Sepsis diagnosis in the laboratory

Sepsis is one of the major challenges in healthcare today, with some statistics predicting over 1 million cases per year in the United States, with mortality rates of about 10%. In a recently published study, between 36.9% and 55.9% of deaths among hospitalized individuals occurred in septic patients [1]. Two other findings of this study are critical to the laboratory. First, they observed that patients with initially less severe sepsis made up the majority of sepsis deaths. Secondly, most patients were already septic at the time they were admitted to the hospital. Thus laboratory testing during the initial emergency department (ED) encounter could be critical to improve sepsis-related mortality.

A systematic review of the literature [2] looked at nearly 200 proposed biomarkers for sepsis. Quoting the study’s final conclusions: “Our literature review indicates that there are many biomarkers that can be used in sepsis, but none has sufficient specificity or sensitivity to be routinely employed in clinical practice. PCT and CRP have been most widely used, but even these have limited abilities to distinguish sepsis from other inflammatory conditions or to predict outcome.” Here we take a look at the key issues the healthcare industry is facing and why physicians still do not have a reliable marker for sepsis to offer for their patients.

by Fernando Chaves

Key factors which can impact outcome in sepsis

In the last decade since sepsis awareness became more prevalent, many institutions have started implementing sepsis treatment protocols, which have been successful in decreasing mortality [3-4]. These protocols call for the collection of multiple blood cultures plus immediate start of intravenous fluids and antibiotics, and were implemented because studies have clearly demonstrated that the single most important factor in decreasing sepsis mortality was early intervention.

Later, a large prospective study comparing variations of these protocols, including invasive patient monitoring did not show any significant differences in mortality rates [5]. This indicates that there is minimal additional decreases in sepsis mortality that can be attained through improvements in treatment.

In contrast there are still options available to improve sepsis mortality through diagnostic testing. An optimal approach for early detection of sepsis still eludes us. Diagnosis today is still based primarily on the clinical recognition of systemic inflammation -- increased heart and respiratory rates, fever, mental confusion, etc. followed by the documentation of a site of infection. When clinicians recognize these signs and symptoms, the window of opportunity to further decrease sepsis mortality by an earlier diagnosis has passed. Therefore, a laboratory test that could allow for earlier recognition of septic patients is a major unmet need for physicians.

What features should a laboratory test have to address this unmet need?

In order to allow for early recognition of septic patients, a laboratory test would need to meet both clinical performance and accessibility criteria. First, it must have sufficient diagnostic performance (measured by area under the curve “AUC” in the receiver operator curve “ROC curve”) to discriminate sepsis not only from healthy individuals, but also from other sick patients with conditions which mimic sepsis, such as systemic inflammatory response syndrome (SIRS). The traditional laboratory tests used during initial evaluation of patients, such as the complete blood count (CBC) fail to achieve this diagnostic performance.

Secondly, it must meet accessibility criteria, meaning it must be a test which can be widely used in all patients coming to the ED, without the need for the clinician to have an initial suspicion for sepsis. As discussed above, waiting for the physician to order the test will likely miss the window of opportunity to further improve mortality. Currently antibiotics and IV fluids are already being initiated before testing, as per the sepsis protocols now becoming increasingly prevalent in hospitals worldwide.

With so many proposed biomarkers for sepsis, which ones have met these criteria?

Unfortunately, although there have been many promises and exciting results in initial studies, results to date have been disappointing.

Early studies often yielded promising results because of their smaller size, and typically they were case-control studies comparing septic patients with healthy individuals [2]. The real challenge is discriminating sepsis from the plethora of mimicking conditions physicians encounter in the ED.

Once the biomarkers were evaluated in real life scenarios, their diagnostic performance, measured by AUC curve, did not match the results of earlier smaller studies. A perfect example was procalcitonin, PCT, the best known proposed biomarker for sepsis which initially showed very good discriminatory ability for sepsis. As PCT became more widely used and systematically studied, it became clear that it was far from the silver bullet it was optimistically thought to be. A systematic literature review and meta-analysis [6] showed an AUC of 0.78, with diagnostic performance upwardly biased in smaller studies, but moving towards a null effect in larger studies. Several years after PCT became available as a reportable test worldwide, its adoption among hospital laboratories is still sporadic, and when it is used, the most common clinical objective is the monitoring of antibiotic therapy for safe discontinuation, rather than initial diagnosis of the sepsis.

Even if the performance of these tests had been excellent, the accessibility challenge would still limit their ability to positively impact patient outcomes. As mentioned above, if the test for sepsis is ordered by
a physician based on observation, the opportunity to start antibiotics sooner was missed, and the positive outcome reduced. Thus, real improvements in patient mortality will only be seen when tests are ordered routinely during initial patient care in the ED, such as the complete blood count with differential (CBC-diff).

Can we diagnose sepsis sooner using only data from a CBC-diff?

To date, there have been multiple attempts to improve the early detection of sepsis using CBC data, either via new parameters or via the creation of index values combining results from multiple traditional parameters. But so far no significant improvement in performance has been achieved — in great part due to the fact that cell counts are also elevated in inflammatory conditions mimicking sepsis. Thus, what is lacking is a parameter which is less sensitive to the inflammatory process, and more specific for the sepsis infection.

Cellular morphologic changes may be the critical tipping point in this quest. As key players in the fight against infection, white blood cells, such as monocytes and neutrophils, get activated and change their morphology. In fact, such changes have been used for years by pathologists and technologists when making their diagnostic decisions at the microscope.

Certain hematological analysers collect cellular morphologic data in their quest to recognize and count cells. Multiple studies have been published over the last decade discussing these parameters and their potential value for the early diagnosis of sepsis. However, as was true for multiple other proposed sepsis biomarkers, the small sample size and retrospective design of these studies limited their value to reliably assess their potential diagnostic performance for sepsis. This limitation has been addressed in a recent large prospective trial, probing the clinical value of morphologic parameters in the early diagnosis of sepsis in the general ED population, as well as in the discrimination between sepsis and its key mimic, SIRS.

The results of this trial will be presented at the Society for Critical Care Medicine (SCCM) annual meeting, and will not be in the public domain in time for publication in this article. But readers are invited to pay close attention to this data once it becomes available in the literature, as this abstract has been selected as one of the “Star Research Presentations” at the upcoming Critical Care Congress in February 2016.

References:

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