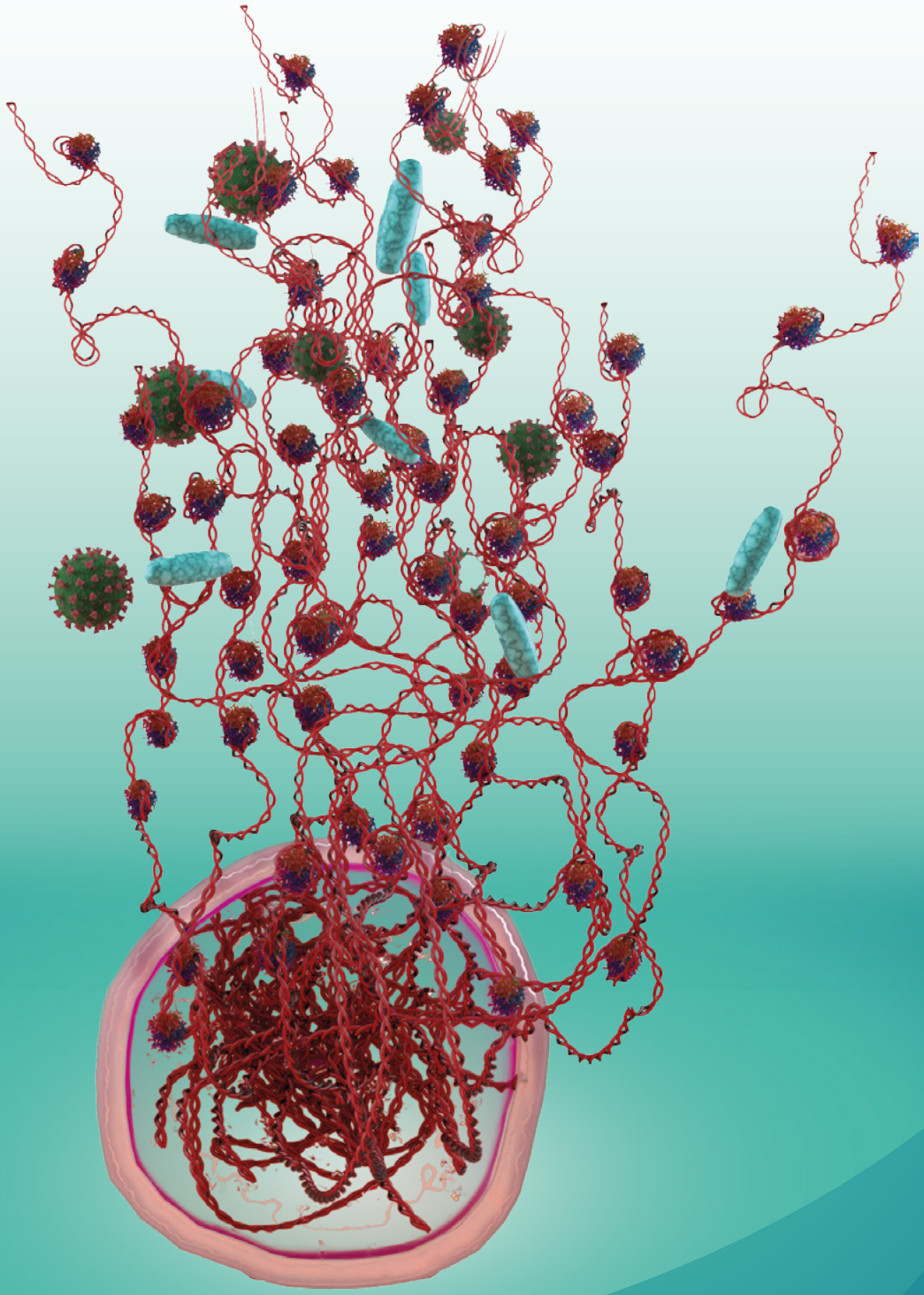
Sepsis: hope of a brighter future.

