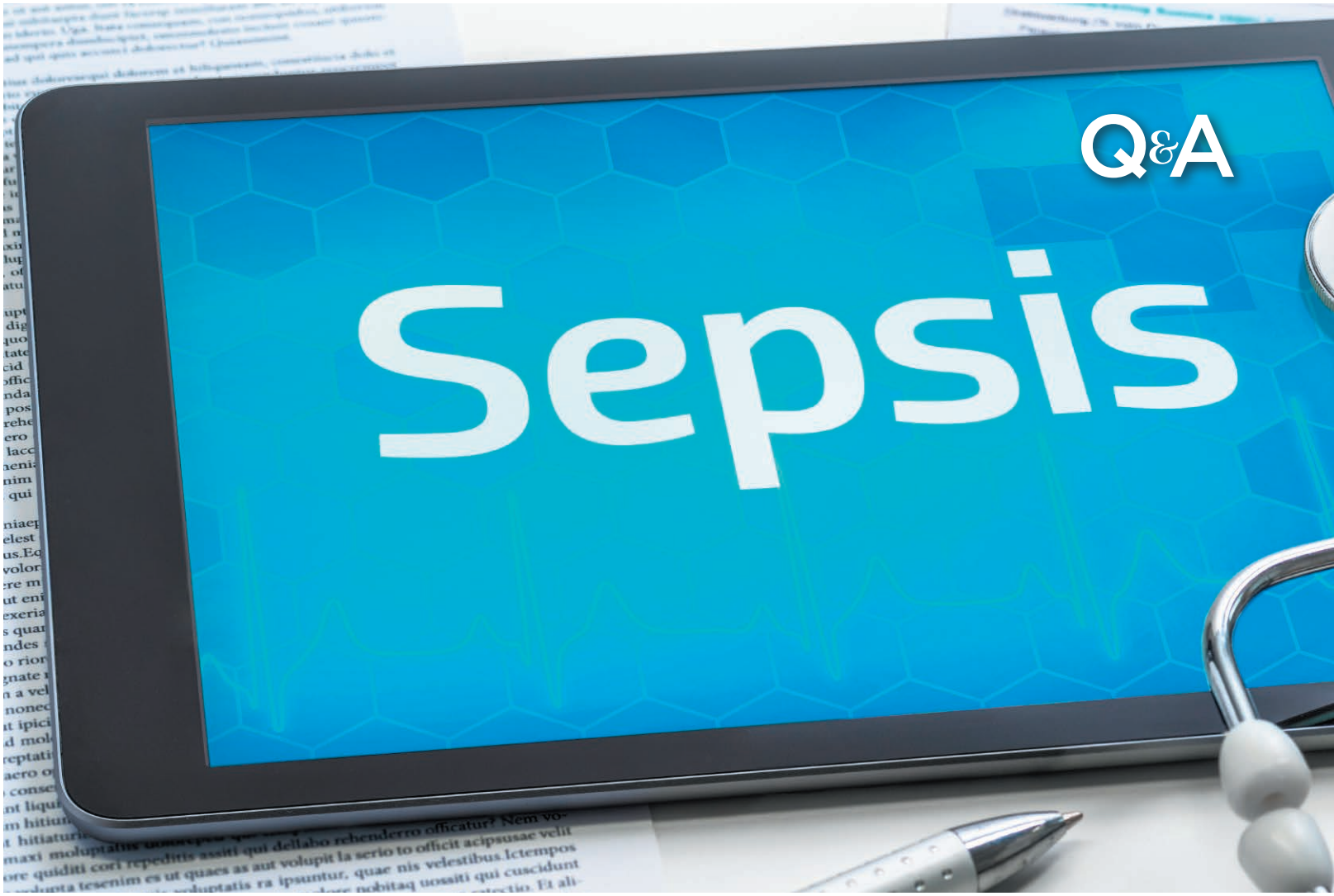


The SepSIGN Trial for Early Detection of Sepsis

An interview with Marie-Angélique Cazalis, Associate Staff Scientist at bioMérieux

SEPSIS IS AN important health issue with considerable socio-economic consequences. In 2017, the World Health Organization (WHO) made sepsis a global health priority, and has adopted a resolution to improve the prevention, diagnosis, and management of sepsis. As noted in Critical Care Medicine,[1] over 970,000 sepsis cases are admitted annually In U.S. hospitals alone with numbers rising year over year. A 20-year study of U.S. hospitalizations identified an increase in the incidence of sepsis among hospitalized patients by 8.7% per year.

