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Microbiome in Critical Illness

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Multiple factors can bring the microbiome out of balance in critically ill patients in the intensive care unit. These include antibiotic use, mechanical ventilation, changes in diet and inflammatory responses. The dysbiosis of the microbiome can alter immunological responses and could potentially have an impact on patient outcomes.

There are approximately 100 billion microorganisms in our body. The microbiome has a diverse role to play in the overall maintenance of human health and wellness. However, very little attention is paid to this microbial community. It is important to study and interpret the microbiome in critically ill patients as this can provide significant insight on how it can be manipulated to improve clinical outcomes.

The goal of addressing the microbiome in critically ill patients is to ensure that it does not transform from a health-inducing entity into a disease-promoting agent. Once we recognise the fact that the composition of the microbiome in critically ill patients evolves rapidly and can become significantly altered with the severity of illness, we will understand the importance of ensuring this does not happen. Multiple factors are at play, and that is why there is a need to apply effective therapeutic strategies for manipulating the microbiome in critical illness.

In this issue, our contributors discuss **Microbiome in Critical Illness.** Francesca Forfori and co-authors explore the many roles of gut microbiota and highlight the importance of targeting therapeutical interventions to restore, preserve and enrich its composition. Nathan Klingensmith and Craig Coopersmith discuss how critical illness alters the intestinal microbiome and how manipulating it could offer a potential treatment approach in ICU patients.

Carmina Guitart and co-authors point out the research gap that exists in the field of the lung microbiome and pneumonia development in the paediatric population and discuss how its study could improve nosocomial pneumonia prevention. Yaroslava Longhitano and co-authors explore the microbiome and probiotics and whether they really work and highlight how the microbiota can play a crucial role in preventing ICU associated complications.

María Guadalupe Olvera-Ramos and co-authors talk about *Clostridioides difficile* infection and how it presents a potentially serious complication in critically ill patients in the ICU, and how it must be identified and diagnosed in time to start early management and treatment. Victor Andrés Bolaños-Toscano and co-authors talk about the role of the microbiome and nutritional therapy in critically ill patients with COVID-19 and how it could be important for the prevention and management of critical disease.

In our Matrix section, Pedro Vitale Mendes and co-authors provide an overview of the available evidence on safe intubation practices in critically ill patients in light of new evidence seen during the COVID-19 pandemic. Benjamin Gladwin and Paul Young discuss methylene blue and highlight the need for more evidence to determine whether it could be a useful treatment for patients with vasopressor-refractory vasoplegia.

As always, if you would like to get in touch, please email JLVincent@icu-management.org.

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Microbiome in Sepsis and COVID-19

Bacteria play a fundamental role in human life. Given the many roles of gut microbiota in critical illness and other pathological conditions, it is important to target therapeutical interventions to restore, preserve and enrich its composition.

Introduction

Bacteria play, for better or worse, a fundamental role in human life. As multidrug resistant bacterial infections are increasing in incidence and mortality, we often consider only the negative impact of bacteria on human life and forget the positive side of the "bacterial coin" - the microbiota. Commensal microbes are critical components that contribute to maintain and promote our health in a complex variety of ways. The gut microbiota is now regarded as an organ with roles in shaping our immunity, host defense and intestinal maturation and function (Moron et al. 2019).

Intestinal Epithelium and Commensal Flora

Intestinal mucosa is composed of epithelial cells closely joined together by tight junctions acting as a barrier to restrict substance passage between cells. Epithelial cells are anchored to a thin layer of connective tissue that hosts immune cells underneath which lies the muscolaris mucosae. Other mechanisms of intestinal defense include gut associated lymphatic tissue (GALT) and mesenteric lymph nodes, mucus production and commensal bacteria; together they compose the intestinal barrier (Assimakopoulos et al. 2018).

Microbiota functions are executed mainly through its composition: commensal microorganisms compete with opportunistic pathogens for adhesion sites and nutrients creating a first line of defense against bacterial translocation (Wang et al. 2019). Additionally, commensal microbes shape the mucosal immune system by regulating T cells expansion and differentiation, dendritic and macrophage activation and B cells produced IgA (Yamashiro 2017). T cells dependent IgA are induced in response to specific microbes in the gut and protect against lethal sepsis following intestinal barrier disruption. Their concentrations depend on a rich and diverse microbiota; in particular Proteobacteria resulted in increased IgA concentrations in murine models (Wilmore et al. 2018).

Alterations in gut microbiota composition may promote a selection of bacteria with the genetic capability to metabolise only specific molecule reducing microbiota protective functions (Moron et al. 2019). Microbial fermentation is necessary both for nutrients uptake and immune system communication and modulation to pathogens. Short chain fatty acids (SCFA) act as mediators for epithelial cells in the gut: propionate, acetate and butyrate are energy sources for epithelial cells as well as modulators of cytokine production (Schirmer et al. 2016). An example is Clostridia, a well-represented commensal microbe, that regulates epithelial permeability to food antigens and, in response to butyrate, induces Treg cells differentiation suppressing inflammatory and allergic responses (Yamashiro 2017; Schirmer et al. 2016). In addition, bacteria-derived butyrate affects epithelial oxygen consumption and results in stabilisation of hypoxia-inducible factor (HIF), a transcription factor coordinating barrier protection (Kelly et al. 2015). All these aspects are essential to establish and maintain gut barrier integrity protecting from infection and regulating immune response.

Dysbiosis

Critically Ill Patients: Antibiotics and Sepsis

There are several reasons for microbiota changes: age, gender, diet and drugs as well as host conditions such as critical illness. Variations in compositions lead to a lack of diversity and richness creating a state of dysbiosis or *pathobiome* characterised by an increased pro-inflammatory profile and decreased protective factors as mucus layer, SCFAs, epithelial integrity

and permeability often associated with decreased nutrients absorption (Moron et al. 2019). On a cellular level macrophages of the lamina propria exposed to acute inflammatory stimuli, in the presence of butyrate, inhibit the synthesis of NF-κB induced pro-inflammatory mediator such as TNF-α, IL-6 IL-12 and increase expression of anti-inflammatory mediators and promote epithelial integrity (Parada et al. 2019). However, in the presence of inflammation, cellular mechanisms are reversed and a vicious cycle takes place: decreased SCFAs production, due to altered microbiota, leads to increased pro-inflammatory mediators and decreased anti-inflammatory mediators causing a decreased epithelial barrier integrity and further inflammation (Parada et al. 2019).

A reduction in intestinal barrier integrity is a high-risk factor for bacterial translocation and subsequent sepsis. Gut microbiota is not only a risk factor – when altered – for sepsis but has also been shown to modulate host response to sepsis in animal models (Adelman et al. 2020). It is quite common for patients, particularly in ICUs, to receive antibiotics and subsequently develop dysbiosis especially considering that hospitalisation alone is associated with gut microbiota alterations and consequent severe sepsis (Prescott et al. 2015). In critical care patients, within 48 hours of admission and throughout hospitalisation, microbial ecosystems of the mouth and skin, not just the gut, are flooded with antibacterial resistant pathogens with large personal and interpersonal variations in composition (Lankelma et al. 2017; McDonald et al. 2016). In a study patients that received antibiotics during hospital stay had a higher risk of developing sepsis within 90 days of discharge identifying third and fourth generation cephalosporines, fluoroquinolones, lincosamides, beta lactam/lactamase inhibitors, oral vancomycin and carbapenems as high risk and first or second generation cephalosporins, macrolide, tetracycline, metronidazole as low risk for developing sepsis after discharge (Baggs et al. 2018). Risk factors for developing sepsis were not limited to the type of antibiotic administered but also included the overall number of antibiotic classes used and therapy duration (Baggs et al. 2018). Other drugs commonly used in ICUs such as proton pump inhibitors and opioids contribute to microbiome changes in different body sites creating, shortly after ICU admission, a loss in specificity and a subsequent constant decrease in colonisation resistance (Haak et al. 2017; Yeh et al. 2016).

> **“the gut microbiota is now regarded as an organ with roles in shaping our immunity, host defense and intestinal maturation and function”**

Mechanisms responsible for “a leaky gut” can both be a cause and a result of sepsis and are not only represented by dysbiosis but extend to incorporate hypoperfusion with tissue inflammation, increased permeability and bacterial translocation (Adelman et al. 2020). Microbial community structures, through opportunism, initiate and drive gut permeability; stress-induced intestinal permeability defects depend on microbial phenotype, though ligands and pathways involved in sepsis remain unknown (Alverdy et al. 2017). Additionally, altered gut flora has been proposed as a potential prognostic marker in patients with SIRS: obligate anaerobes decrease and increase in pathogenic microbes in the gut are associated with septic complications and mortality in SIRS (Shimizu et al. 2011).

Dysbiosis and COVID-19

Commensal microbes are also found in the lungs, but their growth is regulated by mucociliary clearance, surfactants, and lack of nutrients however, in case of injury (i.e., large tidal volumes during mechanical ventilation, ARDS or pneumonia) inflammation causes protein rich fluid deposits in the alveoli providing a new energy source in addition to steep oxygen gradients favouring bacterial growth (Dickson 2016). For instance, catecholamines produced in response to activated innate immunity cells, combined with inflammatory cytokines, alter bacterial composition to favour *P. aeruginosa*, *S. pneumoniae* and *S. aureus* growth in the lungs (Dickson 2016).

Upper respiratory tract infections not only change lung microbiome but also impact gut microbiota. A cross sectional study on the effects of viral respiratory diseases on gut microbiome alterations showed that patients with H1N1 influenza and COVID-19, when compared to healthy controls, have decreased community richness and microbial diversity (Gu et al. 2020). Viral infections weaken the gut-lung axis by decreasing lung immunity, in terms of cell number and function, while simultaneously promoting gut dysbiosis (Sencio et al. 2021). When combined, these factors decrease SCFAs, TLR stimulation, barrier protection and antimicrobial peptides (AMPs) and increase inflammatory cytokines leading to uncontrolled pulmonary and enteric bacterial superinfection (Sencio et al. 2021).

However, this may not be the case when healthy microbiota is present and able to control SARS-CoV-2 lung infection by stimulating production of a large number of immune cells (Rajput et al. 2021). There is evidence suggesting a relationship, either in the form of ‘gut lung axis’ – where the gut microbiota is affecting the lungs – or in the form of immunomodulatory signals released by the gut microbiome (Rajput et al. 2021). After viral infection, immune cells in the airway, such as dendritic cells and macrophages, secrete cytokines to defend against pathogens (Mahooti et al. 2020). In probiotic-receiving subjects, high cytokine concentrations lead to immune cells migration from the gut to the lung

space through the gut–lung axis, resulting in rapid recruitment of activated T and B cells promoting upregulation of virus-specific immunoglobulins and cytokines; on the contrary, in the absence of activated immune cells, respiratory virus can cause severe lung damage due to lack of immediate immune response (Mahooti et al. 2020).

Dysbiosis was found to persist in COVID-19 patients from hospitalisation to recovery, and is characterised by decreased SCFAs producing commensals (*Eubacterium, Faecalibacterium, Roseburia*), and increased opportunistic pathogens (*Clostridium hathewayi, Actinomyces viscosus, Bacteroides nordii*) (Yeoh et al. 2021; Zuo et al. 2020). Disease severity and immune system dysfunction depend on dysbiosis as immunomodulatory commensals depletion contributes to severe forms of COVID-19 (Yeoh et al. 2021; Zuo et al. 2020). In fact, a possible explanation for COVID-19 related multi organ dysfunction is gut barrier disruption – favoured by old age, hypertension, diabetes and obesity – which causes SARS-CoV-2 to seep out of the gut and spread throughout the body causing severe inflammation due to a hyper immune response (Kim 2021). This exaggerated response is supported by altered tight junctions, apoptosis and pro-inflammatory signalling causing endogenous endotoxins passage to the circulatory system boosting pro-inflammatory activity via NF-κB pathways and Spike protein bound to LPS (Belančić 2020).

Therapeutic Approaches

Probiotics and Sepsis

Immune actions of probiotics mainly consist of inflammation response and modulation to pathological stimuli. Immune stimulation causes macrophages, dendritic cells, neutrophils and NK cells to increase their activity, as well as cytokines promoted Th1/Th17 polarisation in the gut mucosa (de Oliveira et al. 2021). On the other hand, anti-inflammatory functions are performed by certain probiotic strains, through dendritic cell modulation, and are capable of inducing regulatory T cells and IL-10, TGF-β production thus enhancing IgA secretion and gut barrier function (de Oliveira et al. 2021). A systematic review on the use of probiotics in critical illness found that the use of probiotics resulted in significant reduction in infection rates particularly in ventilation acquired pneumonia, and further subgroup analysis found the greatest improvement, in terms of infection outcomes, to be in critically ill patients (Manzanares et al. 2016). This may be because microbial fermentation products of a healthy gut – for example, bifidobacterial producing acetate – improve epithelial intestinal defense protecting against lethal infection (Fukuda et al. 2011). Moreover, in critical patients with end organ damage caused by sepsis, acetate was also found to ameliorate sepsis-induced acute kidney injury (AKI) by inhibiting NADPH oxidase signalling and restoring oxidative balance in T cells (Al-Harbi et al. 2018).

Probiotics and Respiratory Tract Infections

As mentioned before, microbiota plays a large role in protecting and modulating responses to respiratory pathogens. A possible therapeutic strategy may include oral administration of lactobacillus rhamnosus which has been shown to control immune response after viral infection by mobilising Th1 cells from the intestine to the respiratory tract to produce IFNγ and recruit local respiratory immune cells (Villena et al 2012). Its role is also supported by a RCT in which lactobacillus rhamnosus reduced rhinovirus infection rates in preterm infants (Luoto et al 2014). Although probiotics are better than placebo in reducing the number of acute episodes of upper respiratory tract infections evidence quality is low (Hao et al. 2015). At this time, unfortunately, there are no systematic reviews examining the effects of probiotics on COVID-19 patients, however, evidence collected by systematic reviews on critically ill patients, particularly those on mechanical ventilation, concluded that probiotics improve outcomes even if evidence was low in quality (Rozga et al 2021). Therefore, due to the lack of direct evidence in COVID-19 patients, the best resources to guide therapeutical approaches using probiotics come from comparable studies (Rozga et al 2021).

Conclusion

The concept of dysbiosis is specific to each person and it can be interpreted as a relative change in composition when compared to others in the community: loss of diversity, increased pathogenic and decreased beneficial bacteria (Bassetti et al 2020). Given the many roles of gut microbiota in critical illness (Dickson 2016), as well as other pathological conditions, we should target therapeutical interventions to restore, preserve and enrich its composition.

Conflict of Interest

None. ■

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Mitigating the Risk of Harm During the Transition From Controlled to Assisted Mechanical Ventilation

Monitoring the strength of the patient's breathing effort, titrating the sedation, and selecting the correct mode of ventilation is vital when transitioning from controlled to assisted ventilation.

Assessing The Transition From Fully Controlled to Assisted Ventilation

One of the key issues with mechanical ventilation is the transition from fully controlled to assisted mechanical ventilation, which must be achieved as soon as possible to improve the patient's outcomes. This transition must be accomplished in a manner that avoids worsening the patient's respiratory problems, thereby forcing the ICU team to resume fully controlled ventilation.

To distinguish between breaths with no active respiratory muscles (fully controlled ventilation) and breaths with active muscles (assisted ventilation), we need to monitor the patient's breathing effort.

Dr Irene Telias is one of the medical world's foremost experts on respiratory physiology, more specifically respiratory effort during mechanical ventilation in intensive care (ICU) and its influence on ventilation-induced lung injury and diaphragmatic dysfunction.

When assessing the transition from fully controlled to assisted mechanical ventilation, Irene always uses monitoring techniques to titrate mechanical ventilation and sedation to avoid potentially injurious effort. "An intermediate range of inspiratory effort is associated with better outcomes for patients and might be a reasonable target for most patients," Irene says.

Evaluating the Transition's Challenges

The transition from full sedation and controlled ventilation to spontaneous breathing is always very challenging, she says. "Why? Firstly, the patient is only partially conscious of what's happening, and usually experiencing sharp discomfort with a tube down their throat," Irene says.

Secondly, under sedation there are many stimuli telling the brain to breathe strongly. Patients are often still very sick. For example, systemic inflammation due to an unresolved or new infection is a strong direct stimulus for the patient to breathe.

"Because the patient is breathing and the ventilator is providing support at the same time during this critical period, matching the timing of the patient's own breathing pattern and that of the ventilator´s insufflation and exhalation is critical. If there is a lack of synchrony between those events, patient-ventilator dyssynchrony occurs, a phenomenon that is associated with increased patient mortality (Kyo et al. 2021)," Irene says.

Irene continues: "This patient-ventilator dyssynchrony can be very uncomfortable for the patient, and potentially injurious for the lungs and the patient's main respiratory muscle, the diaphragm."

How can clinicians adapt or tailor mechanical ventilation to avoid harm to the patient in the process of transitioning from fully controlled ventilation to assisted ventilation?

Personalising Mechanical Ventilation and Sedation

According to Irene, studies have shown that patients with an intermediate range of inspiratory efforts – not excessive, and not too shallow – have better ICU outcomes, including lower mortality rates. However, one size does not fit all and personalising the treatment is necessary.

"There are several important ways to personalise patient care so that the chances of an intermediate range of inspiratory efforts are increased," Irene says. "First, the mode of mechanical ventilation we use is important, as is how much support the ventilator offers, and how we adapt the breathing pattern provided by the ventilator according to the patient's breathing pattern so that the patient is breathing in synchrony with the ventilator while the ventilator is providing the support. That's one element of this lung- and diaphragm-protective ventilation strategy - managing the ventilator setting."

