Evidence-based Pediatric Critical Care Medicine

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Abstract

Evidence-based medicine (EBM) strives to find the optimal course of action for a given clinical question by merging the best available scientific evidence with expert clinical judgment that incorporates a patient's values and preferences. Although learning how to apply the concepts and principles of EBM is not intuitive, most clinicians become facile with modest effort. This chapter will describe the evolution of EBM from clinical and epidemiologic principles and research. We review the process of EBM in detail, including EBM core concepts related to articles on diagnosis, therapy, harm, and prognosis. We conclude by discussing the role of EBM in the PICU, emphasizing challenges and future directions.

Keywords

Evidence-based clinical practice (EBCP) • Evidence-based medicine (EBM) • Critical appraisal, critical care

A Clinical Scenario Raises Important Clinical Questions

Evidence-based medicine (EBM) is the "conscientious, explicit and judicious use of current evidence in making decisions about the care of individual patients" [1]. Despite increasing acceptance of the role of EBM in clinical practice over the last two decades, many clinicians are unaware of EBM's history and do not understand the rigorous systematic approach that the practice of EBM requires. To improve this understanding, we will review the origins of clinical research leading up to the era of EBM to explain why EBM came about. We start this chapter with a clinical scenario to which we will repeatedly refer. We then briefly describe the stepwise approach to some of the EBM core topics as applied to this and other patient encounters. Ways to keep up with the evidence and efficiently find evidence will be reviewed and we will also address challenges to practicing EBM in the pediatric intensive care unit (PICU).

Clinical Scenario

A 7 year-old male is admitted to the PICU after being involved in a motor vehicle accident. At the scene he was hypertensive and bradycardic with asymmetric pupils, an irregular respiratory pattern and a Glasgow Coma Score (GCS) of 6. He was intubated in the field and Emergency Medical Services (EMS) personnel attempted to hyperventilate for suspected elevated intracranial pressure (ICP). Upon arrival to the PICU, he underwent central line placement and was started on an infusion of hypertonic saline and narcotic and benzodiazepine drips for pain and sedation. A few hours after PICU admission, his blood pressure and heart rate normalized.

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This patient's presentation raises numerous types of questions:

- **Etiology**: By what mechanism does traumatic brain injury cause elevated ICP? Why do patients with elevated ICP demonstrate hypertension, bradycardia and abnormal respirations and how often do these findings present as a constellation?
- **Diagnosis**: How likely is the constellation of findings (hypertension, bradycardia and abnormal respirations) indicative of elevated ICP? What is the gold standard for diagnosis of diffuse axonal injury following traumatic brain injury?
- **Treatment**: What is the role of hypertonic saline as an osmotic agent following traumatic brain injury? How does this compare to other osmotic agents like mannitol? Would induced hypothermia be beneficial for this patient?
- **Harm**: Is hypotension after traumatic brain injury causing hypoperfusion associated with worse neurologic outcomes? Is hyperglycemia harmful?
- **Prognosis**: What predictions can be made about survivability following such an injury? What expectations can be given to the family regarding cognitive outcomes if the child survives?

Questions related to etiology or the "background" of the clinical problem are foundational, focusing on the core of our medical knowledge. Questions related to diagnosis, treatment, harm and prognosis are considered 'foreground' questions and are at the core of EBM. Clinicians often rely on expertise – their own or those of consultants – to answer the above questions. One problem with reliance on clinical expertise alone is that it can lead to variable and sometimes contradictory guidance, leaving the clinician unclear about the optimal approach. EBM – also known as evidence-based clinical practice or EBCP – aims to answer "foreground" questions by integrating the best available evidence with clinician expertise taking into account individual patient preferences and values [2].

The Need for EBM

Led by Dr. David Sackett in the early 1980s, a group of clinical epidemiologists at McMaster University published a series of articles in the *Canadian Medical Association Journal* designed to help clinicians interpret clinical research. They coined the term "critical appraisal" to emphasize the need to thoughtfully examine and assess the reliability of research studies and applicability to specific patients [3]. At the time of David Sackett's initial introduction of critical appraisal, the biomedical literature was expanding at a rate of 6–7 % per year, thereby increasing tenfold every 35–50 years [4]. Clinicians were overwhelmed at the exponential expansion of clinical literature yet altering clinical practice with solid evidence occurred very slowly, impeding the probability that the evidence could improve patient's lives.

