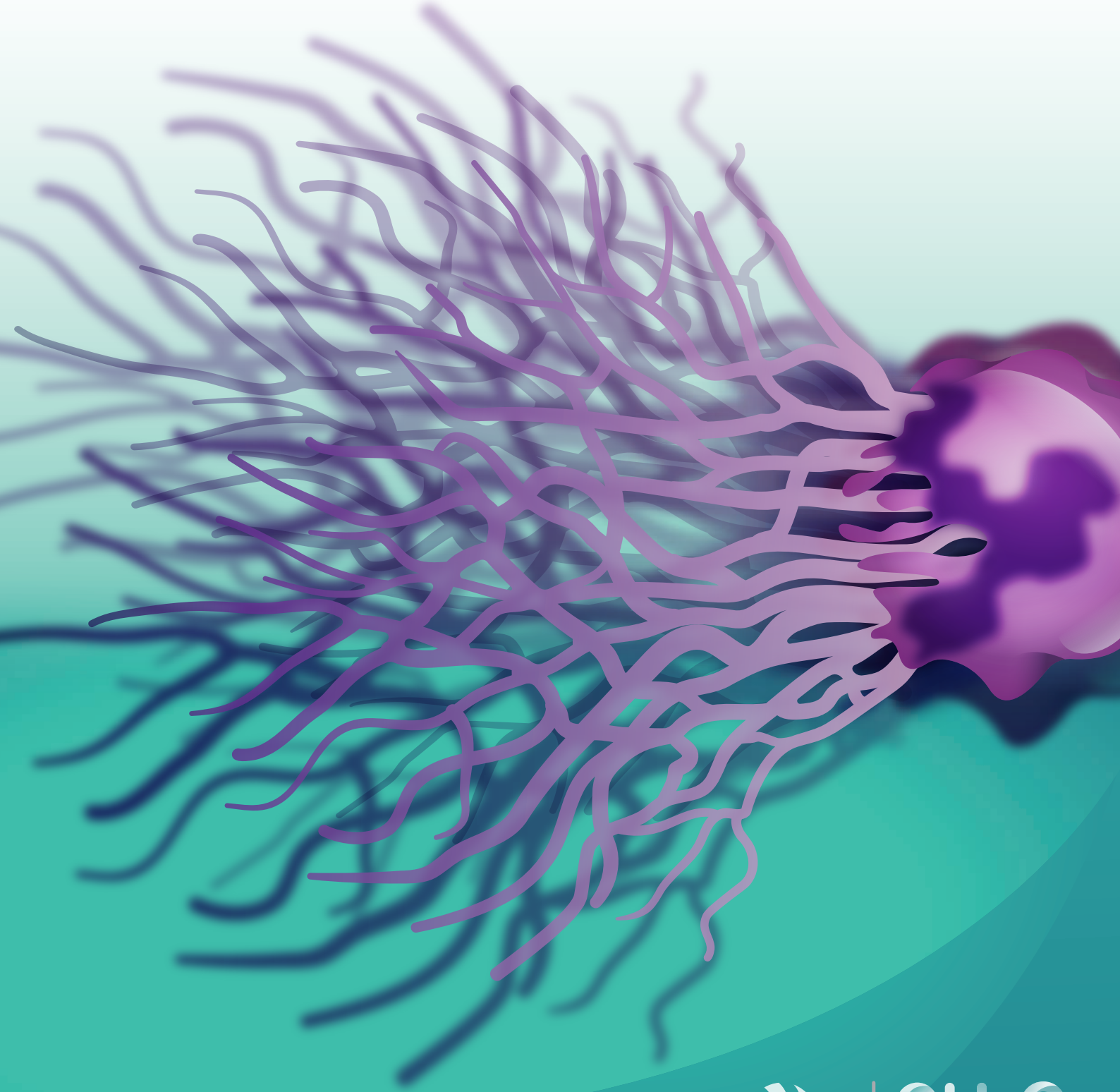
Sepsis: A brighter hope for tomorrow.

