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Interleukin-6 for diagnosis of sepsis in critically ill adult patients (Protocol)

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[Diagnostic Test Accuracy Protocol]

Interleukin-6 for diagnosis of sepsis in critically ill adult patients

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To determine the diagnostic accuracy of interleukin-6 (IL-6) for the diagnosis of bacterial sepsis in critically ill adult patients.

1. To explore the effect of different thresholds in the accuracy of IL-6 for the diagnosis of sepsis

2. To determine whether the pathological source of sepsis (i.e. pneumonia, bacteraemia, urinary infections, among others) or other pre-specified sources have an influence on the accuracy of IL-6 as an diagnostic tool

BACKGROUND

The diagnosis of sepsis in critically ill patients with non-specific findings of an acute inflammatory process can be challenging and non-infectious conditions must be considered in the differential diagnosis (Harbarth 2001). The diagnosis of sepsis, in a significant number of cases, becomes clear after completing the patient medical history and physical examination. However, in other circumstances, such as in comatose patients, the diagnosis of sepsis remains difficult (Abraham 2000). Currently, the reference standard for the diagnosis of sepsis is based on clinical findings and the isolation of microorganisms. However, no single clinical or biological indicator of sepsis has gained unanimous acceptance (Bloss 2014; Boucher 1999).

Target condition being diagnosed

Sepsis is defined as a systemic inflammatory response syndrome in the presence of a documented or suspected infection (Dellinger

2013; Shankar-Hari 2015). Systemic inflammatory response syndrome involves changes, by unknown causes, of clinical baseline parameters, including body temperature > 38.3°C, hypothermia with core temperature < 36°C, heart rate > 90 beats/minute, respiratory rate > 20 breaths/minute or arterial partial pressure of carbon dioxide < 32 mm Hg, a white blood cell count > 12,000/mm^3 or < 4,000/mm^3, or > 10% immature neutrophils (Rangel-Frausto 1995). Sepsis can be severe when it is accompanied by evidence of acute organ dysfunction or tissue hypoperfusion, and septic shock is defined as sepsis-induced hypotension despite of adequate fluid resuscitation (Dellinger 2013). Initially, in patients with symptoms of sepsis, the attending physician uses the term "clinically suspected infection" to indicate the suspicion of an ongoing infection, followed by prescribing immediate initiation of antimicrobial therapy and submitting a request for a complete set of tests to determine the presence or absence of an infection (Rangel-Frausto 1995). Currently, positive cultures are the only objective outcome to confirm this diagnosis (Naafa 2004; Sands 1997).

Sepsis originates as an infection with bacteria, fungus, virus or parasites (Dellinger 2013). One half (52%) of sepsis cases in hospitals in the United States originated from gram-positive bacteria (Finfer 2004). For bacteria to cause infections, they must evade the immune system of the host, either at the site of infection or in the bloodstream. Innate immune cells recognize pathogenic microorganisms by sensing common microbial structures known as pathogen-associated molecular patterns, such as lipoteichoic acid, lipopeptides, lipopolysaccharide and nucleic acids (Christaki 2014). The first barriers to pathogen invasion are the skin and mucosal surfaces. Neutrophils are the primary and most important cells that defend the host against invading pathogens. Other mechanisms of defence include monocytes and macrophages, cytokine storm, and complement activation. The interaction between cells and other mechanisms present unique features in the pathogenesis and they are under the influence of the genetic make-up of the host (Christaki 2014).

The worldwide incidence of severe sepsis is about 1 case per 1000 patients (standard deviation (SD) = 0.5), of which near 10% (SD = 4%) of patients treated at intensive care units (ICUs) are affected (Linde-Zwirble 2004). A retrospective cohort study in seven states in the United States that identified 192,980 cases of severe sepsis, with an estimated incidence of sepsis of three cases per 1000 persons at population level, and 2.26 cases per 100 hospital discharges; the authors projected an increase in severe sepsis by 1.5% per year (Angus 2001).Finfer 2004 reported that 11.8 per 100 patients admitted to an ICU between 1999 to 2000 were diagnosed with severe sepsis, with an incidence of 0.77 (95% confidence interval (CI) = 0.76 to 0.79) per 1000 adult patients. According to Kumar 2011, the mortality rate for severe sepsis decreased from 39% to 27% between 2000 and 2007. However, the rates of mortality were higher in persons with more organ systems failing. In 2011, the average costs for the treatment of severe sepsis were USD$ 22,100 per case and expenses can be even higher depending on patient age, the need for surgical procedures, the presence of organ failure, and variation in costs charged by ICUs (Angus 2001).

