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# Let's Talk About Sepsis

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The current definition of sepsis is based on comparatively contemporary knowledge. However, the disease process is not fully understood and treatment still profoundly challenging. Definitions and guidelines have changed over the recent years, and clinicians are always interested to know what the new and current thoughts on the subject are.

Many papers have been published in the medical press, reporting on definitions, scores, models, cytokines, therapies, new trends, statistics, campaigns, including a sepsis anniversary day-which is not celebrating but fighting against sepsis. Together they signify the enormous interest in the subject.

The American College of Chest Physicians and the Society of Critical Care Medicine met in 1992 and gave the first definition of sepsis and associated organ failure [1]. Eleven years later, American intensivists met European intensivists to evaluate if there was a need for a new definition of sepsis [2].

In 2016 a new and second definition of sepsis was proposed which stated that "sepsis is a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs" [3].

This new definition better illustrates the fact that when we talk about sepsis, we referring to the body's inadequate response to an infection. In effect, the body injures its own tissues and organs in a fight to overcome an "enemy", resulting in self-destruction.

Several models, aimed at understanding sepsis, have been proposed. I think the predisposition, insult, response, organ dysfunction concept (PIRO) that stages sepsis in a similar manner to the tumour, nodes, metastasis (TNM) cancer staging is of interest [4].

This is an exciting perspective, as the sepsis process is described as a dynamic one, with an extension degree that finally affects organs and ultimately results in death.

The model involves compiling a complex picture of the patients, taking into account variables present before the insult, genetic factors, co-morbidities and age. Moreover, the host's response is assessed with regard to all clinical features of sepsis, [5] including the presence of damage/danger-associated molecular patterns (DAMPs), pathogen-associated molecular patterns (PAMPs), resolution-associated molecular patterns (RAMPs), numerous biomarkers [6,7], specific and non-specific pathways of inflammation.

Using such a model, the physician is assisted in assessing the probable effects on organs which may result in failure, death or resolution. The insult or infection is also extensively expressed in order to target appropriate therapy as soon and as efficiently as possible.

The interesting fact is that a lot of novel genetic predisposing factors have been discovered, and future development in the field of genomics and proteomics are subject to further research [8].

Another interesting model that leads to a better understanding of sepsis is the persistent inflammation, immunosuppression, and catabolism syndrome, or PICS concept [9-11]. This model is also dynamic, as it indicates a fluid pathway that that can progress to an adequate host response with resolution of the injury, or to death subsequent to an inadequate host response. The novel concept, embedded in this model, is a predictable, rapid unfavourable fatal outcome occurs rapidly if the insult is severe and the host response is inadequate. However, with most patients seen in an intensive care unit (ICU) death is insidious and occurs when clinicians were hoping to save the patient. The last category of patients have a prolonged ICU stay, suffering multiple infectious episodes, a baseline elevated chronic and persistent inflammatory state, cachexia and sarcopenia, with wounds that do not heal. They typically require a degree of organ support.

I will not elaborate on the inflammatory process *per se*. However, sepsis affects practically all aspects of endothelial cell (EC) function and the inflammatory process targets the endothelium that is altered in sepsis [12]. This is considered to be the critical factor in

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the progression from sepsis to organ failure. This is a sword with a double edge because the endothelium is both a source and target of injury in sepsis. Another feature of the endothelial role in sepsis is that there is a timeline response towards healing or destruction. I would say that the endothelium follows the PIRO model when its numerous functions are adversely affected, allowing spread from local tissue damage to serious organ damage.

A modern therapeutic tactic against sepsis might be to adopt a focused approach, such as targeting a gene or one single mediator. Single-molecules used to treat sepsis have been developed and showed promising results. They have now been withdrawn as their extended resulted in disastrous and unwanted outcomes.

Physicians strive to combat the cytokine storm syndrome, knowing this require rapid diagnosis and treatment to limit the morbidity and mortality caused by the hyper-inflammatory state. Blood purification has been proposed for decades [13]. Antibiotic-coated membranes are by far the option of choice concerning blood purification techniques. Cytokine adsorbers offer a conventional treatment for sepsis in different clinical settings and also for conditions with sepsis-like behaviour. Their suggested mode of action is to re-balance the pro-inflammatory and anti-inflammatory responses. An interesting fact is that this therapy has been shown to be effective in diverse clinical settings including acute liver failure, after cardio-pulmonary by-pass operations and pancreatitis. A proposed hypothesis is that adsorbers clean-up more than cytokines and adsorb micro-particles and other dangerous inflammatory generators. Cytokine adsorbers show promising results, but dose, timing, and length of treatment have yet to be established [14].

It is difficult to conclude when, if ever, physicians will have an ideal set of guidelines and proven methods to rapidly diagnose and cure sepsis. Certainly, the new trend of personalised medicine will have a central role in these issues.

Supportive ICU treatments, organ support, and advanced monitoring are and will be tools to help improving survival of patients with sepsis.

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