Life at the Editorial “COVID Frontline”
The American Thoracic Society Journal Family

We live in extraordinary times, facing the greatest medical crisis of the last century and potentially of all time. The growing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic affects each of us, our families, and our very way of life. Our core American Thoracic Society (ATS) journal readership, making up a significant number of individuals on the clinical and research frontlines, places us in a privileged position: the “editorial frontline” tasked to provide timely, robust, and scientifically sound information to inform clinical practice and research. With this role comes great responsibility and during a global pandemic requires real-time responses, accelerated peer review processes, and a timely, agile governance cadence. Although this is a challenge, the digital era of publication accelerates information availability at speeds inaccessible in past pandemics.

Putting Safety First
Our priority as editors is first safeguarding patient and physician safety by ensuring the scientific accuracy of submitted work: publishing stringently peer-reviewed data using accurate, responsible, and ethical approaches, while ensuring timely publication to facilitate advancements in knowledge and clinical care. Charged by the ATS with the responsibility of transitioning publication to facilitate advancements in knowledge and clinical care. Charged by the ATS with the responsibility of transitioning data into the public domain, our role requires time, focus, and a meticulous approach, in reality, working at the “editorial frontline.” During a global pandemic, we face a set of unique issues where publishing data at speed must be balanced against maintaining standards and rigor. Here we provide a view from that frontline for our international readership.

The Challenges to Publication and the Peer Review Process
Several scientific, peer review, and ethical issues are pertinent in these unprecedented times. Handling the sheer number of daily submissions is a challenge at a family of leading respiratory journals such as ours. We continue to ensure favorable turn-around times, and we must consider decisions about manuscripts where there is a dynamically changing evidence base, sometimes by the hour, analogous in many ways to how this pandemic has evolved. Under no circumstances should peer review be omitted, even during a pandemic. Ensuring adequate fast-tracked peer review with its accompanying time pressure is only possible with dedicated, experienced expert reviewers, the foundation of the editorial process. This is supported by strong statistical assessment, which at such times is critical, as study conclusions are usually drawn from smaller than usual patient numbers. Many expert reviewers themselves are frontline clinical staff, asked to provide opinions in a timely manner and against a backdrop of large clinical and administrative loads. In times of crisis, many look for binary answers to important questions; however, such rigidity belies the very essence of science, which can only appropriately be interpreted taking into account the conditions under which a study was performed. The peer review system exists to ensure that published work clearly acknowledges its limitations from its methodologies, study design, and statistics.

As a family of ATS journals, we are prepared to correct publication errors and are committed to progressing with the rapid advances in scientific knowledge and changes in publication required to respond to this pandemic. Making data open access and available at no charge is no longer simply an idea, it is an ATS Journal Family reality and one we commit to. However, this does come with challenges. A major challenge that we and other journals currently face is avoiding overlapping publication. Several papers, sometimes on the same topic, are submitted to several journals, not necessarily from the same authors or country, but with the same key findings. Messaging between such papers can differ, making it challenging for readers to interpret, especially when published concurrently, which precludes cross-referencing. Addressing this will necessitate formation of a “journal network” where editors can share ideas, messaging, and even manuscripts while ensuring that overlapping publication is avoided. Publication ethics should never be compromised, and trial registration, informed consent, and institutional board approvals must be sought, fast-tracked, or legally waived by country law, and be accessible in documentary form to editors and reviewers.

An innovation in bioscience publishing is preprint servers, with sites such as bioRxiv and medRxiv posting manuscripts online without peer review, a practice long established in nonmedical disciplines such as physics and mathematics. Although immediate data sharing at this critical time has clear value, it is equally important to reiterate that such posts lack peer review and must be interpreted with caution. The clinical and scientific conclusions accompanying such data sets may in fact be entirely different after peer review. Removal of such text from preprint servers once published is a challenge, as the onus remains on authors to correct inaccuracies between the original post and final publication. Social media platforms further compound this, with many tweeting about preprint rather than final versions of manuscripts, which remain cemented, widely shared, and irreversible. Therefore, a delicate balance is required between releasing information quickly and ensuring accuracy, patient safety, and appropriate interpretation, including understanding potential limitations.

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The ATS Journal Family Response and a Call for Clinical Trials

These are key times for teamwork and sharing common goals that bring people, data, and technology together; the ATS Journal Family is no different. Joining the global response to this crisis, the authors, reviewers, editors, and journal staff work closely together to bring the best science to the international respiratory community—science that meets the highest standards focusing on our broad readership, including clinicians, scientists, and patients. As a specialist respiratory society with global outreach, the provision of up-to-date and timely advice, even at the earliest stages of this outbreak, remains a priority (1). Good treatment is based on sound evidence and avoiding patient harm (2, 3). A key exit strategy from this pandemic will be good science. Well-designed, ethical, and properly executed clinical trials are critical, and the ATS Journal Family calls for your best clinical trial submissions.

Akin to a frontline clinician donning personal protective equipment, our evaluation of cutting-edge research during pandemic times does not allow for mistakes, particularly where it influences clinical practice, patient care, and future research. We cannot jeopardize public health and must ensure that the work published is accurate, representative, and useful at the clinical “frontline.” Patient suffering has catalyzed an “information hunger” that has altered the way scientific papers are evaluated, disseminated, and even communicated; no single approach is perfect, and only time will tell if we got things right. As the scale, speed, and strength of this outbreak grows, there is reason to be optimistic: China has recently reported decreasing domestic case numbers, with some aspects of life slowly returning to normality. Although this may currently feel a long time away for colleagues in many other countries working within strained healthcare systems, we at the ATS Journal Family want you to know that we are with you. We are here to provide you with a reliable resource of trusted information from the best science we receive following rigorous evaluation. We express deep gratitude to our peer reviewers, who contribute precious time and expertise that we rely on. A key parallel between clinical and editorial “frontlines” is effective communication; however, they are remarkably different. We wish to acknowledge and recognize all clinical frontline workers who serve as an inspiration for us all at the ATS Journal Family. As we fight this faceless enemy, rest assured that we will continue to do our very best for you at the “editorial frontline.”

