

# ICU

## MANAGEMENT & PRACTICE



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# Sepsis in Critical Care

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# Sepsis in Critical Care

Sepsis is a leading cause of morbidity and mortality in the intensive care unit. Nearly [14 million adults and 2.5 million children](#) survive sepsis each year worldwide. In addition, sepsis survivors are known to experience poor long-term outcomes and often develop functional limitations thereafter. It is thus evident that the long-term impact of sepsis is an issue that must be addressed.

The diagnosis of sepsis in critically ill patients can be quite challenging. At the same, early identification and treatment of sepsis are associated with improved outcomes. To achieve this, it is important to understand the mechanism of sepsis, improve awareness of post-sepsis complications and expand the use of new and improved diagnostic and therapeutic approaches to improve patient outcomes. There is also a need to improve sepsis diagnosis using biomarkers and to recognise that the sepsis response can involve multiple factors during the disease process. The long-term goal of sepsis management in critical care should be to improve diagnostic accuracy, reduce the time to effective treatment, and optimise the use of antibiotics.

In our latest cover story, **Sepsis in Critical Care**, our contributors highlight the prevalence, characteristics

and impact of sepsis in critical care, explore different phenotypes of sepsis and causative factors, and discuss diagnostic approaches and therapies to manage sepsis and its associated complications.

Andreas Edel and Stefan Schaller talk about the different phenotypes of sepsis and provide current research results in relation to an advanced sepsis classification and their implications for new treatment options and research strategies. Girish Nair and Michael Niederman explore optimal management of sepsis in the context of appropriate antimicrobial stewardship and the need for accurate identification of the site of infection, with a focus on the likely pathogens and provision of timely and accurate therapy.

Marc Leone shares the ABCs of sepsis and septic shock based on his clinical experience and choice. Orlando Pérez-Nieto, Mauricio Ambriz-Alarcón, Marian Phinder-Puente and co-authors provide an overview of the haemodynamic management of patients in septic shock and strategies for detection of haemodynamic changes and appropriate therapeutic action to improve prognosis.

Yulia Pinevich, Brian W Pickering and Vitaly Herase-

vich discuss the importance of timely recognition of sepsis for patient survival and explore opportunities to improve this through the use of sepsis screening tools to improve surveillance and treatment of sepsis.

Christopher Noel, Jason Bartock and Phillip Dellinger provide an overview of the presentation, pathophysiology, and potential treatment options for symmetrical peripheral gangrene and limitations in the current literature and a possible strategy for future study.

In other feature articles, Hans Flaatten, Christian Jung and Bertrand Guidet explore publications concerning the very old ICU patients, focusing on publications from the VIP network on elderly COVID-19 patients. Frederic Zimmerman, Gal Pachys, Evan Alpert and Sharon Einav present an overview of the current knowledge and future research directions for CO<sub>2</sub> measurement and clinical application during cardiopulmonary resuscitation.

As always, if you would like to get in touch, please email [JLVincent@icu-management.org](mailto:JLVincent@icu-management.org).

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# 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.

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

### 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

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.

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

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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, adrenergic, 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 overreacting 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).

### **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  $\alpha$ -phenotype had less organ dysfunction with fewer abnormal laboratory findings. In the  $\beta$ -phenotype more chronic comorbidities with an accumulation of chronic kidney disease were seen and the inflammatory parameters were more elevated in the  $\gamma$ -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 inflammatory biomarkers, like interleukin-6 and interleukin-10, were found in the subgroups  $\gamma$  and  $\delta$ . The same was evident in terms of pro-coagulation parameters.

Furthermore, a significant increased mortality was present in the  $\delta$ -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

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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  $\delta$ -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).

## 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 sequencing 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. ■

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# Septic Shock and Vasopressor Initiation: Why Earlier is Better

An overview of vasopressor management, current evidence and when to initiate vasopressor therapy for best possible patient outcome.

Vasopressor management is a cornerstone in the haemodynamic management of septic shock for reversing hypotension by increasing systemic vascular resistance and improving organ perfusion. The Surviving Sepsis Campaign (SSC) guidelines 2021 recommend an initial target mean arterial pressure (MAP) of 65 mmHg with norepinephrine (also known as noradrenaline) as first-line vasopressor agent, vasopressin (also known as argipressin, arginine vasopressin, and anti-diuretic hormone) as recommended second-line vasopressor (Evans et al. 2021). This article will try to address when to initiate vasopressor management for best possible patient outcome, based on the currently existing evidence.

## Hypotension and Poor Clinical Outcomes: Benefits of Early Norepinephrine Initiation

The amount of time spent continuously below a MAP threshold of 65 mmHg is a strong predictor of mortality, with each additional 2-hour increment in the longest episode under threshold being associated with a progressive increase in mortality rate (Vincent et al. 2018). An immediate action for resolving hypotension should be taken as quickly as possible, as the early administration of a first-line vasopressor, namely norepinephrine, is associated with better patient outcomes, such as shorter periods of hypotension and higher survival rate (Bai et al. 2014; Colon et al. 2020). The SSC 1-hour bundle recommends starting norepinephrine within one hour of fluid resuscitation, if fluid administration alone is not sufficient to achieve target MAP (Levy et al. 2018). This can not only prevent prolonged periods of hypotension, but also prevent harmful fluid overload (Hamzaoui and Shi 2020).

## Vasopressin As Second-Line Vasopressor: When and Why

Vasopressin is the only recommended second-line vasopressor to be added to norepinephrine if MAP is inadequate, instead of escalating norepinephrine dose or using any other agents (Evans et al. 2021); this is indicating to catecholamine refractory septic shock, where vascular responsiveness to catecholamines is impaired due to downregulation or decoupling of  $\alpha_1$  adrenergic receptors (Jentzer and Hollenberg 2020). In such cases, when norepinephrine infusion is at 0.25–0.5  $\mu\text{g}/\text{kg}/\text{min}$  and MAP is still inadequate, vasopressin could be added to norepinephrine in order to achieve target MAP and prevent prolonged periods of hypotension (Evans et al. 2021).

In addition to raising MAP, vasopressin also has catecholamine sparing effects, allowing for the reduction of norepinephrine dose while maintaining target MAP (Russell 2011). This early combination of moderate doses of multiple vasopressors with complementary mechanisms of action may avoid the toxicity associated with high doses of a single agent (Jentzer et al. 2018).

In a retrospective, multi-centred, observational study, higher norepinephrine-equivalent dose and higher lactate concentration at vasopressin initiation were each associated with higher in-hospital mortality in patients with septic shock (Sacha et al. 2021). The lowest mortality rates were seen when vasopressin was initiated at lower norepinephrine-equivalent doses and lower lactate concentrations. Initiating vasopressin at a norepinephrine-equivalent dose of 10  $\mu\text{g}/\text{min}$  or initiating when lactate concentrations were below 2.3 mmol/L was associated with a lower likelihood of in-hospital mortality compared with delaying vasopressin initiation until a norepinephrine-equivalent dose of 25  $\mu\text{g}/\text{min}$  or when lactate concentrations exceeded 3.9 mmol/L, respectively. Each 10  $\mu\text{g}/$

min increase in norepinephrine-equivalent dose at the time of vasopressin initiation was associated with 20.7% higher in-hospital mortality, and each 1 mmol/L increase in lactate concentration at the time of vasopressin initiation was associated with 18.4% higher in-hospital mortality (Sacha et al. 2021). These conclusions confirm similar observations in the VASST study, where a subgroup analysis showed reduced mortality when vasopressin was administered at lower norepinephrine doses and lactate levels (Russell 2011).

Retrospective observational data have also shown an association with higher vasopressin response, when vasopressin was initiated at lower lactate and higher arterial pH levels. Vasopressin response was associated with increased in-hospital survival rates and overall better patient outcomes, such as higher MAP and lower catecholamine requirement, further supporting the early administration of vasopressin (Bauer et al. 2022; Sacha et al. 2018).

A post-hoc analysis of the VASST study has shown that the combination of vasopressin at norepinephrine 0.26 $\pm$ 0.27  $\mu\text{g}/\text{kg}/\text{min}$  for patients at risk of renal failure (1.5x serum creatinine based on the RIFLE criteria) significantly decreases the need for Renal Replacement Therapy (RRT) by 55% and reduced the progression to renal failure (Gordon et al. 2010).

In a systematic review of 13 randomised controlled trials (1462 patients), the addition of arginine vasopressin to catecholamine vasopressors compared with catecholamines alone was associated with a significant lower risk of atrial fibrillation (RR, 0.77) (McIntyre et al. 2018). This can be related to a reduction in adrenergic stimulation provided by the catecholamine sparing effect of arginine vasopressin.

Additionally, experimental studies have shown that catecholamines constrict pulmonary arteries, while vasopressin does not, which also supports the use of vasopressin in pulmonary hypertension (Currigan et al. 2014).

### Why Vasopressin

Vasopressin is an endogenous peptide hormone produced in the hypothalamus which is stored and released by the posterior pituitary gland (Evans et al. 2021). Unlike catecholamines, which achieve vasoconstriction through  $\alpha_1$  receptor activation, vasopressin increases blood pressure by activating the  $V_1$  receptors on vascular smooth muscles (Evans et al. 2021). This alternative mode of action allows for the increase in blood pressure in catecholamine refractory septic shock (Evans et al. 2021) and the reduction of catecholamine doses (Russell 2011).

Additionally, serum vasopressin levels in early septic shock

stages have been shown to increase in most patients to reverse hypotension but decrease after 24 hours as shock continues, causing a “relative vasopressin deficiency” due to depletion of hypothalamic-pituitary stores of vasopressin (Russell 2021). This further supports the early administration of exogenous vasopressin during septic shock.

Vasopressin can be administered from doses ranging from 0.01 IU/min to 0.03 IU/min allowing for dose adjustment based on patient’s blood pressure dynamics and needs (Summary of Product Characteristics, Empressin). With a half-life of up to 20 minutes, it offers a high degree of control as the vasopressor effect could be quickly halted once infusion is discontinued (Tanja and Jürgen 2006).

The VASST study has also shown that vasopressin is as safe as norepinephrine when administered at 0.03 IU/min with similar levels of adverse events, with a trend towards digital ischaemia

(0.5% norepinephrine vs 2% vasopressin,  $p=0.11$ ) (Russell et al. 2008).

The SSC guidelines recommend against using terlipressin, a vasopressin analogue prodrug with a half-life of around 6 hours, due to the higher incidence of serious adverse events associated with it (Evans et al. 2021). The 6-hour half-life also makes it impractical for a rapid down-titration or quick stopping in cases of adverse events.

### Conclusion

The early initiation of vasopressors in septic shock has shown to have better patient outcomes in comparison to delayed initiation. MAP response to fluids should guide the initiation of norepinephrine as first-line, while more specific parameters such as inadequate MAP, high catecholamine dose, lactate levels, arterial pH, and serum creatinine should guide the early initiation of vasopressin as second-line vasopressor. ■

### Disclaimer

Point-of-View articles are the sole opinion of the author(s) and they are part of the ICU Management & Practice Corporate Engagement or Educational Community Programme.

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# Sepsis in Critical Care: Effective Anti-microbial Strategies in ICU

ICU sepsis is associated with a mortality rate >25%, with nosocomial infection most lethal, and community acquired infection more common. Optimal management requires identification of the site of infection (lung, abdomen and blood stream most commonly), a focus on the likely pathogens based on risk factors for resistance, and provision of timely and accurate therapy in the context of appropriate antimicrobial stewardship.

man et al. 2020).

Bacterial infections of the lower respiratory tract are the most common cause of sepsis in ICU, although based on other risk factors, such as immunosuppression and exposure to antibiotics within 90 days, other pathogens including fungi and viruses can cause sepsis. Additional common sources of sepsis include intra-abdominal infections, blood stream infections, urinary tract infections, infected vascular access sites, and skin/soft tissue infection. Gram-negative pathogens are identified more commonly in cultures than gram-positives but over the last decade, the percentage of multidrug resistant (MDR) bacterial isolates is on the rise worldwide (Vincent et al. 2020). The most common gram-negative pathogens include *Klebsiella* species, *E. coli*, *Pseudomonas* species, *Enterobacteriaceae*, *Proteus*, *Stenotrophomonas*, *Serratia* and *Acinetobacter* species, whereas Gram-positive isolates include *S. aureus*, *S. pneumoniae*, and *Enterococcus*, and fungal microorganisms were *Candida* species and *Aspergillus* (Vincent et al. 2020). MDR pathogens including extended spectrum beta-lactamase (ESBL) enzyme and Amp C enzyme producing *E. coli*, *Klebsiella* and carbapenem-resistant *Klebsiella* and *Acinetobacter*, and methicillin-resistant *Staphylococcus aureus* (MRSA) are independently associated with a higher mortality in ICU compared to infections with other organisms (Vincent et al. 2020). Risk factors for MRSA include prior history of MRSA infection or colonisation, recent IV antibiotics, history of recurrent skin infections or chronic wounds, presence of invasive devices,

haemodialysis, and recent hospitalisation within 90 days. The risk of 30-day mortality is higher in patients with MDR pathogens and comorbid conditions, such as cirrhosis, immunosuppression or vascular disease but also in those who have received antibiotics, chemotherapy, wound care, dialysis, or surgery within the last 30 days prior to onset of sepsis (Fay et al. 2020). In this review, we focus on the antibacterial management of patients with sepsis admitted to ICU.

## Heterogeneity of Sepsis Syndrome

Recent analysis of big data including 64,000 patients from three different clinical trials have shown that sepsis syndrome can be categorised into four different phenotypes based on demographics, laboratory values, and patterns of organ dysfunction, and this may have implications on clinical outcomes and mortality (Seymour et al. 2019). Gene expression profiling to detect the underlying molecular responses and characterising early septic patients have shown five distinct endotypes, each based on 200 unique gene expression differences and distinct pathways: neutrophilic suppressive, inflammatory, innate-host-defense, interferon, and adaptive (Baghela et al. 2022). Of these, the neutrophilic suppressive and inflammatory endotypes have a propensity to develop severe infection. In another study, investigators found significant differences in key immune and coagulation system pathways based on the source of infection but mortality differences were primarily dependent on

## Introduction

Sepsis is a dysregulated host immune response to infection resulting in acute injury to potentially multiple organs. It is a major cause for morbidity and mortality worldwide (Rhodes et al. 2017). The majority of sepsis patients are from the community but the mortality and associated cost of caring for patients (>50,000 USD) are significantly higher with nosocomial sepsis (Paoli et al. 2018; Rhee et al. 2019; Fay et al. 2020). Surprisingly, even previously healthy patients admitted with sepsis have a higher short-term mortality compared to those with comorbid conditions (adjusted OR 1.99 [95% CI 1.87-2.13]) (Alrawashdeh et al. 2022). There has been an increase in sepsis related hospitalisations in U.S. Medicare beneficiaries from 2012-2018 (Buchman et al. 2020). In that study, authors report that the long-term mortality from sepsis remains high despite advances in management over the last two decades (septic shock mortality at six months is approximately 60%) and the corresponding economic burden of skilled nursing care post discharge, increased over the six years of the study period (Buch-

the source of infection with abdominal and respiratory infections having slightly higher ICU mortality (Peters-Sengers et al. 2022).

