

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

Jeremy E. Orr, M.D.
Robert L. Owens, M.D.
Division of Pulmonary, Critical Care, and Sleep Medicine
University of California, San Diego
La Jolla, California

ORCID ID: 0000-0002-4498-5337 (J.E.O.).

References

- McNicholas WT, Verbraecken J, Marin JM. Sleep disorders in COPD: the forgotten dimension. *Eur Respir Rev* 2013;22:365–375.
- Agusti A, Hedner J, Marin JM, Barbé F, Cazzola M, Rennard S. Night-time symptoms: a forgotten dimension of COPD. *Eur Respir Rev* 2011;20:183–194.
- McSharry DG, Ryan S, Calverley P, Edwards JC, McNicholas WT. Sleep quality in chronic obstructive pulmonary disease. *Respirology* 2012; 17:1119–1124.
- Owens RL, Malhotra A. Sleep-disordered breathing and COPD: the overlap syndrome. *Respir Care* 2010;55:1333–1344.
- Omachi TA, Blanc PD, Claman DM, Chen H, Yelin EH, Julian L, et al. Disturbed sleep among COPD patients is longitudinally associated with mortality and adverse COPD outcomes. *Sleep Med* 2012;13:476–483.
- Köhnlein T, Windisch W, Köhler D, Drabik A, Geiseler J, Hartl S, et al. Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. *Lancet Respir Med* 2014;2:698–705.
- Murphy PB, Rehal S, Arbane G, Bourke S, Calverley PMA, Crook AM, et al. Effect of home noninvasive ventilation with oxygen therapy vs oxygen therapy alone on hospital readmission or death after an acute COPD exacerbation: a randomized clinical trial. *JAMA* 2017;317: 2177–2186.
- Stanchina ML, Welicky LM, Donat W, Lee D, Corrao W, Malhotra A. Impact of CPAP use and age on mortality in patients with combined COPD and obstructive sleep apnea: the overlap syndrome. *J Clin Sleep Med* 2013;9:767–772.
- Marin JM, Soriano JB, Carrizo SJ, Boldova A, Celli BR. Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome. *Am J Respir Crit Care Med* 2010; 182:325–331.
- Redolfi S, Grassion L, Rivals I, Chavez M, Wattiez N, Arnulf I, et al. Abnormal activity of neck inspiratory muscles during sleep as a prognostic indicator in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2020;201: 414–422.
- Arnulf I, Similowski T, Salachas F, Garma L, Mehiri S, Attali V, et al. Sleep disorders and diaphragmatic function in patients with amyotrophic lateral sclerosis. *Am J Respir Crit Care Med* 2000;161: 849–856.
- Struik FM, Sprooten RT, Kerstjens HA, Bladder G, Zijnen M, Asin J, et al. Nocturnal non-invasive ventilation in COPD patients with prolonged hypercapnia after ventilatory support for acute respiratory failure: a randomised, controlled, parallel-group study. *Thorax* 2014; 69:826–834.

Copyright © 2020 by the American Thoracic Society



Bayesian Analysis in Critical Care Medicine

We commend Zampieri and colleagues (pp. 423–429) for their study presented in this issue of the *Journal* (1), in which they conducted a thoughtful Bayesian reanalysis of results from a trial conducted within a developing research network to assess an intervention with broad applications (2). The premise of the ANDROMEDA-SHOCK trial was to compare a novel peripheral perfusion-based resuscitation approach using capillary refill time with a more conventional lactate-based approach to guide resuscitation (2). The trial reported an 8.5% reduction in absolute mortality but failed to reject the null hypothesis, motivating Zampieri and colleagues to repeat the analysis from a Bayesian perspective, which showed a consistently high probability that the intervention improved mortality across a range of prior beliefs. This reanalysis gives us an opportunity to consider the usefulness of a Bayesian approach in critical care medicine.