The second part of the patient personalisation process is the use of sedation to modulate the respiratory drive. The sedative agents that are most often used to do this are propofol and benzodiazepines.

"However, doctors have to very carefully titrate these drugs," Irene says. "If the patient is on very high doses of sedative agents for a long time, they might suffer from respiratory muscle and peripheral muscle atrophy because they haven't moved for several days."

Factors other than management of the ventilator settings and sedation are also important, such as understanding and treating the reason for excessively high or low breathing efforts. For example, patients are often uncomfortable or anxious and these factors must be addressed.

Monitoring Techniques That Help Facilitate the Transition

How do we monitor the strength of the patient´s breathing effort and, therefore, target an intermediate range of effort facilitating the transition from fully controlled to assisted ventilation? There are several monitoring techniques that can help the transition.

Oesophageal pressure (Pes) for example, is the gold standard of measuring a patient's inspiratory effort and the risk of harm (Pham et al. 2020). Pes measures the change in intrathoracic pressure generated by the respiratory muscles.

According to Irene, there are two other techniques that are simpler and less invasive because neither of the two, the Pocc and the P0.1, require the insertion of a catheter (Telias et al. 2020).

"These are measured with the ventilator, so we call them non-invasive monitoring techniques," Irene says. "They both rely on the same principle; that we generate what we call an end-expiratory hold. When the patient breathes in against a closed airway, any change in airway pressure is proportional to the change in intrathoracic pressure. These techniques are used to measure the patient's respiratory drive to check if the efforts are too high or too low. These two techniques, Pocc and P0.1, are screening techniques that can be used in all ventilated patients."

Another available technique to monitor patient´s respiratory drive and effort is the electrical activity of the diaphragm (Edi). Like Pes, it requires the insertion of a naso- or orogastric catheter. However, Edi catheters always contain a feeding tube as well, which is needed in almost all situations. An Edi catheter is connected to, and the signal is processed by the ventilator. The Edi signal is directly displayed on the ventilator´s screen, providing information about the magnitude and timing of the patient´s drive and breathing effort. It therefore allows clinicians to modify ventilator settings and drugs to ensure that the patient exerts a safe amount of effort and there is a better patient-ventilatory synchrony.

Modes of Ventilation of Potential Benefit During Transition

Selecting the best ventilator mode and settings for each patient is one of the most important interventions to achieve a lung- and diaphragm-protective ventilator strategy. NAVA is an important tool for many patients. It is a proportional ventilatory mode that uses the Edi to offer ventilatory assistance in proportion to patient drive and effort.

"The good thing about this mode is that because it is proportionate to the patient's drive and effort, it is very unlikely that the ventilator will provide too much support - what we call over-assistance," Irene says.

Other modes, such as pressure support (PS), can over-assist or under-assist the patient. PS is the mode that is most frequently used during the transition from fully controlled to assisted mechanical ventilation.

"PS provides a fixed amount of support for each breathing effort," Irene says. "If the ventilator provides a fixed amount of support for each breathing effort, the patient's breathing effort is likely to decrease when the ventilator provides support. If the support is too much for the patient, they will take a small inhalation that initiates the breath, but then during the whole breath, the patient is passive. When the patient falls asleep in this situation, sometimes they even become apnoeic, which means they don't take a breath for several seconds. The patient may wake up gasping for breath, something that obviously disrupts sleep. That's called apnoea during PS. Sleep disruption is a major problem in ICU. You can imagine it's very difficult to have a proper restorative sleep in ICU. We think that sleep has a very important physiological function, specifically for healing, so we prefer to use methods that will encourage better sleep quality and quantity."

According to Irene, proportional modes, such as NAVA and proportional assisted ventilation, have the potential to avoid this phenomenon and might result in a better sleep quality and quantity in ICU.

"The amount of support is proportional to the patient's efforts," Irene says, "so this ensures the patient continues to exert some degree of breathing effort, and they rarely become apnoeic, decreasing the risk of sleep disruption, and diaphragmatic atrophy (Delisle et al. 2013). The main potential benefits of this mode are that you improve patient ventilator synchrony, avoid over-assistance and respiratory muscle atrophy, and endure less sleep disruption. Most patients might benefit from NAVA, except those who have excessively high respiratory drive and effort due to an abnormal brain function and will not respond to adjustments in the ventilator settings or sedation. In these circumstances, proportional modes, including NAVA, sometimes provide excessive assistance which might exacerbate patient lung injury."

In conclusion, despite the transition between fully controlled to assisted mechanical ventilation being extremely challenging, current available monitoring techniques, together with the safe implementation of proportional modes of ventilation, can help achieve an effective and personalised lung- and diaphragm-protective ventilation which will ultimately move towards patient liberation.

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The Intestinal Microbiome in Critical Illness

Critical illness alters the intestinal microbiome, resulting in a loss of microbial diversity and induction of a pathobiome. Manipulating the intestinal microbiome offers a potential treatment approach in ICU patients.

The intestinal microbiome is comprised of diverse, robust microbial communities within the intestine, modified by the host's interaction with the environment (Amon and Sanderson 2017). Increasingly, research links alterations in the microbiome to maintenance of health and pathophysiology of disease. Critical illness is no exception. Given the lack of therapies aimed at the host response in critical illness combined with pathologic alterations in the microbiome seen in the ICU, treatment directly targeting the intestinal microbiome serves as a potential avenue for therapy in critically ill patients.

The Intestinal Microbiome in Health

The intestinal microbiome is composed of all microbes (bacteria, fungi, and viruses) that occupy the intestinal lumen. The number of bacteria present in the gut lumen equals the number of the cells in the human body, yet with nearly 100 times the number of genes (Li et al. 2014; Sender et al. 2016). Starting even before birth, the microbiome begins to be established (Younge et al. 2019) and is shaped by every host interaction with its environment. As the host develops, a baseline proportion and diversity of bacteria takes hold for each human, predominantly in the phylogenic families of *Bacteroidetes* and *Firmicutes* (Dethlefsen et al. 2006). The vast majority of these bacteria act as commensal organisms aiding the host in nutrient absorption and vitamin production (Eckburg et al. 2005; Qin et al. 2010), while assisting in enterocyte maintenance and immune function and diversity (Morrison and Preston 2016; Zegarra-Ruiz et al. 2021). Bacterial products can have profound influence on human health. A group of metabolites of particular interest are short chain fatty acids (SCFA) (Pickard et al. 2017). These bacterial fermentation products are found within the lumen of the intestinal tract and are used for signalling between the microbiota and the host and can serve as an energy source for intestinal epithelial cells (Corrêa-Oliveira et al. 2016).

The determinants of microbiome health relate in large part to its ability to maintain microbial diversity and adapt to the host environment in a manner that is mutually beneficial. There is a rapid expansion of microbial diversity in early age (Dominguez-Bello et al. 2019) followed by relative stability for the majority of life (O'Toole and Jeffery 2015). Bacterial diversity within a host (α diversity) and the uniqueness of microbial populations is associated with normal gut function and health. As a person ages, loss of Bacteroides populations, high diversity and uniqueness, and maintenance of rare bacterial taxa are all associated with improved all-cause mortality (Wilmanski et al. 2021).

The Intestinal Microbiome in Critical Illness

Disruption of gut microbial diversity and homeostasis is associated with disease. The intestinal microbiome has been shown to be associated with multiple chronic disease states. Diabetes, atherosclerosis, inflammatory bowel disease, and even cancer treatment are all influenced by the microbiome (Halfvarson et al. 2017; Sivan et al. 2015; Vrieze et al. 2012; Wang et al. 2015).

Notably, critical illness is associated with acute changes in the microbiome (McDonald D et al. 2016). The symbiotic relationship between the host and gut microbiome are altered by both the disease state itself as well as secondarily by treatments instituted in the ICU for other reasons. This results in the commensal microbiome changing in character to one that is detrimental to the host, globally termed the pathobiome (Alverdy and Krezalek 2017). The pathobiome is characterised by a lack of overall microbial diversity and loss of predominant commensal organisms to those in pathogenic phyla *Proteobacteria* (Miniet et al. 2021). The collapse of the normal microbial communities in the setting of critical illness starts nearly immediately (Krezalek et al. 2016). The robust diversity is quickly replaced by ultra-low diversity pathogens that can sense host stress and upregulate their virulence factors (Babrowski et al. 2012). Transition to this low diversity population of intestinal *Proteobacteria* (*Escherichia coli, Pseudomonas spp., Klebsiella spp.*) is associated with higher morbidity and mortality in ICU patients (Freedberg et al. 2018). The mechanisms of these changes are multifactorial. Critical illness, in and of itself, induces rapid

changes to the microbiome as seen in both trauma patients and in pre-clinical models. Many components of ICU management unfortunately also indirectly adversely impact the microbiome. A partial list of treatments initiated in critical illness that have been shown to alter the microbiome include antibiotics, vasopressors (which alter splanchnic blood flow), proton pump inhibitors, opiates and route of/absence of nutrition.

As bacterial populations are lost, their metabolites are also lost. Stool SCFA levels are decreased in critically ill patients (Valdés-Duque et al. 2020). The loss of SCFA-producing resident microbes can potentially have multiple effects during sepsis. Loss of SCFA may contribute to changes in sepsis-induced intestinal hyperpermeability which has been associated with increased sepsis mortality (Feng et al. 2018; Yoseph et al. 2016). Microbiota-derived SCFA also signal with the local immune system to regulate mucosal inflammation through regulatory T-cells providing a protective effect during infection (Bhaskaran et al. 2018). Additionally, in a mouse pneumonia model, antibiotic depletion of the intestinal microbiome leads to higher mortality to *Klebsiella pneumoniae* pneumonia which is reversed when animals are given oral SCFA supplementation (Wu et al. 2020).

Though critical illness induces changes in the microbiome, the baseline composition of the gut microbiome also plays a role in how a host responds to infection. The intestinal microbiome shapes the composition of the mucosal immune system through constant interface and sampling along the luminal border. This interaction facilitates immunological tolerance to commensal organisms, while also preparing the immune system for pathological invasion (Round and Mazmanian 2009). The presence of specific bacteria can directly alter immune function in response to critical illness and potentially alter ICU mortality. We recently demonstrated this in a mouse model of polymicrobial intra-abdominal sepsis, using genetically identical animals from different vendors. Despite having the same genetic composition, mice with different microbiomes had a marked difference in survival from sepsis, with improved mortality in those with a more complex baseline microbiome. This was associated with increased effector and central memory T cells in the animals with a more diverse microbiome. When the animals were co-housed for three weeks, all animals developed a similar microbiome (as mice eat each other's stool), and immunological and mortality differences disappeared (Fay et al. 2019).

> **"the symbiotic relationship between the host and gut microbiome are altered by both the disease state itself and by treatments instituted in the ICU"**

Part of the feedback loop for intestinal microbiome tolerance and establishment of commensal colonisation is through mucosal immunoglobulins, specifically IgA (Macpherson et al. 2018). Intestinal microbiota induce production of IgA and this immunoglobulin is able to bind to pathogens and prevent their binding to mucosal surfaces to prevent disease, as well as allowing for commensal organism proliferation. This IgA induction is specific for bacteria present in the intestinal lumen and can have protective effects in critical illness. Mice exposed to bacteria in the phylum *Proteobacteria*, produce more IgA that is specific to these pathogenic bacteria and are protected against intra-abdominal sepsis (Wilmore et al. 2018).

Manipulation of the Microbiome

Due to its putative role in mediating mortality in critical illness, the microbiome has recently been proposed as a potential target for treatment in the ICU attempting to shift gut dysbiosis back to normal homeostasis. A number of different approaches have been investigated toward manipulating the microbiome including a) probiotics, b) prebiotics, c) fecal microbial transplant (FMT), d) enteral nutrition and e) selective decontamination of the digestive tract (SDD). Probiotics are a group of commensal bacteria that may be beneficial for the gut and systemic health in various disease states including critical illness. Multiple studies have been performed evaluating the impact of probiotics in the ICU. A meta-analysis of 30 studies with nearly 3000 patients involving probiotics and synbiotics in adult critically ill patients demonstrated a decrease in ventilator associated pneumonia seen with probiotics without changes in mortality, length of stay or diarrhoea (Manzanares et al.2016). The benefit seemed specific to probiotics as opposed to synbiotics (a combination of probiotics and prebiotics), although the data for synbiotics was limited. Unfortunately, there was significant heterogeneity in these studies, as there is not a standard protocol between studies for the type of bacteria administered, when they are given, or the dose. In addition, there may be such baseline inter-patient endogenous microbiome variability that it would be hard to know de novo which probiotic regimen may provide a benefit and if that benefit would last (Zmora et al. 2018). Furthermore, patients in the ICU, especially those with sepsis, are given antibiotics which would simultaneously eliminate infecting bacteria as well as the probiotics, limiting their ability to engraft and establish homeostatis. Together, these concerns as well as potential publication bias of studies examining probiotics and critical illness limit conclusions that can be drawn. It is also worth noting the theoretical concern of seeding the recipient patient with any bacteria delivered to the patient. A recent publication used genomic and epidemiologic evidence to demonstrate that enterally administered *Lactobacil-*

lus rhamnosus GG given as a probiotic capsule ended up causing bacteraemia in six ICU patients (Yelin et al. 2019). These concerning findings should give clinicians pause before giving critically ill patients probiotics without additional high quality data supporting their usage.

An alternative strategy involves prebiotics. Whereas probiotics contain live bacteria, prebiotics are nondigestible products intended to promote the growth of beneficial microbes in the intestine. The most common prebiotic that has been studied is dietary fibre. Fibre provides a fuel source for SCFA-producing bacteria and acts to promote improved barrier function. Animals given fibre in their diet show less mucus layer defects after having eaten a high fat, high carbohydrate diet (Schroeder et al. 2018). In septic animal models, mice given pre-treatment of a high fibre diet have improved survival compared to a low or normal fibre diet, and this is associated with a decrease in overall inflammation (Morowitz et al. 2017). Furthermore, a small pilot study of 20 ICU patients receiving broad-spectrum antibiotics randomised to receive enteral fibre or no fibre showed a trend toward increased SCFA-producing bacteria and higher SCFA levels (Freedberg et al. 2020). Together, this demonstrates a potential benefit of fibre (or other prebiotics) in critically ill patients, but this approach should be considered experimental until large well-done studies are performed with patient-centric outcomes.

An alternative approach to giving select bacterial species or promoting microbial growth is to transplant an entire intact gut microbiome. Fecal Microbiota Transplantation (FMT) is a technique in which the contents of healthy donor stool (either in liquid or capsule form) are transplanted into the intestine of a host with a diseased microbiome with the goal of restoring microbial diversity which in turn should restore host metabolism, boost host immunity, and prevent re-colonisation with pathogenic bacteria. The most common use for FMT is in refractory *Clostridium difficile* infection (CDI). The mainstay treatment of initial CDI is still oral antibiotics. However, up to 25% of initial CDI will have a second episode despite treatment, and antibiotic therapy is often ineffective in recurrent CDI (Cornely et al. 2012). Multiple infectious disease societies recommend FMT for multiple recurrent or refractory CDI (Debast et al. 2014; McDonald LC et al. 2018) based upon studies showing complete resolution of CDI between 77% and 100% after FMT. With the success of FMT in CDI, this has led to increased interest in giving FMT in the ICU. The literature is limited only to case reports of ICU patients with refractory sepsis and large volume diarrhoea, but there has been some success in this setting (McClave et al. 2018). The mechanisms underlying potential FMT effectiveness in the ICU are multifactorial and include restoration of SCFA-producing bacteria that stimulate immunity to enhance pathogen clearance. In an animal model of bacterial peritonitis, mice were rescued from sepsis after FMT in an Interferon regulatory factor 3-dependent manner (Kim et al. 2020). These findings were linked to an increase in the butyrate-producing phylum *Bacteroidetes*. There are multiple barriers to using FMT in the ICU that must be overcome however before the treatment can move from its current status as experimental only. First, a large percentage of ICU patients are on antimicrobial therapy, and any antibiotic administration would alter any transplanted bacteria which narrows the population who might benefit from FMT. Additionally, there is no uniform agreed upon standard as related to stool donor, dose or route of administration. Furthermore, there have been two case reports of multidrug resistant organisms making their way into the bloodstream of non-ICU patients receiving FMT, one of which was fatal (DeFilipp et al. 2019). Considering that most ICU patients are immunosuppressed by virtue of their critical illness and the increased risk of bacteraemia in the ICU, this emphasises the need for well-performed studies of FMT in the ICU.

> **despite the numerous obstacles, increasing research suggests that the gut microbiome may be a promising therapeutic target in the ICU**

Nutrition also has the potential to alter the microbiome. In healthy hosts, nutrition directly alters microbial composition and plays a significant role towards maintaining health. In the ICU, the enteral route is the preferred method of administering nutrition for multifactorial reasons including the potential for improved health within the gut microbiome and decreased bacterial translocation (Oami et al. 2019). Unfortunately, not all patients are able to utilise their gut for nutrient absorption secondary to disease states or intestinal procedures, necessitating the use of parenteral nutrition if the inability to feed the gut is expected to occur for an extended period of days. Parenteral nutrition leads to an intestinal proinflammatory state resulting in epithelial barrier dysfunction through tight junction protein downregulation and promoting *Proteobacteria* growth (Ralls et al. 2016).

