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Review

Oxygenation strategy during acute respiratory failure in immunocompromised patients

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ABSTRACT

Acute respiratory failure (ARF) in immunocompromised patients remains challenging to treat. A large number of case require admission to intensive care unit (ICU) where mortality remains high. Oxygenation without intubation is important in this setting. This review summarizes recent studies assessing oxygenation devices for immunocompromised patients. Previous studies showed that non-invasive ventilation (NIV) has been associated with lower intubation and mortality rates. Indeed, in recent years, the outcomes of immunocompromised patients admitted to the ICU have improved. In the most recent randomized controlled trials, including immunocompromised patients admitted to the ICU with ARF, neither NIV nor high-flow nasal oxygen (HFNO) could reduce the mortality rate. In this setting, other strategies need to be tested to decrease the mortality rate. Early admission strategy and avoiding late failure of oxygenation strategy have been assessed in retrospective studies. However, objective criteria are still lacking to clearly discriminate time to admission or time to intubation. Also, diagnosis strategy may have an impact on intubation or mortality rates. On the other hand, lack of diagnosis has been associated with a higher mortality rate. In conclusion, improving outcomes in immunocompromised patients with ARF may include strategies other than the oxygenation strategy alone. This review discusses other unresolved questions to decrease mortality after ICU admission in such patients.

Introduction

The number of immunocompromised patients is increasing steadily, mainly due to therapeutic progress that has resulted in an improvement in their survival and quality of life [1]. These patients may encounter several life-threatening complications warranting intensive care unit (ICU) admission. Among them, acute respiratory failure (ARF) is common and remains the most frequent reason for ICU admission in immunocompromised patients [2–7]. Of patients with the hematologic disease, 10–30% may have a severe respiratory event at the onset or during treatment of their disease [8]. This number can be much higher (almost 50%) for patients with acute myeloid leukemia [2,9] and those with lung tumors (25–30%) [10]. For other patients, the incidence of ARF depends on the underlying disease, immunosuppression, and comorbidities [8].

ARF is a severe complication, associated with a mortality rate of around 50% [5,6,11]. In the TRIALOH observational cohort that included >1000 patients with an hematological malignant disease, ICU admission for ARF was strongly associated with in-hospital mortality [1]. Although significant medical progress has been made [7,12,13], ARF remains a challenging situation for physicians, both in terms of etiological diagnosis and choice of optimal oxygenation strategy. In these patients, in particular, invasive mechanical ventilation (IMV) has been associated with poor prognosis [1,13–15], especially because of a higher risk of infectious complications than in non-immunocompromised patients [16]. As a result, avoiding IMV has become a priority.

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The first strategy used to avoid IMV is non-invasive oxygenation as standard oxygen, non-invasive ventilation (NIV), or humidified high-flow nasal oxygen (HFNO). These devices have been developed over the past 20 years. Nevertheless, the application of each device is still debatable in the setting of immunocompromised patients.

The purpose of this narrative review is to describe the role of each oxygenation strategy in immunocompromised patients with ARF.

Literature Search Strategy

We searched Medline via PubMed by using a combination of specific keywords and free text words including the following: "immunocompromised patients," "immunosuppression," "acute respiratory failure," "ARF," "non-invasive ventilation," "high flow nasal cannula," "HFNO," "ICU," and "intensive care." The search was restricted to articles published in English, between January 1, 2000, and March 31, 2021. The last search was performed on April 15, 2021.

Role of NIV

NIV was first used for the management of patients with chronic obstructive respiratory failure (COPD) [17] and cardiogenic pulmonary edema [18]. In these studies, NIV provided several benefits for respiratory mechanics, as it could decrease inspiratory work, decrease atelectasis, and improve oxygenation [19]. Moreover, non-intubated patients had a lower risk of hospital-acquired infection [20]. For these reasons, NIV was then used in hypoxemic patients without pre-existing pulmonary pathology [21], namely "*de novo* ARF," to reduce the intubation rates [19]. In immunocompromised patients, the risk of infection and mortality under IMV was so high that, in cases of "*de novo*" respiratory failure, NIV has been used as an alternative to intubation for several years.

