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Evidence-based medicine in trauma/acute care surgery- what does that look like?☆

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It is an honor for me to be delivering the Edgar J. Poth Memorial lecture. Dr. Poth was the 15th President of Southwestern Surgical Congress and, as I recently learned, he was interested in identifying and processing data for medical decision-making. In his presidential address[1] he said,

> "The mass of information on which medicine is based is so overwhelming that it is utterly impossible for a person to acquire sufficient depth of knowledge to become truly proficient. Time runs out on all of us long before we can acquire and retain the factual mass."

Mind you, he was speaking 55 years ago. The amount of medical information has grown exponentially over the decades, compounding the challenge of proficiency. Yet we are, justifiably, expected to practice based on the best available evidence.

I am going to discuss evidence-based medicine (EBM) in trauma/acute care surgery. There is indeed a wealth of medical information available; unfortunately, given the difficulties in performing well-controlled prospective randomized clinical trials (PRCTs) in trauma and emergency surgery, only a small fraction of it qualifies as high-quality evidence. Although access to the medical literature is simpler than ever, our challenge is to identify the highest-quality, relevant pieces of information and apply them appropriately to our patients. I recently searched PubMed.gov for papers on "Spleen trauma" and found 72 papers published in just the past 6 months. When I searched "Appendicitis," I found 374 citations from the same time period. And these are problems that I thought we had already figured out how to manage! How can we sift through it all, identify the pertinent literature, reconcile conflicting studies, and apply it to the patient lying on front of us?

As I looked back on my training, I struggled to find many good examples of discussions of EBM during my third year of medical school. As students we were generally directed to the rotation-specific textbook of fundamentals. It was not until my fourth year, on a cardiology rotation, that I first remember the discussions on rounds invoking specific literature-in this case, the "TIMI II" trial-as the basis for clinical decision-making.[2] But it all changed during residency training. I was fortunate to do my surgical training at the University of Colorado, where the explicit expectation was that you read-not just textbooks, but the current literature. My mentors were my Chairman, Alden H. Harken, MD, and the Vice-Chairman and Chief of Surgery at the Denver General Hospital (DG), Ernest E. "Gene" Moore, MD. At DG we had attending rounds in the ICU three days a week. We discussed the latest literature and whether it was robust enough to change our practice. Spirited debates were the norm, and where there were gaps in the evidence, we often studied them. During my first rotation as an intern at DG, Gene Moore challenged the group to review our data and come up with a management plan for the patient with suspected myocardial contusion. I volunteered, and that project became my first paper-which I presented to the Southwestern Surgical Congress in 1994.[3]

One of the things that stood out from my training was that it was never enough to just give the right answer. Just like in third grade math, you can't just write "9"- you have to *SHOW YOUR WORK* to get full credit. In training, you couldn't just say, "Go to the OR!" Why? When? To do what? And how? *WHAT ARE THE DATA*? There is always an alternative approach; we need to understand the options and their associated outcomes in order to choose the best path for an individual patient. To get there, we need to be able to critically evaluate literature and put it in context. Dr. Harken gave us a tremendous opportunity during our training: every Saturday (yes, Saturday School!) we had a resident debate at Grand Rounds. We learned to do research and prepare a talk, and gained public speaking experience. But most importantly, we learned to critically evaluate the literature. The "Conclusions" section of the abstract does not tell the whole story, and even the best papers have limitations. I know this process made me a better surgeon.

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The commitment to fostering critical review of the literature was also emphasized in a recent opinion piece in the New England Journal of Medicine (NEJM).[4] In it, Wenzel highlighted the importance of supporting an environment of intellectual curiosity, in which we identify and question "truths-" i.e., dogma-as well as new information. It is important to recognize that these are not simply academic issues. We owe it to our patients to discuss alternative management strategies and their expected outcomes. This is the foundation of the informed consent process. As the body of evidence evolves, so must our discussions-thus, it is our responsibility to follow the evidence.

Evidence-based medicine

Many authors point to a 1979 publication[5] as one of the first efforts to explicitly characterize the levels of evidence underlying healthcare recommendations, and the strength of those recommendations. In this document, the Canadian Task Force on the Periodic Health Examination had the objective of recommending a plan for lifetime program of periodic health assessments. They graded the effectiveness of interventions according to the quality of the evidence, and it was straightforward: Evidence obtained from at least one properly randomized controlled trial was graded as Level I; "Opinions of respected authorities" were graded as Level III recommendations; and everything in-between was graded Level II. While we see this as an oversimplification today, it was an important contribution.

