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SPECIAL ARTICLE

Annals Clinical Decision Making: Weighing Evidence to Inform Clinical Decisions

Joshua P. Metlay, MD, PhD, and Katrina A. Armstrong, MD, MS

Clinical decisions are ideally based on weighing the best available evidence on the risks and benefits of each option available, tailored to the individual patient in front of us. In many cases, evidence-based practice is well established, and a specific approach is supported consistently across guidelines from professional societies and print and online information sources. We can refer to these situations as "standards of care." But, in some cases, professional guidelines and print and online sources may disagree on the appropriateness and value of different strategies. Moreover, even in areas with broad consensus, new information that challenges the status quo, primarily in the form of peer-reviewed published studies, is available on a frequent basis. Yet, we must still make clinical decisions for the patient in front of us. In this article, we provide a structured approach for interpreting evidence in the absence of consensus or in the face of new and conflicting information.

We use a recent clinical case at our hospital that stimulated an important treatment discussion in response to 2 relatively recently published studies to discuss the steps necessary to make clinical decisions when new evidence conflicts with existing guidelines or current guidelines provide conflicting interpretations of available evidence. The steps are summarized in an algorithm that can be used over time to optimize individual clinical decisions in the absence of broad consensus about the appropriate treatment or test (Table).

Case

A 68-year-old man presents to the emergency department with a 4-day history of fever, anorexia, cough, and sputum production. His medical history is notable for hypertension and hyperlipidemia, with a remote smoking history in his 20s. Medications include a statin and thiazide diuretic. He has had no recent travel, but a family member was diagnosed with influenza illness 1 week ago.

Physical examination is notable for a temperature of 102.3 °F, heart rate of 110 beats/min, and scattered rhonchi on pulmonary examination. Room air pulse oximetry shows an oxygen saturation of 86%, which improves with 4 L of supplemental oxygen via nasal canula. A complete blood cell count demonstrates leukocytosis, but results of the remaining laboratory tests (electrolyte and blood glucose measurement, renal function tests, and liver function tests) are all normal. Chest radiography demonstrates a right middle-lobe consolidation consistent with community-acquired pneumonia.

The patient receives a combination of a β-lactam and macrolide intravenously in the emergency department and is admitted to the regular medical unit of the hospital for further management. The patient is presented by one of the residents during new patient rounds, and one of the medical students asks whether the patient should be started on a corticosteroid, because she heard that steroids reduce mortality in patients with community-acquired pneumonia (1). However, a quick check of the most recent American Thoracic Society/Infectious Diseases Society of America guideline for the management of community-acquired pneumonia reveals that steroids are not recommended in this setting (2).

How Does Existing Evidence Translate Into Individual Clinical Decisions?

For many clinical decisions, guidelines and evidence syntheses provide consistent recommendations across professional organizations, and the recommendations are relevant for the specific decisions in front of us. For example, antibiotic recommendations for empirical treatment of patients with community-acquired pneumonia have been consistent across professional organizations for many years and directly support the antibiotic treatment decision in this case.

However, for other clinical decisions, guidelines do not always address the most recently available evidence or may even provide recommendations that are not consistent with other systematic reviews. Physicians are constantly confronted with the challenge between adopting new approaches as the evidence emerges versus waiting for local and national groups to update existing guidelines before changing practice. But the latter approach is problematic. For one thing, the process of guideline generation or publication of clinical reviews is slow even while information on new diagnostic and treatment strategies is published at a fast pace (3). Thus, individual physicians need to be able to weigh new information in real time and make updated clinical decisions (4).

When Should I Reevaluate My Approach to Individual Treatment Decisions?

