SEPSIS AND THE IMMUNE SYSTEM

PUPIL RESOURCE

SEPSIS RESEARCH FEAT

SEPSIS EVERY HOUR COUNTS

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Your immune system plays a crucial role in maintaining a healthy body by working around the clock to recognise and respond to infection.

Inflammation is part of the immune system's protective response to an infection. It is incredibly powerful, so much so that it can damage your own cells if it is not tightly controlled. Sometimes, inflammation affects the whole body (it becomes systemic) – this is called sepsis. The powerful and complex mechanisms in place to wipe out the infection can cause serious damage to your own healthy cells and tissues. This systemic inflammation can cause irreversible damage to the body's organs (e.g. kidneys) eventually causing them to shut down, which, if not treated rapidly, can lead to death. Here, we describe sepsis from its symptoms to its diagnosis and the current ongoing research being carried out in our groups.

KEY WORDS

- sepsis
- inflammation
- infection
- immune system
- diagnosis

SEPSIS IS RESPONSIBLE FOR ABOUT

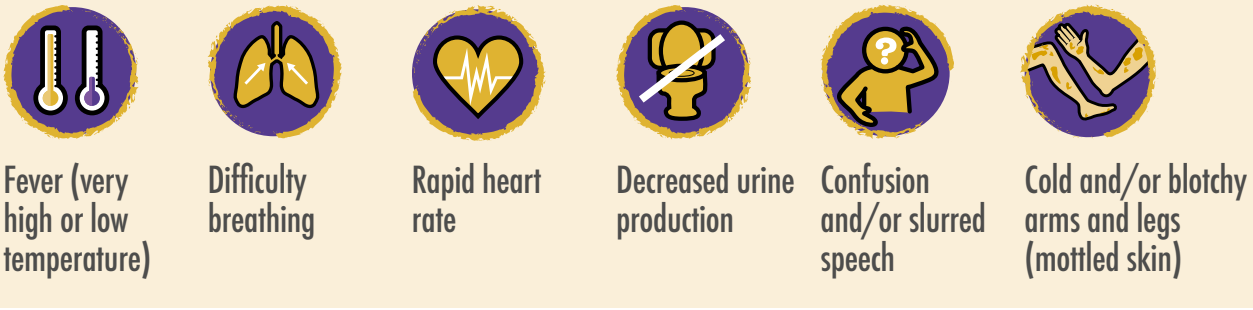
11 MILLION

DEATHS PER YEAR WORLDWIDE

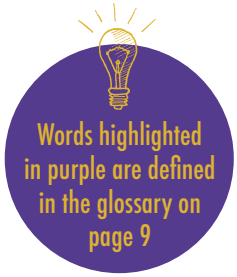
This accounts for roughly 20% of all global deaths which is even more than from breast and bowel cancers combined [1].

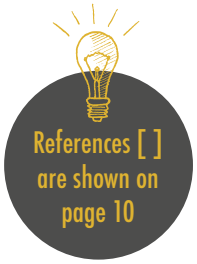
Infections that cause sepsis are a result of **pathogens** such as viruses, bacteria, parasites or fungi which either come from the environment around us or even from within our own body. Common infections which can lead to sepsis include meningitis (inflammation of the linings of the brain), pneumonia (infection of the lungs), urinary tract infections (infections of the bladder or kidneys) and cellulitis (infection of the skin, often affecting the foot and leg); although anywhere in the body has the potential to become infected and could be a source of sepsis.

If a person has sepsis, they may have*:



From the onset of sepsis, a deterioration in physical health can happen incredibly quickly, in just a few hours, so it is crucial to be able to recognise the symptoms of sepsis before it's too late. To be able to understand sepsis and its symptoms, we need to look at the immune system to see how it works normally, and what goes wrong during sepsis.

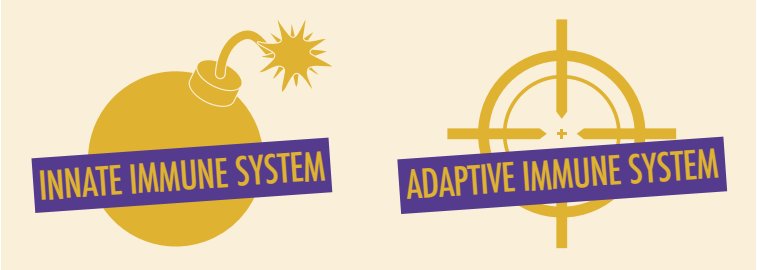




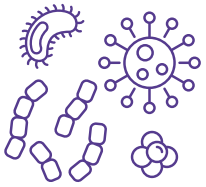
* https://www.sepsisresearch.org.uk/about-us/what-is-sepsis/

WHAT DOES THE IMMUNE SYSTEM DO?