The formal EBM movement is traced back to clinical epidemiologists at McMaster University. In a 1992 paper in JAMA[6] they wrote,

> "A new paradigm for medical practice is emerging. Evidence-based medicine de-emphasizes intuition, unsystematic clinical experience, and pathophysiologic rationale as sufficient grounds for clinical decision making and stresses the examination of evidence from clinical research. Evidence-based medicine requires new skills of the physician, including efficient literature searching and the application of formal rules of evidence evaluating the clinical literature."

Move over Marcus Welby; make way for Doogie Howser!

The EBM advocates pushed practitioners, patients, healthcare managers, and policymakers to pay attention to the best findings form healthcare research-specifically, those that were scientifically valid and ready for clinical application.[7] It was a laudable goal- and recognized by the New York Times Magazine as one of the most influential ideas of 2001.[8] (Notice that it had been nine years since the introduction of EBM-it takes time for movements to gain traction.) But is it that straightforward? What is "valid" research? When are research findings ready for clinical application? Later I'll give some examples of the pitfalls of early adoption. Knowledge is advanced in increments, with mis-steps along the way. Major breakthroughs are few and far between. In fact, only a minuscule fraction of published literature is adequately tested and sufficiently important to make a difference in our clinical practice.

A premise underlying EBM is that an expert or panel of experts are more fallible in their recommendations compared with evidence derived from sound systematic research. To that end, the Cochrane Collaboration was established in 1993. The primary objective was to evaluate available evidence from PRCTs and provide systematic reviews or meta-analyses. The Collaboration has grown over the years and I often read it when I'm researching a topic. But it can be frustrating when the results of seemingly methodologically sound studies offer conflicting results. Or, worse, when the statistical analysis deems findings "inconclusive." An example of this was the review of appendectomy versus antibiotic treatment for acute appendicitis, published in 2011.[9] In this review, 5 PRCTs were analyzed for the primary outcome of cure within two weeks, without major complications (including recurrence) within one year(Table 1A, 1B). Overall, 97% of the appendectomy patients achieved the primary outcome, versus just 73% of the antibiotic treated patients. In only one trial was the absolute difference less than 17%. How is this "inconclusive?" It is this kind of report that leads people to suggest that the most radical protagonists of EBM participate in a randomized, placebo-controlled crossover trial of parachute use to prevent death related to major gravitational challenge-a practice which is still not supported by any Level I evidence![10]

Given the inconsistency in guidelines and how they rated quality of evidence and strength of recommendations, the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system was proposed and has been adopted broadly.[11] In this system, the quality of evidence indicates the extent to which one can be confident that the estimate of effect is accurate. Quality of evidence is based on study design, study quality, consistency, and directness (Table 2). The grade may be further adjusted based on various factors as noted. Ultimately, a high grade of evidence suggests that further research is unlikely to change our confidence in the estimate of the effect. On the other hand, a low grade of evidence suggests that further research is very likely to have an important impact on our confidence in the estimate of effect, and likely to change the estimate. The strength of a recommendation is the degree of confidence that adherence will do more good than harm. To get to a final recommendation-which may be phrased as "Do it/don't do it", or "Probably do/don't do it," several other factors are considered (Table 3).

It has been estimated that the time leg for research evidence to reach clinical practice is 17 years.[12] Francke and colleagues[13] reviewed the factors influencing the implementation of clinical guidelines for healthcare professionals. They concluded that multiple component strategies are usually more effective than single strategies. Further, they highlighted the importance of favorable guideline characteristics (e.g., cheap and easy), professional issues (e.g., awareness of and familiarity with the guideline) patient factors (e.g., comorbidities, compliance) and environmental conditions (e.g., support from peers, superiors; sufficient staff and time). Vander Schaaf et al.[14] suggest reducing the number of publications with a weak evidence base. In addition, they suggest integrating guidelines into electronic health records, and incorporating them into health affairs schools and maintenance of certification activities.

EBM in trauma/acute care surgery practice

Practicing EBM is not as straightforward as is suggested by the above-particularly in my field. I'm going to go over a few examples that illustrate pitfalls in our reading and application of the literature.

