APPLYING EVIDENCE TO THE CARE OF A PATIENT WITH BACTERIAL MENINGITIS: HOW TO EVALUATE A THERAPEUTIC OPTION

Case and Discussion: *Laura J. Nicholson, MD, PhD*

Editor: *John G. Frohna, MD, MPH*

Making decisions about medical therapy is increasingly challenging as new medications arrive on the market and new scientific research outdates previously accepted therapeutic standards. This challenge is especially difficult when a treatment decision must be made urgently due to the high morbidity or mortality associated with a suspected diagnosis. In these situations, information must be quickly accessible and of high quality to ensure prompt institution of therapy based on the best available evidence.

This article uses a case of acute bacterial meningitis to demonstrate how to find, appraise, and apply the best available evidence when faced with making an urgent therapy decision. Most published trials addressing therapeutic options compare one treatment to another, following for defined outcomes. Understanding how these trials are appraised and how to use the resulting information is critical for successful patient care. In urgent clinical settings, time does not always allow us to do this critical appraisal prior to instituting therapy. In these situations, prescreened evidence-based medicine (EBM) resources are becoming a reliable source of critical information. Use of these databases allows fast access to the best clinical evidence during busy clinics or rounds. Treatment decisions thus can be reached during active patient care in much less time than required for individual appraisal of relevant therapy studies.

Assessing the Clinical Problem

You are the medicine resident called to the emergency department (ED) to examine Mr. Johnson, a 72-year-old man who walked into the ED complaining of sudden onset of shaking chills and high fever.

Laura J. Nicholson, MD, PhD, Department of Medicine, University of California San Diego Medical Center, San Diego, CA; and John G. Frohna, MD, MPH, Departments of Internal Medicine and Pediatrics, University of Michigan Medical School, Ann Arbor, MI.

The patient describes a week of left ear discomfort, rhinorrhea, sore throat, and dry cough, which he interprets as a "cold" he got from a sick grandchild. He had no chills or fever until today. His only past medical history is a remote shoulder injury for which he had surgery. He takes no medications and denies any allergies. The patient is married and owns a successful art gallery, where he works full-time. He exercises regularly and does not smoke.

On physical examination, Mr. Johnson is alert and able to describe his symptoms clearly. Vital signs include: temperature, 101.8°F; blood pressure, 154/68 mm Hg; pulse, 116 bpm; respiratory rate, 30 breaths/min, with an oxygen saturation of 94% on 2 L of nasal oxygen; and weight, 145.5 lb. Examination of the head, eyes, ears, nose, and throat is unremarkable except for mild postnasal drainage; the neck is supple, without lymphadenopathy. The lungs are clear, and the heart is tachycardic and regular, with no audible murmur. There is no costovertebral angle tenderness, and the abdomen is benign. Extremity examination reveals well-developed musculature, no edema, and +2 pulses throughout. Neurologically, the patient is fully oriented, with a nonfocal motor examination and a normal gait.

Initial blood chemistries demonstrate mild dehydration, with a sodium of 142 mmol/L, blood urea nitrogen of 23 mg/dL, and creatinine of 1.1 mg/dL. Although the white blood cell (WBC) count is normal at $9.1 \times 10^3/mm^3$, with 79% neutrophils, the radiologist reports a probable early right lower lobe infiltrate on chest radiograph. Urinalysis, anion gap, and liver function tests are unremarkable. You make a diagnosis of lobar pneumonia and admit Mr. Johnson, starting him on ceftriaxone 1 g intravenously (IV) every 24 hours and erythromycin 500 mg IV every 6 hours.

Eight hours later a nurse on the ward calls to say that Mr. Johnson has become confused and agitated. On reexamination, you find his behavior different from that observed in the ED, with increasing somnolence, trouble understanding why he is in the

hospital, and a tendency to pull at his IV lines. He now complains of a headache, and you find his neck has become somewhat stiffer, although the rest of the physical examination remains unchanged. You order immediate repeat complete blood count with differential, a basic metabolic panel, and head computed tomography (CT) with contrast. Within 3 hours you are informed that Mr. Johnson's WBC is now $30.3 \times 10^3/mm^3$, with 89% neutrophils and 4% bands. The CT scan shows high-density material layering within the atria of the lateral ventricles bilaterally, consistent with a small amount of blood or inflammatory cells; brain parenchyma is normal.

You perform a lumbar puncture. A few hours later, now 20 hours since Mr. Johnson presented to the ED, you are notified that the WBC in the cerebrospinal fluid (CSF) is $5820/mm^3$, with 81% neutrophils; 130 red blood cells/mm^3 also are present. Total protein in the CSF is 313 mg/dL, and glucose is 53 mg/dL. The Gram stain shows many neutrophils but no bacteria. The microbiology laboratory then pages you with a preliminary report that all four blood culture bottles sent from the ED are growing a gram-positive organism resembling *Streptococcus pneumoniae*.

