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Acute Exacerbation of Interstitial Lung Disease in the intensive care units: Principles of Diagnostic Evaluation and Management

Acute Exacerbation of ILD

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Abstract

Interstitial lung disease (ILD) is typically managed as outpatient basis. Critical care physicians manage patients with ILD in the setting of an exacerbation (ILD flare, AE-ILD) causing severe hypoxia. The principles of management of AE-ILD are different from those used to manage patients with acute respiratory distress syndrome (ARDS) from sepsis *etc.* Selected patients may be candidates for aggressive measures like extracorporeal membrane oxygenation (ECMO) and lung transplantation, while almost all patients will benefit from early palliative care. This review focuses on the types of ILD, diagnosis, and management pathways for this challenging condition.

Key Words: ILD; Pulmonary Fibrosis; Acute exacerbation of ILD; ECMO; ILD Flare; Interstitial lung disease; immunosuppression

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Core Tip: ILD refers to a heterogeneous group of parenchymal lung disorders. Most patients with ILD receive management in outpatient clinics. Patients with acute exacerbation of ILD (AE-ILD) may experience significant respiratory distress, requiring urgent management in an intensive care unit. Timely diagnosis and management of these patients using a multimodality team approach may improve both morbidity and mortality. When AE-ILD progresses to irreversible end-stage respiratory failure, lung transplantation and/or palliative care may be appropriate treatment options depending on the individual patient's clinical presentation.

INTRODUCTION

Interstitial lung disease (ILD) is a heterogeneous group of approximately 200 disorders affecting lung parenchyma. The classification schema of this group of diseases has

changed over time, with the most current iteration agreed upon in 2013⁶ in a consensus statement from the American Thoracic Society (ATS) and European Respiratory Society (ERS)^[1]. This classification system will be the basis for the nomenclature used in this review (Table 1).

ILD can be more broadly categorized into those with a known cause and those without an identifiable etiology, also known as “idiopathic.” Those ILDs with known causes can be due to drugs and toxins, rheumatic disease, granulomatous diseases such as sarcoidosis, and other forms such as lymphangioleiomyomatosis (LAM), eosinophilic pneumonia, or pulmonary Langerhans cell histiocytosis (PLCH). The major idiopathic ILDs can be distributed into 3 categories: chronic fibrosing (IPF, NSIP), acute/subacute fibrosing (COP, AIP), and lastly, smoking related (DSIP, RBILD)^[1]. Notably, not all ILDs have the propensity to present in acute exacerbation. Moreover, common conditions like pulmonary edema, pneumonia, pulmonary embolism, and aspiration should be considered in the differential diagnosis of acute worsening. Furthermore, patients may present to the ICU with no known history of ILD.

An abnormal chest radiograph may be the initial finding in these patients^[2]. Much attention is paid to the specific patterns noted on chest computed tomography (CT) that, when coupled with clinical history, can sometimes obviate the need for tissue sampling^[3]. It is important to note that the lung³ has a limited and predictable response to injury, and thus, a variety of disease processes may produce similar imaging findings^[4]. Patients will almost universally present in a similar fashion, with dyspnea and acute hypoxemic respiratory failure, and thus computed tomography becomes an essential tool in the differentiation of the diagnosis.

Acute exacerbation of ILD

Definition

The definition of acute exacerbation of ILD has evolved over time. AE-ILD as defined by 2007 IPFnet^[5] as an “acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality typically less than one month’s duration with exclusion of alternative etiologies”¹. The revised criteria in

2016 [2] did not set a definite 30-day duration of onset of symptoms. The critical component of establishing a diagnosis of AE-ILD is excluding other etiologies which could be causing increased respiratory distress such as heart failure, pulmonary embolism, pneumothorax, and infection *etc.* (Table 2). However, in some cases infections and other pulmonary insults might act as trigger for AE-ILD. It is difficult to lump all ILDs into one framework, and important to acknowledge that some of the acute presentations may be exacerbations of a previously unrecognized process [6]. AE-ILD symptoms tend to be shared across the spectrum of the disease, commonly patients will present with worsening cough and dyspnea, but presentations may be more fulminant in the case of some acute interstitial pneumonia (AIP). However, given the nonspecific nature of these symptoms, chest imaging and clinical history play an important role in discerning the diagnosis and, thus, the appropriate management.