Table 1A
Antibiotic treatment for acute appendicitis. Outcome is cure within two weeks, without major complications (including recurrence) within one year.[9]

Study	Subjects	Mean (%)	95% CI %
Eriksson 1995	20	60.0	38.0–78.6
Malik 2009	40	85.0	70.4–93.1
Styrud 2006	96	75.0	66.8–81.7
Turhan 2009	107	81.3	72.6–87.6
Vons 2011	120	60.8	51.8–69.1
TOTAL	415	73.4	62.7–81.9

Table 1B
Appendectomy for acute appendicitis. Outcome is cure within two weeks, without major complications (including recurrence) within one year.[9]

Study	Subjects	Mean (%)	95% CI %
Eriksson 1995	20	95.0	71.8–99.3
Malik 2009	40	92.5	79.2–97.6
Styrud 2006	124	98.4	93.8–99.6
Turhan 2009	183	98.9	95.7–99.7
Vons 2011	119	98.3	93.5–99.6
TOTAL	486	97.4	94.4–98.8

Standard of care, malpractice, or both?

The NEJM is an incredibly influential journal; clinical trials published in NEJM are likely to be adopted quite quickly. This was the case with the study, "A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury," a.k.a. the NASCIS-II study.[15] This study concluded that a bolus dose and 23-h infusion of methylprednisolone improved neurologic recovery if given within 8 hours of acute spinal cord injury. In an accompanying editorial, Ducker[16] stated this was "good news … After 20 years of … research … we now have evidence that a medication can reduce some of the damage that results from acute spinal injury." As trauma residents, the dosing regimen was committed to memory and rolled off of our tongues for every patient with evidence of spinal injury: "30 mg/kg methylprednisolone (MP) followed by 5.4 mg/kg/hr x 23 hours." This intervention was considered the standard of care (I was actually named in a notice of claim, erroneously alleging we had failed to administer steroids to a patient). Critical analyss of this and other NASCIS trials followed, pointing out that the neurologic gains were not as consistent as advertised. More concerning was that the only consistent finding in the NASCIS trials was an increase in harmful side effects. Nevertheless, the practice was endorsed by the Congress of Neurological Surgeons and American Association of Neurological Surgeons as recently as 2002. However, the 2013 guidelines included a level I recommendation AGAINST the use of steroids. The rationale included: a) MP is not approved by the FDA for this application; b) there is no class I or class II evidence supporting a clinical benefit of MP; and c) there is class I, II, and III evidence indicating that high-dose steroids are associated with harmful side effects including death. But the pendulum may be swinging back: a recent review based on GRADE methodology supports a 24 hour infusion of high-dose methylprednisolone being offered to patients within 8 hours of spinal cord injury as an option.[17] This is a "weak recommendation based on moderate quality of evidence". I predict we have not seen the end of this debate.

Where are they now?

I was curious about other high profile papers from NEJM and I performed a search of their most cited PRCTs. Of nearly 1500 research papers, I identified the top 5 (Table 4). Three of the top four happened to fall within our practice in acute care surgery.[18–20] Coincidentally, these three papers were all published in 2001. In the first guidelines proposed by the Surviving Sepsis Campaign for the management of severe sepsis and septic shock in 2004,[21] these papers were all included. The early goal-directed therapy (EGDT) approach of Rivers et al.[19] was endorsed as a Grade B recommendation; recombinant human activated protein C[20] was recommended for patients at high risk of death (Grade B); and glucose control was recommended following initial stabilization, albeit at a slightly more liberal upper limit (<150 mg/dL) than that proposed by Van den Bergh et al.[18] These practices were widely adopted and followed. However, by 2016 the Surviving Sepsis Campaign guidelines[22] differ on all three topics. The recommendation for EGDT was softened as recent studies failed to show survival differences. The targets are still regarded as safe and "may be considered." Recombinant human activated protein C was not shown to be effective in subsequent study and has been withdrawn from the market. The upper target for glucose control has now been increased to 180 mg/dL (strong recommendation, high quality of evidence). This is an important reminder that the highest-quality studies, published in the best journals, may not prove to be the final answer. Early adoption may be reasonable but we must be ready tochange our practce as new compelling data emerge.

Expert opinion: sometimes innovation is the best strategy

Louis Pasteur once said, "Fortune favors the prepared mind." There was no mind more prepared than that of Gene Moore. I was only a couple of months into my career when a young man came in with a gunshot wound in the right upper quadrant of the abdomen. On exploration, I found he had a retrohepatic caval injury. Wanting some seasoned help, I called Dr. Moore. He said he had recently read a case report of venovenous bypass and he thought it would be a good idea to implement that- and to add a superior mesenteric venous cannula to decompress the portal system during the repair. Expert opinion is the lowest quality of evidence- but we did it, the patient did well, and we published our own case report.[23]

EBM versus expert opinion

For many years the Eastern Association for the Surgery of Trauma (EAST) has been publishing practice management

Table 2
Criteria for assessing the quality of evidence, and adjustment factors.[11].