You now are convinced that Mr. Johnson has pneumococcal meningitis, which you know is associated with a high mortality rate and a high rate of neurologic sequelae in survivors. You are uncertain of all the predictors for poor outcome but know that mental status change, which Mr. Johnson is experiencing, is one of them. You recall a meta-analysis presented during your pediatrics rotation in medical school, which found that adjuvant glucocorticoid therapy (to address subarachnoid inflammation) reduced rates of deafness and other neurologic deficits in children with bacterial meningitis [1]. However, you are uncertain whether glucocorticoids have subsequently been shown to benefit adults, or whether a mortality benefit was ever shown in any age-group.

Assessment in Urgent Clinical Settings

To begin the EBM process, we must apply our training and experience in a broad-based assessment step. We need to gather accurate, patient-specific data pertinent to the problem or patient care concern; judge the urgency, timing, and magnitude of the concern for our patient as well as the relevant population; and assess the state of the evidence as well as our own knowledge on the subject. All these considerations help us to choose the next course of action and to define critical information needs.

In the case of Mr. Johnson, we have diagnosed pneumonia and later used our clinical assessment skills to determine that the infection also is present in the patient's central nervous system (CNS). Thus, our next course of action is based on the more dire diagnosis of bacterial meningitis. The central concern is to rapidly institute appropriate therapy that will ensure the best possible patient outcome. In the process of collecting pertinent patient data, we come to know our patient's desires and values, which help us to choose a therapeutic option we believe our patient would wish to pursue. Here, Mr. Johnson works full-time and exercises regularly, allowing us to conclude that he would likely seek treatments preserving life and optimal neurologic function.

In this case, our assessment reveals a question about the treatment of adult bacterial meningitis—whether adding corticosteroids to the therapeutic regimen would be beneficial. Simultaneously, a sense of urgency of the clinical problem exists. Certain clinical situations may be so urgent that attempts to seek additional information should be abandoned. For example, there is no time to explore new approaches to chest tube insertion in the setting of tension pneumothorax. For a patient with bacterial meningitis, short time to antibiotic therapy is critical. If we decide to pursue treatment options before initiating therapy, how serious are the consequences of any resultant delay in treatment? Thus, an important identified information need is to determine whether adding corticosteroids will benefit Mr. Johnson.

Asking a Focused Clinical Question

For treatment of Mr. Johnson's meningitis you order the higher doses of ceftriaxone recommended for penetration into the CSF (ie, 2 g IV every 12 hours). Because the rate of penicillin resistance is reported as 25% of the local pneumococcal isolates, you add IV vancomycin to the treatment regimen and stop the erythromycin at the same time.

While waiting for the antibiotics, you set out to find any information supporting the use of adjuvant corticosteroids in adults with bacterial meningitis. You estimate you have 30 minutes or less to discover whether giving corticosteroids will benefit your patient. In the meantime, you ask that a vial of dexamethasone also be made available to the ward.

Choosing an Information Source to Fit the Need

In an urgent clinical situation, we need to be highly efficient at finding answers to our clinical questions. At this point, we do not know whether our information

need represents a gap in personal knowledge or an unsettled issue in the medical literature. Although a textbook can be quickly consulted for generally accepted information that may be unknown to us personally, it is unlikely to include newer discoveries. In our case, we are interested in relevant evidence about the possible benefit of using steroids in adults with pneumococcal meningitis—information most likely found in recently published well-done clinical trials. A local expert may be consulted more rapidly than doing our own research, for information followed primarily by specialists, but the expert must be quickly accessible lest hours be spent waiting for his or her examination and consideration of the patient. In addition, we have no assurance that the expert's recommendation is based on the best available evidence. An alternative would be to search a computerized database of medical information, preferably a resource containing evidence about therapeutic options screened from the best available studies.

Framing the Need in a Clinical Question

For efficient medical literature searches, it is best to create a focused clinical question. In this way, we save the time it would take to scan through all the "hits" that result if a search is too broad. We also avoid the risk of extrapolating data that might not best apply to the clinical context at hand. If the focused question produces no results, it can be broadened later.

The recommended method for building a focused clinical question is to use the PICO format, where P stands for patient or problem, I for intervention, C for comparison intervention (which may be placebo), and O for outcome [2]. The PICO components for this case may be defined as:

P = adults with pneumococcal meningitis
I = steroid therapy in addition to antibiotics
C = antibiotics alone
O = mortality or neurologic impairment

Using this framework, our focused clinical question in Mr. Johnson's case would be:

> In **adults with pneumococcal meningitis**, does **steroid therapy in addition to antibiotics**, compared with **antibiotics alone**, reduce **mortality or neurologic impairment**?

Combining search terms from some or all of the PICO components produces a more focused search. For example, searching "pneumococcal meningitis" produces 2174 results on PubMed, many of which will not address the question at hand. Searching "pneumococcal meningitis and steroids and mortality" produces only 20 results on PubMed, which are more likely to address the specific question.