Triggers

The incidence of acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) ranges from 2% to 15% per year, depending on the cohort studied. [7-10]. Nonetheless, acute exacerbations appear at a lower rate in non-IPF ILDs [11]. Acute exacerbations are often devastating, with a median survival of usually about 4 mo [12]. If an IPF patient requires mechanical ventilation, mortality exceeds 75% [13]. Given that patients with ILD exist on the fringe between functionality and fulminant worsening, even the most minor perturbations in homeostasis can lead to a significant decline. Intuitively it makes sense that any of the common causes of respiratory failure in the general population also occur in the ILD population, with the implications of such in the latter being far more pronounced.

Risk factors for AE-IPF have been described in several studies but have not been validated in independent cohorts [11]. Whether the acute exacerbation represents a progression of the underlying ILD or an aberrant response to external insults such as aspiration of gastric content, infection, or mechanical stretch remains unknown. Song *et*

al demonstrated that patients with lower baseline lung function as measured by FVC and those who never smoked had a greater risk for AE-IPF [12]. They described a subset of patients with AE-ILD as rapid deterioration (RD) of ILD, where the respiratory failure occurs in shorter duration (days to weeks) requiring hospitalization, with the presence of new radiographic abnormalities. Interestingly, within this cohort, many patients were found to have an infection as a trigger; more than half of those patients had opportunistic infections. The demonstration that AE is the most common cause of clinic deterioration in IPF patients is not a novel discovery [14], thus, acceptance that disease progression may explain the patient's presentation can obviate the need for expensive and possibly morbid diagnostic investigations. Other previously described exposures which can precipitate AE include bronchoalveolar lavage (BAL), cryobiopsy, lung resection surgery, pollution, aspiration, vaccination, and infection [15-21]. Churg and colleagues described the pathologic features found on lung biopsy in patients with fibrotic lung disease who were admitted with worsening respiratory failure. They noted three microscopic patterns found in these patients; **diffuse alveolar damage (DAD), organizing pneumonia (OP), and a pattern of numerous very large fibroblast foci superimposed on underlying fibrosis** [22]. Ultimately, **the** onus on the admitting team is to differentiate idiopathic exacerbations from secondary ones, potentially more amenable to treatment. It has been shown to be related to mortality; that is, patients with suspected AE had worse in-hospital mortality as compared to those patients who had other causes for respiratory worsening [23].

Work-Up

The diagnostic evaluation of patients with ILD admitted to the ICU is largely the same as that for all other patients admitted with acute hypoxemic respiratory failure. A caveat to this approach is for the patient with previously undiagnosed ILD, in which case, they will require a more thoughtful appraisal. It is reasonable to exclude all the common, secondary causes of worsening that can be seen in ILD patients (Table 2).

Chest CT is now routinely utilized in all patients admitted to the ICU with AE-ILD. In those patients without a known diagnosis of ILD, a basic working knowledge of some

of the classic radiographic findings can be helpful. As previously noted, ILDs are both a radiographic and histopathologic diagnosis.

There are several characteristics that can be used to quickly narrow the diagnosis; 1) is increased attenuation present? i.e., reticulation, ground-glass, consolidation, nodules, or linear opacities, 2) are cysts present? 3) Are there areas of decreased attenuation (as is seen with honeycombing) a sign of lung fibrosis? While ILD is considered a rare family of diseases, ⁹ idiopathic pulmonary fibrosis (IPF) is the most common archetype of these rare diseases. The terms non-specific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP) are often encountered in the impression of CT scans of these patients. It should be mentioned that these are both descriptive of radiographic and histologic processes. With the advent of high-resolution chest CT (HRCT), many ILDs can be diagnosed based on imaging alone. Radiologically, in UIP, the prototypical appearance of IPF, honeycombing (which represents areas of the destroyed and fibrotic lung), is a predominant feature with an apical to the basal gradient. It classically involves the sub pleural region and is more often in the middle and lower lungs (Figure 1). Ground glass opacities are minimal or absent, and traction bronchiectasis is often seen, which signifies architectural changes secondary to fibrosis^[4]. NSIP refers to a pattern that is predominantly composed of diffuse, ³ bilateral, ground-glass opacities and, at times, associated with peripheral irregular linear or reticular opacities. The distribution is mainly peripheral and basal and typically spares the sub pleural region honeycombing, if present, is generally mild in comparison to UIP (Figure 3).