### Early Recognition Saves Lives

Surviving Sepsis Campaign 2016 guidelines emphasise early recognition of sepsis with a 1-hour bundle and administration of early appropriate antibiotics plus effective source control (Rhodes et al. 2017). For every hour's delay in antimicrobial administration over the first 6-hrs since diagnosis of septic shock, there is a 7.6% increased risk of death (Kumar et al. 2006). A recent meta-analysis investigating the impact of delay in appropriate antibiotic therapy for hospitalised adult patients with bacterial infections showed significant reduction in treatment failure (OR 0.33, 95% CI 0.16-0.66), reduced mortality rates (OR 0.44, 95% CI 0.38-0.50) and mean hospital costs in those who had appropriate antibiotics (Bassetti et al. 2020). Patients, who received discordant empiric antibiotic therapy based on susceptibility to bacterial isolates had an increased risk of mortality independent of microbial resistance, sepsis or septic shock (adjusted odds ratio 1.46 [95% CI, 1.28-1.66]) (Kadri et al. 2021). The majority of discordant empirical antibiotic therapy and associated mortality were in patients with bloodstream infections caused by *Staphylococcus aureus* or *Enterobacteriales* (Kadri et al. 2021). Data from a large study including 20,026 adults with suspected sepsis in 12 emergency departments showed that both delays in recognition of infection and administration of the antibiotics were associated with increased hospital mortality (Taylor et al. 2021).

The above evidence highlights the importance of rapid recognition and need for broad-spectrum empirical antimicrobial therapy in patients with suspected sepsis, preferably within 6-hours but immediately in patients with septic shock. However, rampant use of broad-spectrum antibiotics in the absence of proven infection is a risk factor for development of antibiotic resistant pathogens and excess mortality (Teshome et al. 2020). Thus, antibiotic stewardship is a key element in the management of sepsis with a commitment to narrow and stop antimicrobials based on culture data during the hospital stay (Wunderink et al. 2020). Another potential opportunity is to develop rapid and cost-effective diagnostics for early identification of the causative pathogen and resistance testing of positive blood culture

using multiplex technologies (She and Bender 2019). Multiplex PCR can detect common bloodstream pathogens within a few hours compared to conventional blood cultures. Several systems including Verigene and FilmArray are commercially available as an adjunct to the conventional microbiology methods, and are used to detect microbial resistance rapidly (De Angelis et al. 2020).

## Antibiotic stewardship is a key element in the management of sepsis

Recently, next-generation sequencing using microbial cell-free DNA has been shown to have better sensitivity in detecting pathogens within hours compared to traditional blood culture in patients with a sepsis (Blauwkamp et al. 2019). Cost effectiveness models show incorporating molecular testing in emergency department in patients with sepsis and septic shock would significantly impact patients receiving inappropriate antibiotic therapy with an incremental cost-effectiveness ratio of negative \$7,302/death averted (Zacharioudakis et al. 2019).

### Biomarkers and Host Response Markers of Sepsis

A different tactic would be to measure the host response to infection rather than direct pathogen detection by using sepsis biomarkers to aide in the decision to start or stop antibiotics. Several markers including procalcitonin (PCT), C-reactive protein (CRP), soluble triggering receptors expressed on myeloid 1, proadrenomedullin, soluble urokinase plasminogen activator receptor and interleukin-6 have been studied in patients with sepsis (Masia et al. 2005; Kruger et al. 2008; Gunsolus et al. 2019). However, the currently available biomarkers lack discriminative diagnostic sensitivity on the decision to start empiric antibiotics in suspected sepsis and generally most societies endorse serial measurement for antibiotic stewardship efforts (Bouadma et al. 2010). In a patient-level meta-analysis, PCT guided antibiotic stewardship programme was able to significantly reduce days on antibiotics compared to controls with significant improvement in

mortality (aOR 0.89, 95% CI:0.8 - 0.99; p = 0.03) (Wirz et al. 2018). Thus, checking serial biomarkers such as PCT and CRP can be of valuable assistance along with clinical judgement on decision to help decide on duration of treatment.

Despite advances in diagnostics and risk stratification, almost 47% of patients with sepsis have a negative-culture and failure to identify the causative pathogen limits opportunities for modification/narrowing of antibiotic spectrum (Gupta et al. 2016). Transcriptomics, targeting host immune gene expression (mRNA) profiling in response to infection is another emerging field with superior diagnostic and prognostic value compared to serum biomarkers in patients with early sepsis (Gunsolus et al. 2019). SeptiCytte LAB is a continuous output of a four-mRNA; CEACAM4, LAMP1, PLA2G7, and PLAC8 (Immunexpress, Seattle, WA) that has FDA clearance for detection of sepsis from systemic inflammatory response syndrome. Increasing scores from 1-10 shows a higher predilection for infectious cause independent of age, sex, race/ethnicity, clinical and other biomarkers, including PCT (Miller et al. 2018; Sweeney et al. 2016). In a study comparing 3-omics models based on host response, including Sepsis MetaScore, SeptiCytte and FAIM3:PLAC8 ratio, all three models showed good discriminative ability in distinguishing patients with sepsis (Maslove et al. 2019). Ultimately, the effectiveness of rapid diagnostics will depend on its ability to reduce days on broad-spectrum antibiotics, prevent delay of appropriate antibiotics, reduce mortality, and length of stay.

### Antimicrobial Considerations

The 2021 Surviving Sepsis International guidelines recommend in adults with sepsis or septic shock at high risk of MRSA and MDR-gram negative organisms to start antibiotics with MRSA coverage and use two antimicrobials with gram-negative coverage for empiric coverage (Evans et al. 2021). However, the guidelines strongly advise against using MRSA coverage or dual gram-negative coverage in patients with low risk for both organisms and once susceptibilities have been identified (Evans et al. 2021). In a recent meta-analysis and trial sequential analysis including thirteen studies, there was no difference in mortality or other patient-related outcomes between mono- vs. combination therapy (Sjovall et

al. 2017). Consideration for targeted therapy should be made after assessment of risk factors for MDR pathogens including prior colonisation in the preceding year, local prevalence, broad-spectrum antibiotic use within 90 days, use of selective digestive decontamination, type of infection – community vs. nosocomial, travel to highly endemic countries and hospitalisations abroad in the last 90 days (Evans et al. 2021).

On any given day, almost 70% of ICU patients receive empirical or targeted antimicrobial therapy (Timsit et al. 2019). The hospital antibiogram can aid in selecting empiric antibiotic treatments with a higher chance of covering pathogens based on prior local knowledge and sensitivity. However, it is not always practical in achieving 90% coverage often based on antibiograms, as it might mean using restricted antibiotics more often driving resistance in the community. Therefore, empiric antibiotic choices should include risk factors related with antibiotic resistance such as comorbid conditions, recent exposure to healthcare, immunosuppression; type of infection: community vs. nosocomial; selection pressure from prior antibiotic use; colonisation with prior drug resistant pathogens; local epidemiology and infection prevention measures (Timsit et al. 2019). Metagenomics with fast sequencing of nucleic acids of all bacterial pathogens and their resistance determinants in the future would aid with this workflow to limit duration and narrow spectrum to monotherapy.

It is imperative to not only use the appropriate antimicrobial agent but to use the appropriate dose based on the pharmacokinetic (PK)/dynamic (PD) properties, and for the optimal duration. Consideration should be given to the minimum inhibitory concentration (MIC) of the pathogen, volume of distribution (usually high in patients with sepsis), augmented renal clearance (ARC), presence of renal or liver failure altering drug metabolism, physiochemical nature of the drug like hydrophilic/lipophilic properties, use of organ support (continuous renal replacement therapy and extracorporeal membrane oxygenation) and the site of infection. Underdosing is common in sepsis due to large volume of distribution and ARC. Hence, an initial large bolus (1.5 x standard dose) loading dose is most often required in severe sepsis

patients regardless of their organ function (De Backer et al. 2019). Beta-lactams work best with time-dependent killing and are usually administered in multiple daily doses or as a continuous infusion to keep the concentration above MIC, while other antibiotics such as aminoglycosides and quinolones exert their antimicrobial effects best by concentration-dependent killing and are usually administered with a single large daily dose.

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Therapeutic Drug Monitoring (TDM) is another measure employed in ensuring appropriate and effective antibiotic use in severe sepsis patients due to the inherent flaws with prediction of PK/PD characteristics in this population (Timsit et al. 2020). TDM is especially beneficial for certain antibiotic classes and should be used with vancomycin and aminoglycosides; however there is lack of evidence on adoption of regular TDM with use of beta-lactams (Timsit et al. 2020). Antibiotics are also chosen based on the site of infection. Lipophilic drugs like quinolones provide high tissue concentrations but hydrophilic antibiotics such as aminoglycosides do not penetrate into tissue space and remain extravascular but often enough to exert their antimicrobial effects (De Backer et al. 2019).

Another important aspect is appropriate source control. Common scenarios include an obstructive stone in patients with sepsis related to urinary tract infection, cholecystitis with cholangitis, post pancreatitis infected phlegmon, skin and soft-tissue infections, infected intra-vascular or cardiac devices, empyema and surgical site infections. This should be followed by antimicrobial de-escalation (ADE) strategies that form the cornerstone for antibiotic stewardship programme to help reduce duration of antibiotics and emergence of MDR pathogens. ADE involves narrowing the spectrum of the

initial antibiotic and/or decreasing the number of agents (Tabah et al. 2020). The majority of patients with sepsis related to pneumonia or post operative intra-abdominal infections can be treated with short course 5–7-day treatment. The Surviving Sepsis 2021 guidelines gave a conditional weak recommendation for limiting antibiotics to a short course in adults with an initial diagnosis of sepsis or septic shock and adequate source control (Evans et al. 2021). However, longer course might be needed with endocarditis and osteomyelitis, and certain MDR pathogens.

### Newer Antimicrobial Agents

Over the last decade several new and combination antibiotics have been developed to treat severe sepsis patients with resistant gram positive and negative pathogens. These include fifth generation cephalosporins, cephalosporin/beta-lactam + beta-lactamase inhibitor regimens including ceftazidime-avibactam, ceftolozane-tazobactam, imipenem-relebactam, meropenem-vaborbactam, and cefiderocol (Sjovall et al. 2017). In general, ceftolozane-tazobactam, ceftazidime-avibactam and imipenem-relebactam are effective choices against highly drug resistant *P. aeruginosa*, whereas with carbapenem-resistant *Enterobacteriaceae*, ceftazidime-avibactam, imipenem-relebactam, and meropenem-vaborbactam are good options (Torres et al. 2018; Kollef et al. 2019; Torres et al. 2019). Ceftazidime-avibactam and cefiderocol are optimal choices for metallo-beta-lactamase producing pathogens (Tamma et al. 2020). Meropenem-vaborbactam has good activity against most gram-negative microorganisms, including those with extended-spectrum beta-lactamases and *K. pneumoniae* carbapenemases and carbapenem-resistant *Enterobacteriaceae* (CRE) (Wunderink et al. 2018). Imipenem-relebactam is another combination regimen effective against most gram-negative microorganisms (Titov et al. 2020). Vancomycin, oxazolidinones (linezolid), telavancin, teicoplanin and streptogramins retain good activity against MRSA infections. Ceftobiprole is a fifth-generation cephalosporin with extended spectrum activity against methicillin-sensitive *S. aureus* (MSSA), *P. aeruginosa* and *Enterobacteriaceae*, but limited efficacy against MRSA and ESBL producing gram negatives, and is not

used in the United States (Cilloniz et al. 2019).

### Antimicrobial Preferences in Pneumonia and Intra-abdominal Infections

Lower respiratory tract infections, both community-acquired pneumonia (CAP) and nosocomial (hospital acquired pneumonia - HAP) and ventilator associated pneumonia (VAP) along with intra-abdominal infections form the bulk of sepsis in the ICU. The guidelines for CAP and nosocomial pneumonias were recently updated and they emphasise initial empiric antimicrobial therapy based on risk factors for MDR pathogens and local resistance patterns.

The 2019 American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) consensus CAP guidelines recommend that patients with severe pneumonia requiring ICU admission, with no risk factors for MRSA or *P. aeruginosa*, be started on either a beta-lactam plus a macrolide or beta-lactam plus a respiratory fluoroquinolone (Metlay et al. 2019). Prior studies have shown a possible survival advantage in severe CAP patients with regimens containing a macrolide with its potential anti-inflammatory effects (Rodriguez et al. 2007; Sligl et al. 2014). However, a more recent systematic review found no difference in outcomes between either a beta-lactam plus macrolide or a beta-lactam plus fluoroquinolone (Vardakas et al. 2017). In general, monotherapy is avoided in severe CAP in the ICU as appropriate dosing and safety of any single agent has not been established. The 2019 ATS/IDSA guidelines recommend empiric MRSA and/or Pseudomonal coverage for CAP patients with risk factors for these pathogens, followed by de-escalation of therapy, if cultures return without growth of these organisms (Metlay et al. 2019). MRSA and Pseudomonas risks as described above are prior positive culture, recent hospitalisations and antibiotic exposure within 90 days. In patients suspected of having *P. aeruginosa*, a two-drug regimen, using an anti-pseudomonal beta-lactam (cefepime, imipenem, meropenem, piperacillin/tazobactam) plus ciprofloxacin or levofloxacin is generally recommended. Another potential combination therapy will be with a three-drug regimen combining an anti-Pseudomonal beta-lactam plus an aminoglycoside plus either an intravenous anti-pneumococcal quinolone (moxifloxacin or levofloxacin) or a macrolide (Mandell et al. 2007). In patients

with suspected MRSA, either vancomycin or linezolid is preferred.

Similarly, the 2016 ATS/IDSA HAP-VAP guidelines also recommend empiric coverage based on MDR risk factors and local antibiogram (Kalil et al. 2016). The majority of patients should receive an initial empiric regimen that includes coverage for methicillin-sensitive *S. aureus* and gram negatives (e.g., piperacillin/tazobactam, cefepime, imipenem, meropenem, ceftolozane/tazobactam). Additional consideration for antibiotics is based on MDR risk factors that include use of IV antibiotics within 90 days, septic shock at the time of VAP, ARDS preceding VAP, at least five days of hospitalisation in the past 90 days, and requirement of acute renal replacement therapy prior to VAP onset. Two anti-Pseudomonal agents from different classes are recommended for VAP patients with at least one risk factor for resistant organisms and where the local prevalence of gram-negative resistance to a single anti-pseudomonal agent is not known or is >10% of gram-negative isolates (Kalil et al. 2016). Empiric therapy includes an aminoglycoside or an anti-Pseudomonal quinolone (high-dose ciprofloxacin or levofloxacin) and an anti-pseudomonal  $\beta$ -lactam such as cefepime, ceftazidime, ceftolozane/tazobactam, imipenem, meropenem, ceftazidime/avibactam, imipenem/relebactam, or piperacillin/tazobactam. Newer combination antibiotics are effective with MDR pathogens. Ceftazidime-avibactam and ceftolozane-tazobactam are effective against most MDR gram-negatives (Torres et al. 2018; Kollef et al. 2019; Torres et al. 2019). Meropenem-vaborbactam has good activity against most gram-negative microorganisms, including those with extended-spectrum beta-lactamases and *K. pneumoniae* carbapenemases and carbapenem-resistant *Enterobacteriaceae* (Wunderink et al. 2018). Imipenem-relebactam is effective against most gram-negative microorganisms with a survival advantage in VAP patients (Titov et al. 2020). MRSA coverage should be included with at least one of these risk factors for antimicrobial resistance and where local prevalence of MRSA is not known, or is >10-20% of *S. aureus* isolates. In those patients a third agent is added using either linezolid or vancomycin.