Many of the illustrative historical clinical research examples given below are excerpted from a book entitled *Clinical Trials* by Pocock [5] and the James Lind Library, "created to help people understand fair tests of treatments in health care" (www.jameslindlibrary.org). Starting in 1753, one of the first published clinical studies was by Lind entitled *The Treatise of the Scurvy* [6]. Below is a modified excerpt of this study:

> I took 12 patients with the scurvy on board the Salisbury at sea. The cases were as similar as I could have them…they lay together in one place…and had one diet common to all. Two of these were ordered one quart of cider a day. Two others took 25 gutts of elixir vitriol…Two others took two spoonfuls of oranges and one lemon given to them each day…Two others took the bigness of a nutmeg. The most sudden and visible good effects were perceived from the use of oranges and lemons, one of those who had taken them being at the end of 6 days fit for duty…The other…was appointed to nurse the sick.

This study is important for two reasons. One is that it was the first strong "evidence" that vitamin C could be used to treat and prevent scurvy. The other is that Lind understood some basic features of good study design. He controlled for differences between patients by identifying those at the same level of illness. He controlled for other influences on outcome by giving patients the same diet, except for the interventions, and the same amount of sunlight and other environmental exposures. He also had two patients in each treatment arm because, although one patient could improve just by chance, the likelihood of two patients improving by chance alone was lower. Interestingly, despite this evidence, it was over five decades before lemon juice became standard fare on British naval ships. Delays in the application of evidence are still a major problem more than two and a half centuries later.

Another early clinical researcher was Louis who established clinical trials and epidemiology on a scientific footing [5]. In the 1800s, bleeding was the standard treatment for numerous serious and minor ailments across the U.S. and Europe. In 1835, Louis urged the need for the exact observation of patient outcome, knowledge of the natural progression of untreated controls, precise disease definition prior to treatment, and careful observation of deviations from intended treatment [7]. Louis' careful comparisons, showed no differences in the outcomes of patients with a variety of disorders who were bled and not bled. His findings led to the slow but eventual decline of bleeding as a standard treatment [5] – although it took over a century before bleeding was completely out of vogue.

In the early days of much of clinical medicine, especially for surgery, anesthesia, and critical care, early procedures and therapies led to dramatic improvements. With such profoundly clear benefits, the need for large numbers and control groups went by the wayside. Lister in 1870 [8] reported

a before-after study of antiseptics for amputation operations, reporting a 43 % rate of mortality in 35 cases before antiseptic use versus a 15 % mortality rate in 40 cases afterwards. Although he focused on the small sample size and erroneously claimed the difference was not statistically significant, a more important problem with before-after studies such as this one is that many other things could have changed in the interim to explain the effect. Newer anesthetic methods, newer surgical techniques, and better basic hygiene could underlie the difference in mortality rates rather than antiseptic use.

The first randomized controlled trial was published in 1948 [9], when streptomycin plus bedrest was compared to bedrest alone to treat pulmonary tuberculosis [10]. The novel features of this trial, besides the randomized assignment to groups, were that outcome assessors were blinded to the treatment allocation and that multiple clinicians assessed outcome and had to come to consensus. This introduces a factor that clinical trials are designed to control for which is called "bias". Bias is a systematic difference between the research question and the actual question answered by the study that may cause the study to give a wrong answer [11]. Carefully designed studies minimize bias. Bias can come from patient variables (e.g., patients in one group being more ill at baseline), predictor variables (e.g., patients in one group are treated differently, besides the intervention), outcome variables (e.g., outcome assessors know patient treatment arm assignment and this influences their assessment), or from the placebo effect. EBM focuses on assessment of study design to ensure that steps were taken to minimize bias to optimize the trial's chances for the real answer to the question to emerge.