Deficiency of the immune system is a risk factor for the development of sepsis, which can be caused by functional asplenia, infectious disease or haematologic malignancy (Dellinger 2013). Moreover, malignancy has been associated with an increase in the incidence of sepsis, with a relative risk of 9.77 (95% CI = 9.67 to 9.88) as compared to non-cancer patients (Danai 2006). Complications associated with the onset of sepsis include acute renal failure, polyneuropathy, cardiomyopathy and multiple organ dysfunction (Latronico 2011; Puthucheary 2013; Romero-Bermejo 2011). Survivors of sepsis report persistent problems that can last for years after hospital discharge. About 50 to 70% of sepsis survivors report physical alterations (weakness and dyspnoea), psychological problems (post-traumatic stress syndrome and depression), cognitive (poor concentration and memory loss) and social issues (delayed return to work and loss of earnings) (Dowdy 2005). Management of septic stages remains a daily challenge for clinicians. Therefore, early administration of effective intravenous antimicrobials is highly recommended due to its association with a reduced mortality (Castellanos-Ortega 2010; Ferrer 2009).

Index test(s)

Interleukin-6 (IL-6) is a cytokine secreted by activated monocytes and macrophages, which mediates a wide range of biological activities. Some studies have shown that administration of cytokines such as IL-1 and tumour necrosis factor (TNF), induce a state of shock with haemodynamic and haematologic alterations, which are classic characteristics of septic stages (Carson 1999; Dinarello 1997; Hauptmann 1991; van der Poll 1990). Both IL-6 and IL-1 play a role in the stimulation of the synthesis of adrenocorticotropic hormone in the pituitary gland. They induce the synthesis of neuronal growth factor, and regulate growth and development of haematopoietic cells and embryonic stem cells (Song 2005). IL-6 is an endogenous pyrogen which play a role in systemic changes associated with infection, tissue injury and in stimulation of hepatic protein synthesis during acute-phase responses (Kishimoto 1995). IL-6 concentrations can be measured with samples at different times during hospitalization, and several commercial assays have been employed to quantify IL-6 in plasma (Thompson 2012).

In healthy adults without an inflammation process, IL-6 concentrations range from 0.2 to 7.8 pg/mL; while IL-6 concentrations in adults with sepsis can exceed 1600 pg/mL (Thompson 2012). However, clinical response and the severity of infection affects the values of IL-6 in adults, but this relationship is not clear in children (Aneja 2011). On the contrary, IL-6 concentrations in newborns are 18 to 26 pg/mL with a significant decrease during the first few years of life without presence of infection (Song 2005). Some authors have reported elevated levels of IL-6 in paediatric burned patients without sepsis (Finnerty 2007).

Clinical pathway

Clinical presentation of sepsis starts with consideration of SIRS and immediate treatment is required. Management of patients with systemic inflammatory response syndrome, and suspected sepsis, includes infusion of solutions to replenish intravascular fluids, the administration of antibiotics, samples taken for cultures, and searching for microorganism(s) usually not found in culture of sterile tissue (Dellinger 2013). Current clinical practice guidelines recommend administration of effective intravenous antimicrobials within the first hour of recognition of septic shock, as well as empiric antimicrobial therapy, including one or more drugs that have activity against most pathogens (Dellinger 2013; Green 2008; Reinhart 2010). However, the problem of this strategy is the overtreatment of patients with noninfectious diseases, which can induce increased economic costs and antimicrobial resistance. Only in cases of difficult-to-culture pathogens or in clinical situations where suspected infection is not clear, the use of biomarkers to guide empiric antimicrobial agents have been suggested (Dellinger 2013).

Prior test(s)

No prior tests for the diagnosis of sepsis have been proposed. Identification of signs of inflammation and/or end-organ hypoperfusion by a clinical assessment are the basis of further tests, including blood tests and microbiological cultures (Dellinger 2013; Rizoli 2002).