The role of NIV in immunocompromised patients was first assessed in the early 2000s. In that period, the intubation rate of such patients admitted to the ICU was almost 80%, and the mortality rate of intubated patients was nearly 90% [14]. In the early 2000s, two randomized controlled trials showed a real benefit of NIV use on hospital mortality. Indeed, the results of a study on 52 immunocompromised patients, randomized between a group receiving NIV and a group receiving only oxygen [22], were strongly in favor of the use of NIV. Another randomized controlled trial on 40 patients with solid organ transplant admitted with ARF and treated with NIV or oxygen confirmed these results [23]. At that time, NIV, when used to avoid intubation, drastically reduced the mortality rate. However, the intubation rate and mortality of immunocompromised patients who need IMV have decreased in more recent years [14]. Thus, the use of NIV and intubation criteria have been modified in the recent period for such patients [3,6,7,14,16,24].

Since 2001, several studies have assessed the impact of NIV [Table 1]. Most have confirmed that NIV success (e.g., without intubation) was associated with a decreased mortality rate. However, intubation after NIV failure was associated with a higher mortality rate, even higher than the one after first-line IMV [25–29]. Further, NIV failure seemed to be more frequent in immunocompromised patients than non-immunocompromised patients [28]. However, a recent analysis using propensity scores did not confirm a higher risk of NIV failure owing to immunosuppression itself [30].

In 2015, a study randomized 374 immunocompromised patients with ARF into a group receiving NIV and a group receiving oxygen. The primary outcome was the 28-day mortality rate. Nearly 40% of total population required intubation during the ICU stay. Mortality rates on day 28 for the standard oxygen and NIV groups were 27% and 24%, respectively ($P = 0.43$). The study did not show any other differences between the two groups of patients with respect to intubation rates and mortality of intubated patients [31]. A *post hoc* analysis from another recent randomized controlled trial confirmed the lack of benefit of NIV for immunocompromised patients [32]. In other words, these recent studies demonstrated that NIV failure is common and leads to intubation for 40–50% of such patients; in recent years, the intubation rate of immunocompromised patients admitted to the ICU for ARF has been closer to 40%; and NIV is no longer associated with a decreased mortality rate in hospitals or ICUs after adjustment for severity criteria [33,34].

For these reasons, and considering the lack of comfort of NIV related to the mask, frequent leaks, and invasive pressure [21], the use of NIV for immunocompromised patients cannot be strongly recommended [35]. If an NIV trial is performed, intensivists should be aware of the high risk of NIV failure.

Role of HFNO

Unlike standard oxygenation systems, HFNO allows constant FiO2, since the gas flow rate delivered is at least equal to the patient's inspiratory flow rate [36,37]. In addition, the high flow rates of inspired gasses create a positive pressure in the airways owing to the Venturi effect, which improves oxygenation and decreases inspiratory work. Physiological studies evaluated this positive pressure to be up to 3.3 ± 1.1 cm H2O [38]. This pressure was largely dependent on the gas flow through the system and whether the patient's mouth was opened or closed [37–39]. Moreover, this system allows a constant renewal of gas in the dead space leading to a decrease in PCO2 [39]. Finally, the use of HFNO seemed more comfortable than that of NIV owing to the absence of a nasal–oral mask, and was superior to standard oxygenation because of the humidification of the inspired gasses [40]. For these reasons, the device seemed suitable for immunocompromised patients in whom intubation was associated with a high mortality rate.

Studies from non-immunocompromised patients confirmed that HFNO leads to an improvement in respiratory parameters [41–43], comfort [40], and outcome [44]. The comfort of the device has been highlighted in several studies [45]. However, in an immunocompromised setting, a randomized controlled trial comparing comfort, dyspnea, and thirst in 100 patients receiving either a Venturi mask or HFNO for 2 h failed to demonstrate any benefit of HFNO use [46].