While probiotics, prebiotics, FMT and nutrition have some commonality in the sense that the goal is to augment beneficial microbial flora, SDD takes the opposite approach by attempting to decrease harmful or pathogenic bacteria in the gut microbiome. SDD has been studied extensively and improves mortality in multiple randomised trials in environments with low anti-microbial resistance (Price et al. 2014). In contrast, a randomised controlled trial of over 8000 patients on mechanical ventilation in ICUs with moderate to high levels of antibiotic resistance failed to show any benefit in a

modified version of SDD (without a four day course of intravenous antibiotics), selective oropharyngeal decontamination, or chlorhexidine mouthwash (Wittekamp et al. 2018). A recent meta-analysis of 41 trials and over 11,000 patients concluded that treatment with topical prophylaxis only likely reduced respiratory infections but not mortality for those on mechanical ventilation whereas combined topical and systemic prophylaxis reduced both (Minozzi et al. 2021). Although data generally do not support SDD leading to increased antimicrobial resistance, concerns continue that intentionally altering microbial flora could potentially lead to microbial resistance, which has limited SDD use in most countries.

Conclusions

The idea of targeting the gut microbiome for therapeutic gain is no longer new. Despite the conceptual appeal of this approach, there are numerous barriers that need to be overcome to translate this into an approach which is commonly used at the bedside. These include identifying the optimal approach(es) in the correct patient population with the correct dose and route of administration of agents intended to alter the microbiome. This is further complicated by the common usage of antibiotics and other agents that directly alter the microbiome in critically ill patients, and the fact that a worsened gut barrier function in an immunosuppressed patient population leads to unique risks to microbiome manipulation in the ICU. Despite the numerous obstacles, increasing research suggests that the gut microbiome may be a promising therapeutic target in the ICU, and the future of microbiome research is promising.

Conflicts of Interest and Source of Funding

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Management of Acute Arrhythmias in Patients With Cardiac Dysfunction - Update of ESC Guidelines

In 2020, the ultra-short acting beta-blocker landiolol was first included in the ESC guidelines with a class I recommendation. The recommendations were based on study results demonstrating the rapid response, efficacy, and safety of this drug. At a recent symposium, during 2021 Heart Failure World Congress, cardiologists were invited to present their daily clinical practice of landiolol use.

The discovery of propranolol in 1964 by British pharmacologist Sir James Whyte Black laid the foundation for one of the pillars of cardiovascular therapy. "It would be easy to assume that since then, there has been nothing new to report in this family of drugs – but every now and then some offspring manages to surprise us, such as landiolol", says Prof Robert Hatala, from the National Cardiovascular Institute and Slovak Medical University, Bratislava (Slovakia).

Highly Selective, Ultra-Short Acting, Good Safety Profile

Prof Helmut Pürerfellner MD, Head of the Rhythmology Department at the Hospital Ordensklinikum Elisabethinen in Linz, Upper Austria, presented the unique features of landiolol: Landiolol is an innovative, highly selective β1-adrenergic receptor antagonist with the highest receptor selectivity of all beta-blockers, namely β1:β2 = 255:1; a short half-life of four minutes and a low volume of distribution. "A lower dose is therefore required to achieve a given plasma concentration, which in turn implies less distribution to tissues and fewer possible toxicities", the cardiologist explains. The onset of action is rapid with less than one minute, the duration of action is short with 10 to 15 minutes, resulting in a good controllability. Steady state is reached after 15 minutes under continuous i.v. infusion, or after two to five minutes after infusion of a loading dose (also possible as bolus) (Nasrollahi-Shirazi et al. 2016; DiPiro 2010; Alpert et al. 2014; Chow et al. 1996; Metoprolol SmPC).

Why is cardioselectivity important? For patients in critical condition "it is important to reduce the heart rate to minimise oxygen consumption while at the same time maintaining cardiac contractility", Prof Pürerfellner elaborates. As innovative beta-blocker molecule, landiolol has limited effect on Ca^{2+} and Na^{+} currents during action potential in cardiomyocytes, "allowing for the stability of stroke volume and blood pressure". Vasculature and bronchi need to be dilated so that the patient receives the maximum amount of oxygen. "All of this is possible with landiolol, thanks to the selective blockade of cardiac β1-receptors." Landiolol is therefore especially beneficial for patients with renal failure (rapid inactivation, no dose adjustment), liver impairment (CYP450 not involved in metabolisation), and lung comorbidities (prevention of bronchoconstriction) (Balik et al. 2018; SmPC Rapibloc). Other advantages include the missing potential for tolerance and the lack of a rebound phenomenon when using landiolol (Nasrollahi-Shirazi et al. 2016).

Effective Heart Rate Reduction Without Decreases of Blood Pressure

What do the clinical data say?

- Safety profile: A prospective observational study on approximately 1100 patients with cardiac dysfunction showed a low rate of adverse drug reactions under landiolol (5.6%) and a rate of <1% of severe bradycardia or hypotension. A good effect on heart rate (defined as ≥20% reduction) was seen in close to 80% of patients; in 888 patients 33.7% achieved cardioversion to sinus rhythm, the median time to cardioversion was 14 hours (Yamashita et al. 2019).
- Similar effects were observed in the J-Land study investigating landiolol vs. digoxin; the primary endpoints were defined as heart rate (HR) of <110 bpm and a >20% decrease of HR after two hours (Nagai et al. 2013). In this respect, landiolol was more effective (48.0% vs. 13.9%), and the safety profile was neutral.
- In patients with acute decompensated heart failure (ADHF), landiolol resulted in a decrease of HR from 141 beats/min (bpm) to 99 after six hours, without a significant decrease of systolic blood pressure vs. baseline (Kakihana et al. 2020).
- In patients with sepsis and persistent tachyarrhythmia, landiolol was compared to antiarrhythmics class I, II, III, IV and digitalis. Under landiolol, the multicentre (54 hospitals), open-label, randomised-controlled

trial showed a higher proportion of patients with low HR of 60-94 bpm (55% vs 33%) after 24h and a lower proportion of patients with new-onset arrhythmia after 168h (9% vs 25%) (Kakihana et al. 2020).

Guidelines: Short-Acting Beta-Blockers Preferable in Haemodynamic Instability

How these findings were incorporated in the current guidelines was the topic of the lecture given by Prof Zlatko Fras MD, Department for Vessel Diseases at the Medical University Center Ljubljana, Slovenia. The European Heart Rhythm Association (EHRA) for instance recommends cardioversion for the acute management of critically ill patients with arrhythmia and haemodynamic instability. Beta-blockers are recommended for haemodynamically stable patients, in case of risk of haemodynamic instability "short-acting beta-blockers may be preferred" (Boriani et al. 2019). In turn, the ESC guidelines for the management of atrial fibrillation (AF) published in 2020 recommend beta-blockers, diltiazem, or verapamil in LVEF ≥40% as first-line therapy; beta-blockers and/or digoxin are recommended to control heart rate in AF patients with LVEF <40%; in patients with haemodynamic instability or severely depressed LVEF, intravenous amiodarone may be considered for acute control of heart rate (Hindricks et al. 2020). "The most important thing in these guidelines however is the first-time inclusion of landiolol", the Slovenian expert stresses. "It is the only agent with a clear dose recommendation in patients with cardiac dysfunction, in particular dosages of 1µg/kg/min up to 10µg/kg/min. A higher dosage is of course possible without cardiac dysfunction."

Prof Fras then illustrates the use of landiolol in clinical practice with the help of a case report. An 82-year-old female patient with multiple pre-existing vascular diseases, comorbidities (including history of pulmonary oedema during amiodarone infusion) and polypharmacy presents with paroxysmal AF. The intervention consists of landiolol in a dosage of 1-7µg/kg/min. After close to six hours, the patient cardioverted into sinus rhythm, target HR was achieved "fairly quickly", and at discharge the patient was haemodynamically stable. "Landiolol was very effective, and in this situation, it was clearly the drug of choice", Prof Fras summarises.

> **"landiolol is an innovative, highly selective β1-adrenergic receptor antagonist with the highest receptor selectivity of all beta-blockers, a short half-life and a low volume of distribution"**

Landiolol

Landiolol is indicated in supraventricular tachycardia and for the rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative, postoperative, or other circumstances where short-term control of the ventricular rate with a short acting agent is desirable. It is also indicated in non-compensatory sinus tachycardia, where in the physician's judgement the rapid heart rate requires specific intervention. In patients with impaired left ventricular function (<40%), lower doses starting from 1µg/kg/min have been used.

Take-Home Messages From the ESC Guidelines

- Landiolol is the only beta-blocker with a specific dose recommendation for patients with cardiac dysfunction and acute AF.
- Landiolol has a class I recommendation: Evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective, the agent is therefore recommended or indicated.
- By contrast, amiodarone has class IIb, meaning usefulness/efficacy is less well established by evidence/opinion. The drug may be considered in patients with haemodynamic instability and severely depressed LVEF for acute control of heart rate. ■

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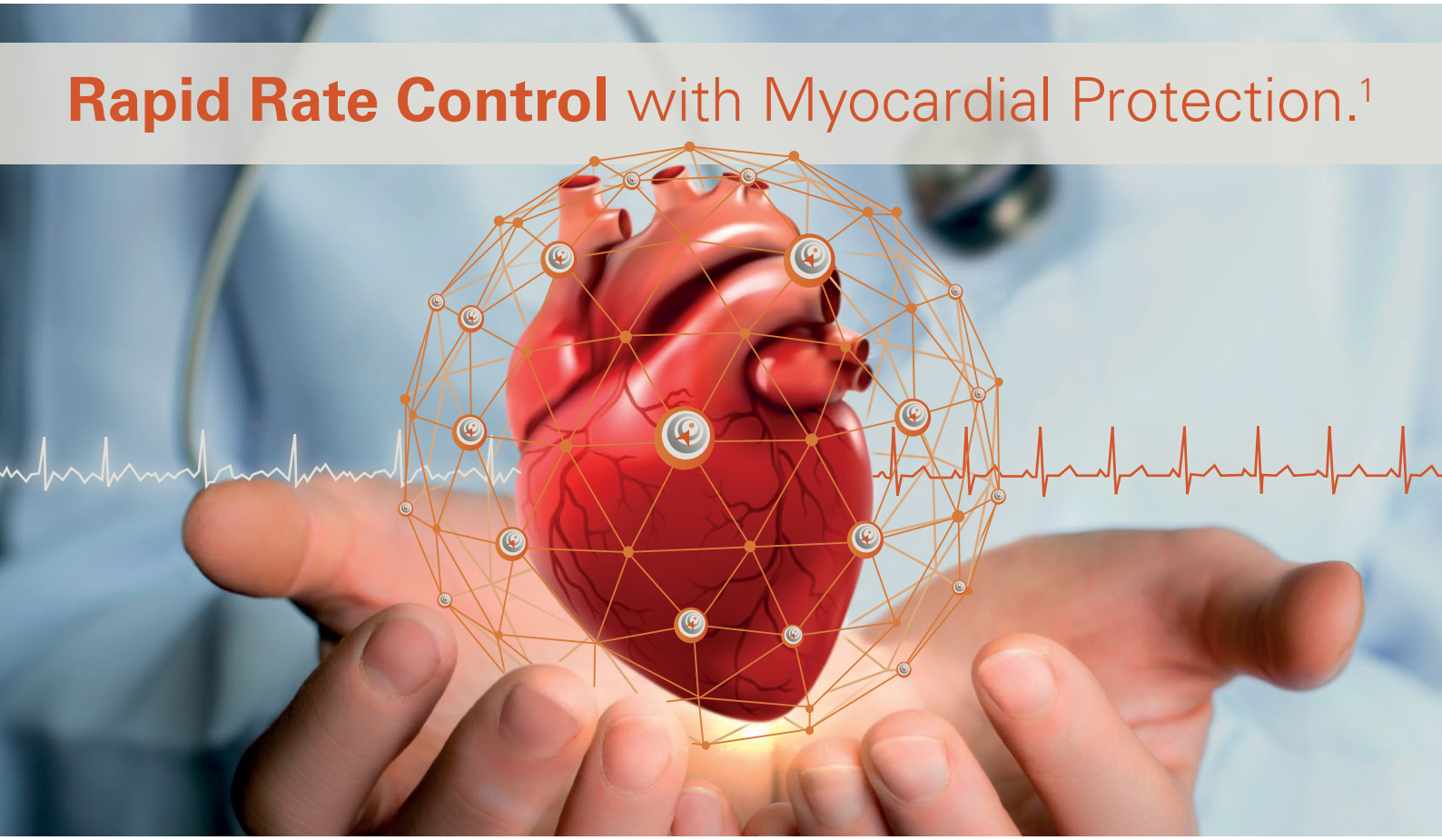

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First-line for patients with cardiac dysfunction[2]

- **Limited effect** on blood pressure and inotropy[3]
- **Favourable safety profile for patients with renal and hepatic comorbidities** due to inactive metabolites and hydrolysis by plasma esterases[1,4]
- **Compatible with pulmonary disorder patients** due to highest cardioselectivity (β1/β2-selectivity = 255:1) among β1-blockers[5]
- **Limited rebound and tolerance effect** due to lack of pharmacochaperoning activity[6]

1 Summary of Rapibloc® Product Characteristics, current version. – **2** Hindriks G., et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). European Heart Journal (2020) 00, 1-126. – **3** Shibata et al. Direct Effects of Esmolol and Landiolol on Cardiac Function, Coronary Vasoactivity, and Ventricular Electrophysiology in Guinea-Pig Hearts. J Pharmacol Sci 118, 255 – 265 (2012). – **4** Yokoyama H. (2016) Stabilization in Off-Pump Coronary Artety Bypass. Springer Tokyo Heidelberg New York Dordrecht London © Springer Japan. – **5** European Heart Journal Supplements (2018) 20 (Supplement A), A1-A24. – **6** Nasrollahi-Shirazi S et al. Comparison of the b-adrenergic receptor antagonists landiolol and esmolol: receptor selectivity, partial agonism, and pharmacochaperoning actions. J Pharmacol Exp Ther 2016; 359:73–81

Rapibloc® 300 mg: Rapibloc® 300 mg powder for solution for infusion. **Composition:** A vial of 50 mL contains 300 mg landiolol hydrochloride. After reconstitution each mL contains 6 mg landiolol hydrochloride (6 mg/mL). List of excipients: Mannitol E421, sodium hydroxide (for pH adjustment). Therapeutic Indication: Landiolol hydrochloride is indicated for supraventricular tachycardia and for rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative, postoperative, or other circumstances where short-term control of the ventricular rate with a short acting agent is desirable. Landiolol hydrochloride is also indicated for non-compensatory sinus tachycardia where, in the physician's judgment the rapid heart rate requires specific intervention. Landiolol is not intended for use in chronic settings. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients, severe bradycardia, sick sinus syndrome, severe atrioven-tricular (AV) nodal conductance disorders (without pacemaker): 2nd or 3rd degree AV block, cardiogenic shock, severe hypotension, decompensated heart failure when considered not related to the arrhythmia, pulmonary hypertension, non-treated phaeochromocytoma, acute asthmatic attack, severe, uncorrectable metabolic acidosis. **Undesirable effects:** Common: Hypotension, bradycardia. Uncommon: Pneumonia, hyponatraemia, cerebral ischemia, headache, cardiac arrest, sinus arrest, tachycardia, hypertension, pulmonary oedema, vomiting, nausea, liver disorder, ECG: ST segment depression, cardiac index abnormal, abnormal laboratory parameters: ALT/GPT, AST/GOT, blood bilirubin, white blood cell count, red blood cell count, haemoglobin haematocrit, platelet count, blood lactate dehydrogenase, blood urea, blood creatinine, blood creatinine phosphokinase, protein total, blood albumin, blood sodium, blood potassium, blood cholesterol, blood triglycerides, protein urine present. Rare: Mediastinitis, thrombocytopenia, platelet disorder, hyperglycaemia, cerebral infarction, cerebrovascular accident, seizure, myocardial infarction, ventricular tachycardia, atrial fibrillation, low cardiac output syndrome, atrioventricular block, bundle branch block right, supraventricular extrasystole, ventricular extrasystole, shock, hot flush, asthma, respiratory distress, respiratory disorder, bronchospasm, dyspnoea, hypoxia, abdominal discomfort, oral discharge, breath odour, hyperbilirubinemia, erythema, cold sweat, muscle spasms, renal failure, acute kidney injury, oliguria, pyrexia, chills, chest discomfort, administration site pain, blood pressure increased, electrocardiogram T wave inversion, electrocardiogram: prolonged QRS complex, heart rate decreased, pulmonary arterial pressure increased, PO2 decreased, neutrophil count abnormal, blood alkaline phosphatase abnormal, leukocyte alkaline phosphatase, free fatty acids abnormal, blood chloride abnormal, glucose urine. Not known: Application site pain, injection site reaction, sensation of pressure. Prescription only/available only from pharmacy. **Date of revision of the text:** 09/2020. Marketing authorization holder: Amomed Pharma GmbH, Storchengasse 1, 1150 Wien, Austria

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Microbiome and Pneumonia in Children

The role of microbiome in nosocomial pneumonia development in critically ill children

A significant research gap exists in the field of the lung microbiome and pneumonia development in paediatric population. Its study may improve nosocomial pneumonia prevention and help to achieve zero pneumonia rates.

Most frequent hospital acquired infections (HAI) in Paediatric Intensive Care Units (PICU), are ventilator associated pneumonia (VAP), catheter-related urinary tract infection and catheter-related infection. All can be the onset of a sepsis or septic shock (Esteban et al. 2013; Goldstein et al. 2005).

What is the VAP Impact in Paediatric ICU?

The incidence of VAP is around 8-9% of ventilated adults and 14% of ventilated paediatric patients (Elward et al. 2002). Two universal criteria required for VAP diagnosis are PICU admission longer than 72 hours and intubation for more than 48 hours. In paediatrics, the criteria of the Centre for Disease Control are the most widely used, and include clinical-analytical, radiological, and microbiological criteria (Horan et al. 2008).

