Intensive Care Med (2015) 41:531–533
DOI 10.1007/s00134-014-3607-y

EDITORIAL

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Multipathogen real-time PCR system adds benefit for my patients: no

Received: 29 November 2014
Accepted: 8 December 2014
Published online: 27 January 2015
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DOI 10.1007/s00134-01-3639-3.

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Introduction

Among the available strategies and recommendations to treat severe infections, namely bloodstream infections, prompt and adequate antibiotic therapy is among the ones with greatest impact on clinical outcomes [1]. “Classic” blood culture results take at least 48–72 h for bacterial culture, 4–24 h for identification, and an additional 24 h for antibiotic susceptibility testing to become available. Besides, blood cultures have suboptimal sensitivity for microorganisms that are phagocytized or that are only present in the infectious focus, and in patients who have already received antibiotics. As a result, new methods have been developed to shorten the identification time of the causative agent and whenever possible its sensitivity pattern. These new methods are based on antigen detection, antibody detection, and molecular detection, namely DNA amplification by real-time polymerase chain reaction (RT-PCR). However, bacteremia is not equal to DNAemia, since RT-PCR technology can detect minute amounts of pathogen DNA in patient blood samples [2]. Besides, sepsis is not only a bloodstream infection, but SeptiFast (the first CE-marked RT-PCR) was developed for pathogen identification only in blood samples.

Multipathogen real-time PCR system

This subject is linked to another issue: how do we trust a positive or negative SeptiFast result? Do we trust all SeptiFast results or only culture-confirmed SeptiFast positives? If both tests, blood cultures and SeptiFast, are concordant, either positive or negative, there is no problem concerning “the truth.” The problem arises (1) when SeptiFast is positive and blood cultures are negative, (2) when SeptiFast is negative and blood cultures are positive, and finally (3) when blood cultures are positive for bacteria not in the SeptiFast panel and as a result the SeptiFast is negative [3]. The last case is a known limitation of the SeptiFast test that could be overcome in the future by the incorporation of a wider test panel of pathogens. The other two situations, i.e., false-positive and false-negative SeptiFast results, are more difficult to interpret, since blood culture results are an inadequate gold standard for identification of pathogens in the blood, but we still do not have any better test. The rates of false-positive and false-negative SeptiFast results are reflected in the specificity and sensitivity of the test. However, to better assess the diagnostic accuracy of a test, we should evaluate the positive and negative likelihood ratios. A test with positive likelihood ratio >5 is a good rule-in test, whereas one with negative likelihood ratio <0.1 is good to

rule out the condition. In several recent studies with large sample sizes [4–9], SeptiFast showed reasonable accuracy to rule in bloodstream infection, with positive likelihood ratios between 5.5 and 13.2. However, it is repeatedly clear that SeptiFast has a poor negative likelihood ratio, between 0.2 and 0.6, and as a result low or very low diagnostic accuracy to rule out a bloodstream infection.

Studies recently published in the journal

In a recent issue of *Intensive Care Medicine*, Dr. Dark and colleagues report the results of two major studies aiming at evaluating the accuracy of SeptiFast in diagnosing healthcare-associated bloodstream infections, and sepsis [10, 11]. The authors should be commended on their excellent work with important potential implications in critically ill patients. In a large multicenter study, they included 795 critically ill patients who developed a total of 922 episodes of suspected healthcare-associated infections [10]. The sensitivity of SeptiFast was only 0.59 at the patient event level and 0.50 at the pathogen concordance level. The likelihood ratio of a negative test for pathogen concordance was 0.69 [95 % confidence interval (CI) 0.50–0.73]. The specificity of SeptiFast was higher than its sensitivity (0.88 and 0.86 at the event and pathogen concordance levels, respectively). However, this value is limited by low pretest probabilities and low positive likelihood ratio at the pathogen concordance level (3.5, 95 % CI 2.7–4.5).

The authors also performed a systematic review and meta-analysis to determine diagnostic accuracy of SeptiFast in the setting of suspected sepsis [11]. They analyzed 41 studies, including a total of 7,727 patients contributing 10,493 episodes of suspected sepsis. Sensitivity and specificity for SeptiFast compared with blood culture were 0.68 (95 % CI 0.63–0.73) and 0.86 (95 % CI 0.84–0.89), respectively. Study quality was judged to be variable with important deficiencies overall in design and reporting.

In spite of the limitations acknowledged by the authors, including the high percentage of patients receiving antibiotics in all studies and the low incidence of positive blood cultures, the results of the two studies published in this issue represent an important contribution to the current literature.

Why SeptiFast is not beneficial for my patient

Based on the low sensitivity (high false-negative rate), antibiotics cannot be stopped in patients with negative SeptiFast results. Despite a higher specificity than sensitivity, the high rate of false-positive results is another limitation for the use of SeptiFast in current practice. Therefore, using SeptiFast to guide antimicrobial treatment would probably result in inadequate antibiotic treatment, and in some cases overuse of antibiotics. Delayed appropriate antibiotic treatment has repeatedly been identified as a risk factor for mortality in septic shock patients [12]. Further, overuse of antibiotics is a well-known risk factor for infections related to multidrug-resistant bacteria, inappropriate treatment, and higher mortality rates in critically ill patients [13–15]. Other points suggesting that implementation of SeptiFast in the intensive care unit (ICU) would not be beneficial for our patients include the absence of good-quality data in infections other than bacteremia, absence of antibiotic sensitivity data provided by this test (other than identifying the *mecA* gene confirming methicillin resistance following detection of *Staphylococcus aureus*), and the absence of data on cost-effectiveness of routine use of SeptiFast in the ICU (Fig. 1). Another important limitation of SeptiFast is its low accuracy in diagnosing fungemia. In their recent meta-analysis [16], Chang and colleagues reported lower sensitivity of SeptiFast in diagnosing fungemia compared with bacteremia. Based on the low accuracy of SeptiFast in diagnosing bloodstream infection, and the above-discussed limitations of this test, we do not recommend its use in critically ill patients to diagnose severe sepsis or to tailor antimicrobial treatment.

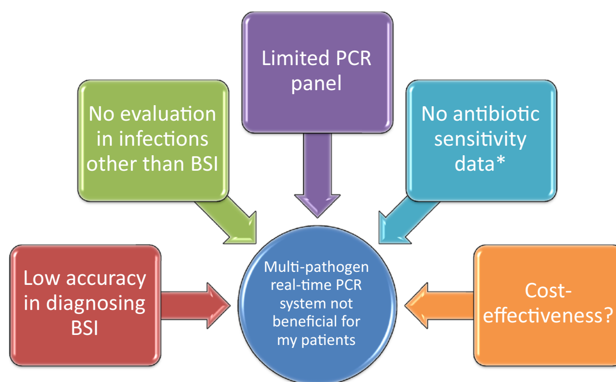

Fig. 1 Limitations of multipathogen real-time PCR system. *Other than identifying the *mecA* gene confirming methicillin resistance following detection of *Staphylococcus aureus*. *BSI* bloodstream infection

Future directions

Future studies should evaluate the accuracy of RT-PCR technology in targeted population with high prevalence of bloodstream infections, such as septic shock and endocarditis; and in samples other than blood, such as

respiratory secretions, pleural fluid, and cerebrospinal fluid. The accuracy of this technology should also be evaluated in patients without prior antibiotic treatment. Increased PCR panel, and antibiotic sensitivity data would represent an important improvement for this technique. Finally, cost-effectiveness and safety should also be evaluated in critically ill patients.

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