Ageing Population

How to reduce the risk of infection due to drug contamination in COVID-19 patients?

E-symposium at e-ISICEM 2020

Moderator **Prof. Marc LEONE** *(Marseille, France)*

Risk infection due to drug contamination during emergency like COVID-19
Prof. Ignacio MARTIN-LOECHES *(Dublin, Ireland)*

Is there an added-value to use prefilled syringes for infusion in COVID-19 patients?
Prof. Marc LEONE *(Marseille, France)*

AGEING POPULATION

The process of ageing cannot be defined by a number. The World Health Organization classifies anyone over the age of 65 as elderly. However, it is important to understand that ageing is a complex process, and we must consider physiological and cognitive vulnerabilities when talking about ageing as they can make some elderly people more prone to disease and acute medical events. Also, comorbidities tend to increase with age and are associated with increased mortality. Hence, older adults are more vulnerable compared to younger people and factors such as disability, frailty, and multimorbidity increase with age.

It is estimated that by 2050, the percentage of population older than 80 years of age will double (Nguyen et al. 2011). And yet, there is limited evidence to guide the treatment and management of older adults in the ICU. There are currently no international recommendations for the admission or treatment of critically ill older patients >80 years of age. There are also no valid prognostic severity scores that would facilitate geriatric assessments (Guidet et al. 2018).

In this issue, our contributors talk about the **Ageing Population** and the treatment and management of elderly patients in the ICU. Hans Flaatten, Bertrand Guidet and Dylan deLange provide an overview of the VIP (Very Old Intensive Care Patients) project that studies patients 80 years or older. Lauren Ferrante and Snigdha Jain discuss the evidence behind the prediction of long-term outcomes in older ICU survivors.

Oana Tatucu-Babet, Kate Lambell and Emma Ridley provide an overview of recommendations for the nutritional management of critically ill older adults while Jayshil Patel and Daren Heyland talk about the deficiencies in communication and decision-making that impact the quality of care provided to older patients with serious illness.

Alice Reid and Paul Young talk about the key domains from geriatric medicine that are relevant to the practice of intensive care medicine, and Christian Subbe, Chris Thorpe, and Richard Pugh explore a system for assessing the quality of care in critically ill elderly patients.

Our contributors also touch upon the COVID-19 pandemic as critical care doctors continue to fight this battle around the globe. I talk about ICU preparedness, ethical issues during a pandemic and the pros and cons of digital congresses while Andrej Michalsen talks about the controversial and much-debated issue of scarce resources and how healthcare systems can respond to this challenge during a pandemic. Orlando Ruben Perez-Nieto and co-authors discuss in detail the challenges in the management of severe SARS-CoV2 infection in elderly patients.

We are living in an era where medical advancement has made it possible for people to live longer. At the same time, the number of older adults who are likely to require ICU care is also increasing. There is a need to adopt geriatric care models in the ICU and integrate geriatric concepts into critical care practice. Critical care professionals must master the skills that will enable them to better manage the elderly patient and to use improved assessment tools and management strategies. The number of elderly patients will continue to increase. Hence, there is a need to give some importance to ageing-related aspects of critical care to help improve the quality of care for the elderly patient in the ICU.

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

Jean-Louis Vincent

Jean-Louis Vincent
Editor-in-Chief
ICU Management & Practice

Professor
Department of Intensive Care
Erasme Hospital
Université libre de Bruxelles
Brussels, Belgium

JLVincent@icu-management.org

@ICU_Management

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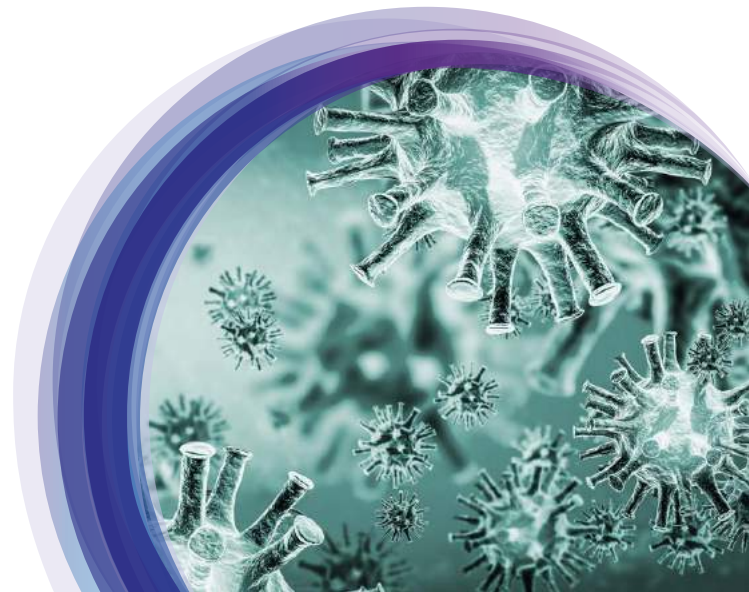
Jean-Louis Vincent
Editor-in-Chief
ICU Management & Practice
Professor
Department of Intensive Care
Erasme Hospital
Université libre de Bruxelles
Brussels, Belgium

JLVincent@icu-management.org

@ICU_Management

Lessons from COVID-19: ICU Preparedness, Ethical Issues and Digital Congresses

Jean-Louis Vincent is a Consultant in the Department of Intensive Care at Erasme University Hospital in Brussels and a Professor of Intensive Care at the Université libre de Bruxelles. He is the editor-in-chief of ICU Management & Practice, Critical Care, and Current Opinion in Critical Care and member of the editorial board of many other healthcare publications. Prof. Vincent has received several awards including the Society Medal (lifetime award) of the European Society of Intensive Care Medicine, the Lifetime Achievement Award of the Society of Critical Care Medicine, College Medalist Award of the American College of Chest Physicians, and the prestigious Belgian scientific award of the FRS-FNRS. ICU Management & Practice spoke to Prof. Vincent about the COVID-19 pandemic and the challenges critical care doctors face across the globe.

The COVID-19 pandemic has brought the world to a standstill. What has been your experience as a critical care professional during this time?
This has been a testing time for all critical care professionals, and indeed all healthcare workers, around the globe. There is no doubt that intensive care teams have done a superb job during this crisis. I am not speaking only about doctors of course, but also nurses, physiotherapists and other healthcare practitioners. It has been a very stressful situation, but our teams have dealt with it extremely well. We can be proud of ourselves.

To what extent do you think the setup of ICUs is likely to change after the COVID-19 crisis?
We have learned a lot about ICU organisation: we managed to open more ICU beds, including in other areas of the hospital, such as coronary care units, recovery rooms or even operating rooms, to increase capacity. We received a lot of

help from other hospital sectors, who provided nurses and doctors to help our ICU teams. We developed new systems for respiratory support (some even using car parts); for keeping and organising material at the bedside; for communication, using walkie-talkies rather than telephones, and providing virtual visits for some relatives. We also increased the use of telemedicine and distant consults. Many of these aspects will continue after COVID-19.

How do you compare the COVID-19 management strategies used in Belgium versus other countries in Europe? Do you have any examples of strategies that were successful and those that failed?
I think that globally people did the best they could under exceptional and unprecedented circumstances. In Belgium, as in several other countries, we had too many deaths in nursing homes, but we had no major 'flooding' of our Belgian ICUs, as was clearly seen in other countries, such as Italy, France and Spain, and managed to

keep our ICU mortality rates relatively low.

Were there any major ethical issues?
Definitely. Ethical problems were present almost everywhere. We were sometimes criticised for denying ICU admission for some elderly patients coming from nursing homes, but these were usually wise decisions. We had to make difficult choices. Ethical guidelines have been published (Azoulay et al. 2020; Vincent et al. 2020), but some did not mention the most important principle: do not apply the 'first come, first saved' principle. And yet the major issues often came when the ICU beds were all occupied and additional patients needed an ICU bed. The next patient to arrive should not necessarily be the one to be 'sacrificed' when some patients who are already in the ICU have much smaller chances of recovering a sufficient quality of life. The most affected regions had many such difficult decisions to make and high rates of withholding/withdrawing life support.

Do you think the mental health of healthcare professionals will be an issue once COVID-19 ends? What would be the best way to deal with this?

Certainly! We all remember the images of Italian doctors weeping at the curbside or the story of the doctor who took her own life after leaving her hospital in New York. In 'normal' times, ICU doctors sometimes have to withhold/withdraw active treatment when it becomes futile, but there is usually time for discussion and preparation of a 'good' death. During this crisis, we have sometimes had to stop therapy quickly, even when futility was not established, but rather to allow a bed/ventilator/ECMO machine to be given to another patient with better chances of recovery. This is a terrible decision for practitioners to have to make, especially when they are relatively unexperienced. In these circumstances, it is essential for senior staff doctors to be around and find the right words to reason, explain, encourage and console. The presence of a psychologist is extremely helpful and although discussions are not always possible in the acute event, consultation should be available for all after such events.

Throughout this pandemic, different treatment strategies have been proposed, many of which are not backed by any clinical evidence. What is your take on it? Do you see any strategy that could be effective?

Unfortunately, we have not been very good at developing new pharmacologic therapies. The only major observation has been the beneficial effects of corticosteroids (primarily from our UK colleagues). Hydroxychloroquine definitely does not work. Remdesivir has only a mild protective effect, which is not worth its high cost. Tocilizumab and other anti-cytokine therapies do not seem to be effective in COVID-19, but patient selection for this drug may not have been optimal. Giving an anti-interleukin (IL)-6 or anti-IL-1

agent to patients who are not evolving into a severe pro-inflammatory phase does not make much sense. This has been a big problem with intensive care therapeutics over the years: we always try and find a 'one size fits all' approach, yet our ICU patients are so very different and we need to determine better which patients are most likely to respond so that treatments can be targeted more individually.

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Could we have done better?

Of course! First, patients and relatives often wanted hydroxychloroquine to be administered 'just in case it may work', but uncontrolled administration of this molecule could prevent inclusion in a clinical trial, especially of course when the study evaluated the effects of hydroxychloroquine. The multicentre trials did not work very well, because of logistic constraints. So, many centres launched their own clinical trials, often including too few patients to allow a meaningful conclusion to be drawn. In the middle of the crisis, clinicians had no time to include patients in trials and when the situation calmed down, the number of suitable patients quickly fell.

As we all try to adjust to the new normal, what do you think are the most important challenges faced by critical care physicians with respect to management and treatment of the critically ill patient?

I think we have all been left with good and bad experiences. Good experiences are those related to the positive dynamism and togetherness of the teams, with a good atmosphere and the clear sentiment of doing the right thing and helping those in need, and of course the positive outcome of some difficult cases… patients we could applaud when they left the ICU. Bad experiences are those related to the frustrations of not being able to do everything we wanted to, and of course the patients we lost despite all the efforts. In a strange way, many people feel that it was globally a good experience, although of course everybody would have preferred to avoid it.

The COVID-19 pandemic has disrupted most healthcare congresses. What was your experience organising your first e-ISICEM?

We were obviously very disappointed that our physical meeting had to be postponed. But we felt it was really important to provide some form of meeting for the critical care community who have been so involved in the pandemic, to share experiences and provide the very latest updates on COVID-19 as well as other aspects of intensive care. But, we had to prepare a programme rapidly to make it as relevant as possible, so had much less time to reach out to new speakers than we would normally have (we did not even have time to reflect on the gender balance of our speakers, a fact that triggered strong criticism from some…). It was also challenging to convince the industry to sponsor a virtual event when there are no physical participants, in particular in the exhibition area.

	Physical	**Virtual**
Programme timing	must be developed early (speaker availability - travel arrangements)	can be finalised quite late (no travel, flexibility if prerecording)
Faculty	usually only from the conference discipline (and several talks)	can include experts outside the main conference discipline (as may give only one talk)
Faculty costs	travel – hotel rooms	usually none
Presentation costs	costly conference rooms	costly recordings/IT support
Last minute speaker cancellations	often several	almost non-existent (if recordings made pre-meeting)
Delayed viewing by participants	often possible	generally possible
Simultaneous sessions	required for big meetings	not necessary (especially if delayed viewing allowed)
Question time	possible (limited duration)	difficult for international meetings (different time zones)
Informal discussions	quite easy	(almost) impossible

Table 1. Major differences between physical and virtual conferences

In your opinion, what are the pros and cons of a physical meeting vs. an e-meeting?

I have listed some of these in **Table 1**. One of the major cons for our participants is the lack of direct discussions and interactions with the experts, not only during question time, which is still possible to a limited extent at virtual meetings, but also in more informal discussions in the hallways or the bar.

Next year you will be celebrating 40 years of ISICEM. What are your tentative plans for ISICEM in the years to come?

Medical meetings evolve over time. Participants are no longer looking for the latest news, as this is immediately available on the internet and shared across social media. What is more important is the associated expert opinion followed by discussions. People like pro and con debates, 'meet the expert' sessions, chances to listen to several sides of an argument and ask questions. We have also made great progress with simulation sessions, and these are taking up a larger part of the programme. ■

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Michael K. Mansour
Assistant Professor of Medicine
Harvard Medical School

Assistant in Medicine
Department of Medicine
Division of Infectious Diseases
Massachusetts General Hospital

mkmansour@mgh.harvard.edu

PCT-Guided Antibiotic Stewardship in COVID-19 Patients

Professor Michael Mansour is a physician-scientist with a research concentration in immune responses against invading pathogens. He attends on the Clinical Transplant Infectious Diseases and Immunocompromised Host Service at the Massachusetts General Hospital - Division of Infectious Diseases, where he cares for solid and stem cell transplant recipients and individuals with weakened immunity. He also directs several COVID-19 clinical trials and sits on committees for the development of treatment guidelines for COVID-19 patients. ICU Management & Practice spoke to Prof. Mansour about the role of procalcitonin in guiding antibiotic use in COVID-19 patients.

Can you please discuss the incidence and role of secondary bacterial infections in terms of risk and mortality?
In the COVID-19 patient population, the incidence of secondary infections appears to be significant. We are beginning to appreciate a few key points:
• One, bacterial respiratory infections appear to be the dominant drivers of secondary infection, although there are a significant number of bloodstream infections as well.
• Two, of the bacteria, there is a mix of gram-positive and negative pathogens. We are looking at this more closely, but gram-positive bacteria such as *Staphylococcus* species are likely to be highly represented.
• Three, despite our improved ICU care, many COVID-19 patients still experience protracted recovery periods, often leaving these patients at risk for secondary infections and prolonged empiric courses of antimicrobials.

Do you think there is an association between PCT values and severe COVID-19 disease?
Yes, I do. PCT does appear to rise in the setting of COVID-19 infection. More precisely, PCT seems to rise as a patient is moving from the viremic phase to a more inflammatory one in the setting of SARS-CoV-2 infection. This rise may reflect the mounting

host immune response, although further investigations are required to understand the association.

The Surviving Sepsis Guidelines and the NIH treatment guidelines both recommend empiric antibacterial therapy in the management of COVID-19 critically ill adults. What is the frequency of usage of antibiotics in COVID-19 patients?
Let's consider this carefully. Initially, in the pandemic, there was a large gap in our experience and management of COVID-19 patients. Many hospitals, including where I practice, witnessed a large spike in antimicrobial usage. In fact, in my experience, the majority of patients being admitted were placed on empiric antimicrobials.

What we have realised is that this practice habit is really unnecessary. While there are a significant number of secondary infections, almost half of COVID-19 patients can be treated without antibiotics.

It is this portion of patients that we should focus our efforts and safely de-escalate antimicrobial therapy. Moreover, for those patients with bacterial superinfection, we need to parse out COVID-related inflammatory pathology from bacterial infection.

Research suggests that only about 10% of COVID-19 patients have bacterial

co-infection but many receive antibiotics. What is your opinion about this?
I think 10% is probably a slight underestimate. A major difficulty in the accurate assessment of secondary bacterial infection stems from clinical judgement of a confusing inflammatory process in CoV-2 pathology. We have significant experience with influenza, for example, where we are more comfortable in judging bacterial superinfection. In the setting of COVID-19, we are still learning and defining the difference in viral versus bacteria pathophysiology. What is progressive COVID-19 versus host response versus bacterial superinfection? These are the clinical struggles that we, as healthcare providers, are faced with daily when managing SARS-CoV-2 infected patients.

What the true superinfection rates are will require careful examination in prospective clinical projects and trials. The careful design of clinical trials must include not only clinical parameters but also the use of additional biomarker tools that will help identify bacterial superinfection and provide insight for the ideal and appropriate usage of antimicrobials.

What could be the consequences of unnecessary antibiotic use use?
This question is incredibly critical and
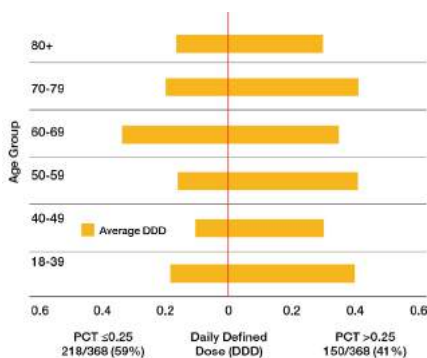
Figure 1. Antibiotic use (DDD) in COVID-19 patients treated in line with a PCT-based guideline recommending to limit antibiotic treatment to patients with PCT >0.25µg/L , if not indicated otherwise by clinical assessment. (Adapted from Williams E.J. et al., 2020; medRxiv preprint doi: https://doi.org/10.1101/2020.06.29.20136572

really the one most central to our discussion. Over the years, we have collected a significant amount of data and experience related to the consequences of antimicrobial overuse. The two most immediate concerns include antibiotic pressure to select resistant pathogens, including MRSA, VRE, multidrug-resistant gram-negative bacteria, and the other is the acquisition of nosocomial infections such as *Clostridioides* (formerly *Clostridium*) difficile.

There are larger, theoretical level impacts that remain under careful research scrutiny, but more and more becoming a reality. A good example of such an impact includes the antibiotic influence on microbiome dysfunction, which is gaining significant evidence in the long-lasting impact on overall health. We need to do our utmost best to avoid the net negative effect of antimicrobial overuse.

What role can PCT play in guiding antibiotic use in COVID-19 patients?
In my opinion, there are two large roles for PCT:
• One, procalcitonin serves as a prognostic indicator of COVID-19 pathogenesis; as patients enter the inflammatory phase, there is a rise in PCT, which can potentially identify patients earlier who may require more intensive care or additional hospital resource allocation.

• Two, PCT can play a role in safely de-escalating antimicrobial usage in COVID patients. I believe the majority of these patients in the milder group can avoid antimicrobial use altogether. Our study, as well as other centres, have demonstrated that most patients with a low PCT safely discharge from the hospital.

While there has been significant data to suggest safe de-escalation, further research studies are required for validation. Randomised controlled trials to confirm the safe stewardship in COVID infection are needed, and in fact, for these reasons, we are currently conducting an RCT, ProSAVE (NCT04158804), to investigate the role of PCT-guided antimicrobial stewardship in US-based hospitals that will include COVID-19 infected patients. We look forward to sharing our results in the near future.

Are there any studies that show the benefit of PCT-guided antibiotic stewardship in COVID-19?
Many studies suggest that PCT can be used for de-escalation, including a recent retrospective analysis performed here at the Massachusetts General Hospital, which we hope to share soon with the community.

In our data, there is good evidence that a low PCT correlates with patients who show no evidence of any concerning microbiology results. I think the most important will be to examine this hypothesis in a prospective clinical trial and define the safety and outcome metrics of a PCT-guided strategy. As mentioned, we have launched such an RCT and hope to answer these important questions in the next year.

The recommended PCT threshold is 0.25. Do you think this is a conservative estimate, and a higher threshold could be adopted safely?
In COVID-19, this question has become interesting because of the nature of COVID-related inflammation that may not typically be seen with other respiratory viral infections. In our data, the majority of patients

who are eventually discharged safely fall below the 0.25 ng/mL cut-off. In addition, those patients with a milder oxygen requirement on the clinical ordinal scale who do not have evidence of concerning microbiology results (blood or sputum cultures) are also successfully identified using a PCT cut-off of 0.25 ng/mL.

On the other hand, when a COVID-infected patient now requires more invasive ventilation and has a higher oxygen requirement based on the ordinal scale, it appears that the 0.25 ng/mL may not provide the discriminatory performance to separate those individuals without significant secondary superinfection. In this sicker cohort, a higher cut-off, such as 0.5 ng/mL may be more appropriate. This analysis is the subject of ongoing research, and we hope to share these results soon.

Overall, what is your opinion about the use of PCT as an antibiotic stewardship tool?
Procalcitonin has a long track record of safety and good performance in lower respiratory tract infections, especially in the area of antimicrobial de-escalation. We are now faced with rising global antimicrobial resistance. It is imperative that we use all available tools, both biomarker and clinical assessment, to appropriately utilise antibiotics.

The COVID-19 pandemic is teaching us that SARS-CoV-2 appears to be settling in as a long-term member of the respiratory viral microbial ecosystem, making it critical that we develop better approaches to identify and treat superinfections, and, importantly, how to then de-escalate antimicrobial use promptly.

I believe PCT can have a significant role to play in the management of these complex patients. ■

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COVID-19 Pneumonia:

Procalcitonin (PCT) for Risk Assessment and Rule-out of Bacterial Coinfection

PCT on admission	PCT during hospital stay
Test PCT as an aid for early risk assessment and prioritization of high risk patients	**Monitor PCT to detect:**
<0.50 µg/L* low risk for bacterial coinfection and adverse outcome	secondary bacterial infections
≥0.50 µg/L high risk patients, bacterial coinfection likely	progression of disease

* Majority of patients with mild disease had PCT values <0.25 µg/L or even <0.1 µg/L. [Ref-1-6]
   Likelihood of bacterial infection and recommendation to start antibiotics in patients with LRTI at PCT 0.25 µg/L. [Ref-7]

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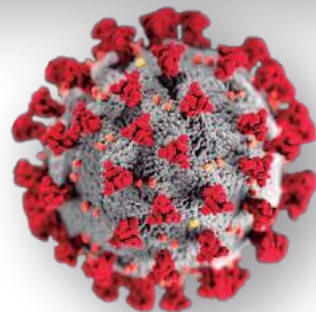
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Thermo Fisher Scientific
B·R·A·H·M·S GmbH
Neuendorfstr. 25
16761 Hennigsdorf
Germany

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+49 (0)3302 883 100 fax
info.pct@thermofisher.com
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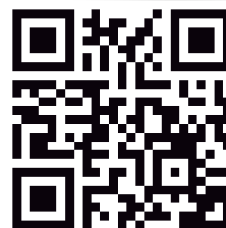
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Andrej Michalsen
Consultant
Department of Anaesthesiol-
ogy, Critical Care, Emergency
Medicine, and Pain Therapy
Konstanz Hospital
Konstanz, Germany

andrejmichalsen@hotmail.de

Predicament Prevention for Pandemics

COVID-19 has resulted in an enormous demand for critical care person-
nel and increased consumption of resources. How can healthcare systems
prepare for the allocation of scarce resources?

Introduction

Health care crises, like the COVID-19 pandemic, can lead to a pronounced regional, national and even supranational discrepancy between the need for medical care and the ability of the health care systems to provide it. Among others, such need can refer to personnel, pharmaceuticals, equipment, nutrition, or transportation capacity. Specifically in the COVID-19 pandemic, the situation has been aggravated by the fact that to date no widely accepted specific treatment is available, leaving only symptomatic and supportive measures (Wiersinga et al. 2020). This has resulted in an enormous demand for critical care personnel as well as a remarkable consumption of resources, such as personal protective equipment, pharmaceuticals, and ventilators (Wiersinga et al. 2020; Grasselli et al. 2020; Emanuel et al. 2020). In general, whatever the particular shortage may be in a pandemic situation, the respective treating teams need to selectively allot the resources available and hence must make prioritisation decisions. An important task is to base such decisions both on the best knowledge available regarding the respective medical aspects and on ethical values and principles.

Allocation of Scarce Resources in Critical Care

When in health care crises resources become scarce despite all efforts of a health care system and its institutions, the general pillars of decision-making, i.e. medical indication and informed consent, become superimposed by a triaging process. The treating teams then must make prioritisation decisions as to the allotment of the resources in need. The focus of care, then, will usually need to shift from patient-centred deontology to population-centred utilitarianism. Clearly, this shift needs to result in

> ❝ in principle, each patient deserves a fair chance of receiving medical care ❞

fair and clinically informed processes about scarce resource allocation, and this may include adapting, conserving, substituting, re-using, and re-allocating resources. Additionally, legal stipulations may direct the allocation of resources and may even overrule medical judgement.

During the COVID-19 pandemic, medical societies in several countries have published recommendations regarding the allocation of scarce critical care resources (Marckmann et al. 2020; Jöbges and Biller-Andorno 2020; Truog et al. 2020; Emanuel et al. 2020). They partially build on recommendations related to former epidemics or on general triage principles, and they are also based on distinct ethical values (Marckmann et al. 2020; Jöbges and Biller-Andorno 2020; White and Lo 2020; Emanuel et al. 2020; Beauchamp and Childress 2019; Nates et al. 2016). Some of these values and recommendations could serve as a general matrix for prioritisation decisions in pandemic situations.

Ethical Values Allotting Scarce Health Care Resources

With regards to the allocation of scarce resources, three core ethical values appear undisputed: treating patients equally; maximising the benefits achievable under the circumstances prevailing; and giving priority to patients with the best odds of success.

Each and every patient is of equal value, and there should be no difference in allocating scarce resources between patients infected with the agent causing the respective pandemic and those not infected with it, but afflicted otherwise. In principle, each patient deserves a fair chance of receiving medical care. However, the odds of success when applying a treatment – i.e. a scarce resource in this context – will not be distributed equally amongst all those in need. Therefore, those with higher odds of success – as defined by transparent and reasoned medical

and ethical criteria in advance – will receive priority for the interventions necessary. Medical determinants with a negative impact on the prognosis need to be described and integrated into the decision-making process as transparent as possible regarding the knowledge available (Marckmann et al. 2020; White and Lo 2020; Emanuel et al. 2020). Neither chronological age alone, though, nor a person's social value, religion, disabilities, or wealth should determine his/her chance to benefit from scarce resources.

Whether maximising benefits means saving more lives – usually measured with mortality predictions – or saving more years of life (in all surviving) – usually assessed by considering co-morbidities – is disputed. Saving more lives is more frequently advocated, though (Marckmann et al. 2020; Peterson et al. 2020; Jöbges and Biller-Andorno 2020; Truog et al. 2020).

A fourth ethical value, giving priority to health care workers and research participants when other factors are equal, has not met the same degree of endorsement, as it raises concerns that those making the rules may be protecting themselves. However, keeping the necessary workforce healthy and alive will benefit others in need, and therefore this notion warrants further deliberation (White and Lo 2020; Truog et al. 2020; Emanuel et al. 2020).

Time and Decision-Making Process of Prioritisation

In clinical practice, there are two primary points in time for prioritisation decisions: **(1)** before scarce resources must be allotted – that is the decision to start or withhold intensive care (life-sustaining) treatments, and

(2) once scarce resource allotment has already been implemented – that is the decision to continue or withdraw such treatments.

Withholding and withdrawing are mostly assessed as equally justified for the same individual. During pandemics, though, the crucial question might arise whether it is justified that one patient be removed from a specific critical care treatment modality for the sake of another patient who has a higher likelihood of successful through this treatment modality. Referring to the COVID-19 pandemic, there is no concordance as to this difficult question (Marckmann et al. 2020; Jöbges and Biller-Andorno 2020; Peterson et al. 2020; White and Lo 2020; Truog et al. 2020; Emanuel et al 2020) and, again, legal stipulations may direct this particular decision.

> ❮❮ **neither chronological age alone, nor a person's social value, religion, disabilities, or wealth should determine his/her chance to benefit from scarce resources** ❯❯

No matter at what point in the course of a pandemic prioritisation decisions must be made, they are complex and challenging. They will bear grave consequences for "denied" individual patients, and they can contribute or lead to conflicts, moral distress and burnout among staff as well as to emotional distress, signs of depression, and complicated grief among patients and their families (Postolache et al. 2020; Lai et al. 2020; Moss et al. 2016). Hence, it is of utmost importance prioritisation decisions not be taken as discretionary decisions, but taken thoroughly, consistently, proportionately, and transparently as to rules based on medical assessment

and ethical values. Furthermore, these decisions need to be re-evaluated regularly and over a length of time adapted to the course of the respective disease.

Core Recommendations for Fair Allocation of Scare Medical Resources in Critical Care During a Pandemic

Based on ethical principles and values as well as on scientific publications on epidemics and pandemics, the following recommendations have been formulated:

1. The appropriateness of critical care treatment measures is assessed for every patient in need (not only for those afflicted by the pandemic). If critical care is not indicated, the patient will not be admitted to an ICU or another high-care unit.

2. The patient's informed consent is obtained or verified. If there is no consent (or not any longer), the patient will not be admitted to an ICU. If the patient's wish cannot be ascertained, he/she will be assessed further as if he/she had consented.

3. Once the need for critical care treatment has been determined, the clinical likelihood of its success is reliably assessed according to reasoned and transparent criteria known at the time. Specifically, indicators for low odds of success are monitored. Patients are then either admitted or not admitted to an ICU, according to the individual odds of success.

4. Decisions to change the goal of therapy from cure to comfort care are considered for each and every patient they may apply to (not only for those afflicted by the pandemic) and are taken without delay. Patients so affected will not be admitted to an ICU or will be discharged from the ICU where they are situated. All prioritisation decisions are re-evaluated regularly in adequate time intervals, and especially when the clinical status of the patient or

the availability of resources changes. After deliberation and decision-making within the treating team, the prioritisation decisions will be explained to the patient (or his/her legal representative) and the family in a transparent manner and then documented appropriately.

5. Psychosocial support for patients, families, and staff needs to be available to help cope with difficult individual courses of the respective disease and/or moral distress.

Conclusion

In a pandemic, many critical care resources may become scarce. All patients still need to be given a fair chance to receive intensive care treatment measures, but the odds of successful treatment will not be distributed equally among all patients in need of the scarce resource. Therefore, in order to prevent predicaments, the treating teams need to selectively allot the resources available and hence must make prioritisation decisions. These decisions must not be discretionary, but consistent, proportional, and transparent – and they must therefore be based on reasoned medical and ethical rules formulated a priori.

Conflict of Interest

None. ■

Key Points

- Pandemics can lead to a pronounced discrepancy between the need for medical care and the ability of the health care system to provide it.
- Prioritisation decisions are then inevitable, and they need to be based on the best medical knowledge available and on ethical values and principles.
- The focus of care will usually need to shift from patient-centred deontology to population-centred utilitarianism.

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Vivantes – Klinikum Neu-
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Berlin, Germany

herwig.gerlach@vivantes.de

Advances in Sepsis Research – New Tools Against One of the Oldest Diseases?

Sepsis and septic shock are the leading causes of death in the ICU. With an estimated mortality rate of 40-60%, septic shock is in the focus of adult critical care medicine. It is broadly accepted that intervention in the very early phase of sepsis before the complex inflammatory host response is initiated should be one major area that clinical research should focus on.

Introduction

Currently, sepsis and septic shock with subsequent multi-organ failure are the leading causes of death in adult intensive care units (ICU). Although surgical and pharmacological approaches in sepsis therapy are continuously improving, epidemiological studies show an increased incidence of sepsis over the last 20 years. The high prevalence of sepsis and its high economic impact have led to the development of several projects in the past decades, intended to allow for better recognition and more accurate description of the course of the disease. Sepsis is a complex and life-threatening syndrome induced by a dysregulated host response to infections. For administrative documentation in daily clinical practice of intensivists, patients are often attributed to different morbidities, although they finally die from the sequelae of sepsis, which makes a reliable generation of epidemiologic data from available intra-hospital data files not easy. Thus, outcome data are often resulting from prospective regional cohorts; recent large studies tried to describe epidemiology on a multi-national level. The most affected organs by sepsis and septic shock are the lungs, the cardiovascular system, and the kidneys. With an estimated mortality rate

of 40-60%, septic shock is in the focus of adult critical care medicine, and implementation of evidence-based methods and individual, goal-oriented strategies are the key approach against this increasingly prevalent and life-threatening disease.

Sepsis – A Typical Disease of the "New World"?

Sepsis is one of the oldest described illnesses. The term sepsis was already used by Hippocrates around 400 BC to describe the natural process through which infected wounds become purulent. After this recognition, it took over 2,000 years until the hypothesis was established that it is not the pathogen itself, but rather the host response that is responsible for the symptoms seen in sepsis. In the last 40 years, one major field of sepsis research was the basic cellular and molecular biology to understand the exact mechanisms, why the body sometimes reacts with an overwhelming inflammation to infections, but sometimes not.

