

Meta-analyses of diagnostic tests in infectious diseases: how helpful are they in the intensive care setting?

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ABSTRACT

In acute-care settings timely and accurate diagnostic tools are critical for patient treatment decisions and outcomes. This review provides an up-to-date look at the meta-analyses of diagnostic test for infections in the ICU setting

There have been 3 meta-analyses investigating the value of procalcitonin as diagnostic marker of sepsis: overall, the performance of procalcitonin test was found moderate-good. Two meta-analyses evaluated methods for diagnosing intravascular device-related bloodstream infections. In general, quantitative catheter segment culture and paired quantitative blood culture showed reliable diagnostic yield, though significant heterogeneity was observed among studies. Criteria of diagnosing VAP in the intensive care unit has been evaluated in 3 systematic reviews. Overall, the cumulative results cast doubts about the usefulness of bacteriological data and quantitative cultures in the diagnosis of VAP; moreover, 2 of these meta-analyses concluded that invasive strategies for VAP diagnosis do not affect mortality.

Keywords: meta-analysis, infectious diseases, diagnostic test, VAP, procalcitonin, sepsis.

INTRODUCTION

Infections in the Intensive Care Unit (ICU) setting constitute one of the greatest challenge of modern medicine. The complexity of ICU care and the compromised condition of many ICU patients yield rates of nosocomial-acquired infections much higher than rates in other hospital wards. Correct and timely diagnosis is an essential point in the management of infections in ICU. Diagnosing nosocomial infections in critically ill patients admitted to the ICU is a challenge because signs and symptoms are

usually non-specific for a particular infection. Moreover, there is no consensus about the ideal method to diagnose some of the common infections in the ICU settings (e.g., nosocomial pneumonia in ventilated patients, sepsis, fungal bloodstream infections) or, more generally, to identify the patient who is truly infected. The diagnostic workup of the febrile critically ill patient should be guided by the underlying condition of the patient, and the clinical suspicion of a specific infection.

Literature evaluating systematic reviews on accuracy of diagnostic tests, including those in the field of infectious diseases, is growing year after year, and these studies can be difficult and time consuming to identify and appraise (1, 2). Systematic reviews of diagnostic studies involve additional chal-

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allenges to those of reviews of randomized clinical trials, and physicians need to be at ease with both type of studies. However, diagnostic studies are observational in nature and prone to various biases. In addition, there is more variation between studies about methods, manufacturers, procedures, and outcome measurement scales used to assess test accuracy than in randomized controlled trials, which generally causes marked heterogeneity in results. The use of statistical methods to combine test accuracy studies is particularly challenging, not least because test accuracy is conventionally represented by a pair of statistics (most often sensitivity and specificity) and not by a single effect measure such as the odds ratio or relative risk.

We have recently reviewed the available meta-analyses of diagnostic test in the field of infectious diseases (3). This overview was designed to summarize the main findings of systematic reviews of diagnostic tests in patients with infections, appraising their quality and highlighting their relative strengths and weaknesses. Fifty-five meta-analyses were included in the review. The mean number of primary studies included in the review was 29 ± 20 (median 23, range 5-96); overall, the 55 meta-analyses reported data from 1,596 primary studies. The reviews covered different types of diagnostic tests and infections. Types of diagnostic test varied, but in the large majority they were laboratory test and to a lesser extent imaging tests, pathology/cytology tests, and clinical examinations. There were 25 meta-analyses investigating diagnostic tests for bacterial infections, 4 for fungal infections (including *Pneumocystis carinii*), 6 for viral infections, 6 for protozoan infections, and 14 investigating diagnostic tests applied to different clinical syndromes and conditions, including sepsis, osteomyelitis, meningitis, acute sinusitis, catheter related blood stream infection and bacteremia, uri-

nary tract infections, and diarrhea. One third of the papers evaluated tests for the diagnosis of tuberculosis.

The first meta-analysis of diagnostic test in infectious diseases we have found is dated 1992. Since then, the number of published papers has increased, and those published in the last 4 years is superior to the number of papers published in the previous years. Some of the meta-analyses we summarized reported data collected in the ICU setting, or included cohorts or subsets of patients admitted to the ICUs.

The key features of these meta-analyses may be of interest for the ICU attending physician, and are reported thereafter.