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Aspirin-exacerbated respiratory disease (AERD) is a unique phenotype of asthma with nasal polyps and characterized by sensitivity to aspirin and nonsteroidal antiinflammatory drugs (NSAIDs) (1, 2). A hallmark feature of AERD is dysregulated function of the 5-lipoxygenase pathway, which leads to overproduction of cysteinyl leukotrienes (LTs) by mast cells (MCs) after exposure to cyclooxygenase inhibitors (3). Although the mechanisms of AERD are not fully established, Laidlaw and Boyce (1) and Boyce (3) have identified dysregulated MC activation as a pivotal component of NSAID-sensitive asthma. In AERD, NSAIDs inhibit cyclooxygenase, shifting 5-lipoxygenase metabolism to generate excessive cysteinyl LTs and large quantities of prostaglandin D2 (PGD2) from MCs, thereby causing acute airflow obstruction (4). A biomarker for dysregulated MC function in AERD is elevated urinary excretion of cysteinyl LT metabolites (i.e., LTE4 and PGD-M).

Interest in regulating MC cysteinyl metabolism in AERD to normalize MC activity and MC-LT production is not new. Researchers have explored a number of MC-stabilizing drugs, such as corticosteroids and Cromolyn sodium (5), in an attempt to reduce MC-LT generation and, consequently, bronchospasm. Omalizumab is a monoclonal antibody that binds and reduces circulating IgE to block MC activation and allergic airway reactions. Reducing free IgE also diminishes expression of high-affinity IgE receptors on MCs and MC activation (6). Consequently, and based on evidence of ongoing MC activation and eosinophil airway inflammation in AERD, Hayashi and colleagues (7) treated 21 patients with AERD; whereas, on placebo, an AERD response to aspirin was observed. These findings of severe disease in patients with AERD but necessary criteria to safely conduct an aspirin challenge were confirmed in a clinical trial of 16 highly selected and carefully managed patients with AERD (9). From 21 patients with AERD screened, 16 participants were randomized into their clinical trial. The subjects had a mean age of 53 years, required high-dose inhaled corticosteroids for asthma control (655 μg/d of fluticasone equivalent), and previously had a positive aspirin challenge reaction to confirm AERD. All enrolled subjects with AERD had asthma control with a mean Asthma Control Questionnaire 6 score of 0.8 (0.3–2.6) and FEV1 of 104.4% predicted (92.7–112.0). Their mean peripheral blood eosinophil count was 370 cells/μL. These are not the typical clinical profiles of severe disease in patients with AERD but necessary criteria for a randomized control trial.

In this issue of the Journal, Hayashi and colleagues (pp. 1488–1498), from Sagamihara National Hospital in Nagoya, Japan, expanded and extended their earlier studies with omalizumab in a placebo-controlled, double-blind, crossover study in 16 highly selected and carefully managed patients with AERD (9). From 21 patients with AERD screened, 16 participants were randomized into their clinical trial. The subjects had a mean age of 53 years, required high-dose inhaled corticosteroids for asthma control (655 μg/d of fluticasone equivalent), and previously had a positive aspirin challenge reaction to confirm AERD. All enrolled subjects with AERD had asthma control with a mean Asthma Control Questionnaire 6 score of 0.8 (0.3–2.6) and FEV1 of 104.4% predicted (92.7–112.0). Their mean peripheral blood eosinophil count was 370 cells/μL. These are not the typical clinical profiles of severe disease in patients with AERD but necessary criteria to safely conduct an aspirin challenge. The study design had two 3-month intervention phases, omalizumab or placebo, with an 18-week washout between the randomized treatment crossover. After each 3-month treatment phase, an oral aspirin challenge was conducted with escalating aspirin doses until either an AERD reaction occurred or the maximal challenge dose of aspirin, 930 mg, was reached. MC activation to the aspirin challenge was determined by measuring LTE4 and PGD-M concentrations in 24-hour urine collections, which also served as the primary study outcome. Aspirin challenge of the subjects with AERD after 3 months of omalizumab treatment did not cause a significant increase of LTE4 and PGD-M in the 24-hour urine analysis compared with placebo (Hayashi and colleagues’ Figure 2). Ten of the 16 subjects achieved the maximal aspirin dose of 930 mg without AERD; whereas, on placebo, an AERD response to aspirin was achieved at doses ranging from 30 mg to 530 mg (Hayashi and colleagues’ Table 3). Furthermore, the mean percent fall in FEV1 was significantly reduced by omalizumab treatment compared with placebo (−4.7 vs. −10.0; P = 0.039) (Hayashi and colleagues’ Table E2).

Hayashi and colleagues (9) also evaluated the kinetics of omalizumab effects on urinary LTE4 and PGD-M concentrations over the 3-month treatment (their Figure 4). Small but significant reductions in urinary excretion of LTE4 and PGD-M began shortly after initiating omalizumab, reached maximal reductions at 1 month, and were sustained at the aspirin challenge (Table 4).