Inflammation in Sepsis – Local vs. Systemic, Pro- vs. Anti-inflammation

During local infections, a physiologic inflammatory response helps to control

the focus, whereas a dysregulated host response leads to macro- and microcirculatory failure, thus inducing organ dysfunction, which determines the symptoms and clinical course of the patients. In other words, in local infections, a normal inflammatory host response controls the focus; a dysregulation of the host response leads to macro- and microcirculatory failure, by which single or multiple organ failure is induced. Hence, inflammation is an essential part of the innate as well as the adaptive immune system. In the initial phase, the inflammation is often a predominantly local syndrome with a more or less pronounced, transient systemic response. On the other hand, this systemic inflammatory response syndrome (SIRS) is potentially harmful, when it is part of a generally overwhelming process. This may lead to circulatory instability by vasodilation due to production of nitric oxide, and to ongoing microcirculatory failure ending with a single or combined organ dysfunction or failure (multiple organ dysfunction syndrome, MODS).

The control of local and systemic pro-inflammatory mechanisms by anti-inflammatory counterbalance is an important protective process against further enhancement of inflammation. If, however,

the anti-inflammatory reaction gets too strong, this may lead to decreased immune competency with so-called "second hit" infections, for example after major surgery. Thus, the local and systemic imbalance between pro- and anti-inflammation is a crucial aspect of pathogenesis of systemic inflammatory response and multiple organ dysfunctions. This is especially important for patients with sepsis, after multiple traumata, or major surgery, who are often in an immunosuppressive phase, and not only in a phase of uncontrolled hyperinflammation. Components taking part in these pro- and anti-inflammatory processes are found in the innate immune system, mainly as endothelial cells, polymorphonuclear cells (PMN), macrophages etc., as well as in the adaptive immune system, represented by specific humoral B cell and cellular T cell immunity. Additional components are the coagulation as well as the complement system, eicosanoid metabolism, and the endocrine system.

Clinical Approaches to Control the Host Response

As the mechanisms of inflammatory host response are becoming better defined, interventions aiming to interfere with the host response have been undertaken, largely with disappointing results. Moreover, it was concluded that immunomodulating approaches in septic patients, altogether named as "adjunctive therapy," have to orientate on the patient's immunologic competence and inflammatory as well as infectious status. Besides low-dose hydrocortisone, and activated protein C, which have been demonstrated to disrupt dysfunctional cascades, thus favourably influencing the course of the disease, the use of intravenous immunoglobulins (ivIG) has been implemented as part of adjunctive therapy.

A source of infection may result in the release of bacterial toxins like components of the cell wall into the blood stream, and these toxins interact with the cells of the immune system, causing the release of endogenous mediators such as tumour necrosis factor (TNF) or Interleukin-1 (IL-1), thus causing cardiovascular insufficiency, hypotension, and decreased end-organ perfusion. A large RCT using a monoclonal antibody against the Lipid A fraction of gram negative endotoxin, however, was disappointing, and it was concluded that more investigation is required before these drugs can be used in patients suspected or having gram-negative sepsis. Later, human monoclonal antibodies against specific antigens of bacteria were also tested, but did not result in any benefit for the patients; altogether, the current view on the development of specific monoclonal antibodies against bacterial antigens for treatment of septic patients is rather skeptical. This short list is far away from being complete, and there are many other experimental approaches to inhibit hyperinflammation. However, no other so-called "adjunctive therapy" could reveal sufficient clinical evidence, such as glycaemic control, selenase, specific antibodies, alkaline phosphatase, thiamine, toll-like receptor inhibitors, nitric oxide inhibitors, glutamine, lactoferrin, statins, and many more, which all were tested in clinical trials, but failed to provide any benefit.

The Early Phase of Sepsis – Still an Option for New Therapies?

In 2017, the results from a large clinical trial were published, presenting data from 149 hospitals including more than 49,000 patients in the USA. It was demonstrated that each hour delay in treating septic patients – measured from the initial time of detecting sepsis – increased mortality by 4% (relative risk). Similar results were found for the single interventions blood culture, antibiotics, and lactate measurement, whereas the effect of early fluid administration was only demonstrated in septic shock patients with a need for vasopressor administration. Hence, it is broadly accepted that intervention in the very early phase of sepsis before the complex inflammatory host response is initiated should be one major option that clinical research should focus on. This latter point supports current discussions that an early fluid challenge might not be favourable in every septic patient (so-called "fluid non-responder"), and that fluid administration should be monitored carefully to avoid a fluid overload with negative effects on the patients' outcome. A recent approach is to absorb pathogens, i.e. bacteria as well as viruses, with special, heparin-coated cartridges (Seraph™ 100 Microbind™ Affinity Blood Filter, ExThera Medical), which are part of extracorporeal circulation devices – either as a stand-alone haemoperfusion or as part of renal replacement therapy (haemofiltration). There are promising experimental data (Mattsby-Baltzer et al, 2011), and first case reports in clinical use are currently published (Seffer et al, 2020). This approach with a more "direct" absorption of pathogens without interfering with the upstream synthesis regulation may be a reasonable alternative to single-hit specific inhibitors, which all keep the risk of a further dysbalance of the immunomodulatory system. A multinational, randomised trial is currently starting to provide the evidence that this new technique is improving the patients' clinical course. ■

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Orlando Ruben Perez-Nieto
Department of Critical Care
Hospital San Juan del Río
San Juan del Río, Queretaro

orlando_rpn@hotmail.com

@OrlandoRPN

Eder Ivan Zamarron-Lopez
Cemain Tampico
Unidad de Cuidados Intensivos

ederzamarron@gmail.com

@dreder_zamarron

Manuel Alberto Guerrero-Gutierrez
Department of Critical Care
Instituto Nacional de Cancer-ología
Mexico City

manuelguerreromd@gmail.com

@cc_yoda

Jorge Lopez-Fermin
Department of Critical Care
Hospital San Juan del Río
San Juan del Río, Queretaro

salemcito1@gmail.com

@MD_FERMIN

Ernesto Deloya-Tomas
Department of Critical Care
Hospital San Juan del Río
San Juan del Río, Queretaro.

deloyajmr@hotmail.com

@e_deloyaMD

Silvio A. Ñamendys-Silva
Department of Critical Care
Medicine
Instituto Nacional de Cancero-logia
Department of Critical Care
Medicine
Instituto Nacional de Ciencias
Medicas y Nutricion Salvador
Zubiran
Mexico City, Mexico

@Snamendys

Challenges in the Management of Severe SARS-CoV2 Infection in Elderly Patients

Elderly patients have damaging and serious complications when they acquire SARS-CoV2 infection. It is thus important to consider this particular age group for better management of COVID-19.

The gradual reversal of the population pyramid that has developed in recent decades has resulted in older adults being mostly affected in a pandemic situation. Senior people are the defenceless group, and the ones who have experienced the severest form of this disease. A patient who is positive for SARS-CoV2, and is over the age of 70 years old is compromised because of age. Since the beginning of this pandemic, 50% of those infected are elderly patients. The elderly also represent 33% of the total admissions in the Intensive Care Unit (ICU) and account for 22% up to 48% of the daily deceased (Bonanad 2020). This could be due to pre-existing comorbidities, geriatric syndromes, disability, dependence or frailty making them more vulnerable to this infection and poor outcomes.

Complications and Comorbidities of Ageing Adults with COVID-19

Up to 60% of senior patients with COVID-19 have at least one of the following comorbidities: hypertension, diabetes, cardiovascular disease, cerebrovascular disease, dementia, cancer, chronic kidney disease and chronic obstructive pulmonary disease (COPD). The most frequent complications of the elderly with severe COVID-19 are acute respiratory distress syndrome (ARDS), shock, delirium, acute kidney injury (AKI), myocarditis, acute

myocardial infarction, heart failure (including Takotsubo disease), arrhythmias and venous thrombosis (Li 2020; Wang 2020).

This link between elderly patients and complications should put us on an awareness mode to detect and evaluate this patient population early. Along with the clinical worsening triggered by the natural progression of the disease, medical management may also contribute to complications through the use of strategies that may not be entirely suitable for this age group. A proposed approach for the detection and diagnosis of complications of SARS-Cov2 infection for elderly patients is shown in **Table 1**.

Special Considerations in the Management of the Critically Ill Elderly Patient Due to COVID-19

Oxygen support, intubation and invasive mechanical ventilation

Oxygen therapy should be initiated when a patient presents hypoxaemia manifested by clinical signs of respiratory failure and a peripheral oxygen saturation ≤92%; in case conventional oxygen delivery devices (low-flow nasal cannulas, facial mask or oxygen reservoir bag) do not provide adequate oxygenation, another advanced type of ventilator support should be considered. Determining the appropriate time to perform intubation is a challenge in elderly patients with previous pulmonary

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Complication	Diagnostic tool			Considerations
ARDS	Berlin and Kigali criteria	Timing Oxygenation PEEP requirement Chest imaging Origin of oedema	**Berlin criteria** Within 1 week of a known clinical insult or new or worsening respiratory symptoms. Mild: PaO_2/FiO_2 >200 mm Hg but <300 mm Hg. Moderate PaO_2/FiO_2 <100 but >200 mm Hg. Severe: PaO_2/FiO_2 <100 mm Hg. Minimum 5 cmH2O PEEP required by invasive mechanical ventilation (non-invasive acceptable for mild ARDS) Bilateral opacities not fully explained by effusions, lobar /lung collapse or nodules by chest radiograph or CT Respiratory failure not fully explained by cardiac failure or fluid overload (need objective assessment, such as echocardiography, to exclude hydrostatic oedema if no risk factor present)	**Kigali criteria** Within 1 week of a known clinical insult or new or worsening respiratory symptoms SpO_2/FiO_2 <315 No PEEP requirement, consistent with AECC definition. Bilateral opacities not fully explained by effusions, lobar/lung collapse or nodules by chest radiograph or ultrasound Respiratory failure not fully explained by cardiac failure or fluid overload (need objective assessment, such as echocardiography, to exclude hydrostatic oedema if no risk factor present)
Shock	Shock index Diastolic shock index Clinical windows Hypotension Serum lactate Capillary refill time	Shock index: heart rate/systolic artery pressure (0.5-0.7) Diastolic shock index: heart rate/diastolic artery pressure (>2) Brain: Altered mental state Skin: Mottled, clammy Kidney: Oliguria The systolic arterial pressure is less than 90 mm Hg or the mean arterial pressure is less than 65 mm Hg. The level is increased (>1.5 mmol per litre) Capillary refill time: >2.5 s		
Myocarditis	Troponin I EKG Echocardiogram Magnetic resonance	Troponin I above the 99th percentile upper reference limit		
Acute myocardial infarction	Chest pain EKG Troponin I	Troponin I above the 99th percentile upper reference limit		
Heart failure	Symptoms. NT pro-BNP	NT-proBNP >450 pg/mL (for patients aged 75-99 years)		
Acute kidney injury	AKI KDIGO			

		AKI Stage	Serum creatinine (SCr)	Urine output
		1	1.5-1.9-fold increase in basal SCr Or increase ≥ 0.3 mg/dl	≤ 0.5 mg/kg/h for 6-12 hours
		2	Increase ≥ 2-2.9 times in baseline SCr	≤ 0.5 ml/kg/h for > de 12 hours
		3	Initiation of renal replacement therapy (RRT), Decrease in GFR ≤ 35 ml/min/1.73 m2 in patients <18 years.	
Deep vein thrombosis	Clinical signs D-dimer Deep vein Ultrasonography	D-dimer > 0.5-1.5 mg/l		
Pulmonary embolism	D-dimer AngioCT AngioMR Echocardiogram Deep vein Ultrasonography Geneva score	**Geneva score** **Variable**		**Score**
		Age		
		60–79 years		1
		80+ years		2
		Previous venous thromboembolism		
		Previous DVT or PE		2
		Previous surgery		
		Recent surgery within 4 weeks		3
		Heart rate		
		Heart rate >100 beats per minute		1
		PaCO$_2$ (partial pressure of CO$_2$ in arterial blood)		
		<35mmHg		2
		35-39mmHg		1
		PaO$_2$ (partial pressure of O$_2$ in arterial blood)		
		<49mmHg		4
		49-59mmHg		3
		60-71mmHg		2
		72-82mmHg		1
		Chest X-ray findings		
		Band atelectasis		1
		Elevation of hemidiaphragm		1
		The score obtained relates to the probability of the patient having had a pulmonary embolism (the lower the score, the lower the probability): **<5 points indicates a low probability of PE** **5-8 points indicates a moderate probability of PE** **>8 points indicates a high probability of PE**		

Severity criteria	Lymphopenia <800 cells/µl
	C-Reactive Protein > 150 mg/l
	D-dimer > 0.5-1.5 mg/l
	Interleukin-6 >40 pg/ml
	Lactate dehydrogenase >350 UI/l
	Ferritin >1000 µg/L
	Creatinine 1.5-1.9 times baseline or ≥0.3 mg/dl increase
	Troponin I above the 99th percentile upper reference limit
	NT-proBNP >450 pg/mL (for patients aged 75-99 years)

Table 1. Approach for early detection and diagnosis of complications of SARS-Cov2 infection in elderly patients.

pathologies like COPD or chronic cardiac failure and could excessively increase the breathing effort and generate fatigue of the inspiratory muscles rapidly compared to young adult patients. The Work of Breathing Scale (Apigo 2020) can be a useful tool. High flow nasal cannula (HFNC) or non-invasive mechanical ventilation (NVMI), can be chosen alone or combined with a prone position in non-intubated patients, however, intubation should not be delayed if necessary; ROX index (Roca 2019) is useful to make the decision in these cases. Protective mechanical ventilation is a cornerstone in the treatment of ARDS. It is recommended to start with a tidal volume of 6 ml/kg of predicted weight and maintain a plateau pressure <30 cm H_2O. An acceptable goal of oxygenation in patients with ARDS is 88 to 94% arterial peripheral oxygen saturation (SaO_2). However, in patients with ischaemic heart disease, it may be more advisable to maintain oxygenation values above 90%.

Analgesia and sedation
In patients with invasive mechanical ventilation (IMV), a target of sedation and analgesia should be established using the RASS scale CPOT scale. Propofol and dexmedetomidine are recommended over the use of benzodiazepines. The use of opioids such as fentanyl as adjuvant treatment with paracetamol is recommended in order to reduce the total dose of morphine derivatives. Long-term use of benzodiazepines and opioids can trigger delirium.

It is recommended to remove sedatives as soon as possible and implement daily sedation withdrawal strategies in patients who present clinical improvement. The use of tramadol and antineuritic medications such as gabapentin may be considered. We suggest avoiding routinary use of NSAIDs due to the high risk of complications such as AKI and gastrointestinal bleeding.

Specific therapies
Dexamethasone is recommended for COVID-19 patients who are hypoxaemic or under IMV. Special care must be taken with increases in blood glucose and weakness in the critically ill patients. Lopinavir-ritonavir, hydroxychloroquine with or without azithromycin are not recommended (RECOVERY 2020) due to greater predisposition to QT prolongation and arrhythmias in this group of patients. Tocilizumab is not recommended either (CONVACTA 2020). Remdesivir and other antiviral drugs are still being tested in clinical trials.

Prophylaxis for venous thrombosis and anticoagulation
It is recommended to use low molecular weight heparin, such as enoxaparin for thromboprophylaxis in all hospitalised patients and to facilitate early mobilisation to avoid venous thrombosis, especially because older adults present comorbidities that generate a higher prothrombotic risk such as immobility, disabling cerebrovascular disease, hip or pelvic limb fracture,

malignancy, etc. In case of clinical data of deep vein thrombosis, it is recommended to perform Doppler ultrasound for diagnosis. If venous thrombotic episode is confirmed, the anticoagulant dose should be increased. The dose should be adjusted based on renal function. Patients receiving oral anticoagulants should be switched to enoxaparin during their hospitalisation and their usual treatment should be restored upon admission.

Fluid therapy
Intravenous fluid therapy has traditionally been considered a standard of treatment in patients with sepsis. However, large volumes of intravenous fluids (as initially recommended by the Guidelines of Surviving Sepsis Campaign) in elderly patients, can lead to fluid overload, increase hypoxaemia, contribute to AKI and other adverse effects. Therefore, fluid restrictive therapy is recommended in patients with ARDS from COVID-19. In case of hypotension and shock, dynamic fluid response manoeuvres are suggested to make the decision to indicate crystalloid infusion, over static manoeuvres, or liberal fluid therapy. Hydroxyethyl starches are not recommended due to the risk of AKI.

Vasopressors, inotropes and adjuvants
In the management of elderly patients in shock, it is recommended to start norepinephrine early to rapidly improve organ perfusion and avoid unnecessary infusions of intravenous crystalloids with

a target of mean arterial pressure (MAP) close to 65 mm Hg, monitoring capillary refilling and other perfusion data obtained by the clinic. Pursuing a target of MAP close to 80 mm Hg can lead to atrial fibrillation in elderly patients and is therefore, not recommended. The use of hydrocortisone and a second vasopressor with a different mechanism of action as vasopressin is also justified given the suspicion of refractory vasodilation. The use of inotropic drugs like dobutamine should be considered when considering cardiogenic shock due to complications such as acute myocardial infarction or septic cardiomyopathy, which are relatively frequent in this group of patients. An echocardiogram is useful for making decisions. Esmolol or ivabradine could be used as adjuvant therapy for refractory shock in the event of suspected diastolic dysfunction due to sepsis, since elderly patients may initially present difficulty in myocardial relaxation due to their age or due to hypertensive heart disease.

Renal replacement therapy
Chronic kidney disease (CKD) is most associated with mortality in patients with COVID-19. When faced with a patient who previously required renal replacement therapy (RRT) (dialysis or haemodialysis) or generates AKI refractory to medical treatment, a renal replacement strategy should be considered. An appropriate option for haemodynamically unstable patients is the use of continuous or intermittent slow therapies. However, adverse events such as thrombocytopaenia, hypocalcaemia (in

case of use of citrate) or rapid intravascular volume removal should be anticipated to avoid complications. The use of sodium bicarbonate could decrease the need for RRT in selected cases (Jaber 2018).

Prevention and treatment of delirium
It is important to use an adapted room without conditions that predispose to delirium: adequate lighting during the day and darkness at night, a visible clock, television, ambient sounds or music, communication tools for visual and digital communication with health personnel, mobile phone to have contact with family and physical therapy and occupational therapy. Avoid unnecessary invasive devices and remove those already used as soon as possible, including catheters, urinary catheters and restrictions. Special caution should be exercised in the prescription of drugs associated with delirium (H2 antagonists, prokinetics such as metoclopramide, some antibiotics, sedatives, analgesics, etc.) Drugs such as olanzapine, quetiapine or risperidone are indicated as specific treatment but lack clinical evidence. Special caution should be exercised with the use of haloperidol in this group of patients. It is recommended to start at low doses with close monitoring of cardiac rhythm.

Palliative care
Being aware of the high lethality of elderly patients with COVID-19, patients with poor prognosis, multiorgan failure, severity scales such as the acute physiology and chronic health disease classification system

II (APACHEII) and sequential organic failure assessment (SOFA) elevated and that do not respond adequately to treatment, the possibility of limiting the therapeutic effort should be considered in order to avoid cruelty. Communication with family members should be established to make the decision properly.

Conclusion
Elderly patients with severe SARS-CoV2 virus infection have higher mortality than other age groups. This is primarily due to their comorbidities. The individualisation of management in this patient population plays an important role and should always be done based on the best available evidence adapted to the clinical setting.

Conflict of Interest
The authors declare no conflicts of interest. ■

Key Points
- Senior people are the defenceless group and the ones who have experienced the severest form of COVID-19 disease.
- Senior patients with COVID-19 have at least one of the following comorbidities: hypertension, diabetes, cardiovascular disease, cerebrovascular disease, dementia, cancer, chronic kidney disease and chronic obstructive pulmonary disease (COPD).
- Frequent complications of the elderly with severe COVID-19 are acute respiratory distress syndrome (ARDS), shock, delirium, acute kidney injury (AKI), myocarditis, acute myocardial infarction, heart failure, arrhythmias and venous thrombosis.
- The individualisation of management in this patient population plays an important role and should always be done based on the best available evidence adapted to the clinical setting.

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Stefan Heinemann
Professor of Business Ethics
FOM University of Applied Sciences
Essen, Germany

Spokesman
Ethics Ellipse Smart Hospital of the University Medicine
Essen, Germany

stefan-heinemann@gmx.de

@s_heinemann001

Patrick Stais
Managing Senior Physician
Lung Clinic Foundation
Bethanien Hospital
Moers, Germany

Patrick.Stais@bethanienmoers.de

Ethics as Superpower Primum Non Nocere Against All Pandemic Odds
Use Case COVID-19-ICU Bethany Hospital Germany

Medicine is an activity of special dignity at all times. Healthcare professionals are responsible actors and have to consider the business of operating ethics. Weighing up values under considerable time pressure, existential fates and critically discussed evidence is a considerable challenge for them, not only in pandemic times but always.

Ethics as Superpower in Medicine

Medicine has been an activity of a special dignity since ancient times and not only in Greek, Roman and Christian context of standards. Principally essential, methodically and, last but not least, ethically. Without being able to clarify the differentiated medical-historical and history of ideas references here, it should be mentioned that the Hippocrates (Bergdolt 2004) -Fan Galenos builds his Definitiones medicae on the τέχνη, in which the ιατρική assumes primary responsibility for his healing action, which is always primarily aimed at the non-harming well-being of the patient: τέχνη ιατρική (Schubert and Leschhorn 2006). With τέχνη both craftsmanship as well as art and science are addressed - a dimensioning that is not only relevant in terms of terminology and academia, which still puts doctors and the surrounding superstructure of politics, society, economy and technology in a relationship that is not always easy to balance. It is not without reason that the ethical dimension is of particular

importance, because it is about people and their ethical essence. Hence: Without ethics, an ethical foundation there is no medicine in the full sense of the word.

Perhaps proper prevention, diagnostics, therapy and aftercare, maybe outcomes in the interest of the patient, maybe also a feasible job in the sense of doctors and nursing staff, in the end maybe even financially affordable, innovative, agile and digital in a cleverly constructed public health system – and there, where organised privately, even linked to efficient, legal and legitimate business models. All that is ostensibly "medicine" within a functionalist health system without ethics. On closer inspection, however, it becomes clear that "medicine" in the full sense can only be legitimate medicine, carried out by actors who bear moral responsibility. Medicine is much more than healing technique.

Therefore, doctors should not be replaced by artificial intelligence or nurses by robots [maybe they could someday (Wandschneider 2020; Crockett (2019)], but should only be supported by them

within the framework of the ethical general mandate in the sense of a positive outcome and experience for the patients (and the doctors and nurses) - as exemplified by the Smart Hospital (Werner, et al. 2020); Heinemann 2018a; Heinemann 2018b) platform as a genuine combination of medical and economic goals with digital means under the clear primacy of humanity. People are not broken and need to be repaired, they need empathic and dignified healing.

"Medicine is one of the areas of life in which the need for ethical action becomes inevitable: Where people are weak, exposed and in need of help, they not only want to be sure that nothing illegal is happening to them, but that everything that is legally required is being done. If people are faced with illness in life, they immediately understand that legal requirements and prohibitions are inadequate and that, beyond the wording of the legal book, it is much more important to follow good laws as intended. This, however, transcends the area of legality, i.e. a hard standardisa-

tion of human action that is threatened with punishment, with regard to ethics" (Heinemann and Miggelbrink 2011).

Medical action is therefore the accomplishment of a skill and duty that cannot be exhaustively recorded in descriptive-real scientific categories, because the sphere of ethics – values, duty, normative realm – cannot be deduced from the facts. Hume and (!) Kant were right: The world is as it is, because in this world it is possible do to what needs to be done for moral reasons (Heinemann 2013; Hösle 1987). Health and illness are not simply facts, but rather states with normative valence (Gethmann-Siefert 1996). In the current situation of a pandemic, which confronts late-modern societies in the West, the already demanding task of the ethical foundation and practical feasibility of effective medical ethics can be characterised as an even more acute challenge for the medical profession (Doctors, and, always included: the nurses; but also the administrative stuff and all professions and basically all occupational groups that are part of the health care system in the broadest sense). On the one hand, because in the field of the long tradition of medical ethics itself, the discourses relevant to ethics as a discipline of philosophy about the nature and validity of ethical propositions are constantly emerging. Between ethical-universalistic and casuistic-relativistic basic orientation, legions of ethics span, sometimes as a large theoretical framework (mostly in the classics such as Aristotle, Kant or in utilitarianism, but not only there, also in the ethics of religions or alternative concepts), sometimes as a deliberately modest, pragmatic approach. Shopping in the Ethics-Supermarket? (Heinemann and Miggelbrink 2011). Well, there is an important difference between freedom and relativism.

However, in addition, these alternative theoretical offers are provoked by factual developments in technological as well as social areas, which mostly ironically

precede ethics as a normative theory of descriptive morality (and even on this point there is no agreement) – just think of the digital transformation of medicine and healthcare. On the other hand, since medicine in its noble basic task – at least as it is understood here – often has little time, too little time for ethical reflections, out of the hard-factual nature of a clinical reality. This explains why, since Hippocrates, those ethical approaches have been popular in medicine that try to grasp medical action neither with hard principles nor with a detailed case report, but with so-called "middle principles" (Potthast 2008; Brenner 2006). However, especially where time becomes critical, and even more critical than perhaps most of the time anyway – namely, especially during the first wave of a pandemic – medical ethics actually becomes the real superpower that once again exceeds the already important professional excellence.

Especially in times of perhaps already over-dynamic scientific development, a research pressure not previously known in this way, and on the other hand socially broad denial of science, associated with an enemy that appears mysterious and still keeps its true nature from us – SARS-CoV-2 – the question is more than urgent how to actually deal with the patients who manifestly suffer from COVID-19. Which ethical considerations play a role here? How can they be justified? Which sound arguments can be given?

In this context, two questions are repeatedly discussed professionally and publicly:

First: The triage in the rationing of intensive care services – which was not yet necessary in Germany – when capacity is overloaded, and the question of how to deal with the therapy of a disease for which no causal therapy is available yet. However, there are always new headlines presenting many ideas, studies, trials and more that at least give hope for a therapeutic perspective (not to mention the question of solid immunity). Fortunately,

the triage pandemic has not yet reached Germany (also because Italy was hit so hard first - and people in Germany were in fear and therefore behave very carefully); Descriptive and ethical balancing between need and prognosis is often a hardly manageable scenario that is difficult to bear for patients and doctors - when need outweighs availability. The basic tendency of rationalisation is ultimately the utilitarian economic form of "medicine" in the dangerous narrow focus on prioritising the prognosis category. The patient-specific, medical decision, on the other hand, will always be based on weighing up neediness and prognosis (under the premise of scarce resources) – which can also be valid if it is considered that, in hardship cases, an extremely poor prognosis would make treatment despite neediness unjust because of the bad situation. If there are enough inpatient beds for ventilation are available (assuming here - for now - that this form of treatment would be the first choice for a COVID-19 patient), not every patient can be treated in the sense of ex-ante triage. Keeping capacities free for expectable COVID-19 patients in the sense of ex-ante triage is again conflicting with the principle of avoiding damage ("Primum non nocere"). Ex-post triage, however, would also not be ethically justifiable because further treatment with prospects of success must not be interrupted in order to initiate a new treatment. The weakest are often not protected by triage in the conflict between non-harm and justice.

Obviously, the old principle of "Primum non nocere" comes into focus. This often-quoted sentence is of course not by Hippocrates, who also hardly wrote Latin (Smith 2005). Not even by Galenos, but probably by the English doctor Thomas Inman (Smith 2005). Whatever the reconstruction of the history of ideas, the question of how this principle can be justified for itself and/or in the context of other principles, and secondly how

those principles can be applied, remains as a systematic return – here with the concrete second example alongside the triage medicine, on the important question of which treatment option for COVID-19 is appropriate to medical ethics in terms of avoiding damage.

The latter example has recently been the subject of wide controversy in a kind of "conflict between the faculties" between clinical pneumologists at the Bethany hospital in Moers (Germany) and professional and other submissions (more on this below in the Bethany case). This is not an easy question, because it has descriptive-technical (data, evidence, etc.) and ethical aspects. The following considerations primarily serve to sort those aspects and develop some arguments for a damage-sensitive initial treatment and then to illuminate the current ventilation debate in this broad context.

Do-No-Harm in the Context of the Big Four: Autonomy, Non-maleficence, Beneficence and Justice

Indeed, as American bioethicists, Beauchamp and Childress (2001) have, in a sense, revived and re-launched a tradition that has shaped the discussion on medical ethics since the late 1970s. The authors clearly saw that on the one hand principles and material contents of norms, i.e. values, are necessary in medicine but nevertheless represent a considerable challenge in concrete application. Beauchamp and Childress do not speak of principles in the sense of the first principles or ultimate, universal foundations of metaphysics, but rather of principles of "medium scope," which generate orientation knowledge and open and advance the discourse, and do not lead to a dissolvable dissent at the beginning, so to speak. Since medical ethical issues are often massively driven by dissent, it certainly makes sense to turn to more pragmatic and, in a sense, more modestly justified theory of ethics. The disadvantage is, of course, that only a

kind of "lowest common denominator" is possible on the basis of well-understood convictions (which of course does not mean that these common beliefs are automatically irrational or simply unacceptable on closer philosophical examination, but these four principles that Beauchamp and Childress have introduced into the debate are, strictly speaking, fungible). And Beauchamp and Childress must assume that most people share common understandings of a basic set of ethical values. But the authors do not articulate any further moral-philosophical claim. The decisive point is that it is not only about beneficence and nonmaleficence in the classic sense, but that the well-known two principles are expanded to include autonomy and justice, and a quasi-system is created; which, however, understandable against the background of the pressure of discourse, does not even have to deal with a hard claim to truth (as a cognitivist ethic would have to do). But all this comes at the price of a complex and thus not easy-to-use relation of beneficence and nonmaleficence (same with autonomy and justice). "Harm" for Beauchamp and Childress means "…thwarting, defeating, or setting back of some party's interest" (Beauchamp and Childress 2001), which in the medical context of course not the same as wrongdoing. "The relationship between the act of doing good and the absence of doing harm is complex, but they seem to be independent concepts. Beneficence and non-maleficence (as well as autonomy and justice) are prima facie duties, which is to say, their violation is ethically wrong unless it is justified by another prima facie duty" (Schwarz 2004). Nonmaleficence is an essential hurdle, a limitation for medical options.

A way is being sought, so to speak, to find an ethic that on the one hand still uses the term "principle" and thus formulates the certain strong claim in the sense of the Kantian tradition that it is not just mere reasoning or thinking, on

the other hand, in the sense of the Aristotelian doctrine of virtue, is formulated sufficiently concrete to motivate action and a productive discourse, but thirdly, in the sense of utilitarianism, allows conceptual elements that are to be weighed up and also to be understood quantitatively. In the end, this mediates between the level of the individual case and the principle in such a way that the actually necessary hierarchy of principles is omitted and these fundamental questions are shifted to the individual level of interpretation and weighting.