Before 2018, studies including immunocompromised patients were scarce. Most were observational or retrospective studies [Table 2]. In 2011, a feasibility study assessed the use of HFNO in 132 patients with solid tumors. Respiratory signs improved without intubation for 41% of patients, were stable for 44%, and required intubation for 15% [47].

Table 1
Studies comparing outcomes related to NIV vs. standard oxygen in immunocompromised patients.

Author	Resource (journal, year)	Study design	Inclusion criteria	Primary objective	Oxygenation devices use, NIV/O_2/IMV first line (*n*)	Failure rate			Mortality			Global mortality after intubation
						NIV group	O_2 group	*P*-value	NIV group	O_2 group	*P*-value	
Antonelli et al. [23]	JAMA, 2000	Randomized	Solid organ transplant	Intubation rate	20/20/NA	20%	70%	0.002	20%	50%	0.005	77.7%
Hilbert et al. [22]	NEJM, 2001	Randomized	All IC patients	Intubation rate	26/26/NA	46%	77%	0.03	50%	81%	0.02	87%
Azoulay et al. [24]	CCM, 2001	Retrospective	Hematological malignancy	D30 mortality	48/0/48	56%	NA	NA	43%	NA	NA	70%
Azoulay et al. [81]	Medicine, 2004	Retrospective	Hematological malignancy	Hospital mortality	79/NA/55	56%	NA	NA	48%	NA	NA	75%
Depuydt et al. [3]	Chest, 2004	Retrospective	Hematological malignancy	Hospital mortality	27/NA/52	69%	NA	NA	65%	NA	NA	71%
Principi et al. [82]*	ICM, 2004	Retrospective (Helmet vs. CPAP)	Hematological malignancy	Hospital mortality	17 helmet/17 CPAP */NA	0	41%*	<0.01	23%	47%*	<0.05	87%
Rabitsh et al. [83]	Leuk Lymph, 2005	Retrospective	Stem cell transplant	Intubation	35/NA/47	68%	NA	NA	80%	NA	NA	100%
Squadrone et al. [84]	ICM, 2010	Randomized	Hematological malignancy	ICU admission	20/20/NA	10%	70%	<0.001	15%	75%	<0.001	100%
Depuydt et al. [85]	JCC, 2010	Retrospective	Hematological malignancy	Hospital mortality	30/107	75%	69%	NA	75%	66%	NA	80%
Canet et al. [86]	Crit Care, 2011	Retrospective	Kidney transplantation	Hospital mortality	64/77/59	53%	43%	NA	23%	22%	NA	41%
Wermke et al. [87]	BMT, 2012	Randomized	Stem cell transplantation	D100 mortality	42/44/NA	14%	25%	NA	61%	68%	NA	100%
Molina et al. [88]	Crit Care, 2012	Prospective cohort	Hematological malignancy	ICU mortality	131/NA/169	60%	NA	NA	65%	NA	NA	75%
Turkoglü et al. [89]	Hematology, 2013	Retrospective	Hematological malignancy	ICU mortality	46/NA/21	78%	NA	NA	74%	NA	NA	86%
Azevedo et al. [13]	Chest, 2014	Propensity score	Hematological malignancy	Hospital mortality	85/NA/178	48%	NA	NA	55%	NA	NA	71%
Lemiale et al. [90]	AOIC, 2015	Propensity score	Hematological malignancy	Hospital mortality	55/55/NA	29%	25%	0.67	27%	20%	0.37	66%
Lemiale et al. [31]	JAMA, 2015	Randomized	All IC patients	D28 mortality	191/183/NA	38.2%	44.8%	0.20	24.1%	27%	0.47	49.7%

* This study compared NIV with Helmet or CPAP through a facial mask.CPAP: Continuous positive airway pressure; ICU: Intensive care unit; NA: Not available; IMV: Invasive mechanical ventilation; NIV: Non-invasive ventilation.