Role of index test(s)

Diagnosis of sepsis is based on clinical symptoms. However, in early stages, classification still remains problematic. Blood cultures remain the standard tests for the diagnosis of sepsis, though the results can take 24 to 48 hours. Likewise, the results of the blood cultures may be undetermined with difficult-to-culture pathogens or when an empiric antimicrobial was administered (Dellinger 2013). Biomarkers used for the diagnosis of sepsis may provide faster results in comparison with microbiology tests, what results in an enhanced initiation of treatment (Boucher 1999). IL-6 appears to be a mediator of sepsis and its secretion is rapidly induced in the course of acute inflammatory reactions (Song 2005). Most patients with sepsis have increased plasma levels of IL-6 at their admission to the ICU (Waage 1989). High IL-6 levels have been directly associated with risk of death, especially death caused by intra-abdominal sepsis (Patel 1994). Likewise, an association between mean plasma IL-6 concentration over time and mortality rate has been shown**.** Persistent elevation of IL-6 appears to be more important than that of the initial or peak levels in terms of outcome (Pinsky 1993). IL-6 could be proposed as an early marker of sepsis. When the detection of IL-6 levels demonstrates high specificity and sensitivity, it could play an important role in replacing other diagnostic tools (i.e. microbiology cultures) that trigger empirical antibiotic treatment, and thus reducing unnecessary patient exposure to antibiotics (Gentile 2013).

Alternative test(s)

Currently, several biomarkers have been evaluated for the diagnosis of sepsis due to they might have the ability to improve early recognition and severity of this condition. For example, the use of C-reactive protein concentrations has been proposed as an acute-phase reactant for the diagnosis of bacterial infections as well as a factor that can lead to a reduction of the mortality rate in septic patients (Onyenekwu; Silva 2014; Simon 2004). C-reactive protein levels are abnormal when the level exceeds 0.8 mg/L and may indicate the presence of a septic process. Likewise, the diagnostic value of procalcitonin has been evaluated in several systematic reviews with contradictory results (Simon 2004; Tang 2007; Wacker 2013). Other biomarkers, such as IL- 8 (Livaditi 2006) and triggering receptor expressed on soluble triggering receptor expressed on myeloid cells 1 (Gamez-Diaz 2011), have been evaluated without conclusive results (de Montmollin 2014). This current review will focus on one biomarker (IL-6) only and not include comparisons of diagnostic accuracy with other biomarkers. This is because there is a Cochrane protocol for a review in process assessing the role of C-reactive protein, procalcitonine and presepsin for sepsis (Onyenekwu in process).

Rationale

Despite the fact that sepsis is one of the first causes of mortality in critically ill patients, it lacks an accurate diagnostic test (Bloss 2014). In order to avoid unnecessary administration of antibiotics and to start appropriate therapy, an opportune differentiation of sepsis from other syndromes is a matter of importance. Some authors have reported higher levels of IL-6 in patients with sepsis and multiple organ dysfunction, but not in other conditions as trauma or cardiac arrest (Bloss 2014; Song 2005). Therefore, the detection of higher IL-6 levels could be useful in early diagnosis of these kinds of infections. Recently Jekarl et found that procalcitonin, IL-6 and protein C reactive might have an important role as diagnostic tests of sepsis from 18 biomarkers assessed (Jekarl 2015). Determining the accuracy of the detection of IL-6 levels as a biomarker for the diagnosis of sepsis might help to provide an adequate and timely management of critically ill patients, and could there with reduce the morbidity and mortality associated with sepsis. Furthermore, an accurate measurement tool may also limit hospitalization costs and potential antimicrobial resistance.

OBJECTIVES

To determine the diagnostic accuracy of interleukin-6 (IL-6) for the diagnosis of bacterial sepsis in critically ill adult patients.

