EDITORIAL

Time for Clinicians to Embrace Their Inner Bayesian?
Reanalysis of Results of a Clinical Trial of Extracorporeal Membrane Oxygenation

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This issue of *JAMA* includes a Special Communication by Goligher et al[1] reporting a Bayesian reanalysis of the results from the recent Extracorporeal Membrane Oxygenation (ECMO) to Rescue Lung Injury in Severe Acute Respiratory Distress Syndrome (ARDS) (EOLIA) trial. This trial, which tested whether routine early ECMO reduced mortality for patients with severe ARDS, was stopped early for futility, and concluded that ECMO was not shown to reduce mortality.[2] In contrast, Goligher et al found it highly probable that ECMO lowers mortality, incorporating various assumptions, although it is unclear whether the benefit is as large as that assumed when the EOLIA trial was designed. How can the conclusions drawn from these 2 analyses of the same trial be so different?

Related article

Frequentist vs Bayesian Inference

Frequentist statistics focus on the probability with which differences in outcomes between 2 groups (one treated with the experimental therapy and the other not), or differences more extreme, would occur by chance alone.[3] In common practice, if the chance (*P* value) is less than .05, the conclusion is that chance alone cannot account for the differences seen and thus the treatment affects outcome. This approach is algorithmic and familiar. Proponents argue the approach also has rigor because it does not rely on subjective assumptions. Its drawbacks include (1) the inability to express the probability of benefit quantitatively when framing a trial as simply positive or negative; (2) the approach is counterintuitive and prone to frequent misinterpretation; (3) findings of no difference between groups may occur because the assumed treatment effect was unreasonably high (a choice that is subjective); and (4) there is limited ability to interpret results in the context of what else is known about the intervention.

In contrast, Bayesian inference directly estimates the probability that a conclusion is true given the data observed in an experiment, without any requirement that the conclusion is binary. Bayes' theorem mathematically combines prior information (prior data and beliefs) with new data (eg, the results of a new trial) to yield an updated summary of knowledge and the remaining uncertainty.[4] Specifically, a prior probability function, summarizing the prior information, is combined with a likelihood function, summarizing all information contained in the new data, to create a posterior probability function that represents the updated information. Bayesian analyses produce probability statements regarding the truth of a conclusion, such as in the analysis of Goligher and colleagues[1] there was a 92% probability that the absolute risk reduction (ARR) in mortality associated with ECMO was greater than 2%. Proponents argue that such statements are more likely than *P* values to be interpreted correctly by clinicians and patients and that Bayesian inference is more intuitive, aligning conceptually with the way humans typically judge whether something might be true.

Bayes' theorem also provides a framework for sequential learning: the current posterior probability function naturally serves as the prior function for the interpretation of future data. Its major drawbacks include (1) relative lack of familiarity within the medical research community; and (2) concerns that the reliance on subjective prior information will render the conclusions suspect or invalid.

The Case for or Against ECMO for Severe ARDS

Severe ARDS can lead to hypoxic death despite mechanical ventilation and intensive care. When first introduced, ECMO was shown to provide effective gas exchange but with frequent complications.[5] ECMO has become safer, but other treatment options for ARDS have also improved. Against this changing clinical landscape, multiple trials and observational studies comparing ECMO with other treatments have yielded conflicting results. Expert opinions are highly variable on the role of ECMO, and EOLIA was intended to settle the debate. The trial was powered to test whether use of ECMO for very severe ARDS would reduce mortality from an anticipated 60% to 40% (ARR of 20%; relative risk [RR] of 0.67) when compared with a supportive care group that permitted late use of ECMO if necessary. The data and safety monitoring board stopped the trial early for futility. With 249 patients randomized, the observed mortality rate was 11% lower in the ECMO group (35% in the ECMO group vs 46% in the control group) but not statistically significant ($P = .09$). Furthermore, 28% of patients in the control group received ECMO. Rather than settling the debate, the study fueled it anew, with multiple conflicting opinions expressed regarding the interpretation of the trial.[6-11]

Bayesian Interpretation of the EOLIA Trial

By using a Bayesian approach, Goligher et al calculated the entire distribution of probabilities regarding the potential benefit of ECMO (eg, the probability that ECMO provides any benefit [RR <1], at least a 2% ARR, at least 4% ARR, and so on up to that tested in the trial: ≥20% ARR and RR <0.67). Their analysis

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incorporated the data from the EOLIA trial, which are fixed and known, and prior information, which must be defined and can be varied. They approached the definition of prior information in 2 ways: mathematical representations of differing opinions (skeptical, neutral, and enthusiastic) and from a meta-analysis of prior studies, further discounting previous results by various amounts to reflect differing estimates of their relevance.