This is quite unusual, because autonomy as well as justice are traditionally associated with extensive conceptual claims. It is particularly striking that Beauchamp and Childress argue more procedurally in the sense of American pragmatism, which in this case is ultimately given an old-continental principle articulation, without shying away from very specific values and their ethical characteristics, which in turn apply to the specific case and thus places the physician under specific responsibility on site. The mid-level ethics of Beauchamp and Childress is a material ethics without a systematic justification framework. The idea of such a middle position is very suggestive, because it promises good results with relatively little discursive use, quite comparable to the Rawls approach, who advocates a reflective equilibrium between principles and applications. To mark the coherence of statements that are mutually justified, but do not understand justification as a strong philosophical system, but much more modestly as only a contentual context, was also the driving force for Rawl's idea, on the one hand, to convey justice with utilitarian logic, and on the other hand bring the rather heterogeneous ideas of justice at least into discussion from an airplane perspective in his "Theory of Justice." There would be no talk of reconciliation here, no synthesis is pursued. Only under the (strict) conditions in the thought

experiment of the "original position" can at least the process be called fair (Rawls 2009). The epistemological challenges that Rawls and ultimately Beauchamp and Childress buy into with this approach, of course, lie in avoiding the last principles and thus also the final foundation. Coherence is the condition for the possibility of a reflective equilibrium; it does not arise from that. Now, to remain in the concrete example of medicine, there are quite a few different variants, to find such a balance of consideration or, as Beauchamp and Childress say, a balance of the principles in their sphere of application: How should one reasonably choose between the different options? Obviously, coherence is certainly important in itself, but does not justify whether reality has to adapt to ethical principles or vice versa. From the basic idea of a balance, no decision can be justified if — what actually happens in medical practice — the ideas of how such a balance should look like are different. "Empirically adopted beliefs become transparent, but ultimately they are only a mirror of the - in the specific case American - belief system in which they are determined" (von Engelhardt (2005), In other words: "The scientific-theoretical decision between induction and deduction is not made in principle — quite comparable to the scientific approach. Standards have to prove themselves in practice, just as a "good theory" in Popper's sense must have the property of failing in practice" (Heinemann and Miggelbrink 2011),

On the one hand, it explains pretty well why Beauchamp and Childress's approach was so successful in medicine as in bioethics (although criticised by the deductivist (Gert, Culver, Clouser) and casuistic (Jonsen, Toulmin) side (Heinrichs 2006). Nevertheless, the differentiation of the four principles remains highly demanding and their weighing up in concrete cases even more. "How such a procedure can give solid, action-focused orientations without ultimately becoming merely arbitrary in its

desired meta-ethics freedom is, however, a core problem of many commonsense ethics (Beauchamp and Childress speak of a "common morality"). In the end, there is a naturalistic fallacy here. This could only be avoided in the long term with an actually 'absolute' — that is, the last-justified — ethics, but admittedly an unpopular alternative even for medical ethicists" (Heinemann and Miggelbrink 2011), On the one hand, the four principles in question are endorsed and applied in practice, for example, when it comes to a concrete case discussion. However, even with these principles, the term "principle" is still criticised, although it was not understood as it was seen — namely that the one principle, which is logically and ontologically more valuable than the other principle, would necessarily abolish the latter principle. Basically, Beauchamp and Childress offer a kind of heuristic in which concrete orientation knowledge can be developed in the discourse. "Certainly, one can complain that every ethical principle (be it a regulatory one like Beauchamp and Childress or constitutive) creates a virtual consensus to a certain extent, a consensus on principles that practically every reasonable person would agree with anyway. But the more material the ethics become, the less likely a consensus is: What to do if a patient prefers a solution that is not optimal for the doctor, or hard diagnoses from the doctor's point of view are unreasonable for the patient, or the doctor in the clinic can only use his working hour once and has to decide at the micro level (Engelhart 1996) where he allocates this resource (a question regarding the principle of justice)?" (Heinemann and Miggelbrink 2011).

With the principle of autonomy, Beauchamp and Childress think of positive and negative freedom. On the one hand, as an absence of coercion and manipulation, on the other hand, of course, as the presence of an emphatic promotion of those conditions, in order to ensure a reasonable,

understandable freedom of decision for the patient. It is precisely in this sense that patient autonomy is absolutely crucial and the patient's right to sufficient, truthful and, above all, understandable, comprehensive information can be derived. The inform consent is the differentia specifica between physical injury and medical treatment and shows how differentiated the autonomy principle can be thought. Especially in times of digital transformation of the medical and healthcare industry, it will become even more important to promote patient sovereignty as a form of autonomy in dealing with health data and new forms of doctor-patient relationship (Heinemann and Matusiewicz 2020).

Apart from emergencies, in which the patient is obviously not able to consent voluntarily and freely, the focus must be on the explanation of possible consequences by the responsible and treating doctor for a patient, who of course also has the appropriate power of judgment. An indirect constraint, for example, because the doctor's reasoning is too strong and suggestive, is also not allowed. Here the challenge of dealing with intensive care medicine immediately arises — like the overall increase in treatments and interventions not medically indicated in the narrow sense.

The principle of justice does not make it easier, at least as long as health needs to be organised under scarcity. On the one hand, this has to do with the fact that the principle-theoretical and very demanding basic questions of justice also resonate in the form of a medium principle, such as the challenge of finding the right criterion (thinking of justice when it comes to the recognition that rights that you ascribe to yourself are also attributed to all equals, the problem arises that "rights" and "equality" cannot be precisely determined by justice itself), on the other hand, the focus is on the question of resource allocation and performance justice move. For example, justice is largely incompatible as a concept

with utilitarian considerations, since justice could only be promoted as a contribution to increasing the overall benefit, while from the Aristotelian point of view it is easily addressable.

In the end, t Especially since the clever distribution also encourages us to think continuously about a certain discipline, which has the best effect for the patient, because in the end medical measures should promote the well-being of the patient. In reality, however, the vast majority of medical measures can be seen in a certain risk context. This means that weighing processes are necessary and the principle of do-no-harm can clearly conflict with the principle of beneficence, the principle of justice and even with the principle of autonomy.

Are there any good arguments for the priority – as the "suprema lex" of the doctor – of the nonmaleficence principle "Primum non nocere" over the other principles of autonomy, justice and beneficence? Which at least do not have to be rebalanced every time, but could at least formulate a cautious universal claim? The case is not quite that simple, because in the present situation, the patient's will (ultimately his autonomy) must first be highly respected, not least because a purely classic-paternalistic doctor-patient relationship will survive itself descriptively. It is not without reason that the free choice of doctor is laid down in the relevant professional regulations and thus, in turn, contract autonomy in medical law. § 223 StGB (German Criminal Code) does not apply to medical treatments precisely because "voluntas aegroti suprema lex" (autonomy, informed consent, posthippocratic Cooperation) is seen on the one hand as a priority over "salus aegroti suprema lex" (beneficience, Hippocratic Paternalism), but on the other hand, this contradiction has become fundamentally questionable in today's patient cooperation with the treating doctor. Salus ex voluntate aegroti suprema lex. Education by the

doctor and compliance and judgment of the patient are only effective together. These relationships are reflected in legitimate laws (there is also illegitimate legality).

"*As a doctor, decide as if you yourself are the patient who does not want to harm themselves or others!*" says Steinvorth (1992) pointedly. In a sense, the principle of nonmaleficence (do no harm) is not to be thought of as independent of the other three principles, as was shown here with the example of autonomy; the same applies, of course, to beneficence, which ultimately depends on the benefit, and even justice (suum cuique), because minimising the risk while at the same time maintaining innovation perspectives (which is by no means an obstacle) potentially promotes it, at least it is not fundamentally excluded. Discussing some recent interpretations, Steinvorth comes up with five sensible reasons for nonmaleficence as a wise priority rule of action for doctors:

1. "Before choosing between risky healing and safe damage reduction, the doctor must choose the damage reduction because they do not bear the risk themselves.

2. Compared to the health conditions of his society or of mankind as a whole, the doctor must prevent the prevention of health damage from the promotion of health perfection, because the prevention of damage is a more urgent moral imperative for all people than the promotion of perfection.

3. Orientation to the reduction in damage binds the doctor to the patient's will without delivering them to it. It also places the patient's will on the condition not to harm. It follows the most general and widely recognized principle of action, not to harm, and at the same time corresponds to the idea of human dignity and the inviolability of his will.

4. The "primum non nocere" assigns the doctor a smaller area of activity than the "utilis esse." It therefore reduces the conflicts between the doctor's obligation to

the individual and to society. At the same time, it encourages a smaller amount of human conditions to be considered illness than the "utilis esse." But if we can assume with Hermann Lübbe (1988) that "the health status of a cultural community, objectively, rises if, subjectively, it uses the predictor 'sick' restrictively," then we have a specific medical reason for the priority of the "primum non nocere."

5. It is easier to see what harms someone than what is good for them or for their well-being. It is often not easy, but easier. We generally know better, both for ourselves and for others, what we do not want than what we want. The more easily recognisable application of a maxim alone cannot give priority to it, but it must confirm it if there is another reason for it" (Steinvorth 1992).

The justification and application perspectives of the "Primum non nocere" are not trivial, and yet there are some reasons to be aware of at least one high-level principle of action of a medical ethic. In the real dissent situations, especially in the pandemic age, however, this theory has to prove itself repeatedly in the collegial discourse practice of conflicting medical concepts of healing. Indeed, in practice it can be observed that – as Sass puts it succinctly – "[…] the academically educated philosopher [but not only those, SH/PS] […], who grew up in school contexts, [finds] […] when weighing up goods […] that different argumentation patterns are used in different situations, without evident justification conflicts or reasons for having to justify them. We argue categorically and rigorously with Kant on questions of the prohibition of killing. On questions of intervention weighing up criteria of quality of life, we calculate with Mill and others in a utilitarian way. On issues of health care allocation according to the Aristotelian principle of equitable justice (everyone their own!). In accident medicine and in acute crises, the rules of paternalism

and its heteronomous concept of interest apply, in triage situations pragmatic rules and explicit unequal preference for some at the expense of others" (Pöldinger 1991). Of course, the ethics in the corona crisis have once again become essential; however promising it may be, current publications by the German Ethics Council (ethikrat.org/fileadmin/Publikationen/ Ad-hoc-Empfehlungen/deutsch/ad-hoc-empfehlung-corona-krise.pdf) or the AEM Academy for Ethics in Medicine e. V. point this out.

Frontline Use Case Bethany Hospital, Moers, Germany – COVID-19-ICU

A current example is the debate on the dissenting of ventilation for acute COVID-19 patients in Germany (the focus here; of course, this debate was and is being conducted internationally).

COVID-19 is a novel disease that was first reported to the WHO in January 2020 as part of the pandemic with the new SARS-CoV-2 virus (Guo et al. 2020). To date, a causal therapy does not exist. Although COVID-19 is asymptomatic to mild in approx. 80 % of cases, approx. 15 % of patients have a severe and approx. 5 % have a critical course with severe pneumonia that can lead to respiratory failure due to a severe oxygenation disorder (Wu and McGoogan 2020). Initial therapeutic recommendations therefore addressed in particular the balancing of hypoxemia with the aim of keeping oxygen saturation above at least 90 % (WHO 2020).

Based on the experience of the first mass attack of patients at the time of the outbreak of the pandemic in China and Italy, recommendations were published – also in Germany by an expert commission – that included a strategy of early intubation and invasive ventilation (Horovitz index of ≤ 200) (Kluge et al. 2020). The entire treatment concept was derived from the principles of ARDS treatment. The treatment results of the critically ill, however,

were very poor. In particular, the group of invasively ventilated patients reported from China was extremely bad with a lethality of up to 97 % (Zhou et al. 2020; Wang et al. 2020); the results from Great Britain (lethality 66 %) (icnarc.org/Our-Audit/Audits/Cmp/Reports) and New York (lethality 88 % (Richardson et al. 2020) were also significantly worse than those from invasive ventilation of a septic shock. Even though some of these results come from studies that were published before all included patients had reached the end point of discharge or death and thus improved results from successful treatments appear to be possible, they give reason to critically question the indication and results of invasive ventilation in patients with COVID-19 pneumonia. The high mortality rate of the critically ill also increases the need for targeted therapy.

Drugs were used early on during the pandemic, which are usually used for other viral diseases and which are intended to inhibit the replication of the virus (e. g., the Ebola drug Remdesivir (Wang et al. 2020) or the AIDS drug Ritonavir/Lopinavir (Tobaiqy et al. 2020) or to dampen an excessive response of the human immune system (e. g., drugs from rheumatology such as dexamethasone (Horby et al. 2020) or hydroxychloroquine (Magagnoli et al. 2020. However, the treatment results were sometimes contradictory or even negative (using the example of hydroxychloroquine (Horby et al. 2020), so that – even if praised as a "breakthrough drug" in the media (aerzteblatt.de/nachrichten/113885/ Dexamethason-Studie-WHO-sieht-Durch-bruch-im-Kampf-gegen-COVID-19) – no general recommendation for the safe use of these drugs could be made. In times of medical uncertainty, however, it makes sense from the risk assessment point of view to rely on reliable knowledge and use analogies. This can and should also include and deliberately reflect the principle of the "Primum non nocere."

At the Bethany Foundation Hospital in

Moers (bethanien-moers.de/krankenhaus-bethanien-moers/infos-fuer-patienten1/ lungenklinik-lungenzentrum), the principle of "primum non nocere" was the focus from the beginning of the COVID-19 treatments. Here, the ethical reflection clearly supported the medical judgment - despite all the uncertainties and challenges. This treatment concept, which has been referred to in the media as the "Bethany Way" or the "Moerser Model" (rp-online.de/nrw/ staedte/moers/corona-moerser-modell-soll-schule-machen_aid-49662005), is based on the one hand on basic pathophysiological considerations, in particular for the treatment of hypoxaemia (Köhler et al. 2005), and on the principle of nonmaleficence by avoiding the use of medication have not been adequately tested in the treatment of the novel disease, which is still largely unknown ex ante, and in the prophylaxis of expected complications such as thrombosis, pulmonary embolism or pneumonia by using appropriate medication. This strategy only provides for invasive ventilation if other measures have not stabilised the patient and intubation seems vitally inevitable. Until then, either oxygen therapy or, if it fails, non-invasive ventilation will be used. The primary goal is to support the patient as long as possible in maintaining his physiological conditions and to maintain spontaneous breathing and vigilance. The effects of positioning techniques such as lying on your stomach or on your side with oxygen therapy and with non-invasive ventilation – similar to invasive ventilation – are systematically checked. It became clear in the brief reconstructive sketch of the technical dissent above that there were deviations from the recommendations made at the outset, since the indication for intubation was not made dependent solely on a limit value for oxygen saturation or the Horovitz index.

The basic pathophysiological relationships speak against this. Accordingly, neither oxygen saturation alone nor the

Horovitz index in pneumonia are suitable for adequately assessing the risk of tissue hypoxia. For this purpose, one should take into account other control parameters such as the oxygen content of the blood or the ejection performance of the heart. The Bethany protocol therefore includes the recording of the basic parameters of oxygen content, cardiac output and respiratory rate. In addition, the patient is continuously monitored for exhaustion by a video camera. In addition to the continuous measurement of the respiratory rate, the ECG is also monitored. To assess the course of the complex inflammatory process, special laboratory parameters such as the CRP and PCT, the LDH, and also the D-dimers are determined daily. The hygiene concept includes a single room, video surveillance, restrictive patient contact through care, thorough ventilation, NaCl inhalations and a non-vented mask with a configuration that prevents the release of infectious aerosols. Neither in this case nor in other cases treated later was there any transfer to the hospital staff. The corresponding results have already been reported elsewhere on a case report. The evidence for the outcome of non-invasive ventilation grows (Karagiannidis et al. 2020). Referring to a current press release of the Bethany Hospital in the context of the visit of Federal Minister of Health Jens Spahn and the Prime Minister of North Rhine-Westphalia Armin Laschet, the mortality of patients under therapy with invasive ventilation would be a dramatic 97 percent in China, 88 percent in New York and still 43 percent in Germany. At Bethany Hospital, the mortality rate for non-invasive therapy would be 1.6 percent. Further data will be published in the near future (bethanien-moers.de/print/krankenhaus-bethanien-moers/ueber-uns/presse/pressemitteilungen/pressearchiv-2020/pe-5720).

The expert recommendation on restrained non-invasive ventilation was given on March 12, 2020 (Kluge et al. 2020), and the WHO guidelines on intubation in the event of failure of oxygen therapy appeared on March 13, 2020 (who.int /docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf). On March 21, 2020 the "Association of Pneumological Clinics (VPK)" chaired by pulmonologist Thomas Voshaar (working in the same Bethany hospital in Moers (Germany) like the second author of this article) recommended "[...] treatment of respiratory complications from acute viral infection outside the intensive care unit" (vpneumo.de/fileadmin/pdf/VPK_Empfehlung_neu_21.03.2020.pdf), which mainly focused on early and intensive breathing support. On April 7, 2020, Voshaar made a similar statement in the FAZ – "It is too often intubated and invasively ventilated" (faz.net/aktuell/gesellschaft/gesundheit/coronavirus/beatmung-beim-coronavirus-lungenfacharzt-im-gespraech-16714565.html) - which was accompanied by a further intensification of the discussion in specialist circles, but also in a wider public. The possible negative consequences (lung damage, etc.) of ventilation, which may not be indicated at all, were subsequently the subject of much controversy (especially since a shortage of intensive care ventilators from a resource perspective had been discussed, with the corresponding triage fears). On April 9, 2020, a corresponding statement was published, "Ventilation at COVID-19: Pulmonologists Announce Recommendations for Seriously Ill Patients" of the German expert association, "German Society for Pneumology and Respiratory Medicine (DGP)," with a clear rejection of the Bethany position: "The significance of invasive and non-invasive ventilation in acute respiratory failure and COVID-19 is currently being much discussed and commented on. A number of aspects are currently being juxtaposed uncritically, and individual opinions have a weight on the Internet that – from the perspective of scientific societies – they should not get" (lifepr.de/inaktiv/deutsche-gesellschaft-fuer-pneumologie-und-beatmungsmedizin-ev/Beatmung-bei-COVID-19-Lungenaerzte-kuendigen-Empfehlungen-fuer-schwer-kranke-Patienten-an/boxid/794408). In the position paper of the DGP dated April 17, 2020 "[...] on the practical implementation of the differential therapy of acute respiratory insufficiency in COVID-19" (Pfeifer 2020), together with Thomas Voshaar, a balancing position is presented, which was essentially incorporated on June 19, 2020 in the S1 guideline "Recommendations for intensive care therapy of patients with COVID-19" (awmf.org/uploads/tx_szleitlinien/113-001l_S1_Intensivmedizinische-Therapie-von-Patienten-mit-COVID-19_2020-06_1.pdf). There, clause 10 states: "The implementation of intensive care treatment for patients with COVID-19 follows the essential ethical principles such as autonomy, beneficence, nonmaleficence, justice and human dignity. An admissible treatment measure must meet two requirements: 1. for the beginning or continuation, according to the treating physicians, there is a medical indication, and 2. the implementation corresponds to the patient's will. If the treatment measure tested meets both requirements, treatment must be initiated or continued. If one of the two conditions are not met, a change in the therapy goal and limitation of the therapy is not only allowed, but even required."

"Primum non nocere" Against All Pandemic-Odds

Medicine is not an easy business. As a patient you ask yourself: "Should I emphatically demand ventilation as a COVID-19 patient, or should I trust doctor A's indication, when doctor B says otherwise and the experts obviously do not agree anyway?" This question arises not only existentially, but already in the case of small sensitivities that motivate some patients to have a very different culture

of dialog with their own doctors. Both ethical and medical reasons are addressed here, doctor and patient. Doctors are not gods, not even half-gods, but as good doctors they are prepared for the daily, often hard, examination of ethical values in dilemma situations (for which very good training is essential) and they can and should cooperate with the patients and vice versa. Asymmetry does not become symmetry – but not least in the digital age, it is another form of discourse. And at the end of the treatment. Innovation and nonmaleficence/beneficence fosters when it comes down to research a special patient-relation, because e.g. "without patients volunteering to participate in clinical research for fear of the possibility of harm, the potential benefits would never be realised and the progress of medicine would come to a halt" (Schwartz 2004). Patients are in turn dependent on a broader base of solid knowledge (beyond fake news) in order to choose the indeed healthy middle of the argument beyond panic and serenity in the spirit of Aristotelian understanding of virtue. "Medicine rests on a broad theoretical basis. But it is not an exact natural science; although it uses scientific methods, it is also philosophy, and above all it is practical action under ethical maxims" (Koslowski 1992). This has to be remembered again and again. The technical debates are not only to be endured individually, but as the core of the

medical ability to be innovative without taking inappropriate risks, to be recognised for ethical reasons. It is important, of course, that it is about the issue and its positive effects (healing and damage prevention) for the patient – not systemic attributions in a hierarchical ordologic of institutionalised medicine that is still top hierarchical. Especially in the current pandemic crisis of an unprecedented socio-economic global extent (and probably also medically very demanding), the position of ethics is being brought to the centre. Obviously, doctors do not have to have the same professional view, and ethical judgments can differ as well. The sensible, open and collegial discourse of the medical profession and related disciplines (such as ethics, computer science, sociology …) is perhaps the best thing that is available for the patient in order to achieve human, effective and low-risk healthcare. In the future, medicine in its application form as medical and nursing activities (and more forms we cannot even imagine today) will continue to work according to rules that are often controversial, but can and should ultimately lead to good outcomes for the patient. As seen, dissent often arises less on the normative than on the descriptive level. The question as to which form of treatment is the one that leads to the maximum possible success for the lowest risk costs for the patient is often disputed. Also, because medical

research needs time to be good. And data to be substantial. Perhaps one perspective of digital medicine of the future is to be able to resolve descriptive dissent more quickly with more and, above all, better data without involving patients in factual treatments in the research. But even these possibilities offered by digital technologies will not be able to relieve the responsible actors in the health care system from the exhausting business of operating ethics. Weighing up values under considerable time pressure, existential fates and critically discussed evidence is a considerable challenge for every responsible person, a real superpower. Not only in pandemic times.

Acknowledgement

Conflict of Interest

None. ∎

Key Points

- Ethics is the Superpower in Medicine
- Do-no-Harm in the Context of the "The Big Four" "middle principles" in medical ethics
- Frontline Use Case Bethany Hospital, Moers, Germany – COVID-19-ICU: "Primum non nocere" against all Pandemic-Odds

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For full references, please email editorial@icu-management.org or visit https://iii.hm/14w0

Hans Flaatten
Department of Intensive Care
KSK
Haukeland University Hospital
Bergen, Norway

hans.flaatten@uib.no

Bertrand Guidet
Sorbonne Université
INSERM
Institut Pierre Louis
d'Epidémiologie et de Santé
Publique
AP-HP
Hôpital Saint-Antoine
Service de Réanimation
Paris, France

bertrand.guidet@aphp.fr

Dylan W. deLange
Department of Intensive Care
Medicine
University Medical Center
University of Utrecht
Utrecht, Netherlands

dlange3@umcutrecht.nl

Lessons From the "Very Old Intensive Care Patients" (VIP) Project

An overview of the VIP project that studies a subgroup of patients ≥ 80 years, the oldest old, since both ICU mortality and morbidity are increased with advanced age.

During the last 10 years, we have observed an increased interest in research into our oldest intensive care patients. This is brought forward with the expectation of a two-fold increase in citizens ≥ 80 years towards 2050 **(Figure 1)**.

"Old" is an ambiguous term with no clear definitions. Hence the age ≥ 65 years is still used by WHO. This threshold for old is not useful for most European ICUs because the median age of our patients is 65 years or above. For this reason, many perceive a particular need to study a subgroup: patients ≥ 80 years, the oldest old, since both ICU mortality and morbidity are increased with advanced age. This, together with the perceived increase in the European population, is the reason our group has targeted to study ICU patients ≥ 80 years. A research network in Canada (Heyland 2015) started early on with a national multicentre group exploring different aspects of outcomes in critically ill elderly (McDermid 2011) and has performed important studies on the topic. Initially, there was some interest for this topic in Europe, mainly in France, the Netherlands and in the Scandinavian countries, but no formal cooperation across borders existed.

Within the European Society of Intensive Care Medicine, the Health Service Research and Outcome (HRSO) section we had discussions during 2015/16 in order to establish a multinational research programme in Europe, which was called the VIP project. Core members from the section with other international researchers published in 2017 a research agenda in the very old **(Table 1)** and the first large prospective multinational European study was planned, the VIP1 study (Flaatten 2017).

The aim of the VIP project is simply to contribute to new knowledge about the very old (≥80 years) ICU patients, in particular to reveal important factors for survival and post ICU quality of life. Up to that time there were several studies on the topic, but most were retrospective, and often single-centre and with a small number of patients. The VIP project used active national coordinators who were able to gather interest from many ICUs in their countries. This resulted in hundreds of active sites across Europe. Many of these sites and countries remained interested and continued to participate in the VIP network. We achieved a very good response from the intensive care community for the initial VIP-study. Obviously, many ICUs regarded the issue with very old ICU patients as important. All were willing to contribute in prospective studies, even without any funding. One of the most important success factors was the development of an easy-to-use website and web-based electronic case report form (eCRF) that prevented time-consuming data-entry. This website annex eCRF has been used for all three VIP studies performed since 2017 (www. vipstudy.org)

The VIP network has so far conducted three large prospective observational studies **(Table 2)**.

The VIP-1 Study
The main purpose of the VIP-1 study was to study the relation between pre-morbid conditions, like frailty and age, in combination with other markers of severity like the sequential organ failure assessment (SOFA) score, on ICU and 30 days outcomes. Frailty was measured

Population pyramids, EU-28, 2018 and 2050
(% share of total population)

Figure 1. 2050 population according to the 2018 projections. Source: Eurostat.

Important research question	Topic covered
Frailty, sarcopenia, ADL and cognition pre and post ICU admission	Good
Opinions among octogenarians about ICU admission in the very old	Poor
Effects of including a geriatrician pre-and post ICU care	Poor
Effects of non-pharmacological approach to delirium	Poor
Burden of intensive care among caregivers	Some
Prognostic tools	Some
Sepsis	Some
Pharmacokinetics of sedatives	Poor
Trajectories after End of Life decisions	Some

Table 1. Proposed research agenda in the very old ICU patients and how the topics are covered in the research by end 2020. There are still many unanswered questions as can be seen.

Study	Patients	Countries	Sites	Published	ICU patients	Age
VIP-1	5021	21	311	2017	All admission ≥ 80y	≥80
VIP-2	3920	22	242	2019	Only acute admissions	≥80
CoVIP	1474[a]	38	268	Not yet	Only COVID-19	≥70

Table 2. All VIP Studies
[a] on August 2. 2020

using the Clinical Frailty Scale (CFS). We found a near linear relationship between increasing frailty and 30-day mortality **(Figure 2)**. Also, in regression analysis we found frailty to be the better predictor of mortality, even when compared with SOFA score for 30-day mortality.

We, as expected, found huge differences in outcomes between acute and planned ICU admissions in the very old ICU patients, and

a sub-study comparing these two groups has been described in more detail (Jung 2019). For this reason, we decided to limit our studies to emergency ICU admission for the coming studies, since we are confident that this is the major challenge concerning the elderly ICU patients.

The VIP-2 Study
The VIP-2 study (Guidet 2020) was launched in 2018 and recruited nearly 4000 patients during a 6-month-period. Having experienced the huge differences between acute and planned admissions the VIP-2 study focussed only on emergency ICU admissions. The main purpose was to study relations between several common geriatric syndromes: cognitive decline, Activity of daily life (ADL), comorbidity/polypharmacy and frailty. For cognitive decline we used the IQCODE questionnaire, which is developed to be answered by close proxies or relatives. Again, we found that frailty, measured with the CFS, was more strongly associated with a poor outcome than the other four geriatric syndromes. A multivariate analysis including all geriatric parameters did not perform better than the model with CFS only. Of note is that the comorbidity/polypharmacy score surprisingly had no discrimination at all between survivors and non-survivors. This emphasises that frailty is not equivalent to the number nor the severity of comorbidities.

The COVIP Study
When we were planning the VIP-3 study the world was hit hard by coronavirus disease. China and Italy were hit first but we anticipated a rapid spread across many European countries. Having a network of very enthusiastic ICUs enabled us to swiftly change plans and start a specific COVID-19 study. We adapted the VIP-1 and VIP-2 study protocols and customised it to fit our knowledge-gaps on COVID-19 in elderly. At that time, many countries were developing treatment and admission protocols and were struggling with survival chances, particu-
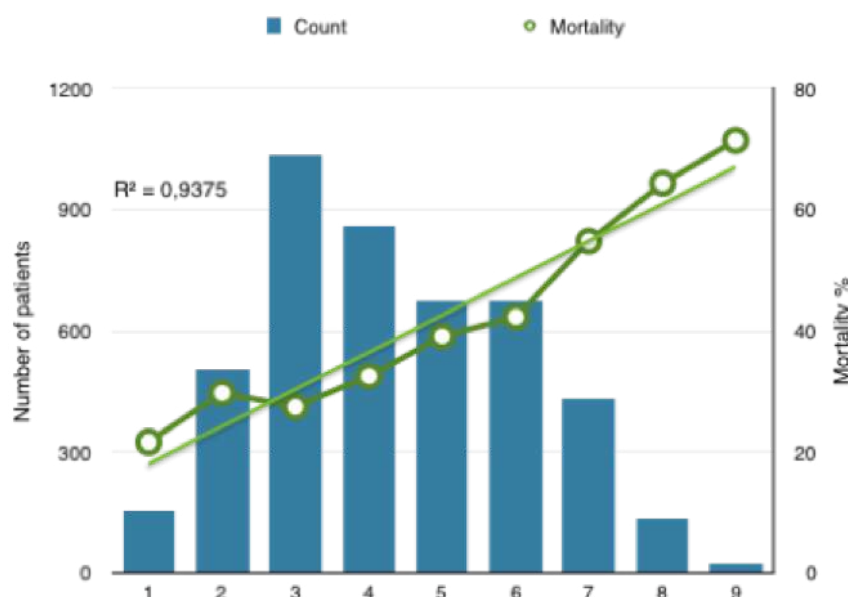
Figure 2. Clinical Frailty Scale

Study	Patients	CFS (median)	CFS >4	SOFA median	LOS	Age (median)	30 d survival
VIP-1	5021	4	44%	4 and 7[a]	1.2 and 2.8[a]	84	93.2% and 62%[a]
VIP-2	3920	4	40%	6	3.9	84	61.1%

Table 3: Comparison of key-variables in VIP-1 and VIP-2.
[a] in planned versus emergency admission

larly for the oldest ICU patients. The CoVIP study (very old COVID-19 ICU patients), started recruitment in March 2020 as the pandemic peaked in Europe. Originally, we planned to study only patients ≥ 80, but since a lot of countries simply did not admit these groups to the hospital nor to the ICU, we decreased the age to patients ≥ 70 years admitted to the ICU.

Our main research question was to describe important predictors for outcomes in a group of elderly patients admitted to the ICU with proven COVID-19. For this study a more detailed eCRF was developed. New end points were a 3 months follow-up with regard to survival and quality of life. The first parts of the study have been completed although the study still includes new patients when a second wave of COVID-19 emerges. We expect to publish the first results from this study towards the end of 2020.

A number of sub-studies from the VIP project has been published **(Table 4)** including individual country data (Germany, Poland, Greece, Norway), and data from the merged databases from VIP-1 and 2. **Table 4** shows some of the most important sub-studies.

Barriers for Observational Studies in Europe

Funding is a problem in cross-country epidemiological studies. It has not been easy to establish funding for such multinational studies in Europe outside the Horizon 2020. Within this system little focus has been on the critical ill elderly patients, although our

estimate is that around 500,000 very old patients are treated in European intensive care units each year. Some of the participating countries have managed to receive funding, but only for their country sites and mainly for development and maintaining a database. At the moment our study group is seeking support of the European Society of Intensive Care Medicine (ESICM) as well as the European Geriatric Medicine Society (EuGMS) in order to create both a scientific cooperation but also to make the critically ill patients even more visible, and to launch joint approach to EU funding.

Another important problem we encountered in the VIP-2 study is the rather strict interpretation of the EU data protection directive (GDPR) in most European countries. This directive was implemented while we were starting up and still recruited participating units. In our first study (the VIP-1), most medical ethical boards in most countries allowed us to recruit patients without upfront written informed consent. As this was just an observational study with no interventions written informed consent was deemed not possible and violation of ethical rights was considered minimal as no patient identifying variables were collected. In some countries, we had to inform ICU survivors that their information had been included in the study and could then in retrospect withdraw from participation. This approach has obvious advantages that we can include patients in all stages of disease, also those unconscious at admission and those that later died.

However, this changed with the implementation of the GDPR in Europe. Now, almost all countries insisted on written informed consent by patient or proxy. This had major implications for recruitment to the study. In many countries, the sickest patients seemed to slip through and were not included in the study. We are now in the process of analysing this in two cohorts: one where informed consent was waived, and one where it was considered mandatory. Our concern is that this obviously may be

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Study	Patients	Clinical findings
Withholding or withdrawing of life sustaining therapy (Guidet 2018)	1356 from the VIP1 study	Limitations implemented in 27.2% (12.2% withdrawal) with large variations in Europe
Cumulative Prognostic Score Predicting Mortality in Patients Older Than 80 Years Admitted to the ICU (deLange 2019)	3720 patients from the VIP1 study	The model developed had an AUC of 0.8
A comparison of very old patients admitted to intensive care unit after acute versus elective surgery or intervention (Jung 2019)	1324 patients from VIP1 admitted after acute or planned surgery	30 days mortality twice as high in acute surgical ICU admissions vs elective surgery in a matched pair cohort study
Sepsis at ICU admission does not decrease 30-day survival in very old patients: a post-hoc analysis of the VIP1 multinational cohort study (Ibarz 2020)	493 patients from the VIP1 study with sepsis at admission	We found similar 30-day mortality in patients admitted with sepsis compared with other admission categories
Huge variation in obtaining ethical permission for a non-interventional observational study in Europe (deLange 2019)	A survey in 16 country coordinators for the VIP1 study	The time to receive ethical approval for the identical protocol varied from 7 to 300 days. In 9/16 countries informed consent at admission was not required.