Secondary objectives

1. To explore the effect of different thresholds in the accuracy of IL-6 for the diagnosis of sepsis
2. To determine whether the pathological source of sepsis (i.e. pneumonia, bacteraemia, urinary infections, among others) or other pre-specified sources have an influence on the accuracy of IL-6 as an diagnostic tool

METHODS

Criteria for considering studies for this review

Types of studies

We will consider diagnostic test accuracy studies which include patients aged 18 years or older with suspicion of sepsis during their hospitalization, where IL-6 levels are evaluated by serological measurement, as well as sepsis confirmation by means of clinical diagnosis and/or identification of microbiological pathogens in cultures. Studies should provide information about the specificity and sensitivity of the results. We will consider abstracts in the initial selection of references. However, if these selected references do not provide enough information for the assessment of the methodological quality, they will be classified as "Awaiting assessment". We will exclude before-after studies and case reports.

Participants

We will include studies evaluating critically ill adult patients aged 18 years or older (requiring mechanical ventilation and vasopressor therapy) with suspected sepsis. These will include participants from different clinical settings, such as emergency departments, hospitalizations wards and intensive care units. We will exclude studies of neonatal or paediatric patients with suspicion of sepsis.

Index tests

We will include articles with a description of the index test as the measurement of IL-6 in plasma as a sign of systemic inflammatory, metabolic, and physiologic activity. We will exclude measurements of IL-6 other than serum (i.e. pleural effusion, peritoneal fluid or cerebrospinal fluid).

Target conditions

As we mentioned earlier in the Background section of this report, sepsis is a systemic inflammatory response syndrome of the host as a consequence of an infection. Currently, the criteria developed by the International Sepsis Definitions Conference has been accepted to define this condition and these are illustrated in Appendix 1 (Levy 2003).

Reference standards

The criteria developed in 2003 by the Society of Critical Care Medicine, European Society of Intensive Care Medicine, American College of Chest Physicians, American Thoracic Society, and the Surgical Infection Society are accepted as the reference standard for the diagnosis of sepsis (Levy 2003).These criteria are described in Appendix 1. For the diagnosis of sepsis it is necessary to confirm the presence of infection in addition to signs of systemic inflammatory response syndrome. The presence of acute organ dysfunction or systolic arterial blood pressure of < 90 mmHg and a mean arterial pressure of < 65 mmHg are considered to be criteria for severe sepsis and septic shock, respectively.

Search methods for identification of studies

Electronic searches

We will search in the following databases:

- MEDLINE via Ovid SP (1956 to search date) (Appendix 2);
- EMBASE via Ovid SP (1982 to search date);
- LILACS via BIREME (1982 to search date);
- CINAHL via EBSCOhost (1980 to search date).

We will design structured search strategies using controlled search terms appropriate for each database as well as free text search terms as outlined in the *Cochrane Handbook of Diagnostic Test Accuracy Reviews* (Deeks 2013). We will not use search filters (collections of terms aimed at reducing the number needed to screen) as an overall limit because those published have not proved being sensitive enough (Whiting 2011a). We will not apply any language restriction to the electronic searches. The Trial Search Co-ordinator of the Cochrane Anaesthesia, Critical and Emergency Care Group will help us run the searches.

Searching other resources

For additional studies, we will screen the reference lists of all relevant papers. We will also contact relevant authors for further details and on-going/ unpublished trials. We will not perform handsearching, as there is little published evidence of the benefits of handsearching for reports of diagnostic test accuracy studies (Glanville 2012).

Data collection and analysis

Selection of studies

Two authors (IAR, DMF) will independently identify potentially eligible studies based on title and abstract. We will resolve disagreements by discussing the paper(s) in question with a third author (MR). We will retrieve the full-text copy of each potentially eligible study identified after which the two authors will independently evaluate each study for inclusion or exclusion according to the selection criteria. We will document the study selection process in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Data extraction and management

Two authors (IAR, MR) will extract the study characteristics from each included study, including data on assessment of quality and investigation of heterogeneity and transfer that information into a study-specific format, as described in Appendix 3. We will resolve any disagreements by discussion with a third author (JZ). We will cross-tabulate the numerical information from the index test results (positive or negative) in 2 x 2 tables against the target disorder (positive or negative) and we will present the results as tables (Appendix 4).