We are constantly making clinical decisions in practice, but the outcomes of these decisions are influ-

See also:

Editorial comment 627

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Table. A Stepwise Approach to Using Evidence to Make Clinical Decisions

Step	Action
1	Clearly state the treatment decision that you are evaluating. A useful approach is summarized in the mnemonic PICO: *patients* (what type of patient are you treating), *intervention* (what treatment are you considering), *comparator* (what is the alternative treatment you are considering), and *outcome* (what is the main outcome you are trying to influence).
2	Determine the quality of the information addressing the PICO. As a start, if multiple guidelines and/or reference sources provide consistent advice about the treatment decision and the treatment effects are likely to be relevant to the patient in front of you, then you can apply the existing guideline to the treatment decision. If new evidence is now available that may alter the recommendation of existing guidelines, you need to evaluate the evidence driving the decision.
3	Evaluate the strengths and weaknesses of the new evidence. Randomized clinical trials provide high-quality evidence and observational studies provide lower-quality evidence of the risks and benefits of a specific test or treatment or management strategy. Studies with bias, small effect sizes, and inconsistent results compared with other available studies are downgraded. Studies with minimal bias, large effects, and coherence with prior information are upgraded.
4	Consider the probability that the patient you treat would be included in the study you are evaluating. Do differences between your patient and the patients in the study matter in terms of the PICO question being addressed?
5	In the face of high-quality evidence that applies to your patient, consider whether the evidence changes the risk–benefit assessment sufficiently to modify your treatment decision. Consider evidence on both benefits and harms.
6	Interpret the actual outcome of your treatment decision in light of the broader evidence. Individual results that contradict the evidence do not invalidate the evidence but should compel you to constantly reevaluate the available evidence.

enced not only by the treatment decisions, but also by many observable and unobservable factors (such as confounders) that influence those treatment decisions. Moreover, each of us can only collect a relatively small number of data points on the comparative risks and benefits of treatments in our own experience, and the outcomes of those experiences can be biased by the spectrum of patients we treat and methods we use to assess outcomes (5). Thus, we need to rely on publicly available evidence, primarily in the form of published studies, which report the outcomes of large studies that minimize the risks of bias, confounding, and chance. Bias reflects systematic error in the study design that influences the types of patients selected for the studies or the types of measures used in the analysis and distorts the true association between an exposure and an outcome. Confounding reflects the influence of a measured or unmeasured factor that affects the observed strength of association between an exposure and outcome. Randomized controlled trials are the gold standard for evidence in medicine, but many important decisions will never be addressed by trials, and we must therefore rely on well-designed observational studies.

How Can I Determine Whether New Evidence Is Strong Enough to Change Practice?

We typically assign the most weight to the design of the study, giving high value to individual-level randomized trials for their ability to balance known and unknown confounders (6). But, randomized trials themselves vary in the quality of randomization and blinding, as well as in the amount of participant attrition and missing data (7, 8). Design flaws in a randomized trial can downgrade the quality of evidence. Even more important, we ultimately rely on the consistency of evidence across multiple randomized trials and other studies to adopt new treatments into practice (or, conversely, discard old treatments). This is, of course, very challenging for individual clinicians to evaluate, because we rarely maintain a high level of awareness of all of the studies addressing a particular treatment, especially for areas outside of narrow bands of expertise. Systematic reviews, meta-analyses when appropriate, and guidelines attempt to address this challenge on our behalf but, as noted above, may be delayed or unavailable in many settings (9). Still, when multiple randomized trials point to a consistent benefit, it is probably time to consider changes in practice.

Can Evidence From Nonrandomized Trials Be Used to Change Clinical Decisions?

Observational studies (for example, cohort studies and case–control studies) can also provide important new information to modify current treatment decisions. For example, safety questions regarding treatments often rely on larger sample sizes than included in the premarketing clinical trials and are therefore observed in larger cohorts of patients after drug approval. Moreover, improved methods for balancing measured confounders, including propensity score matching, can improve the validity of treatment estimates measured in nonexperimental studies and thereby greatly expand the range of studies available to support treatment decisions.

How Do I Decide Whether Individual Patients Should Be Affected by Evidence From New Studies?

We have been repeatedly reminded that clinical trials are often very selective, and the vast majority of patients with a given illness are ultimately not eligible for a trial. Trials frequently exclude patients on the basis of age, comorbid illnesses, and prior treatment exposures. Perhaps most important, trials require informed consent, and many patients decline. It is known that participants and nonparticipants in trials differ in important, and not always easily measurable, ways (10). Thus, the benefits of large randomized clinical trials, which minimize the risks of bias and confounding to maximize the internal validity of the measured treatment effect,

are achieved at the risk of minimizing the external validity of the result (Figure).

