stress. The same goes for the observations of corticosteroid-dysregulated genes. Of note, *ADRB2* gene activity is positively regulated by glucocorticoids. It is difficult to study how these two drug classes impact mechanisms, because both are central to asthma management. Therefore, other ways, including the use of mouse and cell culture models and clinical studies applying different doses of corticosteroids, need to be considered to determine how different doses influence gene expression. The challenge is to decide how best to take these findings forward. Now in its third funding period, SARP continues to show the enormous value and cost-effectiveness of large collaborative research studies to address questions in ways that could never be done by individual academic institutions or pharmaceutical companies. U-BIOPRED has been similarly productive. The findings from both consortia need to be validated, and cross-interrogation of the respective datasets would be of enormous value. We are now well into the era of asthma biologics, and a set of approved monoclonal antibodies that target different pathways is available. To understand how these drugs work on mechanisms, we need to use omics methods like the ones applied in this study. ■

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Ratko Djukanović, M.D.
Faculty of Medicine
University of Southampton
Southampton, United Kingdom
and
NIHR Biomedical Research Centre
Southampton, United Kingdom

ORCID ID: 0000-0001-6039-5612 (R.D.).

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Can Macrolide Antibiotics Prevent Hospital Readmissions?

Exacerbations of chronic obstructive pulmonary disease (COPD) are one of the most common causes of impaired health status and hospital admissions, as well as readmissions that are costly to healthcare services (1). The European COPD audit has shown that after an exacerbation, 35% of patients will be readmitted to the hospital within 90 days (2). Therapy for an acute exacerbation is currently dependent on courses of oral corticosteroids and/or antibiotics, and there is no evidence that this impacts exacerbation readmissions. Other interventions are urgently required, and although some studies have investigated the use of antiinflammatory agents for acute exacerbations, including TNF-α (tumor necrosis factor-α) inhibitors (3) and phosphodiesterase E4 inhibitors (4), no effect has been shown either on exacerbation recovery or on time to the next

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exacerbation or hospital readmission. However, all of these studies have tested short-term exacerbation interventions.

Although most COPD exacerbations recover within 10 days, some of these events may be more prolonged. Seemungal and colleagues showed that at 35 days, 23% of exacerbations had not recovered their peak expiratory flow rate to preexacerbation levels (5), and in a later analysis of the same cohort, 7.3% of exacerbations had not recovered their peak expiratory flow rate by 99 days (6). It is also recognized that COPD exacerbations cluster in time, and thus an index exacerbation increases the patient's susceptibility to subsequent events, especially in the high-risk period of 3 months after hospital admission (7). Thus, to be effective during an acute exacerbation, any novel intervention needs to be administered for at least 3 months. Oral corticosteroids have considerable adverse effects when used in the longer term. Macrolide antibiotics, which are usually administered on top of standard inhaled therapy, have been used successfully to prevent exacerbations (generally in 12-month trials) and introduced into clinical practice (8, 9). However, there have been some concerns that long-term use leads to widespread induction of antibiotic resistance and the development of cardiac toxicity and ototoxicity. A recent subanalysis from the azithromycin trial by Albert and colleagues showed a trend toward a reduction of readmissions, although the number of hospital admissions in that study was relatively small (10). The mechanisms of COPD exacerbation prevention with macrolides are not fully understood; however, the therapeutic benefit may result from interactions of the lung microbiome with the immune system (11).

In this issue of the *Journal*, Vermeersch and colleagues (pp. 857–868) report the results of a well-designed randomized controlled trial performed in Belgium, in which, for the first time, patients with COPD exacerbations who had been admitted to the hospital were treated with a 3-month course of the macrolide antibiotic azithromycin (12). Most of the patients had very severe COPD with frequent exacerbations and were randomized to either placebo or 3 days of loading azithromycin 500 mg daily, administered on top of their usual therapy of antibiotics and oral corticosteroids. Treatment with the macrolide was then continued every 2 days with a lower dose of 250 mg orally for a total of 3 months, with the trial investigators hypothesizing that the antiinflammatory effect of the macrolides would be prolonged. The investigators administered a loading dose of azithromycin to enhance the antibiotic effect, although the patients were already being treated with standard antibiotics and loading was probably unnecessary. Thus, therapy initiated at hospital admission was continued after the patients were discharged from the hospital, and all of the patients were treated with triple inhaled therapy at discharge to standardize the therapy. The primary outcome was the time to first event, and the treatment failure (TF) rate within 3 months was used as a novel primary endpoint. TF was defined as the composite of treatment intensification with systemic corticosteroids and/or antibiotics, a step-up in hospital care or readmission for respiratory reasons, or all-cause mortality. After the 3 months of exacerbation therapy, all patients were followed for a further 6 months.