Acquiring the Current Best Evidence

Considering the historical controversy regarding adjuvant steroid therapy in adult bacterial meningitis, you know a textbook is unlikely to contain any recent data settling the issue. On the patient's ward are several computers with links to the local health sciences library. Being short on time, you click on the library's "Evidence-Based Healthcare" section to search Web sites of clinical information screened by experts for high validity and applicability to patient care.

The first database is the online version of *ACP Journal Club*, which offers structured abstracts and results of clinical trials, followed by brief expert commentaries. You click on this site, enter a search for "pneumococcal meningitis and steroids and mortality," and obtain one match, entitled "Dexamethasone improved disability in acute bacterial meningitis" [3]. The summary is of a study by de Gans and van de Beek [4] published in November 2002. You learn that this was a randomized, blinded, placebo-controlled trial that included 301 adults with bacterial meningitis. According to the conclusion, the study showed that in patients with acute bacterial meningitis, "adjunctive treatment with dexamethasone was more effective than placebo in improving disability and reducing death" [3]. The commentary indicates that the benefit of dexamethasone was "largely restricted to those with pneumococcal meningitis," and that, according to the commentator, "dexamethasone should now be considered the standard of care, provided that it is initiated before or at the same time as antibiotics" [5].

Wondering whether other recent studies may have been included in a Cochrane Systematic Review, you click on the next EBM database, the Cochrane Library. A search of "pneumococcal meningitis and steroids and mortality" produces one systematic review and two controlled trials. Noting that the trials are older, you choose the review, entitled "Corticosteroids in acute bacterial meningitis." You quickly skim the abstract, which cites the de Gans and van de Beek study as the basis for one of the reviewers' conclusions, that "dexamethasone should be given to all adults with bacterial meningitis and should be initiated before or with the first dose of antibiotics" [6].

You estimate that you have about 10 minutes left.

Pleased that you have found at least one relevant study and reviewed two useful summaries of this study, you turn to PubMed to search for any newer trials addressing the use of steroids in pneumococcal meningitis. You search the terms "pneumococcal meningitis and steroids and mortality." Twenty articles return, including cell culture and animal studies. You then limit your search by choosing "Clinical Queries" under PubMed Services, which adds EBM and clinical applicability filters. Clicking the "therapy" category and "specific search" emphasis and searching the same terms as before, you retrieve three articles, the newest of which is the de Gans and van de Beek study. Your online library supplies a link to the full text article, and you print it to skim now and appraise later.

The elements of your PICO question allow you to scan the article title and abstract for inclusion of these components. The authors' stated goal is to examine the effect of dexamethasone on the 8-week mortality and Glasgow Outcome Scale (a measure of neurologic deficit) in adults with bacterial meningitis. Scanning further you note that outcomes are measured for all patients combined and also separately for patients with specific pathogens, including *S. pneumoniae.* Having already seen the trial's results, you skip this section to quickly peruse the discussion section. Here, the authors warn that treatment failures have occurred in adults with penicillin-resistant pneumococcal meningitis, when adjunctive dexamethasone reduced vancomycin penetrance into the CNS.

Mr. Johnson's nurse reports that the antibiotics you ordered are ready to infuse. Time is up, and you decide against giving dexamethasone with the antibiotics because ceftriaxone was started on your patient more than 16 hours ago, albeit at the lower dose, precluding your ability to give steroids with or before the first antibiotic dose as recommended. In addition, you feel strongly that vancomycin must be used until the final antibiotic sensitivities have returned on the cultures.

Seeking Answers to Urgent Therapy Questions

The expanding number of medical information Web sites has enhanced our ability to access clinical information quickly. At times it seems there are too many choices, none of which stands out as the best place to find recommendations on which to base patient care decisions. EBM experts tell us that the majority of what is published in the medical literature does not satisfy accepted standards of research methodology or clinical applicability and therefore should not be used to develop standards of care unless no more valid data are available [7]. For this reason, information resources that have been prescreened for EBM methodology standards and levels of evidence allow us to focus on the best and most recent patient-centered research. Articles with lower quality methods or lack of clinical applicability have been sorted through and discarded, sparing us this chore.

Several databases of filtered evidence are now available. The editors of these resources are committed to filtering useful clinical information out of the available literature, some emphasizing the most recent data and others prioritizing the highest quality research methods. A benefit of these databases is that they can be searched quickly, during active patient care. A limitation, however, is the lag time required for the editors to screen the clinical journals, extract and appraise appropriate studies, and summarize the information. **Table 1** lists attributes and limitations of several filtered evidence sources, some of which were searched for Mr. Johnson's care.

ACP Journal Club. *ACP Journal Club* screens more than 100 clinical journals for articles relevant to internal medicine, applying rigorous standards of evidence-based literature appraisal and then inviting experts to comment regarding the clinical applicability of the studies chosen. Searching this Web site is simple and produces abstracts and commentary for individually published trials or meta-analyses; each article's results are summarized in tables that are easily scanned in seconds. Several months of lag time are created by the screening process, and searching this resource within 6 months of an appropriate article's publication will likely be too early for its incorporation. Another potential drawback of *ACP Journal Club* is its strict EBM methodology criteria, which prevents us from finding less rigorous attempts, however flawed, at answering our PICO question.