Report from ESICM Lives symposium (7 October 2024) on new research into how Nu.Q® NETs could improve the management of sepsis



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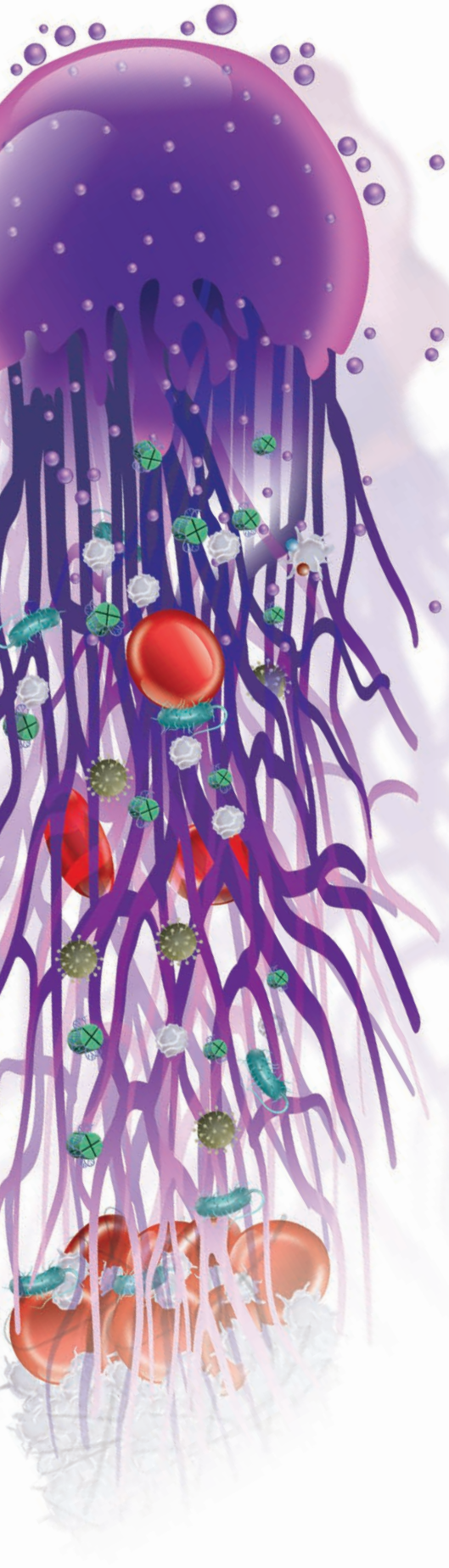

Introduction

Sepsis kills 11 million people a year – that's one in five of all deaths worldwide. Almost half of cases are in children under the age of five and it is the number one cause of death in hospitals.[1]

Of those who do survive, almost half are left with psychological or physical effects. They may struggle to remember everyday things or be unable to dress themselves. Others may develop chronic inflammatory disorders or even autoimmune disease.

Early diagnosis is vital. Patients can deteriorate rapidly and, if sepsis is not treated quickly, it can lead to organ failure and death. But sepsis is hard to identify, and existing treatments frequently aren't enough.

Nu.Q® NETs is a simple, low-cost and rapid blood test for a biomarker of sepsis with the potential to improve the diagnosis and the treatment of sepsis.

We held a symposium at ESICM Lives 2024, the annual conference of the European Society of Intensive Care Medicine, during which experts from around the world presented the results of the latest research into how Nu.Q® NETs could be used in clinical practice.

"On average, one out of three patients admitted to my intensive care unit has sepsis. Of the two who don't have sepsis on admission, one out of ten will develop sepsis, so it really is a daily battle for us."

Prof. Djillali Annane

Introducing the speakers

Djillali Annane

Symposium chair and chief investigator of the RHU RECORDS study

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

Dr. Andrew Retter

Clinical lead for Critical Care Medicine, Consultant in Intensive Care, ECMO and Thrombosis. Chief Medical Officer of Volition, UK.

Terry Kelly, PhD

Chief Innovation Officer at Volition, USA. Holds a PhD in neuroscience, a B.S. in biopsychology and completed a post-doctoral fellowship in epigenetics.

Dr. Caroline Neumann, DESA, EDIC, infectious diseases specialist

A senior Consultant in Intensive Care Medicine at Jena University Hospital. Research interests include biomarkers to improve the diagnosis of sepsis and acute kidney injury.

A brighter tomorrow for sepsis: why NETs are key.

When neutrophils detect invading microorganisms (e.g. bacteria, viruses, or fungi), they release neutrophil extracellular traps (NETs) – sticky webs made of long strings of decondensed chromatin. These trap and kill the invading pathogens, stopping the threat from spreading around the body.