Table 4: VIP sub-studies

an important confounding factor of a prospective pure observation study and may have implications for understanding vital epidemiology in critically ill patients. The GDPR will lead to biased results with an overestimation of the "better outcomes" as only the better or surviving patients can provide written informed consent. Of interest, this is of course not confined only to our studies, but all observation studies in critically ill patients when informed consent is not straight forward.

Future Perspectives

At the moment, our group is conducting a study of the elderly COVID-19 patients, but we are also planning a new multinational VIP study. Several options have been discussed, but most probably, we will study the use of a time limited trial (TLT) in the very old patients (Shrime 2016). In patients with uncertain prognosis it can be particularly difficult to decide whether or not to admit a patient to the ICU. In such circumstances, it can be an option to offer an "ICU-trial of limited time" to see if the patient responds to treatment with improvement of vital functions. This trial should be discussed with the patient (if possible) and/or next-of-kin so this is understood and communicated at admission. If condition deteriorates and there is no sign of response to treatment, the patient may then be given comfort and care with withholding or withdrawing vital organ support as the option. At present, we know very little about how often TLT is used in Europe, and even less about in which patients a TLT is used. The data from this exploratory study will be used in planning a controlled trial if possible.

The VIP-network of very active and enthusiastic ICUs across Europe might also enable us to switch to real-time data collection which can be of use for vigilance purposes. Elderly patients often represent the most vulnerable patient population and they are often more severely ill. This means that an unexpected increase of elderly patients in ICUs across Europe with a particular disease might be the first sign of a pandemic or chemical exposure. Development of such sentinel networks needs support from national governments and European Union legislation.

Conflict of Interest

None. ■

Key Points

- The aim of the VIP project is to contribute to new knowledge about the very old (>80 years) ICU patients, in particular to reveal important factors for survival and post ICU quality of life.
- The VIP network has so far conducted three large prospective observational studies.
- The main purpose of the VIP-1 study was to study the relation between pre-morbid conditions, like frailty and age.
- The VIP-2 study focussed only on emergency ICU admissions.
- When we were planning the VIP-3 study the world was hit hard by coronavirus disease.
- We adapted the VIP-1 and VIP-2 study protocols and customised it to fit our knowledge-gaps on COVID-19 in elderly.

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Snigdha Jain
Post-doctoral Fellow in Geriatric Clinical Epidemiology and Aging-Related Research
Fellow Physician
Section of Pulmonary, Critical Care and Sleep Medicine
Department of Internal Medicine
Yale University School of Medicine
New Haven, Connecticut
USA

Snigdha.Jain@yale.edu

🐦 @snigdhajain89

Lauren Ferrante
Assistant Professor of Medicine
Section of Pulmonary, Critical Care, & Sleep Medicine
Department of Internal Medicine
Yale School of Medicine
New Haven, Connecticut
USA

Lauren.Ferrante@yale.edu

🐦 @LFerranteMD

In Search of a Crystal Ball: Predicting Long-term Outcomes in Critically Ill Older Adults

Older adults who survive critical illness are at risk of adverse long-term outcomes, including long-term mortality and impairment in physical function, cognitive function, and mental health. In this article, we discuss the evidence behind prediction of these outcomes in older ICU survivors, and review risk factors that should be considered in future prediction modelling studies.

Older adults who survive a critical illness are at risk of a host of adverse long-term outcomes, including increased risk of death, readmission, and long-term impairments in physical, cognitive, and mental health domains (Hill et al. 2016; Iwashyna et al. 2010; Marra et al. 2018; Pandharipande et al. 2013; Wunsch et al. 2010). As increasing numbers of older adults are admitted to and survive the intensive care unit (ICU) around the world (Iwashyna et al. 2012; Jones et al. 2020), an understanding of factors that predict these outcomes is crucial to guide decision-making and to identify patients at risk of poor long-term outcomes.

Prediction modelling studies are investigations that utilise multiple known variables to construct a model that allows estimation of the likelihood of a particular outcome (Riley et al. 2013; Steyerberg et al. 2013). While knowledge of individual prognostic factors is useful, prediction models allow for a synthesis of multiple factors from several domains to provide actionable information about outcomes. A prediction modelling

study should 1) provide a model where information of independent variables is used to generate the probability of the outcome of interest, 2) be informed by predictors (factors) that are known before the outcome occurs, and 3) be generalisable (Leisman et al. 2020). In this article, we first review existing prediction modelling studies for long-term outcomes among older ICU survivors, followed by a discussion of factors that may inform future prediction modelling studies based on the current evidence supporting their association with long-term outcomes.

Long-Term Mortality

Older adults who survive a critical illness hospitalisation are at risk of higher long-term mortality compared to their younger counterparts and older adults who are hospitalised for non-critical acute care illnesses (Baldwin et al. 2015; Fuchs et al. 2012; Seethala et al. 2017; Wunsch et al. 2010). This risk is highest in the first year after discharge, but persists for up to three years and possibly longer (Wunsch et al. 2010). For those who become chronically

critically ill (CCI), the risk is even greater; only one-third of CCI patients over the age of 65 were alive at one year in a large American study (Kahn et al. 2010).

Several prediction models have been developed for long-term mortality among older ICU survivors, though only a handful have also undergone external validation. Baldwin and colleagues developed and externally validated a prediction model to estimate 6-month mortality specifically for older adults who survive critical illness (Baldwin et al. 2013). This model included do-not-resuscitate order, older age, comorbidity burden, admission from or discharge to a skilled-care facility, hospital length of stay, principal diagnosis of sepsis and haematologic malignancy, and male sex (area under the curve [AUC] 0.80 in the derivation cohort, 0.71 in the validation cohort). In an older study, age, diagnosis, and physiologic severity of illness were predictive of 1-year mortality in older adults, with an AUC 0.75 in external validation (Djaiani and Ridley 1997; Jandziol and Ridley 2000). A prediction model developed using a multi-centre registry

of older patients in very old adults (age ≥80 years) in Finnish ICUs identified age, male sex, medical (vs surgical) admission, severity of illness, and poor premorbid functional status as independent predictors of 1-year mortality (AUC 0.79 in the derivation cohort), though the model was not validated (Pietilainen et al. 2018). Other prediction models in older adults have identified age, male sex, mechanical ventilation, renal replacement therapy, frailty, diagnosis, and organ dysfunction as predictors of 30-d mortality; however, whether these risk factors can predict long-term mortality remains to be determined (de Lange et al. 2019; Minne et al. 2011).

In addition to true prediction modelling studies, a breadth of studies have attempted to elucidate individual risk factors that may inform prognostication of long-term mortality in older adults. One of the most important factors is pre-ICU functional status, which has been associated with long term mortality in several studies (Chelluri et al. 2004; Haas and Wunsch 2016; Iwashyna et al. 2010; Pietilainen et al. 2018). In a longitudinal cohort study with monthly assessments of functional status, mild-to-moderate and severe pre-ICU functional trajectories were found to be associated with double and triple the risk of death within 1 year of ICU admission, respectively, relative to those with minimal pre-ICU disability (Ferrante et al. 2015).

The evidence base behind frailty and long-term mortality is equally strong. In the same cohort, frailty was found to be independently associated with 6-month mortality with double the risk of death for each one-point increase in frailty count on a scale of 0-5 (Ferrante et al. 2018). This association between frailty and long-term mortality has been observed across multiple studies with 6-month mortality (Le Maguet et al. 2014), 1-year mortality (Bagshaw et al. 2014), and 3-year mortality (Hope et al. 2015).

Characteristics associated with the ICU stay have also been shown to influence long-term mortality. In a study of Medicare beneficiaries, mechanical ventilation was associated with substantially higher risk of long-term (up to 3-year) mortality after ICU discharge, though the risk was concentrated in the first 6 months after discharge (Wunsch et al. 2010). ICU length of stay and severity of illness have also been associated with increased mortality at 6 months and 1 year in an older critically ill population (Chelluri et al. 1993; de Rooij et al. 2005; Le Maguet et al. 2014; Pintado et al. 2016). Notably, the addition of ICU clinician estimates of outcomes may be helpful in improving the performance of prediction models, particularly for long-term mortality. In a prospective cohort study of adults aged 53-71 years in the ICU who were requiring either mechanical ventilation or vasopressors or both, Detsky and colleagues found that when added to an existing model of age, sex, functional comorbidity index, hospitalisations in the prior year, medical (vs surgical) ICU, and severity of illness score, physician and nurse predictions improved the model performance for outcomes of mortality and toileting at 6 months (AUC 0.88 vs 0.80, and 0.85 vs 0.77 respectively), though prediction estimates for ambulation and cognition were not significantly improved (Detsky et al. 2017a).

Long-Term Physical Impairment and Disability

Up to 70% of patients who survive an ICU stay experience new or worsening disabilities (Hopkins et al. 2017; Pfoh et al. 2016). Disability is an important clinical outcome for patients and their families as it is associated with diminished quality of life, increased risk of rehospitalisation, and death (Covinsky et al. 2011; Gill et al. 2010). One study developed and internally validated a prediction model to predict the performance status of very old adults (≥ 80 years of age) at one year after an ICU stay (Heyland et al. 2016). The model included being married, having a primary diagnosis of emergency cardiac surgery or valve replacement, and higher baseline performance status as measured by the Palliative Performance Scale (PPS) to be predictive of a higher performance status (PPS ≥ 60). Being male, a primary diagnosis of stroke, higher severity of illness, Charlson comorbidity index, and higher score on the Clinical Frailty Scale were predictive of a low performance status (<60) at 12-months assessed using the same scale (AUC 0.81 derivation, 0.79 internal validation; good calibration). Only two other studies have described models to predict the risk of physical disability after discharge from the ICU, but these were not specific to older adults. A multi-centre prospective cohort study of middle-aged male adults admitted to medical/surgical ICUs in the United States identified age, medical (vs. surgical) patient, non-white race, higher APACHE III score, hospitalisation in prior year, and past history of cancer, liver disease, neurologic condition, or any type of transplantation in the model as predictive of returning to baseline physical function at 6 months after discharge (AUC 0.78 derivation, 0.73 internal validation; good calibration) (Detsky et al. 2017b). Another single centre study in Europe followed 148 middle-aged adults for 2 months after ICU discharge and identified low educational level, impaired core stability, fractures, and an ICU length of stay of more than two days at discharge as predictive of new-onset physical disability (AUC 0.82 derivation, 0.80 internal validation, good calibration) (Schandl et al. 2014). A recent study developing and externally validating a risk prediction model (the PREDICT model) for persistent functional decline among older ICU survivors is currently under review (Ferrante et al. 2019).

Among older adults, several pre-ICU factors have been found to be strongly associated with post-ICU functional outcomes and should be candidates for inclusion in future prediction modelling studies. Functional disability prior to ICU admission has

been consistently associated with new or worsening disability in ICU survivors of all ages (Hopkins et al. 2017). Among older adults, a quarter of those with minimal pre-ICU disability and 40% of those with mild to moderate pre-ICU disability became severely disabled in the year following ICU stay (Ferrante et al. 2015). A prospective cohort study examining functional recovery 12 months after discharge from the ICU found functional status at discharge as measured by the Barthel Index to be associated with recovery measured by the same index (Sacanella et al. 2011).

Frailty has been consistently associated with post-ICU disability across multiple studies and should be a candidate for inclusion in future prediction modelling studies (Bagshaw et al. 2014; Ferrante et al. 2018; Muscedere et al. 2017). Notably, this strong association exists regardless of which frailty assessment tool is used; most ICU studies have used either the Clinical Frailty Scale (Rockwood et al. 2005) or the Fried frailty phenotype (Fried et al. 2001). Although the Fried frailty phenotype requires patient participation, Baldwin and colleagues successfully demonstrated the feasibility and usefulness of measuring frailty in older ICU survivors prior to hospital discharge (Baldwin et al., 2014). Pre-existing frailty and cognitive impairment have also been shown to interact to amplify the magnitude of post-ICU disability over the 6 months after discharge among older adults (Ferrante et al. 2019). Other pre-admission factors that have been associated with increased disability or functional decline following critical illness include older age (Chelluri et al. 2004; Jackson et al. 2014), coexisting medical conditions (Needham et al. 2014; Pfoh et al. 2016), and sensory impairment including hearing and vision impairment (Ferrante et al. 2016).

Many hospital- and ICU-specific factors are also associated with long-term disability in older ICU survivors. Older adults who received mechanical ventilation were found to have 30% greater disability in activities

of daily living and 14% greater mobility difficulty at one year compared to those who were hospitalised but never received mechanical ventilation (Barnato et al. 2011). In a prospective cohort of patients age ≥80 in Canadian ICUs, younger age, lower severity of illness, lower Charlson comorbidity index, less frailty, and an admission diagnosis of CABG/valve replacement were associated with a greater likelihood of physical function recovery using the Short-Form 36 (SF-36) physical function score (Heyland et al. 2015). A diagnosis of severe sepsis was associated with worse functional limitations compared to non-sepsis hospitalisations in a US based cohort of older adults (Iwashyna et al. 2010). The 7-day post-ICU Functional Independence Measure (FIM), a patient-centred measure of disability that captures both motor and cognitive function, was associated with functional disability over the year after discharge in a cohort of adult ICU survivors that had been mechanically ventilated (Herridge et al. 2016).

Long-Term Cognitive Impairment

Survivors of critical illness are at risk of developing cognitive impairment comparable to that conferred by moderate traumatic brain injury or mild Alzheimer's disease (Pandharipande et al. 2013). Older adults are no exception to this and in fact, because of an increased prevalence of prior cognitive impairment compared to the general population, may be at increased risk for cognitive decline after critical illness hospitalisation and consequences thereof (Gale et al. 2008). There are currently no prediction modelling studies to forecast cognitive impairment in older adults after critical illness (Haines et al. 2020). Most studies on cognitive impairment in critically ill patients have included diverse middle-aged populations with few studies specifically in older adults (Honarmand et al. 2020).

Several studies have evaluated determinants of cognitive decline after ICU

admission in the broader ICU population. The presence and duration of delirium have consistently been identified as risk factors for post-ICU cognitive impairment in systematic reviews (Sakusic et al. 2018; Salluh et al. 2015). Moreover, in a retrospective study of patients age 50-91 who had undergone cognitive testing over time, ICU admission was associated with greater long-term cognitive decline compared to patients without ICU admission; these findings were most pronounced for patients who had delirium while in the ICU (Schulte et al. 2019). Pre-ICU cognitive status, ICU length of stay, and hypoxia are also important factors that have been identified in a prior systematic review in all adult ICU patients (Sakusic et al. 2018) and should be considered as potential predictors of long-term cognitive impairment in future work. Additionally, sepsis should be evaluated as a potential predictor in future prediction modelling studies; in a cohort of older Medicare beneficiaries, of which slightly less than half were in the ICU, severe sepsis was significantly associated with greater odds of cognitive impairment among survivors (Iwashyna et al. 2010).

Long-Term Mental Health Impairment

The consequences of depression and mental health disorders for older adults cannot be understated; in the general older adult population, depression and other mental health disorders have been associated with poor quality of life, worse cognition, reduced physical function, and increased mortality (Callahan et al. 2005; Han 2001; Mehta et al. 2003). Unfortunately, psychiatric morbidity is common after critical illness with increased rates of depression, anxiety, and post-traumatic stress disorders (Davydow et al. 2008), and no prediction models exist to predict onset of psychological impairment after critical illness in older ICU survivors. In middle-aged adults, age, lack of social support, traumatic

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memories and depressive symptoms at ICU discharge predicted depression, anxiety, and post-traumatic stress disorder at 3 months of follow-up (AUC 0.76 derivation, 0.73 internal validation) (Milton et al. 2018). Multiple systematic reviews have synthesised evidence on psychiatric morbidity, depression, and post-traumatic stress disorder in survivors of critical illness; however, none have characterised the older adult population (Davydow et al. 2009; Davydow et al. 2008).

Conclusions

With the ageing of our population, the number of older ICU survivors will only increase. Many of these older ICU survivors are at increased risk of poor long-term outcomes, including long-term mortality and impairments in physical function, cognitive function, and mental health. However, more than half of older ICU survivors will achieve functional recovery within 6 months of a critical illness (Ferrante et al. 2016), and few prediction models exist to distinguish between older adults those

who are at risk of persistent impairments and those who are likely to recover.

To appropriately guide decision-making for geriatric patients and their families, it is helpful for the clinician to be aware of factors associated with long-term outcomes in each of the aforementioned domains. Knowledge of these factors may inform treatment planning discussions using shared decision-making with patients and families. Prediction models that have been developed and externally validated specifically among older adults should be employed by clinicians when faced with the question of long-term mortality and physical performance. However, these studies are limited and do not exist for all domains of impairments, warranting future prediction modelling research for the breadth of adverse outcomes faced by older adults who survive a critical illness.

Conflict of Interest

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Key Points

- Older adults who survive a critical illness hospitalisation are at risk of higher long-term mortality compared to their younger counterparts and older adults who are hospitalised for non-critical acute care illnesses..
- For those who become chronically critically ill (CCI), the risk is even greater.
- Few prediction models exist to distinguish between older adults those who are at risk of persistent impairments and those who are likely to recover.
- These prediction models should be employed by clinicians when faced with the question of long-term mortality and physical performance.
- There is a need for more future prediction modelling research for the breadth of adverse outcomes faced by older adults who survive a critical illness.

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Nutritional Management of the Critically Ill Older Adult

A review of available evidence and an overview of recommendations for the nutritional management of the critically ill older adult.

Oana A. Tatucu-Babet
Australian and New Zealand Intensive Care Society Research Centre
School of Public Health and Preventative Medicine
Monash University
Melbourne, Australia

Oana.Tatucu@monash.edu

🐦 @OanaTatucu

Kate Lambell
Australian and New Zealand Intensive Care Society Research Centre
School of Public Health and Preventative Medicine
Monash University

Nutrition Department
Alfred Health
Melbourne, Australia

kate.lambell@monash.edu

🐦 @KateLambell

Emma J. Ridley
Australian and New Zealand Intensive Care Society Research Centre
School of Public Health and Preventative Medicine
Monash University

Nutrition Department
Alfred Health
Melbourne, Australia

emma.ridley@monash.edu

🐦 @ICUnutrition

Introduction

Worldwide, there is a shift in the distribution of the population towards older ages. This shift is similarly being experienced in the Intensive Care Unit (ICU), with the median age of the entire ICU in some countries above 65 years (Flaatten et al. 2017). Older adults are commonly defined as persons aged 65 years or older, with geriatric medicine not specifically age defined but more frequently guided by the degree of morbidity (EUMS Definition). Nutrition therapy may play an important role in maintaining and optimising functional status and quality of life in critically ill older adults, with prolonged inadequate nutrition associated with poorer patient outcomes and greater economic burden for health care systems (Goates et al. 2016; Rasheed and Woods 2013; Volkert et al. 2019; Ha et al. 2010; Hegerova et al. 2015; Gentile et al. 2013). This narrative review aims to summarise available evidence and provide an overview of recommendations for the nutritional management of the critically ill older adult.

General Considerations for the Nutrition Management of the Older Adult in ICU

Important considerations relevant to the provision of nutrition therapy in the older adult are displayed in **Figure 1**. The majority of these considerations are interrelated and associated with higher morbidity and mortality (Guidet et al. 2018; Schefold et al. 2017; Lew et al. 2017; Shpata et al. 2015; Singer et al. 2019; Wells and Dumbrell 2006; Gomes et al. 2011; Gingrich et al. 2019), with malnutrition, obesity and sarcopenia discussed in more detail below.

Malnutrition

The detection and monitoring of malnutrition are of importance in this patient group, with estimates that malnutrition affects approximately 23% of hospitalised and 23-34% of critically ill older adults (Guigoz 2006; Sheean et al. 2013). The early identification and management of malnutrition are important, with malnutrition associated with adverse patient outcomes including longer hospital length of stay, functional decline, poor quality of life and higher mortality (Rasheed and Woods 2013; Gentile et al. 2013; Esmayel et al. 2013; Alzahrani and Alamri 2017; Liu et al. 2002). A limited number of studies have explored the sensitivity and specificity of malnutrition screening and diagnostic tools in older critically ill patients (Sheean et al. 2013; Tripathy and Mishra 2015). Due to the paucity of studies in this area, the latest 2019 European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines take a pragmatic approach, recommending that all patients (regardless of age) with an admission greater than 48 hours be considered at risk of malnutrition, but do not endorse use of a specific malnutrition screening or assessment tool (Singer et al. 2019). Until tools are appropriately validated in this population, local guidelines or the recent Global Leadership Initiative in Malnutrition (GLIM) criteria can be used to diagnose malnutrition.

Obesity

The prevalence of obesity (body mass index [BMI] >30kg/m2) is increasing in older adults, with a European study reporting an increase from 17.5% in 2005 to 19.2% in 2013 in individuals aged 50 years or older (Peralta et al. 2018). Both the ESPEN and the American Society for Parenteral and Enteral Nutrition/Society of Critical Care Medicine (ASPEN/SCCM) clinical guidelines make specific recommendations for the management of critically ill obese patients (**Table 1**) but are not specific to
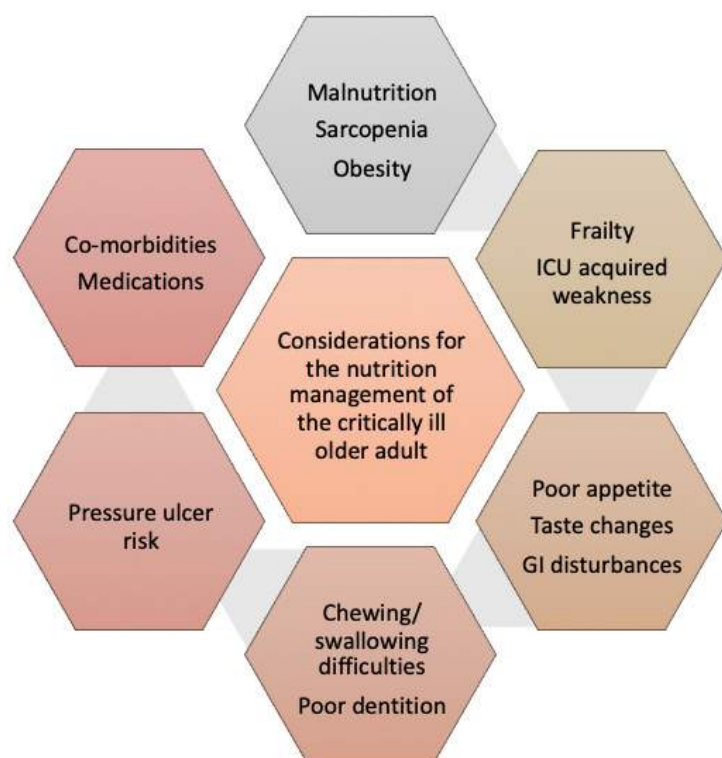
Figure 1. Considerations for the nutrition management of the critically ill older adult.
GI - gastrointestinal; ICU - Intensive Care Unit

Guideline	ESPEN (Singer et al. 2019)	ASPEN/SCCM (McClave et al. 2016)
Energy	Where possible, indirect calorimetry should be used to guide energy delivery **Day 1-3:** Aim <70% estimated or measured energy expenditure **After day 3:** • If using indirect calorimetry, progressively increase to 80-100% measured energy expenditure • If using predictive equations, aim <70% estimated energy expenditure for the first week	Where possible, indirect calorimetry should be used to guide energy delivery **Non-obese:** 25-30 kcal/kg/day **Obese:** • BMI 30-50 kg/m2: 11-14 kcal/kg actual body weight/day • BMI >50 kg/m2: 22-25 kcal/kg ideal body weight/day • If using indirect calorimetry, energy delivery should not exceed 65-70% of measured energy expenditure
Protein	**Non-obese:** 1.3 g/kg/day delivered progressively **Obese:** 1.3 g/kg adjusted body weight/day	**Non-obese:** 1.2-2.0 g/kg/day, and may be higher in burn or multi-trauma patients **Obese:** • BMI 30-40 kg/m2: 2.0 g/kg ideal body weight/day • BMI ≥ 40 kg/m2: up to 2.5 g/kg ideal body weight/day

ASPEN/SCCM: American Society for Parenteral and Enteral Nutrition/Society of Critical Care Medicine;
BMI: Body Mass Index; ESPEN: European Society for Clinical Nutrition and Metabolism.

Table 1: General energy and protein recommendations for all Intensive Care Unit patients

the older obese adult.

A hypocaloric, high protein diet has been proposed for critically ill obese patients and is recommended in the ASPEN/SCCM guideline (McClave et al. 2016; Burge et al. 1994; Choban et al. 1997), but there is minimal evidence to support the use of this intervention in older obese patients. In a retrospective study, nitrogen balance and a range of clinical outcomes were explored in 33 older (≥ 60 years) and 41 younger (18-59 years) obese critically ill trauma patients prescribed hypocaloric, high-protein nutrition therapy (mean protein intake during nitrogen balance: 2.3 g/kg ideal body weight/day for both groups) (Dickerson et al. 2013). Mean nitrogen balance was comparable, with approximately half of patients in each group achieving nitrogen equilibrium or positive nitrogen balance. Clinical outcomes, including ICU length of stay and duration of mechanical ventilation, did not differ between groups (Dickerson et al. 2013). However, older patients had higher mean serum urea nitrogen concentrations (30 ± 14 mg/dL vs 20 ± 9 mg/dL, p = 0.001), although there were no signs of uraemia and no patients required continuous renal replacement therapy (Dickerson et al. 2013). This highlights that the use of high protein diets may be important for maintaining nitrogen equilibrium in the older obese adult, and that renal function should be carefully monitored when this nutrition intervention is delivered.

It is not clear whether there are benefits of implementing hypocaloric versus isocaloric regimens in the older obese critically ill adult. As energy requirements for obese individuals may be higher than recommended targets (Ridley et al. 2020a), and malnutrition and sarcopenia are key considerations in the older adult (which can co-exist with obesity), energy prescription should be carefully considered on an individual basis. The under-prescription of energy needs can result in significant underfeeding over time and this may be further compounded

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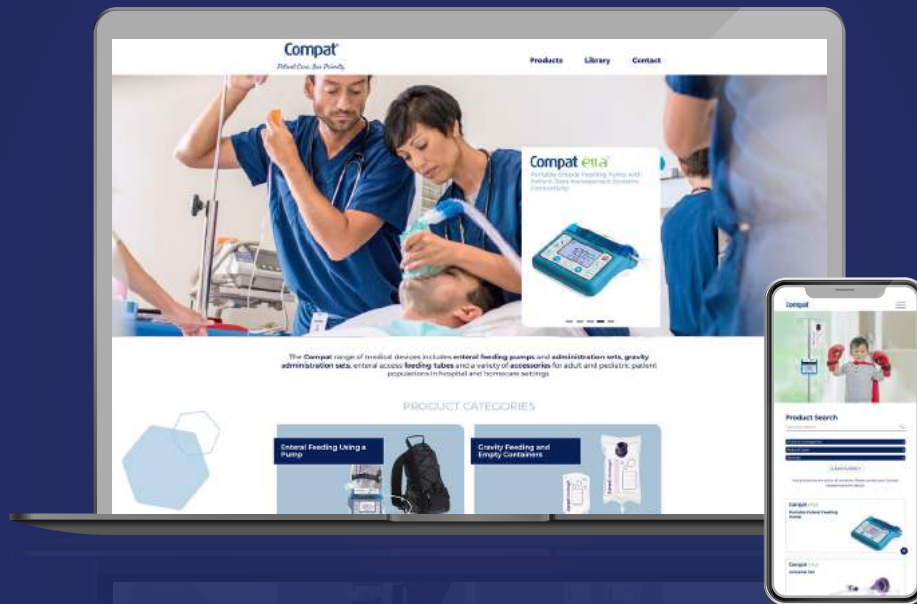
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by the reported delay in the initiation of nutrition support in obese patients (Borel et al. 2014). Conversely, overfeeding has been associated with hyperglycaemia, hepatic steatosis (more likely to occur with parenteral nutrition) and increases in duration of mechanical ventilation which may be more pronounced in obese individuals (Dickerson 2020; Klein et al. 1998). The risks of both should be balanced with the goal of minimising muscle loss and maximising functional recovery.

Sarcopenia

Sarcopenia is generalised loss of skeletal muscle mass, strength and function, occurring primarily due to ageing, and secondary due to disease, inactivity and malnutrition (Cruz-Jentoft et al. 2019). Insulin resistance and anabolic resistance to protein intake (reduced sensitivity to amino acids, with higher quantities likely required to stimulate muscle protein synthesis) contribute to the increased risk of sarcopenia with ageing (Dickerson 2020; Breen & Phillips 2011). There is limited evidence investigating sarcopenia in critically ill patients due to the challenges of measuring both muscle mass and muscle strength in the ICU setting (Kizilarslanoglu et al. 2016). However recent observational studies have reported significantly lower muscularity at ICU admission in older (≥ 65 years) versus younger patients using computed tomography (CT) image analysis (Paris et al. 2017; Lambell et al. 2020). Further, in older trauma patients admitted to the ICU, low CT muscle area was highly prevalent and independently associated with length of mechanical ventilation, ICU stay and mortality (Moisey et al. 2013). In non-ICU hospitalised patients, sarcopenia is associated with a range of poorer health outcomes, and in older hospitalised adults, those with sarcopenia on admission have been found to have higher hospital costs (up to a 5-fold increase) (Cruz-Jentoft et al. 2019; Antunes et al. 2017). Although not specific to older patients, three recent

randomised controlled trials (RCTs) investigated nutritional interventions (high protein, high energy, and bolus feeding) aimed at attenuation of muscle wasting in the first few weeks of critical illness, with mixed findings (Ferrie et al. 2016; McNelly et al. 2020; Fetterplace et al. 2018). While the most appropriate nutrition interventions to limit detrimental changes in muscle health in critically illness (and specifically older adults) remains unclear, strategies such as early mobilisation and high protein intakes (see protein section) may be beneficial but need to be investigated (McKendry et al. 2020). Future studies are required to validate methods for assessing sarcopenia in the critically ill setting, and to determine the most appropriate nutrition intervention to prevent muscle loss and functional decline in critically ill older patients.

Nutritional Requirements for the Older Adult in ICU

Energy

The use of indirect calorimetry (and if not available, oxygen consumption [VO2] or carbon dioxide production [VCO2] measurements) is recommended to determine energy expenditure during critical illness and guide energy delivery where possible (Singer et al. 2019; McClave et al. 2016). In its absence, predictive equations are used. Predictive equation estimates commonly differ from indirect calorimetry measurements in critical illness, and this can be a greater issue at the extremes of age (Segadilha et al. 2017). In the older adult, changes in metabolism, decreases in fat and fat-free mass, medication use (such as the use of sedatives and analgesics in the ICU) and comorbidities likely contribute to this difficulty, as well as the use of predictive equations that were commonly developed and validated using populations with mean ages under 65 years (Walker and Heuberger 2009; Parker et al. 2017). Although various equations have been proposed for use in older critically ill adults (including the Mifflin–St Jeor and Harris-Benedict equa-

tions with applied stress factors) (Segadilha et al. 2017), there is no consensus on the most accurate and precise equation to use in this population.

Where the use of indirect calorimetry is not possible, **Table 1** summarises the current weight-based formula recommendations from key nutrition guidelines in critically ill patients. It should be noted that these recommendations are not specific to the older adult, with the ESPEN guideline on clinical nutrition and hydration in geriatrics recommending that approximately 30 kcal/kg/day is targeted (minimal requirements of 27 and 30 kcal/kg/day estimated during illness) for the older adult (Volkert et al. 2019).

Irrespective of the energy target selected, the latest ESPEN 2019 clinical practice guideline for critical illness recommends the progressive introduction of nutrition **(Table 1)**, due to findings of recent RCTs reporting no benefit (and in some cases harm) with target feeding early in ICU admission (Singer et al. 2019; Arabi et al. 2015; Rice et al. 2012; Casaer et al. 2011; Chapman et al. 2018). Hypocaloric nutrition, with adequate protein provision and progression to isocaloric nutrition where appropriate, has similarly been proposed for the older critically ill adult to avoid complications of overfeeding (McKendry et al. 2020)), nonetheless limited RCTs have been conducted to support this recommendation. Careful monitoring of energy provision is recommended in this patient group to avoid adverse outcomes associated with both under- and overfeeding.