After culture results become available and with clinical stability, de-escalation to a more narrow spectrum agent, reducing the number of antibiotics, stopping therapy altogether in patients not likely to

1. Sepsis should be managed with **prompt antibiotic therapy and source control**.
2. Bacteria are more common than viruses and fungi as a cause of sepsis, with gram-negatives more frequent than gram-positives. Many bacteria are **multidrug resistant (MDR), which should impact the choice of empiric therapy**.
3. Use of initial **appropriate therapy** reduces mortality, length of stay and cost, and **is chosen based on** the suspected source of infection, the likelihood of MDR pathogen infection, and consideration of local microbial susceptibility patterns.
4. **Biomarkers** such as procalcitonin and C-reactive protein may have a role in anti microbial stewardship, rather than in determining **whether to start antibiotic therapy in patients with sepsis**.
5. Successful therapy requires **the correct dose, often higher than usual in septic patients, who can have augmented renal clearance** of antibiotics, along with alterations in volume of distribution, cardiac output and penetration to the site of infection.
6. Empiric therapy for septic patients with pneumonia (CAP, HAP, VAP) **should never be with a single agent**, and is based on risk factors for MDR pathogens. The most important risk factors to consider when choosing empiric therapy are **local microbiology, recent use of broad spectrum antibiotics in the past 90 days, recent hospitalisation for at least five days in the past 90 days, and prior colonisation or infection** by MRSA or *Pseudomonas aeruginosa*.
7. **Complicated intra-abdominal infection (cIAI)** is often polymicrobial, involving gram-negatives, anaerobes and enterococci. **Initial empiric therapy of septic patients should be with a beta-lactam/beta-lactamase inhibitor or a carbapenem, and in some patients, Candida species should be targeted with added coverage**. Management also includes source control.

Table 1. Key Recommendations. Modified from Niederman et al. 2021

have infection, and making efforts to reduce duration of therapy is recommended, and this has been shown to improve mortality and reduce the chance of secondary infection and antimicrobial resistance (Niederman 2006). The majority of VAP patients can be treated with a short course of antibiotics up to eight days (Chastre et al. 2003). In patients with non-responding pneumonia, inhaled colistin or aminoglycosides in addition to IV antibiotics can be used as an adjunct treatment with documented success (Kalil et al. 2016). HAP treatment guidelines are the same as for VAP, with the exception that MDR risk factors in HAP are prior intravenous antibiotic use within 90 days, or high risk for mortality.

Patients with complicated intra-abdominal infection with sepsis and shock can be challenging since most infections are polymicrobial, with both aerobic and anaerobic pathogens. Empirical therapy should include gram-negative with additional anaerobic coverage, using a beta-lactam/beta-lactamase inhibitor combination or a

carbapenem (Martin-Loeches et al. 2019). However, *Enterococcus* is a common pathogen in abdominal infections and is sometimes resistant to beta-lactams. In those patients, treatment is modified to include glycopeptides, oxazolidinones or carbapenems. Another

## Empiric antibiotic choices should include risk factors related to antibiotic resistance

consideration in ICU patients with complicated intra-abdominal infection is fungal infection with candidiasis and empirical antifungal therapy with azoles or echinocandins is generally initiated for severely ill patients (Martin-Loeches et al. 2019). Appropriate source control with percutaneous drainage or open drainage should not be delayed.

## Conclusion

Sepsis is a common, heterogeneous, and life-threatening condition. Successful treatment includes identification of high-risk patients and prompt use of empiric antimicrobial agents directed towards the likely site of infection and the common pathogens, with a clear understanding of underlying risk factors for MDR pathogens. This should be followed by a timely de-escalation strategy once further culture data and clinical stability are achieved, to promote responsible antimicrobial stewardship. Further advances in rapid diagnostics and -omics technology will likely usher a personalised treatment option for sepsis based on endo/phenotypes. Key management principles are summarised in **Table 1**.

## Conflict of Interest

None. ■

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# Rationale Behind Practice: Landiolol in Critical Care

A summary of data regarding the use of landiolol as a potential immunomodulator in septic patients and its effectiveness and safety in the management of new-onset postoperative atrial fibrillation (POAF).

## Cardiovascular Dysfunction and Sepsis

Cardiovascular dysfunction is a common complication of sepsis. Approximately 40 to 50% of patients with prolonged septic shock develop myocardial dysfunction. The changes induced by sepsis in circulating volume and vessel tone can affect cardiac performance. Another feature of sepsis-induced organ dysfunction is mitochondrial dysfunction which places the cardiomyocytes at risk of adenosine triphosphate depletion. Various mechanisms are at play, including downregulation of beta-adrenergic receptors, depressed post-receptor signalling pathways, impaired calcium liberation from the sarcoplasmic reticulum and impaired electromechanical coupling. All these changes are regulated by cytokines and nitric oxide (NO) (Rudiger and Singer 2007). During sepsis, there is an excessive production of NO, which decreases the sensitivity of the myocardium, which in turn affects the protein kinase and cyclic GMP messenger system (Greer et al. 2015).

There is a high level of inflammation during septic shock that leads to vasodilation and capillary leakage. This decreases cardiac output and can trigger sympathetic activation to ensure the maintenance of vital organ perfusion. The hallmarks of this activation are tachycardia and vasoconstriction. Sepsis guidelines recommend intravascular fluid administration as the first step to manage hypotension, but in patients with sepsis who continue to have an elevated heart rate, there is sympathetic overstimulation which is the result of dysregulation of the autonomic nervous system and the effect of exogenous catecholamines (Unger et al. 2018).

In clinical practice, catecholamines have been routinely used to bring the patient's blood pressure back to normal and help their vital organs recover and function normally. The most used catecholamine is noradrenaline. However, noradrenaline is asso-

ciated with significant side effects if given at high doses and for extensive periods of time. The drug may increase blood pressure in the short term, but it can damage the body in the long run. That is why the use of catecholamines in patients with sepsis-induced cardiac dysfunction is being questioned (Lall et al. 2021).

## New-Onset Atrial Fibrillation Post-Cardiac Surgery

Atrial fibrillation (AF) is one of the most reported arrhythmias after cardiac surgery. The incidence of new-onset post-operative AF (POAF) varies between 30 to 50% after cardiac surgery. The time of onset is typically within 1-5 days after surgery, peaking at day 2. Common risk factors for POAF include advanced age, type and complexity of surgical procedures and patient characteristics. POAF can negatively impact patient outcomes in terms of morbidity, hospital stay, long-term outcomes, thromboembolic stroke, and mortality (Boriani et al. 2019).

As per the 2020 ESC Guidelines for the diagnosis and management of AF, beta-blockers, diltiazem or verapamil are recommended as first-choice drugs to control heart rate in patients with LVEF  $\geq 40\%$  and beta-blockers and/or digoxin in patients with LVEF  $< 40\%$ . In patients with haemodynamic instability or severely depressed LVEF, the guidelines recommend intravenous amiodarone for acute control of heart rate. However, for the first time, landiolol is included in these important guidelines. Landiolol is described as the only agent with a specific dose recommendation in patients with cardiac dysfunction (dosages of 1  $\mu\text{g}/\text{kg}/\text{min}$  up to 10  $\mu\text{g}/\text{kg}/\text{min}$ ) (Hindricks et al. 2021).

## Landiolol – Fulfilling an Unmet Medical Need

Landiolol is an ultra-short acting, intravenous  $\beta_1$ -superselective adrenergic receptor antagonist with the highest receptor selectivity of all beta-blockers, a short half-life of four minutes and a low

volume of distribution (0.3 l/kg - 0.4 l/kg) (Rapibloc SmPC; Wada et al. 2016). It has a limited effect on blood pressure and inotropy (Shibata et al. 2012) and has a favourable safety profile for patients with renal and hepatic comorbidities (Rapibloc SmPC; Yokoyama 2016). The drug is compatible with pulmonary disorder patients due to its high cardioselectivity (European Heart Journal Supplements 2018) and it has a limited rebound and tolerance effect (Nasrollahi-Shirazi et al. 2016).

The overstimulation of adrenergic receptors can be treated with beta-blockers as these drugs offer attenuation of inflammatory cytokines, improve cardiac function, counteract metabolic dysregulation, prevent negative consequences from sympathetic overstimulation and prevent dobutamine-induced ventricular arrhythmias. Among septic patients with persistent tachycardia, ultrashort-acting beta-blockers such as esmolol and landiolol are associated with reduced 28-day mortality (Hasegawa et al. 2021). Landiolol, compared to esmolol, has a faster onset of action (1 vs 2 minutes) and a shorter half-life (4 vs 9 minutes). This allows rapid titration and an enhanced control of the substance leading to a better safety profile. In addition, the beta-1 selectivity of landiolol is nearly eight times higher than esmolol (Plosker 2013; Krumpl et al. 2017).

Landiolol has also shown to be effective in treating perioperative tachyarrhythmias and has been reported to be safe in treating patients with heart failure. Post-marketing surveillance studies in Japan illustrated that patients with cardiac dysfunction who received landiolol (continuous infusion, starting at 1  $\mu\text{g}/\text{kg}/\text{min}$ ) for treating AF achieved effective heart rate control without new safety concerns. Landiolol demonstrated to be more effective than digoxin in controlling heart rate in patients with left ventricular dysfunction who had AF. Heart rate control was achieved in 48% of patients treated with landiolol compared with 13.9% with

digoxin (Yamashita et al. 2019).

In the J-Land 3S study, significantly more patients with sepsis-related tachyarrhythmia achieved a heart rate of 60-94 beats per minute at 24 hours and a reduced incidence of new-onset arrhythmia than the control group (Kakikhana et al. 2020).

In patients who developed new-onset AF after open-heart surgery (n=134), landiolol achieved a significantly greater success than other treatments in reducing  $\geq 20\%$  the ventricular rate. It was concluded that this treatment is effective in rate control as well as for conversion of postoperative AF and can be used as a safe, first-line treatment for postoperative AF after open-heart surgery and in patients who have undergone off-pump coronary artery bypass grafting (CABG) (Nishi et al. 2013).

Efficacy and safety of landiolol were also compared with amiodarone in the restoration of sinus rhythm for POAF in ICU patients. Landiolol demonstrated a significantly shorter median time required for conversion to sinus rhythm as amiodarone. Adverse events with bradycardia leading to drug discontinuation were observed only in patients receiving amiodarone. Therefore, landiolol could be considered a favourable drug choice over amio-

darone for the safe restoration of sinus rhythm in ICU patients with POAF (Shibata et al. 2016).

### Conclusion

Controlling the heart rate with landiolol in the ICU often maintains stroke volume. The reduced effects on blood pressure dropping, negative inotropy and the beneficial pharmacokinetic profile of landiolol also decreases the level of complications during treatment. Additionally it is noteworthy to highlight the anti-inflammatory effects of the substance regarding different cytokines, heart tissue damage, and anti-apoptosis effects which can help patients with severe sepsis to avoid cardiac dysfunction.

Overall, a highly selective beta-blocker like landiolol can be considered a first-line treatment for rate control in patients with AF after cardiac surgery and sepsis. Especially the pharmacokinetic and pharmacodynamic profile makes it a favourable choice in critically ill patients. The substance clearly demonstrated sufficient evidence of reliability with regards to efficacy, safety, and handling in the described clinical settings.

### Key Points

- Landiolol, an ultrashort-acting  $\beta$ -blocker, can rapidly control heart rate.
- Controlling the heart rate with landiolol in the ICU can help maintain stroke volume.
- Landiolol has anti-inflammatory effects.
- Landiolol offers effective control of heart rate with minimal impact on blood pressure.
- The safety and effectiveness of landiolol have been successfully assessed in AF with HF.
- The safety of landiolol has been reported to be safe without any major concerns.

### Disclaimer

Point-of-View articles are the sole opinion of the author(s) and they are part of the ICU Management & Practice Corporate Engagement or Educational Community Programme.

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# The Alphabet Book of Sepsis

In this article, the author provides the alphabet review of sepsis and septic shock based on personal clinical experience and choice.

Sepsis and septic shock have been defined in 2016 (Singer et al. 2016) and the management of patients is framed by the Surviving Sepsis Campaign guidelines with its renewed version in 2021 (Evans et al. 2021). Using PubMed, around 15,000 hits respond to the word “sepsis” and “septic shock”, the best match being a review published by Angus and van der Poll in the New England Journal of Medicine in 2013.

As clinicians, we face sepsis and septic shock every day in our intensive care units (ICU). Despite our efforts, the 90-day mortality rate of these patients remains up to 40% in septic shock. We have to fight this high mortality with only antibiotics, one or two vasopressors and a few other drugs that the usefulness of which is still under debate. Each of us has probably their own view of sepsis, depending on several variables.

I provide, thereafter, my alphabet of sepsis and septic shock, based on personal choice. Some of my comments are not evidence-based but reflect my own clinical experience. This is a subjective approach, which does not rely on consensual process, Delphi rounds, or literature-based research.

## The Sepsis Alphabet

**A – Antibiotics** are the key drugs in sepsis, regardless of the lack of randomised controlled trials on their use. They are used either as empirical treatment or as guided treatment, depending on the availability of the microbiological results. In septic shock, they should be administered as soon as possible after diagnosis and sampling (Evans et al. 2021). There is still a debate in sepsis in which few studies suggested an association between early administration and good outcomes (Rüddel et al. 2022), while others showed that a

short delay - 4 to 6 hours - may be acceptable (Naucleur et al 2021). The balance between an overuse leading to resistance emergence and a strategy of large coverage for patients with suspected sepsis is a daily challenge in the ICU.

*Others: albumin; antifungals.*

**B – Breathing** is disturbed in most septic episodes. Increased respiratory rate is a clinical marker of sepsis in several scoring systems, including the concept of systemic inflammatory response syndrome and the quick sequential organ failure assessment (q-SOFA) score. This symptom should be regarded with attention for the diagnosis of sepsis, and one should keep in mind that it does not always refer to pneumonia.

*Others: base excess; beta-lactams; biomarkers; bundle.*

**C – Circulation** is the cornerstone differentiating sepsis and septic shock. The definition of septic shock is a sepsis associated with a vascular failure requiring the introduction of vasopressors and an increased plasma concentration of lactate (Singer et al. 2016). It is a circulatory shock inducing a vasoplegia. However, microcirculation may be impaired in a relative proportion of patients with sepsis (Joffre et al. 2020).

*Others: carbapenems; cardiac; catecholamines; coagulopathy; confusion; crystalloids; colloids.*

**D – Dysfunction** of organ(s) defines the sepsis, based on an increase in the SOFA score (Singer et al. 2016). This score reflects the degree of injury of organs, facilitating the decision-making for clinicians. At the bedside, the number of organs with dysfunc-

tion is probably one of the most relevant predictors of outcomes. However, the “multiple organ dysfunction syndrome” should not be used as cause of death, because this syndrome just reflects another initial injury that has to be clearly identified.

*Others: de-escalation; delivery; dobutamine.*

**E – Early** identification of sepsis is a critical step to improve the outcomes of patient. A large literature supports that early identification of sepsis, early source control and early antibiotic treatment are critical to save lives of patients with sepsis and septic shock (Evans et al. 2021). Different scores like the q-SOFA or strategies, including the use of point-of-care-ultrasound (Zieleskiewicz et al. 2021), may facilitate an early diagnosis. However, while guidelines look for providing specific timing for each step of the management, the word “early” should rather reflect “as soon as possible”.  
*Others: echocardiography; ECMO; epinephrine; examination.*

**F – Fever** is found in most - but not all - patients with sepsis. Fever is one of the variables defining inflammation syndrome (Walter et al. 2016). However, not all patients with sepsis develop fever and those with hypothermia may have worse outcomes. In addition, not all patients with fever have sepsis – a large number have inflammation, cancer-related fever, drug-induced fever, etc. Finally, the fever control in sepsis is an unresolved issue, but a bunch of experimental literature suggest against treating it in these patients. Fever is a critical symptom, but this sign can lead to treatments in excess.

*Others: fibrillation; fludrocortisone; fluid; fluoroquinolone.*

**G – Gas** exchanges are impaired in patients with septic shock mainly due to metabolic acidosis. It is critical in a patient developing sepsis to pay attention to gas exchange by sampling arterial blood. A fine knowledge of gas exchange is a mandatory step to manage the patients with sepsis and septic shock.

Others: *gender; glycopeptides; gram.*

**H – Hydrocortisone** may be used to compensate a relative deficit in steroid production in patients with sepsis. This drug is recommended in patients with a severe vascular failure not responding to first-line vasopressors (Evans et al. 2021). However, despite 20 years of intense research, there is still no consensus on its use in septic shock, with positive randomised controlled trials contradicting negative ones. However, low-doses of hydrocortisone are largely used in patients with septic shock (Téblick et al. 2019).

