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Paradigm Shift in ICU Candidacy for Allogeneic Hematopoietic Stem Cell Transplantation: Who, When, and How Long?

The past 2 decades have seen a paradigm shift in oncologic critical care mortality. Given the therapeutic revolution in cancer care, advancements in infectious disease practices, and progress in the critical care management of immunocompromised patients, candidacy for ICU admission across patients with cancer has become a debate of the past. However, the one population that has not shared the same degree of progress has been recipients of allogeneic hematopoietic stem cell transplantation (allo-HSCT).

Allo-HSCT is a commonly used treatment for different types of hematologic malignancies (1). Patients undergoing allo-HSCT may present several complications, some of which may lead to severe organ dysfunction requiring ICU admission. Historically, these patients had unfavorable prognoses, particularly in the setting of invasive mechanical ventilation, leading to a sentiment of pessimism surrounding their candidacy for ICU admission (2). Although the advances in therapeutic approaches—within both hematology and critical care—have improved their prognosis, thus facilitating access to ICU interventions, they have remained a persistently vulnerable population in the face of critical illness. As such, they have not experienced outcomes as favorable as their other oncology counterparts. Furthermore, preliminary data across patients with hematologic malignancies who survive ICU admission have shown important long-term functional disability and impairment in emotional, physical, and general well-being (3).

It is important to highlight, however, that this population can have great heterogeneity in their ICU outcomes because of frailty and disease status at the time of transplant (3), the specific time period after transplant (governed by distinct mechanisms and depths of immunosuppression) (2), unique allo-HSCT conditions, and graft function (2). Increasingly, we are recognizing that analyzing all critically ill patients receiving allo-HSCT as one entity will not capture their individualized prognosis, as their trajectory and outcomes are much too nuanced.

In this issue of the *Journal*, Lafarge and colleagues (pp. 1017–1024) presented the outcomes of more than 1,000 patients who received allo-HSCT across 14 French ICUs (4). Being one of the largest contemporary studies of this population in the face of critical illness, the study provides valuable insights and raises meaningful considerations for patients undergoing allo-HSCT. First, at ICU admission, 66% of patients presented with multiple organ dysfunction, with acute respiratory failure being the most common complication. Second, a significant proportion of patients survived their ICU stay, with a 90-day survival rate exceeding 50%. Third, it captures the clinical heterogeneity of this population that can impact the variability in their outcome trajectories based on various important factors after transplant. Several determinants of mortality were described, including age, timing of ICU admission relative to transplantation, corticosteroid-refractory acute graft-versus-host disease (aGVHD), and the use of life-sustaining interventions, such as mechanical ventilation and the need for vasopressors. Within patients requiring invasive mechanical ventilation, mortality rates increment based on the presence and number of particular risk factors (namely, age $>$ 56 yr, 30–90 d after transplant, corticosteroid-refractory aGVHD, and the use of vasopressors). Similarly, patients who needed mechanical ventilation, vasopressors, and renal replacement therapy had a 90-day mortality of around 90%, regardless of the presence of aGVHD.

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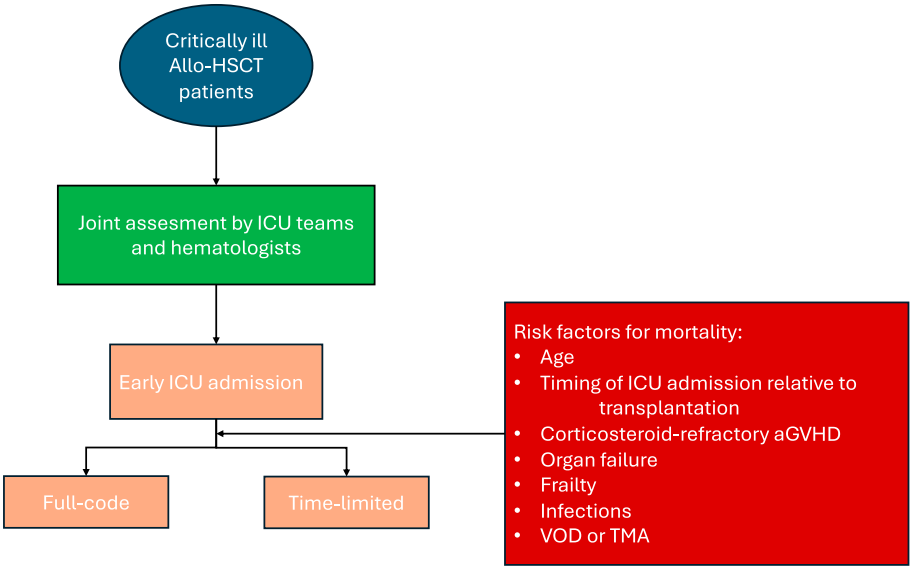

Figure 1. Clinical decision-making processes in critically ill patients receiving allo-HSCT. aGVHD = acute graft-versus-host disease; allo-HSCT = allogeneic hematopoietic stem-cell transplantation; TMA = thrombotic microangiopathy; VOD = venoocclusive disease.

Notably, the study was conducted in a large multicenter population, and it provides a pragmatic approach for assessing the prognosis of allo-HSCT recipients who develop critical illness. These findings enable a personalized strategy for treating these patients according to the number of organ failures, demographics, time after transplant, and aGVHD characteristics. Patients who have only one organ failure upon ICU admission would benefit from a full-code admission. On the other hand, those patients who have more than two organ failures would benefit from a short full-code trial (i.e., 72 h), followed by continuous reevaluation to determine whether life-sustaining interventions should be discontinued.