In the late 1950s through the 1960s, there was a rapid growth of clinical studies and especially of randomized controlled trials. For some therapies such as penicillin, the impact on disease was so great that observational studies of small numbers of patients showing dramatic recovery [12, 13] led to widespread use at the end of World War II saving thousands of soldier's lives. It is also true, however, that dramatic appearing results from clinician observation can be refuted by subsequent randomized trials, and that randomized trials can reveal larger treatment effects that were dampened by non-randomized studies. An example of the first is the rise and fall of "gastric freeze" for duodenal ulcer [14]. This intervention rose to be the standard of care in the 1960s based upon the clinical experience of major opinion leaders and published statements such as "Since April 1961, no patients with duodenal ulcer disease have been operated upon on the senior author's surgical service. This circumstance in itself bespeaks the confidence in the method by patients as well as surgeons" [15]. Thousands of gastric freezing machines were subsequently sold. A proper randomized trial finally led to the abolishment of gastric freeze for duodenal ulcers because there was no difference in rates of subsequent surgery for ulcer disease, gastrointestinal hemorrhage, or hospitalization for intractable pain in patients randomized to the sham treatment versus the gastric freeze [16].

An example of how a randomized trial can lead to more rapid implementation of a promising intervention due to stronger results is from the Salk Polio vaccine trial [5, 17, 18]. In 1954, the annual incidence of polio was 1 in 2,000 people. Polio was epidemic but hit some geographic areas harder than others. Because of this, studies of preventive interventions with control groups within the same geographic regions were needed. Two studies were planned. Some health care regional authorities opted for an observed control approach where second graders were vaccinated while first and third graders served as unvaccinated controls. One million children participated in this study. Health authorities in other regions were concerned that bias could be introduced if the physician diagnosing polio, a diagnosis not always made with certainty, could guess whether or not the child received the vaccine. These practitioners opted for a blinded randomized controlled trial in which 800,000 children participated. The results were clear: in the randomized study the polio vaccine was highly effective with a 70 % reduction in polio and all four deaths occurred in the control group. The observed control study also showed better outcomes in the vaccinated group, however, children in both groups who declined participation in the study had better outcomes, making the results difficult to interpret. The data from the randomized, controlled trial eliminated much of the confusion from this observational control study and therefore provided the impetus for vaccination mandates.

The 1960s through 1980s were years of rapid growth of the clinical literature with the publication of many thousands of clinical trials. Advances in computerization facilitated management of large datasets, the growth of statistical methods, and searching for medical information. Medical practice was still based, however, on the expertise of the individual practitioner and there was no systematic method for practitioners to assess and incorporate published findings into their practice.

The EBM Process and Approaching the EBM Core Topics

McMaster University in Ontario, Canada served as the birthplace of EBM. *Clinical Epidemiology*: *a Basic Science for Clinical Medicine* was authored by Drs. Sackett, Haynes, and Tugwell and published in 1985 [19]. Dr. Gordon Guyatt later coined the term "evidence-based medicine" and with his colleagues published the principles of EBM in a series of articles in *JAMA* starting in 1993 entitled "Users' Guides to the Medical Literature" [20]. Each guide has the same

Table 16.1 Primary validity criteria for articles addressing therapy or prevention, diagnosis, prognosis and risk or harm

Type of study	Validity criteria
Therapy or prevention [21, 22]	Was the assignment of patients to treatments randomized?
	Were all of the patients who entered the trial properly accounted for and attributed at its conclusion?
	Was follow-up complete?
	Were patients analyzed in the groups to which they were randomized?
Diagnosis [23, 24]	Was there an independent, blind comparison with a reference standard?
	Did the patient sample include an appropriate spectrum of the sort of patients to whom the diagnostic test will be applied in clinical practice?
Prognosis [25]	Was there a representative and well-defined sample of patients at a similar point in the course of disease?
	Was follow-up sufficiently long and complete?
Harm [26]	Were there clearly identified comparison groups that were similar with respect to important determinants of outcome, other than the one of interest?
	Were the outcomes and exposures measured in the same way in the groups being compared?
	Was follow-up sufficiently long and complete?

structure: I. Are the results valid? (Using different validity criteria for different types of questions.); II. What are the results? (Including the effect size and its precision.); and III. Are these results applicable to my patient?

