseases].* Geburtshilfe Frauenheilkd, 1985. **45**(12): p. 881-6.
52. Kuse, E.R., et al., *Procalcitonin in fever of unknown origin after liver transplantation: a variable to differentiate acute rejection from infection.* Crit Care Med, 2000. **28**(2): p. 555-9.
53. Lembo, R.M. and C.D. Marchant, *Acute phase reactants and risk of bacterial meningitis among febrile infants and children.* Ann Emerg Med, 1991. **20**(1): p. 36-40.
54. Lorrot, M., et al., *[Procalcitonin in pediatric emergencies: comparison with C-reactive protein, interleukin-6 and interferon alpha in the differentiation between bacterial and viral infections].* Presse Med, 2000. **29**(3): p. 128-34.
55. Marc, E., et al., *[Procalcitonin and viral meningitis: reduction of unnecessary antibiotics by measurement during an outbreak].* Arch Pediatr, 2002. **9**(4): p. 358-64.
56. Marchand, A., F. Van Lente, and R.S. Galen, *The assessment of laboratory tests in the diagnosis of acute appendicitis.* Am J Clin Pathol, 1983. **80**(3): p. 369-74.
57. Matson, A., N. Soni, and J. Sheldon, *C-reactive protein as a diagnostic test of sepsis in the critically ill.* Anaesth Intensive Care, 1991. **19**(2): p. 182-6.
58. Matsuo, S., et al., *[Clinical and laboratory correspondence to outpatients with the extreme value of C-reactive protein].* Rinsho Byori, 1992. **40**(12): p. 1307-11.
59. Meisner, M., et al., *Postoperative plasma concentrations of procalcitonin after different types of surgery.* Intensive Care Med, 1998. **24**(7): p. 680-4.
60. Mercer, L.J., B.S. Block, and S.N. Hajj, *Measurement of C-reactive protein to compare ceftizoxime versus cefoxitin/doxycycline therapy for septic pelvis: a preliminary report.* Clin Ther, 1987. **10**(Suppl A): p. 59-65.
61. Mercer, L.J., et al., *Use of C-reactive protein to predict the outcome of medical management of tuboovarian abscesses.* J Reprod Med, 1988. **33**(1 Suppl): p. 164-7.
62. Miller, P.R., et al., *Systemic inflammatory response syndrome in the trauma intensive care unit: who is infected?* J Trauma, 1999. **47**(6): p. 1004-8.
63. Mimoz, O., et al., *Procalcitonin and C-reactive protein during the early posttraumatic systemic inflammatory response syndrome.* Intensive Care Med, 1998. **24**(2): p. 185-8.
64. Moulin, F., et al., *Procalcitonin in children admitted to hospital with community acquired pneumonia.* Arch Dis Child, 2001. **84**(4): p. 332-6.
65. Muller, B., et al., *Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit.* Crit Care Med, 2000. **28**(4): p. 977-83.
66. Mustard, R.A., Jr., et al., *C-reactive protein levels predict postoperative septic complications.* Arch Surg, 1987. **122**(1): p. 69-73.
67. Nylen, E.S., et al., *Pneumonitis-associated hyperprocalcitoninemia.* Am J Med Sci, 1996. **312**(1): p. 12-8.
68. Oberhoffer, M., et al., *Outcome prediction by traditional and new markers of inflammation in patients with sepsis.* Clin Chem Lab Med, 1999. **37**(3): p. 363-8.

69. Oberhoffer, M., et al., *Sensitivity and specificity of various markers of inflammation for the prediction of tumor necrosis factor-alpha and interleukin-6 in patients with sepsis.* Crit Care Med, 1999. **27**(9): p. 1814-8.
70. Ortqvist, A., et al., *Diagnostic and prognostic value of interleukin-6 and C-reactive protein in community-acquired pneumonia.* Scand J Infect Dis, 1995. **27**(5): p. 457-62.