Bayesian analysis can be intimidating for many clinicians because it uses unfamiliar terms and takes a fundamentally different approach to drawing statistical conclusions from data as compared

with frequentist analysis. However, any increased familiarity that clinicians feel toward conventional (frequentist) statistics is likely a false comfort, given the well-documented problems with the use of frequentist statistics in contemporary science (3). Bayesian analysis is sometimes proposed as an improved way to draw statistical conclusions from clinical data because it allows for the incorporation of information external to the trial (prior information) and makes it easy to answer the question, what is the probability that the intervention has a benefit of at least X%? Incorporating prior information in critical care trials is helpful because critical illness is rare, and so it may be wise to use all available information when analyzing a trial. Calculating the probability of benefit is also useful in critical care medicine, where morbidity and mortality are common, and so it may be helpful to identify interventions where frequentist analysis has failed to reject the null hypothesis but the probability of benefit is still high, as in the case of ANDROMEDA-SHOCK.

One common clinical reasoning approach that is similar to Bayesian analysis is the use of diagnostic tests. Consider a patient with shortness of breath and a swollen leg. A clinician may suspect a pulmonary embolism based on the clinical data (analogous to prior information) and order a diagnostic test such as a D-dimer. The D-dimer test result (analogous to a clinical trial or experiment) will have a different likelihood depending on whether or not a patient actually has a

©This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0 (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). For commercial usage and reprints, please contact Diane Gern (dgern@thoracic.org).

Originally Published in Press as DOI: 10.1164/rccm.201910-2019ED on January 3, 2020

pulmonary embolism—a negative test is very unlikely if a patient does have a pulmonary embolism. The clinician then combines the likelihood of the obtained result with the prior probability of having a pulmonary embolism to compute an updated probability (posterior probability) that this individual has a pulmonary embolism. Clinicians do not make these calculations explicitly, but instead perform them intuitively. By analogy, a Bayesian analysis of a clinical trial combines prior information (analogous to the clinical data that prompts investigation) with the likelihood of the observed trial data (analogous to the result of the diagnostic test) to compute a posterior probability of benefit (analogous to the posttest probability of having the disease).

Prior information is an important component of Bayesian analysis that requires thorough justification and is not included in frequentist analyses. The prior information itself is summarized in the form of a probability distribution, which is an equation that can be used to calculate the chance that an intervention will have benefit. Justification for a prior distribution can consider aspects of the trial design that were not accounted for in the analysis, prior clinical research relating to the specific topic or the general area, and mechanistic information justifying the plausibility of a causal relationship. Relevant prior data can be incorporated into a prior distribution but given less weight if the information is not perfectly pertinent to the situation at hand. For example, in their Bayesian reinterpretation of a recent trial evaluating the use of extracorporeal membrane oxygenation in acute respiratory distress syndrome, Goligher and colleagues used priors based on a meta-analysis of similar studies, giving these studies weights between 0% and 100% (4). Another approach to constructing priors involves querying experts to build empiric distributions, which can yield complex distributions that are not described by a closed form equation (5). Different scientists may weight different aspects of the prior information with more or less importance, yielding some variation in prior distributions.

Just as Zampieri and colleagues have done, a thorough Bayesian analysis should consider multiple prior distributions representing different ways of synthesizing prior information into a distribution, so that readers can see the impact of prior information on the results of the analysis (6). In their Bayesian reanalysis, Zampieri and colleagues selected four priors for the odds ratio, labeling them optimistic, neutral, null, and pessimistic. The optimistic prior encodes belief that the therapy will have clinical benefit, the pessimistic prior encodes belief that the therapy will cause harm, and the neutral prior encodes belief that extremes of benefit and harm are both unlikely. Based on particular details of the mechanism, background literature, and trial, each reader can decide whether the optimistic, neutral, or pessimistic prior best represents their view of the prior information and see how that impacts the results.