From the SepSIGN NCT[2] entry: Despite the *increasing incidence rate* over the past ten years, a decrease in the mortality rate *has been observed,* thanks to improved management, more appropriate intervention approaches in the Emergency Department (ED), and better recognition of organ failure. These observations are based on SOFA (Sequential Organ Failure Assessment) and quick SOFA (qSOFA) scores from the international Sepsis-3 definition. Sepsis-3 can help front-line clinicians detect severe patients with a higher risk of mortality but does not predict clinical deterioration especially in patients without initial organ dysfunction. Furthermore, studies still demonstrate that 20% of patients with infection or uncomplicated sepsis experience disease worsening within 72 hours after ED admission.

Symptoms and signs of sepsis are variable,

which makes clinical recognition and assessment difficult. Unfortunately, no biological marker has yet been validated to predict early deterioration in unselected patients admitted to the ED with acute infection, regardless of their clinical presentation. Sepsis pathophysiology is complex, and some underlying dysfunction could already exist in the early phase of sepsis before patients meet diagnostic criteria. Thus, patients may be clinically asymptomatic at the origin of organ failure. As a result, doubtful patients are often over-hospitalized while they could be treated at home, leading to overcrowding and extra costs for hospitals. In these circumstances, the main challenge of ED clinicians is differentiating mild infections from life-threatening ones in the heavy workload of ED environment.

In response to these growing concerns, bioMérieux has launched SepSIGN,[2] a clinical trial with a goal of validating biomarkers that predict the clinical worsening of adult patients freshly admitted to the Emergency Department with a suspected or confirmed infection. We posed the following set of questions to Marie-Angelique Cazalis to learn more about sepsis and the trial.

Q. What is the current method of assessing a patient for sepsis on admission to an emergency room? How does SOFA and qSOFA play into this assessment?

A. Sepsis is a very heterogeneous syndrome and clinical signs, and symptoms are non-specific.

The early recognition and rapid diagnosis are essential to assess the severity of the infection, predict possible organ failure, identify the pathogen and its possible resistance profile in order to adapt the treatment.

Usually, doctors diagnose sepsis using a syndromic approach combining symptoms (features apparent to the patient like a sore throat, chest pain, etc.) and clinical signs (measurable indicators of disease like fever, blood pressure, heart rate, and respiratory rate).

Along with clinical data, detailed history, physical examination, laboratory testing can provide clues that indicate the presence of or risk of developing sepsis.

These lab tests that check for signs of infection may include samples of blood, urine, wound secretions, respiratory secretions.

To identify the site of infection, especially when it is not readily found, some imaging tests as X-rays (for lungs), ultrasound (for gallbladder and kidneys), computerized tomography (CT) scans (for liver, pancreas, or other abdominal organs), magnetic resonance imaging (MRI) (for soft tissue or bone infections) can be used.

From last decade, it has been recommended to complete the initial diagnosis of infection with diagnosis of potential organ damage. Most of the time, in Emergency department, this assessment is carried out by targeting some specific organ functions and does not make it possible to calculate the complete SOFA score. Alternatively, the qSOFA has been proposed as more appropriate in this population of patient. Nevertheless, even if it is often described as a sensitive predictor of severity and hospital mortality, this score remains not very specific. Also, it has never shown good performances in a population of non-severe patients

Q. Early detection augurs better for patient recovery and survival from sepsis. While the goal is to detect sepsis within 72 hours of admission, what would the shortest feasible target detection time from hospital admission as an outcome for this study?

A. In this study, we want to investigate the potentially prognosis of biomarkers very early in the onset of sepsis. The blood sample is collected as soon as the emergency physician suspects an infection and at the latest within 12 hours after the patient's arrival in ED.