VAP has high morbidity and mortality in PICU, despite the pneumonia zero programmes. Risk factors for developing VAP depend on the patient and prevention measures conducted. The mechanism for VAP apparition are described in three pathophysiological ways: oropharyngeal or stomach secretions aspiration; direct inoculation through the endotracheal tube (ETT); and less frequently through haematogenous dissemination. Preventive measures are targeted against these principles but it's difficult to achieve zero pneumonia rates, especially in paediatric settings (Branch-Elliman et al. 2015; Nair et al. 2015).

Patients with VAP are especially sensible for infections caused by antimicrobial resistance microorganism (AMR), due to patient factors (comorbidities, broad-spectrum antibiotics) as well as external factors (invasive devices, long-term hospitalisation). AMR, and especially multi drug resistance (MDR), are an important public health issue because of the severity of the infections they may cause, the difficulty to establish a correct empiric treatment, the ability for spreading MDR and the absence of new antibiotics against those pathogens (Boucher et al. 2009; Marston et al. 2016; Nathan et al. 2014).

National actions have proposed strategies to prevent VAP and MDR, as the *ENVIN_HELICS* register or "*Pneumonia zero*" programme. National PICUs have collaborated with these projects in order to promote and reinforce the safety culture in the PICU of the National Health System (Grau et al. 2013; Martínez-Martínez et al. 2010; Jordan et al. 2016). Results of these programmes have detected relatively high rates of VAP in paediatrics (5-7 VAP/1000 days VM) (Jordan et al. 2014).

Are There Any Preventive Risk Factors?

Lowest age, previous comorbidities, patient severity, and ETT length are the main risk factors, but most of these are not susceptible to be changed. Strategies to prevent rates follow international bundles, like general strategies (airway manipulation, hand cleansing, use of cuffed tubes -pressure around 20 cmH_2O-, head of the bed at 30-45°) similar than in adults. However, other recommended measures cannot be followed in children, such as the subglottic secretions aspiration (there is no dispositive

for paediatrics), or digestive tube selective decontamination (controversial in children).

Due to the high rates of VAP in paediatric patients and the difficulties in the capacity to modify intrinsic characteristic of the patients, new approaches to this nosocomial infection are required.

Attending to the principal pathophysiological ways of VAP development, oropharyngeal colonisation may be one of the investigation attention points. Either if the respiratory infection is secondary to the oropharyngeal aspirations or by direct inoculation, the microorganism responsible for VAP is commonly one of those colonising the airway. It has been defined that colonisation of the upper airway may be the beginning of the process that can conduce to a tracheobronchitis and even to a VAP. But better understanding might explain why patients develop one of these infections. Bacterial Microbiome (BM) could have an explanation for some of this concern in VAP (Pouline et al. 2017). **Figure 1** shows risk factors and strategies to prevent VAP.

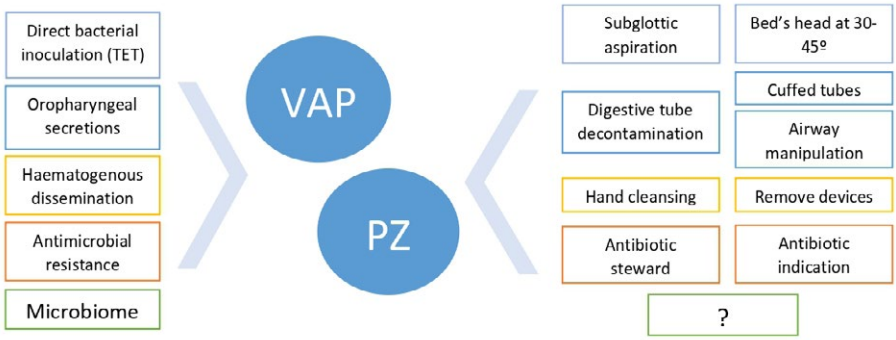

Figure 1. Risk factors and strategies to prevent ventilator-associated pneumonia (VAP), and to achieve pneumonia zero (PZ) rates.

What is Human Microbiome?

The human microbiome is defined as the ecological community of commensal, symbiotic and pathogenic microorganisms found in humans. Microbiota has been found to be crucial for immunologic, hormonal and metabolic homeostasis of their host (The Human Microbiome Project Consortium 2012). It has been defined as a new factor to develop severe community infections and VAP in paediatrics. Not only are the main bacterial microorganism detected on traditional cultures, but also other bacterial commensals (Mourani et al. 2021). A great advantage of Next Generation Sequencing (NGS) analysis for BM detection is its capability to identify hard-to-grow or even uncultivable bacteria, so it would be useful to find another microorganism implicated in VAP development. Even BM could be a risk factor for bacterial resistance.

How Can We Analyse the Microbiome?

The use of next-generation sequencing and multiomic analysis reveals new insights on the identity of microbes in the lower airways blurring the lines between commensals and pathogens. Microbes are not found in isolation; rather they form complex meta-communities where microbe-host and microbe-microbe interactions play important roles on the host susceptibility to pathogens. In addition, the lower airway microbiota exerts significant effects on host immune tone (Wu et al. 2018).

In order to analyse it, there are two types of procedures: metagenomics and analysis of BM. The first relies on the sequencing of all nucleic acid sequences obtained in a sample. It allows to detect a new species in a sample. BM analysis is based on sequencing of specific regions of the DNA genes encoding the 16S ribosomal RNA (rRNA) subunit (Clarridge et al. 2004). This is possible by the presence of regions that are conserved throughout the bacterial kingdom within these genes, which allows PCR amplification using universal primers and permits the determination of bacterial composition in samples.

What is the Role of Microbiome in VAP Development in Children?

Data about mouth/nasopharyngeal (NF)/tracheal microbiome in paediatrics is scarce, but promising. Respiratory mucosa is immediately colonised after birth, by mother's bacteria. The colonisation type may be different depending on genetic and environmental factors and changes during the first years of life. An equilibrium seems to exist between the invasive and commensal bacteria when the patient is healthy, with significantly higher BM diversity. In relation with caries, higher proportion of mouth *Lactobacillus* and anaerobic agents increase its infection, due to higher acids production (Tanner et al. 2018). In other paediatric pathology as bronchiolitis, four clusters of airway microbiota have been identified. Proportion of bronchiolitis was lowest in infants with *Moraxella*-dominant profile (14%) and highest in those with *Staphylococcus*-dominant profile (57%). By contrast, *Corynebacterium/Dolosigranulum*-dominant profile had low proportion of infants with bronchiolitis (17%) (Hasegawa et al. 2017). Other authors note that some viruses' infections, such as influenza, may disrupt interactions between host microbial communities and host defence, thereby contributing to the pathogenesis of secondary bacterial infections (Hanada et al. 2018). In medium otitis the increasing trend in colonisation of otopathogen genera has also been correlated positively with frequencies of upper respiratory tract infection (Chonmaitree et al. 2017).

Two studies showed a decrease in bacterial diversity in the pulmonary microbiome with prolonged MV, with an increase in *Pseudomonas* and *Acinetobacter* species, even if

another pathogen was causing the pneumonia (Mourani et al. 2021). Therefore, development of pneumonia could be possible due to selective pressure on the existing microbiome towards the selection of single bacteria species. One explanation is that commensal bacteria can release lipopolysaccharides and peptidoglycans which go through the oropharyngeal and respiratory epithelium. This capability is increased in inflammation situations, as commonly happens in critical patients. As an example, in children *Respiratory Syncytial Virus* has been determined to cause inflammation which conduces to *Haemophilus* clusters and responsible for a major severity of the viral infection (Rosas-Salazar et al. 2016; Zakharkina et al. 2017).

Longitudinal studies with daily cultures of endotracheal aspirates suggest that in the majority of the patients, the trachea is colonised with causative pathogen at least 1–2 days before pneumonia develops (Miyaki et al. 2005). However, colonisation does not frequently progress to pneumonia and traditional cultures need around three days to be positive. BM surveillance could also help in earlier treatment, which might allow for a shorter course of systemic antibiotics or even the use of inhaled antibiotics alone (Dickson et al. 2014; Kelly et al. 2016; Wexell et el. 2016).

If it was determined that children who develop VAP have different BM than children who do not, especially during the first admission days, some prevention actions could be implemented. It would be local or systemic measures, different than chlorhexidine or floral decontamination now recommended, as lactic inhibitors or anti-anaerobic products. Other decisions may be precociously done, such as antibiotic treatment in individualised cases.

Is There Other Microbiome of Non-Human Origin in Children?

Another focus related to HAI is surface contamination. There are contaminated surfaces in a hospital depending on the setting. In PICU most high-touch points are bed rails, supply cart/bedside table, computer mouse and intravenous pumps (Menis et al. 2011).

There are pathogens associated with each mode of transmission and environmental reservoir, especially multi-resistant microorganisms related with HAI. Environmental contamination may contribute to the transmission of healthcare pathogens when healthcare workers contaminate their hands or gloves by touching contaminated surfaces, or when patients come into direct contact with contaminated surfaces.

> **“the use of next-generation sequencing and multiomic analysis reveals new insights on the identity of microbes in the lower airways blurring the lines between commensals and pathogens”**

There are different methods for evaluating the cleaning of surfaces: the visual inspection (the information is not reliable and subjective); fluorescent marking (not specific, sensitive and the low cost); adenosine triphosphate control system (highly sensitive, not specific and expensive) (Nante et al. 2017); and microbiological analysis and colony counts (sensitive, specific, rapid and accurate but complicated) (White et al. 2007).

Since there are no scientific standards to measure the effect of an individual cleaner, or assess environmental cleanliness, finding the evidence to benefit the control of infection is further hampered. Analysis of microbiota samples of surfaces and medical devices allow the identification of pathogens considered possible reservoir in hospital areas and adoption of new cleaning methods and strategies for prevention and control infections.

What Do We Know From Our Paediatric Population?

Our group conducted a prospective preliminary study about microbiome and infectious disease in paediatric patients. Healthy subjects, cases with invasive pneumococcal disease and children with viral infection were analysed. The sample processing was the same as described in the methodology section, and microbiota was analysed by NGS. Results showed three different nasopharynx microbiota patterns. It was detected that *Dolosigranulum* genera seemed to have a protective profile and was significantly associated to healthy individuals. Second risk pattern was represented by *Streptococcus*, when it was detected together with a high diversity of anaerobic genera; it was associated with pneumococcal invasive disease. Third pattern was rich in *Moraxella* and *Haemophilus* and showed a trend to be related to viral respiratory infection.

What Are We Expecting in the Near Future?

1. **A significant research gap exists in the study of the lung microbiome and pneumonia.** General interest about human microbiome has been increasing during the last ten years. Scientific platforms have references of microbiota in humans since the 70’s but what has changed is the way that this microbiota is analysed, thanks to the NGS method. As previously reported, there have not been new explanations about why a patient develops VAP or not, even when patients have similar risk factors, pathologies or colonisation.
2. **Complex microbial communities exist in the upper and lower airway. Microbe-host interactions blur the line between pathogen and commensal.** If new sequencing methods were useful to diagnostic nasopharyngeal BM (NBM) pattern for VAP developing, a specific NBM panel would be defined

and developed. This research may also allow translating the methodology to other causes of nosocomial infection, such as central line catheter associated infections or urinary tract infections associated with urinary catheter.

3. **Regarding surface bacterial contamination, there is not much information, nor much about the method to be used for the diagnosis.** To define how a PICU is colonised may be an opportunity to analyse if bacterial differences exist along time and if these colonising bacteria are the same that cause VAP. If surface microbiome results are useful, new panels for diagnosis should be developed depending on the bacterial species detected.

Conclusion

The microbial community of the lung may play an important role in pneumonia impacting susceptibility and the natural history of disease. Research interest, focused on determining the influence of NBM in the development of VAP in paediatric critically ill patients, and on analysing PICU surfaces BM colonisation, may improve VAP prevention. Added to previous VAP preventive measures, it may allow to reach zero pneumonia rates.

Conflict of Interest

None. ■

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Microbiome and Probiotics in Critical Care: Do They Really Work?

The microbiota is recognised as one of the most important factors that can worsen the clinical conditions of patients who are already very frail in the intensive care unit. It also plays a crucial role in the prevention of ICU associated complications. It's important to ensure the best functioning of the intestinal immune system.

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The gastrointestinal tract represents one of the barriers between the external environment and the human body. This organ is composed of a wide variety of cells devoted to keep the intestine in balance (McDermott and Huffnagle 2014; Abreu 2010; del Rio et al. 2010; Sun et al. 2007).

The body's microbial composition directly influences the maturation of the immune response by GALT- *Gut-Associated Lymphoid Tissue* (Abreu 2010; del Rio 2010; Sun et al. 2007); and its continued effectiveness, protects against pathogen overgrowth, and modulates the balance between inflammation and immune homeostasis (Lynch and Pedersen 2016; Zhang and Frenette 2019). A few hours after admission to hospital, and especially to the intensive care unit (ICU), the intestinal microbiome switches to pathobiota (Stetcher et al. 2012; Babrowski et al. 2013; Hayakawa et al. 2011).

Sepsis can have a considerable impact on gastrointestinal function, indeed altered permeability and subsidence of normal intestinal flora can lead to systemic infection (Dickson 2015) such as neuropsychiatric disorders, inflammatory bowel disease (IBD), functional gastrointestinal (GI) disorders, cardiovascular disease, liver disease (Longhitano et al. 2020; Nakov et al. 2020) but also multiorgan failure (MOF) and severe sepsis.

The physiological mechanisms altered during hospitalisation in the ICU are responsible for:

- the growth of the pathobiote: colonisation by virulent bacteria;
- hypoperfusion of the intestinal tract leading to the massive release of nitrates and free oxygen radicals;
- the slow transit of faecal material due to various drugs (e.g. antibiotics, intravenous sedatives, opioids, catecholamines) causing a decrease in the normal turnover of about a trillion bacteria (Vincent et al. 2009);
- drugs such as proton pump inhibitors that change the chemical and physical characteristics of intestinal mucous, which neutralises gastric pH and reduces the velocity of gastric emptying (Marshall et al. 1993).

All this leads to the intestine colonisation by the Proteobacteria phylum (the most important are *Pseudomonas aeruginosa* and *Escherischia coli* and other minor gram-negative bacteria); also, other bacteria belonging to Firmicutes phylum (*Staphylococcus aureus, Enterococcus spp* and gram-positive bacteria such as *Clostridium difficile*) can colonise the intestine (Gootjans et al. 2010). The presence of the pathological bacteria described above (Marshall et

al. 1993) is predictive of the development of MOF and systemic infections. Recently, the contribution of the microbiome in the development of coronary artery disease (CAD) has also been reported (Piccioni et al. 2021).

In addition to the above mentioned predisposing factors, the occurrence of contamination of the pulmonary ecosystem is also observed in intensive care patients as a result of the decrease in tussigenic stimulus, the migration of bacteria due to contiguity (Sands et al. 2017) through the orotracheal tube and the effect of micro-aspiration of bacteria from the oral cavity (Dickson et al. 2015; Gleeson et al. 1997; Segal et al. 2013; Sekizawa et al. 1990). All this leads to a subversion of the normal oral flora and leads to its replacement by pathogenic bacteria, such as *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*.

It is obvious that one of the principal therapeutic goals in the ICU is to counterbalance dysbiosis. A number of treatment plans have been proposed: the use of probiotics in patients admitted to the ICU (Hill et al. 2014), faecal microbiota transplantation (FMT) (Fischer et al. 2017; Ianiro et al. 2017) and combination therapies that can help preserve mucosal integrity.

The use of probiotics as co-adjuvants, especially in intensive care patients, is rising exponentially thanks to studies conducted over the last 20 years, which show a statistically significant reduction in infections, in the incidence of VAP and, not least at all, in overall mortality.

A very recent 2020 review by Lukovic et al. (2019) highlighted some strategies that have been applied to reduce the risk of developing ventilator-associated pneumonia (VAP) such as oral decontamination, ETT impregnated with antimicrobials or silver, and probiotics (Spreadborough et al. 2016; Kollef et al. 2008; Muscedere et al. 2011; Manzaneres et al. 2016).

Also symbiotics (e.g. bifidobacterium breve strain yakult, lactobacillus casei strain Shirota, and galacto-oligosaccharides) are used in intensive care patients to prevent the development of sepsis. Conceptually they are a combination of prebiotics and probiotics and can be considered as enhancing compounds between the two and could be the best initial treatment during the conditions of altered homeostasis of the intestinal flora (Shimizu et al. 2018).

> **the use of probiotics as co-adjuvants, especially in intensive care patients, is rising exponentially**

A new strategy in the treatment of chronic diarrhoea due to *Clostridium difficile* infection is FMT which has shown very strong results (Cammarota et al. 2017).

The microbiota is recognised as one of the most important factors that can worsen the clinical conditions of patients who are already very frail in the intensive care unit. At the same time, the microbiota also plays a crucial role in the prevention of ICU associated complications. It's very important to use little but solid knowledge we have on the microbiome to ensure the best functioning of the intestinal immune system.

Also Rello et al. (2021) explained in their editorial the relation between pneumonia and dysbiosis that the traditional paradigm of VAP (that it is a disease caused by a single bacterial pathogen acquired through microaspiration) needs to be replaced by a hypothetical model in which VAP would be associated with dysbiosis. The gut microbiome contributes to protect against opportunistic pathogens. Enriching the microbiota with members of the phylum Proteobacteria, which are considered commensals, increases serum IgA levels. Thus, lung dysbiosis combined with gut dysbiosis might induce local immunosuppression and lung dysfunction, facilitating the occurrence of VAP. The role of the Th17 response provoked by segmented filamentous bacteria, which provides protection from staphylococcal pneumonia, seems crucial. These observations are not only of academic interest. Early identification of patients with dysbiosis associated with a higher risk of developing VAP is an unmet clinical need, and this should lead to innovative, targeted preventive strategies (Cammarota et al. 2017).