The ability to adjust prior distributions based on subjective information is a true strength of Bayesian analyses, even though it is sometimes characterized as a weakness. Clinicians are not swayed by irrational prior distributions that, for example, violate

the principles of equipoise. In analyses of frequentist trials, the same arguments used to justify prior distributions regarding mechanism, trial design, prior research, and external validity appear in the DISCUSSION section instead of the METHODS section, and neither authors nor critics are required to quantify the effect of the study's limitations or areas of controversy on their results. Bayesian analyses with thoughtful prior distributions provide an opportunity for clinicians to quantitatively and transparently incorporate multiple modes of evidence and context into their interpretation of randomized trial data, with the hope of making the best possible decisions for critically ill patients. Broader adoption of Bayesian analyses in critical care medicine trials will promote transparency in combining all available sources of data for clinical decision-making. ■

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

Christopher J. Yarnell, M.D.
Interdepartmental Division of Critical Care Medicine
 and
Institute of Health Management, Policy, and Evaluation
University of Toronto
Toronto, Ontario, Canada
 and
Mount Sinai Hospital
Toronto, Ontario, Canada

John T. Granton, M.D.
Interdepartmental Division of Critical Care Medicine
 and
Division of Respiratory
University of Toronto
Toronto, Ontario, Canada

George Tomlinson, Ph.D.
Institute of Health Management, Policy, and Evaluation
University of Toronto
Toronto, Ontario, Canada
 and
Department of Medicine
University Health Network and Mount Sinai Hospital
Toronto, Ontario, Canada

ORCID IDs: 0000-0001-5657-9398 (C.J.Y.); 0000-0002-9328-6399 (G.T.).

References

- Zampieri FG, Damiani LP, Bakker J, Ospina-Tascón GA, Castro R, Cavalcanti AB, *et al.*; ANDROMEDA-SHOCK Investigators and the Latin America Intensive Care Network (LIVEN). Effects of a resuscitation strategy targeting peripheral perfusion status versus serum lactate levels among patients with septic shock: a Bayesian reanalysis of the ANDROMEDA-SHOCK trial. *Am J Respir Crit Care Med* 2020;201:423–429.
- Hernández G, Ospina-Tascón GA, Damiani LP, Estenssoro E, Dubin A, Hurtado J, *et al.*; The ANDROMEDA SHOCK Investigators and the Latin America Intensive Care Network (LIVEN). Effect of a resuscitation strategy targeting peripheral perfusion status vs serum lactate levels on 28-day mortality among patients with septic shock: the ANDROMEDA-SHOCK randomized clinical trial. *JAMA* 2019;321:654–664.

3. Wasserstein RL, Lazar NA. The ASA's statement on p -values: context, process, and purpose. *Am Stat* 2016;70:129–133.
4. Goligher EC, Tomlinson G, Hajage D, Wijeyesundera DN, Fan E, Jüni P, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome and posterior probability of mortality benefit in a post hoc Bayesian analysis of a randomized clinical trial. *JAMA* 2018;320:2251–2259. [Published erratum appears in *JAMA* 321:2245.]
5. Johnson SR, Tomlinson GA, Hawker GA, Granton JT, Feldman BM. Methods to elicit beliefs for Bayesian priors: a systematic review. *J Clin Epidemiol* 2010;63:355–369.
6. Spiegelhalter DJ, Freedman LS, Parmar MKB. Bayesian approaches to randomized trials. *J R Stat Soc Ser A (Statistics Soc)* 1994;157:357.

Copyright © 2020 by the American Thoracic Society



Evaluating Long-Term Benefits of Chronic Azithromycin Furthering Our Quest for Precision Medicine

Interest in macrolides as a treatment for cystic fibrosis (CF) arose in the 1990s, when the effect of erythromycin on clinical outcomes in diffuse panbronchiolitis, a severe inflammatory airway disease predominantly seen in older East Asian men, was recognized (1). After initial reports of benefit (2), several randomized, placebo-controlled trials of azithromycin were conducted in adults and children with CF, with and without *Pseudomonas aeruginosa* (PA; Table 1).