Assessment of methodological quality

Two authors (MR, IAR) will assess the methodological quality in an independent and duplicate fashion using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool (Whiting 2011b), as recommended by the *Cochrane Handbook of Diagnostic Test Accuracy Reviews* (Deeks 2013). This tool consists of four domains: patient selection, index test, reference standard and patient flow. Each domain will be assessed in terms of risk of bias, and the first three domains will be also considered in terms of applicability. We will report the QUADAS-2 methodological assessment of studies using bespoke tables. Operational definitions describing the use of QUADAS-2 are described in Appendix 5. This format will be piloted against 10 primary diagnostic studies in order to standardize this assessment and to identify any possible disagreement between authors. In case of difficulties, we will make all necessary modifications. We will resolve any discrepancies by discussion with a third author (JZ).

Statistical analysis and data synthesis

For all included studies we will extract data from the 2 x 2 tables (numbers of true positives, false positives, true negative and false negatives) showing the cross classification between binary test results and the binary reference standard. For each study, we will calculate sensitivities and specificities and their 95% confidence intervals (Appendix 4). We will present results graphically by plotting estimates of sensitivities and specificities (both with 95% confidence intervals (CIs)) in a forest plot and in a receiver operating characteristic (ROC) space in order to visually assess the between-study variability. We will consider these findings in light of methodological quality of individual studies. We will use the Cochrane statistical software, Review Manager 2014, to document descriptive analyses.

If data with more than one positive threshold is reported within a same study, we will extract all data and present the findings graphically for each reported thresholds. However, to avoid inclusion of study data in more than one occasion we will analyse thresholds separately for the target population in question. We will perform main analysis with the most common threshold. We will pool studies only if they share a common threshold, are conducted in the same/similar setting and show sufficient clinical homogeneity (i.e. severe sepsis, shock septic). For meta-analysis, we will fit a summary ROC curve using a bivariate random-effects model (Reitsma 2005) and derive summary accuracy indices (sensitivity and specificity) and corresponding likelihood ratios. We will plot 95% confidence ellipse and prediction region around averaged accuracy estimates in the ROC space.

Investigations of heterogeneity

We will investigate heterogeneity initially by visual examination of forest plots of sensitivities and specificities and through visual examination of individual study results in the ROC space. Anticipated sources of heterogeneity include year of publication, country, setting (emergency, intensive care units, hospitalization ward, mixed), baseline diagnosis, origin of infection (pneumonia, urinary infection, meningitis), type of sepsis (severe, septic shock), and type of reference standard. Assuming that an adequate number of studies reporting study level covariates are available, then, we will investigate the effect of these covariates by conducting subgroup analyses in Review Manager 2014 and by including each of these factors as covariates in the bivariate regression model. We will assess model fit by using likelihood ratio tests. This will allow us to test whether sensitivity or specificity, or both, differed in subgroups of studies defined according to these covariates. We will use the Stata software to carry out statistical modelling (Stata 2013).

Sensitivity analyses

We will examine the robustness of the meta-analyses by conducting sensitivity analyses and excluding studies according to different components of the Cochrane's tool for assessing risk of bias (Higgins 2011). Our primary analysis will include all studies; sensitivity analysis will exclude studies of high risk of bias or with important concerns about potential applicability. We will report the

results of the sensitivity analysis for each domain using a summary table.

Assessment of reporting bias

Quantitative methods for exploring reporting bias are not well established for diagnostic test accuracy studies. However, we will explore publication bias by regressing log (diagnostic odds ratios; DORs) on inverse root squared of effective sample size (Deeks 2005). We will interpret this analysis with caution given the lack of statistical power of this test and the absence of consensus about adequate methods to detect reporting bias in diagnostic test accuracy reviews.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Criteria for diagnosis of sepsis