Table 2
Studies comparing outcomes related to HFNO *vs.* NIV or standard oxygen in immunocompromised patients.

Authors	Resource (journal, year)	Design	Patients	Primary outcome	Oxygenation devices use, HFNO/NIV/O_2/HFNO+NIV (*n*)	Mortality rate				Mortality rate of intubated patients
						HFNO	NIV	O_2	NIV+HFNO	
Mokart et al. [91]	ICM, 2015	Propensity score	Cancer	D28 mortality	69 all devices *vs.* 69 HFNO+VNI	54%			36%	62%
Roca et al. [92]	Transplantation, 2015	Retrospective	Lung transplant	Intubation	22/NA/18/NA	50%	NA	83%	NA	79%
Coudroy et al. [50]	AIC, 2016	Propensity score	All kinds of ID	D28 mortality	33/24	15%	42%	NA	NA	59%
Frat et al. [93]	Lancet Respir Med, 2016	Ancillary of a randomized study	All kinds of ID	Intubation	26/NA/30/26	15%	NA	27%	46%	55%
Tu et al. [53]	Transplant Proc, 2017	Retrospective	Kidney transplant	Intubation	20/18/NA/NA	20%	50%	NA	NA	13%
Lemiale et al. [52]	CCM, 2017	Ancillary of a randomized study, propensity score	All kinds of ID except HIV	D28 mortality	90/NA/90/NA	23%	NA	21%	NA	45%
Azoulay et al. [16]	ICM, 2017	Prospective	All kinds of ID except HIV	Intubation	182/136/466/75	38%	39%	35%	38%	56%
Azoulay et al. [94]	JAMA, 2018	Randomized	All kinds of ID except HIV	D28 mortality	388/NA/388	36%	NA	36%	NA	53%

HFNO: High-flow nasal oxygen; HIV: Human immunodeficiency virus; ID: Infectious disease; NA: Not available; NIV: Non-invasive ventilation.

Another observational study on 45 patients conducted in 2015 showed that HFNO improved oxygenation and avoided intubation for 33% of patients. Furthermore, the mortality of patients treated with HFNO was lower than that of intubated patients [48].

Retrospective studies comparing HFNO and standard oxygen in this setting were controversial, showing either a reduction in intubation rates [49–51] or no differences [52]. Compared with NIV, HFNO use did not reduce intubation rates in one study with solid organ transplant patients [53], whereas the intubation rate in the HFNO group was lower than the NIV group in a *post hoc* analysis of a randomized study [51].

A 2018 study on 776 ICU-admitted immunocompromised patients who received HFNO or standard oxygen for ARF did not show any differences in the 28-day mortality rates [54]. The included patients were immunocompromised as a result of malignancy, solid organ transplant, or immunosuppressive treatment. The primary outcome was the 28-day mortality rate. No differences were found concerning other outcomes such as intubation rates, hospital-acquired infection, or mortality of intubated patients.

A recent meta-analysis including all these studies found a reduced intubation rate in patients receiving HFNO. However, this reduction did not translate into an improved survival rate [55]. Moreover, reported cases have raised the question of late failure leading to a higher risk of mortality [56]. Again, when using HFNO, the intensivist should bear in mind the high risk of mortality after late failure and the extended duration of the HFNO trial [14,56].

When is intubation required?

Among intubated patients, the risk of ventilator-associated pneumonia is higher in immunocompromised patients than non-immunocompromised patients [57]. However, ventilator-associated pneumonia remains common and some patients may develop more specific infections such as fungal infection, which is associated with a high mortality rate [58]. Most patients go on to develop acute respiratory distress syndrome (ARDS). In such patients, ventilatory rules concerning ARDS in non-immunocompromised patients should be applied. A recent study from the EFRAIM cohort demonstrated the impact of driving pressure and plateau pressure on hospital mortality. This impact was independent of the severity of ARDS (e.g., Berlin score), but was as high as the impact of the presence of other organ failure or the lack of etiological diagnosis for ARF [59]. Interestingly, in this study, neutropenia and underlying immunosuppressive disease were not associated with mortality. In a recent observational study of ARDS patients, immunocompromised and intubated patients could be managed with the same procedures as non-immunocompromised patients. Nevertheless, hospital mortality was higher in immunocompromised patients than in immunocompetent patients (52% *vs.* 36%) [28]. Additionally, the high rate of hospital mortality in immunocompromised patients may be ascribed to a higher rate of invasive fungal infection in this particular setting of ARDS [60,61].

