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Andreas Edel
Consultant
Intensive Care Unit
Department of Anesthesiology
and Operative Intensive Care
Medicine
Charité - Universitätsmedizin
Berlin
Campus Mitte
Berlin, Germany

andreas.edel@charite.de



Stefan J Schaller
Deputy Clinical Director
Department of Anesthesiology
and Operative Intensive Care
Medicine
Charité - Universitätsmedizin
Berlin
Campus Mitte
Berlin, Germany

stefan.schaller@charite.de

One Sepsis Fits All? Are There Different Phenotypes of Sepsis?

Diagnostic Approaches and Therapies

This article presents current research results in relation to an advanced sepsis classification and their implications for new treatment options and research strategies.

Introduction

Through history, the definition and the term sepsis changed. Since Semmelweis and others formulated the thesis that sepsis was caused by a systemic reaction to bacteria (Funk et al. 2009), the pathomechanism was more and more explored. Today, we know that the devastating response is not only a reaction to bacteria themselves but also a host reaction (Cerra 1985). The first attempts to classify and describe sepsis was the international consensus conference in 1991. During this meeting, sepsis was defined as a systemic inflammatory response to an infection and furthermore the concept of a systemic inflammation response syndrome (SIRS) was invented. Terms like “severe sepsis”, as a clinical picture of additional organ failure, and “septic shock”, as a clinical condition of hypotension or hyperlactaemia were shaped (Bone et al. 1992). The second consensus conference did not change the definition but pointed out that there are more diagnostic conditions than the SIRS criteria for diagnosing a sepsis. An additional list with potential septic symptoms was created and a first attempt of classification and staging were developed (Levy et al. 2003). The most recent and third international consensus conference in 2016 used a data-driven approach based on mortality to specify the

definition of sepsis and septic shock. To differentiate between sepsis and infection, an organ dysfunction due to a systemic infection was obligatory for the diagnosis of sepsis (Singer et al. 2016).

Sepsis as a syndrome is influenced by many factors and manifests itself in a wide variety of presentations, with the final pathway being organ failure. In order to be able to apply individual therapy options, it makes sense to phenotype or group patients into different risk categories at an early stage. Since sepsis is caused by an infection of bacterial, viral, or fungal microorganisms, a first and simple classification is based on the microorganism’s origin. The distribution of these pathogens was well analysed by Martin and colleagues. In their retrospective analysis of 22 years of sepsis cases in the USA they were able to show that gram-negative were replaced by gram-positive bacteria over time. Thus, in 2000 52.1% of the US-American encountered sepsis cases were caused by gram-positive bacteria, followed by the gram-negative strains with 37.6%. Fungal infections were reported with 4.6%. This meant an increasing incidence of gram-positive and fungal infection (Martin et al. 2003). Those numbers differ from country to country, e.g., in Germany the number of gram-positive and gram-negative pathogen was nearly the same (55.7% vs. 54.1%). Later, data showed an increasing number of fungal pathogens (Engel et al. 2007). However, Kern and Reig (2020) recently came to

different conclusions: the main bacteria in high-income countries were *Escherichia coli*, *Klebsiella spp.*, *Staphylococcus aureus* as well as *Pseudomonas aeruginosa*. *Escherichia coli* was described as the most common pathogen in community-acquired infections while *Staphylococcus aureus* and *Klebsiella spp.* were responsible for an increased mortality in healthcare-associated settings. While bacterial sepsis has been the most investigated sepsis type, due to the COVID-19 pandemic we increased our knowledge of viral sepsis tremendously. And finally, fungal infections are mostly associated with the healthcare environment i.e., 93% of candidaemia are nosocomial (Dolin et al. 2019).

Sepsis is an emergency needing fast and adequate therapy, especially in bacterial sepsis. This was demonstrated in 49,331 patients, showing the importance of a structured, timely treatment by investigating a 3h-bundle including adequate antibiotic therapy, collection of blood cultures and measurement of the lactate level. Early antibiotic therapy was associated with a better outcome (OR 1.04 per hour; CI, 1.02 to 1.05; $p < 0.001$) (Seymour et al. 2017).