Others: *heat shock protein; hypotension; hypothermia; hypoxia.*

**I – Intra-abdominal** infection is often identified as the second or third source of infection (Martin-Loeches et al. 2019). This source of infection should be evoked for each patient who develops sepsis without evident site of infection. A delay in diagnosis may lead to delayed source control, resulting in worsened outcome. Of note, intra-abdominal infection is often diagnosed in patients with acute respiratory failure with bilateral basal images on chest x-ray, and then, the wrong diagnosis of pneumonia may cause a fatal delay for the source control.

Others: *insulin; interleukin(s).*

**J – Juniors** should be the target to increase awareness about sepsis in the medical community. We need to sensitise these young doctors to recognise and manage patients with sepsis, which remains an under-known and under-diagnosed syndrome. Education of junior doctors is probably a step to improve patient outcomes in sepsis.

**K – Kidney** function is impaired in a large number of patients with sepsis (Pickkers et al. 2021). It should be determined by using the adequate method. In ICU, the different calculated formula should not be used to assess the creatinine clear-

ance. Creatinine clearance should be measured on the urine collected during 8 to 24 hours using the formula “urine creatinine/plasma creatinine x volume of urine). Acute kidney failure is a strong predictor of long-term outcomes (Al-Dorzi et al. 2021).

Others: *kaliemia.*

## early identification of sepsis is a critical step to improve patient outcomes

**L – Lactate** is the most useful biomarker in sepsis and septic shock (Evans et al. 2021). A serum concentration above 2.0 mmol/L is a variable included in the definition of septic shock (Singer et al. 2016). The increase is due to an imbalance between the needs and the inputs of oxygen to cells, resulting in an anaerobic pathway. However, intensivists should keep in mind that serum concentration of lactate remains the product of its production and its elimination. Thus, in patients with other sources of production, such as muscles (due to epinephrine infusion) (Levy et al. 2015), or those with a decreased elimination, such as those with liver disease, the interpretation of an increased serum lactate deserves a fine analysis. Serum lactate should thus be measured if there is the slightest doubt.

Others: *liver; lung.*

**M – Monitoring** is defined as the maintenance of regular surveillance over time. The level of monitoring required in sepsis and septic shock remains conflicting. It seems safe to use continuous monitoring of arterial pressure in patients at risk of haemodynamic instability (Evans et al. 2021). The use of continuous monitoring of cardiac output is under debate, although a majority of experts would support this statement in septic shock. However, only the devices based on thermodilution seem reliable in these patients (Monnet and Teboul 2017).

Others: *mediators; metabolism; microcirculation; mitochondria; mortality.*

**N – Nitric oxide**, a free radical, is the mediator responsible for vasodilation at the level of endothelium. Its production is related to the pro-inflammatory response and activates the GMPc pathway, which results in the dephosphorylation of myosin phosphatase. Its “chemical” inhibition was assessed in a large randomised controlled trial that found an increased mortality in the group receiving the inhibitor of nitric oxide (López et al. 2004). The reasons for this failure - hypertension in the intervention group, other roles of nitric oxide, etc – are not clearly elucidated.

Others: *norepinephrine.*

**O – Oxygen** may be found abundantly in patients with septic shock, but its use is impaired at the cell level due to several mechanisms including mitochondrial and microcirculatory injuries. This results in poor utilisation of circulating oxygen, and possible high concentration of oxygen found in mixed venous blood samples or superior cava vena blood samples. The elevated values of oxygen central venous saturations have been associated with impaired outcome (Textoris et al. 2011). However, the best management of patients with elevated oxygen central venous saturations remains a matter of debate.

Others: *outcome.*

**P – Pneumonia** is the first cause of infection in the ICU and the first source of sepsis. Different types of pneumonia are defined including community-acquired and hospital-acquired that includes ventilator-associated pneumonia. The definition of pneumonia is based on an evolutive image in the context of infection (Leone et al. 2018). Its management is framed by several guidelines. However, the diagnosis of infection is challenging, which results in frequent mistakes and treatments in excess.

Others: *parasites; patient; penicillin; plasmodium; procalcitonin; pyuria.*

**Q – Q-SOFA** has been suggested to diagnose sepsis in outpatients and in-ward patients. It consists of three variables including mental status, blood pressure and respiratory rate (Seymour et al. 2016). It should serve as a red flag to identify the patients at risk of sepsis to decide both the best treatment, the source control

and the admission to ICU. However, the use of this score outside the field of ICU is disappointing.

Others: quality.

**R – Relatives** of patients with sepsis need attention. This syndrome, despite having a high mortality rate, remains unknown by the public at large. The concept of severe infection reaching several organs and leading to organ dysfunction is difficult to understand, especially in patients with no significant prior medical history. Good communication skills are required and rely on efficient training (Davidson et al. 2017).

Others: reactive oxygen species; responders; resistance.

**S – Source control**, which consists of the reduction of the physical process of infection, is a critical step in the management of septic patients (Martin-Loeches et al. 2019). Any delay, if source control is feasible, is associated with impaired outcome. Mini-invasive procedures should be preferred in those patients.

Others: selective digestive decontamination; survivors; syndrome; systemic.

**T – Trauma** is another inflammatory state that can trigger symptoms close to those of sepsis. It is interesting to underline similarities and differences in the management of patients with trauma and sepsis. First, in the bleeding trauma patient, a systematic investigation to identify the cause of bleeding has been implemented, using whole-body computed tomography scan (Caputo et al. 2014). This strategy should be assessed in patients with sepsis, to improve the identification of the sepsis source. Second, the mortality of trauma patients who develop septic shock is lower than that of non-trauma patients who develop sepsis. The causes of this difference may be age, comorbidities, underlying disease or immune dysfunction (Medam et al. 2017).

Others: terlipressin, tumour necrosis factors.

**U – Ultrasound** is essential to manage patients with sepsis and septic shock. This facilitates the source identification (lungs, kidneys, abdomen), assesses the effect of infection on several organs (lung oedema), provides a close look at the cardiac func-

tion and makes it possible to perform therapeutic interventions like an abscess drainage. The benefit is to use it at the bedside or in the conventional ward patient presenting a respiratory or circulatory failure (Zieleskiewicz et al. 2021).

Others: urine output.

**V – Vasopressors** are the other key treatment in septic shock with antibiotics. They separate sepsis and septic shock in addition to lactate (Singer et al. 2016). They mainly include catecholamines, vasopressin, and angiotensin 2. Among catecholamines, norepinephrine should be the first choice, acting on alpha receptors (favouring vessel contraction) and, with lower effects, on beta receptors (favouring inotropism). Epinephrine tends to be abandoned as first line treatment. Vasopressin is probably the best choice as second line, but the level of evidence supporting this statement remains low. Angiotensin 2 has emerged as an efficient interventional drug, but additional evidence is needed to use it in the best indications (Meresse et al. 2020).

Others: vasopressin.

**W – Withholding and Withdrawal** of life-sustained therapy is a critical issue in sepsis. Studies in the field should always report the rate of withholding and withdrawal of life-sustained therapy among the non-survivors. A multi-professional discussion and an evaluation of patient wishes are required in each case (Sprung et al. 2019). Resuscitation should not be an end in itself; quality of life after ICU discharge is an endpoint that should be constantly discussed with the patient or their relatives.

**X – XXXX** was a drug with anticoagulant and anti-inflammatory properties that created significant hope to improve the outcomes of patients with sepsis. A first randomised controlled trial including patients in septic shock showed a decrease in 28-day mortality rate of around 6% in absolute value (Bernard et al. 2001). Unfortunately, the following randomised controlled trials did not confirm this result, notably in patients with sepsis, which resulted in the withdrawal of the drug by the company.

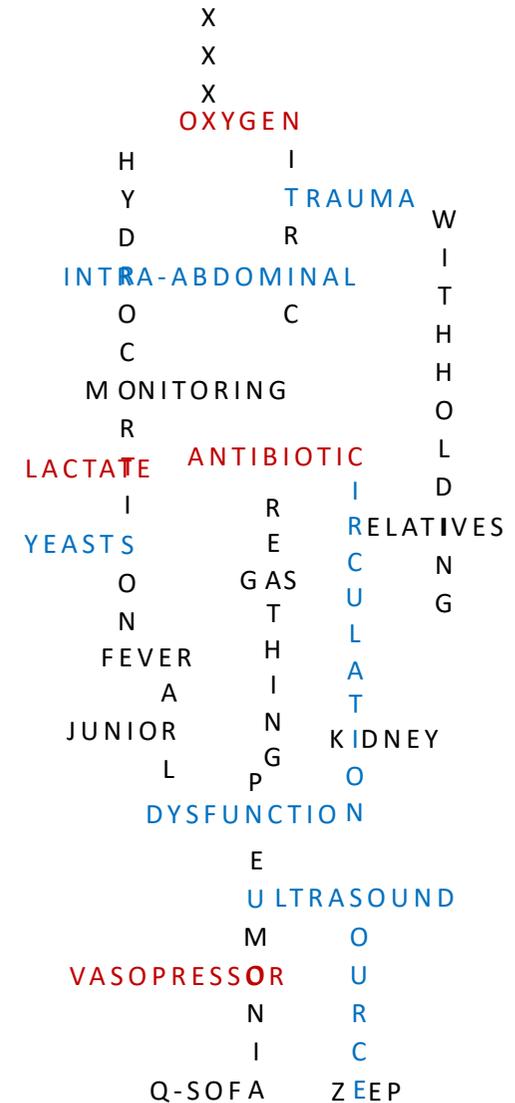


Figure 1. The ABCD of sepsis and septic shock  
Red is critical, blue is important.

**Y – Yeasts** are an agent of infection that can cause sepsis. Among yeasts, *Candida sp.* and *Aspergillus sp.* are the most frequently reported in ICU patients (Vincent et al. 2020). Intensivists should keep in mind the possibility of infection by yeasts, especially in frail patients including those receiving immunosuppressive drugs and those treated with antibiotics for a long duration (Bassetti et al. 2017). Early identification and specific treatments based on guidelines are critical to improve patient outcomes. Simplification is often needed for choosing the best antifungal treatment (Chatelon et al. 2019).

## withholding and withdrawal of life-sustained therapy is a critical issue in sepsis

**Z – Zero End-Expiratory Pressure** is never indicated in the mechanically ventilated patient with septic shock. However, the best positive end-expiratory pressure (PEEP) should be set at the

bedside as a personalised intervention, balancing the positive effects on ventilation and the negative effects on haemodynamics. The first goal with the ventilator setting is not to harm the patient. To this purpose, the strategy of high PEEP versus low PEEP does not really make sense for the clinicians.

### Conflict of interest

Marc Leone received fees for symposium by Amomed and Aspen and for consulting by Ambu, Gilead and LFB. ■

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# Gastric Residual Volume – Monitoring and Management

An overview of critical care guidelines for enteral nutrition (EN) and the use of gastric residual volume (GRV) management and monitoring as an essential component of EN patient care to help prevent complications.

## Malnutrition in Critically Ill and the Use of Enteral or Parenteral Nutrition

Disease-related malnutrition is a common problem among hospitalised patients. Specifically, in critically ill patients, oral food intake may not provide the required nutritional value. This may be due to the illness, nausea, vomiting, difficulty in swallowing and early satiety. Critically ill patients can have their oral intake also affected by mechanical ventilation, gastrointestinal surgery or unconsciousness (Yasuda et al. 2019).

In such patients, enteral nutrition (EN) or parenteral nutrition (PN) may be used to compensate for nutritional intake. Critical care guidelines recommend EN over PN in hospitalised patients who require non-oral nutrition therapy, except in cases where EN is contraindicated. EN is generally a riskless and well-tolerated approach in patients with normal gastrointestinal (GI) function.

## Gastrointestinal Dysfunction and Gastric Residual Volume

GI dysfunction can be an obstacle to EN. Feeding intolerance is an important indicator of GI dysfunction and is caused by delayed gastric emptying. Gastric emptying is assessed in clinical practice by measuring the gastric residual volume (GRV), which is the amount of liquid drained from the stomach following EN. GRV is measured by aspiration using a syringe or gravity drainage to a reservoir (Elke et al. 2015).

GRV management and monitoring are essential components of EN patient care and can help prevent complications. GRV management can allow clinicians to identify patients with delayed gastric emptying earlier to implement strategies that would

minimise the effects of feeding intolerance. As per the SCCM/ ASPEN 2016 guidelines (McClave et al. 2016), patients should be monitored for tolerance of EN, and inappropriate cessation of EN should be avoided. Holding EN for GRV <500 mL in the absence of other signs of intolerance should be avoided. In addition, the time period that a patient is made nil per os (NPO) prior

## GRV management and monitoring are essential components of EN patient care and can help prevent complications

to, during, and immediately following the time of diagnostic tests or procedures should be minimised to prevent inadequate delivery of nutrients and prolonged periods of ileus. Ileus may be propagated by NPO status (ICU Enteral Feeding Guidelines 2012).

The limit for normal GRV was proposed as 200 ml for nasogastric feeding (McClave et al. 1992). While this recommendation has been used in clinical practice, the normal limit for GRV in critically ill patients treated with EN still varies from ICU to ICU. Values between 50 ml to 500 ml can be found in the literature (Montejo et al. 2010). The REGANE study showed that increasing the limit of monitored GRV from 200 to 500 ml did not increase pneumonia (Montejo et al. 2010), while findings from the NUTRIREA1 clinical trial showed that adopting a no-routine monitoring of GRV approach did not increase pneumonia (Reignier et al. 2013). Both these studies included

ICU patients. In another study, Chapman et al. (2009) showed that 24-hour GRV of greater than 250 ml was shown to predict slow gastric emptying, but sensitivity and the negative predictive value was modest.

Overall, ICUs around the world continue to monitor GRV with different frequency, ranging from 4 hours to every 24 hours. European guidelines recommend delaying EN if GRV is above 500 ml/6h and other international guidelines also recommend GRV monitoring in patients with feeding intolerance and/or risk of aspiration (Yasuda et al. 2019).



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## Key Points

- Critical care guidelines recommend enteral nutrition (EN) over parenteral nutrition (PN) in hospitalised patient who require non-oral nutrition therapy.
- Gastrointestinal dysfunction can be an obstacle to enteral nutrition.
- Gastric emptying is assessed by measuring the gastric residual volume (GRV).
- GRV management and monitoring are essential components of EN patient care.
- Compat® DualPort and Compat® Modum are especially designed to ease GRV management and enteral tube feeding in critically ill patients.

## Disclaimer

Point-of-View articles are the sole opinion of the author(s) and they are part of the ICU Management & Practice Corporate Engagement or Educational Community Programme.

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# Challenges in the Haemodynamic Management of Septic Shock

An overview of the haemodynamic management of patients in septic shock and strategies for detection of haemodynamic changes and appropriate therapeutic action to improve the prognosis of these patients.

Treatment of sepsis and septic shock consists of treating the infection with antibiotics and controlling the source of infection while providing adequate multi-organ support. The haemodynamic alterations that accompany septic shock involve a severe decrease in systemic vascular resistance (SVR), an initial increase in cardiac output (CO) due to decreased left ventricular (LV) afterload and increased cellular metabolic needs, in addition to relative hypovolaemia due to leakage of fluid through vessels or absolute hypovolaemia when the patient has had significant fluid loss or intolerance to oral fluids (e.g., sepsis of abdominal or post-surgical origin). In addition, chronic inflammation can lead to (relative) adrenal insufficiency and cardiomyopathy. Despite medical advances, the management of all these alterations remain challenging for the intensivist, who must focus on restoring tissue perfusion to increase oxygen delivery ( $DO_2$ ) to tissues and limit organ failure.