Procalcitonin (PCT) and C-reactive protein (CRP) as diagnostic markers of sepsis, or septic shock

Though bacterial culture is the best method for diagnosis of infection, it does not differentiate between bacterial colonization and invasive bacterial infections or systemic complications (e.g., Systemic Inflammatory Response Syndrome-SIRS). Markers like PCT or CRP respond both to infection and inflammation and therefore reflect both microbiological findings and the host response. There have been at least 3 meta-analyses investigating the value of PCT as diagnostic marker of sepsis (4-6). Of these meta-analyses, two were conducted entirely (4) or mostly (5) in the ICU setting, and the remaining in the emergency department population (6). The gold standard for sepsis diagnosis was microbiological culture (blood culture), or accepted definition by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference (7) in combination with microbiological culture. Overall, the performance of PCT in the diagnosis of sepsis test was found moderate-good. However, PCT cannot reliably differentiate sepsis from other non-infectious causes of SIRS in critically ill

Table 1 - Key features of principal meta-analyses evaluating diagnostic accuracy of tests for infectious diseases syndromes or conditions in the Intensive Care Unit setting.

1 st Author, year (ref)	Object, clinical setting and condition	Index test	Main findings of the review
Siegman-Igra, 1997 (8).	To evaluate the accuracy and cost-effectiveness of methods of diagnosing vascular catheter-related bloodstream infection.	3 categories: catheter segment culture (qualitative, semi-quantitative and quantitative), culture of blood drawn through the catheter (unpaired qualitative, unpaired quantitative and paired quantitative), and a group of miscellaneous methods (including direct staining methods, catheter site skin culture and hub culture).	Quantitative catheter segment culture demonstrated the greatest accuracy for documenting catheter-related bloodstream infection. These conclusions are potentially vulnerable to biases introduced by methodological flaws in the primary studies
Safdar, 2005 (9)	Evaluation of the most accurate methods for the diagnosis of intravascular device (IVD)-related bloodstream infection.	Qualitative, semi-quantitative or quantitative culture of catheter segment, IVD-drawn quantitative or qualitative blood culture, paired quantitative blood cultures, and acridine orange leukocyte cytopsin test.	Paired quantitative blood culture is the most accurate test for the diagnosis of IVD-related bloodstream infection
Uzzan, 2006 (4)	Comparison of procalcitonin (PCT) and C-reactive protein (CRP) as diagnostic marker of sepsis, or septic shock, in ICU, and after surgery & trauma	PCT (LUMItest PCT test only, not assay on Kryptor) & CRP (various methods).	PCT represents a good biological marker for sepsis, severe sepsis, or septic shock in ICU. These conclusions should be interpreted with caution, given the problems with reference standard for the clinical conditions under investigation
Jones, 2007 (6)	Procalcitonin (PCT) as diagnostic marker of bacteremia in the emergency department (ED) population	PCT	The performance of PCT test for identifying bacteremia in ED pts was found moderate
Tang, 2007 (5)	Accuracy of PCT for diagnosis of sepsis in critically ill pts. Most studies were in ICU.	PCT	PCT cannot reliably differentiate sepsis from other non-infectious causes of SIRS in critically ill adult pts
Shorr, 2005 (10)	to evaluate if and how invasive diagnostic strategies in suspected VAP affect important outcomes such as mortality	Protected Specimen Brush (PSB) ± BAL, mini-BAL	Invasive strategies for VAP diagnosis do not alter mortality. Invasive approaches, however, leads to modification in the antibiotic regimen in more than half of the patients
Rea-Neto, 2008 (11)	Accuracy of various diagnostic test and criteria for diagnosing VAP in ICU	Various clinical criteria, microbiological criteria, and biomarkers	Clinical criteria, used in combination, may be helpful in diagnosing VAP. Bacteriological data do not increase the diagnostic accuracy.
Berton, 2008 (12)	To evaluate whether quantitative cultures of respiratory secretions are effective in reducing mortality and other outcomes in VAP pts.	Invasive and non-invasive techniques for respiratory secretions, analyzed quantitatively or qualitatively. Quantitative cultures are used to differentiate the infectious organisms (those with a higher concentration) from colonizing organisms (those with lower concentration), thereby optimizing antibiotic therapy.	Quantitative cultures do not reduce mortality, time in ICU and on mechanical ventilation, when compared to qualitative cultures, and do not affect antibiotic use. Similar results were observed when invasive strategies were compared with non-invasive strategies.

adult patients. One study evaluated CRP as a marker of sepsis (4). PCT was found superior to CRP.