Cochrane Library. The Cochrane Library is a set of seven databases maintained by the Cochrane Collaboration, an international group of volunteer scholars dedicated to discovering and summarizing the best and most up-to-date evidence regarding medical therapies. For each therapy question addressed, the medical literature is thoroughly researched and then summarized as an entry in the Cochrane Database of Systematic Reviews, the Library's primary database. This database is updated quarterly. Each systematic review is in the form of an abstract, from which a quick treatment recommendation can be obtained, followed by a comprehensive description of the background, search strategy, and rationale for the

Table 1. Evidence-Based Medicine (EBM) Resources Amenable to Rapid Searches

Source/Description	Strengths	Weaknesses
ACP Journal Club		
Database of individual articles with high EBM validity, relevant to internal medicine	Strict inclusion criteria for high-quality articles Easily searched Concise article summary and tables of EBM results (RR, NNT, CI) Expert commentary included	Lag time to screen literature Unable to include all clinically relevant articles
Cochrane Library		
Compilation of seven EBM databases	Large number of clinical interventions reviewed Most comprehensive literature review for recommendations	Long lag time to results or recommendations Not a resource for questions other than therapy-type
MEDLINE		
Database of references/abstracts from 4500 biomedical journals	Articles available as soon as published Comprehensive and inclusive Multiple options for search strategy limitations	Limiting search depends on very focused strategy, due to large database size EBM limits vary with platform (PubMed versus OVID) Information has not been screened by EBM experts
PIER		
Compilation of EBM modules organized by diagnosis	Individual search can be further limited to queries regarding prevention, screening, diagnosis, therapy, etc Recommendations made in clear, easy-to-read outlines Level of evidence is reported for each recommendation Rationale, specific research evidence, and expert comments are presented	Lag time for review of topics Limited number of topics included (but growing) Must be ACP member to use it
UpToDate		
Comprehensive textbook-style resource of clinically relevant topics	New peer-reviewed version every 4 months Extensive number of topics reviewed Readable, in narrative style	Difficult to combine terms to narrow search Not every chapter is updated with each 4-month edition (lag time) No specific best evidence commitment for recommendations presented Many overlapping chapters for topics, not always with information consistency

ACP = American College of Physicians; CI = confidence interval; NNT = number needed to treat; RR = relative risk.

conclusion drawn from the data. Lag time can be extensive, and only therapy questions are addressed, but recommendations are backed by the most complete review of the literature of any of the filtered evidence resources.

Other EBM resources. PIER is an EBM tool created by the American College of Physicians (ACP) and restricted to use by ACP members. The Web site allows users to choose from among eight information types for each search, ranging from "prevention" to "drug information." PIER grades the level of evidence presented for each recommendation it makes. In this way, it presents literature that may lack sufficient rigor for inclusion in *ACP Journal Club* and yet

may be the best available information to date. *UpToDate*, as its name implies, commits to keeping information current, releasing a new peer-reviewed version every 4 months. Even with this short lag time, important information can be missed because individual chapters are rarely updated for every new version. However, *UpToDate* is comprehensive and easy to read, resembling a textbook that has a new edition three times per year.

PubMed searches with evidence filters. A search of one or more filtered evidence resources may not always reveal the most recent information critical to our therapeutic decision-making process. The only certain way to find the most recent studies of interest is to search unfiltered databases of medical information (eg, MEDLINE, PubMed). This leaves the appraisal of the information for us to complete on our own. Importantly, there are ways to limit these searches in order to recover high-quality, clinically applicable studies more likely to fulfill EBM criteria. For example, literature searches using the Clinical Queries option under PubMed Services allow the user to recover individual trials or systematic reviews that have been filtered for clinical relevance and high-quality research methodology. Categories for searching include "therapy," "diagnosis," "etiology," and "prognosis." Users can choose to emphasize a sensitive (broad) or specific (narrow) search. For example, choosing "therapy" and "specific search," the search "pneumococcal meningitis and steroids and mortality" produces only three articles, all likely to have sound research methodology and clinical applicability. Recall that the same search under the general PubMed heading produced 20 articles, meaning 17 have been filtered away. PubMed does this filtering by adding terms such as "randomized" and "controlled" to the search, not by expert appraisal of an article's content. In this way, filtering requires no lag time and can be instantaneous, allowing Clinical Queries searches to incorporate trials from date of publication.

Appraising Evidence for Validity and Importance

The following day, Mr. Johnson is gradually improving on IV ceftriaxone and vancomycin. He has regained orientation and knows why he is in the hospital, although he complains of hearing loss in his left ear. Having made your treatment decision for Mr. Johnson, you now have time to more closely examine the de Gans and van de Beek study.