However, there are some radiographic findings that are nearly pathognomonic and, at times, obviating the need for a tissue diagnosis ^[24]. While tissue sampling does provide a definitive diagnosis, surgical lung biopsy is generally not pursued in the setting of AE-ILD as it does not alter the course of treatment ^[25] and the procedure itself carries with it significant morbidity ^[26]. The typical UIP and NSIP CT patterns were outlined above. The findings seen during an acute exacerbation may be of prognostic value. In acute exacerbations, the CT scan may show areas of consolidation, ground glass opacification, or a combination of the two (Figures 2 and 4). In fact, Akira *et al* were able

to demonstrate Kaplan-Meier survival curve differences as it relates to the patterns found on CT scans in patients admitted with AE-UIP [27]. The chest CT will also exclude pulmonary embolism (if protocolled correctly) and pneumothorax.

Laboratory workups should follow the same standard of care as for patients admitted to the ICU with respiratory failure. Sputum and blood cultures should be drawn at the time of admission, urine antigens for *Legionella* and *Streptococcus*, and respiratory samples should be sent for polymerase chain reaction (PCR) to assess for viral infection. Evidence exists that serum procalcitonin may be a helpful marker in differentiating bacterial pneumonia from AE-ILD[28, 29]. Bronchoscopy likely has limited utility in the evaluation of these patients and, if performed, should be done with anticipation that further respiratory decompensation may occur. In the single-center cohort, it was demonstrated that bronchoscopy revealed potential causes of respiratory decline in 13% of patients and a change in management from the initial empiric regimen in 25% of patients. There was no difference in mortality between those with and without bronchoscopy findings. However, bronchoscopy in non-ICU patients led to immediate respiratory decompensation and the need for a higher level of care or invasive mechanical ventilation (IMV) in 25% of patients[30].

In patients without previously diagnosed ILD, there may be a role of assessing autoimmune serology for the purpose of differentiating between IPF and connective tissue disease-related ILD (CTD-ILD) or pulmonary alveolar hemorrhage syndromes. The latter two are more likely to respond to high doses of immunosuppression [31].

Management

Management can be viewed as a multi-faceted approach that is mainly comprised of supportive care for respiratory failure. Given the relative heterogeneity of disease processes, there is not one treatment plan which can be universally applied. Below we will outline the different considerations and treatment modalities that have been applied to patients with AE-ILD. It should be noted that much of this practice is done with a paucity of high-quality evidence and ultimately relies on expert opinion on

consensus guidelines. Figure 5 is a generalized flowsheet that can be used to guide through the various steps of management of AE-ILD patients.

Immunosuppression

Presently there are no proven, effective therapies for the treatment of AE-IPF. Despite this, many patients with AE-IPF receive corticosteroids in accordance with the guidelines, which admit there are no controlled trials to judge efficacy and that the recommendation comes largely from anecdotal evidence of benefit [3]. Given the high mortality associated with AE-IPF, it is reasonable to administer corticosteroids to these patients. However, the dose, route, and duration are of unknown amounts. The same can be said for acute interstitial pneumonia (AIP), which is a rapidly progressing, lethal form of ILD with a dismal prognosis and not responsive to steroids [6]. A general approach adopted is to use daily corticosteroid dosage in the 1-2 mg/kg range in divided doses. In patients who respond to this treatment, a gradual taper is attempted over the course of weeks.