The immune system consists of a very complex network of different chemicals and cells, all working together to recognise the threat caused by pathogens, kill them, neutralise their toxins, and maintain a healthy body. To do this, the body has two weapons which scientists call the *innate* immune system and the *adaptive* immune system.



Think of them like a grenade and a sniper: the innate immune system damages whatever is in range, while the adaptive immune system homes in with precision as a sniper would hunt down an enemy. The innate immune system acts immediately and locally; it rapidly employs a cocktail of potent chemicals and mechanisms to contain the infection before it has a chance to do any significant damage. Our innate immune cells can recognise pathogens by unique patterns on their surface. On recognition of these patterns, immune cells send out chemicals to warn other cells of an invasion and release a host of toxic chemicals to try and kill the invading pathogen.



HOWEVER, PATHOGENS

HAVE FOUND WAYS TO CAMOUFLAGE THEMSELVES FROM THE INNATE IMMUNE SYSTEM. FORTUNATELY, WE HAVE THE ADAPTIVE IMMUNE SYSTEM WHICH IS TRAINED TO TARGET SPECIFIC PATHOGENS.

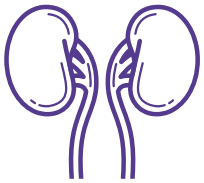
Think of when you get a papercut; microscopic pathogens can enter the wound and it becomes swollen and sore; that means it's inflamed. This is a necessary process to help your body recover from every injury and every infection [2]. An inflammatory immune response causes local **vasodilation** and increased **vascular permeability** at the site of the wound, meaning blood vessels widen and become leaky, causing blood flow to slow down locally.

At the site of inflammation, special proteins, termed receptors, are produced on the inside of your blood vessels and act like hooks to capture inflammatory cells as they pass by. Slower blood flow makes it easier for more inflammatory cells to get to the site of injury/infection and the leaky blood vessels help them to pass through the blood vessel cell wall into the site of infection.

WHAT GOES WRONG DURING SEPSIS?

The exact cause of sepsis is not known. Most of the time your immune system is able to efficiently take care of an infection without you even knowing about it. However, during sepsis, the innate immune system fails to localise its response and goes rogue, leading to a systemic inflammation. Instead of being contained at the site of infection, chemical signals are released into the bloodstream and travel around the body where they cause widespread vasodilation and increased vascular permeability in your blood vessels. The result of this is a decrease in blood pressure which causes inadequate blood flow to the body's tissues and major organs. Blood transports oxygen to the organs, which they require to function; a lack of blood flow decreases the amount of oxygen the organs receive. Systemic inflammation and a decrease in blood flow affect the body in a variety of ways, causing a whole host of serious symptoms.

In the case of sepsis, each of the organs can be affected in their own way. In the following paragraphs we will present some examples with words highlighted in blue, these refer to the symptoms of sepsis shown on page 3. To compensate for the inadequate blood flow, the heart and lungs have to work much harder to supply the tissues with oxygenated blood, resulting in a **faster heart rate** and **breathing difficulties**. Furthermore, blood oxygenation becomes less efficient as inflammation causes fluid to collect in the lung cavities and tissues, making it even harder for blood to take up the oxygen needed for normal body function.