## Fluid Therapy

Sepsis generates vasodilatation mediated by several proteins and toxins from microorganisms, leading to capillary leakage and decreased effective circulating blood volume with reduced venous return. These macro-haemodynamic effects lead to impaired tissue perfusion and organ dysfunction (Durgar et al. 2020). Considering these haemodynamic alterations, the management with intravenous (IV) fluids in these patients is currently debatable. The Surviving Sepsis Campaign 2021 guidelines were recently published, suggest-

ing that during initial resuscitation for patients with sepsis-induced hypo-perfusion or septic shock, intravenous crystalloids should be administered at a dose of at least 30 ml/kg within the first three hours of resuscitation (Evans et al. 2021). While the document emphasises a change in the strength of recommendation and quality of evidence (from a strong recommendation with low quality of evidence in 2021), its appearance in the guideline as a standard dose may lead to incorrect prescribing of fluids, with potential harm to patients, especially those with comorbidities. There is limited evidence to recommend initial bolus IV fluids, most of which is based on retrospective studies. Recent studies on the initial bolus of IV fluids have reported contradictory results (Wang et al. 2021; Lee et al. 2021).

In recent years, there has been increasing evidence of the deleterious effect of IV fluid boluses and persistent positive fluid balance for more than two days, contributing to global increased permeability syndrome (GIPS) and multi-organ oedema, association with higher incidence of acute kidney injury (AKI), increased days under mechanical ventilation (MV) and more days of hospital stay which can lead to multi-tissue oedema, thereby directly impacting ICU length of stay and mortality (Acheampong and Vincent 2015; Koonrangsomboon et al. 2015; Sakr et al. 2017; Shen et al. 2018; Tigabu et al. 2018; Zhang et al. 2021; Pérez-Nieto et al. 2021).

Experts recommend that the dose of fluids needed for initial and subsequent resuscitation in patients with septic shock should always

## Introduction

Sepsis is one of the main causes of admission to the Intensive Care Unit (ICU). It is defined as a life-threatening organ dysfunction, caused by dysregulated host response to infection (Singer et al. 2016). Septic shock is a public health problem, impacting millions of people worldwide every year, killing between one in three and one in six sufferers (Evans et al. 2021). It is one of the world's leading causes of death. Overall mortality in patients hospitalised with sepsis can be up to 24.2% and is higher in patients with comorbidities (33.1 vs 19.1%) (Kaukoken et al. 2014). Septic shock has a mortality rate of ~40% (Singer et al. 2016).



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be individualised according to the clinical characteristics of the patient and based on dynamic assessments of fluid responsiveness. An example of this is that a young patient without comorbidities is more likely to tolerate the administration of a large volume of fluid compared to a frail elderly patient with chronic cardiac or renal disease (Vincent et al. 2021). One of the many limitations of maintaining a fixed dose of fluids for patients with sepsis and septic shock is that the response to fluids decreases significantly over time elapsed from initiation of resuscitation (liquid responders: at 0 hours, only 57%; 2 hours, only 22%; 4 hours, only 11%; 6 hours, only 10%; and 8 hours, only 3%) (Hernández et al. 2019).

Physicians should avoid using static measures to assess volume status (e.g. central venous pressure) and volume response in these patients. To identify those patients who will or will not respond to fluid administration, it is advisable to use dynamic measures to estimate the effect of the additional volume on cardiac filling pressures and stroke volume (SV). Practical options are to administer a bolus of crystalloid fluids (usually no more than 500 ml, e.g., 3–4 ml/kg) or to passively raise the legs (which would produce a return of 200–300 ml of venous blood from the lower limbs), and then directly measure the change in systolic volume (e.g., with thermodilution, echocardiography, or pulse wave analysis). A 10–15% increase in SV is associated with an adequate fluid response. These changes can also be assessed by heart-lung interaction in patients on MV based on changes in intrathoracic pressure during the inspiratory and expiratory cycle, using pulse pressure variation (PPV), systolic volume, velocity-time integral (VTI) with Doppler ultrasound at LV outflow tract or arterial vessel level (e.g., carotid artery), and variation in the diameter of the inferior vena cava (ICV) or internal jugular vein (IJV) (Dugar et al. 2020). The greater the variability of any of these parameters (PPV, SV, VLT, etc), usually above 10–15%, the greater the response to IV fluids (in the absence of right ventricular dysfunction, common arrhythmias, significant tachycardia, and spontaneous and forceful ventilations). A recent randomised clinical trial in patients with sepsis, hypotension, and shock found that physiologically reported fluid and vasopressor resuscitation using passive leg raise induced systolic volume change to guide

treatment was safe and effective in reducing net fluid balance, with reduced risk of renal and lung injury (Douglas et al. 2020).

Regarding the type of solutions to be administered, there is no benefit when comparing 0.9% saline versus balanced solutions (Finfer et al. 2022), the latter of which are more expensive. IV albumin may be useful when a significant dose of crystalloid solutions has already been administered or for patients with significant hypoalbuminaemia (Joannidis et al. 2022).

## Vasopressors

### Catecholamines

Since vasodilatation is the main cause of shock—not hypovolaemia—the administration of vasoconstrictive agents should be considered. The decision to initiate vasopressor therapy to achieve mean arterial pressure (MAP) goals must be balanced against potential adverse effects, including tachyarrhythmias and cardiac, intestinal, or peripheral ischaemia. Norepinephrine has been considered the first-choice vasopressor for more than a decade due to its effect on vascular alpha receptors to generate vasoconstriction and cardiac beta receptors which cause a modest inotropic effect. Patients with MAP <66 mmHg and those who require >2,000 ml of IV fluids are at a higher mortality risk (Sivayoham et al. 2020). Early initiation of norepinephrine has been shown to be safe and could limit the amount of fluid required during resuscitation, thereby improving patient outcomes (i.e., faster resolution of shock, reduced mortality) (Permpikul et al. 2019; Ospina et al. 2020). Epinephrine is considered a second-choice vasopressor agent that should be used in the absence of response to norepinephrine (with or without added vasopressin or in the absence of vasopressin availability) with caution due to its association with tachyarrhythmias, hyperlactataemia and ischaemia. Dopamine is currently not recommended as the vasopressor of choice in septic shock for its higher incidence of tachyarrhythmias compared with norepinephrine.

### Vasopressin and analogues

Vasopressin is commonly considered a second-line agent, commonly used in vasoplegia. The VANISH clinical trial directly compared the

use of vasopressin versus norepinephrine in patients with septic shock (in addition to hydrocortisone) and failed to demonstrate significant differences in a 28-day mortality; however, the use of vasopressin significantly reduced the risk of renal replacement therapy (Gordon et al. 2016). In terms of combination therapy, the VASST randomised clinical trial compared norepinephrine versus norepinephrine plus vasopressin (at low doses), finding no significant differences in mortality, neither at 28 days nor 90 days. However, in a subgroup analysis, patients with milder shock who received norepinephrine at doses  $<15 \mu\text{g}/\text{min}$  had increased survival with the addition of vasopressin (Russel et al. 2008). For adults in septic shock who are on norepinephrine administration while maintaining inadequate mean arterial pressure levels, the Surviving Sepsis Campaign 2021 suggests adding vasopressin rather than progressively increasing the dose of norepinephrine (when the dose of norepinephrine is in the range of 0.25-0.5 mcg/kg/min, as a weak recommendation with moderate quality of evidence). Terlipressin and selepressin are synthetic vasopressin analogues used in the management of patients with septic shock. Terlipressin was associated with reduced mortality in septic shock patients less than 60 years old and may also improve renal function but cause more peripheral ischaemia (Huang et al. 2020).

There are other vasopressor agents for the management of septic shock including IV methylene blue and angiotensin II. Despite their vasoconstrictor effect and increase in blood pressure, their availability is limited, and clinical trials have not shown a greater benefit in survival or days of shock when compared with norepinephrine. More studies are needed to assess their clinical utility (Scheeren et al. 2019).

The combination of persistent diastolic hypotension and its correlation with heart rate (HR) may reflect severe vasodilatory conditions. The diastolic shock index (heart rate/diastolic blood pressure) calculated before and during vasopressor use is an early identifier of patients at high risk of mortality when its value is above 2 (Ospina et al. 2020).

### Corticosteroids

“Critical illness related corticosteroid insufficiency” has been

defined as a condition in which the patient may not be able to produce the required amount of cortisol for survival. Patients in septic shock with a prolonged stay in the ICU have a particular risk of developing septic shock (Annane et al. 2017). It has recently been shown that the amount of cortisol produced by patients during critical illness is not much higher than that produced by healthy patients. The increased availability of systemic cortisol during critical illness is mostly driven by decreased binding proteins, reduced binding affinity of these proteins and suppression of cortisol degradation (Téblick et al. 2019). Randomised clinical studies have compared the use of corticosteroids versus placebo in patients with septic shock without direct survival benefits (Sprung et al. 2008; Venkatesh et al. 2018); however, these studies had an impact on vasopressor-free days and lower undesirable effects. Only one multicentre randomised clinical trial found a reduction in 90-day mortality with the administration of hydrocortisone combined with fludrocortisone for 7 days (no stepdown) (Annane et al. 2018).

Considering resource requirements, cost of intervention, and feasibility, the Surviving Sepsis Campaign 2021 gives a weak recommendation in favour of the use of low-dose corticosteroids in adults with septic shock who continuously require norepinephrine or epinephrine at doses  $\geq 0.25 \text{ mcg}/\text{kg}/\text{min}$  for at least 4 hours after initiation (Evans et al. 2021).

### Inotropic Drugs

Sepsis induced myocardial dysfunction is recognised as an important contributor to the haemodynamic instability of persistent septic shock. It can manifest in multiple forms and affect both ventricles through primary myocardial cell injury (Beesley et al. 2018). It is characterised for being acute and reversible within the first 7–10 days and for presenting global biventricular dysfunction (systolic and/or diastolic) with contractility impairment and may present left ventricular dilatation. Septic cardiomyopathy is associated with decreased fluid and catecholamine response, contributing even more to haemodynamic deterioration (L’Heureux et al. 2020). After adequate fluid therapy and use of vasopressors, inotropic agents may be required if sepsis or septic shock leads to decreased

cardiac output with persistent hypoperfusion.

There is no inotropic drug of choice, but epinephrine and dobutamine are the most employed drugs despite their lack of clinical benefit in multiple indirect comparison studies. It should be noted that both should be stopped in the absence of improvement of hypoperfusion or in presence of adverse events (Belletti et al. 2017; Wilkman et al. 2013). Despite scarce strong evidence in favour of their use to improve clinical outcomes in patients with septic shock, experts recommend their use when there is low cardiac output with clinical signs of hypoperfusion. Dobutamine is recommended as the inotrope of choice (Scheeren et al. 2021). According to the Surviving Sepsis Campaign 2021 update, in adults with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and blood pressure, they suggest adding dobutamine to norepinephrine or using epinephrine alone (weak recommendation with low quality of evidence). They do not suggest using levosimendan due to the absence of benefit in clinical studies, in addition to its undesirable safety profile (e.g., increased risk of supraventricular arrhythmias), cost, and limited availability (Evans et al. 2021).

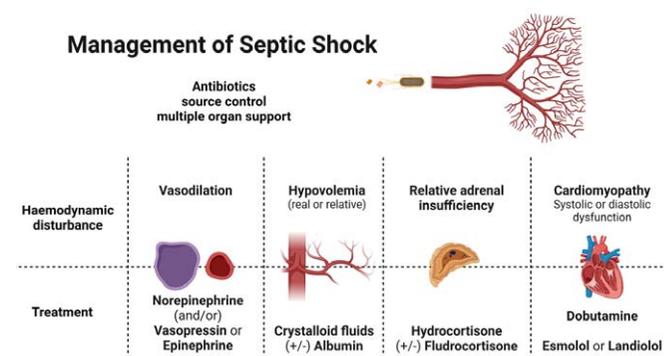


Figure 1. Haemodynamic management of septic shock

## Negative Chronotropic Drugs

In the clinical stage of sepsis, the adrenergic system functions as an initial adaptive response to maintain homeostasis. However, excessive increases in catecholamines can cause adverse effects such as persistent tachycardia, which can lead to altered cardiovascular haemodynamic with worsening prognosis. There are multiple factors for tachycardia in sepsis (e.g., inflammatory state, fever, pain, etc.), but persistent tachycardia is likely to manifest as a non-compensatory arrhythmia due to sympathetic overstimulation (Hasegawa et al. 2021). A randomised clinical trial in patients with septic shock compared the use of esmolol (short-acting selective beta-1 blocker) against a control group, finding that esmolol was associated with reductions in heart rate to achieve primary endpoints without an increase in adverse events and lower mortality (Morelli et al. 2013). Several clinical studies have now been published with similar pharmacological interventions. A systematic review with meta-analysis of six randomised clinical studies (including 572 patients) on the effect of ultra-short-acting beta-blockers in patients with sepsis and persistent tachycardia despite initial resuscitation showed that the use of esmolol or landiolol in patients with sepsis and septic shock was significantly associated with lower mortality at 28 days, with no significant heterogeneity between the studies analysed (Hasegawa et al. 2021). Ivabradine has also been studied in patients with septic shock and persistent tachycardia, being safe but with questionable efficacy (Datta et al. 2021).

## Discontinuation of Therapy

Intravenous fluids should be suspended as soon as possible. Fluid intake in the form of nutrition, drug vials, transfusions and so on should be considered. Positive fluid balance should be avoided for longer than two days. Regarding vasopressor withdrawal, the DOVSS study (prospective, randomised) evaluated the incidence of hypotension according to the order of vasopressor withdrawal in septic shock, demonstrating that gradual reduction of norepinephrine instead of vasopressin was statistically significantly associated with a higher incidence of hypotension (Jeon et al. 2018). A recent systematic review with meta-analysis that evaluated the effects of the order of norepinephrine and vasopressin

Drug	Dose	Mechanism of Action	Adverse Effects	Comment
<b>VASOPRESSORS</b>				
Norepinephrine	0.025–3.3 µg/kg/min	α1 receptor agonist β1,β2 receptor agonist (mild effect)	Intestinal and renal hypoperfusion (uncommon) Bradycardia (uncommon) Tachyarrhythmia	First-choice vasopressor. Associated with lower mortality. Early treatment recommended.
Vasopressin	0.01–0.04 units/min	V1a, V2, and V1 <sub>b</sub> receptor agonist.	Intestinal, hepatic, and splenic hypoperfusion (uncommon) Thrombocytopenia (uncommon) Hyponatraemia (uncommon)	Second-choice vasopressor. Treatment for vasoplegia. Infusion is usually stopped after retiring norepinephrine.
Epinephrine	0.01–2 µg/kg/min	α1, β1, and β2 receptors non-selective agonist	Tachyarrhythmia, hyperglycaemia, splanchnic ischaemia, and hyperlactaemia.	Second-choice vasopressor. Higher incidence of tachyarrhythmia compared with dopamine and norepinephrine.
Dopamine	2–20 µg/kg/min	Dose-dependent agonist of α1, β1, and β2 D <sub>1</sub> , and D <sub>2</sub> receptors	Tachyarrhythmia, peripheral ischaemia, splanchnic hypoperfusion, delayed gastric emptying.	Consider in patients with shock and bradycardia. Higher incidence of tachyarrhythmia than norepinephrine. Does not diminish the incidence of acute kidney injury.
Terlipressin	1.3–5.2 µg/min	Synthetic arginine-vasopressin analogue with higher selectivity for receptors V1 <sub>a</sub> and V1 <sub>b</sub> > V2.	Peripheral vasoconstriction. Mesenteric ischaemia. Bradyarrhythmia.	Higher incidence of adverse effects than vasopressin. Longer half-life.
Selepressin	1.7–5 ng/kg/min	Selective V1 <sub>a</sub> receptor agonist	Arrhythmia, myocardial ischaemia, mesenteric ischaemia.	Not superior to norepinephrine and vasopressin. Low availability worldwide.
Angiotensin II	1.25–40 ng/kg/min	ATR <sub>1</sub> and ATR <sub>2</sub> receptor agonist in smooth muscle cells.	Thromboembolism, thrombocytopenia, delirium, hyperglycaemia, tachycardia.	Not superior to norepinephrine. Low availability worldwide.
Methylene Blue	2 mg/kg bolus 0.25–2 mg/kg/h infusion	Nitric oxide synthesis inhibitor.	Blue-green pigmentation of skin, mucosa, and secretions. Arrhythmia (uncommon).	Contraindicated in chronic kidney disease without renal replacement therapy.

interruption in the recovery phase of septic shock showed that norepinephrine interruption, before vasopressin, resulted in less hypotension, with no difference in mortality or length of hospital stay (Hammond et al. 2019). As for inotropic drugs used for myocardial dysfunction caused by sepsis, it is known that this complication is usually reversible within days and should be suspended upon evidence of improvement in IV systolic function, for which echocardiography can be very useful.