Observational studies reduce the problem of external validity by typically including a much wider range of patients that reflects the types of patients seen in usual clinical practice, but these studies may consequently reduce internal validity, specifically by increasing the presence of bias and confounding. Ultimately, we must identify the key differences between study participants and the patients in front of us, and then decide whether these differences are likely to affect the treatment risks and benefits. In truth, the bulk of the evidence from past trials suggests that treatment benefits do extend to the broader patient population seen in clinical settings, so given basic agreement on disease and major exclusion criteria, it is probably very reasonable to apply the results of relevant clinical trials and well-designed observational studies to the patients we see in clinical practice (11).

How Do I Translate New Information Into Individualized Treatment Decisions?

Even if a new study provides valid evidence of a treatment benefit that would apply to the patient you are treating, the outcomes measured in the study may or may not be relevant to the patient in front of you. For example, many treatment benefits are expressed in terms of mortality benefits, but those benefits may be much less relevant for patients with very-low-severity forms of a disease, because the effect of nontreatment is much lower. This heterogeneity of treatment effect occurs independent of the quality of evidence available and ultimately requires the use of additional clinical information to tailor treatment decisions to individual patients. Such an approach is the subject of another article in this series (12).

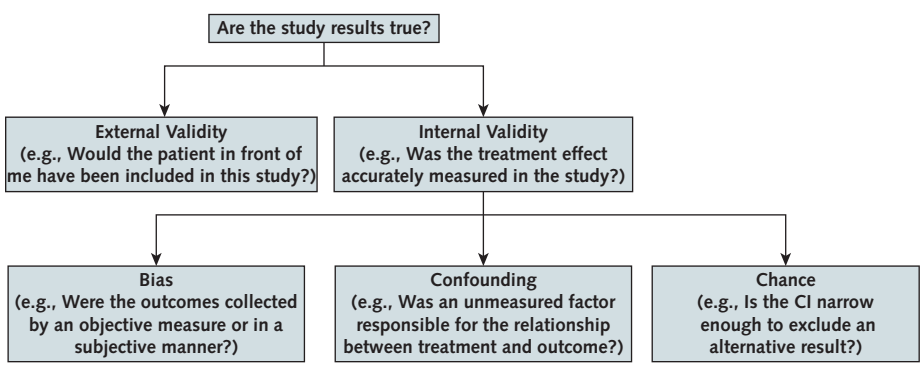
In addition, some benefits may be of limited relevance to the patient themselves (for example, issues of resource utilization, such as length of hospitalization) and should not influence decision making from the patient perspective even if they are relevant to other stakeholders (payers or health systems, for example). Another article in this series (13) addresses approaches for reconciling different decision maker perspectives in clinical decision making when the perspective alters the decision. Finally, treatment benefits can be challenging to consider at an individual patient level because they are typically measured and expressed at population levels, in terms of the number needed to treat or the absolute risk reduction. In health care, we evaluate treatments from a probabilistic framework, but each patient will experience a binary result (treatment benefit, yes or no) (12). Certainly, as the absolute risk reduction becomes smaller, we can infer that the individual patient is less likely to benefit, and yet, there remains the reality that each patient will experience a binary result (treatment benefit, yes or no; treatment harm, yes or no).

Reviewing the Evidence in This Case

It is unlikely that most clinicians will be familiar with all the randomized trials that evaluated the effect of corticosteroids on survival for patients with community-acquired pneumonia. However, a meta-analysis identified 12 separate trials addressing this question, and when the data for all the trials were pooled, there was an overall mortality benefit for patients assigned to the corticosteroid treatment group, though it was essentially restricted to the subgroup of patients with severe pneumonia (1). Of note, there was significant heterogeneity in the trial results. Moreover, only 2 of the included trials individually demonstrated a statistically significant benefit of corticosteroids. Thus, others have concluded that the level of evidence is insufficient to warrant routine use of corticosteroids for patients with community-acquired pneumonia (14).

