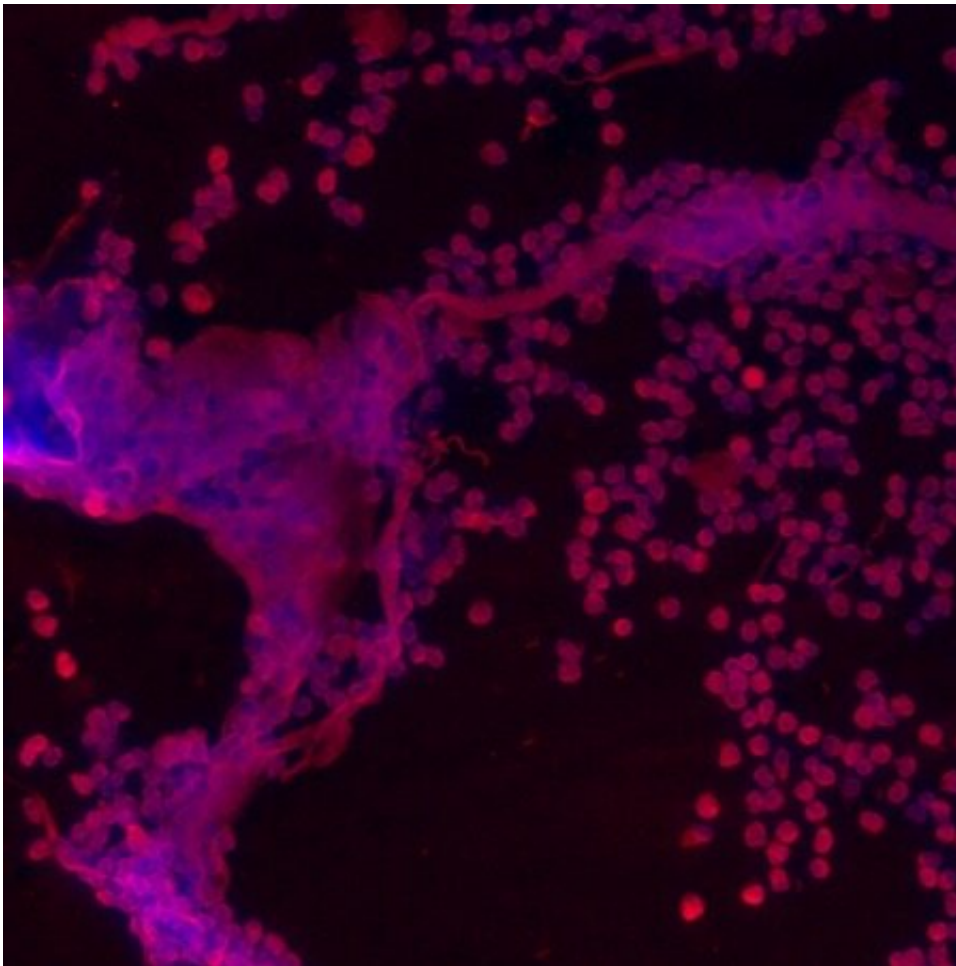


New non-antibiotic strategy for the treatment of bacterial meningitis

April 10 2019



Seen here are the white blood cells (neutrophils) in the spinal fluid during bacterial meningitis. The nuclear material DNA is stained blue and proteins in neutrophils are stained red. The large aggregates as represented by overlapping areas of blue (DNA) and red (protein) portrays the extracellular DNA-protein networks called neutrophil extracellular traps (NETs). NETs are released as a defence response against invading bacteria in bacterial meningitis. Credit:

Tirthankar Mohanty

With the increasing threat of antibiotic resistance, there is a growing need for new treatment strategies against life-threatening bacterial infections. Researchers at Lund University in Sweden and the University of Copenhagen may have identified such an alternative treatment for bacterial meningitis, a serious infection that can lead to sepsis. The study is published in *Nature Communications*.