### Goals of Macrohaemodynamic Resuscitation in Septic Shock

Recommendations indicate to maintain a mean arterial pressure target >65mmHg, compared to higher targets (as a strong recommendation with moderate quality of evidence (Evans et al. 2021)); however, patients with systemic hypertension or chronic kidney disease may require a target >80 mmHg MAP for better results.

The ANDROMEDA-SHOCK study evaluated the use of capillary refill time (CRT) compared to serum lactate levels as a resuscitation strategy in patients with septic shock, finding that 28-day mortality was not statistically different between the two groups (Hernández et al. 2019). Nevertheless, a post-hoc analysis using Bayesian mixed logistic regression showed that peripheral perfusion-guided resuscitation can reduce mortality and lead to rapid resolution of organ dysfunction compared to lactate-guided resuscitation, the latter being associated with over-resuscitation with fluids, vasopressors, and inotropes (Zampieri et al. 2020).

Serum lactate has been strongly associated with mortality in critically ill patients, however, its usefulness in monitoring patients with sepsis is controversial. Although the Surviving Sepsis Campaign 2021 suggest guiding resuscitation to lower lactate levels in septic shock (Gómez and Kellum 2015), other causes associated with lactate elevation should be ruled out or assessed (e.g., acute liver failure, intestinal ischaemia, diabetic ketoacidosis, adrenergic effect, etc.). It has also been shown that hyperlactataemia is often caused by impaired tissue oxygen utilisation (bioenergetics failure) in sepsis, rather than oxygen transport impairment as the single main cause. Thus, the current resuscitation strategy could be modified according to the origin of lactate excess (Marik

INOTROPES				
Dobutamine	2–20 µg /kg/min	β-adrenergic receptor agonist	Tachyarrhythmia, vasodilation.	First-choice inotropic drug in sepsis-associated cardiomyopathy with hypotension.
Levosimendan	0.05–0.2 µg/kg/min in continuous IV infusion	Enhances sensitivity to calcium of proteins in contractile cells through binding of troponin C.	Headache, nausea, extrasystole, hypotension.	Not superior to dobutamine. Contraindicated in kidney disease with creatinine clearance <30 ml/min.
NEGATIVE CHRONOTROPICS				
Ivabradine	5–7.5 mg orally every 12 hours	Selective inhibitor of the If current in nodal heart cells.	Phosphenes, bradycardia, atrial fibrillation.	Useful for diastolic dysfunction.
Esmolol	0.05–0.2 mg/kg/min	Selective antagonist of short-acting β1 receptor	Hypotension	Easy to titrate.
Landiolol	1–20 µg/kg	Super-selective β1-adrenergic receptor antagonist of ultra-short action.	Hypotension	Lower impact on blood pressure lowering. Faster onset than esmolol. Shorter half-life.
CORTICOSTEROIDS				
Hydrocortisone	50 mg every 6 hours or 200 mg/day continuous IV infusion	Increased vascular reactivity.	Hyperglycaemia	Corticosteroid of choice. Widely available.
Fludrocortisone	50–100 µg orally every 24 hours	Increased vascular reactivity.	Oedema, hypernatraemia, hypokalaemia.	Can be used alongside hydrocortisone. Low availability worldwide.

Figure 1. Cardiovascular pharmaceuticals used for the treatment of septic shock

2019). Central venous oxygen saturation ( $ScvO_2$ ) has prognostic value in critically ill patients. Levels  $<70\%$  are associated with increased mortality; however, despite the recommendation to maintain a  $ScvO_2$  greater than this level (Rivers, 2008) through IV fluids, vasopressors, inotropes, transfusion of red blood cell concentrates and increased inspired oxygen fraction ( $FiO_2$ ) have no impact on mortality.

Other invasive and minimally invasive monitoring strategies to improve the prognosis of patients in septic shock have been proposed (intrapulmonary and transpulmonary thermodilution, pulse wave analysis, etc.), but the perfect monitoring strategy that represents an improvement in outcomes, with the least possible

## ■ ■ sepsis induced myocardial dysfunction is recognised as an important contributor to the haemodynamic instability of persistent septic shock ■ ■

invasiveness and at the lowest cost has not yet been developed. The best monitoring is done by the clinician who is aware of the haemodynamic changes in the patient and who takes appropriate actions based on the best available evidence.

### Conclusion

Haemodynamic management of patients in septic shock is a challenge for the clinician. Detection of haemodynamic changes and appropriate therapeutic action with fluids, vasopressors, inotropes, corticosteroids and/or beta-blockers, combined with infection control can improve the prognosis of these patients.

### Conflict of Interest

None. ■

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Sepsis is a critical healthcare problem, associated with high mortality rates, and considerable financial and resource burden. At the end of 2021, new Surviving Sepsis Campaign international guidelines were published. Although updated guidelines have incremental updates bringing some new insights into geographic and gender diversity, haemodynamic management, early administration of steroids, antimicrobial choice, and post-ICU care, there are no real game-changers for either the diagnosis or treatment of sepsis and septic shock (Evans et al. 2021). Timely recognition of sepsis is the foundation of improved patient survival. There are opportunities to improve this in multiple areas.

# Sepsis Surveillance (Sepsis Sniffer): Where We Are Now and Where We Are Going

Timely recognition of sepsis is the foundation of improved patient survival. This article will discuss opportunities to improve this in multiple areas and the use of sepsis screening tools to improve surveillance and treatment of sepsis.

## Public Awareness and Pre-Hospital Recognition of Sepsis

Knowledge about sepsis has increased but remains lower than awareness of other more lethal conditions such as acute myocardial infarction or stroke (Jabaley et al. 2018). Members of the public may know the word “sepsis” and some of the signs but they are not always aware of the devastating consequences of organ failure if prompt medical intervention is lacking. Unlike, cardiac arrest or stroke, the early signs of severe sepsis are relatively non-specific and may be of gradual onset making it difficult to educate the public about triggers for medical intervention.

## In-hospital Recognition and Treatment of Sepsis

Once the patient enters a health system, we have more tools at our disposal but still encounter delays or failure of diagnosis and treatment with significant negative impact on patient outcomes, health costs and resource utilisation.

In the last 15 years, there have been many efforts to use Electronic Medical Records (EMR) data for the early recognition of sepsis. Multiple systematic reviews on sepsis surveillance showed no breakthrough progress on that for the past 15 years in hospitalised patients (Alberton et al. 2017) and emergency departments (Hwang et al. 2020). One early “sepsis sniffer” demonstrated sensitivity of 48% and specificity of 86%, and a positive predictive value of 32% (Herasevich et al. 2008) and was based on established sepsis definition criteria. Later tuning of the algorithm improved performance with sensitivity of 80% and a specificity of 96% when applied to

the validation cohort (Harrison et al. 2015). In parallel, Artificial Intelligence (AI) and Machine Learning (ML) in medicine have resulted in a new generation of AI-based sepsis detection/prediction models. Despite their potential, the prediction performance of those models is suboptimal in the real world compared to the controlled development environment, where they do about as well as traditional rule-based system using Systemic Inflammatory Response Syndrome (SIRS) criteria. For example, a prospective study of a sepsis detection algorithm utilising 160 clinical features relevant to sepsis achieved a sensitivity 65% and specificity 88% (Yuan et al. 2020). Recent prospective validation of a widely implemented sepsis prediction model from a commercial EMR vendor, similarly demonstrated poor performance. In this example, the system failed to identify 67% of patients with sepsis while simultaneously generating an alert for 18% of all hospitalised patients (Wong et al. 2021) undermining the primary intent of alerting, which is to call attention to a developing situation and to drive a behaviour or response that averts or mitigates the negative impact of that event. However, even in situations where machine learning algorithms demonstrate good predictive performance, clinician response to alerting is limited and results in minimal changes of patient care and outcomes (Giannini et al. 2019).

What can we learn from more than a decade of active sepsis surveillance research?

1. **EMR Data:** The way we capture and store clinical data in electronic form through the EMR is not ideally suited to

the development of predictive models. Infrquent and delayed data capture or charting presents a major barrier to the performance of real time predictive models. Most physiological charting does not occur in real time. This is particularly true during busy times when patient care takes precedent over charting. Unfortunately, this is precisely the time when automated detection of sepsis may be most useful and is a major contributor to poor performance and impact of alerts in the working environment.

2. **Continuous reliable automated data capture is not common:**

Time is of the essence in sepsis. Given the broad differential in the early stages of disease, it is essential that predictive models reliably identify the point where sepsis is highly probable as early as possible. For this, a model needs data at a frequency greater than commonly captured with usual workflows. Hospital based nurse observation data is not often captured at high frequency - every 4-6 hours would not be unusual in the average general care area. When combined with inconsistent data charting practices these organisational factors can lead to missing or very delayed data with significant downstream delays impeding the performance of model based sepsis alerts. These constraints are not accounted for by models developed on static retrospective datasets.

3. **Pre-test probability:** Compounding all of this is the fact that most predictive models are trained to recognise sepsis using diagnostic labels found in the EMR that have been generated by clinical staff. This means that most sepsis algorithms depend on data gathered when sepsis is suspected by clinical staff. An excellent example of how this impact model performance is lactate measurement. Lactate is measured most often when sepsis is suspected by a clinician. This has two implications for performance in the setting of a patient with sepsis. In the first, the clinician suspects sepsis, orders lactate and the sepsis alert triggers, calling the attention of the clinician who already suspects sepsis to the fact that sepsis may be present - annoying and distracting; in the second, the clinician does not suspect sepsis, does not order lactate and the alert doesn't trigger - the clinician and algorithm are

both blissfully unaware of the fact that the patient has sepsis until some other events intercede. These model development choices dramatically decrease the impact of alerts on clinical outcome.

## It is evident that AI alone cannot produce a perfect algorithm based on EMR data alone

4. **Testing and reporting the usefulness of an alert:** Most sepsis alerts are tested for diagnostic performance (sensitivity, specificity etc.) but almost never for action following an alert. Rarely are the impact on diagnostic performance or treatment choices reported. This obscures the essential value of the alert and underrepresents failures in essential follow-up actions that can lead to clinically meaningful delays in recognition and intervention.
5. **Prediction lead time and risk-benefit analysis:** Every diagnostic or treatment intervention for sepsis carries a risk or cost. Prediction is valuable only if the risk of early action outweighs the risk of delay while waiting for certainty. The inflection point for such risk-benefit analysis is very poorly understood for predictive models of sepsis. If this is layered on top of the other contributors to suboptimal performance of sepsis alerts outlined above, the probability that such alerts will generate unnecessary interventions or be ignored is very high.

As we discover all the ways not to build and deploy sepsis sniffers, are there approaches or combinations of approaches we can take to deliver truly useful alerts?

1. **Failure to rescue alerts:** An approach that has been pioneered in security systems and more recently applied to clinical sepsis is the failure to rescue model of alerting. In this approach alerts are considered meaningful only

if they prompt useful actions that otherwise would be missed or delayed. For this to be effective, the alerting platform monitors both system state and system processes. Alerts are issued only when there is a mismatch between the state and expected process. In the case of sepsis, this would correspond with an alerting platform that detects the condition of sepsis, confirms it with a clinician and then monitors for expected events or actions such as timely administration of antimicrobials. Notifications are only generated when expected actions are not detected. This acts as a guardrail for the quality of care delivered once the condition of sepsis is confirmed to be present.

2. **Ambient data cues:** Clinicians utilise all their senses when evaluating the patient. Many of the visual and tactile cues clinicians use to make decisions are not recorded in the EMR and are not readily available to analytic models. Advances in computer vision could be applied to this problem. Computer vision models could be trained to monitor patients 24/7 and recognise important visual clinical cues as they emerge. Applying machine learning algorithms on such data may be able to achieve recognition of emerging sepsis performance similar to that of an expert clinician. This approach could be extended to other sensors such as accelerometers or sound.
3. **Physiological waveforms:** As continuous physiologic monitoring becomes more common outside of traditional high acuity environment such as the ICU, the potential for high frequency data capture increases. This can potentially reduce dependence on EMR charted data and address some of the sepsis detection algorithm performance issues associated with delayed data availability. The application of machine learning to the problem of false alerts and noise is a particularly fertile area for improvement that may accelerate their application to sepsis monitoring.
4. **Alert delivery:** Using real time locations services and accelerometer data, information on computer network activities and other augmented data from providers could

be used to deliver alerts directly to the right person in the right location and position to act. The acceptance of such an approach to providers is unclear and merits further study.

5. **Control tower:** There is no doubt, that sepsis screening tools should be implemented systematically and hospital-wide to improve surveillance and treatment of sepsis for all patients. With the recent interest in telepresence, there

is an opportunity to integrate sepsis surveillance and management into clinical control towers under centralised supervision. This will help to mitigate some of the challenges associated with implementation and training of large numbers of staff in new processes of care.

Electronic sepsis detection is suboptimal. It is evident that AI alone cannot produce a perfect algorithm based on EMR data alone. To be able to produce useful sepsis surveillance, additional

investment in data capture and health system responsiveness need to be made.

### Conflict of Interest

Mayo Clinic and Dr Herasevich hold the USA patent on sepsis sniffer technology – sepsis monitoring and control (US 8527449B2). Technology licensed to Ambient Clinical Analytics - <https://ambientclinical.com>. ■

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## Introduction

Symmetrical peripheral gangrene (SPG) refers to the development of tissue necrosis in an acral distribution without vasculitis and often without loss of arterial pulses. It is a rare but devastating clinical syndrome associated with significant morbidity and mortality, often leading to amputation of digits or limbs in patients who survive.

SPG is most commonly seen with sepsis, but has been described in a wide variety of clinical conditions. A typical presentation would be in a patient with septic shock and disseminated intravascular coagulation (DIC) who initially develops skin mottling

# Symmetrical Peripheral Gangrene

In this article, the authors describe the presentation, pathophysiology, and potential treatment options for symmetrical peripheral gangrene. Limitations in the current literature and a possible strategy for future study are highlighted.

temporally related to a sudden and progressive drop in platelet count. Evidence of diffuse acral cyanosis and tissue loss then follow.

The pathophysiology is incompletely understood but thought to result from a DIC driven microvascular thrombosis often paired with impaired perfusion, and relative deficiency in anti-coagulant factors such as protein C and antithrombin secondary to impaired production and consumption (Warkentin and Ning 2021). Ischaemic hepatic injury as a source for the reduction in the aforementioned liver produced anti-coagulant factors is thought to play a significant role (Warkentin and Ning 2021). DIC is likely the final common pathway of SPG. SPG has in fact been described as the cutaneous marker of DIC (Sharma et al. 2004).

While vasopressor administration has been associated with SPG, a causative or contributory role has never been established. One reason that SPG remains poorly understood is the rarity of its presentation. Research has been limited to animal models, case reports, and small single-centre case series of patients with a wide spectrum of clinical illness. Modifiable risk factors and effective treatment options remain poorly defined.

In this article, we briefly review the pathophysiology, potential treatments, and areas for future research.