Non-invasive oxygenation devices alone do not decrease mortality

As described above, the prognosis of immunocompromised patients with ARF has improved over the last decades. Although

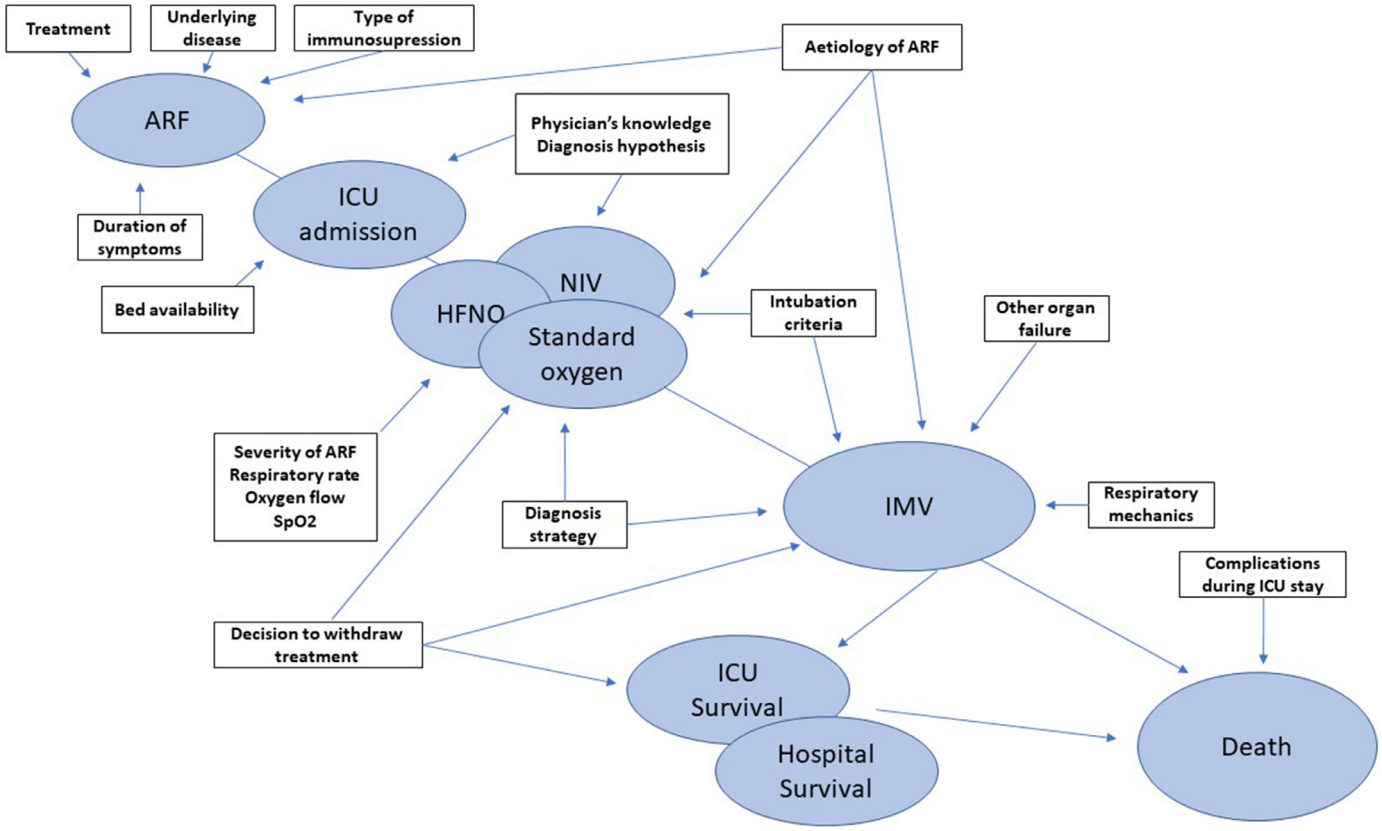

Fig. 1. Factors potentially influencing the outcome of immunocompromised patients with ARF eventually admitted to the ICU. ARF: Acute respiratory failure; HFNO: High-flow nasal oxygen; ICU: Intensive care unit; IMV: Invasive mechanical ventilation; NIV: Non-invasive ventilation; SpO2: Oxygen saturation.

the meta-analyses of recent studies in that setting have shown a reduction in intubation rate with HFNO [55,62,63], none of the first-line oxygenation strategies demonstrated any reduction in mortality rate [16].

Some factors could explain these results.

First, although mortality is an important endpoint, several factors could influence the mortality, such as patient severity at baseline, recruiting centers' experience, ICU practices, and end-of-life decisions, which sometimes make it difficult to understand the treatment effect [Fig. 1]. As shown in Fig. 1, patients may follow complicated trajectories during the ICU course and later, of which oxygenation strategies are only a part. Further, endpoints such as late mortality could only partially reflect the effect of initial oxygenation strategies.

Second, the immunocompromised population comprises a heterogeneous group of pathologies with important variability in ARF etiologies and outcomes [31,54]. Indeed, the heterogeneity of this population was illustrated in a recent study on the risk of intubation. In a cohort of 649 patients with ARF, we found that in addition to baseline severity, intubation risk varied across ARF causes [34]. This is an important point because the same oxygenation strategy is usually used in studies (as in clinical practice) without any distinction of the clinical and radiological