As early diagnosis is crucial, "delay between ED presentation and inclusion that does not exceed 12h" is our first inclusion criteria.

Q. Can you comment on the plans to "biobank" samples (presumably to mine biomarkers later)? What are the plans for samples collected in PAXgene tubes? Would the plans include expression profiling?

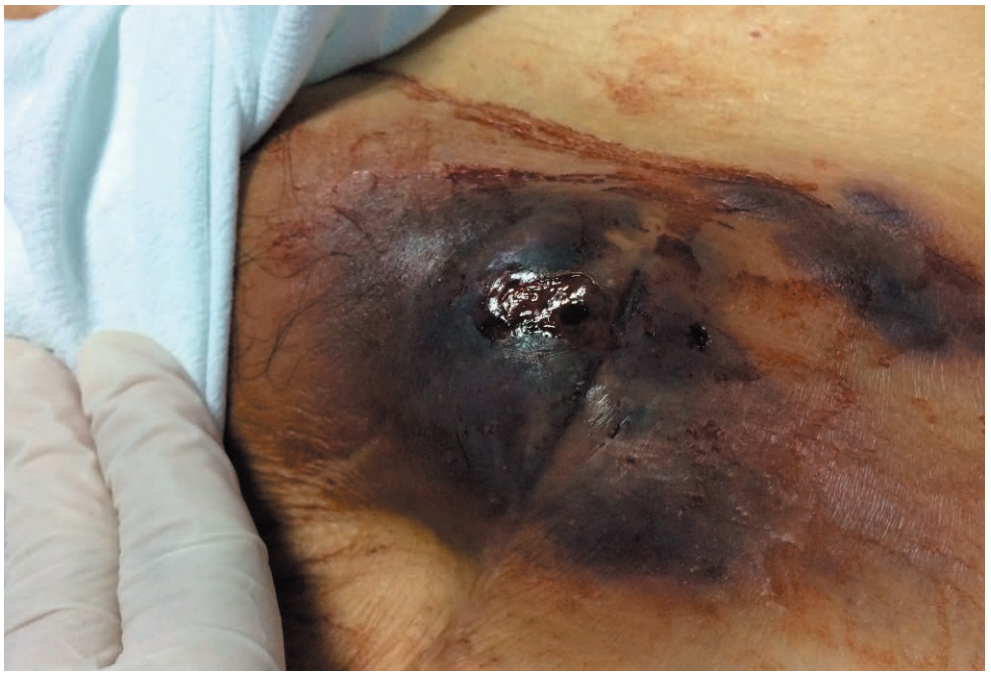
A. We collect serum, plasma, urine and PAXgene tubes. At this stage, we only defined the use of samples related to our main objective that is to confirm the relevance of previously identified biomarkers that can predict the clinical worsening of patients. Nevertheless, thanks to this large biobank, we will also be able to investigate new candidates either with proteomic or transcriptomic approaches. Of course, PAXgene tubes, combined with genome-wide approaches, are powerful tools to better understand of pathophysiology of sepsis development and to generate new hypothesis that could be validate in further studies. Thus, taking advantage of these tools, it could be an additional opportunity to valorize the valuable database in ancillary studies. »

Sepsis

Infections can put you or your loved one at risk for a life-threatening condition called sepsis. Anyone can get an infection, and almost any infection, including COVID-19, can lead to sepsis. In a typical year:

- At least 1.7 million adults in America develop sepsis.
- Nearly 270,000 Americans die as a result of sepsis.
- 1 in 3 patients who die in a hospital has sepsis.
- Sepsis, or the infection causing sepsis, starts outside of the hospital in nearly 87% of cases.

From Get Ahead of Sepsis – Know the Risks. Spot the Signs. Act Fast. https://www.cdc.gov/patientsafety/features/get-ahead-of-sepsis.html#:~:text=At%20least%201.7%20million%20adults,in%20nearly%2087%25%20of%20cases.



Q. Can these biomarkers potentially be used to determine nosocomial infections – that is, opportunistic sepsis that may develop while a patient is already in hospital? Or post-surgery monitoring? Or due to medical tubes or catheters for prolonged admissions?