Protein

Protein provision is thought to be important for maintaining functionality, decreasing the degree of ICU-acquired weakness and promoting recovery from illness, however the impact of protein intake on outcomes in critical illness is yet to be elucidated (Singer et al. 2019; Bauer et al. 2013; Preiser 2018). Protein intake recommendations in critical illness are summarised in

Table 1, however these are not specific to the older adult. For adults aged 65 years or older, 1.0–1.2 g/kg/day of protein is recommended in health, with increased quantities of 1.2-1.5 g/kg/day or higher recommended for older people with a severe illness in key position papers (Bauer et al. 2013; Deutz et al. 2014). In a recent review, protein intakes up to 2.5 g/kg/day have been proposed for critically ill older adults in severe catabolic states, such as patients with severe trauma and burns (McKendry et al. 2020).

In the stable non-critically ill patient, protein source (animal > vegetable protein), feeding pattern and timing of protein to exercise may play an important role in enhancing optimal protein synthesis (Bauer et al. 2013). Pulse-feeding (the inclusion of most protein at midday) (Bouillanne et al. 2013) and consuming high-quality protein immediately following exercise (Jordan et al. 2010; Esmarck et al. 2001) are some strategies that may be beneficial but require investigation in the stable critically ill older adult.

Fluid

For non-critically ill patients, 30-35 ml/kg/day of fluid is recommended for adults, nonetheless, this is a general recommendation that can vary significantly depending on factors including extra losses (e.g. drains) and extra input (e.g. intravenous drugs) (National Collaborating Centre for Acute Care, Queensland Health 2017). In the older adult (particularly frail and malnourished patients), fast and high volumes of fluid resuscitation may not be well tolerated with recommendations of providing less intravenous fluid (approximately 20-25 ml/kg/day) (NICE 2013). As with younger critically ill patients, fluid requirements are dependent on the clinical situation and should be individualised. When prescribing oral nutrition supplements, enteral and/or parenteral nutrition, fluid requirements should be considered and discussed with the medical team.

In the stable older adult, constipation is a common complaint which becomes more prevalent with ageing (Schuster et al. 2015). This in part can occur due to neurodegenerative changes in the enteric nervous system related to ageing and changes to rectal sensitivity and anal function (McCrea et al. 2008). Fluid intake should be considered when managing constipation in the ICU, with critical illness likely to increase the risk of constipation further for several reasons including the use of sedatives, opioid agents and changes in diet (de Azevedo and Machado 2013).

Considerations for the Ventilated Patient

Where nutrition targets cannot be achieved orally or in cases where swallowing is proven unsafe, artificial nutrition support should be considered (Singer et al. 2019). Post-pyloric enteral nutrition (or temporary parenteral nutrition where post-pyloric enteral nutrition is not possible) may be necessary in cases of severe dysphagia with a very high aspiration risk (Singer et al. 2019).

When commencing enteral nutrition, early commencement within 48 hours of ICU admission is recommended in key guidelines for critically ill adults (Singer et al. 2019; Burge et al. 1994; Heyland et al. 2003). Avoiding delays in the commencement of artificial nutrition support is important for at-risk patient groups, including malnourished and frail older adults. In all critically ill patients, enteral nutrition is the preferred and most common delivery route. However, when both oral and enteral nutrition are contraindicated, parenteral nutrition should be considered within three to seven days of ICU admission (Singer et al. 2019). Furthermore, as only approximately 50-60% of prescribed nutrition targets are usually delivered (Ridley et al. 2018), particular attention to energy and protein adequacy should be made as large deficits can quickly accumulate. This is an important consideration in this potentially vulnerable population that may have pre-existing malnutrition.

Another key consideration for patients receiving artificial nutrition support is refeeding syndrome, characterised by potentially fatal extreme fluid and electrolyte shifts (in particular, hypophosphatemia) (Mehanna et al. 2008; Aubry et al. 2018). Older adults, particularly malnourished elderly, are considered a high-risk population for developing refeeding syndrome due to the increased likelihood of comorbidities and reduced physiological reserves. Careful progressive introduction of artificial nutrition in all critically ill patients within the first week of ICU stay is recommended in the ESPEN 2019 guideline (**Table 1**) which is likely to assist in limiting the occurrence of refeeding syndrome (Singer et al. 2019). However, if refeeding syndrome is detected, detailed recommendations of management are outlined in the ESPEN 2019 guideline (Singer et al. 2019).

Considerations for the Non-Ventilated Patient in ICU

In the non-ventilated critically ill older adult, where possible, energy and protein targets should be met via oral diet and oral nutrition supplements (Singer et al. 2019). However, in practice this is challenging, with increasing evidence highlighting that energy intake is likely to be suboptimal, and frequently, under 60% of predicted requirements (Rowls et al. 2016; Peterson et al. 2010; Chapple et al. 2020). Refeeding syndrome risk should also remain a key consideration in patients consuming an oral diet, although the risk of occurrence is likely to be lower than in patients receiving artificial nutrition support.

The reasons contributing to suboptimal intake in the older adult are likely multifactorial and may include; decreased appetite, alterations in taste and smell, gastrointestinal factors (including delayed gastrointestinal motility, nausea, vomiting), physical barriers (including weakness, impaired vision) and psychological factors

(including delirium), all of which may be heightened in the ageing population (Wells and Dumbrell 2006; 14, Naithani et al. 2008; Reid and Allard-Gould 2004; Bryczkowski et al. 2014; Ridley et al. 2020b). Post-extubation dysphagia is also a concern for the older critically ill patient, with a recent study reporting that 41.4% of 111 patients aged 65 years or older were found to have clinically significant dysphagia following liberation from mechanical ventilation (Regala et al. 2019).

For patients consuming an oral diet, oral nutrition supplementation should be strongly considered in this population (Singer et al. 2019; Singer 2019). Albeit not in the ICU, a double-blinded RCT of 652 malnourished hospitalised older adults (≥ 65 years), found that consumption of two high-protein supplements containing beta-hydroxy-beta-methylbutyrate (700 kcal and 40 g protein per day) from 72 hours of admission to 90 days post discharge compared to a placebo led to a lower 90-day mortality (4.8% vs 9.7%; relative risk 0.49, 95% confidence interval, 0.27 to 0.90; p = 0.018) and improved odds of better nutritional status at day-90 (Duetz et al. 2016). In addition to assisting in meeting energy and protein targets, oral nutrition supplements have also been reported to assist in optimising quality life, muscle function and decreasing the incidence of pressure ulcer development in acutely ill older adults (Ha et al. 2010; Bourdel-Marchasson et al. 2000; Gariballa & Forster 2007). Despite these findings, the prescription of oral nutrition supplements in non-ventilated ICU patients has been reported to be low (offered to <50% of patients consuming an inadequate diet) (Jarden et al. 2018). It is crucial that the oral intake of critically ill older adults is closely monitored and escalation to artificial nutrition support is considered when intake is inadequate.

The Post-ICU period

Nutrition support in the post-ICU period is likely to play an important role in recovery, but limited research exists in the area in general and specifically in older patients. In a study conducted in 32 patients in the post-ICU hospitalisation period (mean age 56 ± 18 years), nutrition intake was assessed second daily until day 28 or hospital discharge (Ridley et al. 2019). The median [interquartile range] energy and protein intake was 79% [41–108%] and 73% [44–98%], respectively, with intake lowest in patients receiving oral intake alone without oral nutrition supplements (median [interquartile range] energy and protein intake: 37% [21– 66%] and 48% [13–63%] of predicted requirements, respectively) (Ridley et al. 2019). No studies to our knowledge have assessed nutrition intake solely in older patients following ICU discharge, however studies in the acute care setting support the notion that intake may be suboptimal and that oral nutrition supplements should be prescribed and encouraged as discussed earlier (Ha et al. 2010; Bourdel-Marchasson et al. 2000; Gariballa and Forster 2007; Shahar et al. 2002; Young et al. 2018). In older adults, combined nutrition support and physiotherapy may also be beneficial for physical and muscle function as well as improving body composition (Hegerova et al. 2015; Fiatarone et al. 1994), but this needs to be explored in the ICU.

Conclusion

The physiological changes encountered with ageing present many complexities to consider when assessing and managing the nutrition needs of critically ill older adults. A thorough assessment of patients' pre-ICU condition ensures that potential nutritional risks are identified (e.g. risk of re-feeding syndrome and malnutrition) and that the nutritional management is appropriate for the individual. Following ICU discharge, adequate nutrition follow-up is likely to be important for supporting recovery and a return to premorbid function. With limited evidence available, critical care trials investigating nutrition therapy in the older adult would assist in guiding and enhancing nutrition care in this vulnerable population. ■

Key Points

- The median age of the entire ICU in some countries is above 65 years.
- Malnutrition affects approximately 23% of hospitalised and 23-34% of critically ill older adults.
- The prevalence of obesity is increasing in older adults.
- Careful monitoring of energy provision is recommended to avoid the development of refeeding syndrome and adverse outcomes associated with under- and overfeeding.
- The oral intake of critically ill older adults should be monitored closely and escalated to artificial nutrition support when intake is inadequate.
- In older adults, combined nutrition support and physiotherapy may be beneficial for physical and muscle function.

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For full references please email editorial@icu-management.org or visit https://iii.hm/14jh

Jayshil J. Patel
Division of Pulmonary & Critical Care Medicine
Medical College of Wisconsin

jpatel2@mcw.edu

Daren K. Heyland
Department of Critical Care Medicine
Kingston Health Science Centre

Clinical Evaluation Research Unit
Kingston Health Science Centre

Department of Public Health Sciences
Queen's University
Kingston, Ontario

dkh2@queensu.ca

Unmasking the Triumphs, Tragedies, and Opportunities of the COVID-19 Pandemic

The COVID-19 pandemic has resulted in many changes to society and the practice of critical care medicine. Perhaps now is the time to address deficiencies in communication and decision-making that impact quality of care provided to older patients with serious illness.

The COVID-19 pandemic has created a juxtaposition of triumph and tragedy. In triumph, the pandemic has metaphorically brought humans together like nothing else we have observed in recent times. The international community has been mobilised to provide the best patient care while simultaneously protecting health care workers by identifying solutions to local problems like workforce and resource shortages. Research priorities have shifted to rapidly test novel therapies, to identify a vaccine, and to establish 'best practices' for managing patients with COVID-19. With temporary obscurity of the electronic health record, doctors and other healthcare providers are talking with one another. The chatter is ripe with novel clinical observations and teeming with pearls and stories of how individuals and healthcare systems are innovating during a crisis. Thanks to social media, many communities, industries, and organisations have banded together to procure personal protective equipment

(PPE) for front-line healthcare workers.

In tragedy, over 25 million people have been infected and the death toll continues to climb, reaching nearly 850,000 worldwide, and unfortunately, older individuals bear the burden of severe disease, hospitalisations, and mortality (Johns Hopkins University 2020). Outcomes data demonstrate afflicted hospitalised individuals 80 years of age or higher survive less than 15%, and survivors often require more than three weeks of mechanical ventilation and prolonged hospital stay (Cummings et al. 2020). Pre-COVID-19, longitudinal post-critical illness follow-up studies suggest only 25% of older patients return to pre-critical illness level of functioning while 25% endure a significant reduction in their quality of life and functional status and the remainder will die (Heyland et al. 2016a). Not yet available, but longitudinal outcomes data from survivors of COVID-19 related critical illness are likely to be grim owing to the prolonged nature of illness. Death, while tragic, may overshadow the real tragedy, which is dying (or surviving) in a personally unacceptable manner. Here, we cast a light on problems with communication as it relates to decision-making for older individuals suffering from critical illness (no communication, insufficient communication, and ineffective communication) and how the COVID-19 pandemic has further impaired the decision-making process by

serving as a barrier to timely and effective communication. We offer pragmatic tools to enhance the decision-making process to ensure the older patient with COVID-19 disease transitions through the healthcare system in a personally acceptable manner.

Caring for critically ill patients with COVID-19 disease has called for clustering care, preserving personal protective equipment, limiting interactions with patients, and prohibiting visitors into an ICU. The intended consequences of these measures are to protect healthcare workers and limit the spread of SARS-CoV-2 virus. The unintended consequences are unknown. However, communication between the healthcare team and families may be sub-optimal. Due to the prohibition of visitors, families are updated via telephone and unable to witness their loved one physically and emotionally suffering. Consequently, decision-making is marred and incomplete, without consideration of the subjective bedside experience gained by families, and decisions made with incomplete information opens a pathway for medical errors to occur, including the receipt of unwanted treatments.

Reviewing the consequences of inadequate communication from the pre-COVID era may provide insight into the magnitude of the problem. For example, older hospitalised patients were interviewed to identify their values and preferences for CPR and

compared those preferences to CPR orders in the medical chart (Heyland et al. 2016b). The chart indicated the patient prescribed CPR when, in fact, the patient did not identify it as a preference on average 35% of the time and this error rate ranged in 14-82% of hospitals surveyed. These data suggest older patients had the potential to receive a life-sustaining therapy (CPR) that was unwanted. In another study, families of 600 incapacitated patients aged 80 or older were interviewed throughout the patients' ICU stay. Families were interviewed to elucidate patients' underlying values and preferences. Preserving comfort and 'to suffer as little as possible' were the most common responses (Heyland et al. 2015). In fact, 24% of families expressed that the preferred medical treatment plan be 'comfort measures only.' Yet, all the older patients had been admitted to an ICU for aggressive treatments that increased their pain and promoted discomfort. Just over 50% of families acknowledged that a doctor had talked to them about treatment options. Approximately half of these older patients died in the hospital, on average, after two weeks of intensive care. Families were most dissatisfied with communication and decision-making and the amount of 'control' they had over what happened to their loved one.

Arguably, these results suggest the health care system's decision-making superseded patients' and critical care services served to prolong the dying experience, which seems inconsistent with a 'quality finish' from the patient's point of view. Finally, by analysing audio recordings of approximately 250 patient-clinician interactions in the ICU setting, Scheunemann and colleagues provided us with greater insights into how values and preferences are elicited from family members of critically ill patients (Scheunemann et al. 2019). Overall, 63% of family conferences contained no information exchange or deliberation about patient values or preferences and clinicians made treatment recommendations informed

by patient values and preferences in less than 10% of the conferences. These results suggest ICU family conferences to establish treatment plans often lack important elements of shared decision-making and 'patient-centred care.'

Overall, these data suggest poor-quality communication negatively impacts decision-making, which can lead to overutilisation of ICU services for older individuals who did not want them in the first place, or

> ❝ **over 25 million people have been infected with COVID-19 and the death toll continues to climb .... older individuals bear the burden of severe disease, hospitalisations, and mortality** ❞

who, once in an ICU, had their dying experience unnecessarily prolonged, and thus, the ICU experience merely served to enhance discomfort and suffering. Not only do unwanted treatments harm patients and add stress on families, but during the COVID-19 pandemic, they (unnecessarily) expose health care providers to a greater risk of SARS-CoV-2 virus transmission. For some older patients, protracted critical illness represents a far worse state than death and data suggest many older individuals would rather choose conservation and dignity-preserving treatment pathways in lieu of aggressive supportive care system technology when faced with serious illness (Rubin et al. 2016). For older persons with SARS-CoV-2 infection requiring critical care services, the disease state has left them in isolation, tethered to machines, at-risk of never speaking again nor hearing a familiar voice or seeing a

recognisable face, which for many may be an unacceptable way to live or die. When the COVID-19 pandemic settles, it will be unclear how many older critically ill patients with SARS-CoV-2 infection will have received a life-sustaining therapy when their values and preferences would have suggested otherwise, merely due to inadequate or ineffective communication.

Fortunately, triumph and tragedy converge on opportunity. In continuing to triumph, when the COVID-19 pandemic dust finally settles, perhaps the exercise in masking and physical distancing will stoke and sustain a collective yearning for human connection, where we seize opportunities to build bridges, instead of silos, to enrich our lives through meaningful interactions with our families, colleagues, and communities. In remediating the tragedies, the pandemic presents us with opportunities to innovate. Not isolating SARS-CoV-2 infected individuals increases the risk to healthcare workers and the burden on healthcare systems, and thus the tragedy of dying alone may be inevitable. Many centres have installed bedside videoconferencing technology for loved ones to hold virtual bedside vigils, and where available, compassionate use of PPE for families to visit dying patients. As the pandemic rages, addressing inadequate communication and incongruent decision-making may be the most important opportunity to tackle, to ensure healthcare systems do not breach the boundary of patients' values and preferences. The core of patient-centred care asks: how do we ensure right treatments are applied to the right patient at the right time to derive the right benefit?

To address inadequate communication surrounding decision-making, some experts call for more 'end of life' conversations or the traditional form of advance care planning (Rubenfeld 2020; Shajahan 2020). Unfortunately, these approaches are likely not helpful during the COVID-19 pandemic. Planning for death under conditions of certainty (like advanced cancer) is not

the same as planning for unexpected and serious illness (like SARS-CoV-2 pneumonia), where prognosis may be uncertain (Heyland 2020).

The basic tenets of clinical decision-making include providing information on the prognosis and possible treatments, learning about patients' personal values and preferences, and using language of shared-decision making. We do not believe "in the moment" clinical decision-making is as simple as asking patients their values and preferences. We have previously shown eliciting values in an open-ended, unconstrained manner, like what often happens in the real world, whereby the patient does not explicitly see the conflict between competing values, may not be helpful in determining the best plan of care for seriously ill patients (Heyland et al. 2017). Lay people's expressed values often conflict with each other and bear little relationship to their preferences for medical care (Heyland et al. 2017). A statement like, "My mom is a fighter" could imply she should be given every chance at curative treatment without acknowledgement of risks and alternatives. What is not transparent in such a statement is the collateral damage of this value-driven choice: survivors of prolonged critical illness experience significant reductions in their physical, psychological, and cognitive functions which impair quality of life. Some patients even consider survival from critical illness a health state 'worse than death' (Rubin et al. 2016). The early experiences with SARS-CoV-2 infected patients requiring critical care services demonstrate their mortality rate exceeds 50%, and survivors often require weeks of mechanical ventilation (Livingston and Bucher 2020; Wu and McGoogan 2020). We do not know the long-term health outcomes of survivors of critical care with SARS-CoV-2 pneumonia but early experiences suggest survivors will be similar to other survivors of prolonged critical illness and will experience significant reductions in their quality of life (Servick 2020). For
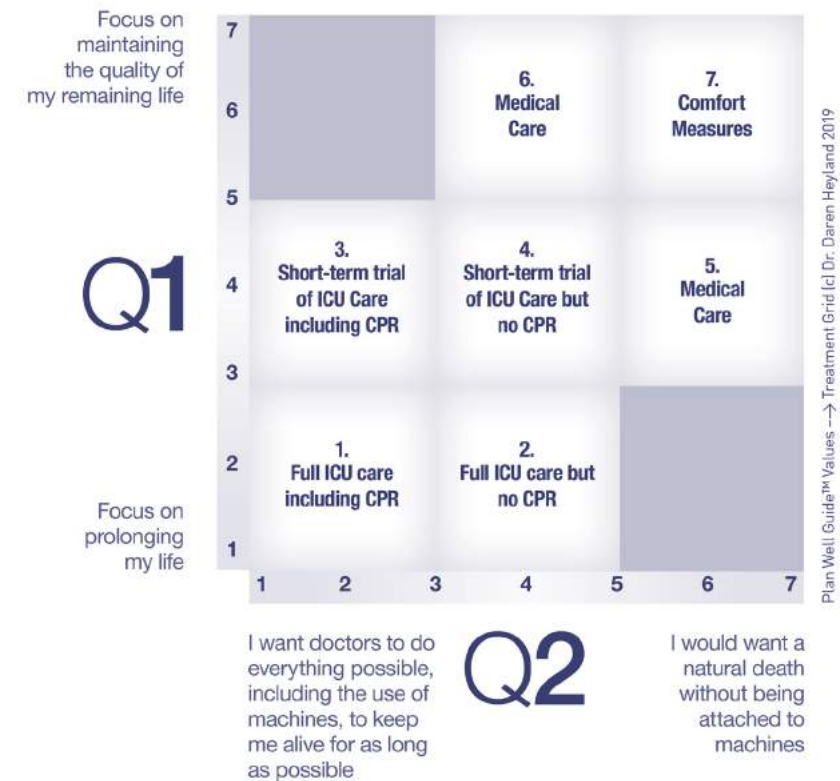
Figure 1: Values-Preferences Grid
The cell that is at the intersection to the answers to the values question may be indicative of the medical treatment plan that might be right for the patient.

many older patients or those living with chronic or life-limiting illnesses and barely maintaining their independence, further reductions in quality of life may not be an acceptable form of living.

Next, many healthcare providers may unfortunately treat patients as informed consumers and, after describing the various treatment options, ask them "What do you want us to do?" Such a strategy violates the principles of shared medical decision-making where most people want to share in decisional responsibility with their healthcare providers. Moreover, most people are ill-informed about the risks, benefits and possible outcomes of life-sustaining treatments and should not be treated as informed consumers.

We suggest a new approach to planning for serious illness called Advanced Serious Illness Preparations and Planning (ASIPP),

which aims to prepare patients (or their surrogates) for 'in the moment' clinical decision-making (Heyland 2020). Ideally, before a crisis, ASIPP calls for asking patients their values in a way that highlights the trade-off with competing values. Questions like, "Are you the kind of person that wants medical treatments to focus on prolonging your life or enhancing the quality of your remaining days?" and "Are you the kind of person who prefers a natural death or are you willing to accept the use of machines, such as breathing machines, to prolong your life, for as long as possible?" allows doctors to link stated values to medical treatments that could be proposed to treat serious illness in a reliable and transparent way, thus reducing medical errors **(Figure 1)** (Heyland 2020). Complementary decision aids, such as the Plan Well Guide, are useful in helping

patients clarify their authentic values and informing patients about the risks, benefits and possible outcomes of these different treatment options and have been shown to improve the quality of serious illness decisions (Heyland et al. 2020).

Once informed, asking patients, "Are you willing to put up with the risks and possible outcomes of critical care treatments?" will help doctors then propose the 'acceptable' treatment plan for the seriously ill patient using the language of shared decision-making. In a recent randomised clinical trial, this approach improved decision-making quality, patient and physician satisfaction, and reduced time physicians spent on their interactions with patients compared to usual care (Heyland et al. 2020). If there is not time to 'prepare' the patient in advance of clinical decision-making, as often is the case, the Plan Well Guide provides a worksheet, which enables clinicians to optimally elicit values and transparently link them to acceptable treatment preferences (Plan Well Guide 2020). A similar decision-aid tool aimed at family members of critically ill patients, called "My ICU Guide," has been developed and undergoing clinical evaluation (Van Scoy et al. 2017).

In the midst of the COVID-19 pandemic, addressing deficits in serious illness communication and decision-making may seem like a far-fetched idea. We argue, if our aim is to reduce the demand on precious and finite critical care services, there is no better time than now to address these deficits. Importantly, the crucial conversation may ensure patients get the care that is right for them, which may preserve autonomy, enhance justice and fairness of allocation, and reduce the potential to minimise exposing health care professionals to the SARS-CoV-2 virus. The alternative, and foregone conclusion, is the "rationing conversation," where only patients who have the best chances of surviving are going to get ICU care. We worry the rationing conversation is threatening to lay individuals. They fear beneficial treatments may be withheld from them or their loved ones and that their lives are unworthy of saving. We believe a focus on efforts to restore 'patient-centredness' to health care decision-making ("What are your authentic values and informed treatment preferences?") would be welcomed and embraced, as opposed to the rationing conversation. Perhaps, by prioritising 'patient-centred' care and optimal commu-

nication and decision-making practices, we could reduce unwanted ICU admissions, preserve resources, and delay, minimise, or even omit the 'rationing' conversation to ensure the right patient receives the right treatment at the right time to derive the right benefit.

Conflicts of interest

Neither author has any conflicts of interest to report. ■

Key Points

- The COVID-19 pandemic has created a juxtaposition of triumph and tragedy.
- Poor-quality communication negatively impacts decision-making, which can lead to overutilisation of ICU services for older individuals.
- Limiting the spread of disease is the intended consequence of quarantine, strict hospital isolation, and prohibiting hospital visitors during the COVID-19 pandemic. However, the fault lines from fractured communication during the pre-COVID era may deepen during the COVID-19 pandemic and lead to the unintended consequences of impoverished decision-making and improper and perhaps unwanted resource utilisation.
- Now is the time to put new processes and procedures in place to improve communication and decision-making with seriously ill older patients regarding the use of life-sustaining treatments.

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For full references, please email editorial@icu-management.org or visit https://iii.hm/14n8

Alice Reid
Research Fellow
Medical Research Institute of
New Zealand
Geriatric Registrar
Wellington Hospital
Wellington, New Zealand

alice.reid@ccdhb.org.nz

Paul Young
Deputy Director
Medical Research Institute of
New Zealand
Co-Clinical Leader
Intensive Care Unit
Wellington Hospital
Wellington, New Zealand

paul.young@ccdhb.org.nz

@dogICUma

What Intensivists Can Learn From Geriatric Medicine

In this article we discuss mind, mobility, medications, multi-complexity, and what matters most. These are key domains from geriatric medicine that are relevant to the practice of intensive care medicine.

The notion that advanced age is a sufficient reason to decline admission to the Intensive Care Unit (ICU) is no longer widely accepted by clinicians, patients, or their families. In many settings, older adults are now admitted to the ICU in situations where they once would not have been (Tripp et al. 2015). Globally, we have an ageing population and live in an era where advances in medicine mean people live longer. Accordingly, there is an increasing potential for overlap between the groups of patients who require geriatric care and those who require intensive care.

In some respects, geriatric care and intensive care are very different specialties. Geriatricians often have the luxury of time to consider chronic issues in an outpatient setting or while supporting a patient's recovery from illness, while intensivists typically deal with acute issues that are an immediate threat to the patient's life. Despite these differences, the specialties have similarities. Both deal with the care of complex patients. Both involve the management of disease syndromes with a range

of specific aetiologies, such as sepsis in the ICU and dementia in the geriatric setting. Both geriatricians and intensivists work with families in situations where patients may be unable to advocate for themselves. In doing so, both communicate complex clinical information, typically as part of a multidisciplinary team. Given these similarities, the principles that underpin geriatric medicine may be relevant for practising intensivists. This editorial outlines these principles within the "5Ms framework" that includes mind, mobility, medications, multi-complexity, and what matters most (Molnar and Frank 2019).

Mind

Delirium, Dementia, Depression
Delirium affects a third of hospitalised older adults (Marcantonio 2017), and a third of ICU patients (Salluh et al. 2015). There are many different causal pathways that result in the "brain failure" syndrome of delirium (Marcantonio 2017). Although geriatricians and intensivists both encounter delirium commonly, there are substantial differences in manifestations of disease they encounter, which may reflect differences in underlying pathophysiology. The underlying pathophysiology of delirium in a normally fit and well 30-year-old who is intubated following trauma is probably different to that of delirium in a comorbid older adult in a geriatric ward. Moreover, the management approach to delirium in

the ICU setting and in the geriatric setting differs in many fundamental ways. The care of a patient with hyperactive delirium in the ICU is more likely to require the use of sedatives to preserve lifesaving endotracheal tubes and invasive lines. That said, with the possible exception of dexmedetomidine in the ICU setting (Reade et al. 2016), there is little evidence that pharmacological interventions are effective at aiding the resolution of delirium in either setting (Burry et al. 2019, Nikooie et al. 2019). In both the ICU and in the geriatric ward, the best treatment for delirium remains to treat the underlying cause and to provide good supportive care (Ely 2017).

One issue that geriatricians are acutely aware of is that a diagnosis of delirium can sometimes signal that a patient has underlying dementia (Marcantonio 2017). Older patients with dementia have an increased risk of developing complications when they are hospitalised (Watkin et al. 2012). Because dementia is a risk factor for delirium (Marcantonio 2017), and the presence of delirium confounds the assessment of baseline cognition, establishing the degree of underlying cognitive impairment may be important when assessing whether ICU admission is in a patient's interest. If a patient has seen a geriatrician, the geriatrician may be well placed to provide important collateral information that can guide clinical decision making. The possibility that the presence of delirium heralds

underlying dementia probably receives less attention in the ICU than it does in the geriatric ward. In part this is probably because in the ICU setting delirium sometimes occurs in young patients who have a very low risk of dementia. However, even in older adults in the ICU who have an episode of delirium that represents the first manifestation of an evolving cognitive disorder (Marcantonio 2017), the degree of dementia present is rarely sufficiently severe to require specialist geriatric follow-up. Moreover, while tools such as the AD8 Dementia Screening Interview (Duggan et al. 2017) or the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) (Jorm 2004), which can be administered on an "informant" such as a family member, are useful screening tools to identify cognitive impairment, formal evaluation is best undertaken when the patient is well. Despite this, intensivists are well positioned to educate families if delirium occurs.

Once a patient has recovered from their acute illness, a primary care physician or an intensivist in a dedicated ICU follow-up clinic should address concerns about underlying cognitive impairment and attempt to identify other psychiatric sequelae of critical illness like anxiety and depression, which are common in patients of all ages (Nikayin et al. 2016). If there is diagnostic uncertainty about the possibility of dementia, a referral for assessment by a geriatrician may be appropriate at that stage.

Mobility

Immobility is associated with poor outcomes for ICU patients and older adults who are general hospital inpatients. However, such associations are confounded by indication bias, because patients who are less sick are the ones who are able to mobilise. While physiotherapy has an established role in the ICU (Hodgson and Tipping 2017), and we may feel compelled to get the patient out of bed and moving, the evidence-base that supports any specific approach to physiotherapy in the critically ill is lacking. Randomised controlled trials, predominantly those involving older adults with exacerbations of chronic obstructive pulmonary disease (Greening et al. 2014) and stroke (AVERT trial group 2015) provide a salutary lesson that when it comes to mobility more is not necessarily better in the acute phase. While consensus guidelines (Hodgson et al. 2014) support mobilisation in many critically ill patients, further evidence from randomised controlled trials is urgently needed.

> **there is an increasing potential for overlap between the groups of patients who require geriatric care and those who require intensive care**

Medications

Much of the evidence in support of therapeutics for chronic medical conditions comes from studies that exclude older adults with multiple co-morbidities. Despite this, around 30% of adults aged 65 and older take five or more medicines. Such polypharmacy increases the risk of adverse events occurring and for some older adults, in particular, there is a risk of the consequences of the treatment being worse that the disease. In such circumstances, de-prescribing, the process of tapering or stopping drugs to minimise polypharmacy, may improve patient outcomes (Scott et al. 2015). ICU discharge is the perfect de-prescribing opportunity. Intensivists can potentially capitalise on the disruption to a patient's usual medication regimen that occurs as a consequence of acute illness.

They can work collaboratively with a patient's family physician, geriatrician or pharmacist to evaluate the appropriateness of each medicine. Ongoing indications for all medicines should be considered taking into account the patient's wishes, the potential harms of each medicine, and whether they will add benefit to the patient's remaining years. In the case of drugs that are commonly initiated in the ICU like amiodarone, stress ulcer prophylaxis, sedatives, and antipsychotics, careful consideration should be given to whether these medicines should continue beyond the ICU. If ongoing use of these medicines is required then a date to review or stop them should be documented.

Multi-complexity
Multimorbidity, complex biosocial situations
Multimorbidity means having two or more long term conditions that can be managed but not cured. It is associated with reduced quality of life, increased healthcare use, and increased mortality (Yarnall et al. 2017). Patients with multimorbidity are potentially more vulnerable to acute illnesses like sepsis, and are at high risk of multiorgan dysfunction and death when these illnesses occur (Zador et al. 2019). ICU clinicians are well versed in recognising the complex interplay between age, multimorbidity, and frailty. The accumulation of long-term health conditions (multimorbidity) as we age leads to frailty. The presence of frailty in turn can be used to identify older adults with multimorbidity who are vulnerable (Yarnall et al. 2017). Thus, measuring frailty using the clinical frailty scale (Flaatten et al. 2017) may help intensivists recognise patients who are at risk of adverse outcomes, and who may derive greater benefit from speciality older adult consultation. Conceptually, the presence of multimorbidity and frailty are important for intensivists because they affect the likely number of years of life that a patient has remaining. Considering each patient

in ICU in terms of the expected number of years until death rather than just their chronological age, may be useful in framing complex decisions and in considering what matters most to a given patient.

Matters Most

"What matters most to you?" is a way of approaching end of life care conversations, and managing multi-complexity in a patient-centred way (Fried et al. 2020). Patients and their families benefit from clear communication about planned ICU admission and therapy (Cardona et al. 2019). Such advanced planning benefits patients and intensive care teams alike. Advance care planning such as advanced directives or care guides can help inform decision making when patients are referred during a medical or surgical emergency. However, despite the potential usefulness of such planning, there are ethical, legal, cultural, societal and individual patient factors that must be considered in each case (Metaxa 2020).