characteristics or the reason for ARF. Currently, data are lacking to identify the predictive criteria of failure and therefore the elements to guide the choice of a strategy according to the patient characteristics. Only trials with adaptive design may potentially identify which patient could benefit from a given diagnostic or therapeutic strategy, as well as a better stratification of specific risks through machine-learning advances.

Taken together, the most recent data are now suggesting that the strategies to improve survival should not target only oxygenation and ventilation strategies. These strategies must be included in a multimodal approach, including the optimal diagnostic strategy and ideal prevention of ICU-acquired events.

Unresolved questions in decreased mortality in immunocompromised patients with ARF

Early admission

Identifying patients at high risk for subsequent aggravation and reducing the delay of ICU admission could be an interesting way to improve patient prognosis. For example, in the TRIALOH cohort [1], 56.8% of hematological patients were classified as high-risk patients at ICU admission (e.g., without any organ failure), but 20% died in the ICU within 28 days [64].

Early ICU admission policy has been evaluated in some case-control studies, at first in specific settings such as acute leukemia or post-chemotherapy neutropenia [65–67], with promising results. A recent meta-analysis, with a high level of heterogeneity, concluded that early ICU admission was associated with a lower mortality rate than later admission to the ICU [68]. Some factors could mitigate these results. First, the center's experiences and volume of ICU admission can make it difficult to generalize practices [69–71]. Furthermore, all those studies, included only patients who were referred to the ICU team. Some patients may improve with first-line treatment without ICU admission