The [immune system](#) has several important defenders to defend against infections of the central nervous system. The researchers have mapped what happens when [white blood cells](#) called neutrophils intervene in [bacterial meningitis](#). The neutrophils deploy to the infected area in order to capture and neutralise the [bacteria](#). It is a tough battle, and the neutrophils usually die, but if the bacteria are difficult to eliminate, the [neutrophils](#) resort to other tactics.

"It is as though in pure frustration, they turn themselves inside out in a desperate attempt to capture the bacteria they have not been able to overcome. Using this approach, they capture a number of bacteria at once in net-like structures, or neutrophil extracellular traps (NETs). This works very well in many places in the body, where the NETs containing the captured bacteria can be transported in the blood and then neutralised in the liver or spleen, for example. However, in the case of bacterial meningitis, these NETs get caught in the cerebrospinal space, and the cleaning station there is not very effective," explains Adam Linder, associate professor at Lund University and specialist in Infectious Diseases at Skåne University Hospital.

By using advanced microscopy, the researchers observed that the cerebrospinal fluid of patients with bacterial meningitis was cloudy and

full of lumps, which proved to be NETs. However, among patients with viral meningitis, the cerebrospinal fluid was free from NETs. When captured bacteria are caught in the cerebrospinal fluid, it adversely affects the immune system's work of clearing away bacteria and also impedes standard antibiotics from getting at the bacteria, says Adam Linder.

Would it be possible to cut up the nets so that the bacteria are exposed to the immune system, as well as to antibiotics, making it easier to combat the infection? As the NETs consist mainly of DNA, the researchers investigated the concomitant use of drugs that cut up DNA, so-called DNase.

"We gave DNase to rats infected with pneumococcus bacteria, which causes bacterial meningitis, and show that the NETs dissolved and the bacteria disappeared. It seems that when we cut up the NETs, the bacteria are exposed to the immune system, which finds it easier to combat the bacteria single-handed. We were able to facilitate a significant reduction in the number of bacteria without antibiotic intervention," says Tirthankar Mohanty, one of the researchers behind the study.

Before antibiotics, the mortality rate for bacterial meningitis was around 80 percent. With the advent of antibiotics, the mortality rate quickly fell to around 30 percent.

In the 1950s, Professor Tillett at the Rockefeller University in the U.S. found lumps in the [cerebrospinal fluid](#) of patients with bacterial meningitis. Professor Tillett discovered that these lumps could be dissolved using DNase. This was effective in combination with antibiotics, and reduced the mortality rate for meningitis from around 30 percent to about 20 percent. However, this treatment had side effects, as the DNase was extracted from animals and could therefore trigger

allergic side effects.

"At that time, everyone was so happy about the antibiotics—they reduced mortality for the infections, and it was thought that we had won the war against bacteria. I believe we need to go back and take up a part of the research that took place around the time of the breakthrough for antibiotics. We can, perhaps, learn from some of the discoveries that were then flushed down the drain," says Adam Linder.

"The development of resistance in bacteria is accelerating, and we need alternatives to [antibiotics](#). The drug we used in the studies is a therapeutic biological product derived from humans and has already been approved for human use. They are not expensive, and have also been tested against many different bacteria and infections. Bacterial meningitis is a major challenge in many parts of the world. In India, for example, it is a major cause of death among children, so there would be significant benefits there from using such a treatment strategy," says Tirthankar Mohanty.

The researchers want to set up a major international clinical study and use DNase in the treatment of patients with bacterial meningitis.

More information: Tirthankar Mohanty et al. Neutrophil extracellular traps in the central nervous system hinder bacterial clearance during pneumococcal meningitis, *Nature Communications* (2019). [DOI: 10.1038/s41467-019-09040-0](https://doi.org/10.1038/s41467-019-09040-0)

Provided by Lund University

Citation: New non-antibiotic strategy for the treatment of bacterial meningitis (2019, April 10) retrieved 27 April 2024 from

<https://medicalxpress.com/news/2019-04-non-antibiotic-strategy-treatment-bacterial-meningitis.html>

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