Report from World Leaders in sepsis care meeting (17-18 September 2023) – discussing how Nu.Q® NETs could best be used in clinical practice



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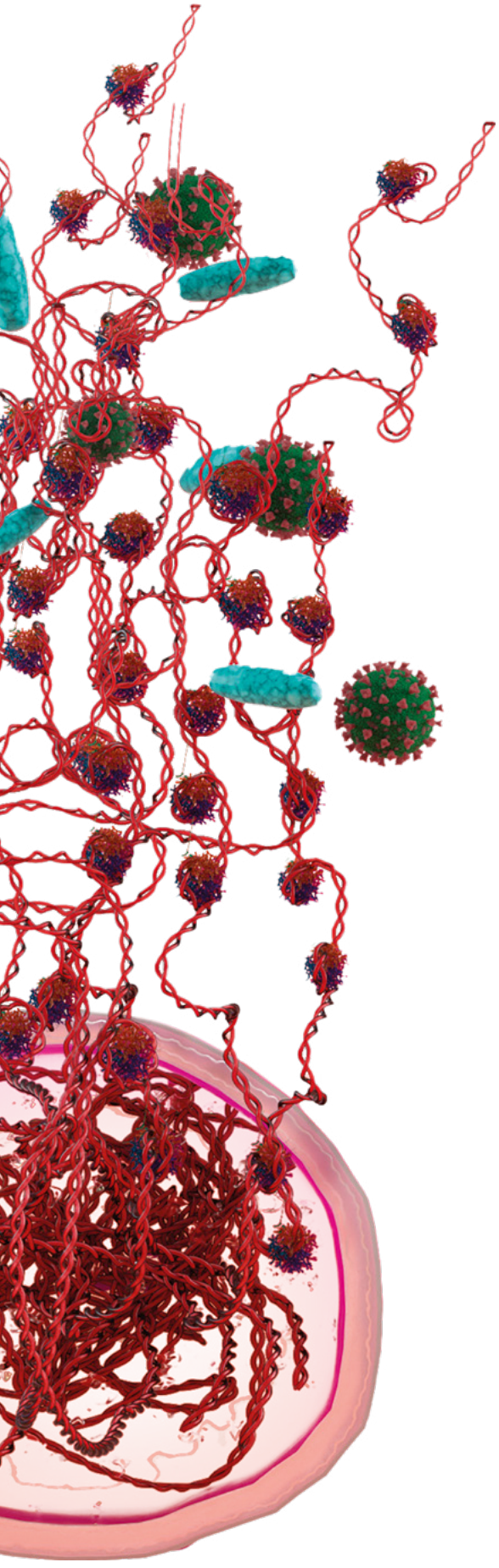


Introduction

Sepsis is the number one cause of death in hospitals worldwide. It kills an estimated 11 million people a year[1], which is more than cancer or coronary disease. Almost half of cases are in children. In 2017, there were an estimated 20 million cases and 2.9 million deaths under-fives.[2]

Half of survivors are left with psychological and/or physical sequelae. They may struggle to remember everyday things, no longer be able to walk or be unable to dress or bathe themselves without help.

Early detection and treatment of sepsis has the potential to improve survival – and improve the quality of life of survivors. But sepsis can be hard to spot early; it is a syndrome with many faces and many of its symptoms mimic those of other conditions.

Once it is diagnosed, existing treatments – antibiotics, plus supportive therapies such as ventilation, IV fluids and vasopressors – are often not enough.

Imagine if a simple blood test could help diagnose sepsis and identify those patients more likely to deteriorate. We brought together a panel of world-renowned experts in sepsis to explore the potential of Nu.Q® NETs, a rapid, low-cost and routine blood test, in clinical practice.

"A lot of patients come into the emergency room, are not recognised as having sepsis and are sent home. Eventually some of them worsen and they come back to the hospital in a poor condition or even die at home."

Prof. Djillali Annane

Introducing the panel

Djillali Annane
Panel chair

Professor in medicine at University Paris-Saclay and University Versailles SQY and Chief Counsellor of the French Minister of Health.

Michael Bauer

Professor and Chair of the Department of Anaesthesiology and Intensive Care Medicine at Jena University Hospital.

Evangelos J. Giamarellos-Bourboulis
Event host

Professor of internal medicine and infectious diseases at the National and Kapodistrian University of Athens and chair of the European Sepsis Alliance.

Guillaume Monneret

A professor of immunology at Hospices Civils de Lyon.