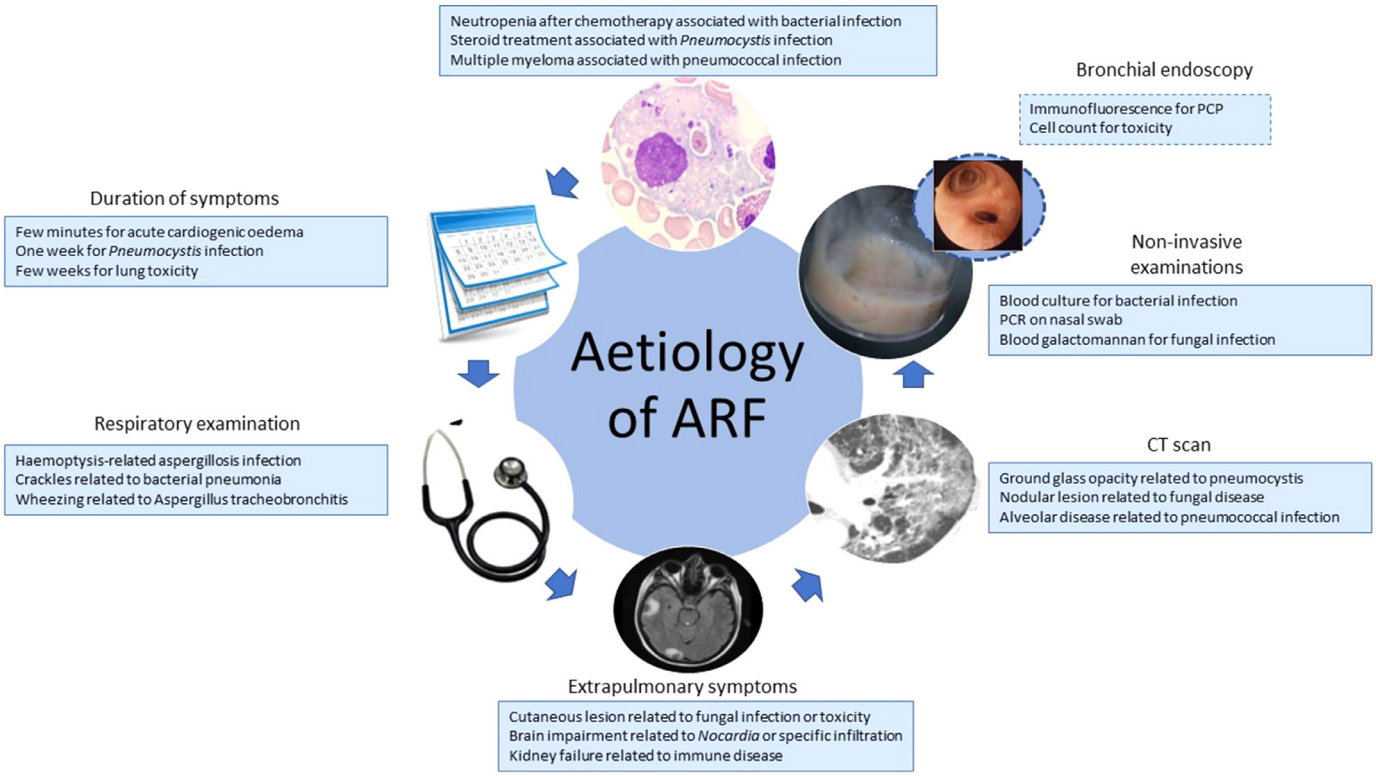

Fig. 2. Diagnostic strategies in immunocompromised patients with ARF. ARF: Acute respiratory failure.PCP: Pneumocystis Jirovecii pneumoniae.

and were not included in the studies. Although they may be difficult to conduct, prospective studies in this field remain warranted.

Avoid late failure of oxygenation strategy

Despite significant advances over time, recent reports showed that patients who have failed first-line NIV strategy could experience a higher mortality rate than patients who were first-line intubated [14]. This excess mortality may be due to lack of improvement or deterioration in clinical status, with a higher risk of cardiac arrest during the intubation procedure [72]. The deleterious effect of the non-invasive strategy has recently been demonstrated in patients receiving NIV sessions with high respiratory drive [73]. Moreover, the mortality rate in immunocompromised patients who require IMV has decreased over time, contrary to the 90% mortality rate reported in the early 2000s [22,23]. In that setting, the challenge to avoid intubation should not be a major goal.