You proceed with critical appraisal of the study following the criteria recommended by the authors of the Users' Guides (**Table 2**) [8]. The abstract and methods sections note that patients were randomized, with double-blinding of the allocation. You review the article's first table, which shows that groups were similar at the start of the trial except for more seizures at baseline in the dexamethasone group. You decide that this may mean these patients were more neurologically impaired, so any result showing better outcomes with dexamethasone retains validity. At the beginning of the results section you find an explanation of who was lost to treatment, noting that the last clinical observations of the lost patients were carried forward so that they were included in the results using an *intention-to-treat* analysis. Three patients were lost from the dexamethasone group and four from the placebo group, comprising less than 3% of patients overall. In addition, lost patients were similar in that six of seven had Glasgow Outcomes Scores of 5, and one had a score of 4.

Criteria for Appraising Validity

To begin critical appraisal of a therapy study, it is important to evaluate whether the authors used sound research methodology to ensure validity of the results. The Users' Guides outline specific questions that can be applied to an individual therapy study to ensure its methods will have the least possible bias toward any result (Table 2).

Randomization. The first of these questions addresses randomization (ie, the placement of a consenting patient into a treatment group randomly to avoid any bias introduced by choosing treatments for specific patients). Like team captains choosing players for sides in basketball, it would be impossible for a researcher to fully ignore his desired outcome while personally placing evaluated patients into treatment groups. Therefore, this method is not permitted for best evidence standards. An example of this bias occurs when patients stable enough for surgery are chosen for a surgical intervention, such as coronary artery bypass, while those not stable for surgery are treated medically. Comparing outcomes in these two groups will nearly always produce results showing surgery is better than medical treatment, but these results are biased unacceptably by healthier patients being chosen for the surgery group. Randomization of enough subjects produces groups expected to be similar at the start of the trial. The authors should always compare group characteristics for the reader, as important differences may occur by chance.

Double-blinding. Double-blinding means both the study subjects and the clinicians who are treating

them are not aware of the group assignment and therefore the treatment received. Blinding the patients prevents subjective reporting of outcomes that might be influenced by the patients' beliefs or expectations about the treatment. Blinding clinicians and other study personnel prevents biased reporting of outcomes based on expectations about treatments or hopes for the study's success. It also allows all subjects to be treated equally, since the clinicians have no information about their assigned treatment group.

Intention to treat. Analyzing patients in the groups to which they were randomized is called intention to treat. This principle means that if a patient did not complete a treatment because of side effects, or received a counteracting treatment for a nonstudy reason, or perhaps left the study altogether, that patient must be analyzed with the original group assigned. These confounding issues represent real-world occurrences and help the study represent the real-world population.

Follow-up. The more patients who are lost to follow-up in a study, the more validity will be compromised, since lost patients' outcomes are unknown. There is no set threshold for an acceptable percentage of patients lost to follow-up, but validity is helped if authors can show that the lost subjects were similar and how their outcomes were estimated. To discover the extent to which lost patients may alter the presented conclusions, results can be recalculated making the assumption that lost experimental patients had the worst outcome and lost placebo patients the best. This represents the worst case scenario for the authors' hypothesis, and if their conclusion holds despite this, validity is preserved.

Table 2. Criteria for Appraising and Applying an Individual Therapy Study

Are the results valid?

Did experimental and control groups begin the study with a similar prognosis?

- Were patients randomized?
- Was randomization concealed (blinded or masked)?
- Were patients analyzed in the groups to which they were randomized?
- Were patients in the treatment and control groups similar with respect to known prognostic variables?

Did experimental and control groups retain a similar prognosis after the study started?

- Were patients aware of group allocation?
- Were clinicians aware of group allocation?
- Were outcome assessors aware of group allocation?
- Was follow-up complete?

What are the results?

- How large was the treatment effect?
- How precise was the estimate of the treatment effect?

How can I apply the results to patient care?

- Were the study patients similar to my patients?
- Were all clinically important outcomes considered?
- Are the likely treatment benefits worth the potential harm and costs?

Adapted with permission from Guyatt G, Rennie D. Users' guides to the medical literature: a manual for evidence-based clinical practice. Chicago: AMA Press; 2002:58.

Satisfied with the study methodology, you proceed to appraise the results. Examining mortality, you find amongst all bacterial meningitis patients combined that 11/157 died in the dexamethasone group. This produces a mortality rate (or *experimental event rate* [EER], since this group received the experimental intervention) of 7% for patients receiving dexamethasone. In the placebo group, 21/144 died, producing a *control event rate* (CER) of 14.6%. The *relative risk* (RR) of death comparing the dexamethasone rate with the placebo rate is EER/CER, or 7%/14.6%, which equals 48%. This means that mortality from bacterial meningitis when dexamethasone is used is only 48% of what it would have been had no dexamethasone been used. You note that the authors also report a 95% confidence interval (CI) of 24% to 96% for this RR, demonstrating significance. *Relative risk reduction* (RRR) is not presented in the paper, but you compute it since you like to think of a reduced risk of death as a way to interpret the results:

$$RRR = 100\% - RR\ (48\%) = 52\%$$

You are impressed that this paper shows a 52% reduction in the rate of death from bacterial meningitis when dexamethasone is added to the treatment regimen. For the subgroup with *S. pneumoniae*, the authors compute an impressive RR as well, but you accept this only as a probable trend since patients were not randomized according to causative agent.