Conflict of Interest

None. ■

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Clostridioides difficile Infection: A Serious Complication of Intestinal Microbiome Alteration in Critical Patients

Clostridioides difficile (C. difficile) infection is a potentially serious complication in critical patients admitted to the Intensive Care Unit (ICU). It generally occurs because of an alteration of the intestinal microbiota due to antibiotic exposure that must be timely identified and diagnosed to start proper and early management.

Clostridioides difficile (*C. difficile*) is a Gram-positive anaerobic, spore-forming, toxin-producing rod. Previously known as Clostridium difficile, it was renamed in 2016 to its current name, which reflects the taxonomic differences between this species and other members of the Clostridium genus. Spores, present in the environment, are spread by the fecal-oral route. Five percent of adults and 15-70% of infants are colonised by *C. difficile* and there is a prevalence in hospitalised patients or nursing homes residents. After the introduction of antibiotics, the role of *C. difficile* in the pathogenesis of large-intestine diseases increased. The mortality rate directly related to *C. difficile* infection (CDI) is estimated at 5%, while the mortality associated with CDI complications reaches 15% to 25% and up to 34% in intensive care units. Currently, CDI has become one of the most important nosocomial infections, affecting all hospital wards (Czepiel et al. 2019).

Pathophysiology

The digestive tract extends from the mouth to the rectum. Its covering mucosa, with an approximate 300 m^2 surface, acts as a barrier against microbial invasion, mainly through three levels of control: first, gastric acid is responsible for eradicating ingested microorganisms; secondly, the mucosa, which has a single layer of columnar epithelial cells (0.1 mm thick), acts as a physical barrier, blocking the bacteria and toxins movement into circulation; and, finally, the reticuloendothelial system traps and destroys the microorganisms that cross the mucosa (Martínez-Rodríguez et al. 2018).

The gastrointestinal tract is widely colonised, being the large intestine the most populated region, which reaches up to 1012 bacteria per gram of fecal matter (1-1.5 kg per weight). Knowing this fact has allowed us to understand the important protective role that this intraluminal ecosystem plays, which prevents invasion by pathogenic microbes capable of causing disease. The effect of antibiotics on the intestinal microbiota is well documented. These show a long-term reduction in bacterial diversity after their use, which decreases resistance to colonisation. Furthermore, this microbiota modification after antibiotic treatment facilitates the transfer of drug-resistance genes (Portillo et al. 2002; Meyer et al. 2014).

C. difficile is a bacterium that forms

acid-, antibiotic-, and heat-resistant spores that spread through fomites or directly by the oral-fecal route. The bacillus does not survive gastric acid; however, the spores are resistant to its effects and germinate when exposed to bile salts in the small intestine. These spores later colonise the large intestine with bacilli, causing disease in susceptible people. The use of antibiotics is the main associated factor. At this site, it acts by releasing two protein exotoxins, toxins A and B, whose effects lead to pseudomembranes or even megacolon formation (**Table 1** and **Figure 1**) (Meyer et al. 2014; Barra-Carrasco et al. 2014).

The following are characteristics of *C. difficile*-induced pseudomembranous colitis.

1. Early or type I lesion: the patchy necrosis of the epithelium forms fibrin and fibrinous exudate in the lumen of the colon.
2. The exudative lesion, or type II lesion, is a volcano-type epithelial ulceration with intact surrounding mucosa.
3. Type III lesion: diffuse epithelial necrosis and ulceration with development of a pseudomembrane containing cellular debris, leukocytes, fibrin, and mucin.

C. difficile initiates a sporulation process that consists of producing spores that are spread into the environment in stools, a unique and sophisticated strategy to persist in the colonic environment of the host. This occurs when environmental conditions are unfavourable for its survival (Portillo et al. 2002).

Risk Factors

Risk factors for CDI include being 65 years or older, previous hospitalisation, recent antimicrobial therapy (particularly third-generation cephalosporins, amoxicillin-clavulanate, clindamycin, and newer fluoroquinolones), immunosuppression, and proton pump inhibitors.

Likewise, there are factors associated with the patient themselves, related to advanced age, such as chronic diseases and multiple comorbidities of which

Effect	Result	Shared effect
Enterotoxin "A" • Fluid retention • Inflammatory cells (macrophages, mast cells, lymphocytes, and neutrophils) • Mediator release (prostaglandins, leukotrienes, platelet activating factor, nitric oxide, and cytokines).	Pseudomembranous colitis.	They facilitate bacterial adherence and penetration through the intestinal epithelial barrier. They increase vascular permeability and promote bleeding.
Cytotoxin "B" A thousand times more potent than toxin A. It causes morphological and electrophysiological modifications of the colonic mucosa.	Increased hostility to the colonic mucosa.	

Table 1. *Clostridioides difficile* pathogenic toxins and their main effects

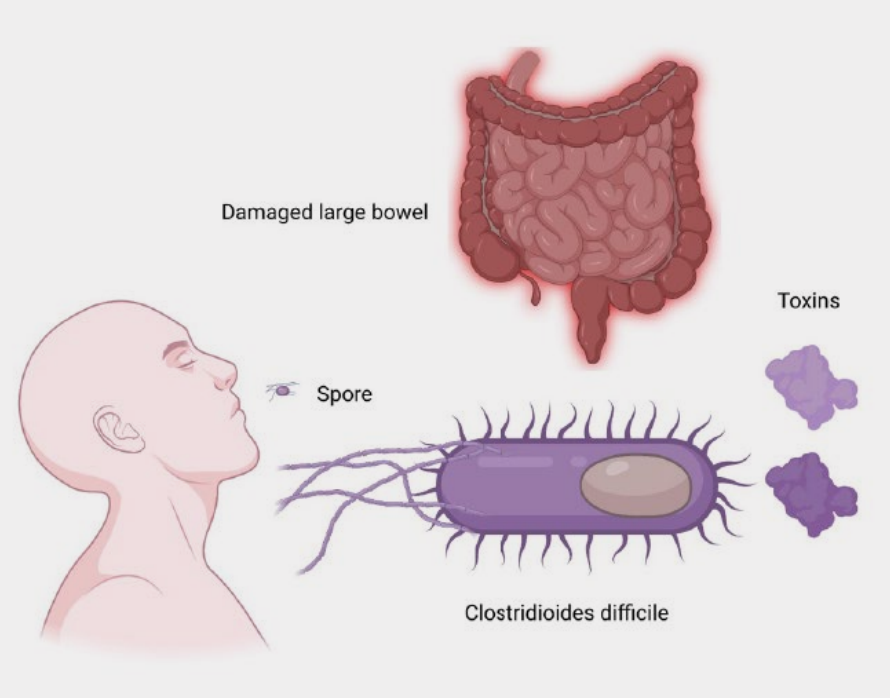

Figure 1. Pathophysiology of *Clostridioides difficile* infection

inflammatory bowel disease, chronic liver disease, and immunosuppression stand out (De Roo and Regenbogen 2020).

Clinical Conditions

The CDI clinical conditions are highly heterogeneous, ranging from asymptomatic carrier status, mild to moderate diarrhoea, to life-threatening fulminant colitis. Although the incubation period is not precisely described, some reports suggest it lasts from 2 to 3 days, but more recent studies show that it can be longer than 3 days, and it depends on each individual. The CDI can affect all parts of the colon, but the distal segment is the most commonly infiltrated. Most patients with CDI have mild diarrhoea and experience spontaneous recovery after 5-10 days of completing the course of antibiotics (Samore et al. 1994; McDonald et al. 2018).

To make an effective diagnosis of CDI, both clinical symptoms and a positive lab-test result are required (Zhong et al. 2018). The clinical condition ranges from mild diarrhoea to severe illness or fulminant colitis. Up to 30% of patients can develop a recurrent CDI. Although diarrhoea is the characteristic symptom, it may not be present at the onset of the disease, possibly due to colon dysmotility, either from previous underlying conditions or from the disease process (Sartelli et al. 2019).

Mild to Moderate CDI

Diarrhoea is defined as loose stools corresponding to types 5-7 of the Bristol Stool Chart. The patient must present at least three diarrhoeal stools for 24 consecutive hours or more frequently than normal for the patient. Diarrhoea must be accompanied by mild abdominal pain and cramps. If prolonged, it can cause an alteration of the water and electrolyte balance as well as dehydration (Zhong et al. 2018).

Severe CDI

Severe CDI is associated with increased abdominal pain and cramps, as well as systemic symptoms such as fever, leukocytosis, and hypoalbuminaemia. The absence of diarrhoea may indicate the progression of fulminant disease. Although a wide variety of predictors of poor prognosis have been described, there is still no international consensus for the severe CDI definition. Progression to fulminant colitis is relatively uncommon (1-3% of all CDIs). Mortality remains high due to the development of toxic megacolon with colonic perforation, peritonitis, septic shock, and subsequent organ dysfunction (Sartelli et al. 2019).

Severity markers include advanced age (≥65 years), leukocytosis (> 15 × 109/L), lower blood albumin levels (< 2.5 g/dL), elevated serum creatinine levels (≥ 133 μM or ≥ 1.5 times the baseline), temperature > 38.5, severe underlying disease or previous immunodeficiency (Zhong et al. 2019). In a recent study, it was shown that human serum albumin is capable of binding to the IIa domain of toxins A and B of *C. difficile*, which prevents its internalisation in host cells. This could partially explain the hypoalbuminaemia with a CDI severity marker.

Recurrent CDI

In 10-30% of cases, a recurrence of symptoms develops after initial therapy for *C. difficile* and it becomes a clinical challenge. For a patient who has presented 1 to 2 cases, the risk of more recurrences is 40-65%. Recurrent CDI may result either from the germination of resident spores that remain in the colon after completing the antibiotic treatment or from reinfection from an environmental source. Recurrence is present when the CDI reappears within 8 weeks of the onset of a previous episode and after its symptoms resolve once the initial treatment is completed. In daily practice, it is difficult to distinguish between recurrence due to relapse or reinfection (Di Masi et al. 2018).

When a patient has diarrhoeal stools that correspond to Bristol stool types 5-7 and has other CDI risk factors together with the absence of a different cause of diarrhoea, a stool sample should be collected for laboratory analysis. However, for paralytic ileus, formed stool samples should not be tested for CDI (Di Masi et al. 2018).

Diagnosis

Only toxigenic strains, which produce toxins A and B, are pathogenic. According to the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) guidelines, CDI is defined as a condition compatible with CDI plus microbiological evidence of toxins A and B that produce *C. difficile* in stool, without evidence of another cause of diarrhoea, or patients with pseudomembranous colitis (Di Masi et al. 2018).

Currently, there is no single stool test to be used as a standalone test for diagnosing CDI. Several laboratory tests detect free toxins in the stool (enzyme immunoassay (EIA), cell cytotoxicity neutralisation assay (CCNA), *C. difficile* presence (EIAs that detect glutamate dehydrogenase (GDH)), or the presence of a toxigenic *C. difficile* strain (toxigenic culture (TC)), and nucleic acid amplification tests (NAAT) (Di Masi et al. 2018).

Among these methods, stool TC or CCNA have been considered the gold standard for the diagnosis of CDI for the past 30 years. Paradoxically, neither of these are used routinely due to technical problems and the prolonged time of results (Di Masi et al. 2018).

1. Toxicogenic culture (TC) is a two-step method that first isolates *C. difficile* strains on a selective medium, and then evaluates *in vitro* toxin-producing capacity. Different selective media are available and are generally derived from cycloserine-cefoxitin fructose agar. Currently, additives such as sodium taurocholate or lysozyme have been added to stimulate germination. Chromogenic media have also been developed since it has been shown that they are as sensitive as other selective media, which allows

identification within 24 hours after incubation. Plates are incubated in an anaerobic atmosphere for 48 hours at 36 ± 1 °C. After isolating a strain, its pathogenic potential is determined by testing for in vitro toxin production. TC is considered the gold standard for detecting toxigenic *C. difficile* and for evaluating new molecular methods. Although TC results take too long for routine diagnosis (2 to 5 days), culture is essential for subsequent strain typing, molecular analysis, and antimicrobial susceptibility determination (Di Masi et al. 2018; Crobach et al. 2016).

2. Nucleic Acid Amplification Test (NAAT) for *C. difficile*: *C. Difficile* toxin genes were introduced in 2009. NAATs are based on a PCR method or isothermal amplification. They have a higher sensitivity (80-100%) and specificity (87-99%) than EIA tests, so they can be used as a CDI standard diagnostic test. NAAT, as a one-step algorithm, can increase the detection of asymptomatic colonisation; therefore, it should be performed in patients with high suspicion of CDI, or included in a two-step algorithm starting with toxin detection. This test has limitations such as its high cost and some difficulties in its interpretation. PCR detects the presence of a toxin-encoding gene, thus confirming the presence of toxin-producing *C. difficile*, but this does not necessarily mean that the strain is producing toxins at that time, resulting in false positives (Crobach et al. 2016).
3. Glutamate dehydrogenase (GDH) tests: Glutamate dehydrogenase is a metabolic enzyme expressed in all *C. difficile* strains. A positive result only indicates the presence of *C. difficile*, without predicting the strain's ability to produce toxins. GCH can be detected by immunoenzymatic assays (ELISA) or immunochromatography. At present, different guidelines propose GDH EIA tests as a detection method for diagnosing CDI. Due to its high negative predictive value (NPV) of 80-100%, a negative test will rule out infection. However, a positive result must be confirmed by a second, more specific test that detects toxins (Di Masi et al. 2018; Crobach et al. 2016).
4. Toxin A/B enzyme immunoassay (EIA): EIA is a fast test that provides results in about 1 to 2 hours, and has a 75-85% sensitivity and a 95%-100% specificity. Due to its low cost and ease, it is the most popular in laboratories. However, many studies have highlighted its lack of sensitivity (ranging from 29% to 86%) in comparison to CCNC, which excludes its use as a stand-alone test for the diagnosis of CDI (Crobach et al. 2016).
5. Cell culture cytotoxicity neutralisation assay (CCNA): It is considered the gold standard for detecting free toxins (mainly toxin B) in stools. For this method, stool filtrates are inoculated onto a cell culture which is then observed for a cytopathic effect evaluated at 36 ± 1 °C after 1 or 2 days. The specificity of the cytopathic effect is evaluated by the neutralisation with *C. difficile* antitoxin or *Clostridium* sordelli antitoxin sera, which share the same antigens. Despite CCNA's good sensitivity, specificity, and low cost, this method is currently used by a very limited number of laboratories due to the lack of standardisation and prolonged response time (Di Masi et al. 2018).

According to the ESCMID, no test is suitable as a stand-alone test for diagnosing CDI since they have a low positive predictive value. The best way to optimise the CDI diagnosis is by combining two tests in a two-step algorithm (**Figure 2**). The first test should be a high negative predictive value test (GDH or NAAT). The second test should be a high positive predictive value test (toxin A/B EIA). If the first test is negative, DCI is excluded; if it is positive, a second test should be performed to confirm the diagnosis. If the second test is positive, the CDI diagnosis is confirmed; if it is negative, the case must be clinically evaluated. In this scenario, the possible cause can be related to 3 situations: CDI with toxin levels below the threshold of detection, false-negative result, or *C. difficile*

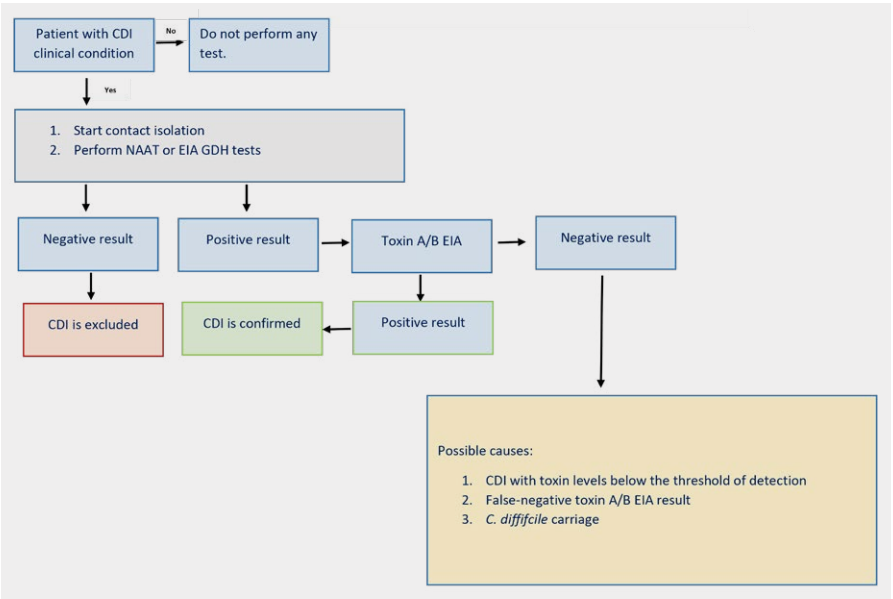

Figure 2. Diagnostic algorithm for *Clostridioides difficile*
CDI: *C. Difficile* infection, EIA: enzyme immunoassay, NAAT: Nucleic acid amplification tests, GDH: EIA detecting glutamate dehydrogenase

carriage (**Figure 2**) (Crobach et al. 2016).

Proper handling in the preanalytical phase is extremely important as it can lead to wrong results. The toxin present in a stool sample breaks down easily at room temperature and can no longer be detected after 2 hours. Thus, when the sample is obtained it should be stored at 4 °C temperature and the test must be performed within the next 24 hours. The test should only be performed on a diarrhoeal stool sample. If the patient has ileus, a rectal swab can be used. Tests in asymptomatic patients are not recommended, unless for epidemiological purposes. Repeat testing for *C. difficile* after successful completion of treatment is also not recommended, as some patients may have positive results without requiring continued or repeat treatment (Czepiel et al. 2019).