71. Panichi, V., et al., *Plasma C-reactive protein in hemodialysis patients: a cross-sectional, longitudinal clinical survey.* Blood Purif, 2000. **18**(1): p. 30-6.
72. Parnaby, R.M., et al., *The value of serum C-reactive protein levels as a marker of sepsis in intensive care unit patients.* Clin Intensive Care, 1994. **5**(3): p. 106-13.
73. Peltola, H.O., *C-reactive protein for rapid monitoring of infections of the central nervous system.* Lancet, 1982. **1**(8279): p. 980-2.
74. Penel, N., et al., *[Fever and solid tumor: diagnostic value of procalcitonin and C-reactive protein].* Rev Med Interne, 2001. **22**(8): p. 706-14.
75. Pettila, V., et al., *Predictive value of antithrombin III and serum C-reactive protein concentration in critically ill patients with suspected sepsis.* Crit Care Med, 2002. **30**(2): p. 271-5.
76. Philip, A.G. and P.C. Mills, *Use of C-reactive protein in minimizing antibiotic exposure: experience with infants initially admitted to a well-baby nursery.* Pediatrics, 2000. **106**(1): p. E4.
77. Pinilla, J.C., et al., *The C-reactive protein to prealbumin ratio correlates with the severity of multiple organ dysfunction.* Surgery, 1998. **124**(4): p. 799-805; discussion 805-6.
78. Pinkola, K. and K. Darvas, *[Procalcitonin rapid test in surgical patients treated in the intensive care unit].* Magy Seb, 2001. **54**(6): p. 368-70.
79. Povoa, P., et al., *C-reactive protein as an indicator of sepsis.* Intensive Care Med, 1998. **24**(10): p. 1052-6.
80. Pulliam, P.N., M.W. Attia, and K.M. Cronan, *C-reactive protein in febrile children 1 to 36 months of age with clinically undetectable serious bacterial infection.* Pediatrics, 2001. **108**(6): p. 1275-9.
81. Putto, A., et al., *C reactive protein in the evaluation of febrile illness.* Arch Dis Child, 1986. **61**(1): p. 24-9.
82. Racine, A., et al., *[The value of the C-reactive protein assay for the early diagnosis of neonatal infection at the maternity ward and pediatric service of a general hospital center].* Ann Pediatr (Paris), 1989. **36**(4): p. 253-7.
83. Rothenburger, M., et al., *Detection of acute phase response and infection. The role of procalcitonin and C-reactive protein.* Clin Chem Lab Med, 1999. **37**(3): p. 275-9.
84. Ruiz-Laiglesia, F.J., et al., *[Value of C-reactive protein for detecting bacteremia in febrile patients].* Presse Med, 1996. **25**(24): p. 1105-8.
85. Ruokonen, E., et al., *Procalcitonin and neopterin as indicators of infection in critically ill patients.* Acta Anaesthesiol Scand, 2002. **46**(4): p. 398-404.
86. Sabat, R., et al., *Massive elevation of procalcitonin plasma levels in the absence of infection in kidney transplant patients treated with pan-T-cell antibodies.* Intensive Care Med, 2001. **27**(6): p. 987-91.

87. Schwarz, S., et al., *Serum procalcitonin levels in bacterial and abacterial meningitis.* Crit Care Med, 2000. **28**(6): p. 1828-32.
88. Selberg, O., et al., *Discrimination of sepsis and systemic inflammatory response syndrome by determination of circulating plasma concentrations of procalcitonin, protein complement 3a, and interleukin-6.* Crit Care Med, 2000. **28**(8): p. 2793-8.
89. Sheldon, J., et al., *C-reactive protein and its cytokine mediators in intensive-care patients.* Clin Chem, 1993. **39**(1): p. 147-50.
90. Shortland, D.B., et al., *Evaluation of C. reactive protein values in neonatal sepsis.* J Perinat Med, 1990. **18**(3): p. 157-63.