Pathophysiological Pathway in Sepsis

In general, the pathophysiology of sepsis is driven by the idea that an overreacting host immune reaction leads to organ failure and if untreated consequently to death. Additionally, Bone et al. (1997) described

an anti-inflammatory phase after a pro-inflammatory phase which can lead to recovery, but to secondary injury as well (Angus and van der Poll 2013; Bone et al. 1997; van der Poll and Opal 2008). The first line of defence mechanism against an infection is the innate immune system which recognises the special microbial structures - so-called "pathogen-associated molecular patterns" - with specialised receptors e.g., toll-like and other receptors (Takeuchi and Akira 2010). The interaction on those receptors induces an activation of several pro-inflammatory pathways, like activation of leukocytes as well as the complement and coagulation system (Angus and van der Poll 2013). As a side effect, the inflammatory response and defence system results in necrotic cell death. This cell scrap or "damage-associated molecular patterns" is then delivered to the environment (Chan et al. 2012), where it stimulates the immune system once again. A vicious circle is starting. As a result of the potentially harmful pro-inflammatory pathway, the immune system activates several anti-inflammatory pathways using neuroendocrine, humoral, and cellular regulation systems (van der Poll and Opal 2008; Rosas-Ballina et al. 2011; Andersson and Tracey 2012). If the organism survives the pro-inflammatory phase, the following immunosuppression can cause other opportunistic infections like latent viral reactivation (Boomer et al. 2011; Limaye et al. 2008). Consequently, this immunosuppression is the main reason for death after surviving the pro-inflammatory phase (Rittirsch et al. 2008).

Added to the above, vasodilation and hypotension - due to vascular leakage caused by a release of pro-inflammatory cytokines - as well as thrombosis caused by sepsis coagulopathy, are leading to an impaired tissue oxygenation and consecutive to organ dysfunction (Goldenberg et al. 2011; Angus and van der Poll 2013; Rittirsch et al. 2008). Without appropriate treatment more cell damage and finally death is the consequence.

Differentiation of Sepsis Phenotypes According to the Underlining Pathogen

Bacterial sepsis

Bacterial infections are the main reason for sepsis in intensive care medicine (Martin et al. 2003). The most common gram-positive germs are *Staphylococcus aureus* and *Streptococcus pneumoniae*, and the most common gram-negative pathogens are *Escherichia coli*, *Klebsiella spp.*, and *Pseudomonas aeruginosa* (Nannan Panday et al. 2019; Opal et al. 2003). Especially gram-negative strains are known microorganisms with the potential to quickly deteriorate the clinical condition of the patient.

■ ■ sepsis as a syndrome is influenced by many factors and manifests itself in a wide variety of presentations, with the final pathway being organ failure ■ ■

The pathology of bacterial sepsis consists of several different factors such as the bacterial virulence factors - the microbiologic weaponry against the host - reflecting the complex pathogen-host-interaction (Jenner and Young 2005; Merrell and Falkow 2004; Moine and Abraham 2004). Bacterial toxins, like superantigen of the gram-positive strain, can cause an enormous direct damage to host cells. While on the other hand lipopolysaccharides, a surface toxin of gram-negative bacteria, can stimulate specialised toll-like receptors, that lead to a destructive immune response (van der Poll and Opal 2008). Another crucial factor for the virulence of bacteria is quorum sensing, i.e. the ability of bacteria to determine their own density depending on the current phase of infection (van der Poll and Opal 2008; Bassler 2002; Pearson et al. 2000; Parsek and Greenberg 2000).