The goal of repeating the analysis with differing prior information is to determine the sensitivity of the results to differing prior beliefs that might be held by diverse clinicians or other stakeholders. If the qualitative interpretation of the trial is dependent on a particular prior, then individuals with different prior beliefs would reasonably interpret the trial results differently. Alternatively, if the results change minimally, the conclusion is that the findings should be interpreted consistently. Broadly speaking, the probability estimates regarding whether ECMO had any effect (RR <1) were independent of choice of prior (ranging from 88%-99% probability that ECMO reduces mortality).[1] Meanwhile, the probability that ECMO reduced mortality by at least 20% was low and variable (range, 0%-48%).[1] Thus, the Bayesian analyses support a consensus that ECMO lowers mortality but, at the same time, demonstrate that there remains substantial variability in the conclusions to be drawn regarding whether ECMO confers a large benefit. In contrast, the original frequentist analysis was silent with regard to whether ECMO had any effect and only supported the conclusion that the results from the EOLIA trial cannot support a finding of large benefit.[2]

Caveats to the Bayesian Approach

A Bayesian analysis is only transparent to the degree that individuals understand the information represented in the prior distributions—both the magnitude of the assumed treatment effect and the strength of that assumption. Thus, although Goligher et al calculated the probability of benefit across a range of priors, an important issue is whether the range represents the full diversity of informed prior opinion. For example, a prior distribution may indicate a belief that ECMO is protective but allow for tremendous uncertainty and thus convey very little information. There are no standard prior distributions for summarizing clinical opinions, and terms like *strongly enthusiastic* or *moderately pessimistic* may be applied to markedly different probability distributions. Therefore, communicating the strength and content of a prior is often best done graphically or by stating the number of equivalent patient outcomes and the associated treatment effect that the prior distribution represents (see Table 1 of Goligher et al).

In the article by Goligher et al, the use of prior information derived from a meta-analysis of prior trials illustrates the type of sequential updating of knowledge that is a strength of the Bayesian approach.[4] However, given ubiquitous differences in the details of trials (eg, differences in patient populations, settings, interventions, and outcome measures), prior and current trials may not be estimating the same treatment effect. To account for differences in opinion regarding the similarity of prior ECMO trials with the EOLIA trial, Goligher et al downweighted the prior information from the meta-analysis by decreasing the effective number of patients by 0%, 25%, 50%, and 75%. This downweighting maintained the same mean treatment effect but widened the uncertainty around it. By providing a range of downweighting, Goligher et al permitted readers to see all information and select that which corresponds to their personal belief regarding the degree with which prior trials and the current trial are similar.

What Next?

Even though Goligher et al focused on ECMO, there are many therapies in medicine for which there is conflicting evidence and varying opinion. Using ECMO as an example, it is clear that a Bayesian framework provides a wider, and arguably more informative, set of interpretations than that typically provided by a frequentist analysis. The Bayesian approach also provides an explicit quantitative display of factors that are often weighed internally and subjectively by experts when forming treatment recommendations.

Although the Bayesian approach appears explicit, much must be specified to understand its assumptions. Thus, if Bayesian analyses are to be used more commonly, 2 specific conditions are important. First, investigators should outline their proposed approach explicitly, in detail, and ideally before launching any new clinical trial. In that way, their analysis plan could undergo peer review, their selection of prior information may be vetted, and the design of the trial may be improved. Second, for consistency, rigor, and reproducibility, it is important to develop a set of standards for both the conduct and reporting of Bayesian analyses, similar to those widely adopted for other assessment methodologies, like clinical trials, meta-analyses, and cost-effectiveness analyses.[12-14]

The debate should not be cast as frequentist vs Bayesian inference: there is no need to choose. Rather, a better goal may be simply to promote greater and more rigorous use of Bayesian analyses as either a primary or a complementary tool for clinicians, patients, and policymakers. In addition, the findings of Goligher et al may help those evaluating ECMO to think differently about what questions are next. Clinicians and researchers should no longer ask "Does ECMO work?" because that question appears to be answered. Instead, the key question that should now be asked is "By how much does ECMO work, in whom, and at what cost?"

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