ICU

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Caring for critically ill immunocompromised patients

We can do better!

Élie Azoulay, MD, PhD, is Professor of Medicine in Specialty Pulmonary Medicine and Critical Care at Saint Louis Teaching Hospital and Université Paris Diderot in France. He is the Director of the medical intensive care unit (ICU). He leads the French programme for the care of critically ill immunocompromised patients, and is part of the national reference centre for thrombotic microangiopathies. In 2005 he established a research network, the Groupe de Recherche en Réanimation Respiratoire du patient d'Onco-Hématologie (GRRR-OH), to improve practices in critically ill patients with malignancies. GRR-OH includes more than 30 ICUs in France recruiting a high volume of immunocompromised patients. In 2014 GRRR-OH experts joined multinational experts to create the Nine-i (Caring for Critically Ill Immunocompromised Patients, Multinational Network), whose aim is to improve the care of critically ill immunocompromised patients. Professor Azoulay is also Director of the French FAMIREA study group aimed at improving effectiveness of communication with family members of ICU patients. He serves as Editor-in-Chief of *Intensive Care Medicine*.

What are the major challenges in treating critically ill immunocompromised patients?

Thank you for starting with the most important question. It is now demonstrated that critically ill immunocompromised patients are sicker and exhibit higher mortality rates compared to general intensive care unit (ICU) patients. However, managing these patients requires some knowledge related to the underlying disease (this group is highly heterogeneous), related treatments (time before effectiveness, patterns of toxicity, alternative regimen), specific emergencies (i.e. tumour lysis syndrome, cytokine releasing syndrome or acute humoral rejection), or specific clinical vignettes (febrile neutropenia).

There are two other challenges in treating immunocompromised (IC) patients: the first is to know how to work closely with referring clinicians (haematologists, oncologists, transplant specialists), and the second is to apply to IC patients all recent diagnostic and therapeutic advances validated in non-IC patients (in studies where IC patients were mostly excluded).

Is it clear which immunocompromised patients will benefit from intensive care?

Let me answer the other way. It is clear that some patients cannot benefit from intensive care. These are patients who have a very poor performance status (bedridden or dependent) and those in whom no lifespan expanding therapy is available. Here, patients have to be managed together with the palliative care team, and ICU admission is non-beneficial. In all other situations, ICU management can benefit immunocompromised patients, but the goals of care are of course different from one situation to another.

When you look at 100 patients, who are admitted to our ICUs, 80 have a full code status, 15 are undergoing a time-limited trial, and 5 may have other goals such as palliative ICU admission (noninvasive ventilation or high flow oxygen in patients who are 'Do Not Intubate') or exceptional ICU admission (patients with advanced disease receiving newly released biotherapy, immunotherapy or any targeted therapy).

When should immunocompromised patients be admitted to ICU?

Patients should be admitted early enough to be able to undergo a noninvasive diagnostic or therapeutic strategy. Several studies have shown that delayed ICU admission was associated with higher mortality. For example, in a study from our group, mortality doubled from 20 to 40% in patients who were admitted after day 3 of the onset of the acute respiratory failure (Mokart et al. 20013).

Are there adequate triage criteria?

Triage criteria are not reliable and clinicians need to be aware that patients with limited goals of care can benefit from ICU admission, even when it comes to outcomes such as

mortality or quality of life. At the same time, studies have shown that when death occurs in the ICU, both patient and family burden are among the highest possible. Thus we do not encourage ICU admission for patients with irreversible conditions or when death is the only expected outcome.

Should there be guidelines?

It is certainly time to release international guidelines for the standard of care to manage critically ill immunocompromised patients; nothing is available to date.

What has led to improved care of immunocompromised patients?

I would classify these into three different domains:

Advances in the care of IC patients overall

We know that the number of averted deaths from cancer is huge and increasing: today 5% of the population is a cancer survivor. The number of new steroid-sparing agents in transplantation, chronic inflammatory or autoimmune diseases is growing, so that these diseases are much better controlled.

Advances in the management of general ICU patients

We are all enthusiastic for positive trials and are upset when physiology or observation-driven interventions fail to improve outcomes. Nevertheless, over the last two decades, adjusted mortality has decreased in patients with acute respiratory distress syndrome (ARDS), sepsis or acute kidney injury (AKI). However, with changing definitions of ICU syndromes and varying case mix, this remains controversial.

Several advances in the ICU management of IC patients have translated into improved survival.

Namely, noninvasive diagnostic and therapeutic strategies have allowed faster and safer management of patients with acute respiratory failure, typhlitis or other sources of sepsis. Also, a better understanding of organ dysfunction at the earliest phase of haematological malignancies has helped manage the patients with a more targeted way. Other advances include early admission to the ICU, antibiotic stewardship, antifungal prophylaxis, management of drug-related toxicity etc.

What can further improve outcomes for and survival of immunocompromised patients? What should the research priorities be?