To diagnose a bacterial sepsis, an increased number of neutrophils and elevated concentration of procalcitonin (PCT) are appropriate parameters (Limper et al. 2010). The advantage of PCT was demonstrated in a meta-analysis comparing PCT with C-reactive protein (CRP) in infective endocarditis (Yu

et al. 2013). Promising new biomarkers are the soluble subtypes of the CD-14 receptors, presepsin and pro-adrenomedullin (pro-ADM). Due to the specificity of presepsin this marker could help to differentiate between non-infectious and infectious causes (Yaegashi et al. 2005). Pro-ADM is a ubiquitous peptide synthesised by many different cell types. Suberviola et al. (2013) demonstrated in their observation study with 49 septic patients that pro-ADM level correlated well with illness severity and mortality. Furthermore, pro-ADM itself can cause beneficial and adverse effects on the vascular integrity (Temmesfeld-Wollbrück et al. 2007; Kita et al. 2010; Müller-Redetzky et al. 2014; Nakamura et al. 1997). In addition, adre-cizumab, an antibody against adrenomedullin, was positively evaluated in a phase I study in humans (Geven et al. 2018).

Viral sepsis

Although, the clinical presentation of a viral sepsis is similar to a bacterial sepsis, the underlining immune reaction is different. Macrophages as part of the innate immune system stimulate the production of type I and type II interferon after virus contact. These pro-inflammatory cytokines play a key role in the host's defence system against the virus by activating neutrophils and lymphocytes as part of the adaptive immune system. This process was recently well described in COVID-19 disease (Chau et al. 2021). These interferons contribute to organ failure via the same septic signalling pathway that results in vascular leakage and hypotension (Levy and García-Sastre 2001; Baccala et al. 2014; Steinberg et al. 2012). Moreover, viruses have the properties to downregulate the immune response in the early phase of invasion resulting in an over-reacting immune system with a maximal increased pro-inflammatory cytokine level so-called "cytokine storm". This cytokine storm is probably an expression of this delayed immune response (Chau et al. 2021). Before the COVID-19 pandemic, viral sepsis accounted for less than 5% of all documented sepsis cases (Mayr et al. 2014), which demonstrated the minor role of viral sepsis till then.

Fungal sepsis

Fungi - especially candida - are part of the normal microbiome of a healthy subject. Only an immune imbalance enables fungi to invade deeper tissue and cause an infection or sepsis (Spellberg and Edwards 2002). Unlike the other described pathogens, fungal infections are typically associated with an immunosuppressive condition and therefore commonly occur as hospital acquired infection (Dolin et al. 2019). Compared to viral and bacterial sepsis, fungal sepsis has a higher mortality rate (Delaloye and Calandra 2014; Upperman et al. 2003; Dolin et al. 2019). Possible causes could be an increased level of anti-inflammatory interleukin-10 or different cytokine profiles in fungal sepsis (Taylor et al. 2014). For example, interleukin-17 is being increasingly produced in mice with candida infection (Netea et al. 2015). This increased interleukin level causes a pro-inflammatory immune response with host cell injury (Huang et al. 2016). Fungal microorganism can produce metabolites that can also be toxic. Gliotoxin, for example, can destroy enterocytes and consequently the gut barrier (Upperman et al. 2003).

Another virulence factor is the ability of fungi to switch between yeast and hyphal state, which makes elimination difficult if the fungi is once inside the body. This allows candida to escape the leukocytes (Louria and Brayton 1964; Spellberg and Edwards 2002). In addition, the diagnosis of fungal sepsis remains challenging in an early phase of disease. Besides positive blood cultures detection of fungal components can be a useful tool for diagnosing fungal infection. Beta-d-glucan (BDG), a cell wall component of candida, is one of these compounds. However, a meta-analysis of ten studies demonstrates that BDG had only a sensitivity of 0.81 (CI, 0.74 - 0.86) and a specificity of 0.60 (CI, 0.49 - 0.71) in an intensive care setting. Due to the great heterogeneity of the included studies, this result is just moderate with a great risk of false positive results. For aspergillus, the other main fungal pathogen, positive results of galactomannan, a polysaccharide released by aspergillus, can be a useful tool detecting this fungus. A meta-analysis showed a moderate to even

high sensitivity and specificity of 0.84 (CI, 0.73 - 0.91) and 0.88 (CI, 0.81 - 0.91) for a positive galactomannan finding in the bronchioalveolar lavage (Haydour et al. 2019).