- •Study Design
  - o PRCT = High
  - o Observational = Low
- •Study Quality (Methods and execution)
  - o Decrease grade if serious (−1) or very serious (−2) limitation to study quality
  - o Decrease grade if Imprecise or sparse data (−1)
  - o Decrease grade if High probability of reporting bias (−1)
- •Consistency (Similarity of effects across studies)
  - o Decrease grade if important inconsistency (−1)
  - o Increase grade if strong evidence of association (significant relative risk of >2 based on consistent evidence from two or more observational studies, with no plausible confounders) (+1)
  - o Increase grade if very strong evidence of association (significant relative risk of >5 based on direct evidence with no major threats to validity) (+2)
  - o Increase grade if evidence of a dose-response gradient (+1)
  - o Increase grade if all plausible confounders would have reduced the effect (+1)
- •Directness (Similarity to the patient/population, interventions, and/or outcomes of interest)
  - o Decrease grade if some (−1) or major (−2) uncertainty about directness

Table 3
Factors for consideration before recommendations.[11].

- Quality of evidence for each outcome
- Relative importance of outcomes (Only consider Important or Critical)
- Overall quality of evidence (Based on lowest quality of evidence for any critical outcome)
- Balance of benefits and harms
- Balance of net benefits and costs
- Values and preferences
- Strength of recommendation

guidelines, and they follow EBM principles. These guidelines are widely quoted, and in many trauma centers they form the basis for institutional practice guidelines. The Western Trauma Association (WTA) created a "Critical Decisions in Trauma" ad hoc Committee in the early 2000s, with the goal of providing evidence-based decision tools at the point of care. Recognizing the paucity of high-level evidence in trauma, the WTA group decided to create algorithms, based on the best available evidence adjudicated by the expert opinion of experienced trauma surgeons. The algorithms offer a safe approach for various scenarios within a topic area. I'm going to use the example of resuscitative thoracotomy to illustrate the differences between the two approaches.

The 2015 EAST guideline for emergency department resuscitative thoracotomy (EDT)[24] addresses six clinical scenarios: patients with or without signs of life, and after blunt; penetrating thoracic; or penetrating extra-thoracic injury. The existing literature was reviewed and recommendations were made based on the strength of the evidence. Of the six scenarios, there is only one strong recommendation: to perform EDT in a patient with signs of life after penetrating thoracic injury. The remainder of the recommendations are conditional, with one of the five being against performing EDT: in patients without signs of life after blunt injury. I respect the EBM process; however, for the practitioner at the bedside of a mostly-dead patient, it needs to be a "Go/No Go" situation. There can't be a lot of head-scratching. The WTA algorithm[25] offers a step-by-step approach, including indications for EDT (profound refractory shock, or undergoing CPR without signs of life); conditions under which EDT is not performed and a patient is pronounced dead on arrival (e.g., CPR beyond a certain time limit, based on mechanism and location of injury); and criteria for declaring futility (e.g., inability to achieve systolic blood pressure >70 with an aortic cross-clamp applied). I often find this more useful at the bedside of the individual patient.

Are we asking/answering the right question?

As we read the literature and determine whether to apply it to an individual patient or group of patients, we must consider whether we are asking and answering the right questions. The inclusion and exclusion criteria, the outcome measures, and the generalizability should all be assessed. I'll offer an example of an actively-developing body of evidence that is affecting practice. I'll go back to a WTA algorithm on the management of complicated diverticulitis.[26] When this was published in 2012, the group recommended laparoscopic lavage and drainage (LLD) for the management of grade 3 diverticulitis (i.e., perforated diverticulitis with purulent peritonitis). This recommendation was based on promising results from several case series, and was felt to be a safe, less invasive alternative to resection (which is associated with ostomy in the majority of cases). Since the publication of that algorithm, three PRCTs were performed comparing laparoscopic lavage versus Hartman's procedure for acute perforated diverticulitis.[27–29] The first PRCT published was from the LOLA (Laparoscopic Lavage versus Sigmoidectomy) group of the Ladies trial.[27] In this study the primary endpoint was major morbidity and mortality within 12 months, and the study was terminated early based on a significantly higher rate of in-hospital major morbidity or mortality in the LLD group (35% vs 18%). The authors concluded, "laparoscopic lavage is not superior to sigmoidectomy for the treatment of purulent perforated diverticulitis." In the Scandinavian Diverticulitis trial (SCANDIV), there was no difference in the rate of death or severe complications between the groups. The secondary endpoints did differ: 90-day rates of reoperation (20% vs 6%) and secondary peritonitis (12% vs 0%) were higher in the LLD group, leading the authors to conclude, "These findings do not support laparoscopic lavage for treatment of perforated diverticulitis." Do I hear a death knell for LLD?