Mervyn Singer

A professor of intensive care medicine at University College London. Co-chaired Sepsis-3 Definitions International Task Force; past-Chair, International Sepsis Forum; Sepsis Topic Adviser to NICE; Emeritus NIHR Senior Investigator.

Lea Payen

A professor in molecular biology and toxicology at the University of Lyon I and Hospices Civils de Lyon.

Adrienne Randolph

A paediatric critical care physician at Boston Children's Hospital, Professor of Anaesthesia and Paediatrics at Harvard Medical School and chair of the International Sepsis Forum.

Dr Andrew Aswani

A consultant in intensive care medicine and anaesthesia at Guy's and St Thomas' Hospital in London and co-founder and Chief Medical Officer of Santersus AG.

Dr Tanya Novak

A PhD scientist at Boston Children's Hospital and an instructor at Harvard Medical School.

Dr Andrew Retter

An intensive care consultant at Guys and St Thomas' Hospital in London and a medical consultant to Volition.

A brighter future for sepsis: are NETs the key?

A growing understanding of the biology of neutrophils and, in particular, neutrophil extracellular traps (NETs) could improve the diagnosis, monitoring and treatment of sepsis.

Released by neutrophils when they detect bacterial, viral or other threats, these webs of decondensed chromatin can be "angels" or "devils". They play an important role in the body's response to infection; they trap and kill invading pathogens, stopping the threat from spreading around the body. Excessive NETs production is associated with a dysregulated immune response and poor patient outcomes in a range of life-threatening conditions.

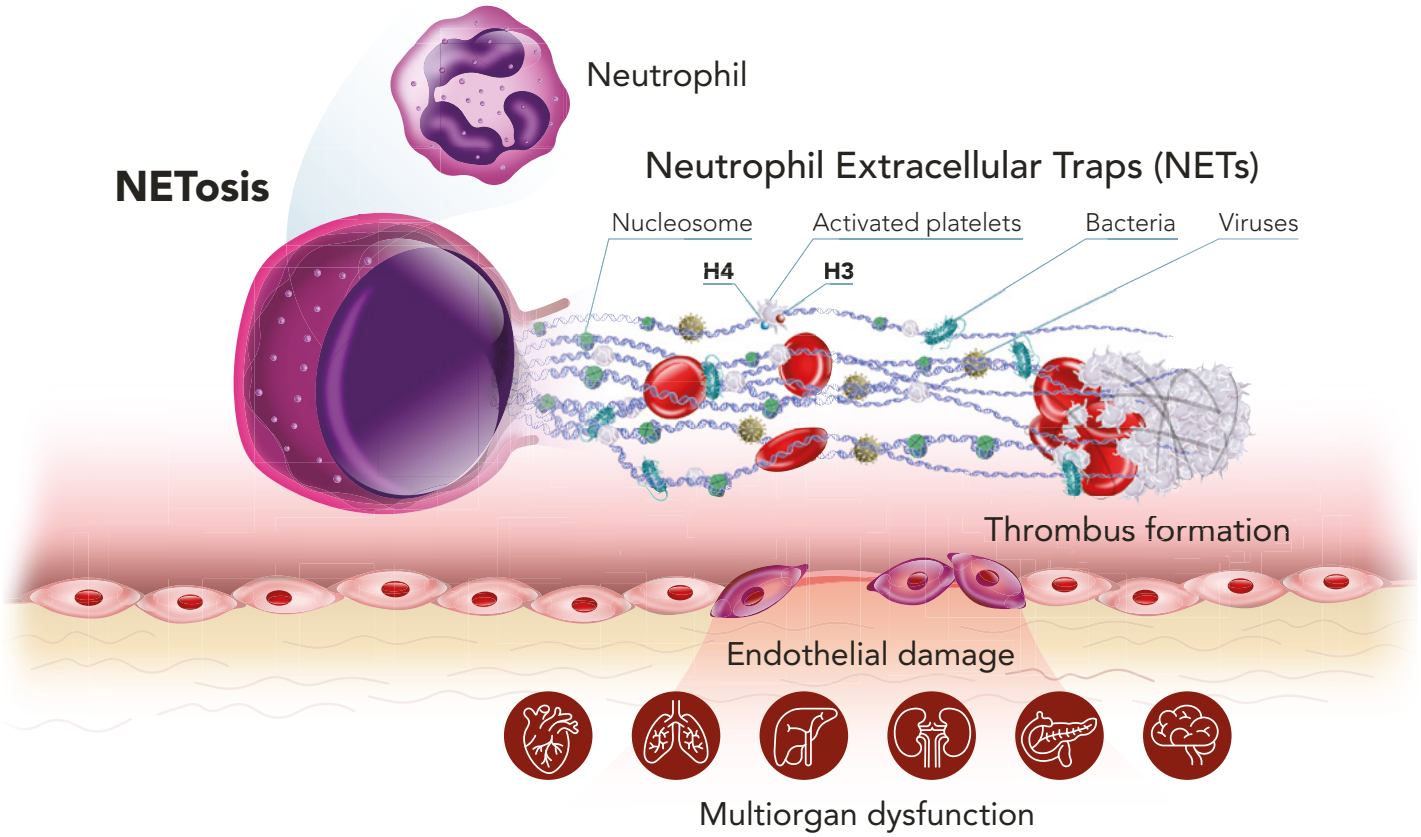
This includes sepsis, in which the excessive host immune response to an infection can cause widespread organ damage.