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New Ways of Characterising Sepsis - From Machine Learning to Improving Practical Sepsis Therapy

Besides the traditional classification based on the underlining pathogen new attempts have been initiated to differentiate sepsis phenotypes according to their clinical presentation. As previously described, a subdivision based on pathogens alone is too simple, as the different immunological responses are not considered. The application of other classifications, however, is complicated by the fact that immunological factors and their measurement are not yet part of routine laboratories. A possible solution was shown by Seymour et al. (2019) who analysed a retrospective cohort of 20,189 patients to discover clinical phenotypes of sepsis. Out of three randomised control trials and three observational cohorts, they performed a machine-learning analysis using 29 routine parameters and found four phenotypes. Patient in the α -phenotype had less organ dysfunction with fewer abnormal laboratory findings. In the β -phenotype more chronic comorbidities with an accumulation of chronic kidney disease were seen and the inflammatory parameters were more elevated in the γ -phenotype. Overall, the most severely ill patients with an elevated lactate level and severe organ dysfunction were summed up in the last group. Interestingly, an increase of inflam-

matory biomarkers, like interleukin-6 and interleukin-10, were found in the subgroups γ and δ . The same was evident in terms of pro-coagulation parameters.

Furthermore, a significant increased mortality was present in the δ -phenotype. In comparison to traditional classification parameters like APACHE or SOFA score an overlap between the phenotypes was evident (Seymour et al. 2019). This indicates that the classification model of Seymour et al. differentiates differently than classical severity scores. Ma et al. (2021) also recognised the need of a further characterisation based on routinely measured values. This Chinese study group analysed a retrospective study cohort of 1,437 patients with septic shock. Their aim was not only to identify subclasses of septic shock but also to find an optimal individualised treatment strategy for fluid and vasopressor application. After running a finite mixture and K-means clustering model, five subclasses were identified. Interestingly, similar structures as described above were recognised. Thus, a critical subclass with an impaired tissue perfusion and elevated lactate concentration was found, which could be compared with the δ -phenotype of Seymour et al. (2019). Furthermore, a renal as well as a respiratory dysfunction subclass were described. In a second step, Ma et al. (2021) used a dynamic treatment regime model to find an optimal treatment strategy for fluid and vasopressors. They compared the optimal with actual treatment and identified risk factors for either fluid or vasopressor overload. Their model suggested an optimal therapy pattern starting with an increased fluid application at the beginning of the septic shock followed by a reduced volume application in the subsequent treatment phase (Ma et al. 2021). This result matches clinical considerations, like the concept of salvage, optimisation, stabilisation and de-escalation (SOSD) described by Vincent et al. (2013). Comparing actual with calculated therapy, larger differences were also associated with an increased hospital mortality (Ma et al. 2021). While studies investigating the best way of starting the de-escalation phase are still missing (Bakker et al. 2022), a new adaptive enrichment study design using

precision medicine in sepsis could help identify new treatment options.

Interestingly, similar subgroups with clusters of an elevated level of inflammation and organ dysfunction are found in acute respiratory dysfunction syndrome (ARDS). Liu et al. (2021) demonstrated in their analysis of ARDS patients that one phenotype was associated with less dysfunction of other organs, while another phenotype was related to an increased inflammatory reaction and younger patient age. Finally, a third subgroup was linked to kidney impairment and older age. From this, similarities in phenotypes between sepsis and ARDS can be observed, indicating pathophysiological similarities. In the same study, the heterogeneity effect of the included randomised controlled trials was analysed and showed different treatment effects if the different phenotypes were separately analysed. For example, in one included RCT comparing liberal vs. restrictive fluid therapy in ARDS patients, a restrictive volume therapy in the subgroup of patients with kidney impairment was associated with increased mortality (Liu et al. 2021). This offers an explanation why large trials are not always the best choice to test treatment effects in critically ill patients.