This process plays a critical role in our normal response to infection but when NETs are produced faster than they can be removed, they are associated with an excessive or dysregulated immune response and can lead to tissue damage and, in severe cases, sepsis, organ failure and death.

In his presentation, Dr. Retter explained that excessive levels of NETs are directly toxic to the endothelial layer and can cause inflammation and organ damage. In this regard excessive NETs are considered to be damaging.

NETs are the natural bridge between our innate immune and our blood clotting systems. The trapping mechanism of NETs is called immunothrombosis. When NETosis goes into overdrive the 'excessive' amount of NETs can block blood vessels damaging organs and causing micro blood clots. This process is called thromboinflammation. This causes worse tissue damage and the worsening of sepsis.

- Nu.Q® NETs is the only commercially available, validated assay to quantify the level of NETs. It does this by measuring levels of the nucleosome H3.1, a building block of NETs.
- The test is done on samples collected in standard purple-top tubes for full blood counts and doesn't involve any additional testing for patients.
- Dr. Kelly presented data from immunoassays, DNA methylation and fragmentation patterns and other work that confirm that Nu.Q® NETs is detecting H3.1 and that the H3.1 comes from neutrophils.[2]
- She has also shown that H3.1 levels are not affected by the patient's height, weight, age or sex.[3] Nor are they affected by circadian rhythm.[4]
- The symposium heard that H3.1 correlates poorly with neutrophil count.[3–5] This means that measuring H3.1 provides information that isn't available from the full blood count alone.

"H3.1 isn't affected by someone's sex, someone's height, someone's weight and there's no circadian rhythm – it doesn't fluctuate during the course of the day. These are simple things but really critical things to help make a test clinically usable."

Dr. Terry Kelly

"The test uses blood collected in standard purple-top tubes and doesn't require any new technology or major investment."

Dr. Andrew Retter

Nu.Q® NETs:
The latest research findings.

The symposium explored the latest research findings from three large independent studies carried out at centers of excellence in three different countries and involving more than 3,000 sepsis patients. All used Nu.Q® NETs to measure levels of H3.1.

Study	Country	Description	Cohort size
SISPCT	Germany	Retrospective analysis of prospectively collected cohort	971 intensive care patients
Amsterdam UMC	Netherlands	Retrospective analysis of prospectively collected cohort	1,713 intensive care patients
RHU RECORDS	France	Prospective, multi-center, placebo controlled, biomarker-guided, adaptive Bayesian design basket trial	1,500 intensive care patients (interim analysis of 416 patients)

Their findings are **clear** and **consistent**: they show that sepsis patients with an elevated H3.1 level on admission to ICU are at greater risk of deteriorating. In general, a reading of 1,000ng/ml or above, predicted poor outcomes (a healthy adult typically has a reading of under 30ng/ml).

All three studies found that an elevated H3.1 level was associated with **mortality**. For example, Volition's analysis of the SISPCT data found that every patient with an H3.1 level over 20,000ng/ml on admission to ICU died within 14 days. Patients with a level of 10,000-20,000ng/ml had a 25% mortality risk and those with readings of 1,000-10,000ng/ml had a 12% risk.[3]

The studies also show a clear link between an elevated H3.1 level and **organ failure** and, in particular, **renal failure** and **respiratory failure**.

About half of patients with sepsis will develop acute kidney injury (AKI), with a mortality rate of about 40%.[6] NETs can contribute to sepsis-associated AKI, by infiltrating the kidneys, where they cause direct and indirect damage.

Dr. Neumann presented results from the SISPCT study that show that H3.1 levels correlate with AKI severity. The likelihood that patients would need renal replacement therapy (RRT) also correlated with H3.1 levels on admission and H3.1 levels were superior to creatinine in predicting which patients would require RRT.