It isn't yet clear whether elevated NETs are a key actor in sepsis – if they are part of the dysregulated host immune response to infection that drives sepsis – or if they are a useful bystander – a sign of, rather a contributor to, the dysregulated response.

We do know, however, that excessive activation of NETs is a critical juncture bringing together the innate immune system, the complement system and the adaptive immune system, which suggests that high levels of NETs are indeed part of the dysregulated host immune response.

Nu.Q® NETs is the first approved clinical assay to assess disease severity by quantifying circulating nucleosomes, a critical component of NETs.

The role of NETs in endothelial damage and the formation of microthrombi and resultant multiorgan failure.



Adapted from Henry Ng. Arteriosclerosis, Thrombosis, and Vascular Biology. Circulating Markers of Neutrophil Extracellular Traps Are of Prognostic Value in Patients With COVID-19, Volume: 41, Issue: 2, Pages: 988-994, DOI: (10.1161/ATVBAHA.120.315267) and Vélez-Páez JL, Rueda-Barragán FE, Dueñas-Andrade S, Rodrigez-Morales A, Kyriakidis NC. The role of platelets and neutrophil extracellular traps (NETs) in sepsis: A comprehensive literature review. Microbes Infect Chemother. 2023; 3: e1595

"Detecting sepsis early is critical to saving lives. Mortality increases as much as 8% for every hour that treatment is delayed."

Dr. Andrew Retter

The potential of Nu.Q® NETs: how the technology could be best used in clinical practice.

The panel explored the potential of using Nu.Q® NETs to enhance the management and outcome of sepsis patients.

Early diagnosis of sepsis

One of the key themes of the discussions and presentations included whether measuring NETs would assist in the **early diagnosis** of sepsis.

The first step in successfully treating sepsis and ensuring a brighter future for patients and their families is to find it. Sepsis pays no respect to age, social status, prior health and can occur in any setting, from the community to hospital (ED, ward and ICU). Currently, physicians use a combination of clinical signs and blood, microbiological and other tests to make their diagnosis. However, the process is time-consuming and far from foolproof; the symptoms of sepsis overlap with those of many other conditions and even in the sickest patients only about a third of blood cultures are positive.

"Measurement of NETs could potentially identify severe illness that may not be apparent yet clinically."

Prof. Adrienne Randolph

Nu.Q® NETs is a simple, low-cost and routine blood test which can be deployed throughout the hospital, including the Emergency Department. It measures levels of the histone H3.1, a building block of NETs. Studies that demonstrate the potential of measuring NETs in the diagnosis of sepsis include one published in Biomolecules in August 2022 which found a correlation between NETs levels in septic shock patients and the SOFA score, a measure of organ dysfunction.[3]

For a biomarker test to be widely adopted, it has to be practical in routine settings. A recent validation study by Professor Payen found the Nu.Q® NETs assay to be compatible with existing biochemistry robots. It also showed that blood can be collected in citrate and EDTA tubes and samples can be kept for up to 24 hours, allowing reflex testing.[4]

"Sepsis is the number one cause of death globally amongst young children."