Important limitations to this study that could further enhance personalized decisions and help distinguish those who may or may not benefit include the incorporation of frailty status (3), the presence of invasive fungal infections or viral infections (5, 6), the presence of conditions associated with endotheliitis (e.g., venoocclusive disease, thrombotic microangiopathy after transplant) (7), center-volume effect, and optimal duration of time-limited trials. Furthermore, understanding long-term functional and cognitive status would be an important consideration for future studies. Importantly, external prospective validation of these findings will be needed to ensure their generalizability.

Nevertheless, these findings have important implications. This research exemplifies the importance of a data-driven approach to critical care for allo-HSCT recipients incorporating distinct characteristics. The detailed multivariable analysis conducted by the authors aids in not only understanding the complex interplay of risk factors but also delineating clear targets for improving clinical practices and patient outcomes. Although the timing of ICU admission (early or late) was not specifically measured, it is likely that implementing standardized protocols that emphasize early intervention could revolutionize outcomes and optimize resource allocation in ICUs. Centers should implement local guidelines that define specific admission ICU criteria for allo-HSCT recipients. In addition, collaborative patient evaluation, in the ward and during their ICU stay, by both hematologists and intensivists should be implemented. This would enable the early identification of those patients at risk of deteriorating, assuring their immediate transfer to the ICU, which may lead to improved outcomes. For certain patients, conducting time-limited trials in the ICU with predetermined criteria for not increasing treatment, such as do-not-intubate or do-not-resuscitate orders, may be a suitable choice until a final decision is made (Figure 1).

As we move forward, it is crucial for ICU teams and hematologists to integrate these insights into their clinical decision-making processes. The road ahead involves embracing these new paradigms and continuing to challenge our assumptions with solid research and reflective practice. This will be the only way to improve the outcomes of these patients and to efficiently use the healthcare resources. ■

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Air Pollution and Bronchitis: Childhood Exposure, Lifelong Consequences

Cough and mucus hypersecretion are common respiratory symptoms in adults. Persistence of these symptoms, driven by chronic airway epithelial inflammation and mucus metaplasia, can lead to a diagnosis of chronic bronchitis, a condition associated with reduced quality of life, increased risk for chronic obstructive pulmonary disease (COPD), and higher mortality rates (1). Exposure to air pollution has been linked to a higher prevalence and incidence of chronic bronchitis and bronchitic symptoms in adults (1–3). The adverse effects of air pollution on the lungs are linked to diverse pathogenetic processes, including the activation of proinflammatory signaling cascades in airway epithelial cells and the generation of reactive oxygen species (1).

There is increasing awareness that chronic diseases have their origins early in life. Childhood disadvantage factors, including maternal smoking, can accelerate lung function decline and increase COPD risk (4). Lifelong consequences of early-life air pollution exposure have been documented for several respiratory outcomes. The Dutch Prevention and Incidence of Asthma and Mite Allergy (or, PIAMA) study found a higher incidence of asthma up to age 20 in children and young adults who were exposed to higher levels of air pollution at their birth residential address (5). Higher exposures to particulate matter with an aerodynamic diameter $\leqslant$2.5 μm ($PM_{2.5}$) and ozone (O_3) in the first decade of life were related to increased asthma attacks in the Respiratory Health in Northern Europe, Spain and Australia (RHINESSA) study, which was performed in North European countries with low to moderate air pollution levels (6).

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Research conducted in diverse populations (Poland, Sweden, Norway, and Australia) using various study designs indicates that childhood air pollution exposure can lead to lower FEV_1 and FVC in adolescence and young adulthood (6–9). The FEV_1/FVC ratio appears to be less affected by air pollution (7, 9), suggesting an early alteration of lung development that tracks with age rather than faster lung function decline. With regard to low lung function, the Swedish BAMSE study identified the first year of life as a period of greater susceptibility compared with ages 1–8 years and 8–16 years (8).

In this issue of the *Journal*, Garcia and colleagues (pp. 1025–1034) advance our understanding of how early life exposures impact respiratory health in adulthood (10). They investigated the association between childhood air pollution exposure and the risk of reporting bronchitic symptoms in adult life. The study sample consisted of 1,308 individuals (mean age in yr: 32 $\pm$ 5), from 16 southern Californian communities, who took part in an online follow-up survey. These were part of the 2,267 participants in the Southern California Children's Health Study, originally recruited when they were 5 to 10 years old and previously assessed up to the age of 17 $\pm$ 2 years. The authors reconstructed residential histories and assigned annual exposures to particulate matter with an aerodynamic diameter $\leqslant$10 μm (PM_{10}) and nitrogen dioxide (NO_2) (daily 24-hour mean concentrations), and to O_3 (daily maximum 8-hour mean concentrations) to the geocoded addresses. Mean exposures to air pollutants were 41.9 μg/m^3 for PM_{10}, 26.1 ppb for NO_2 (U.S. Environmental Protection Agency standard: 49.1 μg/m^3), and 49.1 ppb for O_3 (96.7 μg/m^3), largely exceeding the annual air quality guideline levels recommended by the World Health Organization in 2021 (11).

Approximately 25% of adult participants reported having had one or more of four bronchitic symptoms. Of them, 62% reported usual congestion in the chest or bringing up phlegm; bronchitis or persistent cough in the morning or at other times of the day