In addition, a clinical model that combined three variables – an H3.1 level of over 2,600ng/ml, a low platelet count and a low urine output – could identify 84% of the patients who would go on to require RRT.[3]

The Amsterdam UMC and RHU RECORDS studies found a similar link between H3.1 levels and AKI.[4,5] RHU RECORDS also found H3.1 levels to be associated with the need for RRT.[4]

Dr. Retter explored research that links H3.1 with **organ failure**. He described a recent study by Mittendorfer et al in which the removal of H3.1 restored lung function in pigs with acute respiratory distress syndrome (ARDS).[7]

He also presented the results of Volition's analysis of the SISPCT data which showed that the patients with the most severe ARDS had the highest H3.1 levels.[3]

Meanwhile, the Amsterdam UMC study found the higher a patient's H3.1 level, the greater their risk of **multiple organ failure**.[5]

And the RHU RECORDS data indicates that H3.1 levels can be used to distinguish between patients with sepsis and those with **septic shock**. Those with septic shock had a median H3.1 level of just over 1,000ng/ml. This compares with a level of 700ng/ml or so in those with sepsis.[4]

"Patients with sepsis-associated AKI, and especially those staying on renal replacement therapy, endure a huge impact on their lives. Long-term dialysis patients need to visit the dialysis center several times a week and are also at increased risk of suffering cerebrovascular and cardiovascular complications. Their immune system is substantially depressed, meaning they are also at risk of developing new infections."

Dr. Caroline Neumann

"This is the first time I have seen so much data, so quickly, on a sepsis biomarker with consistent findings. The consistency of data across different teams, across different countries, across different types of sepsis is extremely reassuring."

Prof. Djillali Annane

How using Nu.Q® NETs to measure H3.1 could improve the management of sepsis.

There are numerous ways in which using Nu.Q® NETs to measure H3.1 could improve the treatment of patients with sepsis.

The research findings suggest that a high level of H3.1 may be a **"treatable trait"** – in other words, lowering levels of the biomarker may be a much-needed new way of treating sepsis.

If so, lowering H3.1 may improve patient outcomes by, for example, preventing organ failure or the need for organ support like RRT.

How could H3.1 be lowered? The Santersus AG's NucleoCapture "blood-cleansing" device has been used to lower H3.1 levels in the lungs of pigs.[8] Others have used small molecule inhibitors of NETs to protect against renal failure in sheep with sepsis.[9] Another option could be to give a therapy that prevents neutrophils from releasing NETs into the bloodstream.

It is also possible that an H3.1 reading over a certain threshold could be used to personalize treatment. For example, if a high H3.1 is a sign of a hyperinflammatory immune response, corticosteroids might be helpful.

Or perhaps some old treatments could be revisited. Might some treatments that failed in clinical trials or were withdrawn from use be effective when given to a particular group of patients, such as those with high levels of H3.1? Activated protein C, for example, has previously been shown to bind and clear histones and therefore could be worthy of exploration.

These are all ideas for the future. In the here and now, elevated levels of H3.1 could assist in the early diagnosis of sepsis. They could also be used to identify those who are going to deteriorate, allowing them to be admitted to ICU earlier and be monitored more closely. Treatment plans could be reevaluated, and the level of organ support increased.

"There are already biomarkers available, but they haven't been game-changers, they haven't been able to, for example, be treatable traits. What we are likely to see with H3.1 is a high likelihood of getting a treatable trait, a game-changer in modifying patients' trajectory."

Prof. Djillali Annane

Conclusions and next steps.

There is now a wealth of data that offers sepsis patients real hope for a brighter tomorrow.

The results of three, large independent studies involving thousands of patients have demonstrated, with real consistency, that Nu.Q® NETs can predict which patients will deteriorate.

It is clear that an elevated level of H3.1 in sepsis patients reflects a dysregulated immune response and is associated with an increased risk of mortality, renal failure, respiratory failure, multi-organ failure and septic shock.

Importantly, H3.1, the Nu.Q® NETs biomarker could be a "treatable trait" – and lead to new ways of treating sepsis, improving the survival of patients and the quality of life of survivors.

The Nu.Q® NETs test is simple to do and can be introduced into most hospital labs easily and without the need for major investment; it uses blood taken for standard tests.

Volition is currently seeking to commercialize Nu.Q® NETs and the findings from these latest studies will support ongoing licensing discussions with key industry stakeholders.

"Being able to predict a patient's clinical course early on would give you a bit more time to intervene and improve their outcome. That's what we all want to do as doctors."

Dr. Andrew Retter

"I believe that Nu.Q® NETs has the potential to bring about a paradigm shift in sepsis management. A year or two from now, physicians like me will very likely be using it routinely to help ensure more patients survive and survive in good health."

Prof. Djillali Annane

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Volition

About Volition

Volition is a multi-national epigenetics company 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.

Get in touch for more information:

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