Assessing the validity of a study as the initial step can save the reader time. Fancy statistics will not fix a weak study design. If the study is not valid, there is no reason to read further. If the study design is of high quality and the study reports a statistically significant result, the next step is to ensure that the confidence interval around the treatment effect increases our confidence that the treatment is beneficial. If the study reports no effect, it is important to ensure that the study had sufficient power to test the hypothesis. Even if the study is valid, the sample size was large enough, and the confidence interval appropriately narrow, the study may not be applicable to your specific patient's situation based upon differences in their demographic or clinical status as well as their individual preferences and values.

Table 16.1 shows the Users' Guide primary validity criteria for questions about therapy or prevention [21, 22], diagnosis [23, 24], prognosis [25], and risk or harm [26] showing how criteria differ for each question type. To practice EBM, it is important to focus the clinical question and to choose and apply the correct Users' Guide criteria. There are over 25 Users' Guides currently available for different topics. Many are included in a series of articles edited by Dr. Deborah Cook that were published in *Critical Care Medicine* using critical care examples [27]. The *JAMA* Users' Guide series has also been incorporated into a book and pocket guide entitled Users' Guides to the Medical Literature [28].

To practice EBM is more than accessing and understanding the Users' Guides. EBM is defined as the conscientious, explicit and judicious application of current best evidence to the care of individual patients [29]. The practice of EBM requires the integration of clinical expertise and critical appraisal to determine the applicability and quality of available evidence. Practitioners of EBM make a commitment to use a systematic approach to search for, critically appraise, synthesize, and apply evidence in their clinical practice [29]. To do this requires a five-step approach called the Evidence Cycle [28] often referred to as 'The 5 As':

1. **Assess** the patient and the problem to determine the pertinent issues (e.g., differential diagnosis, treatment, prognosis, risk of harm).
2. **Ask** a clear answerable clinical question that guides your search for the best available evidence.
3. **Acquire** the best evidence through efficient searching and from appropriate sources.
4. **Appraise** the evidence you have retrieved using a systematic method to evaluate it for validity, importance, and usefulness.
5. **Apply** the evidence to a particular patient and to their unique values and preferences.

Step 1: Assessing the Patient

The method of EBCP relies first on clinical expertise to assess the patient and incorporate all of the relevant clinical data. Clinical expertise is essential. With a comprehensive understanding of pathophysiology and by taking a thorough history and performing a rational clinical examination, the clinical problem(s) will be identified. The problem could involve a differential diagnosis, a treatment decision, a determination of prognosis, or a weighing of risk and benefit. Using clinical skills forms the basis for moving forward to the next steps in the Evidence Cycle.

Step 2: Asking Effective Clinical Questions

A critical step is to identify one or two key issues arising from the assessment to develop a focused and answerable clinical question. Doig and Simpson [30] put forth the mnemonic 'PICO' to detail the critical aspects of a well-formulated clinical question. The question should clearly entail the ***P***atient/***P***opulation of interest, the ***I***ntervention (or exposure) and its ***C***omparison/***C***ontrol in evaluating an ***O***utcome of interest. (Some have advocated expanding this to 'PICOT' to stress the importance of considering what ***T***ype of study is most desirable, considering the