## Pathophysiology

SPG has been described as its own clinical entity, but exists along a spectrum of other related thrombotic disorders that lead to tissue necrosis. These include purpura fulminans, venous limb ischaemia, warfarin skin necrosis, and heparin induced thrombocytopenia (Warkentin 2015). Purpura fulminans is most closely associated,

and is the term used to describe the presence of both acral and non-acral gangrene in a relatively symmetrical distribution.

All of these disorders involve coagulopathy with coagulation factor consumption and anti-coagulant insufficiency resulting in thrombosis and tissue gangrene (Warkentin 2015). Yet, while venous limb ischaemia, warfarin skin necrosis, and heparin induced thrombocytopenia have well recognised precipitants – deep vein thrombosis, coumadin administration, and heparin-platelet factor 4 antibody development, respectively – conditions precipitating SPG are more varied.

SPG was first described by J Hutchinson in a 37-year-old male with shock (Hutchinson 1891). It has since been described in association with sepsis, COVID-19 infection (Sil et al. 2022), myocardial infarction (Caserta et al. 1956), pancreatitis (Liao et al. 2015), trauma (Tan et al. 2018), and envenomation (Shastri et al. 2014), among others. While SPG is most commonly reported in patients with hypotension, it has also been reported in individuals without overt hypotension (Kurup and Simpson 2019).

The shared common pathway in SPG is thought to be a triad of 1) end organ shock, 2) disseminated intravascular coagulation, and 3) depletion of natural anticoagulants through consumption and impaired production (Warkentin and Ning 2021) leading to small vessel fibrin thrombosis (Robboy et al. 1973) and tissue necrosis. Liver dysfunction due to ischaemic hepatitis is observed in many cases (Warkentin and Ning 2021), but dilution of anti-coagulants may also occur through colloid volume expansion (Warkentin et al. 2020).

Vasopressors are often cited as having a significant role in developing SPG (Hayes et al. 1992; Ruffin et al. 2018). However, such causality has never been established. Several observations argue

against it. First, the majority of patients on high dose vasopressors never develop SPG. Second, there may be a significant time delay between vasopressor initiation and the onset of distal tissue ischaemia (Warkentin and Ning 2021). Third, there are patients who develop SPG prior to ever receiving vasopressors. Ghosh et al.

(2010) reported a case series of 14 consecutive patients presenting with SPG. None of them received vasopressors immediately prior to or during the development of tissue gangrene.

It is possible that vasopressors exacerbate SPG. However, the evidence for this is very weak. Kwon et al. (2018) performed a small retrospective matched case-control study comparing 36 patients with SPG with 42 controls. They found that weight adjusted mean dose of dopamine and the weight adjusted peak doses of norepinephrine, dopamine, and epinephrine correlated with SPG. However, the SPG group was more haemodynamically unstable, thrombocytopenic, and had lower Glasgow Coma Scale (GCS) scores than the control group (Kwon et al. 2018). Coagulation markers were also not reported. Many other case reports attribute SPG to vasopressor use. But association does not mean causality. Of note, vasopressors have not received the same level of attention as a contributing factor in purpura fulminans.

### Proposed Treatment Options

Various treatment strategies have been described for SPG. Most of these treatments are based on sound theory, but lack robust evidence to support their efficacy or safety. Proposed interventions can be broadly classified in terms of 1) anti-coagulation, 2) replacement of natural anti-coagulant factors, 3) improving circulation, and 4) reduction in systemic inflammation.

#### Anti-coagulation

Several case reports describe using systemic anti-coagulation to treat SPG (Tripathy and Rath 2010; Kurup and Simpson 2019). However, the role of this remains uncertain and must be weighed against bleeding risk in the setting of thrombocytopenia (Warkentin and Ning 2021). This is in line with variable society recommendations for anti-coagulation in DIC without bleeding (Wada et al. 2014).

If systemic heparin anti-coagulation is used, monitoring and dosing requirements may be affected by DIC related elevations in partial thromboplastin time and reductions in antithrombin, respectively (Warkentin and Ning 2021).

#### Replacement of anti-coagulant factors

Replacement of anti-coagulant factors has also been proposed as a treatment strategy for SPG. This is largely based on case series suggesting possible benefit of administering protein C concentrate to patients with purpura fulminans from sepsis (Rintala et al. 1998; Schellongowski et al. 2006) or congenital protein C deficiency (Manco-Johnson et al. 2016).

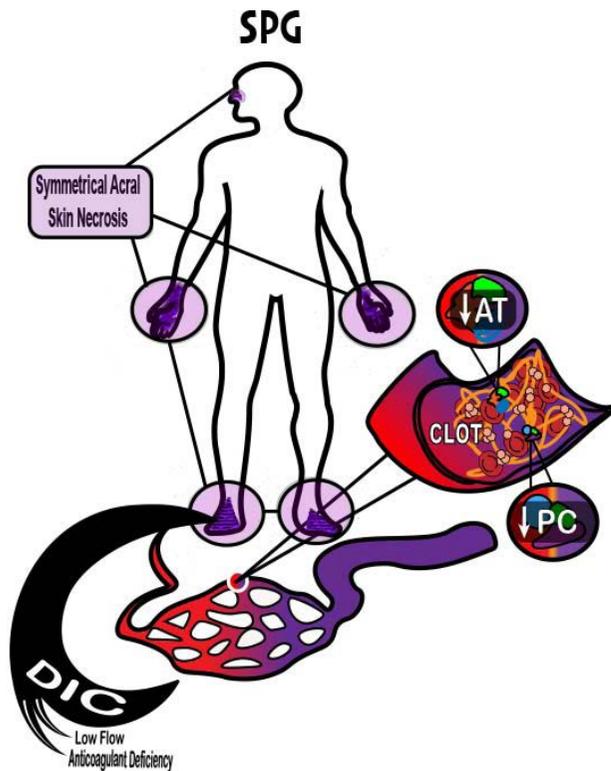
Antithrombin III may also be depleted in patients with SPG and severe sepsis in general. However, antithrombin III repletion has not been shown to reduce mortality or the incidence of new organ dysfunction in patients with severe sepsis, and may increase the risk of bleeding (Warren et al. 2001).

#### Improving circulation

Various methods to improve circulation in the microvascular bed have been described. These include administering systemic or topical vasodilators (e.g., topical nitroglycerin ointment), alpha receptor or sympathetic blockade, volume expansion, and reduction in vasopressor dosing (Willis et al. 2001; Foad et al. 2018; Kurup and Simpson 2019). None of these therapies have proven efficacy. Since in septic shock associated DIC vasopressors are primarily used to combat mediator induced systemic vasodilation, the addition of vasodilator therapy would seem counterintuitive. In addition, several of these interventions have the potential to further worsen haemodynamics for patients already in shock. Colloid volume expansion may also worsen natural anti-coagulant deficiency (Warkentin et al. 2020).

#### Reducing systemic inflammation

Limited case reports also cite haemofiltration (Smith et al. 1997) or haemoabsorption (Uncu Ulu et al. 2021) as helping to reduce or reverse peripheral tissue changes of SPG. These are based on the idea that such methods cause reductions in circulating inflammatory mediators that may be contributing to the syndrome. However, such methods have not shown improvements in mortality or organ dysfunction in a general septic shock population where inflammatory mediators are thought to be a driver of organ dysfunction (Dellinger et al. 2018).



**Figure 1: Symmetrical peripheral gangrene (SPG)**

SPG, driven by disseminated intravascular coagulation (DIC) with potential contribution of low flow state and anticoagulant deficiency (anti-thrombin AT, protein-C PC), presents as mostly symmetrical diffuse acral skin necrosis due to microvascular thrombosis within the terminal arteriole-capillary-venule network.

Ultimately, early identification and aggressive treatment of the underlying cause should remain the management priority in all patients with SPG.

### Future

Research on SPG is limited by the infrequent occurrence of this syndrome and the yet to be defined clinical markers that precede visual ischaemic changes. Cases may also go unreported due to rapidity of progression and when SPG is seen as an unavoidable consequence of multi-organ dysfunction or attributed to vasopressor administration. Research is likely to remain limited to sporadic case reports and small case series that often combine multiple treatment strategies, describe subjective clinical improve-

ment without control comparisons, are subject to publication bias, and occur over prolonged periods of time when clinical

## early identification and aggressive treatment of the underlying cause should remain the management priority in all patients with SPG

practices may have changed.

Registry data collection may offer a solution. A registry would

allow for centralised collection of standardised data to improve understanding of the modifiable risk factors, treatments, and natural course of SPG. More informed prospective studies could then follow. Brunkhorst and Patchev (2014) recognised this in creating The Sepsis-associated Purpura Fulminans International Registry – Europe. While this registry was ultimately closed due to challenges with funding and enrolment, it highlights the need to better understand this important clinical syndrome.

### Conflict of interest

None. ■

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# ICU Management of the Very Old: The Evidence Base Anno 2022

This overview explores the publications concerning the very old ICU patients since 2011 and with a focus on publications from the VIP network on elderly COVID-19 patients.

## Introduction.

In 2017, an international group of intensivists with a particular interest for geriatric intensive care published a statement paper (Flaatten et al. 2017). This paper discussed the status of research in the very old critical ill patients, and what should be the priorities for such research in the coming years (**Table 1**). In this overview we seek to find out where this area of research stands five years later. Are any of the suggested topics better described and have new and important issues emerged?

If we look at the absolute numbers of related clinical research in this group, we see a considerable increase from 2011 until today, in total 2124 publications, but the number of publications has stabilised the last five years around 300 publications per year (**Figure 1**). Hence publications on the very old ICU patients measured as published paper seems still to attain a high interest.

The topics of the publications are more diverse. With the same research string but adding 11 specific topics found either in the title or the abstract, we found a more diverse picture. The topics of interest spread from low interest like severity score (n=20) to high interest like outcome (n=485) (**Figure 2**). One topic occurred and peaked in 2020 and 2021 - COVID-19. We found this despite only covering two years to be overall the third most popular topic over the 5-year period and was by far the highest in 2021 with 142 papers. The topics within the COVID-19 subgroup naturally varied to cover a broad spectrum.

Comparing these findings with **Table 1** reveals that several items found to be important in 2017 are poorly covered. This goes for the more soft items like the study of opinions among elderly

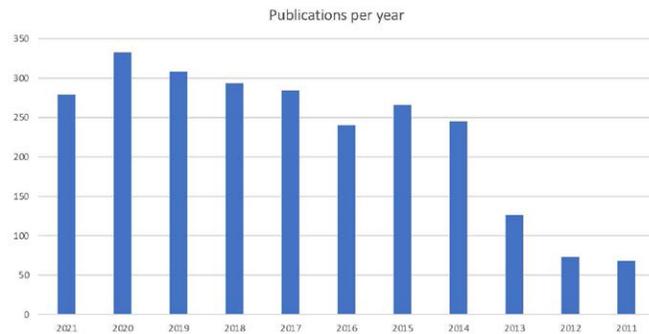
about intensive care, end-of life issues, frailty and sedation. These are all important topics that merit more focus.

## COVID-19 and the Elderly Group of ICU Patients

Old patients have paid a severe tribute to COVID with a disproportionate number needing admission to an intensive care and a large proportion succumbing from the disease. In the beginning of the pandemic, several countries issued recommendations for admission and treatment of the most severe cases. However, little was known about the validity and applicability of such recommendations for the group of old critically ill patients. Since most of the interventional studies excluded old patients or included only a small number, there is doubt for extrapolating data to an old population.

Our VIP network has been active since 2017 and it was straightforward to adapt our CRF to the COVID surges and to motivate centres to participate. As a result, the COVID-19 in very old ICU patients (COVIP) study recruited 3140 patients older than 70 years from 19 March 2020 to 4 February 2021 in more than 150 ICUs across 15 European countries. COVIP is a prospective observational study looking at patient demographics, treatment modalities in ICU and outcomes included health related quality of life up to three months after admission to the ICU.

We confirmed the poor prognosis in this old population with only 39% of the patients surviving up to 90-days (Jung et al. 2021a). Further, we documented that the effect of crude age is less important than the degree of frailty in this group. Outcome in patients above 70 in the presence of frailty was not influenced



**Figure 1. Publications (PubMed) 2011-2021** Search [(Intensive care [title or abstract]) OR (Critical care [title or abstract])] AND (["2011"[Date - Publication] : "2021"[Date - Publication]]) with filters Clinical study and Age 80+

by age. In our quality analysis of outcome within the group of surviving patients 48% (n = 592) experienced ‘severe problems’ or ‘extreme problems’ in at least one of the five domains of the EQ-5D-5L questionnaire (Soliman et al. 2022). ‘Severe problems’ were mentioned by 41% (n = 496), and ‘extreme problems’ on one of the five domains in 30% (n = 371).

Another important issue included in the COVIP study was an analysis of the use of steroids. It was commonly acknowledged that systemic steroids were beneficial for hospitalised patients with COVID-19, but with insufficient documentation to conclude in the very old patient group. In a comparison of patients receiving steroids or not during the first and second surge in Europe, we found an independent association of steroids with increased mortality from 14 days after ICU admission (Jung et al. 2021b).

Early tracheostomy was not found to be of benefit, and we documented huge variability in the use of this procedure across European countries (Polok et al. 2021). We were expecting improved prognosis from severe COVID-19 from the first to the second surge in parallel with optimisation of oxygenation therapy, avoidance of early invasive mechanical ventilation and use of steroids. In fact, we found treatments to differ during the

second wave with less invasive mechanical ventilation and more use of steroids. However, these differences did not translate into better outcomes since the mortality was significantly higher in the second wave compared to the first one (Jung et al. 2021c). This higher mortality could be related to different admission policy and pressure on ICU beds (Jung et al. 2021c) and to the above mentioned use of steroid treatment that was detrimental in old patients.

We have further shown that pressure on ICU beds increased the number of decisions to limit life-sustaining treatment (LST) (Jung et al. 2022). We will claim that information on withholding and withdrawing LST is crucial to interpret survival curves and have been missing in most outcome papers including critical ill elderly patients (Flaatten et al. 2022).

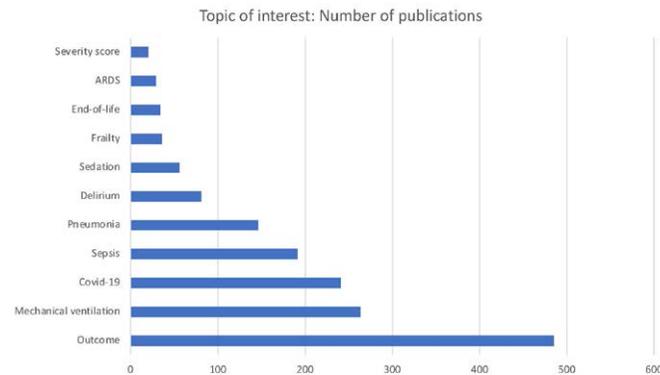
We also took advantage of information from a previous cohort in patients without COVID (VIP2 study) to compare patient characteristics, treatment and outcome between COVID and non-COVID patients older than 80 years admitted for acute respiratory failure (Guidet et al. 2022). This was obtained with matching the propensity score and regression analysis patients from the two cohorts. In this study we found elderly COVIP patients to be less sick (lower SOFA score), less frail (lower CFS) but with more decision to forgo LST and with a higher one-month mortality.