Criteria 1. Confirmation of infection 1.1. Diagnosis of an infection on the basis of microbiological evidence or clinical criteria
Criteria 2. Systemic inflammatory host response (at least two criteria) 2.1. Fever (> 38°C) or hypothermia (< 36°C) confirmed by rectal, intravascular or intravesical assessment 2.2. Tachycardia: heart rate > 90 bpm 2.3. Tachypnoea (frequency > 20/min) or hyperventilation (PCO_2< 4.3 kPa/<33 mmHg) 2.4. Leukocytosis (>12000/mm) or leukopaenia (<4000/mm) or >10% immature neutrophils in blood cell count
Criteria 3. Acute organ dysfunction (at least one criterion) 3.1. Acute encephalopathy: reduced alertness, disorientation, agitation, delirium 3.2. Relative or absolute thrombocytopenia: decreased in count platelet by more 30% or count of less 100.000/mm 3.3. Arterial hypoxaemia: PaO_2 < 10kPa (<75 mmHg) while breathing ambient air or PaO_2 < 250 mmHg on administration O_2 3.4. Renal Impairment: Diuresis < 0.5 ml/kg/hr for at least 2 hrs 3.5. Metabolic acidosis: Base excess < 0.5 mmol/Lt or lactate concentration > 1.5 upper limit of normal
Severe sepsis criteria • Sepsis induced hypotension • Lactate above upper limits laboratory normal • Urine output < 0.5 mL/kg/hr for more than 2 hrs despite adecuade fluid resuscitation • Acute lung injury with PaO_2/FiO_2 < 250 in the absence of pneumonia as infection source • Acute lung injury with PaO_2/FiO_2 < 250 in the presence of pneumonia as infection source • Creatinine > 2.0 mg/dL • Bilirrubin > 2 mg/dL • Platelet count < 100.000 uL • Coagulopathy (international normalized ratio > 1.5)

Based on information from Levy 2003

Appendix 2. MEDLINE (Ovid SP) search strategy

1. exp Interleukin-6/ or exp Receptors, Interleukin-6/ or exp Cytokines/ or (interleukin* or IL?6* or (diagnostic adj3 marker*) or procalcitonin or cytokin*).ti,ab.
2. exp Bacteremia/ or exp Sepsis/ or exp Shock, Septic/ or exp Systemic Inflammatory Response Syndrome/ or Critical Illness/ or (sepsis or septic* or bacter?em* or (critical* adj3 ill*)).ti,ab.
3. 1 and 2
4. (child* or neonat*).af.
5. 3 not (4 not (4 and adult*.af.))
6. 5 not (animals not (humans and animals)).sh.

Appendix 3. Data extraction

Study name / date	Authors, publication date and number.
Setting	• Emergency department • Intensive care unit (medical, surgical, mixed) • Hospitalization ward.
Participants	Sample size. Characteristics if reported: • demographics; • gender; • baseline diagnosis. Origin of infection: Pneumonia, urinary infection, meningitis, bacteraemia, abdominal sepsis Use of antibiotics (empiric management).
Study design	Sampling strategy. Duration of follow-up.
Target condition	Proportion of people with sepsis in sample. Subtype of sepsis (severe, septic shock), if available.
Reference standard	Culture. Clinical diagnosis. Type of culture. Culture and clinical diagnosis. Time between IL-6 assessment and reference test. Relationship between IL-6 value and initial empirical antibiotics Blinding of operator to IL-6 levels. Was any subset subject to a different reference test? Positive cultures: microorganism isolated. Clinical diagnosis: composition of expert panel, training.
Index test	Kit Name - commercial name, batch number. Who did the test? Training provided to operator. Thresholds used to define positive and negative levels for sepsis

(*Continued*)

Index and reference standard test results	Missing results for index and reference. Uninterpretable results for index and reference. Borderline results for index and reference. True and false positives. True and false negatives. Sensitivity and specificity of index tests.

Appendix 4. Results of the two by two tables cross-relating index test results of the reference standards

Index test information	**Reference standard information**	
	Sepsis present	**Sepsis absent**
Index test positive	IL-6 positive & Sepsis (True Positives) at baseline.	IL-6 positive & No sepsis (False Positives) at baseline.
Index test negative	IL-6 negative & Sepsis (False Negatives) at baseline.	IL-6 negative & No sepsis (True Negatives) at baseline.

Appendix 5. Anchoring statements for quality assessment of IL-6 for diagnosis of sepsis.