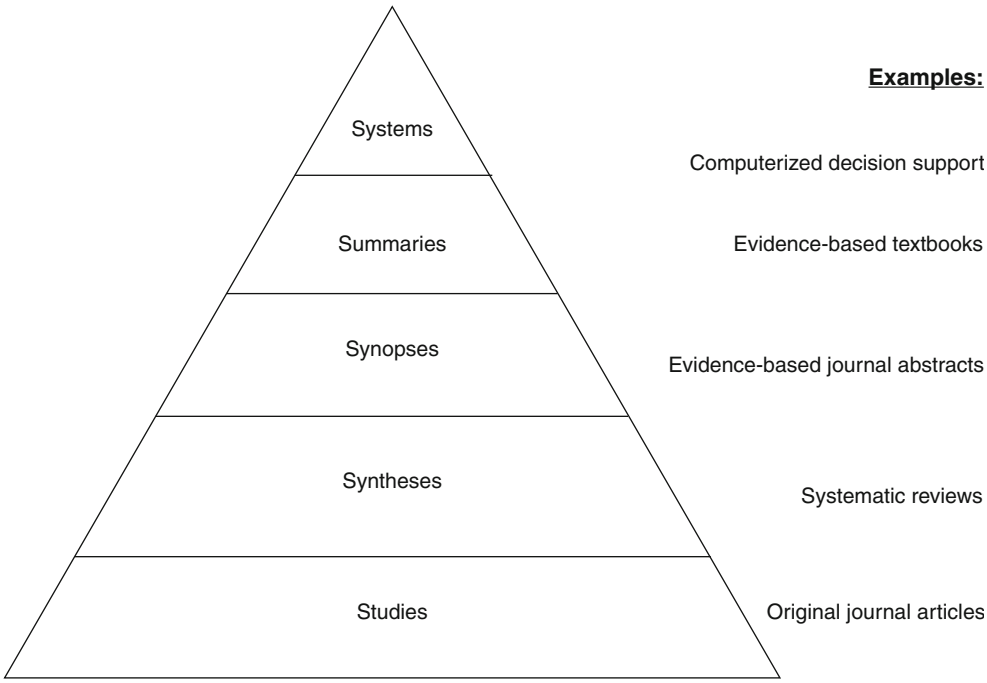

Fig. 16.1 Hierarchy of evidence. The "5S" evolution of information services for evidence-based healthcare decisions is a hierarchy of evidence designed to demonstrate the progression from original scientific articles all the way to the individual patient whereby escalating levels of evidence synthesis results in patient-specific decision support based upon best-existing evidence (Based on data from Haynes [49])

hierarchy of evidence shown in Fig. 16.1. Asking the most specific question for a given patient scenario allows for the most efficient acquisition of available literature.

Step 3: Acquire (Finding and Keeping Up with the Evidence)

High-quality systematic evidence reviews, when available, save an enormous amount of time [4]. Although reviews that do not take an evidence-based systematic approach can be helpful in describing the physiology and pathology of a problem, they often present data in ways that are slanted to support the opinion of the expert author. Using a systematic approach to search for, critically appraise, synthesize, and present the results minimizes the potential for bias. The Cochrane Collaboration publishes an updated database of systematic reviews – all referenced in PubMed – that uses a rigorous and standardized review methodology developed and refined by expert methodologists (www.cochrane.org).

Efficiently finding evidence in online medical search engines such as PubMed, a National Library of Medicine platform for searching MEDLINE, requires using the right terminology such as Medical Subject Headings (MeSH). There are search criteria developed by Dr. Brian Haynes for using PubMed to identify relevant articles that will yield a higher sensitivity (retrieving all relevant articles) and specificity (not retrieving irrelevant articles) [31–34]. PubMed has a special search feature found under Clinical Tools on the home page called "Clinical Queries" This search tool is based upon the work of Dr. Haynes and colleagues that automatically filters searches based on the type of clinical study and searches specifically for systematic reviews allowing the clinician to set the search criteria broadly or narrowly.

Information overload is a constant problem plaguing clinicians. Given that research relevant to the pediatric intensive care setting may be found in the areas of internal medicine, neurology, surgery, trauma, infectious disease as well as hospital epidemiology, neonatology, pediatrics, radiology, oncology, and many other specialties, it can seem impossible to keep up with the literature [35]. Journal clubs that critically appraise relevant studies can save time. The PedsCCM Evidence-Based Journal Club (http:// PedsCCM.org) identifies articles across a range of medical journals, reviews them using the Users' Guide approach, and now publishes a select number in *Pediatric Critical Care Medicine*.