Treatment

Once a CDI diagnosis is confirmed and if the patient is symptomatic, the first step is to stop all antimicrobials. The selection of antibiotics should be based on the severity criteria, considering whether it is the first occurrence or a recurrence. For mild to moderate initial infection, treatment with oral vancomycin at a 125 mg QID dose for 10 days is recommended (Abreu et al. 2019). Treatment with fidaxomicin (a narrow-spectrum antibiotic of specific antibacterial activity due to its inhibition of bacterial RNA polymerase) at a 200 mg BID dose for 10 days is an alternative to vancomycin. Recent clinical trials have shown the non-inferiority of fidaxomicin compared to vancomycin; it even has a lower recurrence rate than vancomycin (Polivkovaa et al. 2021). If vancomycin or fidaxomicin are not available, it is recommended to use metronidazole as an alternative treatment, which is prescribed at a 500 mg TID dose for 10 days. In patients who cannot tolerate the oral route, this antibiotic can be administered intravenously. The lack of response to metronidazole after 5 days of treatment is an indication for a change from the antibiotic to oral vancomycin at a 125 mg QID dose for 10 days (Abreu et al. 2019; Johnson et al. 2021; Antonelli et al. 2020).

In severe complicated CDI, combination treatment of oral vancomycin at 250 to 500 mg QID doses combined with metronidazole 500 mg TID intravenously for 14 days is the treatment of choice. In severe-complicated cases with abdominal distention or ileus, it is recommended to administer vancomycin at a 500 mg QID dose via a rectal tube (Abreu et al. 2019; Johnson et al. 2021; Antonelli et al. 2020).

For patients with multiple recurrences, vancomycin is recommended at a 125mg QID dose for 10 to 14 days, followed by rifaximin 400 mg TID for 20 days or fidaxomicin 200 mg BID for 10 days (Abreu et al. 2019; Polivkovaa et al. 2021).

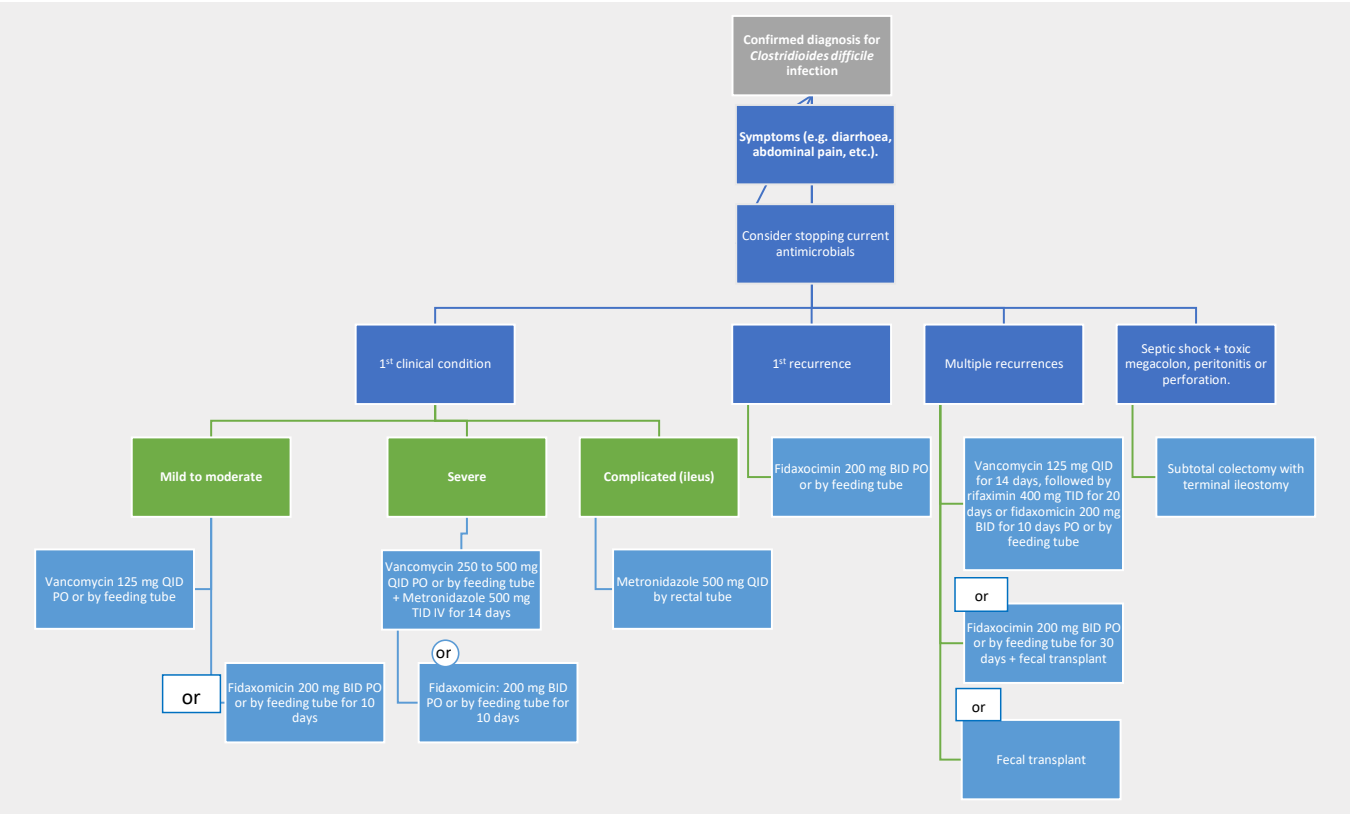

Figure 3. Treatment algorithm for *Clostridioides difficile*
PO: by mouth or orally

Patients with a septic shock, or multiple organ failure (with clinical evidence of toxic megacolon, peritonitis, or perforation), who have failed treatment are candidates for surgical intervention. Surgery should also be considered in patients with severe CDI who do not respond to antibiotic treatment. The surgical intervention of choice is subtotal colectomy with terminal ileostomy since segmental colectomies have a worse prognosis (**Figure 3**) (Sartelli et al. 2019).

Fecal microbiota transplant (FMT) is a safe and effective option in CDI patients with two recurrences or severe episodes, when antimicrobial treatment fails. It consists of the infusion of stool (containing the entire community of the intestinal microbiota) from a healthy donor to the digestive tract of the patient to cure or improve a disease. The purpose of FMT in CDI treatment is to restore the diversity of microorganisms in the colonic microbiota and to stop *C. difficile* growth.

FMT is indicated for the following cases:

- Recurrent *C. difficile* infection.
  - 3 or more episodes of mild to moderate CDI (1 initial and 2 recurrences) when treatment with vancomycin for 6 to 8 weeks fails, whether combined with another alternative antibiotic (fidaxomicin, rifaximin, nitazoxanide) or not.
  - 2 or more episodes of CDI with hospital admission and significant morbidity.
- Severe or fulminant CDI that does not respond to standard treatment within 48 hours.

The microbiota donor can be a known donor (family member, friend, spouse) or a universal donor (anonymous). The donor must be a healthy subject without digestive or extradigestive comorbidities, and risk of transmitting an infectious agent, and have not used antibiotics in the last three months. Routes of FMT administration include nasogastric tube, colonoscopy, enema, or capsule, which all have been shown effective (Abreu et al. 2019; Chun-Wei et al. 2021).

Bezlotoxumab can be used as a co-intervention with antibiotics for patients with a recurrent CDI in the past 6 months to reduce the risk of a subsequent CDI recurrence after initial clinical recovery. In patients with a history of congestive heart failure, the US Food and Drug Administration (FDA) advises that bezlotoxumab should be reserved for use only when the benefit outweighs the risk. There are comparative trials of different anti-CDI recurrence strategies using narrow-spectrum antibiotics that target *C. difficile*, restoration of the microbiota by biotherapeutics or FMT, or increase of host immune response with single-administered agents, such as bezlotoxumab (Johnson et al. 2021).

In conclusion, *C. difficile* infection is a serious disease that must be appropriately recognised and treated due to its high risk of spread and its potentially serious complications. Therefore, avoiding the indiscriminate use of antibiotics for hospitalised patients is crucial.

Conflict of Interest

None. ■

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The Role of the Microbiome and Nutritional Therapy in Critical COVID-19

Dysbiosis has been closely related to inflammation and severe-to-critical COVID-19, a reason why nutritional therapy could be important in the prevention and management of critical disease.

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Introduction

Infection by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease (COVID-19), involves the recognition of the cell's angiotensin converting enzyme 2 (ACE2) receptor through its Spike protein. ACE2 is not only expressed in the respiratory tract, but also in the gastrointestinal tract, especially enterocytes of the ileum and colon (An et al. 2021). The interactions between enterocytes, ACE2 receptors and the gastrointestinal microbiome are believed to be involved in health and disease, possibly leading to gastrointestinal symptoms in patients with COVID-19 (Pan et al. 2020). Since SARS-CoV-2 RNA has been identified in stools of patients with COVID-19, viral infection of enterocytes could play a role in its pathogenesis (Xiao et al. 2020). Understanding the role of intestinal dysbiosis and nutritional therapy in patients with COVID-19 could be important to improve management of patients with critical disease.

Human Microbiome and SARS-CoV-2 Infection

SARS-CoV-2 has been detected in nasopharyngeal and oropharyngeal swabs, and faecal samples of patients with COVID-19 (Xiao et al. 2020). Increased ACE2 expression has been associated with facilitation of viral infection, impaired immune responses, and intestinal dysbiosis during SARS-CoV-2 infection (Aguirre García et al. 2021). Alterations in the intestinal microbiome may influence lung immunity, response to respiratory infections, and development of concomitant gastrointestinal and respiratory symptoms (Chunxi et al. 2020). This link would be of importance since COVID-19 patients with gastrointestinal (GI) symptoms experience greater respiratory distress compared with patients without GI involvement (Mao et al. 2020). Furthermore, chronic conditions which are often associated with intestinal dysbiosis (i.e. obesity, diabetes mellitus, cardiovascular diseases and other age-related disorders) (Durack and Lynch 2019) are associated with greater risk of experiencing severe-to-critical COVID-19 and short-term mortality (Mancilla-Galindo et al. 2020; Vera-Zertuche et al. 2021).

Dysbiosis and Inflammation in COVID-19

Dysbiosis refers to any changes in the composition of the microorganisms which shape the human microbiome, with respect to that found in healthy individuals (Petersen and Round 2014). Therefore, dysbiosis may occur in different forms, including reduced microbial diversity, loss of beneficial microbes, or increased relative abundance of pathogens. Like the chicken-and-egg dilemma, directionality and causality of dysbiosis in the context of COVID-19 remains to be determined since it is not

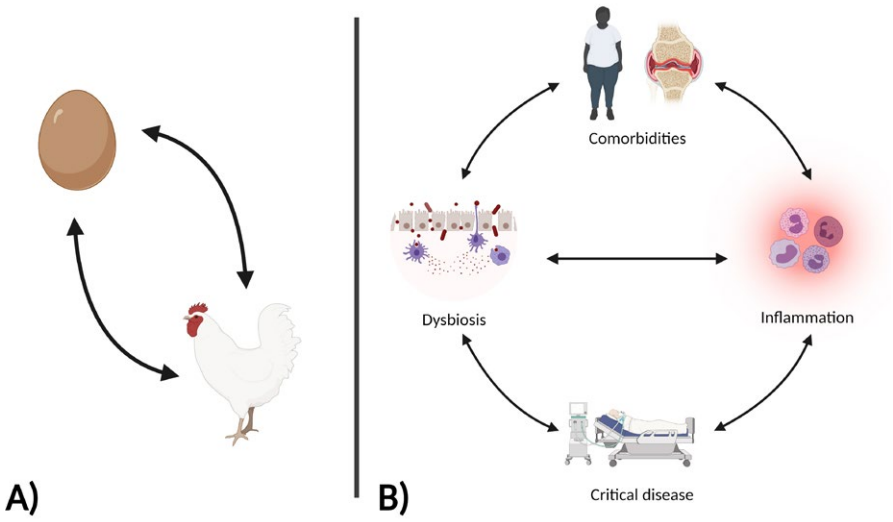

Figure 1. Like the A) chicken-and-egg dilemma, the B) dysbiosis-and-COVID-19 dilemma remains unsolved since there are numerous factors which interplay during viral infection of which causality and directionality have not been elucidated. Created with BioRender.com.

clear yet if dysbiosis puts patients at risk of disease progression, if altered immune responses favour dysbiosis, if dysbiosis promotes inflammation, or if dysbiosis is an incidental finding in severe-to-critical COVID-19 since patients with comorbidities are inherently at increased risk of adverse outcomes. We depict interactions involved in the dysbiosis-and-COVID-19 dilemma in **Figure 1**, which do not necessarily have to be unidirectional but could be bidirectional.

There are various ways by which the microbiome could have its interplay with the immune system and other organs. For instance, metabolites, such as short chain fatty acids (SCFAs), play an important role in modulating immune responses (Gonçalves et al. 2018). These SCFAs can efficiently minimise exaggerated inflammatory responses through T helper (Th) cells, regulatory cells and Th17 effector cells (Li et al. 2018). Furthermore, intestinal dysbiosis is correlated with a lower production of metabolites from intestinal bacteria such as butyrate, leading to increased intestinal permeability (Mosca et al. 2016). Consequently, the integrity of the intestinal barrier is compromised, which facilitates translocation of microbial products, activating the immune system and triggering inflammatory responses. This could be associated with favouring the increased proinflammatory cytokine signature (IL-6, IL-10, and TNF-α) found in patients with severe-to-critical COVID-19 (Del Valle et al. 2020).

Risk Factors

During the patient's stay in the Intensive Care Unit (ICU), there are numerous factors which may promote dysbiosis in critical patients. These include glucose and electrolyte alterations, the use of exogenous opioids, sedatives, catecholamines, and muscle relaxants, poor oral hygiene, invasive devices, body positioning, transport and mobilisation of patients, among others (Bao et al. 2020; Fernández-Barat et al. 2020). Mechanical ventilation in itself promotes airway stress, which affects mucociliar activity and clearance of secretions, with inexistent or diminished cough reflex, which favour overgrowth of opportunistic and pathogenic microorganisms (Dickson 2016).

Comorbidities

Conditions like obesity, cardiovascular disease, hypertension, diabetes, rheumatoid arthritis, and cancer have been associated with higher levels of proinflammatory cytokines and decreased intestinal barrier function, which increases the risk of infection and intestinal dysbiosis (Aguirre García et al. 2021).

Antibiotics

Antibiotics are important therapeutics often used in patients at the ICU which have the potential of reducing mortality, although their irrational use is not uncommon (Ali et al. 2019; Mancilla-Galindo et al. 2021). Use of antibiotics in patients with COVID-19 has been reported to be high (three quarters of patients regardless of receiving ambulatory or hospital care) (Langford et al. 2021). The use of antibiotics is associated with important changes in the GI microbiome with the consequent increase in susceptibility to GI infections by nosocomial pathogens (Dickson 2016). Thus, regeneration of the intestinal microbiota during and after hospitalisation in patients exposed to antibiotics could be considered as part of their rehabilitation.

Sedatives, analgesics, relaxants and inotropes

Increasing evidence has pointed out that sedatives, analgesics, opioids, and muscle relaxants may be involved in favouring dysbiosis. For example, opioid receptors are found not only in the central nervous system but also in the GI tract, thereby having influence on the host-microbe relationships. Also, inotropes have been associated with increased relative abundance of pathogens in the gut. Thus, prescription of these drugs in the ICU must be well founded without forgetting that their prolonged or irrational use may have a negative impact in the microbiome (Rueda-Ruzafa et al. 2020).

Opportunistic Pathogens and COVID-19

A recent study showed that faecal samples from COVID-19 patients tested positive for SARS-CoV-2 up to 6 days after clearance of the virus from the respiratory tract (Zuo

et al. 2020a). In addition, these faecal samples had an increased abundance of bacterial pathogens: *Collinsella aerofaciens, Collinsella tanakaei*, *Streptococcus infantis*, and *Morganella morganii*. Among these species, *C. aerofaciens* is associated with loss of integrity of the intestinal epithelium by increasing the expression of the proinflammatory cytokine IL-17 and chemokines CXCL1 and CXCL5 (Kalinkovich and Livshits 2019). Similarly, higher levels of *Klebsiella, Streptococcus*, and *Ruminococcus gnavus* in COVID-19 patients have been associated with increased proinflammatory cytokines (IFN-γ, TNF-α) and Th1 cell activation (Zuo et al. 2020b).

Opportunistic pathogens (*Streptococcus, Rothia, Veillonella, Erysipelatoclostridium*, and *Actinomyces*), along with bacteria which favour inflammation (*Coprobacillus, Clostridium ramosum, Clostridium hathewayi*) have also been found to be increased during the course of COVID-19 (Zuo et al. 2020a). The number of common opportunistic pathogens of the genus *Enterococcus*, phylum *Firmicutes* such as *E. faecalis*, and Enterobacteriaceae family, which includes *Escherichia coli* and *Klebsiella pneumoniae*, have also been found to be increased in critically ill COVID-19 patients, whereas faecal samples that had low or no SARS-CoV-2 traces were reported to have a higher abundance of SCFAs-producing bacteria like *Parabacteroides merdae, Bacteroides stercoris, Alistipes onderdonkii*, and *Lachnospiraceae bacteria* 1_1_57*FAA* (Tang et al. 2020).

In summary, early evidence has shown that SARS-CoV-2 is associated with dysbiosis, possibly by favouring changes on the microbiome through yet uncharacterised mechanisms.