In contrast to these two trials was the "DIverticulitis- LAparoscopic LAvage vs resection (Hartman procedure) for acute diverticulitis with peritonitis (DILALA)" trial.[29] The initial publication of the DILALA trial examined short-term outcomes and found no significant differences in either mortality or significant complications. They concluded, "Laparoscopic lavage as treatment for patients with perforated diverticulitis was feasible and safe in the short term." A subsequent longer term follow-up of the study[30] found that significantly fewer patients in the LLD group had reoperations in 12 months (28% vs 63%), and total length of hospital stay was 35% shorter. Fewer LLD patients had a stoma at 12 months (7% vs 28%).

I heard many surgeons opine that LLD was not a viable option, but what is the desired outcome? If it's me, I'd like to have my sepsis controlled and avoid a colostomy. To that end, LLD appears to be a good option. In the SCANDIV trial, 16% of LLD patients had an ostomy, compared with 69% of the resection group. Although stomas are often placed with the intention of closure, we know that 30–40% are never taken down. In DILALA, 100% of resection patients had a colostomy (of which 53% were closed), versus 5% of LLD patients. At one year, the LOLA group participants were alive without a stoma in 78% of LLD cases and 71% of resections. To get to that point with fewer surgical procedures and lower costs, as

Table 4
Five most frequently cited PRCTs, New England Journal of Medicine, 1827–2018.

- Van den Berghe G, Wouters P, Weekers F et al. Intensive insulin therapy in critically ill patients. N Engl J Med, 2001; 345:1359–1367.
- Rivers E, Nguyen B, Havstad S et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med, 2001; 345:1368–1377.
- The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting enzyme inhibitor, Ramipril, on cardiovascular events in high-risk patients. N Engl J Med, 2000; 342:145–153.
- Bernard GR, Vincent J-L, Laterre P-F et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med, 2001; 344:699–709.
- Llovet JM, Ricci S, Mazzaferro V et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med, 2008; 359:378–390.

indicated by the results of DILALA,[29–31] is superior in my mind.[32] Quality of life assessments were similar in both groups in all 3 trials. In sum, patient-centered outcomes appear to be quite acceptable after LLD, and I suggest it to appropriate patients. At the least, it should be discussed as an alternative in the informed consent process.

Patients/families and EBM

Informed consent is central to our interactions with patients. Shared decision making is the expectation. Many patients entrust us with making a recommendation; some, on the other hand, have read what they can about their disease and will have many questions- and occasionally requests for their care.

Given the complexities of care, it is best when we and are patients are on the same page. But there are times when we are not. One example that stands out for me involves an adolescent girl with acute appendicitis. I was called by the emergency physician about a girl with a classic presentation, leukocytosis, and ultrasonography demonstrating a noncompressible 13 mm appendix with localized peritoneal irritation. I went into the room with a surgical consent form in hand- but that's not where we ended up. The parent requested a CT scan to “make certain” of the diagnosis. We discussed radiation. The parent questioned the need for surgery. I quoted the available literature-which the time consisted primarily of the Cochrane review I presented earlier.[9] But the family had accessed the abstract of a paper published that month, reporting 93% success with antibiotic treatment-at 30 days![33] I'm not in the position of “selling” surgery to patients, but I really felt it was the best course in this young, good-risk patient. Needless to say, the parents were committed. Regrettably, the course did not go well. The poor girl spent too many days in the hospital, and returned to the ED at least once after discharge (she was lost to follow-up). I don't know how it ultimately turned out, but I believe she would have been back to her normal life far sooner if she had undergone laparoscopic appendectomy on the day of presentation.

Evidence-based medicine is a good thing. But finding and applying the best evidence for an individual patient is not always easy. Just because a paper was published recently does not mean it can or should supplant previous work on the topic. Everything must be put in context. And as a word of caution about reading only the abstract of a paper, I point to a paper by Arunchulam and colleagues.[34] Upon review of PRCTs with nonsignificant primary outcomes, they found evidence of “spin” in the title in 7%. In addition, the level of spin was high in 14% of abstract and 19% main-text “Conclusions” sections. Of note, 23% of the articles recommended the treatment despite a nonsignificant primary outcome. This highlights the important of reading the entire paper to assess its quality and give it context. We may find enough there to recommend it, depending on the alternatives. Ultimately, we owe it to our patients to inform them of how we are coming to a decision, and do our best to align it with their goals of care.

Conflict of interest statement

I have no financial or personal conflicts of interest that have influenced this work or its publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2018.09.017.

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