A recent trial looked at the addition of cyclophosphamide to corticosteroid for the management of AE-IPF and showed that 3-month mortality was increased in the treatment arm, which provides further evidence against its use in this setting [32, 33]. Another drug of interest is cyclosporine which has been investigated in conjunction with corticosteroids in several non-randomized, retrospective studies in a patient with AE-IPF and has shown potential benefits though larger randomized controlled studies are needed to confirm this [34]. It has been postulated that immune dysregulation may lead to autoantibody production, which may drive the progression of IPF or the development of AE. As such, rituximab, in conjunction with plasma exchange, has been investigated as a potential therapeutic with promising results [35]. Currently, there are ongoing, prospective, randomized controlled studies STRIVE-IPF [NCT03286556] and Europe Exchange -IPF [NCT03584802] testing the efficacy and safety of combination plasma exchange, rituximab, intravenous immunoglobulin, and corticosteroids for the treatment of AE-IPF based on the hypothesis that auto-antibody reduction might help in its management. Regarding patients with AE of other ILDs, stronger evidence of

benefit from corticosteroids exists, as is the case for fibrotic hypersensitivity pneumonitis (HP), connective tissue related ILD, and organizing pneumonia, to name a few. We recommend the engagement of a pulmonologist familiar with the role of immunosuppression in CTD-ILD if this is suspected. Depending on the condition, the choice of agents may range from corticosteroids alone to consideration of agents like cyclophosphamide, rituximab, and even plasma exchange if the alveolar hemorrhage is suspected. These decisions are best undertaken in a multi-disciplinary discussion to facilitate the best outcome for the patient.

Antifibrotic Therapy

Currently, there are two medications available on the market, Nintedanib and Pirfenidone, which are classified as antifibrotics that are approved for the treatment of IPF. Nintedanib is a tyrosine kinase inhibitor that blocks the processes that propagate fibrosis. In the clinical trial, which ultimately led to its approval, it was shown to reduce the decline of lung function and thus slow disease progression [36]. Pirfenidone works by inhibiting the transforming growth factor beta, which plays a role in collagen-directed fibroblast formation. While there is no reversal of disease, this medication has also shown the ability to slow the progression of lung decline. Both medications have been shown to reduce the rate of exacerbations [3]. Many patients with IPF will be on these medications at the time of hospitalization. Polke *et al* looked at the management practices of AE-IPF in specialized and non-specialized ILD centers worldwide. They found that 80% of physicians in specialized centers continue antifibrotics during hospitalization, and 66% initiate therapy during AE [33]. These therapies have not been investigated specifically for use in the setting of AE-IPF or other ILDs, for that matter. There is, however, a growing body of evidence for the use of these drugs in other fibrosing lung diseases other than IPF [37].

Antibiotics

Antimicrobial agents are used routinely in patients with AE-ILD in conjunction with a thorough infectious workup. Antimicrobial coverage should be tailored to the specific pathogens and sensitivities at each respective institution. Azithromycin is a familiar

drug, and its use in the management of acute exacerbations of chronic obstructive lung disease (COPD) is well documented. Azithromycin is postulated to exert its benefits through anti-inflammatory and immunomodulatory effects in the lung [38, 39]. Evidence does exist that there may be a benefit to macrolide use in patients with AE-IPF. However, these studies are small and confounded by other therapies patients received [40, 41]. Other patient-specific considerations, such as recent hospitalization, prior culture data, and immunosuppression, should also play a role in determining the most appropriate therapy. In a Chinese cohort of patients with idiopathic inflammatory myopathy (IIM) related ILD, they found that roughly one-third of patients admitted with clinical worsening (mainly respiratory) had what they deemed to be concomitant infection and exacerbation of the IIM. Nearly half of those patients with documented infections had a fungal infection with either *Aspergillus* or *Pneumocystis* [42]. This highlights the importance of considering opportunistic infections in patients with ILD who are admitted to the ICU.

Antacids

It's postulated that microaspiration might play a role in the incitement of lung fibrosis. Studies have frequently demonstrated a higher prevalence of gastroesophageal reflux disease (GERD) in ILD patients; however, this association cannot be interpreted as causation [43, 44]. The role of acid-reducing therapy in AE has not been formally investigated; however, many physicians will continue antacids during hospitalization, and at the very least, the patients will qualify for alimentary prophylaxis based on mechanical ventilation and corticosteroid administration.