Based on these trials, the Cystic Fibrosis Foundation (CFF) guidelines recommend chronic azithromycin (AZM) for individuals with persistent PA and consideration of its use for those without PA (3). However, antagonism between AZM and inhaled tobramycin has been observed *in vitro* and in a secondary analysis of inhaled aztreonam trials, raising concern about its safety and efficacy (4, 5).

AZM's mechanism of action in CF appears to be primarily immunomodulatory, rather than anti-infective. *In vitro*, AZM downregulates neutrophil chemotaxis and IL-8 and GM-CSF production by bronchial epithelial cells (6, 7). In clinical trials, AZM use was associated with decreased neutrophil elastase and IL-8 in PA-infected subjects (8) and reduced C-reactive protein, serum amyloid A, calprotectin, and absolute neutrophil count in PA-negative subjects (9). The only changes in microbiology noted in clinical trials were increased AZM resistance among *Staphylococcus aureus* and *Haemophilus influenzae*; no treatment-emergent pathogens were noted (10), although AZM's potential effect on the microbiome is unknown.

Although clinical trials have demonstrated short-term efficacy of AZM and led to its widespread adoption in patients with CF with chronic PA and, to a lesser degree, those without PA (11), long-term studies of the effectiveness of AZM have been lacking until now (12). In this issue of the *Journal*, Nichols and colleagues (pp. 430–437) report an analysis of the CFF Patient Registry (CFFPR) showing a significant AZM-associated reduction in FEV₁ percentage predicted (pp) decline over the course of 3 years in patients with chronic PA compared with those not prescribed AZM (difference, 0.88 pp; 95% confidence interval [CI], 0.30–1.47

pp) (13). Among patients without chronic PA, a small nonsignificant reduction in FEV₁ pp decline was found. Addressing the concern regarding AZM-tobramycin antagonism, the effect on FEV₁ pp decline in patients prescribed AZM and inhaled tobramycin was not significant, whereas those prescribed AZM and inhaled aztreonam had slower decline (0.49 pp; 95% CI, –0.11 to 1.10 pp).

The study found no benefit in reduction of exacerbations. One plausible explanation, offered by the authors, is that their analysis considered only exacerbations treated with intravenous antibiotics, whereas previous trials considered those treated with oral antibiotics as well (10). However, other explanations that address the validity of their methodologic approach are worth discussing.

Observational data from CF registries can provide insights into associations of outcomes with exposures (including therapeutics) that cannot be obtained from randomized clinical trials for ethical or pragmatic reasons. The use of these data for comparing effectiveness of therapeutics in real-world practice is attractive, but also challenging: potential methodologic pitfalls and threats to validity must be acknowledged and their consequences explicitly weighed (14). The CFFPR is an especially successful patient registry, with high-quality data on approximately 95% of the CF population in the United States and a notable history of impactful publications (15). However, studies that use any preexisting database must make pragmatic methodologic compromises to adapt and format the data set to their own needs. For example, in the current study, AZM treatment was dichotomized into low and high AZM use because CFFPR data collection does not granularly address how patients were truly prescribed AZM (3). Similar problems and solutions involved the determination of inhaled tobramycin and aztreonam use (13). Furthermore, in the real world, adherence to chronic CF therapies is about 50% (16). These challenges to appropriate classification of exposures likely bias the estimate of effect downward.

In addition, preexisting databases such as the CFFPR do not include all pertinent confounding variables relevant to a particular analysis. For studies of therapeutics, this is especially challenging because of the problem of indication bias. In clinical practice, clinicians' perception of illness severity and prognostic factors influence treatment choice. Typically, therapies are prescribed preferentially to patients deemed at high risk. This may lead to the appearance of no effect, or even an adverse effect, in population-wide analyses unadjusted for these considerations.

©This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0 (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). For commercial usage and reprints, please contact Diane Gern (dgern@thoracic.org).

Originally Published in Press as DOI: 10.1164/rccm.201911-2234ED on December 6, 2019