Criteria for Appraising Importance of Results

Relative risk and relative risk reduction. The above computations demonstrate how RR and RRR are derived from raw outcomes data by calculating event rates first. RR and RRR represent effects of a

treatment on population outcomes; that is, a population of patients can exhibit a 52% lower death rate, but an individual obviously cannot be 52% less dead. The individual will reach a single defined outcome, and the use of steroids in bacterial meningitis appears to decrease the likelihood that this will be death. RR and RRR always add up to 100%. RR expresses the outcome as a percentage of what it would have been, whereas RRR expresses the outcome as a reduction of what it would have been. A good example is an item on sale. One can say that the cost is 75% what is was last week, or 25% reduced. Either way, the same information is expressed.

Confidence interval. The CI is a method of measuring the precision of a result. In a therapy study, the study population is meant to represent the population at large. However, the study outcome is unlikely to be exactly what the entire population would experience if the intervention were applied universally. The RR computed for the study is simply a point estimate of the true RR for the whole population, which can never be known. The CI is the range of values within which there is 95% certainty that the real result lies. In the example above, the authors report a RR of 48% and a CI of 24% to 96%. Statistically, there is 95% certainty that the actual RR is between 24% and 96%, with 48% being the point estimate. An RR of 100% would mean that the EER and CER are equal, and an intervention has no measurable effect. Therefore, a CI that crosses 100% would indicate that within the 95% confidence range there is the chance that the groups have no real outcome difference. Thus, CIs crossing the boundary of equivalence between the experimental and control groups indicate insignificant results.

Probability value. Another way to express significance is the probability (*P*) value. The *P* value is the probability that the difference shown between the two groups was due to chance. The lower the *P* value, the less likely it is that the groups are different by chance. In the de Gans and van de Beek study, the *P* value for the RR for mortality comparing the steroid and placebo groups is 0.04. This means there is a 4% probability that these two groups showed an outcome difference by chance rather than a true effect of the dexamethasone. The standard for showing statistical significance between groups is a *P* value of 0.05 or less (ie, 5% or less probability that group differences are by chance). Authors and their statisticians should compute CIs or *P* values to show which of their experimental interventions produced statistically different outcome rates. These computations should be considered beyond the scope of the general reader.

Another end point examined in the study is "unfavorable outcome," defined as any score other than 5 on the Glasgow Outcome Scale. Quickly checking the methods, you find that a Glasgow score of 5 means mild or no disability (able to return to work or school) and scores of 1 to 4 indicate various ranges of disability, from death to moderate dysfunction.

For the unfavorable neurologic outcome (score of 1 to 4), the RR presented for all bacterial meningitis patients is 59% (95% CI, 37% to 94%). However, according to the data presented, the unfavorable outcome benefit seems to be nearly entirely due to prevention of mortality. This is because death (equal to a Glasgow score of 1) appears to occur at significantly different rates between the dexamethasone and placebo groups, but scores of 2 through 4 occur at similar rates. Therefore, the significant difference claimed for two separate outcomes—death and unfavorable Glasgow outcome—might simply be measuring the same mortality end point, albeit an important one.

Because Mr. Johnson has been complaining of some difficulty hearing during his recovery, you also examine results for the study's end points of focal neurologic abnormalities and hearing loss. No group of patients showed significant benefit from dexamethasone for either of these end points.

You conclude that on the basis of this study, steroids should be given at or before the first antibiotic dose in bacterial meningitis, to lower mortality from this disease. This was not a treatment option for Mr. Johnson, because he received antibiotics for his pneumonia before meningitis was suspected.

To help you understand the impact dexamethasone may have on future meningitis patients, you decide to compute the *number needed to treat* (NNT). The article does not do this for you, so you consult the Users' Guides [8] to be sure of your calculations. NNT is 100% divided by *absolute risk reduction* (ARR), and ARR is equal to the absolute difference in outcome rates between two groups. For the mortality end point, ARR is the rate of death in the placebo group (CER) minus the rate of death in the dexamethasone group (EER), or 14.6% minus 7%, which equals 7.6%. You then compute the NNT required to prevent one death, which is 100%/7.6%, or 13.

Number needed to treat. NNT is our clinical bottom line, as it represents the number of patients who need to receive the intervention before one outcome change occurs. NNT is derived from ARR, because ARR is the absolute difference in outcome

rates between two groups and reveals the proportion of the population that stands to benefit from the intervention.