Additionally, a recent scoping review by Duffett et al. is an excellent consolidation of the available RCTs in pediatric critical care. The authors have made these accessible to clinicians and researchers at epicc.mcmaster.ca and have underscored the need for more high-quality evidence in order to support clinical decision-making in our patient population [36].

Returning to the patient presentation at the beginning of this chapter, suppose that the question we seek to answer is the role of hyperosmolar therapy in the management of pediatric TBI. Following the hierarchy of evidence, individual studies provide the foundation by which stronger evidence is based. Optimally, the practitioner would find a systems-level body of evidence in the form of practice guidelines, clinical pathways, or evidence-based textbook summaries that are frequently updated as new evidence arises. Turning to the question of hyperosmolar therapy and its role in the treatment of pediatric TBI for example, a clinician may stop after a literature

search that reveals one of several individual articles pertaining to the use of hyperosmolar agents in severe TBI. However, more optimal evidence exists in the form of a set of guidelines published in 2012 which address the role of multiple treatments and management approaches and would be discovered upon a more exhaustive literature search [37, 38]. Updated from the 2003 set of guidelines, this revised clinical guide incorporates the GRADE approach to rate topics [39], providing a starting point for our clinical question. Chapter 8 of the pediatric TBI guidelines [38] specifically addresses the question of hyperosmolar agents in severe pediatric TBI and provides a summary of relevant articles. This allows a clinician to review the strength of the recommendation based upon the available evidence up to the time of the publication of the guideline. Because there is a 2 month to 1 year gap between development of a guideline and the timing of publication, it would be important to review further articles published after 2011 and determine if they would influence the recommendations in the guideline.

Step 4: Critical Appraisal

Appraisal of the acquired literature is unarguably the most important step in the application of evidence to clinical practice. Poorly designed studies, publications wrought with bias or unaccounted-for confounders and studies with improper statistical analysis or unfounded conclusions can lead clinicians to the wrong conclusion. As shown in Table 16.1, each type of study – therapy, diagnosis, prognosis, harm, etc. – should be appraised for validity using the validity criteria relevant for the type of study in question.

Returning to the hyperosmolar therapy question in severe pediatric TBI, we will review the EBM criteria (Table 16.1) for a therapy article. The first aspect of appraisal involves the validity of results and incorporates several key components to strengthen the findings. One must ask if patients in the intervention and control groups started with the same prognosis. While there may be confounders that are difficult to control for or even unknown to the investigating team, all attempts should be made to ensure prognostic equality between the groups in order to ensure that any difference is truly due to the intervention studied. Patient randomization is the optimal method for ensuring equal distribution of known factors that can influence patient outcome between the groups. Randomization can be done in multiple ways and to be most effective, should be a concealed process by which allocation into study arms cannot be affected by clinician bias. Following initial prognostic balancing at time of enrollment, the reader should consider whether enrollees maintained prognostic balance throughout the duration of the study. This is accomplished through blinding at as many levels as possible (i.e., study participant, investigator, data collector, and statistician). Finally, prognostic balance can be assessed at the conclusion of the study by evaluation of how complete follow-up was, whether patients were analyzed in the groups in which they were randomized (intention-to-treat analysis) and whether or not the trial was stopped early.

Once you are convinced the results are likely to be valid, it is now worth your time to review them identifying the point estimate and the confidence interval around it. A point estimate is simply the observed treatment effect from the study with the knowledge that the "true" treatment effect is likely different from that observed, secondary to a multitude of factors (i.e., confounders). To address this discrepancy between the point estimate and what may be a different "true" effect, a confidence interval is calculated. The confidence interval is simply a range of values within which the reader can be confident that the true effect lies. It is standard to use the 95 % confidence interval which defines the range that includes the true effect 95 % of the time, provided that the study was well-designed and executed with minimal bias [40].