Unfortunately, due to financial limitations and slow recruitment (especially as only approximately 15% of the screened patients were eligible for study enrollment), the initial target of 500 patients was not reached and the study was terminated when 301 patients had been recruited. The composite primary outcome, the TF rate, was lower in the azithromycin-treated group (49%) than in the placebo-treated group (60%), although this just missed statistical significance with a P value of 0.0526. However, a number of key secondary endpoints studied, such as treatment intensification with corticosteroids and antibiotics or a step-up in hospital care, suggested a statistically significant benefit of the macrolide compared with placebo. ICU length of stay was also reduced in the macrolide group, during both the first 90 days and the subsequent follow-up period. Interestingly, the exacerbation-prevention effects of the macrolide were reduced over the next 6 months after cessation of therapy, suggesting that macrolide therapy needs to be administered longer term or possibly also seasonally during the winter months, when COPD patients have the highest risk of exacerbation (13) and hospital admissions are most frequent. This would target therapy in patients during the time of their highest exacerbation risk while also reducing the chance of adverse effects.

The limitations of the study are discussed and include the early trial termination and the insufficient number of sputum samples obtained to allow a full study of antibiotic resistance. Patients were only enrolled if the investigator considered they had an "infectious" exacerbation, but it is not clear whether this was accompanied by purulent sputum or an increase in sputum volume or other features of infection. However, if we believe that the main action of macrolide therapy is antiinflammatory, then a wider group of patients hospitalized with exacerbations would benefit from the intervention. The study also highlights that a more traditional exacerbation outcome incorporating ICU length of stay may be valuable in future studies.

The authors should be commended for a well-designed trial that for the first time has produced encouraging preliminary data on how we can prevent readmissions for patients with COPD. Concerns regarding global widespread macrolide resistance mandate a more targeted approach for treating patients who have the highest risk for exacerbations and who still develop exacerbations despite receiving triple inhaled COPD therapy. Additional study of this approach is required to best determine whether macrolides may provide a valuable approach to preventing readmissions, to define how macrolide antibiotics should be used, and to establish whether they should be started at hospital admission in the highest-risk patients or given prophylactically during the time of highest seasonal risk. ■

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Jadwiga A. Wedzicha, M.D.*
Andrew I. Ritchie, M.B.*
National Heart and Lung Institute
Imperial College
London, United Kingdom

Fernando J. Martinez, M.D.*
Department of Medicine
Weill Cornell Medical College
New York, New York

*J.A.W. is Editor-in-Chief, F.J.M. is Deputy Editor, and A.I.R. is Editorial Coordinator of *AJRCCM*. Their participation complies with American Thoracic Society requirements for recusal from review and decisions for authored works.

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NET Gain for Sepsis Research: A New Approach to Assess Neutrophil Function in Patients

Neutrophil extracellular trap (NET) formation, a feature of neutrophils that involves extracellular release of a DNA web with attached histones and proteolytic enzymes, plays a critical role in the immune response to infection by trapping and preventing the dissemination of pathogens (1, 2). However, it is now well recognized that the release of NETs can also contribute to tissue injury in several pathologic conditions, including acute lung injury (3), thrombosis (4), and sepsis (5). Thanks to decades of research, we now have a deep understanding of the characteristics of NETs and subsequent effects on different organ systems in experimental models. However, there is still a gap in our knowledge regarding how we can use this information to improve clinical outcomes, especially during a critical illness. Although many assays have been developed to detect circulating NET components, including cell-free DNA, MPO (myeloperoxidase), and histones (6–8), these markers of already released NETs are not specific and may not always correlate with disease severity or outcomes. Furthermore, they are subject to degradation and clearance, which limits their potential to provide meaningful clinical information.

In an elegant study in this issue of the *Journal*, Abrams and colleagues (pp. 869–880) developed a novel assay to test the potential of plasma from patients with sepsis to stimulate healthy human neutrophils to release NETs (9). They then used this approach to prospectively test the association between plasma NET-forming capacity and clinical outcomes of ICU patients with sepsis. Using this new method, the authors discovered that the NET-forming capacity of plasma was independently associated with disease severity, the development of disseminated intravascular coagulation, organ injury, and mortality during critical illness. Importantly, the NET-forming capacity of plasma does not seem to be dependent on the neutrophil donor, and no plasma from healthy donors stimulated NETs. The assay procedure is relatively simple and straightforward, assuming that someone with the necessary expertise in neutrophil isolation, immunofluorescence, and microscopy, as well as fresh donor neutrophils, would be available when needed. An inability to meet these requirements could be a potential shortcoming of the assay. In addition, the time requirement of the assay (at least 4 h for stimulation of neutrophils, in addition to sample collection, neutrophil isolation, staining, and imaging) may not necessarily be an improvement from the predictive scoring mechanisms already in place, especially considering that the investigators found no significant improvement in the predictive capacity of this assay compared with Acute Physiology and Chronic Health Evaluation (APACHE) II or Sequential Organ Failure Assessment (SOFA). Nevertheless, this outside-the-box approach could provide additional insight into patient outcomes, as well as underlying pathological processes during a critical illness.

When they further investigated the NET-forming capacity of individual plasma samples, the authors identified IL-8 as a key component. In fact, blocking IL-8 using an antibody or receptor antagonist, or downstream mitogen-activated protein kinase signaling, removed the ability of patient plasma to induce NETs,

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