Patient Selection	
Was a consecutive or random sample of patients enrolled?	"Yes" if it is well described in the paper (e.g. consecutive or a random sample from consecutive patients) "No" if the sample was non-random or patients were not consecutively recruited "Unclear" if there is insufficient information to make a judgment on the selection of patients
Was a case control design avoided?	Self explanatory
Did the study avoid inappropriate inclusions?	"Yes" if inclusion and exclusion criteria clearly described and appropriate "No" if inclusion and exclusion criteria clear but include inappropriate subjects "Unclear" if there is insufficient information to make a judgment on the inclusion of subjects

(*Continued*)

Could the selection of patients have introduced bias?	"Yes" if it is clear that bias is introduced through, for example, non-random selection "No" if the selection of patients is clearly described and does not introduce bias "Unclear" if there is insufficient information to make a judgment on the impact of selection on bias
Are there concerns that included patients do not match the review question?	"Yes" if included patients are inherently different from the cohort of patients who would be expected to receive IL-6 "No" if there are no such concerns. "Unclear" if patient characteristics are not sufficiently clearly explained to make a judgment on patient inclusion
Index Test	
Were the index test results interpreted without knowledge of the results of the reference standard?	"Yes" if the paper states that the index test is interpreted by individual(s) who did not know the results of the reference test(s) "No" if the results of the index test were known by the individuals performing the reference test, or if the same individual performed both tests Unclear if there is insufficient information to make a judgment about test result interpretation
If a threshold was used, was it prespecified?	
Could the conduct or interpretation of the index test have introduced bias?	"Yes" if a subset of index tests were conducted or interpreted in a different manner, or under different conditions, or by people with differing levels of training "No" if it is clear that the conduct and interpretation of all index tests was appropriate and could not have introduced bias "Unclear if there is insufficient information presented to assess the potential of conduct and interpretation of the index test to introduce bias
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	"Yes" if the index test is not IL-6 analysis for sepsis or if the conduct of test or its interpretation is not applicable to the review question "No" if there are no concerns based on the information presented
Reference Standard	
Is the reference standard likely to correctly classify the target condition?	"Yes" if the reference standard (culture or clinical diagnosis) used in the paper matches those chosen in this protocol "Yes" if the culture or clinical diagnosis is interpreted by appropriately trained/accredited individuals "No" if either of the above criteria is not met. "Unclear" if insufficient information is presented.

(*Continued*)

Were the reference standard results interpreted without knowledge of the results of the index test?	"Yes" if the paper states that the reference test is interpreted by individuals who had not seen the reference standard results "No" if the result(s) of the IL-6 analysis were known to the individual performing the reference test
Could the reference standard, its conduct, or its interpretation have introduced bias?	"Yes" if a subset of reference standard tests were conducted or interpreted in a different manner, or under different conditions, or by people with differing levels of training "No" if it is clear that the conduct and interpretation of all reference standard tests were appropriate and could not have introduced bias "Unclear" if there is insufficient information presented to assess the potential of conduct and interpretation of the reference standard test to introduce bias
Are there concerns that the target condition as defined by the reference standard does not match the review question?	"Yes" if the target condition is not sepsis or it is not clearly stated "No" if it is clearly stated that the target condition is sepsis
Flow and timing	
Was there an appropriate interval between index test(s) and reference standard?	"Yes" if the time between IL-6 results and reference standard was less than 48 hours "No" if the time is longer than 48 hours for a significant proportion of patients
Did all patients receive a reference standard?	"Yes" if all patients who received the index test also had the reference test "No" if not all the patients who received the index test also received the reference standard, or if a non-random sample was selected "Unclear" if this cannot be determined from the information presented in the paper
Did all patients receive the same reference standard?	"Yes" if the same reference standard was used for all patients "No" if different reference standards were used. "Unclear" if this cannot be determined from the information presented in the paper
Were all patients included in the analysis?	"Yes" if there were no withdrawals or exclusions, or if those reasons are adequately explained with a flow chart "No" if withdrawals or exclusions are not explained or accounted for "Unclear" if withdrawals or exclusions cannot be determined or if there is insufficient information to judge this
Could the patient flow have introduced bias?	"Yes" if subsets of patients or samples were treated, included or excluded in systematic ways which could have introduced bias "No" if patient flow is reported clearly and does not have the potential to introduce significant bias

CONTRIBUTIONS OF AUTHORS

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Develop and run the search strategy: IAR-DM

Obtain copies of studies: DM- IAR

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DECLARATIONS OF INTEREST

Ingrid Arevalo-Rodriguez has no conflicts of interest to declare.

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