**Conclusions**

This overview reveals an increase in publications about critically ill ICU patients during the last five years. However, the topics of interest for publications follows traditional patterns with

TOPIC	
1	The occurrence of pre- and post-ICU admission frailty and sarcopenia and its effects of functional outcomes
2	What is the opinion of octogenarians towards use of critical care resources in acute, severe vital organ failure? A European survey among 10,000 octogenarians
3	The effects of including a geriatrician in the early assessment and discharge of octogenarians
4	The effects of non-pharmacological interventions to reduce delirium in the ICU
5	The burden of intensive care, a prospective study in caregivers of octogenarians in the ICU
6	Development of a prognostic tool for the very old ICU patients
7	Sepsis in the very old ICU patients: incidence and outcomes
8	Dementia development after ICU discharge of octogenarians
9	Pharmacokinetics of midazolam, propofol and dexmedetomidine
10	End of life trajectories in the very old

**Table 1. Priorities for research in very old critical ill patients**



**Figure 2. Major topics in the studies of the very old intensive care patients from 2017 to 2021**

outcome, sepsis, and mechanical ventilation as the most popular issues. An exception is the large number of publications following the COVID-19 pandemic. Specific age-related issues like frailty, end-of life issues and prognostications (severity score) are less frequently published. We could not find any publications related to the wishes of elderly persons or their family with regards to receiving intensive care.

We hope our VIP network will continue to reveal new knowledge about the very old ICU patients also in the future. More knowledge of this group is crucial if we want to overcome the challenge of the rapid increase in the population of elderly across the globe, and concomitant huge increase in very old ICU patients. We should not stop to treat elderly critical ill patients, but we need to know more about those who will not profit from such intervention for the benefit of the elderly themselves and their families.

### Conflict of interest

None. ■

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# Understanding Carbon Dioxide in Resuscitation

Peri-arrest CO<sub>2</sub> measurement may serve to assess resuscitation efficacy and guide clinical decisions. This paper reviews current knowledge and future research directions for CO<sub>2</sub> measurement and clinical application during CPR.

Sudden cardiac death (SCD) necessitating cardiopulmonary resuscitation (CPR) is a substantial driver of morbidity and mortality. In the United States, approximately 450,000 deaths annually are associated with SCD and CPR, with 400,000 such deaths annually in the European Union (Atwood et al. 2005; Callans 2004). Current guidelines call for the use of carbon dioxide (CO<sub>2</sub>) measurement to guide resuscitative efforts (Link et al. 2015; Soar et al. 2021). This paper reviews current knowledge and directions of future research for measurement and clinical application of CO<sub>2</sub> during CPR.

## Carbon Dioxide During Normal Heart-Lung Function

CO<sub>2</sub> is produced by the mitochondria as a major end product of tissue aerobic respiration. Approximately 70% of CO<sub>2</sub> produced by the mitochondria undergoes a chemical reaction with water catalysed by carbonic anhydrase to form H<sub>2</sub>CO<sub>3</sub>, dissolved in the plasma as its component ions, HCO<sub>3</sub><sup>-</sup> and H<sup>+</sup>. Another 23% of CO<sub>2</sub> produced by the mitochondria binds to haemoglobin to form carbaminohaemoglobin. The remaining 7% is dissolved directly in the plasma. CO<sub>2</sub> is highly soluble in the blood and therefore has a high diffusion coefficient. The dissolved CO<sub>2</sub> is transported to the lung, thus maintaining the mixed venous partial pressure of CO<sub>2</sub> (PmvCO<sub>2</sub>) – as measured in the pulmonary artery – at around 45 mmHg.

In the healthy individual with normal cardiac output and lung physiology, pulmonary ventilation matches pulmonary perfusion. This allows maintenance of the partial pressure of CO<sub>2</sub> in the alveoli (PACO<sub>2</sub>) at approximately 40 mmHg, thus maintaining a CO<sub>2</sub> diffusion gradient between the pulmonary capillaries and alveoli of 5 mmHg. The high diffusion coefficient of CO<sub>2</sub> and efficient alveolar perfusion and diffusion across the alveolar membrane

in the patient with normal heart and lung function result in an arterial partial pressure of CO<sub>2</sub> (PaCO<sub>2</sub>) which approximates the PACO<sub>2</sub> – about 40 mmHg.

As direct measurement of PACO<sub>2</sub> is complex, PACO<sub>2</sub> is usually evaluated indirectly via the end-tidal CO<sub>2</sub> (PetCO<sub>2</sub>). In patients with normal heart and lung function, the PetCO<sub>2</sub> is usually less than 5 mmHg below the PACO<sub>2</sub>. Thus, in the healthy patient, the PetCO<sub>2</sub> is also less than 5 mmHg below the PaCO<sub>2</sub> (Hall 2016).

## Carbon Dioxide During Decreased Cardiac Output and the No-Flow State

Changes in cardiac output result in substantial changes in arterial and venous CO<sub>2</sub> levels, as well as in the alveolar CO<sub>2</sub>.

A decrease in cardiac output decreases blood flow to both peripheral tissues and the lungs. In peripheral tissues, this results in less effective removal of CO<sub>2</sub>, leading to its accumulation in tissues and venous blood. In the lungs, decreased cardiac output decreases pulmonary perfusion pressures, resulting in a ventilation/perfusion (V/Q) mismatch. Thus, CO<sub>2</sub> transport to the lungs is reduced, decreasing CO<sub>2</sub> alveolar concentration (West 1974).

Cardiac arrest results in a no-flow state, with no organ perfusion despite ongoing cellular metabolic activity. These circumstances lead first to cellular hypoxia and subsequently to a transition to anaerobic cellular respiration, resulting in release of cellular by-products of this process to the extracellular space. These include carbon dioxide, lactate and hydrogen ions, thus resulting in a combined respiratory and metabolic acidosis (Ahn et al. 2011; Prause et al. 2001; Takasu et al. 2007). In the no-flow state of cardiac arrest, no changes in CO<sub>2</sub> are initially noted, as the cellular by-products from unperfused tissue remain in-situ (Tucker et al. 1994).

### Carbon Dioxide During the Low Flow State – Initiation of CPR

During CPR, chest compressions, along with positive pressure ventilation, restore organ perfusion and oxygenation to some extent. In ideal conditions, CPR can achieve as much as 25% of normal cardiac output, converting the no-flow state of cardiac arrest to a low-flow state (Bellamy et al. 1984; Johnson and Weil 1991; Link et al. 2015).

The low-flow state that occurs during CPR results in an increase in  $P_{mv}CO_2$  – reflecting poor systemic perfusion. It also leads to a decoupling of the  $P_{et}CO_2$  and the  $P_{a}CO_2$ , with a decrease in the former and an increase in the latter, both due to poor alveolar perfusion (De Backer et al. 2015; Nowak et al. 1987; Steedman and Robertson 1992). These can be expressed in the ventilation – perfusion ratio equation (Idris et al. 1994; West 1974).

Given that CPR effectiveness is directly related to patient survival (Ashoor et al. 2017; Sell et al. 2010) and that the  $CO_2$  changes noted during CPR can be partly reversed with effective CPR (Hartmann et al. 2015; Kim et al. 2016; Niemann et al. 1985; Ornato et al. 1985; Spindelboeck et al. 2016; von Planta et al. 1991; Yakaitis et al. 1975), the measurement of partial pressures of  $CO_2$  at various points in the systemic and pulmonary circulation, as well as measurement of alveolar  $CO_2$  as reflected by  $P_{et}CO_2$ , may be useful for optimising CPR performance, as well as for prognosticating CPR outcomes. Thus, a detailed understanding of  $CO_2$  changes in various compartments is important in assessing and optimising the quality of an ongoing resuscitation.

#### End-tidal $CO_2$

When cardiac output is 5 litres per minute, as in the healthy, sedentary adult, the  $P_{et}CO_2$  ranges between 36–40 mmHg. For every one litre decrease in cardiac output, this value decreases by 4–6 mmHg, assuming constant ventilatory conditions (Askrog 1966; Leigh et al. 1961; Maslow et al. 2001; Shibutani et al. 1994). Under constant and optimal ventilation conditions, the  $P_{et}CO_2$  may therefore serve as an effective surrogate measure of pulmonary blood flow (Isserles and Breen 1991; Jin et al. 2000; Ornato et al. 1990). Consistent with this, animal and human studies have shown a direct correlation between quantitative waveform capnography pressure during resuscitation, cardiac output and

coronary perfusion (Link et al. 2015).

Furthermore, a meta-analysis examining the relationship between  $P_{et}CO_2$  values and resuscitation outcomes demonstrated that patients eventually achieving return of spontaneous circulation (ROSC) had a mean  $P_{et}CO_2$  of  $25.8 \pm 9.8$  mmHg versus a mean  $P_{et}CO_2$  of  $13.1 \pm 8.2$  mmHg in those not achieving ROSC ( $p=0.001$ ). In contrast, administration of sodium bicarbonate, changes in minute ventilation and varying resuscitation protocols were not associated with  $P_{et}CO_2$  changes (Hartmann et al. 2015).

**▲ a detailed understanding of  $CO_2$  changes in various compartments is important in assessing and optimising the quality of an ongoing resuscitation ▲**

Resultantly, American Heart Association and European Resuscitation Council guidelines recommend use of quantitative waveform capnography in all cardiopulmonary resuscitations in order to optimise chest compressions and identify ROSC (Kodali and Urman 2014; Link et al. 2015; Soar et al. 2021).

#### Arterial $CO_2$

Arterial  $CO_2$  has been studied during CPR, immediately after ROSC and at a later stage, after ICU admission.

Multiple studies in both humans and animals have shown that the level of arterial and venous acidosis during resuscitation is determined mainly by partial pressures of  $CO_2$  (Angelos et al. 1992; Grundler et al. 1986; Martin et al. 1985; Nowak et al. 1987; Ornato et al. 1985; Sanders et al. 1988; Weil et al. 1986), with a more profound acidosis in venous versus arterial blood (Gabielli et al. 2005; Martin et al. 1985; Nowak et al. 1987; Ralston et al. 1985).

Profound acidosis during CPR has been associated with resuscitation failure (Niemann et al. 1985; von Planta et al. 1991; Yakaitis et al. 1975), though some earlier studies have noted poor correlations between arterial blood gas values and tissue metabolism (Nowak et

al. 1987; Steedman and Robertson 1992). Nevertheless, a study of 136 out-of-hospital cardiac arrest (OHCA) patients transported to the hospital during cardiac arrest showed less profound acidosis in blood samples obtained during CPR from patients who eventually achieved ROSC versus those who did not ( $pH=6.96$  versus  $6.85$ ;  $P=0.009$ ).  $P_{a}CO_2$  and lactate levels were also lower in the former versus the latter group ( $74.0$  versus  $89.5$  mmHg,  $P=0.009$ ;  $11.6$  versus  $13.6$  mmol/L,  $P=0.044$ , respectively). Thus,  $P_{a}CO_2$  during resuscitation may be a marker of ischaemia severity (Kim et al. 2016). Similarly, less acidosis and lower  $P_{a}CO_2$  at emergency room arrival were noted in patients achieving ROSC in the pre-hospital setting versus those admitted to the emergency room in ongoing resuscitation (Ornato et al. 1985).

Greater arterio-alveolar  $CO_2$  difference ( $AaDCO_2$ ) has also been associated with resuscitation failure. A multicentre study examining  $AaDCO_2$  during or immediately post-CPR in OHCA showed an association between increased  $AaDCO_2$  and failure to achieve sustained ROSC. No patients with an  $AaDCO_2$  greater than 33.5 mmHg during CPR achieved sustained ROSC (Spindelboeck et al. 2016). Similar findings were noted in those with an elevated  $AaDCO_2$  an hour after ROSC (Moon et al. 2007).

In contrast, in post-OHCA patients hospitalised in an ICU, lower levels of  $P_{a}CO_2$  were associated with poorer prognosis (Helmerhorst et al. 2015; Schneider et al. 2013), and, in such patients, a relatively increased  $CO_2$  was associated with improved cerebral function (Roberts et al. 2013; Vaahersalo et al. 2014; Wang et al. 2015), possibly due to the injurious effects of hypocapnia on the brain (Aufderheide and Lurie 2004; Buunk et al. 1996; Coles et al. 2007; Schneider et al. 2013). However, it should be noted that hypercapnia, as well, has been associated with increased mortality in some studies (Roberts et al. 2013).

In conclusion, a higher  $P_{a}CO_2$  during and immediately post-resuscitation appears to be associated with a poorer prognosis; whereas, in the later post-resuscitation period, a lower  $P_{a}CO_2$  is associated with a poorer prognosis.

#### Pulmonary artery/mixed venous $CO_2$

Though pulmonary artery sampling can provide information regarding tissue oxygen consumption in the tissues and cardiac output, use of pulmonary artery catheters has not been associated

with improved patient outcomes and is therefore not recommended in most critically ill patients (Binanay et al. 2005; Harvey et al. 2005; Marik 2013; Rajaram et al. 2013; Richard et al. 2003) and is generally not possible nor recommended during CPR. Thus, PmvCO<sub>2</sub> is generally not available during resuscitation.

In non-cardiac arrest hypoperfusion states (e.g. septic shock), Pv-aCO<sub>2</sub> can assist in evaluation of cardiac output, tissue perfusion and anaerobic metabolic activity (Mallat et al. 2016), and increased values have been associated with increased mortality (Ospina-Tascon et al. 2013; Ospina-Tascon et al. 2015; van Beest et al. 2013).

Small retrospective studies showed substantial differences in PaCO<sub>2</sub> and PmvCO<sub>2</sub> during CPR due to OHCA (Nowak et al. 1987; Steedman and Robertson 1992). Indeed, PmvCO<sub>2</sub> may differ substantially from PaCO<sub>2</sub>, as the latter reflects pulmonary gas exchange and former tissue perfusion, with differences being especially prominent in states of low cardiac output and especially during CPR (Bloom et al. 2014; Byrne et al. 2014; Kelly 2010; Spindelboeck et al. 2016). As PmvCO<sub>2</sub> may more accurately reflect tissue perfusion it may be a better clinical decision tool than PaCO<sub>2</sub> during resuscitation (Adroque et al. 1989; Nowak et al. 1987; Steedman and Robertson 1992; Weil et al. 1986).

Indeed, multiple studies have noted an association between PmvCO<sub>2</sub> levels and resuscitation outcomes (Niemann et al. 1985; von Planta et al. 1991; Yakaitis et al. 1975). Differences between PaCO<sub>2</sub> and PmvCO<sub>2</sub> (Pv-aCO<sub>2</sub>) may also be associated with prognosis, and thus may also serve as a useful tool during and after resuscitation (Ospina-Tascon et al. 2015).

## Measurements of CO<sub>2</sub> during and after resuscitation may serve to assess resuscitation efficacy

### Peripheral venous CO<sub>2</sub>

Peripheral blood sampling is a simple procedure and is the common practice in most departments of emergency medicine (Kelly 2016). As such, PvCO<sub>2</sub> may be more useful clinically as an index of resuscitation efficacy than PmvCO<sub>2</sub>. Several studies have also noted substantial correlation between PmvCO<sub>2</sub> and PvCO<sub>2</sub> (Abdelmoneim et al. 1999; Byrne et al. 2014). However, PvCO<sub>2</sub> may be confounded by the location of sampling as there may be relative ischaemia of the tissue being drained by the sampled

vein. Therefore PvCO<sub>2</sub> may not accurately reflect global tissue perfusion (Abdelmoneim et al. 1999; Bloom et al. 2014; Byrne et al. 2014; Kelly 2010; Toftegaard et al. 2008). Unfortunately few data are available on the association between PvCO<sub>2</sub> and other measures of CO<sub>2</sub> during resuscitation, nor between PvCO<sub>2</sub> and resuscitation outcomes.

### Conclusion

In conclusion, measurements of CO<sub>2</sub> during and after resuscitation, including PetCO<sub>2</sub>, PaCO<sub>2</sub> and PmvCO<sub>2</sub>, may serve to assess resuscitation efficacy. Such measurements may therefore be useful adjuncts in clinical decision-making during resuscitation as they have been shown to correlate overall with patient prognosis. Given that PmvCO<sub>2</sub> is rarely available during resuscitation, research is needed regarding the usefulness of substituting PvCO<sub>2</sub> for PmvCO<sub>2</sub>. More research is needed into effective interventions towards modifying PCO<sub>2</sub> indices during resuscitation and their possible effects on outcomes.

### Conflict of Interest

None. ■

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