Diagnosis of vascular catheter-related bloodstream infection

Central venous catheters (CVC) are the most frequent cause of nosocomial bloodstream infection. The spectrum of infections ranges from local asymptomatic infection to blood-stream infections with septic shock. Due to the high attributable mortality rate, accurate and early diagnosis of CVC-related infections is essential. Two meta-analyses evaluated the methods for diagnosing intravascular device-related bloodstream infections (8, 9). Various reference standards were used across the studies, including microbiological methods in combination with clinical symptoms and signs of infection. Methods requiring catheter removal included qualitative, semi-quantitative, and quantitative catheter segment culture. Methods not requiring catheter removal included qualitative or quantitative blood culture through the device, paired quantitative blood cultures, differential time to positivity (peripheral blood vs blood through the device), and direct stain of blood from the catheter. The first of these meta-analysis included data from 22 primary studies (8). The results of this meta-analysis show that quantitative catheter segment culture demonstrated the greatest accuracy for documenting catheter-related bloodstream infection. By contrast, the results of the meta-analysis by Safdar, Fine and Maki, based on 55 published studies, show that paired quantitative blood culture (1 drawn percutaneously from a peripheral vein and 1 through the suspected catheter) is the most accurate test for the diagnosis of CVC-related bloodstream infection (9). Moreover, the authors conclude that catheters should not be cultured routinely but rather only if CVC-

related bloodstream infection is clinically suspected.

Significant heterogeneity in pooled sensitivity and specificity was observed among studies.

Diagnosis of ventilator associated pneumonia

Ventilator-associated pneumonia (VAP) remains a major challenge in the intensive care unit. The role for invasive diagnostic methods (e.g., bronchoscopy) remains unclear. Few trials have systematically examined the impact of diagnostic techniques on outcomes for patients suspected of suffering from VAP. The results of a meta-analysis show that invasive strategies do not affect mortality (10). Invasive sampling, however, leads to modifications in the antibiotic regimen in more than half of patients.

Another systematic review has compared various criteria of diagnosing VAP in the intensive care unit (ICU) with a special emphasis on the value of clinical diagnosis, microbiological culture techniques, and biomarkers of host response (11). A total of 64 articles fulfilled the inclusion criteria and were included. Clinical criteria, used in combination, may be helpful in diagnosing VAP; however, the considerable inter-observer variability and the moderate performance should be taken into account. Bacteriologic data do not increase the accuracy of diagnosis as compared to clinical diagnosis. Quantitative cultures obtained by different methods seem to be rather equivalent in diagnosing VAP.

Blood cultures are relatively insensitive to diagnose pneumonia. The rapid availability of cytological data, including inflammatory cells and Gram stains, may be useful in initial therapeutic decisions in patients with suspected VAP.

More recently, a Cochrane review evaluated whether quantitative cultures of respiratory secretions are effective in reduc-

ing mortality and others secondary clinical outcomes in immunocompetent patients with VAP, compared with qualitative cultures (12). The review evaluated diagnostic procedures not in terms of diagnostic yield, but the effect of interventions on clinical outcomes. Only 5 randomized clinical trials were included: 3 studies compared invasive methods using quantitative cultures versus non-invasive methods using qualitative cultures; 2 studies compared invasive versus non-invasive methods, both using quantitative cultures.

All 5 studies were combined to compare invasive versus non-invasive interventions for diagnosing VAP. The studies comparing quantitative and qualitative cultures (1240 patients) showed no statistically significant differences in mortality rates. The analysis of all 5 studies showed there was no evidence of mortality reduction in the invasive group versus the non-invasive group. There were no significant differences between interventions with respect to the number of days on mechanical ventilation, length of ICU stay or antibiotic change.

Diagnosis of Invasive fungal infections

Invasive candidiasis continues to present major diagnostic challenges to the clinician, and there is critical need for improved diagnostics that will provide clinicians the opportunity to intervene earlier in the disease course.

Conventional microbiologic and histopathologic approaches are neither sensitive nor specific, and they usually do not detect invasive fungal infection until late in the course of disease.

Up to now the diagnosis of *Candida* infection in practice remains a clinical decision based on inference. Since early diagnosis may guide appropriate treatment and prevent mortality, there is considerable interest in developing non-culture approaches to diagnosing fungal infections. These ap-

proaches include detection of specific host immune responses to fungal antigens, detection of specific macromolecular antigens using immunologic reagents, amplification and detection of specific fungal nucleic acid sequences, and detection and quantitation of specific fungal metabolite products. Among these methods, measurement of β -D-glucan, a major component of the fungal cell wall, has been object of several clinical trials conducted in haematological patients and in ICU patients. Preliminary results from a meta-analysis show that β -D-glucan hold promise for an adjunct diagnostic strategy for invasive fungal infections, including candidiasis and aspergillosis (13).

CONCLUSIONS

In acute-care settings timely and accurate diagnostic tools are critical for patient treatment decisions and outcomes.

This review provides an up-to-date look at the meta-analyses of diagnostic test for infections in the ICU setting. Although the diagnostic tests we have considered cannot be regarded as perfect, they do have practical consequences for management of ICU patients at risk of infections.

However, further data from well designed and adequately powered clinical trials are needed to refine the diagnostic strategies and to identify, in the heterogeneous ICU population, the subgroups of patients who might most benefit from these strategies.

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