A. This is not an objective of this study, as we target non-severe patients at ED and we focus on the first 72 hours after enrollment, but many other studies at bioMérieux have attempted to answer to this question that remains very important for clinicians.

Q. Given the critical nature of sepsis and speed of onset, is there a metric for a time-to-result for a future biomarker assay (assuming success in finding markers in the trial)?

A. A biomarker will never give you any information if you don't use it a clinical context. So, our test (as many others) will be used in conjunction with others clinical parameters and clinicians' judgment.

Q. Given the urgency of the condition, is bioMérieux targeting a future biomarker assay as an in vitro diagnostic or a laboratory test that could be run in hospital? Or will this be targeted as a point-of-care assay in the ED? Or even at at-home test for bed-ridden patients?

A. At this stage, we are exploring the value of the biomarkers and not yet evaluating the which platform will be the best fit. This could be done in an additional study analyzing the added value of using the real-time biomarkers.

Q. Can you comment on the inclusion/exclusion criteria regarding ensuring diversity in age and other population profile measures? Would a patient be excluded if the patient were taking, say, an antibiotic medicine for an unrelated condition?

A. In this study, we include all adults (18 years or older) with a suspected or confirmed non-severe infection (JAMA 2017) and at risk of deterioration. Risk of deterioration is defined as any patient that the physician has admitted or intends to admit as an inpatient to the hospital or patients discharged home (outpatient) who are either i) >65 years old or ii) diagnosed with pneumonia. To target a population of non-severe infections that could progress to sepsis, we focus on patients with a delta SOFA under 2 from baseline as defined in JAMA 2016.

Exclusion criteria are limited to i) inability to obtain written consent, ii) known pregnancy, iii) patients with isolated uncomplicated pharyngitis, throat infection, sinusitis, or otitis media, and iv) Infectious symptoms present for > 5 days prior to presentation.

With these inclusion exclusion criteria, we really wanted to match the real-life of ED, without too many restrictions. Thus, if a patient arrives with some treatment (antibiotic, immune suppressor, etc.), which often happens, the condition will be listed in the eCRF but the patient will not be excluded.

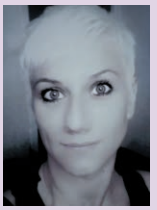
Q. Does bioMérieux plan any follow up assay on banked samples to determine the most likely pathogen that leads to sepsis?

A. With this cohort we will not have enough information to respond to this question

Q. Why identify patients at risk of deterioration? and What will doctors do with these results?

A. Anyone can get an infection, and almost any infection can lead to sepsis. Thus, early identification of patients at higher risk of worsening is crucial to avoid organ dysfunctions that can lead to death or long sequelae. On another hand, as most hospitals suffer from overcrowding, space constraints and sometimes shortage of nurses and physicians, there is also great value in identifying patients who could be safely rule-out from hospital.

So, identifying patients at risk for deterioration could help prevent sepsis and better allocate resources according to the degree of severity. It could also indirectly lead to lower hospital costs and greater patients' satisfaction, as low-risk patients will undergo fewer tests and could be discharged sooner. JoPM



Marie-Angélique Cazalis

I am an Associate Staff Scientist at bioMérieux, a world leader in *in vitro* diagnostics, in the Open Innovation and Partnerships (OIP) department. I have over 15 years of experience as a Scientific Leader and Project Manager, with a strong focus on medical needs in emergency medicine, critical care, and infectious diseases. I have spent half of my career in the Joint Research Unit established between bioMérieux and the Hospices Civils de Lyon, France's second university hospital center. Over the years I have developed a strong ability to interact with cross-functional teams, made up of program managers, immunologists, biostatisticians, and physicians. In addition, my strong hands-on laboratory experience (i.e., test design and SOP establishment in molecular biology, genomics, and immunoassays) has given me the opportunity to train over 30 people, including technicians and PhDs, in laboratory techniques. Having a deep understanding of industrial priorities and hospital constraints has helped me ensure alignment between medical needs and implementation in hospital clinical routine, which has led to the successful conduct of several multi-center international clinical trials in emergency and intensive care units.

References

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