High-Flow Nasal Cannula (HFNC)

The COVID-19 pandemic has changed the way non-invasive ventilation (NIV) is viewed and utilized. With the popularization of high-flow nasal cannula (HFNC) the oxygen demands of severely hypoxemic patients can be met without the need for endotracheal intubation. Invasive mechanical ventilation (IMV) carries with it a dismal prognosis for patients with AE-ILD [45] and thus a trial of HFNC is warranted. The benefit and feasibility of using HFNC for acute hypoxemic respiratory failure were

shown by Frat and colleagues, and the caveat however was that patients with chronic hypoxemic respiratory failure were excluded from this study. While the patients that were randomized to HFNC ¹⁰ *vs* continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BPAP) devices did not result in less need for intubation, there was a reduction in mortality at 90 days in the HFNC group. HFNC can deliver a fraction of inspired oxygen up to 100% with high flow rates that can match the patients' respiratory demands. Given the high flow rates, there is also a degree of dead-space washout that results in decreased work breathing. There is limited high-quality evidence regarding the matter, but it has been shown in several retrospective studies that it is a safe and well-tolerated modality with comparable outcomes to CPAP and BPAP ⁴ [46, 47]. HFNC has been shown to have salutatory effects in idiopathic pulmonary fibrosis patients without an acute exacerbation, specifically decreased minute ventilation and respiratory rate, and capillary carbon dioxide was seen. The minor increase in PEEP seen with it is also considered beneficial [48, 49]. Finally, there is the added advantage of the patient able to eat and communicate with HFNC *vs* IMV.

Non-Invasive Ventilation

NIV is often applied in patients with acute hypoxemic respiratory failure in the hopes of staving off endotracheal intubation. There is robust evidence for the utility of its use in respiratory failure secondary to COPD and congestive heart failure; however, the benefit is less certain in AE-ILD. Yokoyama and colleagues demonstrated that NIV might have potential benefits in patients with acute hypoxemic respiratory failure secondary to AE-ILD. 11 patients received CPAP therapy; of those patients, 6 failed and required IMV but did not survive, the remaining 5 patients survived and were alive at 3-month follow-up [50]. Similar results were shown in another study that also used NIV for patients with IPF [51, 52]. These studies are not without limitations, given small sample sizes and retrospective nature that may not be representative of the general AE-ILD population. Further, it may reflect a selection bias that patients who benefitted from the use of NIV may have had less severe diseases. Nonetheless, it is proof of concept

that perhaps for a subset of AE-ILD patients, a trial of NIV is a potential alternative to an otherwise morbid intervention which in some cohorts sees a mortality rate of up to 90% for ICU patients [51].

Mechanical Ventilation

The outcomes for ILD patients that require IMV are so poor that outside of transplant candidates, some experts have advised against endotracheal intubation for these patients apart from those patients that have clearly reversible causes for respiratory decompensation [53]. The lungs of ILD patients are plagued by two detrimental factors: significant V/Q mismatch and poor compliance. No specific guidelines dictate the optimal way to provide IMV to this subset of patients. The intrinsic substrate properties of ILD lungs make them especially prone to ventilator-induced lung injury (VILI) with decreased compliance making the lung more prone to both barotraumas as well as atelectrauma [54, 55]. Therefore, it is reasonable to utilize strategies from the ARDSNET group ⁵ for the management of patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) [56]. Some authors use this fact as a caution against absolute denial of IMV for ILD patients, given that some of the data were collected before the publication of the landmark trial in 2000, which demonstrated the mortality benefit of low tidal volume ventilation [13]. There have been studies that looked at the lung mechanics of stable ILD patients and found that based on both static and dynamic lung compliance, the lung is less distensible than normal. Furthermore, it was demonstrated that the elastance of the mechanically ventilated IPF patient was four times higher than even those patients with ARDS [57]. This is further corroborated by retrospective studies that have shown that higher levels of PEEP have been associated with higher mortality in AE-ILD patients [54].

In conclusion, the outcomes of ILD patients requiring IMV are extremely poor, with cohorts that report up to 100% mortality[58]. As such, the decision to proceed with endotracheal intubation should not be made lightly and should only occur after thoughtful discussion with the patient and family members. In the case of transplant

candidates, IMV can be seen as a bridge therapy. Otherwise, early involvement in palliative services are advised.