Machine learning not only has potential in therapy optimisation, but can also provide interesting results through study design modelling or re-evaluation. For example, Seymour et al. (2019) demonstrated that a change in phenotype distribution can influence the outcome of a previously non-significant controlled randomised trial. By increasing the subclass with severe organ failure and signs of impaired tissues perfusion to 50% of the ProCESS population - a RCT analysing early-goal therapy in sepsis - resulted in harmful study results (Seymour et al. 2019). Therefore, the American Thoracic Society recommended using new methods of data science to create new studies design taking the heterogeneity of treatment effect into account (Shah et al. 2021).

References

Andersson U, Tracey K J [2012] Reflex principles of immunological homeostasis. *Annu Rev Immunol.* 30:313-35.

Andriolo BN, Andriolo RB, Salomão R, Atallah ÁN [2017] Effectiveness and safety of procalcitonin evaluation for reducing mortality in adults with sepsis, severe sepsis or septic shock. *Cochrane Database Syst Rev.* 1, Cd010959.

New Ways of Characterising Sepsis - From Transcriptome to Precise Medical Therapy

Not only routine data, but also genes arrays can enrich the understanding and classification possibilities of sepsis. In the last decade, the technical improvement of sequencing a large amount of RNA simultaneously opened the possibility of analysing thousands of transcripts of specific genes. Wong et al. (2012) could differentiate two different phenotypes of septic shock in their patient cohort of 168 paediatric patients by using computer-assisted image analysis and microarray-based reference mosaics. They verified these result in a prospective cohort as well. One of the identified subclasses was characterised by a decreased expression of a specific gene pattern. These patients had an increased risk of mortality, if corticosteroids were prescribed (OR 4.1; CI, 1.4-12.0; $p = 0.011$) (Wong et al. 2015). These findings were further supported by a post hoc analysis of the VANISH trial, a study comparing vasopressin and norepinephrine in the initial therapy phase of septic shock. After running gene expression profiling in that trial two transcriptomic response signatures were found. These two subclasses also had different reactions towards additional hydrocortisone application. The patients with a more immunocompetent profile had an increased mortality if hydrocortisone was applied (Antcliffe et al. 2019). These results must be verified in a prospective study setting but these findings underline the importance of individualised precise medicine in future research.

New Diagnostic Approach

Next-generations sequencing (NGS)

Although the gold standard for detection of fungal and bacterial germs is still the culture growth, next-generation sequence has become more and more available in the last years. Next-generation sequenc-

ing is culture-independent PCR-based method detecting cell-free microbial DNA. Compared to traditional blood cultures NGS has the advantage of a faster detection in hours (Grumaz et al. 2016). In a small study of 50 patients with septic shock and 20 control patients without an infection undergoing elective surgery, NGS had a higher positive rate than traditional blood culture (72% vs. 33%) at sepsis onset (Grumaz et al. 2019).

The transcriptomics of white blood cells

A promising early sepsis detection method is not based on the detection of a pathogen but searching for special gene expression signatures of circulating leukocytes. This analysis is based on the new generation sequencing technology but instead of DNA, RNA is sequenced. This transcribed RNA reflects the host gene expression and is also called "transcriptomics" (Holcomb et al. 2017). This gene expression was analysed in acute infection and special expression signatures were found (Ramilo et al. 2007). First studies were able to distinguish between sepsis and non-infectious systemic inflammation (Miller et al. 2018; McHugh et al. 2015).

Conclusion

After finding a definition for sepsis, the pathophysiology is still not fully understood. Although the final pathway of sepsis with organ failure is ultimately the same, the underlying pathophysiological pathways are different. First attempts in using machine-learning system have started, showing promising results and that phenotyping might be possible. By using new classification models and new study designs, the heterogeneity effect can be overcome in some randomised controlled trials.

Conflict of Interest

None. ■

Baccala R, Welch MJ, Gonzalez-Quintal R et al. [2014] Type I interferon is a therapeutic target for virus-induced lethal vascular damage. *Proc Natl Acad Sci.* 111:8925-30.

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