Developments in the field of perioperative medicine have broadened our view of what constitutes a successful surgical outcome to include preservation of performance, functionality, autonomy, and quality of life (Olotu et al. 2019). Such considerations are important because they allow for holistic planning with patients who may need ICU care post procedure. Such planning may include deciding in advance not doing a procedure if it will not enable a patient to spent their remaining years as they had planned.

Conclusions

In the future, increasing numbers of older adults will require care in the ICU. The 5Ms of geriatrics "Mind, Mobility, Medications, Multimorbidity, and Matters Most" offer a guide to reframe that care using geriatrics principles. These principles include careful screening for delirium; providing appropriate education and follow up of patients to identify neuropsychiatric sequelae of critical illness; consideration of mobility and functional recovery; de-prescribing where appropriate; recognising that frailty and comorbidity are potentially more important than age in determining how much longer a given patient is expected to live; and, above all else, taking the time to appreciate what matters most to patients and their families.

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Conflicts of interest

The authors report no conflicts of interest. ■

Key Points

- Globally, we have an ageing population and live in an era where advances in medicine mean people live longer.
- Geriatric care and intensive care are very different specialties but at the same time share many similarities.
- The 5Ms framework outlines the principles that underpin geriatric medicine and that may also be relevant for practicing intensivists.
- These include mind, mobility, medications, multicomplexity and what matters most.
- The 5Ms of geriatrics offer a guide to reframe care using geriatrics principles.

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For full references, please email editorial@icu-management.org or visit https://iii.hm/14m6

Christian Subbe
Senior Clinical Lecturer in Acute
and Critical Care Medicine
School of Medical Sciences
Bangor University

christian.subbe@wales.nhs.uk

Chris Thorpe
Consultant Intensive Care/
Anaesthetics
Ysbyty Gwynedd
Bangor, UK

chris.thorpe@wales.nhs.uk

Richard Pugh
Consultant Intensive Care/
Anaesthetics
Glan Clwyd Hospital
Bodelwyddan
Denbighshire, UK

richard.pugh@wales.nhs.uk

Ageing and Critical Illness: What Does Quality Care Look Like?

This article explores a system for assessing quality of care in critically ill elderly patients.

Decision-making processes around the admission of critically ill elderly patients have been put into sharp focus in 2020. The urgent need to meet the demands associated with large numbers of acutely ill patients during the COVID-19 pandemic has quickened discussions about prioritisation of resources with a focus on objective benefits. In providing high quality care to the elderly we certainly need to look at hard evidence on mortality and morbidity, arguments that have been widely debated during recent months, but it is also essential to look at the many other important aspects that affect the patient experience. In interrogating these aspects, it is helpful to have a framework where we can explore the many aspects of care that go beyond simple mortality figures.

The Institute of Medicine's [IoM] "Crossing the quality chasm: a new health system for the 21st century" was published nearly twenty years ago (Institute of Medicine 2001). Its intention was to provide perspective on the aims of healthcare systems, the inter-relation between clinicians and patients, responsiveness to individual needs, and the structures and processes within which clinical services operate. Facing an ageing population with increasingly complex clinical needs, the Society of Critical Care Medicine have argued that the need for change set out in "Crossing the quality chasm…" has only increased (Nates et al. 2016). The IoM dimensions of quality - safety; effectiveness; patient centred care; timeliness; efficiency; and health equity - remain a relevant framework for considering the organisation of healthcare systems: they are referenced within the latest UK Guidelines for the Provision of Intensive Care Services (Faculty of Intensive Care Medicine/Intensive Care Society 2019), for example. We now begin to consider some specific examples of how these dimensions relate to critical illness in an older population.

Safety

Risk of deterioration increases with age, co-morbidity, frailty and severity of acute illness. Very recent data from ICNARC in the UK indicates that in the short-term, hospital mortality has improved over every age cohort for those admitted to critical care over the last twenty years (Jones et al. 2020). In the wider hospital setting, however, outcomes following in-hospital cardiac arrest are improving at different rates among different age cohorts; this may of course reflect underlying reserve, but despite having a greater proportion with underlying cardiac disease, older cohorts were less likely to have arrested in a higher acuity ward or to have had telemetry in situ (Wiberg et al. 2020). Similarly, the METHOD study found that frail acute hospital admissions (who triggered the attendance of a rapid response team) had a significantly lower nurse: patient ratio than non-frail counterparts, despite their greater vulnerability and illness severity (NEWS and qSOFA) (So et al. 2018). Facing lack of certainty over treatment benefits, quality care needs to look at a wider understanding what is important to the individual patient in terms of treatments, priorities and goals. Elderly and frail patients are more vulnerable to physiological and psychological disturbance, both as an inevitable result of the illness and therapies, but also as a consequence of adverse incidents. This needs to be taken into account when planning care, with meticulous attention over everything from medications through to family interactions. From a professional perspective, we also need to be able to communicate not just the long-term outcomes, and chance of

survival but also the critical care environment the patient is likely to experience during their illness.

Effectiveness

Individuals in many countries around the world can expect to live longer and to survive with chronic illness and functional dependency. In some healthcare settings, there is evidence that static critical care capacity is leading to rationing, and subsequent exclusion of older patients and those with significant levels of comorbidity; in other settings, critical care expansion appears to allow critical care admission trends to follow national demographic trends; indeed, in relatively resource-rich environments, where critical care beds are conjectured to create their own demand, debate has moved on to the consideration of critical care bed reductions as "a safe and effective way to reduce ICU-related spending" (Wallace et al. 2015).

The Eldicus study demonstrated that older patients have greater mortality, and are also less likely to be admitted to critical care. The study however also found a greater reduction in mortality for admitted vs. rejected patients in the elderly compared with the young, suggesting that critical care admission appears to have greatest "mortality benefit" for the elderly (Sprung et al. 2012). Systematic admission might be considered to help, but in one study of patients aged 75 years or more (who were cancer-free, with preserved nutrition and functional status) had a similar risk of death at six months to those subject to conventional admission processes (Guidet et al. 2017). Furthermore, long-term outcomes among older patients who have required significant organ support in critical care can be disheartening (Biston et al. 2014).

Although age is clearly important when anticipating outcomes from critical illness, the interaction of age with comorbidity, the nature and severity of acute illness, and frailty, necessitate more nuanced clinical consideration for the individual. For critical

care clinicians interested in "physiological reserve," the concept of frailty has been a leading development in the last decade. Frailty is considered the consequence of a decline of physiological systems during a lifetime, and a vulnerability to poor resolution of homeostasis after a stressor event (Clegg et al. 2013). It can be reliably assessed in the critically ill, has strong predictive validity in the short-term, and provides a platform on which to investigate longer-term outcomes from critical illness. However, it must be remembered that frailty is not a dichotomous state, and

> ❝ in some healthcare settings, there is evidence that static critical care capacity is leading to rationing, and subsequent exclusion of older patients and those with significant levels of comorbidity ❞

that it may be relatively dynamic.

Clearly, there is a need to personalise in order to identify likely benefit of critical care admission, which takes into account longer-term outcomes, and those outcomes of particular value to the individual patient.

Patient–Centred Care

Recent evidence would suggest that only a minority of critical care patients have been asked about their treatment preferences; furthermore, many families (when asked) have not discussed their relative's treatment options with the clinical team. As Darren Heyland and colleagues have pointed out, shortfalls in communication and decision-making may lead to prolonged use of intensive care treatments in elderly critically ill patients, many of whom ultimately die (Heyland et al. 2015). Frailty

is associated with a lower life-expectation and towards the end of life the priorities of patients might not be the same as those of younger patients. Many frail patients if confronted with the perspective of critical illness and possible death will answer "I had a good innings;" indeed Fried and colleagues' exploration of the health outcome priorities of older patients with multiple chronic conditions suggests that many would rank the preservation of independence and symptom relief above staying alive (Fried et al. 2011).

Timeliness

The window of opportunity to influence outcome from acute illness is short among patients who are frail. Prolonged periods of instability are poorly tolerated in the context of limited physiological reserve, and the balance between likely benefit and burden of invasive therapy shifts with progression from single to multiple organ dysfunction. Recent international guidelines for the metric of Rapid Response Systems stipulate decisions about escalation of care within 24 hours of triggering a local track and trigger tool as a quality metrics (Subbe et al. 2019).

Efficiency

Healthcare efficiency can be defined as the ratio of system output to input; an efficient system achieves high output (e.g. survival to hospital discharge) with low input (e.g. in terms of bed days). Numbers needed to treat is another common representation of efficiency. Efficiency of critical care might be lower in frail patients than in less frail patients. For patients admitted with low levels of frailty at comparable level of illness, as measured by APACHE II or comparable score, the chance of surviving with a minimal level of disability is significantly greater than that of a patient with mild or moderate frailty (though long-term outcome data is currently limited). Furthermore, the resource (e.g. in terms of length of stay) required to achieve this outcome may

be substantially less. By necessity, critical care services operating within resource constraints will tend to take an efficient approach and will be inclined to admit and provide ongoing care for those most likely to benefit. Bench-marking processes (which do not take account of frailty within the case-mix) have historically tended to reinforce this. However, in an efficient system, individuals who may have benefitted from critical care intervention in another healthcare setting suffer as a consequence of reduced access. This brings us to the final dimension of equity.

Health Equity

"Health equity" or "equity in health" implies that ideally everyone should have a fair opportunity to attain their full health potential and that no one should be disadvantaged from achieving this potential (World Health Organization 2020). During the COVID-19 pandemic this principle of care has been a cause for passionate debate between healthcare providers and policy makers. While frail patients might deserve similar access to critical care, decision-making has focused strongly on the full future health potential of deteriorating patients. With severe mismatch of supply

and demand, concerns shift from the individual patient to a utilitarian objective of "equitable concern for all." Beyond critical care, this benefit looks different for a patient with a life-expectancy of 1-3 years and a patient with a life-expectancy of 40-50 years. Faced with extraordinary demands, UK professional ethical guidance considered that "the capacity to benefit quickly" would represent "a proportionate means of achieving a legitimate aim" – appreciating that although "everyone matters and everyone matters equally… this does not mean that everyone will be treated the same" (British Medical Association 2020).

Conclusion

We have used the IoM framework to explore a number of issues relating to the provision of quality care to an ageing population. The issues are wide-ranging: from the prioritisation of resources within healthcare systems, through public and patient expectations, the organisation of healthcare services to enable timely identification of those at risk, knowledge of clinical outcomes, transparent discussion, and shared decision-making. To borrow from Professor Ken Rockwood and colleagues, "Frailty is not synonymous with end-of-life" (Hubbard et al. 2020). We

have come some way over the last decade in our understanding of the impact of frailty on critical care – and its interaction with comorbidity and severity of acute illness - but we need to adapt further to meet the needs of an ageing population, and we need to be clear that we understand the consequences of ageing and frailty from the perspectives of those who may use our services and those close to them.

Conflicts of Interest

None. ■

Key Points

- Risk of patient deterioration increases with age, co-morbidity, frailty and severity of acute illness.
- Elderly and frail patients are more vulnerable to physiological and psychological disturbance, both as an inevitable result of the illness and therapies, but also as a consequence of adverse incidents.
- Although age is clearly important when anticipating outcomes from critical illness, the interaction of age with comorbidity, the nature and severity of acute illness, and frailty, necessitate more nuanced clinical consideration for the individual.
- Our understanding of the impact of frailty on critical care has increased but we need to adapt further to meet the needs of an ageing population.

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INFOGRAPHIC

AGEING POPULATION

IMPORTANT FACTS

- BY 2050, THE PERCENTAGE OF POPULATION OLDER THAN 80 YEARS OF AGE WILL **DOUBLE**.

- BY 2050, PEOPLE 80 YEARS OR OLDER WILL ACCOUNT FOR **9.6%** OF THE POPULATION IN **EUROPE, 9%** IN **NORTH AMERICA, 6.5%** IN **OCEANIA, 5.5%** IN **LATIN AMERICA** AND **CARIBBEAN, 4.4%** IN **ASIA** AND **1.1%** IN **AFRICA.**

- THERE HAS BEEN A **SIGNIFICANT INCREASE** IN THE ELDERLY POPULATION **ADMITTED TO THE ICU** DURING THE LAST 20 YEARS.

- IT IS EXPECTED THAT THE PROPORTION OF THE **VERY OLD CRITICALLY ILL PATIENT** (80 YEARS OR OVER) WILL **INCREASE FASTER THAN ANY OTHER COHORT** IN THE ICU.

Sources: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3224497/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6261095//

PROBLEMS ASSOCIATED WITH AGEING

1 ALTERATION IN RESPIRATORY PHYSIOLOGY

2 INCREASED RISK OF ACUTE RESPIRATORY FAILURE

3 IMMUNOSUPPRESSION AND INFLAMMAGING (IMMUNOSENESCENCE)

4 FRAILTY

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6261095/

COMPLICATIONS OF CRITICAL ILLNESS IN THE ELDERLY PATIENT

- Increase in Psychological Symptoms
- Sleep Cycle Alterations
- Delirium
- Cognitive Impairment
- Ventilator-Induced Lung Injury
- Acute Respiratory Distress Syndrome (ARDS)
- Sepsis

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6261095/

GAPS IN TREATMENT OF CRITICALLY ILL OLDER PATIENTS

- There are currently no international recommendations for the admission or treatment of critically ill older patients >80 years of age.
- There are also no valid prognostic severity scores that would facilitate geriatric assessments.
- Elderly patients often receive a lower level of treatment intensity compared to younger patients.
- Older patients discharged from the ICU are often victims of poor handovers and poor monitoring.

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6261095/

Karin Amrein
Department of Internal Medicine
Division of Endocrinology and
Diabetology
Medical University of Graz
Austria

karin.amrein@medunigraz.at

Paul Zajic
Medical University of Graz
Austria

paul.zajic@medunigraz.at

Magdalena Hoffmann
Department of Internal Medi-
cine/Research Unit for Safety
in Health
Medical University of Graz

Executive Department for Quality
and Risk Management
University Hospital Graz
Graz, Austria

**magdalena.hoffman@meduni-
graz.at**

Jean-Charles Preiser
Université Libre de Bruxelles
Belgium

**jean-charles.preiser@erasme.
ulb.ac.be**

Patrick Meybohm
University Hospital Würzburg
Department of Anaesthesiology

meybohm_p@ukw.de

Dhruv Parekh
University Hospitals Birmingham
United Kingdom

d.parekh@bham.ac.uk

Dayre McNally
University of Ottawa
Canada

dmcnally@cheo.on.ca

Vitamin D in Critical Illness – Fifty Shades of VIOLET

Did the VITDALIZE study and the VIOLET study manage to answer some of the questions regarding vitamin D deficiency and its impact on critically ill patients? Experts compare the findings and present an overview.

Introduction

Vitamin D deficiency is very common in the ICU (usually >60%) because many critically ill patients were already chronically ill before their acute illness. Current guidelines recommend low doses < 1000 IU daily for supplementation and standard diet for critically ill patients contains less vitamin D than recommended for healthy individuals. Vitamin D is not a vitamin at all but a steroid hormone - it possesses its

> **❝ is it really conceivable that an inconspicuous substance such as vitamin D can have a mortality benefit in the event of serious illness? ❞**

own nuclear vitamin D receptor which is expressed in many cell types; with sufficient UV-B exposure the body can produce enough endogenous vitamin D from cholesterol in the skin.

A large number of epidemiological studies link vitamin D deficiency to many diseases across a wide variety of organ systems. Following the publication of a letter in the New England Journal of Medicine in 2009, the vitamin D hype also reached the intensive care unit (ICU)

(Lee et al. 2009).

Starting in 2011, several randomised controlled intervention studies were published; the Austrian VITDAL-ICU study (n=480) (Amrein et al. 2014) was the largest study on this topic until the recent publication of VIOLET. Results of the VITDAL-ICU study showed no difference in the primary endpoint regarding the length of hospital stay (LOS). A surprisingly large mortality benefit in the predefined subgroup with severe vitamin D deficiency was found (25-hydroxyvitamin D (25OHD) <12ng/ml, n=200).

The logical next step was to plan the VITDALIZE study, which started in Austria in 2017 and was extended to Belgium in 2019 (protocol: Amrein et al. 2019). In parallel, the VIOLET study was started in the USA in 2017, which was prematurely terminated in 2018 and recently published. The results were rather sobering. Were all important questions answered? Is the hype over?

The VIOLET Study: A Short Summary

The VIOLET study was a randomised controlled, double-blind, placebo-controlled phase III trial within the US PETAL network. Patients with vitamin D deficiency and high risk of developing ARDS and mortality were administered enteral vitamin D3, recruiting mainly in the emergency department (ED), likely because 1) early administration was considered to be better and 2) the PETAL network focuses on ED patients.

The protocol adopted the same enteral loading dose of cholecalciferol as VITDAL-ICU and the same definition of vitamin D deficiency (25OHD < 50nmol/l). In total, 3000 adults with vitamin D levels of 25(OH)D≤20ng/ml were to be recruited in the emergency room when ICU admission was "scheduled" and patients meet criteria for being at risk for ARDS and mortality. Vitamin D levels were measured at inclusion using a POCT device but only individuals with mass spectrometrically verified D deficiency (25(OH)D<20ng/ml) were included in the final analysis. Subjects were randomised in a 1:1 ratio and treated with high-dose enteral vitamin D3 (once 540,000 IU) or a placebo. The primary endpoint 90-day mortality was 23.5% in the vitamin D group (125 of 531) and 20.6% in the placebo group (109 of 528), (95% confidence interval, -2.1 to 7.9; p=0.26). There were no clinically relevant differences between the groups in terms of secondary clinical, physiological or safety endpoints (National Heart, Lung, and Blood Institute PETAL Clinical Trials Network et al. 2019). On the positive side, a loading dose of 540,000 IU of vitamin D has not led to any negative consequences for patients.

While the VIOLET study originally specified a sample size of 3000, the publication only reports on the findings from 1360 patients who were recruited and randomised. The target number of 3000 was not reached because the study was prematurely terminated after the first interim analysis (which was obviously conducted later than planned) due to "futility." Ultimately, only 1078 patients met all inclusion criteria.

In a subgroup of patients with 25(OH)D levels <12 ng/ml, the placebo group seemed to perform better. This is in complete contrast to VITDAL-ICU's results and appears contradictory to the large body of evidence suggesting stronger effects of vitamin D in more severe deficiency. The subgroup analysis did not show clear signals. Ironi-

cally, however, especially in the group with ARDS before study entry, mortality seemed to be lower in the placebo group. However, it should be noted that due to the unadjusted multiple testing with 21 subgroup analyses in two populations, the probability of type 1 error is very high.

Discussion

Although with only a cursory inspection the VIOLET and VITDALIZE studies appear to be very similar, there are important differences **(Table 1)** that continue to spark hope for benefit from vitamin D administration in the ongoing European VITDALIZE study. The studies also answer different questions. The protocol of the VITDALIZE trial was recently published in BMJ Open in 2019 (ClinicalTrials.gov Identifier: NCT03188796).

There are a number of substantial differences between VIOLET and VITDAL/VITDALIZE which could explain the outcome difference:

Single ultra-high loading dose without maintenance doses
An appropriately high loading dose is absolutely necessary in acute situations in order to quickly increase vitamin D levels.

However, it is extremely unphysiological to administer a high loading dose without a maintenance dose. Recent findings demonstrated shorter effects of some metabolites. Vitamin D catabolism is also stimulated and it is conceivable that there is less at the end than at the beginning. Several studies also showed a higher risk of falls and fractures; Martineau et al. (2017) demonstrated a lack of effect on respiratory infections (compared to daily or weekly doses). For these reasons, paradigms shifted away from – admittedly handy – high-dose treatments with long intervals.

Study population
In the VITDAL-ICU study, a mortality benefit was only found in the subgroup with severe vitamin D deficiency with an initial value of 25-hydroxyvitamin D level <12ng/ml (200 of 480 patients). These findings were not taken into account in VIOLET.

Work highly relevant on this matter was published by London pulmonologist Adrian Martineau (2017) in the BMJ. In an individual patient data meta-analysis of almost 11,000 people, he was able to show that vitamin D can prevent respiratory tract infections, but only if administered daily or weekly.

	VIOLET	VITDALIZE
SITES	USA, > 40 sites	Europe (Austria, Belgium, Germany, UK)
Population	Patients planned for ICU	ICU patients
Vitamin D at inclusion	25(OH)D<20ng/ml	25(OH)D<12ng/ml
Intervention	Cholecalciferol 540,000 IU enterally	Cholecalciferol 540.000IU enterally. Maintenance: 4000IU enterally once daily up to day 90
Placebo	Placebo (MCT)	Placebo (MCT)
Primary Endpoint	90-day mortality	28-day mortality
Sample size	planned n=3000 actual n=1078 (stopped at first interim analysis)	planned n=2400 current: >450 (recruiting)

Table 1. Factbox: VIOLET vs. VITDALIZE

The strongest effect with a number needed to treat (NNT) of only 4 (!) was observed in people with severe vitamin D deficiency at baseline.

The "Goldilocks" Effect

For an endpoint such as mortality, it must be assumed that an intervention can only be effective for people with a moderate disease severity - individuals who are "too healthy" may recover with or without intervention. Conversely, individuals "too ill" may die with or without intervention. This is similar to potential benefits of wearing a helmet in case of rockfall, where the size of the falling rock may determine the usefulness of said helmet.

Although an ultra-early intervention seems to make sense in principle, it probably makes it very difficult to assess the trajectories of the individual, i.e. whose outcome could potentially be altered (just as, for example, the duration of ventilation and the usefulness of a tracheotomy is very difficult to predict).

Is it really conceivable that an inconspicuous substance such as vitamin D can have a mortality benefit in the event of serious illness? There is already a Cochrane meta-analysis that showed a mortality benefit of several percent (6% for all-cause and 12% for cancer mortality) in healthier individuals (mostly older women in osteoporosis studies) (Bjelakovic et al. 2014). For critically ill patients with a higher event rate

> ❝❝ the topic of vitamin D deficiency and vitamin D in diseases requiring intensive care is and will therefore remain a hot topic ❞❞

and a high risk of "second hits" such as nosocomial infections, a mortality benefit seems possible.

The topic of vitamin D deficiency and vitamin D in diseases requiring intensive care is and will therefore remain a "hot topic." Even a mortality benefit of 1% would be relevant (however, much larger studies are still needed for this; VITDALIZE is "only" powered to an absolute difference of 5%). In any case, vitamin D is too harmless and too inexpensive not to be investigated seriously.

In Canada, the VITDALIZE Kids study has recently been launched, which is a multi-centre study to investigate the effect of vitamin D on morbidity endpoints (@ vitdalizekids, ClinicalTrials.gov Identifier: NCT03742505).

VITDALIZE and VITDALIZE kids will hopefully shed more light on this important topic in the next years. ∎

Key Points

- Vitamin D deficiency is very common in the ICU because many critically ill patients were already chronically ill before their acute illness.
- A large number of epidemiological studies link vitamin D deficiency to many diseases across a wide variety of organ systems.
- VITDAL-ICU study was the largest study on this topic until the recent publication of VIOLET.
- The VIOLET study was a randomised controlled, double-blind, placebo-controlled phase III trial conducted with patients with vitamin D deficiency and high risk of developing ARDS.

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Nathan S. Cutler
Commander
Medical Corps
United States Navy
Department of Pulmonary and
Critical Care Medicine
Naval Medical Center
Portsmouth, Virginia

Nate.cutler@outlook.com

Jason W. Signorelli
Critical Care Medicine Fellow
Department of Anesthesiology
Section on Critical Care
Medicine
Wake Forest School of Medicine
Wake Forest Baptist Medical
Center
Winston-Salem, North Carolina

Jsignore@wakehealth.edu

Patrick M. Wieruszewski
Pharmacist
Cardiothoracic Surgery/Anesthesia ICU
Department of Pharmacy
Mayo Clinic
Rochester, MN

Multidisciplinary Epidemiology
and Translational Research
in Intensive Care (METRIC)
Laboratory
Mayo Clinic
Rochester, MN

wieruszewski.patrick@mayo.edu

Marc Reichert
Clinical Manager
Critical Care, Transplant, Emergency Department
Department of Pharmacy
Wake Forest Baptist Medical
Center
Winston-Salem, North Carolina

mreicher@wakehealth.edu

Ashish K. Khanna
Associate Professor
Section Head for Research
Department of Anesthesiology
Section on Critical Care
Medicine
Wake Forest School of Medicine
Wake Forest Baptist Medical
Center
Winston-Salem, North Carolina
Outcomes Research Consortium
Cleveland, OH

akhanna@wakehealth.edu

Angiotensin II in Post Cardiopulmonary Bypass Vasoplegia – The Experience So Far

Post cardiopulmonary bypass vasoplegia is common, and associated with poor outcomes. Traditional management strategies involving escalating doses of catecholamines, vasopressin and adjuncts such as methylene blue and hydroxycobalamin or ascorbic acid have not shown promising results. Since ACE enzyme dysfunction, high serum renin and low endogenous angiotensin II may be a common problem in these patients, synthetic Angiotensin II is a physiologically viable option. Both post hoc results from the ATHOS-3 trial and prospective outcomes from the real world use of Angiotensin II has shown encouraging results. More data is needed to map the renin angiotensin cascade in post cardiac surgery patients with vasoplegia and large prospective randomised trials should be done to validate these findings.

Introduction

Postoperative vasoplegia is a form of distributive shock, physiologically similar to the shock caused by sepsis. It is diagnosed when hypotension after surgery is due to low systemic vascular resistance (SVR), with cardiac output either preserved or adequately augmented, and adequate circulatory volume. The distinction is important since postoperative shock may be multifactorial, especially after cardiac surgery. Though estimates of prevalence vary, the condition affects 20% or more of patients who have undergone operations requiring cardiopulmonary bypass (CPB), particularly those with predisposing factors such as longer bypass times and higher comorbid disease burden (Shaefi et al. 2018). Patients with vasoplegia after CPB are at increased risk of death and other major complications (Busse et al. 2020).

Pathophysiology

The mechanism for vasoplegia due to CPB is not precisely known, but is thought to be multifactorial. This begins with an inflammatory response to the bypass circuit and involves ischaemia-reperfusion injury, cytokine release, and excess production of vasodilatory molecules such as nitric oxide (NO), with eventual depletion of endogenous vasopressors including angiotensin II (ANG-2) (Shaefi et al. 2018). Further, prolonged exposure to the bypass circuit is known to impair angiotensin-converting enzyme (ACE) activity in pulmonary epithelia resulting in a relative endogenous ANG-2 deficiency, and potentially diverting the renin-angiotensin-aldosterone system (RAAS) to pathways which produce vasodilatory metabolites including angiotensin 1-7. Lastly, hydrogen sulfide, an additional vasodilatory mediator, is upregulated during CPB and may inhibit residual ACE activity (and thereby ANG-2 generation) as well as further activate NO generating pathways (Lambden et al. 2018). Treatment of the condition can be challenging and is fraught with potential adverse effects, particularly in the immediate postoperative period when the myocardium is already under significant stress. The most common interventions, similar to those for other distributive shock states, are volume

resuscitation, catecholamine vasopressors (typically norepinephrine [NE]), and arginine vasopressin (AVP). In severe cases, the vasculature becomes poorly responsive to NE (Hajjar et al. 2017). NE may also be limited by toxic potential when very high doses are required, specifically via end-organ injury from peripheral and mesenteric vasoconstriction and tachyarrhythmia due to excessive beta stimulation of the myocardium (Chawla et al. 2014). AVP also is not universally effective; in one single centre retrospective study, only 45% of 938 patients receiving catecholamines for septic shock who were given fixed-dose AVP were classified as AVP "responders," defined as able to maintain MAP ≥ 65 mmHg while permitting a reduction in catecholamine dose (Sacha et al. 2018). Lastly, excessive fluids can also become problematic, as the extravasation of excess intravenous crystalloid leads to dysfunction in congested organs (Claure-Del Granado and Mehta 2016). When the therapeutic benefit of these traditional therapies is exceeded, adjunctive therapies such as methylene blue, hydroxocobalamin, high dose ascorbic acid, and hydrocortisone have been used in efforts to augment blood pressure or reduce the requirement for vasopressors. The data supporting adjuncts is minimal and the level of evidence is poor for most.

Methylene blue and hydroxocobalamin are thought to work by inhibiting excess synthesis of NO and to serve as NO scavengers (Weinberg et al. 2009; Hosseinian et al. 2016). Use of methylene blue to improve haemodynamics during post-CPB vasoplegia is supported by several small prospective trials (Hosseinian et al. 2016), but data regarding outcomes is contradictory. Its use has been retrospectively tied to worse outcomes (Weiner et al. 2013), and there are several case reports of serotonin syndrome due to methylene blue's monoamine oxidase inhibitor (MAOI) activity (Schumacher et al. 2017). It is also a cause of haemolysis in patients with G6PD deficiency. Hydroxocobalamin is less proven
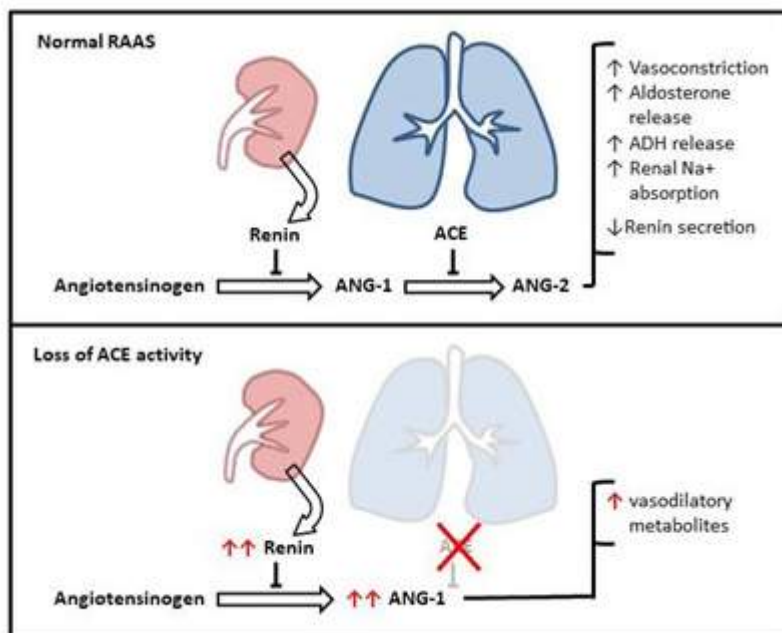

Figure 1. Normal RAAS versus loss of ACE activity.
ACE= Angiotensin Converting Enzyme-1; ADH = Antidiuretic hormone; ANG-1=Angiotensin 1; ANG-2= Angiotensin II. RAAS= Renin-angiotensin-aldosterone system. Source: Santos et al. 2019; Bussard and Busse 2018.

than methylene blue, but has shown some promise in observational studies (Shapeton et al. 2019). High dose ascorbic acid, of recent interest in the treatment of septic shock, has demonstrated a potential vasopressor sparing effect for post-CPB vasoplegia in a case series (Wieruszewski et al. 2018), but was not associated with faster resolution of shock in a small prospective study (Yanase et al. 2020). Intravenous hydrocortisone is often added during treatment for severe refractory vasoplegia, with supporting data largely extracted from the use of corticosteroids in septic shock, but has not been prospectively studied for vasoplegia due to CPB. The success of these adjunctive therapies is variable. Often, multiple are used concurrently, and in some cases postoperative hypotension is refractory even to high doses of vasopressors and adjunctive therapies.

Role of the Renin-Angiotensin-Aldosterone System
The renin-angiotensin-aldosterone system (RAAS) plays a key role in blood pressure

homeostasis, and is of increasing interest as an additional potential target in the treatment of shock. ANG-2, a naturally occurring hormone in this system, has activity throughout the cardiovascular, renal, endocrine, and nervous systems. In addition to the regulatory role in aldosterone production, ANG-2 has direct arterial and venous vasoconstriction activity via Type 1 ANG-2 receptors in the vascular smooth muscle (Chawla et al. 2014). Use of ANG-2 in the treatment of shock has increased following the Angiotensin II for the Treatment of High Output Shock (ATHOS) trials, which found the addition of ANG-2 effective in patients with vasodilatory shock, for increasing mean arterial pressure (MAP) and allowing the reduction in doses of other vasopressor agents (Khanna et al. 2017). Endogenous ANG-2 begins as angiotensinogen, a precursor protein produced and constitutively released by the liver, which is catalysed into ANG-1 by renin, which is primarily secreted from the kidneys. ANG-1 is then converted to ANG-2 by angiotensin

converting enzyme-1 (ACE), an membrane-bound enzyme predominantly found on lung endothelium (**Figure 1**) (Santos et al. 2019). In the setting of profound inflammation, relative ANG-2 deficiency is thought to occur through decreased ACE activity, either by signaling mechanisms or due to pulmonary endothelial injury, furthering the state of shock (Bellomo et al. 2020a).While decreased ACE activity is difficult to measure directly due to the enzyme being membrane-bound, increased ANG-1 to ANG-2 ratio has been proposed as a surrogate test, and in recent studies has been linked to catecholamine-resistant vasodilatory shock and poor outcomes (Bellomo et al. 2020a).