Prof. Adrienne Randolph

Monitoring treatment

Sepsis patients can deteriorate rapidly. If patients who aren't responding to treatment could be identified earlier, they could be changed to a new line of treatment earlier, improving outcomes.

Research led by Professor Monneret and presented at ESICM 2023[5] found a correlation between high H3.1 levels and 28-day mortality in septic shock patients. This suggests that Nu.Q® NETs could be used to identify the sickest patients; their treatment could then be reevaluated.

"There have been no new treatments or therapies for sepsis really since antibiotics were invented about 70 years ago."

Dr. Andrew Retter

Guiding treatment

There was a lot of interest among the panel in how NETs could be used to guide treatment of sepsis. Preliminary results of the RECORDS trial[6] presented by Professor Annane indicate an association between high levels of H3.1 and the need for mechanical ventilation and vasopressors. The early data also points to elevated H3.1 being predictive of mortality.[7]

The panellists discussed how Nu.Q® NETs could be used to stratify patients for treatment, by for example, helping physicians decide whether to move a patient into ICU. There was also interest in whether the assay could be used to triage and prioritise discharge, to help planning with both admissions and discharge from critical care.

"From the data I have seen, it looks like high circulating levels of H3.1 are associated with a higher risk of requiring mechanical ventilation, requiring vasopressors and are even associated with mortality, so if the test is rapidly accessible, it will be helpful for triage."

Prof. Djillali Annane

Another important theme was whether the results of Nu.Q® NETs could guide the use of treatments beyond the current standard therapies. Fundamental to this is the role of NETs in sepsis – whether they are main actor or a bystander.

If it is the former and NETs are part of the dysregulated host immune response, they could be a valuable treatment target. For example, therapies that clear them from the blood could be helpful. In animal studies, Santersus AG has shown that its NucleoCapture™ technology can remove NETs from the blood of pigs with sepsis.[8] The "blood-cleansing" device has also been successfully used in the regeneration of damaged lungs – a finding that further demonstrates the association between NETs and organ damage.[9]

Another option could be giving treatments that prevent the activation of neutrophils and the release of NETs into the bloodstream. The panel discussed ongoing research which has identified TNF-α to be crucial for the activation of neutrophils, suggesting TNF blockers could be useful.

Personalised medicine

If NETs are, however, not directly toxic but sign a particular subtype of sepsis, this could allow the personalisation of treatment. For example, if high levels of NETs signify a hyperinflammatory endotype, patients might benefit from corticosteroids or complement inhibitors.

Our growing knowledge of the biology of NETs also raises the possibility of revisiting some old treatments. There have been more than 100 phase 3 trials in the last 20 to 25 years but none have led to therapies that are still used today. One reason for this is thought to be that many trials failed to take into account that sepsis is a complicated condition made up of many different sub-types.

"Patient-centred benefit based on a biomarker guiding personalised intervention would be the holy grail."

Prof. Michael Bauer

What if some treatments that either failed in trials or were withdrawn from use could improve outcomes when directed at patients with high levels of NETs? For example, NETs are known to down-regulate natural anti-coagulant mechanisms, which suggests that the treatment of patients with excessive levels of NETs with activated protein C is worthy of exploration.

"Enrichment with a biomarker is key to minimise the systemic effects that will stymie new drugs."

Dr Andrew Aswani

Conclusions and future research

There was agreement among the panel that, while more work needs to be done, NETs represent a very interesting avenue to early diagnosis of sepsis and to guiding and monitoring response to therapy.

Valuable sources of further data will include EPICTETUS, a one-year prospective study evaluating Nu.Q® NETs in 500 patients with sepsis or septic shock.[10]

Launched in October 2023, the observational study will assess how the Nu.Q® NETs assay performs in diagnosis, clinical course prediction and prognosis of sepsis.

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Volition

About Volition

Volition is a multi-national epigenetics company powered by Nu.Q,® its proprietary nucleosome quantification platform. Volition is developing simple, easy to use, cost effective blood tests to help diagnose and monitor a range of life-altering diseases including some cancers and diseases associated with NETosis such as sepsis.

For details go to:
https://volition.com/nu-q-nets