There is a large margin for improvement. For instance, we can expect a lot from diagnostic strategy in acute respiratory failure, from fluid management, antibiotic de-escalation and combination, transfusion policies, as well as for specific management of patients with neutropaenia and sepsis from undetermined source. We should move away from ideas that oxygenation and ventilation management are going to save lives, that intubation is always mortal, or that the ICU is a bad place to start chemotherapy. In the September issue of *Intensive Care Medicine* we published a research agenda in oncology and haematology patients (Azoulay et al. 2017). Worldwide experts have shared their opinions about research priorities in this area of critical care, and this review article summarises these issues very well.

> “patients should be admitted early enough to be able to undergo a noninvasive diagnostic or therapeutic strategy”

Should immunocompromised patients be treated only at high-volume centres?

The answer has to be no. For several reasons. First, with the growing number of cancer survivors and the numerous toxic events with immunotherapy, it is likely that the number of cancer patients admitted to the ICU will grow significantly. Also, in patients with transplants or chronic inflammatory diseases, age increases steadily over time. Overall, every ICU clinician should acquire skills to manage IC patients. We are now developing a telemedicine programme where experts guide management of patients remaining in low-volume centres. In the close future, alternatives to patients' referral to high-volume centres will develop. Everything should be done to maintain patients where they are, unless of course they need to receive urgent chemotherapy and the centre cannot do it, or if it's a complication related to the transplant, in which case the patient needs to be transferred to the referring centre.

How can oncologists, haematologists, infectious disease specialists and intensivists best work together for better outcomes for immunocompromised patients?

They are committed to do so. They have the same goals: improving the care of IC patients, and not only when they become critically ill. They have to learn from each other and develop collaboration in both clinical and translational research. A paper from Brazil that was published last year reported that when haematologists, oncologists, clinical pharmacists and intensivists were working closely together and discussing the patient's management on a daily basis, this was associated with reduced mortality (Soares et al. 2016). Over the last few years, critical care management of IC patients at high risk of being critically ill has become the rule. This is true at the earliest phase of sepsis and of respiratory events; it is also true in patients with high tumour burden such as hyperleukocytic leukaemia or bulky lymphoma and with the fantastic expansion of targeted therapies.

Are intensivists well-prepared for this increasing group of patients—is current training and education sufficient?

There is an increasing awareness that among patients admitted to the ICU, the first comorbidity will be cancer and other sources of immunosuppression. Critical care curricula are increasingly including specific training. Also ICU specialists are seeking to improve their skills managing these patients. Last, it is very likely that in the hospital of tomorrow, hospital wards and specialists will not be able to manage high-risk patients. ICU specialists will have to learn and to be prepared.

The Efraim cohort study found an association between failure to identify acute respiratory failure (ARF) aetiology and higher rates of intubation and mortality. Please comment.

The Efraim study was a fantastic collaborative work from the Nine-I (Azoulay et al. 2017b). 1611 acute respiratory failure (ARF) patients from 16 countries (68 ICUs) were enrolled and followed until day 28. This study

is unique for several reasons: it is the only multinational study on ARF in immunocompromised patients and is the largest study to date. It is a high-quality study with few missing variables and the analysis allowed identification of both risk factors for intubation and mortality. The finding that oxygenation/ventilation strategies have no impact on mortality, but that ARF from undetermined aetiology is associated with both intubation and mortality, allows appraisal of the literature and putting the patient at the right place. It opens avenues for further research. In addition to this published paper, several substudies are about to be submitted.

The Early non-invasive ventilation for acute respiratory failure in immunocompromised patients (IVNIctus) randomised controlled trial appeared to rule out noninvasive ventilation as a therapy for immunocompromised patients with acute respiratory failure (ARF), although the study was underpowered. Please comment.

This multicentre randomised controlled trial (RCT) published in 2015 showed no benefit (and no harm) from noninvasive ventilation (NIV) in IC patients with ARF (Lemiale et al. 2015). It helps to reserve NIV to hypercapnic ARF and pulmonary oedema. We are not using NIV anymore in hypoxaemic ARF, more especially now that in more hypoxaemic patients the Frat trial (Frat et al. 2015) and the Lungsafe study (Bellani et al. 2016) both reported that in the most severely hypoxaemic patients NIV was associated with mortality. We then do not recommend the use of NIV in immunocompromised patients with hypoxaemic ARF. We also do not consider that NIV is a safe comparator in trials. We state so, being aware that perhaps the use of continuous NIV, or continuous positive airway pressure (CPAP) using the helmet, may be beneficial for some patients. Until large studies have demonstrated benefits from these techniques, we recommend not delaying intubation in patients failing standard or high flow oxygen.

What is the HIGH trial A Randomised Controlled Trial of High-Flow Nasal Oxygen Versus Standard Oxygen Therapy in Critically Ill Immunocompromised Patients (HIGH) designed to investigate?

We have just ended recruitment in the HIGH trial (NCT0273945 - **clinicaltrials.gov/ct2/show/record/NCT02739451**. In this trial that recruited 778 patients from 31 ICUs in France standard oxygen was compared to high flow oxygen. The primary endpoint is day 28 mortality. ■

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Abbreviations

ARF acute respiratory failure
IC immunocompromised
ICU intensive care unit
Nine-i Caring for Critically Ill Immunocompromised Patients Multinational Network
NIV noninvasive ventilation
RCT randomised controlled trial