Bowel Dysfunction

GI symptoms during SARS-CoV-2 infection are usually mild and non-specific, including nausea, vomiting, diarrhoea and abdominal pain (Kariyawasam et al. 2021). Patients with GI symptoms present fever, shortness of breath and body aches more often. As mentioned earlier, the presence of GI symptoms has been associated with greater disease severity, hospitalisation, ICU admission, and intubation (Reintam Blaser et al. 2020). In critically ill patients, gastrointestinal dysfunction is highly prevalent and associated with adverse outcomes. A study in patients with acute respiratory distress syndrome found an increased occurrence of potentially serious GI complications like ileus and mesenteric ischaemia, as well as high risk of GI thrombosis due to increased clotting activity (Helms et al., 2020). Inflammation of the endothelium and increased cell death have been described for GI tissues from patients with COVID-19 (Stahl et al. 2020; Varga et al. 2020).

> **“early evidence has shown that SARS-CoV-2 is associated with dysbiosis, possibly by favouring changes on the microbiome through yet uncharacterised mechanisms”**

Probiotics and Prebiotics

The use of probiotics (live microorganisms able to provide potential health benefits), prebiotics (nutrients that stimulate growth or activity of beneficial microorganisms) and synbiotics (combination of probiotics and prebiotics) have been used to treat intestinal dysbiosis with the intention of allowing proliferation of protective bacteria, potentially attenuating inflammation (Hemarajata and Versalovic 2013). These products may have protective effects by enhancing epithelial barrier function, improving intestinal diversity, and preventing colonisation with opportunistic pathogens. The use of probiotics in critically ill patients could improve outcomes in patients with COVID-19 (Walton et al. 2021), although randomised controlled trials evaluating them should be performed. Nonetheless, the Chinese National Health Commission has advocated for the use of probiotics to treat patients with severe COVID-19 to mitigate intestinal dysbiosis and possibly reduce bacterial translocation and secondary infections ((Tian and Rong 2020). Currently there are multiple lines of research involving probiotics which will allow to elucidate their utility in critical patients.

The Role of Nutritional Support in Dysbiosis

Omega 3

The effect of Omega-3 polyunsaturated fatty acids (omega-3 PUFAs) like eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from fish oil, have the potential to attenuate the inflammatory response related to metabolites released by macrophages (cytokines, chemokines, prostaglandins and leukotrienes) (Gutiérrez et al. 2019), by contributing to the synthesis of eicosanoids and specialised lipid mediators such as resolvins and protectins which lower inflammatory activities. The daily intake of Omega-3 PUFAs produces an increase in SCFAs, resulting in a protective effect for the intestinal microbiome (Watson et al. 2018). In a small randomised study where 1000 mg of omega-3 (400 mg EPA, 200 mg DHA) were administered for 14 days after admission to the ICU, patients had greater survival compared with the control group (Doaei et al. 2021). Therefore, omega 3 PUFAs could be used in critical patients to improve outcomes, although further prospective studies are warranted.

Enteral nutrition

Enteral nutrition (EN) remains the preferred method of nutritional therapy when oral ingestion fails since it promotes GI stimulation. The lack of contact with nutrients in the GI tract of critically ill patients is an important factor associated with intestinal dysbiosis. Resulting alterations of the intestinal mucosa could lead to atrophy of

lymphoid tissue and functional deterioration of the immune system, as well as bacterial proliferation and translocation (Szefel et al. 2015). For this reason, nutritional intervention therapy could play an essential role to prevent such complications. The use of early enteral nutrition has been associated with better immune function, less bacterial translocation, and greater mucosal integrity (Zaher 2020).

The intestinal microbiota is normally preserved through food and its dietary components in adequate proportions and concentrations. Thus, EN should contain protein, a moderate amount of carbohydrates, and the use of fibre once the intestine has recovered functionality, to produce SCFAs that may confer anti-inflammatory benefits (Martindale et al. 2020). With this in mind, inadequate dietary composition of EN may also alter the composition of the intestinal microbiota and increase the growth of opportunistic pathogens (Zaher 2020), whereas overfeeding produces gastrointestinal complications when there is risk of refeeding syndrome (i.e. haemodynamically unstable patient).

Diet as a protective factor

When diets are low in fibre and high in fat and/or carbohydrates, intestinal dysbiosis is more frequent. The intestinal microbiota is responsive to both acute exposures and long-term dietary exposures, with an ability to respond rapidly in a matter of hours (Thaiss et al. 2016). Therefore, eating habits including daytime, duration, and frequency of meals influence the composition and functionality of the intestinal microbiota (Thaiss et al. 2014).

Conclusion

The human microbiome may influence how the immune system responds to viral infections. Dysbiosis has been closely related to inflammation and severe-to-critical COVID-19, although more research is needed to understand the directionality and potential causality of these associations. Nutritional intervention can be helpful to reduce the risk of presenting dysbiosis through regular consumption of foods, nutrients and bioactive molecules with potential anti-inflammatory effects, to promote a healthy microbiome in the absence of critical disease. Nutritional therapy is also of primary importance in critically ill patients with COVID-19.

Conflict of Interest

None. ■

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Safer Intubation Practices in Critically Ill Patients

What we learned during the COVID-19 pandemic that should not be forgotten

An overview of the available evidence on safe intubation practices in critically ill patients in light of new discoveries due to the coronavirus pandemic.

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Introduction

Orotracheal intubation is a life-saving procedure in critically ill patients with acute respiratory failure, but complications during the procedure are frequent and life-threatening situations still occur in almost 45% of the procedures (Simpson et al. 2012; Russotto et al. 2021). The vast majority of clinical evidence on intubation is mainly focused on the operating room (OR). As opposed to traditional anatomical challenges, orotracheal intubation in the intensive care unit (ICU) imposes further risks due to the high prevalence of a physiological difficult airway (Mosier 2020).

The COVID-19 pandemic brought new challenges for intubation in the ICU. Severe respiratory failure and hypoxaemia, commonly present in COVID-19 patients, impose an increased risk of cardiovascular collapse and cardiac arrest during intubation. Besides, the procedure may expose healthcare professionals to contamination and changes in usual practice aiming at staff protection may unduly increase procedure difficulty (Feldman et al. 2020). Thus, while COVID-19 imposes challenges to intensive care physicians, it also creates opportunities for improvement in relation to intubation practices in the ICU.

Our objective with this piece is to summarise the available evidence about safe intubation practices in critically ill patients in light of new discoveries due to the coronavirus pandemic.

Intubation in Critically Ill Patients – Prior Evidence

Severe adverse events occur in 1 of 22.000 cases of orotracheal intubation in the operating room. On the other hand, the incidence of life-threatening complications may be as high as 45% during intubation in the ICU (Simpson et al. 2012; Russotto et al. 2021). It must be highlighted that this high incidence of complications in the ICU cannot be attributed solely to the lack of the anaesthesiologist. In a prospective comparison of intubation attempts for 208 patients intubated first in the OR and later in the ICU, both by anaesthesiologists, the incidence of difficult airway and complications were higher in the ICU, while first-time intubation success was lower when compared to the OR (Taboada et al. 2018). Intubation strategies – and risks – may vary among elective surgery and critically ill patients, but most of the clinical evidence is mainly focused on the OR.

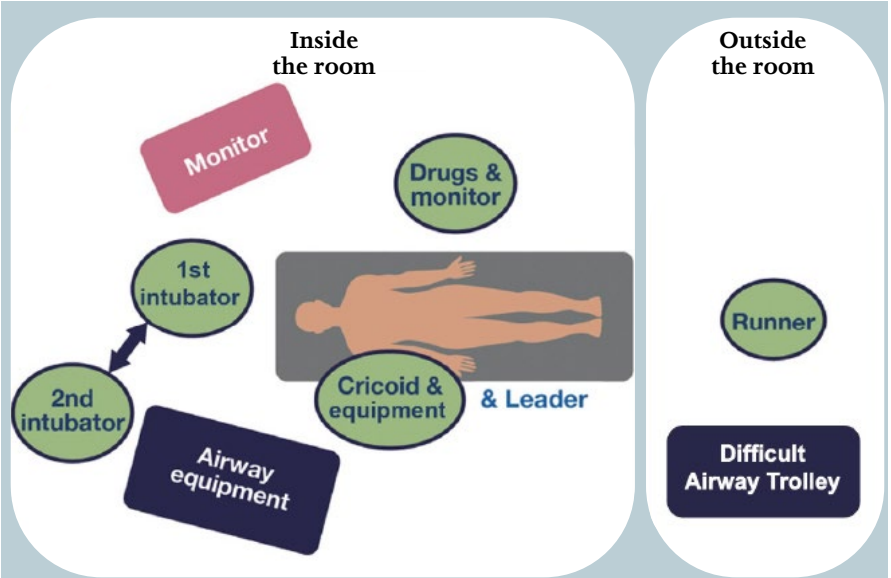
The differences between airway management in the OR and ICU begins with the evaluation of the airway. Several predictors of difficult laryngoscopy, such as the 3-3-2 rule or the upper lip bite test depends on patient collaboration and may be unfeasible in the critically ill (Detsky et al. 2019). So far, the only validated airway assessment tool in ICU patients is the MACOCHA score, which still depends on the patient being able to sit for the Mallampati evaluation (De Jong et al. 2013). However, despite these limitations, assessing potential difficulties is advisable before all intubations in the ICU environment.

When it comes to efforts in preparing the scene to increase first attempt success, it is worth noting that the use of a checklist to ensure protocol adherence was not superior to standard care in a randomised controlled trial (Janz et al. 2018). Neverthe-

less, specific strategies during each step of the procedure can increase patient safety and must be implemented when possible.

Preparing the scene and patient positioning

Experienced staff is advisable for a safer procedure. Ideally, the presence of two airway operators with the presence of a senior physician can reduce the risk of overall complications (Schmidt et al. 2008). The leader must also plan and verbalise the primary and rescue strategies to be adopted to share their mental model with the team should any difficulties ensue during the procedure. Sedative agents, rescue devices and ventilation equipment must be checked and readily available. Two experienced operators and an easy access to a difficult airway trolley is advisable. One should not expect a *bolus* of fluid to be enough to manage hypotension or cardiovascular collapse. In a randomised controlled trial, routine infusion of a 500ml crystalloid solution did not prevent the occurrence of hypotension during intubation in the ICU in the absence of hypovolaemia (Janz et al. 2019). Therefore, norepinephrine must be readily available if hypotension is expected. Finally, sniff positioning must be optimal and is superior to other strategies of patient positioning during intubation in the ICU (Semler et al. 2017). **Figure 1** exemplifies scene preparation before orotracheal intubation.



During orotracheal intubation, there are some roles that each team member can have (and sometimes more than one role at a time): (a) the 1st intubator, (b) drug administrator (drugs), (c) an observer of the patient's clinical state (monitor), (d) cricoid force applier or BURP manoeuvre (cricoid), (e) airway equipment assistant (equipment), (f) a runner to call for help or provide additional equipment if necessary, (g) a 2nd intubator (if possible/available), (h) a team leader/coordinator (leader), and (i) a manual in-line stabiliser (MILS). Usually, at least 4 members are necessary: the 1st intubator (physician), someone for drugs & monitor (the nurse), someone for cricoid & equipment (a respiratory therapist or a physician) and a runner (in the context of the risk of aerosol generating usually outside of the room with advanced devices available in a difficult airway trolley). A 2nd intubator (physician) can or cannot be present. Ideally, at least two physicians proficient in airway management should be present during the procedure with one of them assuming the leader role (avoid this role for the 1st intubator).

Figure 1. Scene preparation before Orotracheal intubation. Adapted from Higgs et al. 2018.

Pre-oxygenation

Pre-oxygenation before intubation aims at prolonging the period of safe apnoea after sedation and neuromuscular blockade. Offering 100% oxygen for 3 to 5 minutes reduces the risk of desaturation in comparison to standard of care. Strategies for proper pre-oxygenation includes the use of noninvasive ventilation, high-flow nasal canula, bag-valve-mask ventilation with 15 L/min oxygen and nonrebreather mask with a flush-rate oxygen delivery (>40 L/min). A randomised controlled trial suggested that bag-valve mask ventilation before first intubation attempt improved patient oxygenation without an increased risk for aspiration of gastric content. Although not definitive, these results suggest that ventilation before intubation is not harmful as previously reported and may be interesting in severely hypoxaemic patients (Casey et al. 2019). On the other hand, apnoeic oxygenation during intubation with nasal catheter or high-flow nasal canula seems ineffective and should not be routinely performed (Vourc'h et al. 2015; Bailard et al. 2006; Simon et al. 2016; Semler et al. 2016).

Sedation strategies and use of neuromuscular blockade

There is not enough evidence to support the use of a specific sedation strategy over another during intubation in the ICU. In an observational cohort in 34 institutions, etomidate, propofol, midazolam and ketamine were the most used drugs by intensivists (Groth et al. 2018). The patient baseline condition is usually determinant in the choice of sedation strategy. Propofol and midazolam are more commonly used in a situation of haemodynamic stability, while etomidate and ketamine are preferred in a clinical scenario of shock (Mendes et al. 2020).

The use of neuromuscular blockade during intubation in the ICU is still a matter of debate. While several randomised controlled trials support the use of neuromuscular blockade and rapid sequence induction in the OR (Lundstrøm et al. 2018), the evidence in the ICU is based solely on observational studies (Li et al. 1999; Mosier et al. 2015; Wilcox et al.

2012). Potential risks of eliminating patient effort and respiratory drive with the use of NMB includes the risk of a rapid fall in patient oxygenation and a high risk of cardiovascular collapse in a do-not-intubate, do-not-ventilate scenario.

However, despite the lack of randomised trials and potential risks, available evidence suggests that the use of neuromuscular blockade can increase first attempt success and reduce overall complications during intubation in the ICU. So far, the use of NMB in the ICU may vary from 20 to 90% of intubations in different cohorts (Simpson et al. 2012; Yamanaka et al. 2010; Doig et al. 2009). In a recent survey regarding practices of airway management in the ICU, physicians reported the use of NMB in the minority of cases (Mendes et al. 2020).

Auxiliary devices and airway manipulation

Two recently published randomised controlled trials evaluated the use of auxiliary devices to increase first-attempt intubation success in the intensive care unit. The Styleto trial has shown that the routine use of a tracheal tube plus a stylet during intubation is superior to the tracheal tube alone to achieve first-attempt intubation success. Although this trial was not powered to evaluate possible differences among serious adverse events between groups, the use of a stylet did not increase traumatic injuries related to tracheal intubation in the ICU (Jaber et al. 2021). Similarly, a randomised trial evaluated the use of a bougie versus tracheal tube and stylet on first-attempt emergency intubation success. The rate of success was higher in the bougie group with similar rates of procedure related complications (Driver et al. 2018). Nevertheless, we believe adequate training about the caveats of using these devices is strongly advisable to avoid as much as possible preventable (and eventually fatal) complications associated with these devices, such as tracheal tears and posterior wall injuries, specially by inexperienced physicians.

When it comes to airway manipulation during intubation the most readily available strategy for dealing with difficult laryngoscopy is posterior displacement of the larynx by backward pression. The Sellick manoeuvre is largely adopted during intubation but it was originally described to "control regurgitation until intubation with a cuffed endotracheal tube was completed" and should not be the first strategy (Sellick 1961). On the contrary, the displacement of the larynx backward, upward and rightward with the so called BURP manoeuvre can improve vocal chords visualisation and may be adopted to improve intubation success (Takahata et al. 1997).

Direct laryngoscopy X Video laryngoscopy

Video laryngoscopy (VL) has emerged as a new standard of care or best practice during intubation in the ICU. It is supposed to provide a better view of the vocal cords even when difficulty is expected due to anatomical reasons. It does not demand a perfect alignment of the structures and can magnify the image, facilitating the intubation process. It also allows concurrent visualisation by a second operator that can immediately aid in airway management. However, it is more expensive and less available than direct laryngoscopy (DL). More important, previous knowledge of the intubation with DL is not directly transferrable to VL and variable learning curves can be expected.

In a small single center randomised trial, the use of VL improved first attempt success during urgent endotracheal intubation (Silverberg et al. 2015). However, in a larger trial published, VL compared with DL did not improve first attempt success rate and, unexpectedly, was associated with higher rates of severe life-threatening complications. The reasons for intubation failure varied among both strategies. In the DL group, the inability of glottis visualisation was the main reason for intubation failure. On the other hand, in the VL group, glottis visualisation was not possible in only 22% of the cases and failure of tracheal intubation was the most reported reason despite proper vocal cord visualisation. It is possible that the absence of previous training and proper skill may have contributed to the trial results (Lascarrou et al. 2017).

Confirmation of intubation

The use of waveform capnography to confirm intubation is mandatory and should not be considered as an optional auxiliary device. Lung auscultation and visualisation of chest wall movement are not reliable signs and cannot be used as single strategy to check intubation success, especially in the absence of neuromuscular blockade (Whitaker and Benson 2016; Linko et al. 1983).

The Need to Recognise and Anticipate the Physiologically Difficult Airway: A Life-Threatening Situation

As previously discussed, the occurrence of severe complications is much higher in the ICU setting than in the operating room. Cardiac arrest may occur in up to 4% of the patients and haemodynamic instability along with hypoxia are the most common reasons for this event (Russotto et al. 2021; Heffner et al. 2013). Moreover, life threatening situations may occur even with first attempt success in patients with severely deranged physiology and pre-intubation status is important to identify patients at increased risk for complications (Heffner et al. 2013). In a large retrospective cohort of intubation in critically ill patients, arterial hypotension prior to intubation, hypoxia prior to

intubation, absence of pre-oxygenation, age and obesity were independently associated with cardiac arrest and death (De Jong et al. 2018). Three of these may be modifiable risk factors in case of proper recognition before initiating the procedure.