To demonstrate this, envision a population of 100 bacterial meningitis patients to whom antibiotics alone were given. According to our appraised study, 14.6% of them, or about 15 patients, would be expected to die of bacterial meningitis. Now envision the same 100 patients given dexamethasone before antibiotics, instead of antibiotics alone. According to our appraised study, 7% or seven patients are expected to die. This means that of our entire population of 100 patients, eight would be saved from death by the addition of dexamethasone. These eight patients are measured by the ARR of 7.6%. Unfortunately, we cannot identify these eight patients ahead of time. Therefore, a group of patients must be given the intervention in order to catch one of the eight who will benefit. This group is the NNT and is measured by dividing 100% (the whole population) by ARR (the proportion who actually experiences the intervention's benefit). From our example, 100%/7.6% equals 13, meaning 13 people will need to receive dexamethasone before or with antibiotics before one death from bacterial meningitis will be prevented. The other 12 will not experience a change in outcome from the dexamethasone; one will die anyway (the 7% represented by EER), and 11 will live anyway (the 85.6% who survived even with control treatment).

There is no rule of thumb for what is an acceptable NNT. The smaller the NNT, the greater the impact of the experimental treatment on the outcome examined. However, we also must consider patient values and the cost of the intervention. Cost may include actual dollars but also means physical cost in side effects or recovery time. For example, we might be willing to give a relatively benign medication to 50 patients to save one life but unwilling to perform a risky procedure 50 times to save the same life.

Applying Evidence to Patient Care

Encouraged by the NNT of 13, you plan to use dexamethasone with the first dose of antibiotics the next time you suspect bacterial meningitis in an adult patient. However, three issues are bothering you.

First, you are unsure whether to use steroids in every case of suspected meningitis. In your experience, most of these patients receive antibiotics even before lumbar puncture is performed, missing the inclusion criteria of positive CSF findings used in the de Gans and van de Beek study. The authors do not comment on the group ultimately found to have aseptic meningitis, who comprise the majority of your past meningitis patients.

Your second concern is whether gastrointestinal (GI) bleeding will be increased by steroid therapy, and you find that GI bleeding was an end point considered by the authors of the study. They found no significant difference in this complication, which occurred in two dexamethasone patients and five placebo patients (P value = 0.27). However, they excluded patients with a recent history of peptic ulcer disease, something you will need to consider if you hope to have similar outcomes when using steroids in this setting.

Your third and most bothersome issue is what to do when vancomycin should be part of the treatment. For this question, you decide you will take your article to morning report, hoping to stimulate discussion about whether to give dexamethasone to adults with bacterial meningitis when pneumococcus is known to be the most common etiologic agent and 25% of the local isolates have some level of penicillin resistance. The article does not fully discuss this question, saying only that patients on vancomycin and dexamethasone should be "carefully observed." Perhaps some of the infectious disease attendings will be invited to morning report by your chief resident, since treatment failure due to poor penetration of vancomycin into the CSF would be of enormous concern.

Criteria for Appraising Applicability

Once a relevant therapy study is appraised for validity and importance, we need to examine whether the results apply to our patient at hand or to future patients we are likely to encounter. Patients enrolled in the study must be similar to the patients to whom the treatment will be applied locally, or they must be sufficiently great in number and diverse in presentation to represent any patient who may acquire this disease. Since the latter is rarely possible, we should be reasonably convinced that our patients are well represented by the study population in their baseline characteristics and mode or timing of presentation. In addition, exclusion criteria should not be overly lax or strict in comparison to the circumstances that would warrant the treatment in our practice.

The patient at hand. The de Gans and van de Beek study included patients with age, inclusion, and exclusion criteria that match Mr. Johnson. Furthermore, about a third of the study patients were diagnosed with the same infecting agent, *S. pneumoniae*. Once patient similarity is satisfied, we must consider whether the

outcomes examined in the study are similar to those of concern to our patient. The outcomes of mortality and neurologic deficit were of primary importance in the PICO question pertaining to Mr. Johnson. During the course of the patient's recovery, hearing deficit became a concern as well, changing the O in PICO to hearing loss. All of these outcomes were considered in the therapy study we found.

Future patients. We are interested in additional outcomes as we contemplate applying dexamethasone to future patients with suspected meningitis. Some of these outcomes suggest potential harm to the patient by the intervention, such as GI bleeding or vancomycin treatment failure. The article allows estimation of the GI bleeding effect, since this outcome is reported, although this estimation was made in a population of patients limited by the exclusion of peptic ulcer disease. What to do in the case of suspected bacterial meningitis and known peptic ulcer history is unclear. What to do when vancomycin is part of the antibiotic regimen is even less clear. These issues require further discussion, or perhaps further study, to reach an accepted treatment standard. Trials including patients with peptic ulcer disease and penicillin-resistant pneumococci may be warranted, with interventions adjusted for these possibilities. Until then, we must carefully exclude those patients whom we believe might be harmed additionally.