This could offer a new research agenda. First, there is a need to define consensual intubation criteria. For more severe patients with multiple organ failure, the decision to intubate may be quite simple and should not be delayed because of the immunosuppressed status of the patient. However, for several patients without clear intubation criteria, this decision remains difficult. In that setting, center effects in the multicenter studies [69, 74]clearly demonstrated differenes in physician'decisions.

Second, accurate identification of early predictors of non-invasive oxygenation/ventilation failure is a major challenge. Still, two indices have been studied. Factors associated with early NIV failure have been summarized in an easy-to-use mnemonic, called the HACOR score, which stands for Heart rate, Acidosis, Consciousness, Oxygenation, and Respiratory rate [75]. However, it remains difficult to use because each item could in itself be a major criterion for intubation. Furthermore, the ratio of oxygen (ROX) index (ROX saturation [SpO2]) which includes respiratory rate, SpO2, and FiO2, maybe an interesting tool to identify patients at high risk for HFNO failure [76]. Although some of these indices have been assessed in immunocompromised patients, none could be fairly used as intubation criteria alone [77].

Diagnosis

The diagnosis of ARF could be challenging in immunocompromised patients, specifically due to the wide range of potential etiologies which have to be evoked [57]. Avoiding unknown ARF etiology should be a priority. Indeed, undetermined diagnosis (a situation that affects 12–15% of patients in the recent studies [8]) was an independent factor associated with mortality [57,61], as well as associated organ failure or hypoxemia severity [59].

Therefore, the implementation of a diagnostic strategy is of great importance. Fig. 2 summarizes some diagnostic strategies used in our setting. As shown, the time from symptoms onset, a careful analysis of the underlying immunosuppression, respiratory and extra respiratory manifestations, and chest imaging lead to an etiological hypothesis [78]. This careful analysis makes it possible to develop hypotheses that can be supported by non-invasive examinations and/or broncho-alveolar lavage (BAL), a procedure that is not without the risk of intubation. In this way, a randomized trial performed by the Grrr-OH research group that compared an invasive strategy with BAL and a non-invasive strategy [79], found no differences in terms of mortality, diagnosis, or intubation rates between the two arms. This was an important finding because BAL could be associated

with both intubation risk and mortality, especially in the most severe patients [80]. Moreover, BAL is no longer the cornerstone of ARF diagnosis in immunocompromised patients, especially since the development of some recent diagnostic tools such as polymerase chain reaction (PCR) and antigen testing with good accuracy on various samples (e.g., blood, serum, BAL). These new tests may increase the diagnostic ability and modify the need for BAL. However, the role of BAL remains to be discussed in certain situations (in particular to investigate *Pneumocystis jirovecii* pneumonia or drug-related pneumonia) depending on the patient's ability to receive this invasive procedure [79,80].

Conclusion

ARF is a challenging situation for the clinician, both in terms of choice of best oxygenation/ventilation and diagnosis strategies. This situation is associated with a high rate of case fatalities, in particular when intubation is needed. Oxygenation and ventilation strategies to avoid IMV have been widely evaluated in this setting, with conflicting results. The data available thus far are based on a large number of patients and seem to suggest that the ways to improve survival should not target only oxygenation and ventilation strategies. At the same time, immunocompromised status as such should not be a reason to manage patients in different ways regarding the non-invasive oxygenation strategies when ARF occurs. In this setting, early ICU admission, implementation of diagnosis strategy, and delineating intubation criteria to avoid late failure of first-line oxygenation strategy may improve survival. Further studies should confirm these points.

Conflicts of Interest

The Grrr-OH research group received non-financial support from FISCHER PAYKEL for studies. The research group received fees from Gilead, Alexion, Pfizer, Celgene, MSD, Baxter.

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Virginie Lemiale had travel expences paid by Biomerieux for Congress, outside this work

The other authors declare no conflict of interest.

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