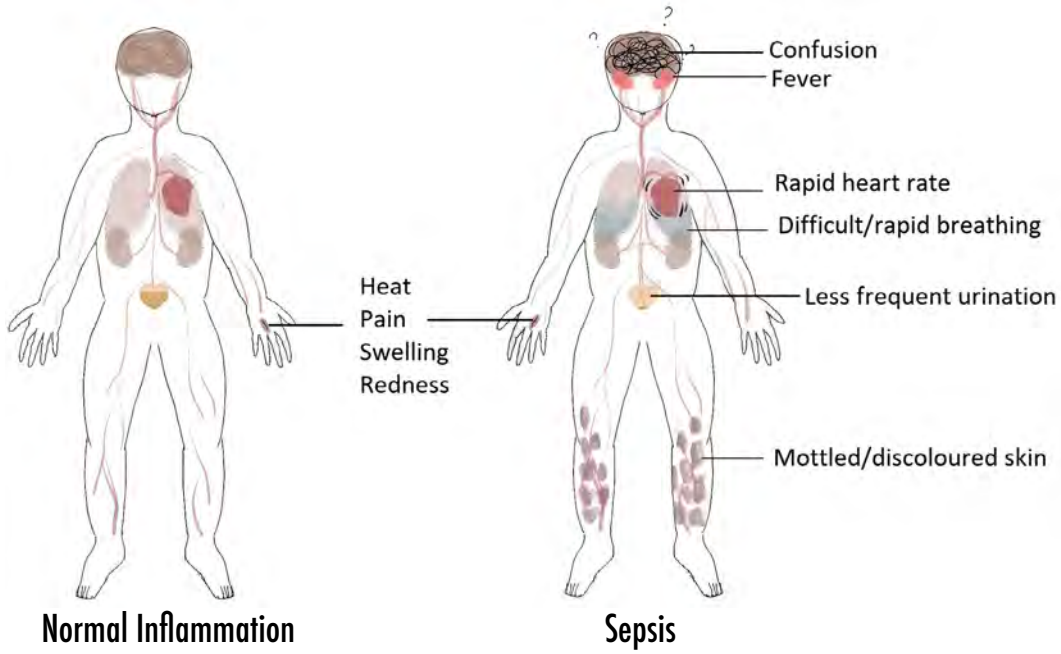
YOUR KIDNEYS

ARE RESPONSIBLE FOR FILTERING EXCESS WATER AND TOXINS, LIKE EXCESS ACID, OUT OF THE BLOOD, WHICH LEAVE THE BODY AS URINE.

Sepsis-associated inflammation and impaired blood flow affect the **kidneys' ability to clean the blood and make urine**. **Pale or mottled skin** is a sign that it isn't getting enough oxygenated blood. **Confusion and slurred speech** in sepsis patients are related to changes in the brain. The brain is difficult to study so scientists don't know for sure why people get confused, but they think it might be to do with the brain not getting enough oxygen, or immune cells releasing chemicals [2]. When inflammatory signals reach the hypothalamus, an area of the brain that regulates the body's temperature, it causes a **fever**. Fever is a common sign of an inflammatory response to infection; the patient will have an **elevated temperature whilst feeling hot and flushed or cold and shivery** [3],[4].

These are all examples of ways sepsis can affect the body (Figure 1), but sepsis is much more complex than that. Importantly during sepsis, normal organ functions can only be sustained for a limited time before they become irreversibly damaged and start shutting down, eventually leading to death.

Figure 1. A comparison between the inflammatory immune responses of two people: a healthy immune response of a person who has injured their hand (left) and a dysfunctional immune response affecting the entire body; this is typical of sepsis (right).



HOW DO WE DIAGNOSE AND TREAT SEPSIS?

Scientists have shown that time is critical in treating patients with sepsis. The earlier the treatment, the better their chances of survival. Figure 2 provides a summary of the diagnostic process.

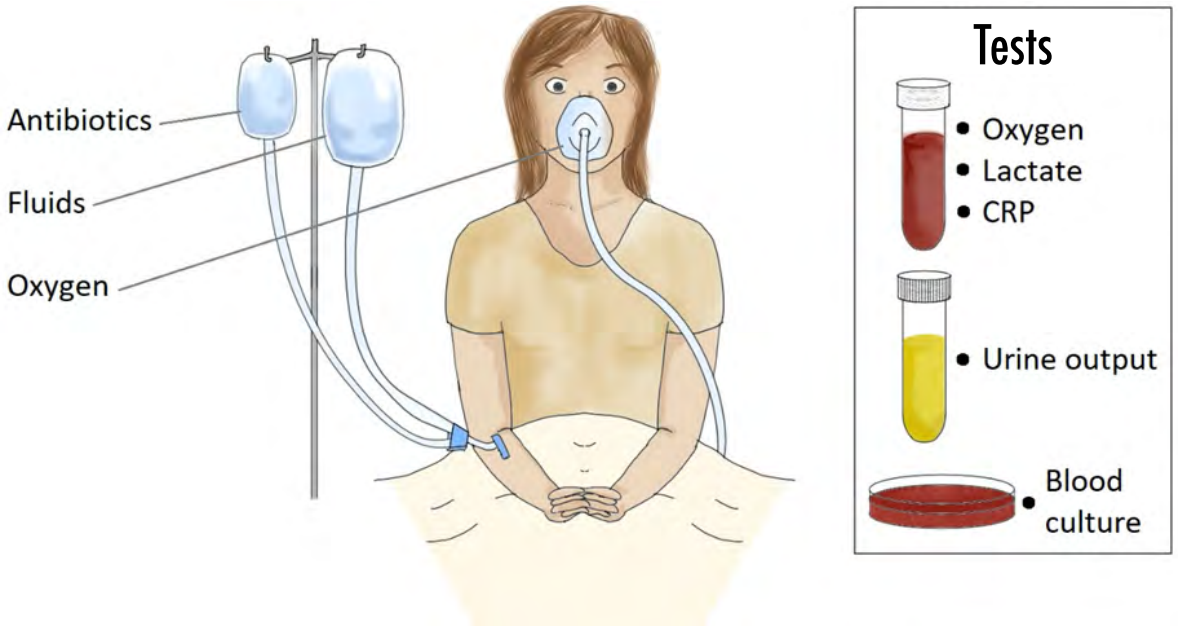
Patients suspected of having sepsis are kept under close observation. Blood pressure and oxygen content are monitored, as well as urine output to make sure the kidneys are functioning properly. They will immediately be treated with broad-spectrum antibiotics to try to kill the pathogens that might be responsible for the infection and they might receive oxygen or fluids depending on their status. A blood sample will also be taken because a variety of laboratory tests are helpful in the diagnosis of sepsis.