Occasionally, a trial is published that suggests a new standard of therapy for an illness commonly encountered in our patient population. When the illness has high morbidity and mortality, such as bacterial meningitis, there is some urgency to reach a consensus regarding the application of this purportedly improved therapy. Many adults will present to EDs with the inclusion criteria used in the de Gans and van de Beek study (ie, cloudy CSF, bacteria on CSF Gram stain, or CSF leukocyte count greater than $1000/mm^3$), for whom risk of death or neurologic deficit will be significantly reduced by dexamethasone, according to these authors. Given that this treatment has been discussed in the literature for more than 20 years without a conclusive recommendation regarding its use in adults, should we now apply it to our patients based on this single trial? The resident in our case example has notable concerns, which he or she appropriately plans to bring to local experts. While the resident's institution is considering changes in protocols of meningitis care, consensus statements are likely being formulated internationally by clinical organizations responding to the important new data.

Weighing our patients' wishes and values is very important and must be done on a patient-specific basis. It is hard to imagine a patient who would refuse dexamethasone and its improved survival rates unless choosing comfort care alone. More importantly, in the particular setting of bacterial meningitis, little time is available to discuss treatment options, and patients may be too cognitively impaired to entertain those options. When this occurs, we must act in our patient's best interest as quickly as possible, preserving life and cognitive function as values assumed to be desired by any patient choosing treatment.

Conclusion

Table 3 summarizes the five-step EBM approach as it applies to the decision whether to add steroids to the treatment of Mr. Johnson's pneumococcal meningitis. This case serves to illustrate the search for a therapeutic option supported by the best available evidence. In our example, three EBM resources allowed us rapid review of high-quality evidence during active patient care. Using prescreened EBM Web sites allowed us to avoid the critique and elimination of less valid information, saving time and optimizing clinical decision making.

The information obtained ultimately could not be applied to Mr. Johnson, since he did not meet the clinical similarity requirement, having already received parenteral antibiotics. However, by being able to appraise the de Gans and van de Beek article and use its results to plan changes in therapy, we are better prepared to care for future patients like Mr. Johnson. Having these skills means that, in the setting of an illness with high morbidity and mortality, we can avoid the delay caused by waiting for others to appraise scientific data that may save lives. Following these steps leads to the most specific and efficient searches of available literature.

In this case, a search of filtered evidence sources was successful in quickly revealing useful summaries of a relevant and recent clinical trial. If this search had been performed less than a year earlier, however, this would not have been the case, due to the screening time required by the filtered resources. Thus, individual article appraisal becomes important for evaluation of recently published trials, which can only be recovered with certainty by searching bibliographic databases such as MEDLINE. Acknowledging the need for high-quality evidence, bibliographic search sites have incorporated evidence-based limits of their own, such as Clinical Queries on PubMed. Using all of these EBM strategies, we are able to rapidly cull important and highly valid data from the enormous quantity of published medical information. In this way, we regularly update our own medical knowledge

Table 3. Summary of the Evidence-Based Medicine Approach to Making a Treatment Decision for Mr. Johnson.

Assess	Mr. Johnson has likely pneumococcal bacteremia, new symptoms of meningismus, and lumbar puncture results consistent with bacterial meningitis. He has already received parenteral antibiotics.
Ask	In adults with pneumococcal meningitis, does steroid therapy in addition to antibiotics, compared with antibiotics alone, reduce mortality or neurologic impairment?
Acquire	• *ACP Journal Club*—1 hit: summary and commentary for 2002 RCT recommending dexamethasone at or before antibiotics for adult bacterial meningitis • Cochrane Library—3 hits: one is systematic review recommending dexamethasone at or before antibiotics for bacterial meningitis, including adult cases • MEDLINE—2002 RCT (same as found on *ACP Journal Club*) on steroid use for adult bacterial meningitis, with no newer study
Appraise	Appraisal of RCT indicates randomization of subjects, double-blinding, intention-to-treat analysis, similar prognostic factors, and adequate follow-up. Mortality and "all unfavorable outcomes" are reduced with the use of steroids given before or with the first antibiotic treatment of bacterial meningitis. NNT to prevent one death is 13 for all bacterial meningitis cases. Reducing "all unfavorable outcomes" appears to be primarily reducing mortality, since lesser unfavorable outcomes did not appear measurably different. Focal neurologic deficit and hearing loss were not significantly reduced by dexamethasone.
Apply	Study patients are similar to Mr. Johnson in having definitive evidence of bacterial meningitis. However, they all received steroids before or at the time of the first dose of antibiotic. Since Mr. Johnson has already received antibiotics, he may not benefit from steroids. In addition, he requires vancomycin and there are concerns that the CSF level of this antibiotic may be reduced by steroids. The intervention in the article is therefore not applied to Mr. Johnson but may be applied to future patients with evidence of bacterial meningitis who have not yet received the first dose of antibiotics.

CSF = cerebrospinal fluid; NNT = number needed to treat; RCT = randomized controlled trial.

and apply the best available evidence to daily patient care, improving outcomes and increasing satisfaction for patients and practitioners.

Address correspondence to: Laura J. Nicholson, MD, PhD, UCSD Hospital Medicine, 9300 Campus Point Drive MC 7828, La Jolla, CA 92037-7828 (e-mail: lnicholson@ucsd.edu).

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