Step 5: Apply the Evidence

The final aspect of a critical appraisal for a therapy article addresses the applicability of the results to patient care [41]. This can perhaps become one of the more challenging aspects of EBM since many well-developed studies work to minimize confounders by studying a relatively homogenous group, thereby limiting generalizability to a broader patient base. In assessing the applicability to patient care for a therapy article, there are three key questions to address:

1. Were those patients being studied similar to my patients?
2. Were all of the patient-important outcomes considered?
3. Are the likely treatment benefits worth the potential harms and costs?

The subspecialty of pediatric critical care in the specialty of pediatrics is a small and relatively new field. Although the amount and quality of evidence are improving, practicing evidence-based pediatric critical care medicine can be challenging, often requiring assessment of evidence collected in critically ill adult populations or non-critically ill children, and then determining if it is applicable to your critically ill pediatric patient. For the patient presentation at the beginning of this chapter, some questions have an evidence-base in critically ill children while for other questions, extrapolation from best-available literature must suffice until more studies specific to pediatric critical care are conducted.

Even in valid studies reporting therapeutic efficacy, incorporation of a patient and family's preferences and values is essential to the practice of EBM. How to elicit preferences of critically ill patients and their families and how to incorporate them into clinical encounters is a chal-

Table 16.2 Ten steps to changing behavior to implement evidence in practice

Start with a manageable problem and specify an achievable goal
Key ingredients: teamwork and leadership
Do an environmental scan
Develop a formal proposal
Understand the current behavior
Create a data collection system
Decide how to report results to your target audience
Select and introduce behavior change strategies
Reevaluate performance and modify behavior as necessary
Conclusion and the final step (or "move on to the next project!)

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lenging frontier for pediatric critical care EBM meriting much further study [42].

Evidence-Based Clinical Practice in Pediatric Critical Care: Challenges and Next Steps

There are numerous challenges to practicing EBM in the PICU. As we have shown, learning the principles of EBM is a time-consuming but clearly surmountable task. Although evidence focused on critically ill children is still sparse, the amount of high quality evidence is growing. Most clinical interventions have a modest effect yielding a 25 % or lower relative risk reduction. This means that clinical trials powered to identify a reduction in mortality requires enrollment of over 700 patients per group or 1,400 patients for two groups even if baseline mortality is as high as 25 % (assuming alpha 0.05, 80 % power, 25 % risk reduction). Finding 1,400 children with severe sepsis or acute respiratory distress syndrome is a challenge even if 50 or more pediatric centers are enrolling subjects [43, 44]. Fortunately, research networks such as The Pediatric Acute Lung Injury and Sepsis Investigator's (PALISI) Network (http://palisi.org) [45, 46] are facilitating performance of trials across large numbers of PICUs.

One aspect of practicing evidence-based pediatric critical care medicine involves the assessment of whether we are actually doing so. The gap between the availability of strong evidence and the application of evidence in practice is huge. It is likely that as few as 20 % of effective interventions actually reach patients [47]. Changing clinician behavior is one of the most challenging aspects of implementing EBM. Cook and colleagues have developed a pragmatic approach and in Table 16.2 we list their ten steps for changing clinician behavior and implement evidence into clinical practice [48].

EBM is a paradigm shift away from the practice of medicine based on clinical expertise alone. Uninformed colleagues sometimes misinterpret EBM and accuse it of being "cookbook medicine" and potentially harmful to the patient. This is an uninformed opinion. Prior to widespread acceptance of EBM, developers of guidelines and protocols rarely graded the level of evidence underlying each recommendation. Knowing how strong the evidence is behind clinical recommendations allows clinicians to make informed decisions prior to application. It also helps to reassure colleagues that although clinical expertise is hard to define, one cannot effectively practice EBM without sound clinical judgment that comes from a wealth of patient experience.

Although our introduction to EBM has been brief, we attempted to highlight the foundational principles as well as the challenges to practicing evidence-based pediatric critical care medicine. One website developed to help clinicians practice EBM in the PICU and other specialties is JAMA Evidence (http://www.jamaevidence.com). This website includes learning tools, calculators, podcasts and education guides and contains links to other options such as applications for smartphones and PDAs. We hope that this brief introduction to EBM has supplied high quality sources for learning more about EBM.

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