

Current therapies for patients with acute exacerbation of idiopathic pulmonary fibrosis

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Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, and generally fatal fibrotic lung disease with a median survival of 2 to 3 years after diagnosis.^[1,2] Acute exacerbation of IPF (AE-IPF) is defined as an acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality. Nearly 46% of deaths in IPF are caused by AE-IPF, and the median survival of patients with AE-IPF is approximately 3 to 4 months.^[3] Over the past 27 years, great efforts have been paid to find therapies that might work for patients with this condition. We herein summarize current therapies for patients with AE-IPF.

AE-IPF is an acute and severe complication of IPF. Glucocorticoids alone or combined with other therapies have been empirically used in treating patients with this condition.^[3] However, the pathogenesis of AE-IPF is unknown and AE may represent an intrinsic acceleration of the underlying fibrotic lung, and it is generally accepted that glucocorticoids should not be recommended for IPF patients.^[2,3] It remains unclear whether glucocorticoids can truly bring benefits to patients with this condition. A retrospective single-center study reported that the survival of an exacerbation event in AE-IPF patients without glucocorticoids was 75%, while the survival of patients ever treated with glucocorticoids was 25%.^[4] There is debate regarding the use of glucocorticoids in AE-IPF, and randomized controlled trials (RCTs) are needed to examine the role of glucocorticoids in AE-IPF.

Glucocorticoids combined with cyclophosphamide have been reported in treating patients with AE-IPF [Supplementary Table 1, <http://links.lww.com/CM9/A234>]. It was reported that 1-and 3-month survivals of patients with glucocorticoids and cyclophosphamide were 100% and

55%, which seemed higher than those with glucocorticoids alone in previous studies.^[5] But a recent study showed that glucocorticoids and cyclophosphamide did not significantly improve survival in these patients, compared with glucocorticoids alone.^[6] Naccache *et al*^[7] carried out a RCT (NCT02460588) to evaluate the efficacy of glucocorticoids and cyclophosphamide compared with glucocorticoids alone in treating patients with AE-IPF. The final results are yet to be released, they will potentially impact treatment strategy of AE-IPF.

There are reports of glucocorticoids combined with cyclosporine A or tacrolimus in treating patients with AE-IPF [Supplementary Table 1, <http://links.lww.com/CM9/A234>]. It was reported that patients with glucocorticoids and cyclosporine A had longer survival duration than those with glucocorticoid alone.^[8] But the study conducted by Aso *et al*^[9] did not find significant difference in mortality during hospitalization between patients with and those without cyclosporine A. As for tacrolimus, a study showed that patients who received glucocorticoids and tacrolimus not only had improved survival rate and duration, but also had reduced AE recurrence, in comparison with patients who received glucocorticoids alone.^[10] These studies are small and retrospective, and we need high-quality evidence to further evaluate the efficacy and safety of calcineurin inhibitors added on glucocorticoids in AE-IPF.

Direct hemoperfusion with polymyxin B immobilized fiber column (PMX-DHP) has been used in treating patients with AE-IPF [Supplementary Table 1, <http://links.lww.com/CM9/A234>]. And it was reported that the 12-month survival was longer in patients with glucocorticoids and PMX-DHP than those with glucocorticoids alone.^[11] PMX-DHP could potentially bring benefits to patients

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with AE-IPF, but further investigations in RCTs are still warranted.

Recombinant human soluble thrombomodulin (rhTM) has been tried in treating patients with AE-IPF, the typical dosage and durations are 0.06 mg/kg daily or 380 U/kg daily for 6 or 7 days [Supplementary Table 1, <http://links.lww.com/CM9/A234>]. A study indicated that 3-month mortality of AE-IPF patients with and those without rhTM was 30% and 65%, respectively.^[12] However, a RCT conducted by Kondoh *et al*^[13] showed that 90-day survival of patients with and those without rhTM was 72.5% and 89.2%, respectively. It is the first completed RCT in investigating therapies for AE-IPF, and these results show that rhTM should not be recommended in patients with AE-IPF.

It was reported that critically ill AE-IPF patients were treated with glucocorticoids combined with plasma exchanges, rituximab and intravenous immunoglobulin (IVIG) [Supplementary Table 1, <http://links.lww.com/CM9/A234>]. The study showed that patients with autoantibody-targeted treatment had better 60-day survival than historical controls who received glucocorticoids alone.^[14] It was retrospective, and a RCT (NCT03584802) was sponsored by Assistance Publique-Hôpitaux de Paris to evaluate the efficacy and safety of glucocorticoids combined with plasma exchanges, rituximab, and IVIG *vs.* standard glucocorticoid therapy in patients admitted in intensive care unit with severe AE-IPF. Because of the coronavirus disease 2019 epidemics, the study has been suspended.

Pirfenidone and nintedanib are currently the only drugs shown to slow down the progression of IPF.^[2] It was reported that AE-IPF patients were treated with high dose glucocorticoids and appropriate supportive measures, median survival time of patients with and those without pirfenidone was 137 and 16 days, respectively.^[15] A case report showed that a patient with AE-IPF treated with nintedanib alone survived.^[16] With the gaining experience of using anti-fibrotic drugs in patients with IPF, there will be more evidence about their therapeutic values for AE-IPF which is a deadly complication of IPF.

Patients with idiopathic AE-IPF are generally prescribed broad-spectrum antibiotics with other pharmacotherapies and non-pharmacotherapies.^[3] However, the use of antibiotics in idiopathic AE-IPF patients is still controversial. A retrospective single-center study showed that azithromycin improved survival in patients with idiopathic AE-IPF.^[17] Deciding or not to prescribe antibiotics in patients with idiopathic AE-IPF remains to be a problem, and more evidence is needed to evaluate the efficacy of azithromycin in AE-IPF.

AE-IPF is characterized by refractory hypoxemia with high mortality, the decision to use mechanical ventilation in patients with AE-IPF is best made by the patient, clinician, and family ahead of time.^[3] A multi-center retrospective study showed that the mortality of IPF patients with invasive mechanical ventilation and non-invasive mechanical ventilation was 51.6% and 30.9%, respectively.^[18] So

non-invasive ventilation is likely to be a better option for AE-IPF patients requiring mechanical ventilation.

Oxygen via high-flow nasal cannula was reported to bring benefits to patients with AE-IPF who did not respond to conventional oxygen therapy.^[19] Extracorporeal membrane oxygenation (ECMO) is now regarded as a lifesaving option for patients who are candidates for lung transplantation, because it is unable to reverse the progression of interstitial lung disease and acute respiratory failure.^[20] So oxygen via high-flow nasal cannula can be of benefit for those unable to undergo lung transplantation, whereas invasive mechanical ventilation and ECMO are acceptable rescue tools to bridge to transplant.

As there is no proven pharmacotherapy for patients with AE-IPF, lung transplantation is a potential lifesaving therapy. However, patients with AE-IPF who underwent lung transplantation had significantly worse short-term and long-term survivals compared with patients with stable IPF who underwent the procedure.^[21] Available lungs for transplantation are scarce,^[22] and outcomes for patients with AE-IPF after lung transplantation are poor.^[21] Is it appropriate to do lung transplantation for patients with AE-IPF?

The prognosis of patients with AE-IPF is unsatisfactory. A completed RCT suggests that rhTM not be recommended for AE-IPF patients. The results of another two RCTs are not available now. Currently, there is no proven pharmacotherapy for these patients and lung transplantation is the only potential lifesaving therapy. Further prospective work to assess existing and novel treatment regimens for AE-IPF is needed.

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Conflicts of interest

None.

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