Renin release, the rate limiting step in the RAAS cascade, receives negative feedback from ANG-2 (Bussard and Busse 2018), so that renin levels would be expected to increase in the setting of ANG-2 deficiency. Renin levels may be easier and more practical to check than an ANG-1/ANG-2 ratios, and these have been found to correlate (Bellomo et al. 2020b). In a recent prospective observational study, renin levels were found to be useful as a marker of tissue perfusion, and elevated renin levels were prognostic for increased ICU mortality (Gleeson et al. 2019). While it is unclear to what extent refractory shock is due directly to decreased ANG-2 activity or to increased ANG-2 precursors and their metabolites, both renin and ANG-1 appear to be suppressible by exogenous ANG-2 (Bellomo et al. 2020b). Further, in a post hoc analysis of the ATHOS-3 trial, treatment with ANG-2 was associated with reduced 28-day mortality among patients with renin levels above the study population median (Bellomo et al. 2020b).

Patients undergoing CPB may be particularly vulnerable to relative deficiency in ANG-2. In addition to the inflammatory cascade provoked by CPB, bypassing the pulmonary circulation effectively bypasses the primary site of ACE activity, which may result in less catalysis of ANG-1 to ANG-2,

at least temporarily (Busse et al. 2020). Elevation in plasma renin activity has been observed both during and after CPB (Lehot et al. 1992; Barta et al. 1980) though the precise relevance of this to vasoplegia is not clear. ATHOS-3, which primarily enrolled patients with septic shock, did include 19 patients with postoperative vasoplegia, of whom 9 received ANG-2 after CPB compared to 7 who received placebo after CPB. The remaining 3 of 19 did not undergo CPB. In a post hoc analysis, target MAP was achieved in the majority of the ANG-2 group (8 out of 9

> **◀◀ patients undergoing CPB may be particularly vulnerable to relative deficiency in ANG-2 ▶▶**

subjects), compared none in the placebo group (Klijian et al. 2020). Of note, the authors of that study confirmed circulating levels of ANG-1 and the median ANG-1/ANG-2 ratios in the group were elevated relative to healthy controls. Although ACE inhibitor use prior to CPB has been cited in some studies as a risk factor for vasoplegia, only 3 of the 19 had prior exposure to ACE inhibitors. Renin levels were not reported in this analysis.

Review of Literature

The United States Food and Drug Administration (U.S. FDA) approved synthetic human ANG-2 in December 2017. Prior to this, the agent had been approved for compassionate use in the summer of 2017. The European Medicines Agency (EMA) allowed use of the drug in summer 2019. Therefore, published data with this new vasopressor in the setting of post CPB vasoplegia is limited to the last two years. PubMed, Ovid, and Web of Science databases were searched for articles published

through Sept 2020, with the search terms "vasoplegia," "cardiopulmonary bypass," and "angiotensin." Any articles were considered which addressed the use of synthetic human ANG-2 for the treatment of vasoplegia related to CPB. The authors identified a total of 15 articles, of which 4 were individual case reports, 2 were small case series, 5 were review articles on post-CPB vasoplegia which mentioned the potential of ANG-2 as an adjunctive therapy, one was a review article on ANG-2 that mentioned its potential use following CPB, one was a post hoc analysis of CPB patients enrolled in ATHOS-3, and one was a retrospective review of ANG-2 use which included one patient who received the drug after CPB. Additionally, a retrospective study was identified which included 270 patients who received ANG-2 for refractory shock, of which 55 occurred after cardiothoracic surgical procedures, though these were not analysed separately (Wieruszewski et al. 2020).

From the case reports, case series, and ATHOS-3 post hoc analysis, we assessed patient age, sex, type of surgery, start time and reported effect of ANG-2, and any postoperative events discussed (**Table 1**). Among these cases, use of ANG-2 to treat vasoplegia during or after CPB is reported in 22 patients, with some demonstrating dramatically improved haemodynamics or reduced need for other vasopressors, and some for whom the apparent effect was more subtle. This variable response is consistent with the findings of the retrospective study mentioned, which identified 181 of 270 total patients (67%) to be "responders" to ANG-2, meaning MAP ≥ 65 mmHg was achieved and vasopressor doses were stabilised or reduced after initiating ANG-2; 159 (59%) of the total cases were able to reduce vasopressor doses once ANG-2 was initiated (Wieruszewski et al. 2020). Predicting which patients will most benefit is of great interest; in this study responders were significantly more likely to be receiving AVP, and to

have lower lactate levels, and those who responded were more likely to survive at 30 days (Wieruszewski et al. 2020)

Aside from the ATHOS-3 subgroup, components of the RAAS were not reported in the majority of cases identified. Among the case reports, however, one patient who suffered refractory vasoplegia after pneumonectomy had renin levels checked serially, including prior to initiation of ANG-2. While markedly elevated initially, renin levels trended downward during the ANG-2 infusion, closely mirroring the downward trend in catecholamine requirement (Trethowan et al. 2020). In a separate case series, one heart transplant patient was tested and found to have significantly elevated renin activity both during and after ANG-2 infusion, and this patient appeared to have a very favourable response to ANG-2(Cutler et al. 2020). Finally, one patient was presumed to have abnormally low levels of renin after coronary artery bypass graft (CABG) due to history of bilateral nephrectomies, and this patient also appeared to have a very favourable response (Cutler and Khanna 2020). All three of these cases could be postulated to have a relative ANG-2 deficiency prior to treatment, two due to decreased ACE activity and one due to decreased renin activity. Of note, one additional article was identified which described a series of 7 patients who received ANG-2 for shock in conjunction with extracorporeal membrane oxygenation (ECMO), which shares some physiology with CPB (Ostermann et al. 2018). The authors found overall that ANG-2 permitted reduction in dose of catecholamine vasopressors, reporting one case of digital ischaemia and one case of bowel ischaemia and death among that cohort, none of which were attributed to ANG-2. Some of those patients received ANG-2 in the context of the ATHOS-3 trial, including one who had undergone CPB earlier in their hospital course. However, CPB was apparently not associated with vasoplegia in that case, so it does not appear in Table 1 and was not included in the post hoc by Klijian et al. (2020).

The burden of organ injury is relatively high among available published cases of post CPB vasoplegia, which is likely a consequence of current ANG-2 use primarily as a rescue therapy in refractory shock. Reported complications were consistent with what might be expected in cases of severe shock, with none attributed to ANG-2 by the authors cited. In ATHOS-3, thrombotic events occurred more frequently overall in the ANG-2 group (12.9%) than the placebo group (5.1%), and Wieruszewski and colleagues identified venous thromboembolism in 4 of 270 patients during their retrospective study (Wieruszewski et al. 2020). Although ANG-2 may have a pro-thrombotic effect at receptors in certain cell types including the vascular endothelium (Bauer et al. 2018), no arterial or venous thromboses were reported among the group of cases reported in **Table 1**. The relevance of this in the context of cardiac surgical patients who may already be receiving antithrombotics for new grafts or devices, remains unclear.

Angiotensin II use protocol at the Wake Forest University Medical Center

The authors present the current protocol for the use of ANG-2 in the treatment of post CPB vasoplegia at our tertiary care 900 bedded university hospital. Eligible patients are adults who have undergone cardiac surgery and had vasoplegia intraoperatively or postoperatively, which was not responsive to traditional high dose vasopressors, and which in the past would lead to the administration of methylene blue as salvage therapy at our facility. Vasoplegia in our population is defined as an inability to maintain a MAP ≥ 65 mmHg in the presence of high dose vasopressors, as measured via invasive arterial blood pres-

Authors	Year	Study type	Case Numbers (n)	Age, sex	Procedure	Start POD #	Effect	Postoperative events**
Evans et al.	2019	Case report	1	81, M	CABG	0	Improved MAP, reduced NE	-
Wieruszewski et al.	2019a	Case series	4	47, M	Heart transplant	0	Reduced NE	
				57, M	CABG/AVR	0	Improved MAP, reduced NE	Digital ischaemia
				37, M	Lung Transplant	8	Reduced NE	-
				64, M	LVAD implant	0	Transiently reduced NE	Death
Wieruszewski et al.	2019b	Case report	1	34, F	Heart and Liver Transplant	14	Improved MAP, reduced NE	-
Wong et al.	2019	Retrospective review	1	76, M	MV replacement	0	Brief infusion, no apparent effect	-
Cutler and Khanna	2020	Case report	1	70, M	CABG	0	Improved MAP, reduced NE	Ischaemic bowel
Trethowan et al.	2020	Case Report	1	57, M	Pneumonectomy	0	Improved MAP, reduced NE	VAP
Cutler et al.	2020	Case series	4	62, M	Heart Transplant	0	Transiently stabilised NE	Optic neuropathy, wound complication
				61, M	Heart Transplant	0*	Transiently stabilised NE	Renal failure, VAP, wound complication
				69, M	Heart Transplant	0	Reduced NE	Liver injury
				60, M	Heart Transplant	0	Transiently stabilised NE	-
Klijian et al.	2020	Post-hoc ATHOS-3 subgroup	9 (vs. 7 placebo)	57, M	TV and MV repair	1	Transiently improved MAP	-
				48, M	MV replacement	1	Improved MAP, reduced NE	-
				64, M	CABG	1	Improved MAP, reduced NE	-
				67, M	CABG	1	Improved MAP, reduced NE	-
				80, M	CABG and MV replacement	1	Improved MAP, reduced NE	VF arrest
				72, M	AV replacement	1	Improved MAP, reduced NE	Liver and kidney injury, septic shock
				60, M	CABG	1	Improved MAP, reduced NE	Cardiogenic shock, death
				52, M	AV replacement	1	Improved MAP, reduced NE	-
				88, M	AV replacement	1	Improved MAP, reduced NE	-

Table 1. Summary of Cases for use of ANG-2 after CPB since U.S. FDA approval†

ANG-2 = Angiotensin II. ATHOS-3 = ANG-2 for the Treatment of High Output Shock trial. AVR = Aortic valve replacement. CABG = Coronary artery bypass graft. CPB = Cardiopulmonary bypass. LVAD = Left ventricular assist device. MAP = Mean arterial pressure. MV = Mitral valve. NE = norepinephrine requirement. POD= postoperative day. TV = Tricuspid Valve. VF = Ventricular fibrillation. †Wieruszewski and colleagues recently report using ANG-2 in 55 patients post CPB, however the data published is part of a retrospective multi-institutional effort of all comers with vasodilatory shock of different etiologies. The reader is referred to (Wieruszewski et al. 2020) for complete details. *ANG-2 was initiated intraoperatively prior to wean from CPB. **None of these events are complications attributed to ANG-2 use.
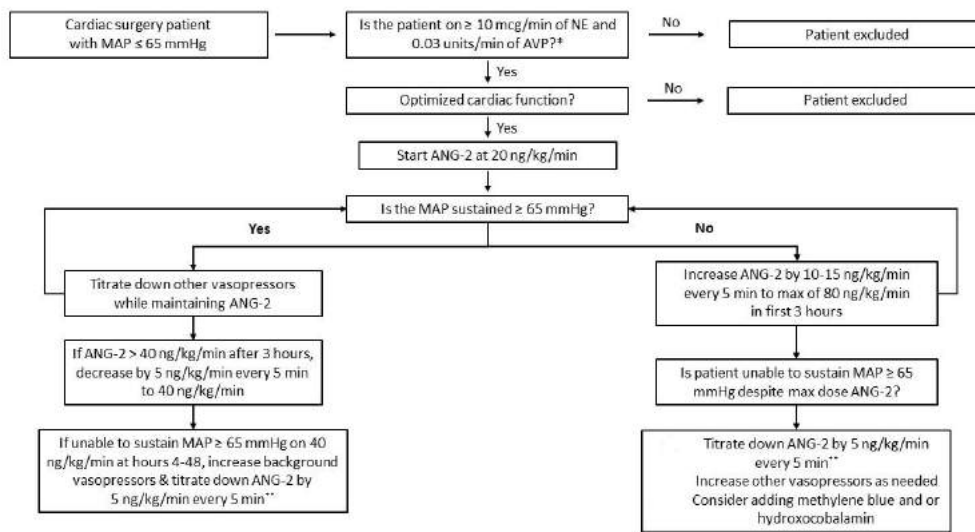
Figure 2. ANG-2 = Angiotensin II. AVP = Arginine vasopressin. NE = norepinephrine. *Total 0.2 mcg/kg/min NE equivalents for an 80kg patient. **Leave ANG-2 at lowest dose 20ng/kg/min and let run out over 24 hours

sure monitoring, despite optimised cardiac function. The definition of optimised cardiac function has been loosely worded to allow for the clinical judgement of the cardiac intensivists and cardiac surgical teams. This would be a combination of the exclusion of low cardiac output and or hypovolaemic states, and the clinical background of a vasoplegic state (prolonged bypass run, pre-existing reduced ejection fraction, patients with infective endocarditis, or those with a mechanical circulatory support device, to name a few). High dose vasopressors are defined as NE ≥ 10 mcg/min plus AVP ≥ 0.03 unit/min (total NE equivalent ≥ 0.2 mcg/kg/min for an 80 kg patient). All clinical care providers were provided training regarding initiation and titration of ANG-2 (**Figure 2**). Upon meeting inclusion criteria ANG-2 is initiated at 20 ng/kg/min and up titrated to a maximum of 80 ng/kg/min, within the first three hours, with a target MAP of ≥ 65 mmHg. This dose is maintained for up to three hours as needed and then titrated downward to a maximum maintenance dose of 40 ng/kg/min for up to 48 hours total. In our previous experience and based on published literature most patients are able to sustain adequate blood pressures at a dose of ANG-2 between 20-40ng/kg/

min. Other vasopressors are maintained at their pre-ANG-2 initiation dose during this time. If the patient is unable to maintain MAP ≥ 65 mmHg while on ANG-2 (at a maximum of 80ng/kg/min) within 4 hours of initiation, they are considered to have treatment failure, and ANG-2 is titrated off to a low dose (with the aim of stopping at 24 hours) while other interventions continue. These could include the escalation of catecholamine vasopressors and AVP, and the use of methylene blue and or hydroxycobalamin. If patients are determined to respond to ANG-2, then other vasopressors are decreased as tolerated until the patient remains solely on ANG-2. If allowable, serum renin and lactate levels are drawn at initiation of ANG-2 and at regular intervals during the 48 hours afterwards.

Future work
Early data from the prospective utilisation of ANG-2 and post-hoc analysis of the ATHOS-3 population have shown very encouraging signals for use in post-CPB vasoplegia. There is a well-established pathophysiologic cascade of events that lead to dysfunctional ACE and low endogenous ANG-2 in post CPB patients. The data obtained from our protocol will be

reviewed annually for research and quality control purposes. The best evidence requires a large randomised double-blind placebo-controlled trial of ANG-2 versus standard of care in this population. However, we hope for a large dataset of prospective and protocolised ANG-2 use in established post CPB vasoplegia patients. By mapping biomarkers, we aim to establish the need for specific vasopressor therapies in these patients, and in conjunction with parallel work at other institutions, anticipate the ability to identify populations for whom the addition of ANG-2 will be most beneficial. Knowing the well-established utility of serum renin as a prognostic marker in shock, personalised use of vasopressors that target the RAAS should be the unstated rule in most critically ill patients. Herein, future research should focus on detailing all aspects of the RAAS, including angiotensin 1-7 and angiotensin 2-9, along with renin, ANG-1, and ANG-2 levels in several different clinical phenotypes of shock.

Conclusion
Vasoplegia is relatively common following cardiothoracic surgery, and is associated with significant morbidity. Treatment of severe cases can be challenging. ANG-2 is of increasing interest in this role for

improving blood pressure and reducing the requirement for catecholamine vaso-pressors, but its appropriate place in the hierarchy of adjunctive therapies is not yet clear. Some cases described in the literature have experienced dramatic improvement, and the limited prospective data from ATHOS-3 is promising. ANG-2 may be uniquely beneficial to patients following CPB, particularly in subgroups of patients with specific patterns of RAAS dysfunction. Potentially, markedly abnormal renin levels will indicate greatest need or benefit, but further data is needed to clarify this in the setting of CPB. Personalised vasopressor management is the need of the hour, and the one-size-fits-all approach to increasing blood pressure in the ICU may become a thing of the past.

Conflict of Interest

The views expressed in this article reflect the results of research conducted by the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the United States Government.

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Key Points

- Postoperative vasoplegia is a form of distributive shock, physiologically similar to the shock caused by sepsis.
- Though estimates of prevalence vary, the condition affects 20% or more of patients who have undergone operations requiring cardiopulmonary bypass (CPB).
- Treatment of the condition can be challenging and is fraught with potential adverse effects, particularly in the immediate postoperative period when the myocardium is already under significant stress.
- The most common interventions, similar to those for other distributive shock states, are volume resuscitation, catecholamine vasopressors (typically norepinephrine(NE)), and arginine vasopressin (AVP).
- The authors present the current protocol for the use of ANG-2 in the treatment of post CPB vasoplegia at our tertiary care 900 bedded university hospital.

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Gianluca Paternoster
Research coordinator and
consultant
Cardiothoracic and Vascular
Anesthesia and Intensive Care
U.O.C. Cardiac Anaesthesia and
Cardiac-Intensive Care
San Carlo Hospital
Potenza, Italy

**paternostergianluca@gmail.
com**

Ádám Nagy
U.O.C. Cardiac Anaesthesia and
Cardiac-Intensive Care
San Carlo Hospital
Potenza, Italy;

Károly Rácz School of PhD
Studies
Semmelweis University
Budapest, Hungary

nagyadam05@gmail.com

Promising Techniques in Sepsis After Cardiac Surgery

The purpose of this article is to give an up-to-date, comprehensive review on the utilisation of extracorporeal blood purification techniques and immunostimulation in septic patients after cardiac surgery.

Introduction

Sepsis is a potentially life-threatening state caused by an infection and an inadequate, dysregulated host immune response. In general, sepsis ranks in the top ten causes of death and is potentially harmful for the whole population of our planet (Lever and Mackenzie 2007; Martin et al. 2003). From the aspect of the intensive care unit, sepsis is one of leading causes of mortality despite the huge efforts and many different type of treatments (Mayr, Yende, and Angus 2014). Focusing on cardiac surgery, the prevalence of sepsis is low, after procedures situated between 0.39% and 2.5%. Nevertheless, the current life-expectancy of septic patients is poor, with mortality varying from 65% to 79% (Oliveira et al. 2010; Yaroustovsky et al. 2014).

A dysregulated interaction between the infection and the host immune system possibly lead to sepsis. During perioperative period of cardiac procedures, several additional, special factors are presented such as: (1) surgical trauma; (2) shear stress; (3) blood contacts with a huge artificial surface in cardiopulmonary bypass;

(4) internal drainage system; (5) need for blood transfusion related to surgery; and (6) reperfusion after ischaemia. Reperfusion after ischaemia can lead to an increased endothelial permeability. In the gastrointestinal tract it possibly results in endotoxin or lipopolysaccharide (LPS) release. These factors together can provoke a dynamic systematic immune response (Paternoster and Guarracino 2016).

The pathophysiology and immunopathology of sepsis is still unclear. We were witnesses of several paradigm shifts during the last decade. Actually, we consider sepsis as a dynamic process with two different sides. Both immune hyperactivity and immune suppression are presented during the progression (van Ton et al. 2018). Immunomodulation is not a fresh idea in the treatment of sepsis. In order to develop a successful method in immunotherapy we should understand the progress of sepsis from the aspect of the immune system (Antonopoulou and Giamarellos-Bourboulis 2011; Cohen 2002).

Currently the diagnosis of sepsis is based on clinical signs. The biomarkers and molecular diagnostic tools are insufficient

(Rhodes et al. 2017; Levy et al. 2018). Traditional prevention and treatment strategies have not changed significantly in the last decades and mortality is still alarmingly high.

During the last few years, several new approaches were studied. A large part of these approaches are based on immuno-modulation, two of which are immunostimulation and extracorporeal blood purification techniques (Antonopoulou and Giamarellos-Bourboulis 2011).

The purpose of this article is to give an up-to-date, comprehensive review on the utilisation of extracorporeal blood purification techniques and immunostimulation in septic patients after cardiac surgery.

Immunopathophysiology of Sepsis After Cardiac Surgery

The actual concept of immunopathophysiology in sepsis is based on the idea of a dynamic parallel immune response; both pro- and anti-inflammatory processes are presented from the beginning (Annane et al. 2005). The innate immune system is responsible for the initial detection of potentially harmful factors, like microor-

ganisms and special inflammatory stress factors related to the perioperative period of cardiac surgery. Gram-negative and positive bacteria contain numerous structures (endotoxin, or lipopolysaccharide {LPS}, lipoprotein, peptidoglycans, peptidoglycan-associated lipoprotein, lipoteichoic acid, flagellin, fimbriae) that can lead to intense immune response. We call them pathogen-associated molecular patterns (PAMPs) (Kumar, Kawai, and Akira 2011). Surgical trauma and cardiopulmonary bypass cause a release of danger-associated molecular patterns (DAMPs). PAMPs and DAMPs are recognised by the pattern recognition receptors (PRRs) presented on dendritic cells, monocytes and macrophages. Toll-like receptors (TLRs) are one type of PRR. Binding of PAMPs and DAMPs to a PRR initiates the immune response of the host. The activation of different intracellular signalling cascades ends-up in a general activation of the innate immune system. The magnitude and type of primal response is influenced by many individual factors like age, type and amount of bacteria, comorbidities, genetic factors (Leentjens et al. 2013).

Proinflammation and antiinflammation walk hand-in-hand from the zero time point of the immune response. In the early phase, proinflammatic environment dominates. Mononuclear cells play an important role with the release of proinflammatory cytokines IL-1- IL-6, TNF-α. These classic proinflammatory mediators can lead to a fast and intense activation of the immune system called hyperinflammation (van Ton et al. 2018; Cohen 2002). Nevertheless, the immune system tries to maintain balance and launches a complex system of counter-regulatory mechanisms at the same time (Cohen 2002). These counter-regulatory attempts can end-up causing a phenomenon called "sepsis-induced immunoparalysis" (Venet et al. 2013). After the hyperinflammatory early phase, this immunosuppression possibly opens the field for secondary, opportunistic infec-

tions. Dominating molecules of this period are soluble TNF receptor antagonists, IL-1 receptor antagonists, IL-4, IL-10 and IL-13. Immunoparalysis is caused by impaired cytokine producing function of leukocytes, apoptosis of different type of immune cells, low absolute lymphocyte count and diminished expression of important cell surface antigens like HLA-DR on monocytes. The phenomenon of "sepsis-induced immunoparalysis" is supported by several studies and experiences. (1) Frequent occurrence or reactivation of less-virulent bacteria, viruses and fungi in the late phase of septic patients despite

◀◀ in order to develop a successful method in immunotherapy we should understand the progress of sepsis from the aspect of the immune system ▶▶

aggressive therapeutic efforts. (2) Mortality distribution of sepsis shows three peaks. Approximately a quarter of patients die in 4-5 days. From the remaining survivals one-third can bear with primal infection and restore immunocompetence - mortality of this group is 10%. The other two-third develop immunoparalysis and have a mortality rate of around 65% (Venet et al. 2013). (3) Studies with the application of antiinflammatory therapies show lack of positive effect on sepsis outcome (Leentjens et al. 2013).

Equilibrium may be the key in the immune response of sepsis. Immune system tries to maintain the homeostatic environment during sepsis via pro- and antiinflammatory processes. In case of an unbalanced, dysregulated and radical (in both directions) response, mortality

becomes frightfully high. Of course, in reality it is more complicated and there are no clear borders between phases and extremities, like pro- and antiinflammation. Cytokines do not behave in a dichotomised manner; function and contribution to survival or death can depend on the context. A single cytokine possible act pleiotropically depending on the actual molecular microenvironment. The final effect of an inflammatory mediator is therefore diverse and highly depends on numerous different interactions (Denstaedt et al. 2018).

Treatment: New-Approaches Based on Immunomodulation

Infection source control, adequate antibiotic therapy and organ support are the three corner stones in the treatment of sepsis since the definition of sepsis was created (Zimmerman et al. 2004). Nowadays, the insufficiency of these treatments is clear and there is a need to improve clinical outcomes, especially in the late phase of sepsis. In the development and progression of sepsis, host immune response is an extremely important component. Complexity and heterogeneity of our immune system makes it clear that we will never be able to find a general answer for every septic patient; rather we should search for individual treatment modalities based on the clinical picture and immune-pathophyisiological background, patient-by-patient (Rello et al. 2017; Leligdowicz and Matthay 2019). Although these techniques are performing well in the early phase of sepsis, new adjuvant therapies are needed to prevent or treat the effects of the immunoparalytic phase of sepsis (Leentjens et al. 2013).

In our review we would like to add a detailed overview on two promising modalities of immunomodulation: (1) extracorporeal blood purification; (2) immunostimulation. Early days of sepsis is ruled by a hyperinflammatic state with DAMPs, PAMPs and proinflammatory cyto-

kines circulating in the body. Extracorporeal blood purification may represent a useful technique by removing these molecules from the circulation. In the late phase of sepsis immunoparalytic state appears in the majority of patients. To maintain equilibrium immunostimulation may offer a suitable opportunity (Antonopoulou and Giamarellos-Bourboulis 2011). Pro- and antiinflammatory responses and innate and adaptive immune systems may represent equal importance and become potential targets for immunomodulation strategies to improve outcome (Delano and Ward 2016).

Based on the nature of the immunopathophysiology of sepsis and our therapeutic goals with immunomodulation to maintain immune equilibrium, we must recognise the possible intervention points early and precisely. Appropriate immunomonitoring seems unavoidable and has a huge importance to recognise the patients with an overturned immune system as soon as possible (Venet et al. 2013; Denstaedt et al. 2018). Unfortunately, a detailed description of these methods is beyond the scope of this present review.

Extracorporeal Blood Purification

Extracorporeal blood purification techniques have a history of 15 years in the treatment of critically ill patients. A serious inflammatory host response includes an immune hyperactivity and an excessive release of proinflammatory cytokines. It leads to organ damage, dysfunction and immune-paralysis which possibly end up, in adverse outcomes, with death. This phenomenon summoned the original idea of blood purification (Honoré and Matson 2004; Di Carlo and Alexander 2005; Rimmele and Kellum 2011). Removing or reducing the blood concentrations of inflammatory mediators, bacterial toxins (endotoxin, LPS) and tissue degradation products from the systemic circulation with a special device can provide beneficial effects (preventing multi-organ dysfunc-

tion and immune- paralysis). Through that period numerous different strategies were studied, such as haemofiltration, haemoadsorption, plasmapheresis etc. Studies report promising results; these approaches can significantly reduce the blood concentration of the targeted molecules and are well tolerated by patients (Born et al. 2017). However, the details (appropriate technique, patient selection, timing, duration etc.) and the effect on clinical endpoints (mortality, organ dysfunction) is unclear yet. In technical aspects we can distinguish three different types: (1) haemofiltration (high volume haemofiltration, very high volume haemofiltration,

◀◀ in the late phase of sepsis immunoparalytic state appears in the majority of patients ▶▶

high cut-off membranes); (2) adsorption (Toraymyxin, EMiC2, Cytosorb, Oxiris, LPS adsorber and HA 330) (3) coupled plasma filtration adsorption (Ankawi et al. n.d.). These methodologies can be applied with appropriate renal replacement therapy devices as an adjuvant treatment or alone.

Haemofiltration techniques are feasible and safe in the setting of sepsis. Probably they can improve haemodynamics. Nevertheless, the effect on mortality is unclear, despite promising early results. Adsorption strategies are well-tolerated and feasible in septic patients. Currently we lack robust evidence, however, a positive trend seems to be emerging with improved haemodynamics and decreased mortality. Coupled plasma filtration adsorption technique is complex, expensive and associated with multiple technical issues. Evidence suggests feasibility and ineffectiveness

in clinical endpoints; to date the power of these trials are limited (Ankawi et al. n.d.). Overall, the magnitude of currently available evidence on these techniques are admittedly insufficient, further efforts are warranted to ascertain the beneficial effects.

Utilisation of Cytosorb is one of the most promising and actual field among extracorporeal blood purification techniques. Cytosorb treatment is already tested in different clinical settings. It seems significantly effective in reducing toxic molecules and may improve the clinical outcome (Calabrò et al. 2019; Nemeth et al. 2018). Three small RCTs in the setting of sepsis and septic shock showed significant reduction in IL-6 concentration and significant reduction in vasopressor need, but no significant difference in mortality (D Schädler et al. 2013; Dirk Schädler et al. 2017; Hawchar et al. 2019). Each study confirms the safety and feasibility of the method. The international registry on the use of Cytosorb with 135 septic patients reported an improvement in observed mortality compared to predicted mortality, however, the number of patients is still a huge barrier to make further conclusions (Born et al. 2017). Several smaller studies and case series also support the above mentioned beneficial trends in haemodynamics and survival (Friesecke et al. 2017; Kogelmann et al. 2017).

Immunostimulation

Immune response during the dynamic process of sepsis is complex and contextual, however, a robust body of evidence remark a relationship between the presence of sepsis-induced immunoparalysis and poor clinical outcomes (Denstaedt et al. 2018). Numerous pre-clinical and clinical study report that sepsis leads to an overall state of immune depression with T cell dysfunction, impaired antigen presenting cell functions (monocytes, macrophages, dendritic cells) (Williams et al. 1998; Fan et al. 2015). Approximately 70% of sepsis related mortality occurs in later phase

of progression, which is defined by the persisting primary infection and sepsis related immune suppression with serious secondary opportunistic, nosocomial infections (Otto et al. 2011). Therefore, the development of novel strategies to augment host immunity may represent useful tools in the treatment of sepsis. Several diverse agents are already tested, although our current knowledge is based on animal studies and few clinical studies (Patil et al. 2016).

Granulocyte colony stimulating factor (G-CSF) and Granulocyte-macrophage colony stimulating factor (GM-CSF) are cytokines, which can stimulate stem cells to produce macrophages, monocytes and neutrophils and also improve release and function. Several clinical studies reported promising results and also a meta-analysis of 12 clinical studies demonstrated a significantly reduced rate of secondary infections (Francisco-Cruz et al. 2014; Bo et al. 2011). G-CSF and/or GM-CSF potentially become useful in the eradication and prevention of infections (Delano and Ward 2016).

Interferon gamma (IFN-γ) is one of the key cytokines responsible for appropriate monocyte and macrophage function, which are important factors in microbial elimination. Recombinant IFN-γ therapy increase antigen presenting capacity and proinflammatory cytokine production in septic patient without therapy related adverse outcomes (van Ton et al. 2018). Beneficial effects are already proofed in different patient population with an impaired immune system (Dries et al. 1994). Careful utilisation of IFN-γ may provide a therapeutic intervention for septic patients.

IL-7 is one of the most important cytokines in T cell production and function and also inhibits lymphocyte apoptosis. Therefore, recombinant IL-7 might offer benefit in lymphopenic septic patients (Rezoagli et al. 2019). A recent phase IIb randomised controlled trial results are suggesting recombinant IL-7 is a safe and feasibly option to enhance the adaptive immune response in septic patients (Francois et al. 2018).

Immunoglobulins (Ig)

Immunoglobulins are produced and secreted by B-cells that are activated and propagated by the T cells. Igs are constituted by heavy (H) and light (L) chains and Ig isotypes are classified into IgG, IgA, IgM, IgD and IgE (Shankar-Hari et al. 2011). Both H and L chains are divided into one variable and one constant domain (Shankar-Hari et al. 2011). It is well known that Igs are the major effectors of the humoral immune response, nevertheless, the exact mode of action of Ig remains largely unexplored. On one hand, Igs have the role to protect the host from infection, but on the other hand they may play a dual antithetical role as pro-inflammatory or anti-inflammatory agents (Berlot et al. n.d.).