For example, molecules in the blood, known as **acute-phase proteins**, can indicate what is happening in the body. These include **C-reactive protein** (CRP), **procalcitonin** (PCT) and **lactate** (lactic acid); CRP is produced by innate inflammatory cells, PCT suggests the presence of a bacterial infection (as opposed to viral or fungal), while high levels of lactate are produced by the body's cells when they are under stress.

Another test done for patients with suspected sepsis is to try to find pathogens in their blood sample. Because a blood sample has a really high number of blood cells, finding pathogens can be like finding a needle in a haystack; the sample must first be **cultured** for 1-5 days until the number of pathogens reaches a concentration high enough that they can be identified. Only at this point can a patient be placed onto targeted antibiotics specific to the pathogen responsible for the infection. This is a time-consuming process that we, as researchers, aim to improve. By being able to quickly identify what might be the pathogen causing the infection, patients would be able to receive the best treatment more rapidly.

Figure 2. Summary of the clinical diagnostic tests and treatment of sepsis. A patient with suspected sepsis may be given intravenous fluids and oxygen to increase blood pressure and blood oxygen levels, respectively. Simultaneously, oxygen, **lactate** and **C-reactive protein** (CRP) levels in the blood, in addition to the patients' urine output, are monitored to follow the severity of the infection.

Broad spectrum **antibiotics**, drugs that can kill as many types of bacteria as possible, are used as a first line of defence. In order to identify the pathogen responsible for the infection, a blood sample is **cultured** for 1-5 days before the elusive pathogen reaches a concentration high enough to be detected. Only at this point can the patient be treated with specific antibiotics.