High-risk situations other than hypotension and hypoxaemia may also behave as physiologically difficult airway. Pulmonary hypertension or right ventricular dysfunction, severe acidosis, intracranial hypertension and the full stomach scenario may all impose a greater risk of complications, even in the absence of traditional anatomic predictors of difficult airway (Mosier 2020). **Table 1** highlights physiologically difficult situations and possible strategies to overcome them.

Respiratory failure

- Pre-oxygenation with positive pressure ventilation
- Routine bag-valve-mask ventilation after induction and before laryngoscopy in the absence of a high risk of aspiration
- Consider apnoeic oxygenation if high risk of aspiration

Haemodynamic instability

- Prepare push dose vasopressors
- Prepare a norepinephrine infusion should hypotension be anticipated
- Ensure fluid replacement if hypovolaemia is likely, but don't rely on routine fluid boluses to correct or avoid hypotension

Metabolic acidosis

- Administer sodium bicarbonate before intubation
- Ensure adequate minute-ventilation after intubation (at least 2X100 mL/Kg of predicted body weight)

Acute brain injury and intracranial hypertension

- Avoid even short-term desaturation and hypotension episodes
- Avoid severe hypertension during the procedure
- Avoid long intubation attempts that risk acute hypercapnia

Abdominal distension / Vomiting / Upper gastrointestinal bleeding / Full stomach

- Have a rigid aspirator readily available
- Consider awake intubation or avoid neuromuscular blockade
- Place a nasogastric tube in case of suspected bowel obstruction or ileum
- Avoid videolaringoscopy unless judged extremely necessary

Pulmonary hypertension / Right ventricular dysfunction

- Avoid hypercapnia and low minute ventilation
- Avoid hyperinflation and start with low PEEP (5 – 8 cmH_2O)
- Start norepinephrine pre-emptively and avoid (even short term) hypotension episodes

Table 1. Physiologically difficult situations and preventive strategies

Intubation in COVID-19 patients poses as a major challenge when it comes to physiologically difficult airway. Hypoxaemia is common and safe apnoea time may be as short as 60 seconds in lungs with a poor compliance (Mosier 2020). Moreover, the combination of severe hypoxaemia due to pneumonia and hypercapnia due to increased dead space ventilation further increases the risk of acute *cor pulmonale* and right ventricular dysfunction (Mekontso et al. 2016).

Intubation of the COVID-19 Respiratory Failure

Given that COVID-19 is a disease transmitted predominantly by droplets, intubation and airway management are procedures with high level of exposure of healthcare workers and increased risk of contracting the illness. Some proposed changes in usual practice due to the COVID-19 pandemic affected all steps of intubation, from preparation to checking proper tube position. Therefore, protective measures are important but may increase the risk of severe complications and it is necessary to balance the risks and benefits of each of these measures.

What has changed that increased the procedure risk

To reduce staff exposition, guidelines and recommendations suggested to limit the number of people inside the room (Cook et al. 2020; Orser 2020). However, previous publications also suggested that two operators can reduce complications during the procedure. Therefore, a reduced number of people is adequate but the presence of two airway operators is still advisable (Jaber et al. 2006). Also, initial recommendations suggested changes in patient preoxygenation to reduce staff exposure to aerosol. Non-invasive ventilation and high flow nasal canula were contraindicated by some (Cook et al. 2020). Moreover, low flow non-rebreathing mask, which is incapable of providing 100% oxygen, was suggested as a possible alternative. Although the concern with aerosolisation is understandable, poor preoxygenation can reduce the safe apnoea time and decrease first attempt success. Desperate rescue manoeuvres due to severe desaturation is probably more problematic than the use of proper preoxygenation, eventually leading to cardiac arrest and a crash scenario where any concerns about staff safety are forgotten. Another common reason for crashing after intubation is to forget about the necessary trade-off of increasing respiratory rates when using low tidal volume ventilation for acute hypoxaemic respiratory failure. This has been a frequent observation in our practice, especially with physicians inexperienced with a physiologically difficult airway. Finally, the use of bag mask ventilation and even the use of certain supraglottic devices were discouraged during intubation in COVID-19 patients. However, emergent surgical access of a failed first attempt is probably more difficult and riskier for the patient and staff than traditional algorithms in "do-not-intubate" situations (AMIB 2020).

What has changed that improved patient safety

On the other hand, some recommendations during intubation in COVID-19 should come to stay as the new standard of practice in the ICU. The presence of a runner outside the room with an easy access to rescue devices is advisable and can accelerate the process of accessing an urgent or crashed airway. Moreover, COVID-19 has brought the best experienced airway manager to the patient room. In any intubation, even if a less experienced operator is primarily managing the airway, a senior staff must be present to ensure a low rate of complications (Cook et al. 2020). Despite initial recommendations, recent trials evaluating the use of noninvasive ventilation and high flow nasal canula in COVID-19 patients have facilitated personnel acceptance of using these resources during intubation (Grieco et al. 2021). Adequate preoxygenation with available devices, especially positive pressure ventilation, must remain as the gold standard in preparation for intubation. The routine use of neuromuscular blockade to reduce cough and aerosol dispersion brought the experience of the operating room into the ICU. Although not tested in a randomised trial, available evidence suggests that this strategy can increase first attempt success (Li et al. 1999; Mosier et al. 2015; Wilcox et al. 2012). Fnally, some have suggested a faster escalation to senior physicians and between devices (such as the adoption of the Vortex approach) instead of repeat attempts (3 or more) with the same operator and/or device. With adequate preparedness and sharing of the mental model of the most experienced physician, sharp decision-making during airway management is a desired consequence to improve procedural safety.

Current Approach to Airway Management – Suggested Do's and Don'ts

In **Table 2**, we suggest current do's and don'ts on airway management for critically ill patients, COVID-19 or not, based on current literature, and the authors' previous and acquired experience during the pandemic.

Conclusion

The COVID-19 pandemic brought several challenges to airway management practices in the ICU. The fear of staff contamination changed the usual practice with positive and negative effects to staff and patient safety. Now, after the experience with COVID-19 patients, it is important to filter which

DO	DON'T
Share the mental model and back-up plans of the most experienced operator beforehand	Repeat three attempts with the same device or less experienced operators
Evaluate for a difficult airway	Adopt a one-size-fits-all approach
Aim for first attempt success (with higher order devices in the primary strategy if necessary)	Always use direct laryngoscopy as the primary strategy
Include at least two operators, with at least one more experienced	Operate the airway without a second knowledgeable operator
Fastly escalate between devices should any unanticipated difficulties arise	Avoid bag valve mask ventilation should it be necessary (even in COVID-19)
Anticipate and prepare for physiological difficulties	Proceed to a surgical airway without considering suitable alternatives
Position the patient in a sniffing position attentive to ear-to-sternal notch alignment	Routinely use ramped patient positioning unless necessary to improve ear-to-sternal notch alignment
Pre-oxygenate with positive pressure ventilation in respiratory failure	Rely solely on apnoeic oxygenation to avoid desaturation
Check positioning with capnography	Check positioning solely with auscultation or chest expansion
Prepare a norepinephrine infusion beforehand	Rely on fluid boluses to avoid hypotension or haemodynamic collapse
Use neuromuscular blockers more liberally	Avoid neuromuscular blockers without a clear justification
Aim for an adequate post-intubation minute-ventilation to avoid severe hypercapnic acidosis and cardiac arrest	Start mechanical ventilation with low tidal volumes (≤ 6 mL/kg) without a higher respiratory rate (≥ 25–30 ipm) from outstart.

Table 2. What to do and not to do in airway management of the critically ill

recommendations should be left aside and which ones must stay for good. As with other expert recommendations based on few observations that have led to suggestions of non-evidence informed approaches to the management of known syndromes in critically ill patients, we believe that airway management strategies should also have been maintained to current standards, actually taking them to higher standards if necessary. While protecting healthcare workers is a top priority (and should be done with proper protective equipment), lowering airway management standards for staff protection is both unacceptable and unadvisable. The main lesson we learned in airway management during the pandemic is to keep the highest possible standards informed by the best available evidence to avoid potentially catastrophic and lethal complications.

Conflict of Interest

None. ■

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Methylene Blue for Vasoplegic Syndrome Post Cardiac Surgery

Post-operative cardiac surgical patients are encountered commonly in the intensive care unit. Methylene blue might be a useful treatment for patients with vasopressor-refractory vasoplegia but high quality evidence is lacking.

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Cardiac surgery is one of the most frequently performed major surgical procedures, with more than 1 million operations annually. Major cardiac surgery requiring cardiopulmonary bypass commonly results in post-operative haemodynamic instability and requires specialised management in Intensive Care Unit (ICU). As many as half of all patients requiring cardiopulmonary bypass develop a degree of shock following surgery. In patients responsive to first line vasopressor therapy, the duration of time in ICU and the overall mortality is relatively low. Significant vasoplegia refractory to vasopressors may be seen in between 5 and 25% of patients and increases to 40% in high risk groups (Lenglet et al. 2011a; Fischer and Levin 2010; Lenglet et al. 2011b; Argenziano et al. 1999). Patients like this are considered to have vasoplegic syndrome and often require prolonged ICU care and prolonged hospitalisation (Lenglet et al. 2011b; Ortoleva et al. 2020). Patients with vasoplegic syndrome have high risk of developing renal failure and of adverse neurological, cardiac outcomes and death (Shaefi et al. 2018; Levin et al. 2004; Ortoleva and Cobey 2019; Lenglet et al. 2011b; Liu et al. 2017; Gomes et al. 1998). Given the increasing frequency of invasive cardiac surgery, the investigation and effective management of post-cardiac surgical vasoplegic syndrome is of critical importance.

Definitions of vasoplegic syndrome vary (Lenglet et al. 2011b; Stawicki et al. 2008; Gomes et al. 1998; Donati et al. 2002; Lambden et al. 2018; Orozco Vinasco et al. 2019). In addition to the requirement for the condition to develop within 24 hours of cardiopulmonary bypass, a combination of clinical parameters including low blood pressure, low central venous pressure and pulmonary capillary wedge pressure, elevated cardiac index, and low peripheral resistance combined with a minimum vasopressor requirement are used in the literature to define the syndrome. In practical terms, clinicians recognise vasoplegic syndrome when they encounter a patient with a combination of high cardiac output and low blood pressure.

Pathophysiology of Vasoplegic Syndrome

Cardiopulmonary bypass-induced vasoplegia results from a combination of inciting factors including the immunological response to ischaemia reperfusion injury of the heart and lung, endotoxin release from mucosal surfaces, and complement activation after exposure of blood to the cardiopulmonary bypass circuit (Shaefi et al. 2018; Hall et al. 1997). These processes result in increased production of oxygen free radicals, thromboxane A2, interleukin-1 (IL-1), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF). Inducible nitric oxide synthase is stimulated via these cytokines and leads to an overproduction of nitric oxide (NO) (Lenglet et al. 2011b). NO increases vasodilation primarily via activation of guanylyl cyclase, which results in production of cyclic guanosine monophosphate (cGMP) (Booth et al. 2017). The normal role of cGMP is inhibition of calcium entry via voltage-gated channels and therefore cardiopulmonary-bypass induced NO production leads to a rapid reduction in intracellular calcium and vasodilation. NO also activates ATP-sensitive potassium channels causing membrane hyperpolarisation which causes a further reduction in vascular smooth muscle tone (Ortoleva and Cobey 2019; Ortoleva et al. 2020).

In addition to this well accepted pathway, other NO-independent pathways resulting from the cascade of factors above have been proposed. Cardiopulmonary bypass-induced release of IL-1 and IL-2 results in vasodilation in the absence of NO via direct guanylate cyclase activation and this effect can be reversed with administration of methylene blue (Beasley and McGuiggin 1994; Samlowski et al. 2011). Endogenous soluble guanylate cyclase activating factors such as carbon monoxide (CO) and the hydroxyl free radical (OH) also contribute to vasoplegia by direct activation of guanylate cyclase (Schmidt 1992). Lastly, vasopressin deficiency due to haemodilution during cardiopulmonary bypass has been suggested as an exacerbating feature of post cardiac surgical vasoplegia.

Management of Vasoplegic Syndrome

Accurate pre-operative determination of patients who will develop vasoplegic syndrome is not possible at present. Risk factors which are associated with vaso-

plegic syndrome include pre-operative use of angiotensin-converting enzyme inhibitors or beta-blockers, higher comorbid disease burden before surgery (Shaefi et al. 2018; Riha and Augoustides 2011), low pre-operative left ventricular ejection fraction (Shaefi et al. 2018), preoperative use of heparin, congestive heart failure, prolonged duration of cardiopulmonary bypass, advanced age, and the use of opioid analgesia (Ortoleva et al. 2020).

Early recognition and differentiation of vasoplegic syndrome from other common causes of shock in the post-operative cardiothoracic setting is complex as cardiogenic, obstructive, hypovolaemic and vasoplegic shock often coexist. Fluid responsiveness and post-operative anaemia should be treated with combination of blood product replacement, crystalloid and colloid with a focus on restrictive resuscitative targets (Murphy et al. 2015). Early use of vasopressors and simultaneous investigation and elimination of reversible causes is necessary. Ultimately, the identification of vasoplegic syndrome requires a high index of suspicion and remains a diagnosis of exclusion.

The action of soluble Guanylate Cyclase represents an important target for the management of vasoplegic syndrome. Methylene blue is a low cost therapy which acts via both direct and indirect mechanisms to counteract the vasoplegic effects of cardiopulmonary bypass (Omar et al. 2015). The direct action of methylene blue is via oxidation of both inducible nitric oxide synthase and endothelial nitric oxide synthase resulting in significantly reduced NO levels. Secondly, methylene blue acts via indirect pathways by binding to the haem complex of the guanylate cyclase enzyme. This further reduces vasoplegia by targeting the common final pathway of both nitric oxide dependent and independent mechanisms, reducing the formation of cyclic GMP and increasing intracellular calcium levels and vascular tone.

Only one previous randomised clinical trial has evaluated the use of methylene blue in patients with post cardiac surgery vasoplegia (Levin et al. 2004). A total of 56 patients with post cardiopulmonary bypass vasoplegia were included. Of these, 28 received an infusion of 1.5 mg/kg of methylene blue over 1 hour and 28 received placebo. Mortality in the group treated with methylene blue was 0% compared with 21.4% in the placebo group respectively (P=0.01). There was also a significant difference in the duration of vasopressor support with all patients in the methylene blue group successfully weaned from vasopressor support within 4 hours of the treatment (Levin et al. 2004).

> **“methylene blue is a low cost therapy which acts via both direct and indirect mechanisms to counteract the vasoplegic effects of cardiopulmonary bypass”**

Another randomised clinical trial compared the use of a single 2mg/kg dose of methylene blue given 1hr prior to surgery in patients at high risk of developing vasoplegia (Ozal et al. 2005). In this study, vasoplegic syndrome was not observed in any patients in the treatment group but occurred in 26% of the control. In a second prospective randomised controlled trial, a dose of 3mg/kg vs placebo was given immediately post cardiopulmonary bypass and was observed to significantly reduce post-operative phenylephrine and noradrenaline requirements (Maslow et al. 2006).

Finally, a single centre retrospective analysis evaluating the use of 2 mg/kg of intravenous methylene blue followed by a 12-hour infusion at 0.5 mg/kg/h demonstrated that the use of methylene blue was associated with significant reductions in major adverse events defined as permanent stroke, renal failure, reoperation, deep sternal wound infection, and prolonged ventilation in addition to operative mortality (in-hospital or 30-day) (Mehaffey et al. 2017).

Despite these encouraging data, further research is now needed to establish whether methylene blue can be effectively applied to severe post-operative cardiothoracic vasoplegia to reduce both mortality, duration of vasopressor therapy and ICU length of stay. Given how rapidly the burden of cardiac disease and the frequency of cardiac surgical intervention is increasing, a large randomised controlled trial to determine the safety and efficacy of this therapy is a high priority.

Conflict of Interest

None. ■

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AGENDA

For a full listing of events visit https://iii.hm/icuevents2021

OCTOBER

3-6
ESICM 34th Annual Congress, LIVES 2021
Virtual event
https://iii.hm/1c6i

7-9
10th Europaediatrics 2021
Hybrid event, Zagreb, Croatia
https://iii.hm/1c6j

8-12
ANESTHESIOLOGY 2021 Annual Meeting
San Diego, USA
https://iii.hm/1c6k

12-15
44th Annual Conference on Shock 2021
Portland, USA
https://iii.hm/1c6l

25-28
ACEP 2021 - American College of Emergency Physicians
Boston, USA
https://iii.hm/1c6m

26-29
39th Vicenza Course on AKI & CRRT
Virtual event
https://iii.hm/1c6n

26-29
19th Annual Meeting Neurocritical Care Society 2021
Virtual event
https://iii.hm/1c6o

27-30
The 15th European Conference on Pediatric and Neonatal Mechanical Ventilation EPNV (2021)
Montreux, Switzerland
https://iii.hm/1c6p

27-31
EUSEM 2021
Lisbon, Portugal
https://iii.hm/1c6q

NOVEMBER

4-6
10th Annual Johns Hopkins Critical Care Rehabilitation Conference
Virtual event
https://iii.hm/1c6r

11-13
16th Annual Conference German Society for Interdisciplinary Emergency and Acute Medicine (DGINA)
Kassel, Germany
https://iii.hm/1c6s

25
Ortho Masterclass - Interdisciplinary Acute Care
Virtual event
https://iii.hm/1c6t

DECEMBER

5-8
Critical Care Canada Forum 2021
Toronto, Canada
https://iii.hm/1c6v

6-8
ICS State of the Art 2021
Virtual event
https://iii.hm/1c6w

17-19
Euroanaesthesia 2021
Hybrid event, Munich, Germany
https://iii.hm/1c6x

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