ECMO

Veno-venous extracorporeal membrane oxygenation (VV ECMO) is presently viewed as a salvage tool in the management of patients with refractory hypoxemic respiratory failure. When the known ² strategies, such as low-tidal volume ventilation, prone positioning, and neuromuscular blockade, all fail to improve oxygenation and/or refractory acidemia due to impossible ventilation in the capable centers, VV ECMO is often employed. ECMO helps to diminish ventilator-induced lung injury in these patients. There is no consensus recommendation on the use of VV ECMO for ARDS, and the data supporting its use leaves most intensivists with a great deal of uncertainty regarding the degree of and who will benefit [59, 60]. There is even less certainty regarding its use in AE-ILD patients. Trudzinski and colleagues showed that ECMO is a viable option for patients who are suitable for a lung transplant. However, it should not be offered to those who are not, given that it does not reverse the otherwise poor prognosis faced by patients who are not transplant candidates [61]. In an international poll, roughly 50% of physicians at specialized centers offered ECMO as a bridge to patients who were suitable for transplantation [33]. To summarize, ECMO should be considered for patients with AE-ILD with a clear reversible cause (e.g., infection or pulmonary embolism) or as a bridging therapy for patients appropriate for lung transplant.

Lung Transplantation

ILD particularly IPF is now the most common indication for lung transplantation worldwide [62]. The median post-transplant survival for patients with idiopathic interstitial pneumonia, which includes IPF, is 5.2 years ⁸ and 6.7 years for all other ILDs transplanted between 1992 and 2017 [63]. Current guidelines recommend that transplant only be offered to those patients with a > 80% likelihood of 5-year post-transplant

survival ^[64]. There are several relative contraindications to transplant, such as severe psychosocial problems or life-threatening extrapulmonary organ dysfunction. The latter may frequently be encountered in AE-ILD patients who require ICU admission. The need for IMV and/or ECMO for respiratory failure pre-transplant are associated with adverse post-transplant outcomes, which may prevent some of the sickest patients from undergoing transplantation. ^[64]. For those patients who were already listed for transplantation and who experienced an acute exacerbation, ECMO as a bridge to transplantation could be considered on a case-by-case basis. The emphasis in these patients is to avoid the development of critical illness myopathy and extra-pulmonary organ damage. For denovo patients, performing invasive tests like heart catheterization and screening colonoscopies can be perilous, though. Ultimately, candidacy for an organ transplant will be a decision made in a multidisciplinary fashion incorporating the values of the patient and family, transplant surgeons, and transplant pulmonologists.

Palliative Care

Palliative care (PC) medicine specialists are dedicated to improving patients' quality of life with serious illnesses. In a recent survey, it was shown that the majority of ILD providers use PC and are comfortable discussing PC with their patients ^[65]. Given the poor prognosis that ILD patients face when they are admitted to the ICU, it warrants early involvement of PC services. Furthermore, the median life expectancy for all patients with IPF is between 2-7 years, which hastens in the AE setting. The ATS/ERS guidelines go so far as to recommend that advanced directives and end-of-life issues be addressed in the ambulatory setting in all patients with IPF ^[3]. A subset of patients will require ICU level of care due to AE-ILD that was not previously diagnosed and will require more nuanced discussions given the emotional burden of a new, life-limiting diagnosis. In one IPF cohort, it was found that the hospital was the place of death for 80% of the patients, and most of these patients (93%) were hospitalized for an average of 30 days during the last 6 mo of their life. More striking was the statistic that 42% had a do not resuscitate order (DNR) that was decided upon in ≤ 3 days prior to their death

[66]. This further confirms the importance of early and thoughtful communication with these patients and their families to ease the emotional and physical suffering they may endure at the end of their lives.

CONCLUSION

Flares or acute exacerbations of ILD have feared complications of these disease entities, owing both to their poor prognosis and uncertain management. The mainstay of therapy is supportive care and early recognition of a potentially reversible cause. Immunosuppression plays a role in a subset of patients; however, the optimal dosage and duration have not yet been defined. It behooves the intensivist to trial NIV forms on respiratory support to avoid the highly morbid effects of mechanical ventilation in these patients. The most aggressive therapies, such as IMV and ECMO, should be reserved for those patients who are potential transplant candidates. Early involvement in palliative care will assist in managing complex discussions and minimize suffering for patients with a high propensity for mortality.

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