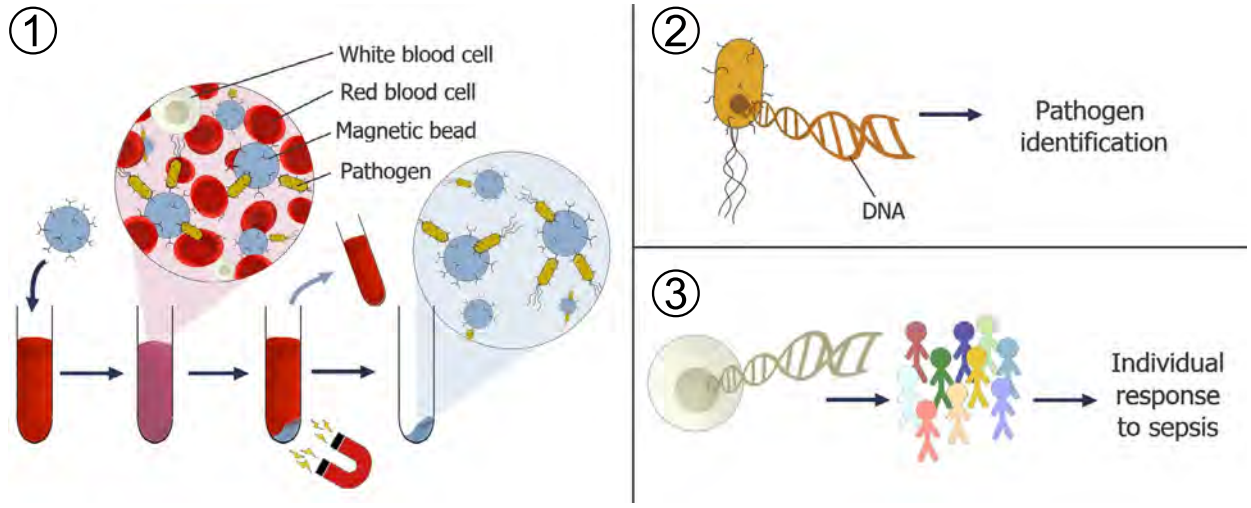


In order to find pathogens in a blood sample, we are engineering microscopic magnetic beads that can recognise them. When we mix these beads with a sample from a patient, the receptors will bind to the pathogens and thanks to the magnetic properties of the beads, we can remove them and the pathogens with a magnet directly (① in Figure 3). Although our beads will bind to the pathogens, we still need to identify them once they are separated from the blood sample. We do that by extracting and **sequencing DNA** and then looking for genetic information (similarly to reading a barcode) that is unique to pathogens (② in Figure 3). With the help of some sophisticated software tools [5], we can link that information to the identity of the pathogen but also to how it might react to different treatments.

This part of our work aims to help doctors know, as quickly as possible, what might have caused sepsis and what's the best treatment for a patient. Importantly however, clues to a patient's survival don't just lie in the identity of the pathogen. We are still trying to understand why an infection might turn into sepsis for one person and not for another. To do this, we are studying human DNA sequences from a large number of sepsis patients to see if we can recognise specific patterns for people who have had sepsis and using powerful computers we are trying to identify what these patients have in common (③ in Figure 3).

The goal of our research is consequently to better understand why some people are more at risks of sepsis than others and also make sure they can have access to the best treatment as quickly as possible if they do have sepsis.

Figure 3. ① Magnetic particles are being developed to capture pathogens in a sample. The particle will bind to the pathogen surface and can be separated from the sample using a magnet. Using equipment already in hospitals the pathogen can be identified. ② We extract **DNA** from the pathogens and 'read' it – this is called **DNA sequencing**. By looking at the specific genetic information of the pathogen, their resistance to drugs can also be studied [5]. ③ Patterns in human DNA can also be studied to better understand why some people survive sepsis and others don't. DNA from large populations is studied to identify patterns that might help predict a patient's response to sepsis.



CONCLUSION

The immune response is crucial to maintaining a healthy body. Systemic inflammation can cause some very serious problems, as is the case with sepsis. A prolonged systemic immune response will eventually cause multiple organ failure; this can be avoided with rapid diagnosis of sepsis so that doctors can prescribe the right treatment to target the pathogen. The good news is that if doctors give the right treatment quickly, most people will get better; this is why it is incredibly important that everyone can recognise the signs of sepsis.

GLOSSARY

Acute-Phase Proteins A type of protein in the blood that increases or decreases in concentration in response to inflammation.

Antibiotic A drug that targets bacteria. There are lots of different kinds of antibiotics; some are broad spectrum (they work on lots of bacteria) whereas some are more specific.

Culture or cultured cells A laboratory method used to maintain tissue cells, pathogens etc. in conditions that are suitable for their growth. Culturing a pathogen enables scientists to grow more of the pathogen, increasing the pathogen concentration within the culture and therefore making them easier to detect and identify.

C-reactive protein (CRP) A molecule found in the blood that corresponds to the level of inflammation. Doctors measure this when monitoring sepsis.

DNA & Sequencing 'Deoxyribonucleic acid', it is the code that makes us who we are, a long series of genetic building blocks that instructs the body how to function. DNA sequencing is a method that reads the precise order of genetic building blocks (adenine "A", thymine "T", guanine "G" and cytosine "C") also known as "bases" that make up DNA.

Lactate When cells are under stress, they produce lactic acid (lactate). This is one of the things health professionals can look at in the blood.

Pathogen Infectious agent that can make us sick and cause disease. Bacteria, fungi, parasites and viruses are examples of pathogens.

Procalcitonin (PCT) Doctors can look for PCT in the blood as an indicator of a bacterial infection.

Vascular permeability This means blood vessels become leaky, allowing inflammatory cells to get out into the surrounding tissue as part of an inflammatory immune response.

Vasodilation This is when the blood vessels become wider as part of the inflammatory immune response.

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