Corticosteroids for Pleural Infection: Should We STOPPE Studying?

Pleural infection is a challenging condition to manage, and, unlike other infectious diseases, outcomes have improved little over the past decade (1). Pleural infection results in extended hospital stays, a mortality rate of 15%, and a considerable healthcare burden, given the potential requirement of chest tube drainage, intrapleural fibrinolytics, or thoracic surgery. Preventing the development or progression of pleural infection is a very worthwhile venture. In this issue of the *Journal*, Fitzgerald and colleagues (pp. 1093–1101) describe the STOPPE (Steroid Therapy and Outcome of Parapneumonic Pleural Effusions) trial, the first randomized trial of corticosteroids in adults presenting with parapneumonic effusions (2).

The rationale behind corticosteroids in parapneumonic effusions is sound. Numerous laboratory studies have demonstrated that effusions are rich in proinflammatory cytokines even in the early stages. Bacterial replication adjacent to the pleural space sets off an inflammatory cascade that results in a spectrum of fluid volume and complexity, from small, simple parapneumonic effusions to grossly loculated, fibropurulent collections. The cytokines upregulated within infected fluid include IL-6 and IL-8, TNFα (tumor necrosis factor-α), VEGF (vascular endothelial growth factor), and MCP (monocyte chemotactic protein), which theoretically could be attenuated by systemic corticosteroids (3). Arresting the inflammatory cascade at an early stage might avoid the derangement of fibrinolysis and resultant loculation development that can hamper subsequent pleural fluid drainage (4). Whether persistence of bacteria or inflammation alone drives ongoing fluid accumulation and loculation is uncertain, although the notoriously low yield of causative microbes from pleural fluid (just 10% in this trial) would point to the latter.

A previous trial by Tagarro and colleagues in a pediatric population demonstrated a benefit from administering intravenous dexamethasone in terms of clinical recovery from parapneumonic effusions (5). As the first trial in adults, the STOPPE trial was designed as a pilot study without a primary endpoint, with the aim of capturing a wide range of clinical outcomes. Adult patients hospitalized with community-acquired pneumonia were screened for the presence of an associated pleural effusion in the first 3 days of admission. Eligible patients were randomized 2:1 to receive either 4 mg of dexamethasone intravenously every 12 hours up to a maximum of four doses or the same course of normal saline. This was a regimen extrapolated from the pediatric study. Importantly, the whole spectrum of parapneumonic effusions were eligible for study, from simple, small effusions to frank empyema.

From six Australian centers over a 2-year period, 80 patients were randomized from the 374 screened (52 dexamethasone vs. 28 placebo). Most exclusions were owing to patient factors such as lacking capacity or requiring intensive care on admission. The study was not powered to detect a difference between the groups and indeed did not find one. There were no significant differences in terms of time to or relapse from clinical stability, Day 30 chest X-ray appearances or inflammatory markers, hospital length of stay, or antibiotic use. However, just half had radiological resolution by Day 30, suggesting an extended follow-up might be indicated. Less than half of the cohort (37 of 80) required any form of pleural drainage during their hospital admission, indicating that the majority of randomized patients had a simple parapneumonic effusion or indeed one related to another etiology (i.e., cardiac dysfunction exacerbated by infection) because pleural fluid diagnostics did not form part of the inclusion criteria. Crucially, the STOPPE trial has shown that giving corticosteroids to this population does not result in significant harm, with adverse events similar between groups. Hyperglycemia was more common in the dexamethasone group, but no patients required intravenous insulin.

Without a trend toward benefit from steroids in parapneumonic effusions, does this shut the door on any future trials in this area? We would argue that it should not. As a first-of-its-kind pilot study, its authors should be commended. Interventional pleural studies are inherently difficult, as evidenced by the attrition from screening to randomization owing to patient factors alone. As a pilot study should, it has generated many questions that need addressing before future trials are performed.

A key issue is that of the optimal target population. In an era of large platform trials, overly restrictive inclusion criteria should be avoided. However, the spectrum of parapneumonic effusions is so wide that the fundamental aim of steroid therapy is affected. Are we trying to prevent the development of pleural infection? In that case, we should target only simple parapneumonic effusions at the earliest possible time point, especially given that corticosteroids seem to benefit adults hospitalized with community-acquired pneumonia with or without an effusion (6). This is a valid approach, but only a minority of simple parapneumonic effusions progress to pleural infection, so the trial size needed to demonstrate a difference would be large, and the potential benefit-to-risk ratio of steroids could be marginal (7, 8). Alternatively, one could argue for an approach of targeting established cases of pleural infection to augment the inflammation that is driving fluid production and loculation. Such a trial might include patients in whom initial medical management had already been performed, and the potential role of steroids would be to reduce ongoing symptoms, or hospital length of stay, or persistent pleural thickening, all endpoints that were deemed feasible to collect within the STOPPE trial.

Beyond trial design, the choice of steroid, dosing, and route is an important area. The investigators very reasonably chose dexamethasone for its strong antiinflammatory effects with minimal mineralocorticoid effect and long duration of action. However, 8 mg daily in divided doses is a relatively small dose compared with other inflammatory conditions related to infection, such as bacterial

Originally Published in Press as DOI: 10.1164/rccm.202201-0057ED on February 9, 2022

meningitis, for which 40 mg daily is administered (9). The RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial demonstrated that just 6 mg daily reduced mortality in severe coronavirus disease (COVID-19) but is currently testing doses of 20 mg daily after promising results from other trials (10, 11). In addition, the intravenous route might not be necessary, given the bioavailability of oral dexamethasone, which would reduce adverse effects (e.g., phlebitis), costs, and complexity of intravenous administration (12).

In summary, as the first of its kind, the STOPPE trial has shown that it is both safe and feasible to randomize adult patients with parapneumonic effusions to steroids. Future trials are certainly indicated, but careful consideration should be given to their aim. Should we aim to prevent pleural infection development, or instead attempt to dampen inflammation in already established disease to reduce immediate symptom burden and/or improve longer-term outcomes? ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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Prime Time for Proteomics in Pulmonary Arterial Hypertension Risk Assessment?

Precision-based approaches to pulmonary vascular disease have been a focus of research over the past decade (1, 2). The goal is to reclassify pulmonary hypertension (PH) in a way that more accurately aligns with pathobiology and precisely identifies patients at risk or those likely to respond to established and investigational therapeutics. One strategy to address these aims is to combine blood biomarkers and computational modeling to provide more robust and deeper phenotyping than can be achieved with clinical PH classification alone. Genomics, transcriptomics, proteomics, and metabolomics in isolation or combined in systems biology–based networks have, to date, uncovered novel insights into disease mechanisms and questioned how we clinically characterize patients (3–8). In this issue of the *Journal*, Rhodes and colleagues (pp. 1102–1111), who have been at the forefront of these efforts in pulmonary vascular disease (3, 4), build on a previous proteomics study (9) and present the largest unbiased analysis of plasma protein expression to date in idiopathic, heritable, and drug-induced pulmonary arterial hypertension (PAH) (10).

The burden that precision-based approaches in PAH bear is against established markers of disease progression and prognosis,

Supported by NIH grant R01-HL141268 (C.E.V.).

Originally Published in Press as DOI: 10.1164/rccm.202201-0040ED on February 10, 2022