91. Singh, U.K., et al., *C-reactive protein as an indicator of complications in bacterial meningitis.* Indian Pediatr, 1996. **33**(5): p. 373-6.
92. Smith, R.P., et al., *C-reactive protein. A clinical marker in community-acquired pneumonia.* Chest, 1995. **108**(5): p. 1288-91.
93. Soderquist, B., et al., *Interleukin-6, C-reactive protein, lactoferrin and white blood cell count in patients with S. aureus septicemia.* Scand J Infect Dis, 1995. **27**(4): p. 375-80.
94. Somech, R., et al., *Procalcitonin correlates with C-reactive protein as an acute-phase reactant in pediatric patients.* Isr Med Assoc J, 2000. **2**(2): p. 147-50.
95. Suprin, E., et al., *Procalcitonin: a valuable indicator of infection in a medical ICU?* Intensive Care Med, 2000. **26**(9): p. 1232-8.
96. Torre, D., et al., *Acute-phase proteins and levels of interleukin 1B, interleukin 6, tumor necrosis factor alpha, and interleukin 8 in children with pertussis.* Am J Dis Child, 1993. **147**(1): p. 27-9.
97. Tschaikowsky, K., et al., *Coincidence of pro- and anti-inflammatory responses in the early phase of severe sepsis: Longitudinal study of mononuclear histocompatibility leukocyte antigen-DR expression, procalcitonin, C-reactive protein, and changes in T-cell subsets in septic and postoperative patients.* Crit Care Med, 2002. **30**(5): p. 1015-23.
98. Ugarte, H., et al., *Procalcitonin used as a marker of infection in the intensive care unit.* Crit Care Med, 1999. **27**(3): p. 498-504.
99. Unkila-Kallio, L., M.J. Kallio, and H. Peltola, *The usefulness of C-reactive protein levels in the identification of concurrent septic arthritis in children who have acute hematogenous osteomyelitis. A comparison with the usefulness of the erythrocyte sedimentation rate and the white blood-cell count.* J Bone Joint Surg Am, 1994. **76**(6): p. 848-53.
100. van den Broek, P.J., A.M. Radder, and J. Hermans, *[The significance of body temperature, sedimentation, C-reactive protein, leukocyte count and differential for the diagnosis of infections in an internal medicine emergency department].* Ned Tijdschr Geneeskd, 1990. **134**(52): p. 2536-40.
101. van Langevelde, P., et al., *Endotoxin, cytokines, and procalcitonin in febrile patients admitted to the hospital: identification of subjects at high risk of mortality.* Clin Infect Dis, 2000. **31**(6): p. 1343-8.
102. Vanlieferinghen, P., et al., *[C-reactive protein and orosomucoid determinations in a neonatal pathology unit].* Pediatrie, 1986. **41**(2): p. 121-5.

103. Viallon, A., et al., *Serum and ascitic procalcitonin levels in cirrhotic patients with spontaneous bacterial peritonitis: diagnostic value and relationship to pro-inflammatory cytokines.* Intensive Care Med, 2000. **26**(8): p. 1082-8.
104. Virkki, R., et al., *Differentiation of bacterial and viral pneumonia in children.* Thorax, 2002. **57**(5): p. 438-41.
105. von Heimburg, D., et al., *Procalcitonin--a sepsis parameter in severe burn injuries.* Burns, 1998. **24**(8): p. 745-50.
106. Wanner, G.A., et al., *Relationship between procalcitonin plasma levels and severity of injury, sepsis, organ failure, and mortality in injured patients.* Crit Care Med, 2000. **28**(4): p. 950-7.
107. Whang, K.T., et al., *Serum calcitonin precursors in sepsis and systemic inflammation.* J Clin Endocrinol Metab, 1998. **83**(9): p. 3296-301.
108. Yentis, S.M., N. Soni, and J. Sheldon, *C-reactive protein as an indicator of resolution of sepsis in the intensive care unit.* Intensive Care Med, 1995. **21**(7): p. 602-5.

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