Immunoglobulins are mandatory elements of adequate pathogen recognition and clearance. They inhibit the transcription of immune mediator genes and have anti- apoptotic effect (Vincent and Mongkolpun 2019). Sepsis is associated with decreased circulating immunoglobulin levels (especially IgG and IgM) levels (Taccone et al. 2009; Venet et al. 2011). Even if the mechanisms of action are still not fully elucidated, basic immunology and more recent studies indicate that endogenous Ig as well as the possible Ig supplementation may play a fundamental role in the host inflammatory-immune response to infection. Not only Ig (particularly IgM) can facilitate the rapid pathogen and toxin clearance in the early phases of infection and modulate the excessive pro-inflammatory host response, but they may be also beneficial in the late phases of sepsis characterised by a profound depression of innate and adaptive immunity. Ig exert a direct anti-apoptotic effect on lymphocytes and facilitate the clearance of apoptotic cells by an IgM-mediated mechanism that may counteract sepsis-induced immune- dysfunction (Schwab and Nimmerjahn 2013).

A recent meta-analysis with trial sequential analysis (TSA) for the primary and secondary outcomes which included 15 RCTs, involving 712 patients, and four cohort studies, involving 818 patients, assessed the use of intravenous (IV) IgGM preparations in adults with sepsis. IV IgGM administration significantly reduced mortality rates, with an RR of 0.60 (95% CI 0.52–0.69). Subgroup analysis showed that these results were generally consistent, regardless of duration of treatment, daily dose, total dose, variety of disease severity scores, follow-up duration, study design and year of publication. However, use of IV IgGM shortens mechanical ventilation days but not length of intensive care until stay or length of hospital stay (Cui et al. 2019).

Therefore, the possibility of direct immunoglobulin supplementation seems to be a worthwhile attempt. On one hand, results of recent studies are inconsistent (Kakoullis et al. 2018; Welte et al. 2018). On the other hand, the body of evidence is still insufficient for making further conclusions.

Immunostimulation in sepsis is currently in the scope of high scientific interest with great efforts to develop further progress. Numerous ongoing projects are investigating for other possible therapeutic interventions (IL-3, IL-15, anti-PD-1 antibody, anti-PD-L1-antibody, anti-BTLA antibody, anti-CTLA4 antibody, Flt3 ligand, CAR T cell therapy) (Patil, Bohannon, and Sherwood 2016).

Conclusion

Sepsis already has a long history, the intention to cure septic patients probably far older than the first definition of sepsis. During the last decade the potential outcome of sepsis in different patient population has not improved significantly.

Nevertheless, studies revealed the complexity and diversity of the immune response in septic patient. Numerous individual factors are recognised, which can lead to different progression patient-by-patient. Different types of immunomodulation techniques have a great prospect. However, the potentially beneficial utilisation may require a bigger and stronger body of evidence and an individualised approach for every single septic patient. A more accurate understanding of the immuno-pathophysiology of sepsis can lead to new approaches in treatment to improve the currently poor outcome.

Conflict of Interest

None. ■

Key Points

- Sepsis ranks in the top ten causes of death.
- The current life-expectancy of septic patients is poor and mortality varies from 65% to 79%
- Pathophysiology and immunopathology of sepsis is still unclear.
- Different types of immunomodulation techniques have a great prospect. However, their utilisation may require a bigger and stronger body of evidence and an individualised approach for every single septic patient.
- Understanding the immunopathophysiology of sepsis can lead to new approaches in treatment and improved patient outcomes.

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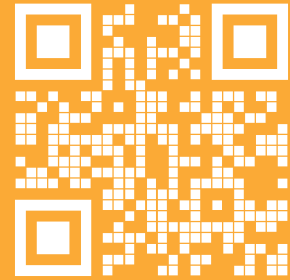
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Matthias P. Hilty
Institute of Intensive Care
Medicine
University Hospital of Zurich
Zurich, Switzerland

Department of Intensive Care
Erasmus MC
University Medical Center Rotterdam
The Netherlands

matthias.hilty@usz.ch

🐦 @matthiashilty

Can Ince
Department of Intensive Care
Erasmus MC
University Medical Center Rotterdam
The Netherlands

c.ince@erasmusmc.nl

Microtools to Identify and Resuscitate Microcirculatory Dysfunction in Critically Ill Patients

An overview of real-time digital assessment of microcirculation and quantification of tissue perfusion and the physiological and technical considerations that may, in the near future, change the way we look at circulatory shock in critically ill patients.

The Challenges of Detecting Circulatory Shock

Despite recent advances in the timely restoration of impairments in the oxygen supply chain to the tissue (Yealy et al. 2014; Peake et al. 2014; Mouncey et al. 2015), circulatory shock remains a major contributor to mortality in critically ill patients. The lung and pulmonary circulation, the right and left heart, and the systemic circulation consisting of arteries, veins, and microvessels, provide oxygen to the target cells by perfusing the tissue with red blood cells saturated with oxygen (Guven et al. 2020). In the systemic circulation, two overarching categories of circulatory shock may be differentiated by the primary mechanism of circulatory failure. On one hand, tissue red blood cell hypoperfusion may be secondary to a reduction of blood flow within the large arteries and veins, or a reduction of the oxygen-carrying capacity of the blood. Such dysfunction of the macrocirculation may be caused by primary pump failure in the form of forward or backward failure of the heart, hypovolemia as the cause of a reduction in cardiac output, or haemodilution which

may reduce tissue red blood cell perfusion even in the presence of otherwise sufficient cardiac output. These types of shock result in tissue hypoxia through insufficient delivery of oxygen by the macrocirculation and — if present long enough — in cell death and damage to the microvasculature, the interstitium and the parenchymatous cells within the tissue. Treatment aims at restoring cardiac output and tissue red blood cell perfusion before such irreversible damage ensues. On the other hand, circulatory shock may primarily manifest as dysfunction of the microvasculature within the tissue. In septic and inflammatory shock, the precipitation of an infectious or inflammatory agent has been demonstrated to directly cause dysfunction of red blood cells and the endothelial cells and induce disseminated intravascular coagulation, which together result in functional heterogeneity of the microcirculation and a deficit in the capacity of the tissue to extract oxygen culminating mainly through microcirculatory shunting and consecutive regional tissue hypoxia (Ince and Mik 2015; Ince 2015). In such a case, the timely restoration of oxygen

delivery to the tissues and elimination of the precipitating infectious or inflammatory agents may limit the additional damage caused by tissue hypoxia.

Both categories of circulatory shock, if allowed to progress, can result in a state of permanent microcirculatory damage and malfunction. The enabling step for the successful treatment of patients in circulatory shock is therefore the achievement of timely diagnosis and understanding of the underlying pathophysiology to identify and administer effective treatment strategies. However, the detection of circulatory shock is often challenging, especially in patients with effective compensatory mechanisms of the macrocirculation where parameters such as arterial blood pressure, blood haemoglobin concentration or even advanced haemodynamic measurements such as cardiac index may remain within the normal range despite the presence of severe tissue hypoxia. Direct insight into the function of the microcirculation in patients, on the other hand, may reveal deficiencies in tissue red blood cell perfusion and abnormal leukocyte kinetics from the onset. Such insights have been

achieved by the introduction of handheld vital microscopes for direct observation of sublingual microcirculatory alterations in critically ill patients (Ince et al. 2018). Even though the technological and methodological prerequisites to measure and interpret sublingual microcirculatory function have been demonstrated in a growing body of evidence (Ince 2015; Aykut et al. 2015; Ince 2014; Legrand et al. 2018), the applicability in clinical settings has been limited by complex and time-consuming data analysis processes (De Backer et al. 2007). Recent developments in advanced computer vision software such as realised in MicroTools are for the first time enabling the application of these technologies at the bedside (Hilty et al. 2020; Hilty et al. 2019; Hilty and Ince 2020).

The Microtools Advanced Computer Vision Algorithm Enables Quantification of Microcirculatory Function and Tissue Red Blood Cell Perfusion

The convective and diffusive capacity of the microcirculation are important determinants of the ability to deliver adequate amounts of oxygen to the tissue, through the movement of oxygen carrying red blood cells through the capillaries and the distance between the oxygen carriers and the parenchymatous cells (Guven et al. 2020). While surrogate parameters for both properties can be directly or indirectly measured using methods such as laser Doppler or near-infrared spectroscopy (Li et al. 2015), these only provide a partial insight. With the advent of handheld vital microscopy employing side stream or incident dark field microscopy, the imaging of individual red blood cell movement through the capillaries was made possible. Based on the principle that when observed for a long enough period, the total locus of moving red blood cells over time approximates the location of the capillary walls involved in

red blood cell transport, parameters such as the total length of capillaries divided by the field of view (total vessel density, TVD) and the total length of actively perfused capillaries divided by the field of view (functional capillary density, FCD) were formerly extracted from these images using manual analysis, providing insight into the microcirculatory diffusion capacity (De Backer et al. 2007). The quantification of red blood cell movement had initially relied on subjective scores in the absence of automated analysis algorithms (Naumann et al. 2016; Boerma et al. 2005). Early attempts at automatic analysis of HVM image sequences were not further developed to provide reliable measurements of such parameters and not validated in clinical settings (Eden et al. 2005; Bunyak et al. 2008; Bezemer et al. 2011; Behnke et al. 2012; Demir et al. 2012; Chao et al. 2015).

The development and validation of MicroTools using advanced computer vision algorithms utilising principal curvature-based region detection on equalised time-based mean images allowed automatic measurement of TVD and FCD (Hilty et al. 2020). In addition MicroTools allowed generation of space-time diagrams of the red blood cells moving through the detected capillaries (Ince et al. 2018), from which red blood cell velocity (RBCv) could be calculated to provide a reliable parameter reflecting the microcirculatory convection capacity in HVM image sequences (Hilty et al. 2019). MicroTools was further developed to compute capillary haematocrit (cHct), which next to FCD is a second major factor determining the diffusive capacity of the microcirculation (Hilty et al. 2019). With these quantitative parameters, HVM image sequences now provide a full overview of the parameters determining the perfusion of the tissue by red blood cells, which may thus be quantified as the displacement of red blood cell volume divided by the observed tissue volume which we have termed tissue red

blood cell perfusion (tRBCp) (Hilty and Ince 2020). Of major significance it that MicroTools allows the automatic calculation of these functional parameters of the microcirculation including tRBCp at the bedside in real-time and independent of the operator.

Automatic Analysis of the Sublingual Microcirculation Using Microtools Allows Systematic Analysis of Large Datasets

While the quantification of the determinants of oxygen delivery to the tissue provides the prerequisites for early recognition of circulatory shock and to guide resuscitation in critically ill patients at the bedside, algorithm-based analysis of HVM image sequences using MicroTools also for the first time opens large datasets of such measurements to the systematic analysis of the movement of red blood cells. In the first such use an analysis of a multicentral database consisting of 1525 measurements of the sublingual microcirculation, evaluating information on multiple trillion discrete red blood cell positions using the MicroTools algorithm was accomplished (Hility et al. 2020). Such a systematic analysis marks the transition of the in-vivo examination of microcirculatory function to a data-driven realm and may, for example, provide the basis for identifying the defining characteristics of circulatory failure in the setting of different diseases in critically ill patients. Hypotheses generated from such analyses will serve to prospectively test the diagnostic power of HVM measurements and the possibility to assess the effect of therapeutic measures using real-time analysis of the sublingual microcirculation. Further, it enables the application of more complex methods such as latent cluster analysis or the training of neuronal networks using the parameters derived from red blood cell tracking within HVM image sequences using MicroTools.

Alterations in Sublingual Microcirculatory Diffusion and Convection Capacity Correspond to the Presence Of Circulatory Shock and the Success of Resuscitation

In the population of the above mentioned systematic, algorithm-based study in a multicentral microcirculation database, the combination of RBCv and FCD as measures of the microcirculatory convection and diffusion capacity were found to indicate the presence of circulatory failure in patients with septic, cardiogenic and obstructive shock, hypovolemia and haemodilution (Hilty et al. 2020). The sublingual microcirculatory measurements included in that database were collected from 145 patients hospitalised in an intensive care unit, 82 perioperative patients and 40 healthy volunteers, and the observed conditions represent the main causes of a failure to deliver oxygen to the tissues. At the same time, longitudinal analysis in subgroups of the database encompassing those patients that underwent interventions to potentially recruit the microcirculation demonstrated that an increase in cardiac output mainly recruited the microcirculatory convection capacity as represented by RBCv, while systemic vasodilation favored the recruitment of the microcirculatory diffusion capacity by increasing the density of the perfused capillary network. These results thus not only establish that the early diagnosis of circulatory shock may be aided by the assessment of the sublingual microcirculation at the bedside in critically ill patients, but they also confirm the hypothesis that the effects of resuscitation procedures result in changes in microcirculatory function that are detectable by the algorithm-derived parameters of microcirculatory convection and diffusion capacity.

In the future, the hypothesis may be tested that different interventions steer the microcirculatory function in specific ways, for example, that certain vasopressors may primarily increase the precapillary arteriolar tone while others could prioritise action on the postcapillary venules, resulting in capillary perfusion recruitment instead of de-recruitment. Similarly, volume resuscitation may recruit microcirculatory delivery of oxygen through an increase in convection capacity, but may be associated with capillary de-recruitment through haemodilution even when macrocirculatory parameters such as stroke volume are still volume responsive (Hilty and Ince 2020).

Conclusion

Automatic, algorithm-based analysis of HVM image sequences using Software such as MicroTools has been made possible by the rapid evolution of advanced computer vision libraries and processing hardware, has been validated in large clinical datasets and provides real-time insight into the microcirculatory function at the bedside. Mathematical models allow the calculation of tRBCp in the sublingual microcirculation as a quantitative measure of microcirculatory delivery of oxygen, providing a novel treatment target for resuscitation in circulatory shock. Patterns in the parameters of microcirculatory convection and diffusion capacity and red blood cell movement within the capillary system may provide insight into the presence of circulatory shock before it manifests in organ dysfunction or in macrocirculatory aberrations, and reveal information on the underlying pathophysiological processes.

Conflicts of interest

Can Ince (CI) has developed SDF imaging, which is a hand-held vital microscope, and is listed as the inventor on related patents commercialised by MicroVision Medical (MVM) under a license from the Academic Medical Center (AMC). He receives no royalties or benefits from this license. He has been a consultant for MVM in the past but has not been involved with this company for more than five years now and holds no shares or stock. Braedius Medi-

cal, a company owned by a relative of CI, has developed and designed a handheld microscope called CytoCam-IDF imaging. CI has no financial relationship with Braedius Medical of any sort, i.e., never owned shares, or received consultancy or speaker fees from Braedius Medical. The MicroTools software is being developed by Mathias P. Hilty (MPH) and owned by Active Medical BV of which CI and MPH are shareholders. Active Medical runs an internet site called microcirculationacademy.org which offers educational courses and services related to clinical microcirculation and provides more information regarding MicroTools. ∎

Key Points

- Circulatory shock remains a major contributor to mortality in critically ill patients.
- The enabling step for the successful treatment of patients in circulatory shock is timely diagnosis and understanding of the underlying pathophysiology.
- Direct insight into the function of the microcirculation in patients may reveal deficiencies in tissue red blood cell perfusion and abnormal leukocyte kinetics from the onset.
- Recent developments in advanced computer vision software such as realised in MicroTools are, for the first time, enabling the application of these technologies at the bedside.

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Serene Ho
Cavendish Clinic
UK

serene.ho@doctors.org.uk

Adrian Wong
Consultant Intensive Care Medi-
cine and Anaesthesia
King's College Hospital
London, UK

avkwong@mac.com

🐦 @avkwong

Anda Butnar
Department of Anaesthesia and
Intensive Care
Royal Surrey County Hospital
Guildford, UK

butnar_anda@yahoo.com

Manu L.N.G. Malbrain
ICU Director
Intensive Care Unit,
University Hospital Brussels
(UZB)
Jette, Belgium

Professor
Faculty of Medicine and Phar-
macy, Vrije Universiteit Brussel
(VUB)
Brussels, Belgium

Manu.Malbrain@uzbrussel.be

🐦 @manu_malbrain

The Future of Critical Care: The Human Capital

This article will focus on the non-clinical, human aspects of critical care, namely the patient and the ICU team. The modern concepts of humanising ICU care, the healing environment and future-proofing the ICU team will be discussed.

Introduction

Despite being a relatively young specialty, critical care has made remarkable progress since its inception during the polio epidemic in Copenhagen in the 1950s. Though the iron lungs and medical students ventilating patients via tracheostomies have been replaced by modern ventilators complemented with other extracorporeal devices such as haemofilters, cardiac and lung support devices, the intensive care unit (ICU) remains the place where we care for the sickest patients.

Through a series of articles in this journal, colleagues discuss several aspects of critical care. Whilst our improved scientific knowledge will provide the basis for future therapies, these interventions are likely to gradually evolve rather than undergo abrupt major advances (Vincent and Creteur 2015). Rather, we anticipate that it will be the evolution of holistic care delivery which drives improvement in patient outcomes, with the emphasis on quality of care **(Figure 1).**

'It is not what we do, it is how we do it.'

This article will focus on the non-clinical, human aspects of critical care, namely the patient, who is central to all our endeavours, and us, the ICU team. In particular we will consider the modern concepts of humanising ICU care, the healing environment and future-proofing the ICU team. Given

the breadth of topic, only select aspects will be discussed.

Humanising ICU Care

The average human lifespan is increasing, with obesity and lifestyle-related illnesses becoming more common. 'Frail' patients are undergoing more complex and invasive procedures; medical advances have led to novel surgical procedures and chemo/immunotherapy agents for previously untreatable illnesses. These changes are reflected in the hospital and ICU patient population, with ICU admissions of longer duration and involving more complex management.

Sometimes, we lose sight of the human being behind the machines, paraphernalia and clinical syndromes. Dehumanisation tends to creep in, and can occur in many forms, including the loss of personal identity, control and privacy, all of which are significant stressors for the patient. To counter this, 'Humanising the ICU' is a relatively recent cultural swing in critical care based on a range of patient-focused behaviours and environment-related measures **(Figure 2 and 3)** (Wilson et al. 2019).

Simple measures to promote understanding of the patient as an individual and provide reminders to facilitate interaction e.g. appropriate use of glasses, hearing aids or communication aids are important.

WHAT DO WE MEAN BY
Quality Healthcare?

Quality Healthcare

Person Centred

Efficient

Effective

Safe

Timely

Equitable

Figure 1: Quality Healthcare. Source: aquanw.nhs.uk/membership/delivering-high-quality-care.htm

How to humanise the ICU

Flexible visiting hours

Open communication between patient, family and staff

More dignified end-of-life care

Focus on the well-being of the patient

Humanised approach to treating patients

Better management and less sedation
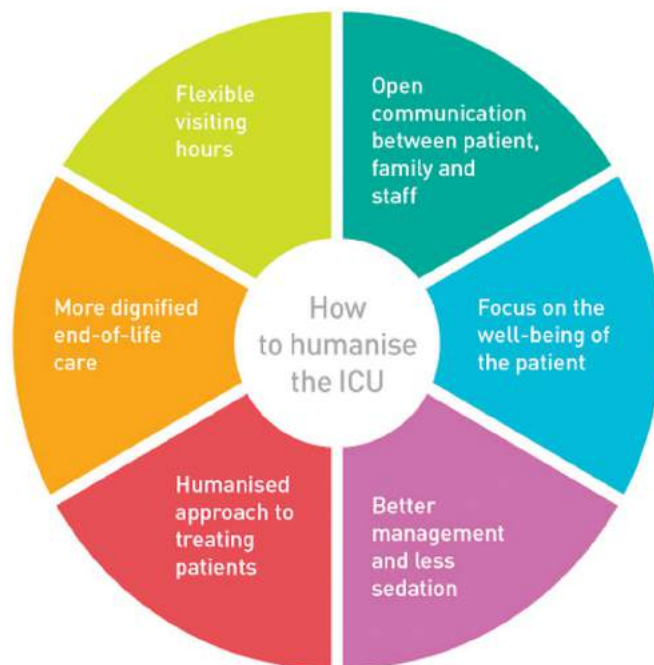
Figure 2. How to humanise the ICU

Helping the patient participate in basic self-care encourages feelings of independence and control.

Communication with patient and family is frequently challenging for various reasons, including complexity of illness, limited retention of facts and fragmented care. Multi-source input ICU diaries are increasingly recognised as a relatively inexpensive intervention to orientate and empower the family to actively communicate and support patient care, whilst helping ICU professionals identify areas requiring improvement and/or resources. Studies looking at the effect of ICU diaries on post-traumatic stress disorder have shown mixed outcomes (Jones et al. 2010; Garrouste-Orgeas et al. 2019). The implementation format, patient selection criteria and follow-up period still require further investigation. Despite this, future efforts to improve patient and family wellbeing will likely be embedded in open, transparent dialogue to help the patient make sense of the ICU experience with early family engagement in this process.

As more patients survive ICU admission, the scale of Post-Intensive Care Syndrome (PICS) and its crucial role in functional outcomes are becoming a stark reality - physical and neuropsychological (non-physical) debilitation can persist for years, with profound long-term effects on patients and carers (Rawal et al. 2017). The ABCDEF bundle consists of elements which individually and collectively reduce long-term consequences of ICU admission, improving functional outcomes (Marra et al. 2017). Early multidisciplinary rehabilitation during ICU admission, while the patient is on life-support therapies, may reduce physical and mental health impairments associated with PICS (Parker et al. 2013). Post-ICU clinics and survivor peer groups can identify patients requiring further support, although there are few evidence-based interventions for PICS.

Approximately 30% of family members can develop neuropsychological symptoms similar to PICS, often related to the severe

Dehumanisation of ICU Patients
• Loss of identity (and appearance)
• Loss of ability to communicate
• Loss of ability to advocate for oneself
• Loss of family presence
• Loss of control
• Loss of respect
• Loss of modesty/privacy
• Purposeful exploitation (e.g. for research)

Humanising Behaviours
• Unrestricted family visitation
• Knowing the patient as a person (non-medical facts)
• Physical touch (e.g. holding a hand)
• Communicate with the patient (not just about or above the patient)
• Common courtesy communication, especially to delirious/ comatose patients (introduction, explanation of what is about to happen, permission to touch)
• Attending promptly to patient needs
• Individualising communication modalities
• Giving patients some locus of control of their environment
• Use eyeglasses, hearing aids, dentures as feasible
• Personal hygiene (hair care, oral care, etc.)

Figure 3: Humanising and Dehumanising of ICU Patients

stress of having a critically ill family member and being involved in difficult decisions etc. Such families are less able to support and care for the ICU survivor, with wider repercussions on society. We anticipate that efforts and resources will be directed towards prevention and screening of ICU survivors and family members for PICS, with early referral for comprehensive multidisciplinary follow-up to support their recovery.

In some situations, preservation of life at the expense of quality of life is inappropriate. The challenge with end-of-life decisions is often identifying the point at which to stop futile measures. We believe the traditional paternalistic approach to clinical decisions will soften as we turn our focus to what really matters to the patient. Advance directives or discussions with family about the patient's values and preferences will provide guidance in the absence of capacity. End-of-life care can have significant impact on the family as well as the healthcare professionals involved. Timely involvement of palliative care specialists and support for the family at this time, as well as follow-up after bereavement are important; a good death

can be a good outcome.

> ❝❝ dehumanisation tends to creep in, and can occur in many forms, including the loss of personal identity, control and privacy, all of which are significant stressors for the patient ❞❞

The Healing Environment

Traditional ICU designs prioritise functional and logistical issues of clinical care. Restricted visiting hours, immobility and lack of privacy have been cited as significant stressors during ICU admission, compounded by environmental stressors e.g. unfamiliar and uncomfortable environment, machine alarms and light levels (Gültekin et al. 2018). Prolonged ICU admissions continually

erode the emotional and psychological reserves of patients and families.

Excessive ambient noise and light can lead to sleep disturbance and delirium, both of which are common and often co-exist in ICU patients (Cavallazzi et al. 2012). Sleep deprivation has physiological consequences including altered immune, metabolic, endocrine function, as well as effects on psychomotor performance and mood (Watson et al. 2012). It is considered a potentially modifiable risk factor for delirium which, apart from its association with increased morbidity, mortality and length of stay, is also a significant risk factor for PICS (Rawal et al. 2017).

A humanised ICU environment prioritises comfort for the patient and family, with essential clinical care designed around them. The patients are no longer nursed in bays - individual rooms provide privacy and space for visitors; visiting hours are much less restrictive to engage the family in care and support for the patient. There is emphasis on natural light during the day and limiting ambient noise. The clinical feel of the ICU is tempered with decorative art and streamlined medical equipment. An innovative example of this is presented by the consciously-designed critical care unit at King's College Hospital. Here, the patient has control of the environment, turning the bed to take in views of a park, accessing music/films and communicating with loved ones utilising monitors as video-call screens. A fully-equipped rooftop garden makes it possible for patients to be wheeled outdoors to enhance the recovery journey. The design process incorporates feedback from previous ICU patients and addresses common important issues raised, creating a healing environment for rest and recovery.

Future-Proofing the ICU Team
Staff wellbeing
The ICU environment is demanding, with difficult decisions frequently made under time pressure. Burnout is common in critical care, with a prevalence of 30-60% in ICU

professionals (Chuang et al. 2016). It did not gain prominence or invite open discussion until recently, partly because healthcare professionals are expected to be impervious to it. Crucially, burnt-out healthcare professionals are often high-functioning individuals who would have originally contributed substantially to workplace morale, productivity and improvement - the impact of burnout extends beyond the individual to affect the patients, hospital and healthcare system (Brindley 2017). In particular, desensitisation to the human aspects of patient care, which occurs as part of burnout, is counter to the goal of humanising the ICU.

The manifestation and course of burnout are variable, subjective and frequently underreported. There is no quick fix and therefore, as with most things, prevention is probably better than cure. Burnout occurs as a result of internal and external factors. Its management requires the individual to self-care, self-assess, report and seek help as appropriate but realistically, a significant part of the responsibility of burnout prevention lies with the employing organisation. Efforts to prevent burnout tend to be positive interventions that promote staff awareness and wellbeing, reinforced by strong leadership that recognises hard work, supports those that are struggling and actively listens to its employees. Several professional societies such as the Society of Critical Care Medicine and American Thoracic Society now prioritise and actively campaign for physician wellbeing. 'Resilience' is oft-quoted as the most desirable characteristic in NHS workers nowadays; resilience training is increasing in demand within NHS leadership circles (Lake 2016). This may represent the first step to make this resource widely available for healthcare workers. Borrowing from lessons learnt in other industries, a happy workforce is a high performing one and more likely to go above and beyond their specified duty (Seppälä and Cameron. 2015).

Competent management of burnout

can help reduce staff illness and turnover, enabling trained professionals to successfully remain in their chosen specialty. Since staffing is the most expensive resource in healthcare settings, the cost savings, though hard to quantify, will usually be significant.

Assembling a Multidisciplinary ICU team of the Future

Caring for the critically ill patient on ICU is the epitome of multidisciplinary teamwork. There is a move away from the hierarchical structure of the medical team towards an open, collaborative culture of healthcare

> ◀◀ **desensitisation to the human aspects of patient care, which occurs as part of burnout, is counter to the goal of humanising the ICU** ▶▶

professionals combining their skills and expertise. When faced with the shortage of ICU doctors and duration of specialist training, the creation of the critical care practitioner role (increasingly commonplace in USA) has not only provided a practicable solution to address the staffing shortfall, it has also broken down the traditional dichotomy of physician and nursing roles. This strategy produces results while challenging status quo and is an example of thinking-outside-the-box which, when appropriate, can be desirable and advantageous in various aspects of critical care practice.

Traditional forms of training mean that doctors, nurses and other allied health professionals undergo training in separate streams until qualification, beyond which they are abruptly expected to work together in a multidisciplinary ICU team. This collaboration can fail at several junctures - inefficiency, poor understanding

of colleagues' roles and responsibilities, ineffective communication etc. The logical approach to improving team performance should involve team-based training - this can take place in a realistic yet safe environment of a simulation (both high- and low-fidelity) setting. A variety of scenarios can be practised and assessed, ranging from single tasks e.g. patient intubation to complex situations e.g. managing a multi-trauma patient through the resuscitation phase into the operating room. Analogous to the seamless collaboration within the motorsport pit-team, the ICU team of the future should comprise individuals who recognise their unique roles, communicate clearly and work together confidently and synergistically.

The increasing availability and popularity of simulation workshops at international conferences and high-fidelity simulation training courses are strong indicators that the future of ICU training will be team-based. Further research into psychosocial phenomena influencing team effectiveness and a better understanding of performance indicators will give us a foundation for teamworking that is excellent not by chance, but by design (Ervin et al. 2018).

Future tools

The role of cognitive aids and tools should also be considered. Protocols, standard operating procedures (SOPs) and checklists reduce variability in practice and ensure that high-quality care and standards are consistently achieved. However, detractors argue that this approach favours data-generated guidelines over personalised care which is specifically tailored for the patient. The protocolised versus personalised approaches represent extreme ends of patient care and a happy medium is probably the best way forward. Our improved understanding of genomics and metabolomics will better equip us to personalise therapy e.g. select suitable patients for specific treatments, while

protocols and SOPs reduce cognitive demand, allowing us to focus on other important aspects of patient care (Patel and Buchman 2016).

The ICU is also becoming more reliant on computers to deliver and record care. A key issue is that the human-computer interface is rarely seamless and has lagged behind the experience in personal technology platforms such as smartphones and other consumer devices. Wasted working time due to poor user interface and/or clumsy processes is a recurring theme in healthcare. However, recent advances in digital healthcare innovation are placing more emphasis on streamlining work and increasing the efficiency of the ICU team.

Conclusion

With more patients surviving ICU admission, we have begun to appreciate the psychological impact of critical illness and its burden on ICU survivors, their families and society. We recognise that humanised ICU care and a healing environment can improve functional outcomes. There will be emphasis on quality of life, not necessarily quantity, with more research focusing on holistic patient care.

The growing complexities of critical care, unrelenting pace and expectations will take a toll on all ICU health professionals - smarter ways to train and work can improve teamworking efficiency and job satisfaction. We are more accepting of the fact that healthcare professionals are not resistant to burnout and welcome measures that promote staff wellbeing and resilience. A happy well-functioning team is far more likely to deliver an excellent quality of care.

Focusing on the human aspects of patients, family members and healthcare professionals is a significant cultural shift — this, we firmly believe, is the future of critical care. ■

Key Points

- Advances in medicine and increasingly complex procedures in frail patients are resulting in longer and more complicated ICU admissions.
- 'Humanising the ICU' reminds us to focus on the human being behind the machines, paraphernalia and clinical syndromes.
- As more patients survive ICU admission, the scale of Post-Intensive Care Syndrome (PICS) and its crucial role in functional outcomes are becoming a stark reality.
- Burnout is common in critical care, with a prevalence of 30-60% in ICU professionals.
- The growing complexities of critical care, unrelenting pace and expectations will take a toll on all ICU health professionals - smarter ways to train and work can improve teamworking efficiency and job satisfaction.

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AGENDA

For a full listing of events visit https://iii.hm/133l

OCTOBER

2-5
ANESTHESIOLOGY 2020
Virtual conference
https://iii.hm/14ri

4-7
Critical Care Canada Forum
Virtual conference
https://iii.hm/14rj

16-19
EAPS 2020 - European Academy of Paediatric Societies
Virtual conference
https://iii.hm/14rk

NOVEMBER

2-6
38th Vicenza Course on AKI & CRRT
Virtual conference
https://iii.hm/14rl

5-7
9th Annual Johns Hopkins Critical Care Rehabilitation Conference
Virtual Conference
https://iii.hm/14rm

13-15
e-SMART - 31º SMART 2020 - Anaesthesia, Resuscitation & Intensive Care
Virtual conference
https://iii.hm/14rn

19-21
WCID 2020 - World Congress on Infectious Diseases
Rome, Italy
https://iii.hm/14ro

21-22
Zagreb Spring Symposium Of Applied Cardiovascular Physiology And Treatment
Zagreb, Croatia
https://iii.hm/14rp

28-30
Euroanaesthesia 2020
Virtual conference
https://iii.hm/14rq

DECEMBER

1-4
10th World Congress of the World Federation of Pediatric Intensive & Critical Care Societies
Virtual conference
https://iii.hm/14rr

2
4th World Day of the Critical Lung
Virtual conference
https://iii.hm/14rs

5-9
ESICM LIVES 2020 - 33rd Annual Congress
Madrid, Spain
https://iii.hm/14rt

MARCH 2021

16-19
40th ISICEM
Brussels, Belgium
https://iii.hm/14ru

24-26
25th EAHP Congress - Hospital Pharmacy 5.0 - The Future of Patient Care
Vienna, Austria
https://iii.hm/14rv

29-31
9th EuroELSO Congress
Montreux, Switzerland
https://iii.hm/14rw

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