Of course, treatment decisions involve the risks of benefits and harms. Interestingly, a separate meta-

Figure. Validity assessment diagram.



The diagram illustrates that the interpretation of the results of any study requires an assessment of internal and external validity. Internal validity addresses the degree to which the study results are true for the patients included in the study. Threats to internal validity include bias in patient selection and outcome measurement, confounding, and random error. External validity addresses the degree to which the study results can be extrapolated to other patients with the same or similar conditions. Randomized clinical trials often emphasize the importance of internal validity at the cost of external validity.

analysis assessed the risks and benefits of corticosteroids in patients with influenza (15). (Recall that the patient was exposed to someone with influenza at the onset of his illness.) No randomized trials had addressed this question, but a pooled result of 12 observational studies indicated a significant increase in mortality in patients with influenza treated with corticosteroids. The authors acknowledged that the quality of the evidence is low, given significant study heterogeneity and concerns about confounding by indication, a form of confounding that occurs when treatment decisions are influenced by the severity of illness of patients, falsely raising or lowering the estimate of treatment harm or benefit.

Changing our standard treatment strategies in the face of new cases of illness is challenging. We clearly wish to avoid harming a patient by being too quick to adopt a new treatment. Yet, concern about withholding valuable new treatments, especially when life-saving, is equally and at times even more powerful. The more we can identify subgroups of patients who benefit from treatments, the more precise we can be in assigning new therapies. Genetic and physiologic markers hold much promise in that approach, though we are still often in the setting of initially evaluating new therapies among relatively broad groups of patients. For example, inflammatory markers in patients with pneumonia (such as an elevated C-reactive protein level) can identify a subgroup with an excess of proinflammatory mediators (16). It is possible that corticosteroid treatment for that subgroup will further magnify the benefit.

Returning to the case in this article, we should acknowledge that patients admitted to the hospital with community-acquired pneumonia continue to face significant mortality risk, despite the availability of effective antibiotic therapy and other supportive interventions. Thus, the availability of multiple studies pointing toward a mortality benefit with the use of corticosteroids for patients with pneumonia is a relevant outcome. Moreover, although this patient may not meet strict criteria for severe pneumonia (17), his age and compromised respiratory status are poor prognostic signs. On the other hand, the hospital did not have the capacity for point-of-care testing of C-reactive protein or procalcitonin, limiting the utility of measuring inflammatory markers to guide early treatment decisions. Finally, although influenza infection was not confirmed in this patient, the history of exposure was concerning, especially in light of the data suggesting harm of corticosteroids in these patients.

In the clinical case presented here, corticosteroids were not administered, and the patient had an uneventful recovery from pneumonia. This individual outcome does not, of course, invalidate the consideration of using steroids in future cases of pneumonia, especially if future research identifies a better subgroup of patients for treatment with corticosteroids. Such is the challenge of making individual decisions based on individual case experiences and the limitations of extending data from clinical trials and observational studies to individual decisions (as discussed in other articles in this series [5, 12]). But decisions still must be made, and those decisions will be better the more we understand the data behind the treatment benefits and risks and learn how to apply those results to our patients.

From Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts (J.P.M., K.A.A.).

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Corresponding Author: Joshua P. Metlay, MD, PhD, Division of General Internal Medicine, Massachusetts General Hospital, 100 Cambridge Street, 16th Floor, Boston, MA 02114; e-mail, jmetlay@mgh.harvard.edu.

Current author addresses and author contributions are available at Annals.org.

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Current Author Addresses: Dr. Metlay: Division of General Internal Medicine, Massachusetts General Hospital, 100 Cambridge Street, 16th Floor, Boston, MA 02114.
Dr. Armstrong: Massachusetts General Hospital, Gray-Bigelow 7, 55 Fruit Street, Boston, MA 02114.

Author Contributions: Conception and design: J.P. Metlay, K.A. Armstrong.
Analysis and interpretation of the data: J.P. Metlay.
Drafting of the article: J.P. Metlay.
Critical revision of the article for important intellectual content: J.P. Metlay, K.A. Armstrong.
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Collection and assembly of data: J.P. Metlay.