EVIDENCE-BASED RESOURCES FOR CLINICAL PRACTICE

LESLIE ST. JACQUES, BHSC (PA), MES, MSW

Abstract:
A key clinical skill in evidence-based practice is the ability to obtain accurate, quality clinical information quickly. Also crucial are empathy and communication skills to enable shared decision-making with the patient, toward formulation of practical treatment decisions. How do clinicians find and use the most current evidence-based resources to answer clinical questions? This article draws from Thomas Agoritsas et al's chapter "Finding Current Best Evidence", and explores the search for and utilization of evidence-based resources, using Clostridioides (formerly Clostridium) difficile infection as an example.

Introduction

An abundance of information exists at our fingertips – how do we access the best clinical evidence quickly? As clinicians an equally important skill is being able to translate this information to patients and families, to ensure their understanding and agreement, coming to treatment decisions that can be implemented in the context of the patient's situation. Thomas Agoritsas et al provide an overview of different categorizations of evidence, and discuss strategy for finding answers to clinical questions in detail.[1] This article draws on their approach, exploring the search for and utilization of current best evidence for Clostridioides difficile infection (CDI) treatment as an example.

Evidence-based medicine (EBM) arose from the need to make treatment decisions based on clear clinical reasoning. Complexity is acknowledged as "uncertainty about clinical research evidence intersects with an individual patient's predicament and preferences."[2] EBM's three fundamental principles involve acquisition of the best available evidence; determination of the trustworthiness of that evidence and the level of certainty; and decisions made with patients integrating consideration of risk, cost, benefit, patient values and preferences.[3]

Agoritsas et al suggest formulating your clinical question in the PICO format, to aid your search.[4] PICO stands for:

- Patient or population
- Intervention(s) or exposure(s)
- Comparator
- Outcome[5]

An example:

Patient: Adult female with Clostridioides difficile infection (CDI)
Intervention: antibiotic therapy
Comparator: antibiotic therapy with probiotics
Outcome: resolution of watery diarrhea

Starting with a clear question will help find resources that relate more closely to your patient. The closer the study population resembles your patient, the more applicable the findings may be.

What is meant by "best evidence" in clinical practice?

A search for the best evidence begins by looking for guidelines and decision-analyses, systematic reviews, and pre-appraised research, leaving non-pre-appraised studies to the end. There are clear expectations for guidelines, decision analysis, systematic reviews and databases of pre-appraised research, including assessment of included studies for methodological quality and avoidance of bias. Excellent resources for those interested in guideline development include Schunemann et al, "Guidelines 2.0: systematic development of a comprehensive checklist for a successful guideline enterprise",[6] and Alonso-Coelle et al, in Evidence to Decision (EtD) frameworks.[7]

The GRADE Working Group created a "framework for judging confidence in" the estimates produced by systematic reviews and health technology assessments, determining the quality of evidence, particularly with respect to guideline development. GRADE refers to: Grading of Recommendations Assessment, Development and Evaluation.[8]

In brief, the design of a study significantly impacts the confidence rating in its results. Randomized control trials engender more confidence that an observational study, however many factors influence the confidence rating including "increased risk of bias, inconsistency, *imprecision, indirectness,* or concern about *publication bias*."[9] When a systematic review includes multiple studies that contain a lot of unexplained heterogeneity, this can also lower confidence.[10]

Types of evidence-based resources

Clinical practice guidelines are created in a process involving multiple researchers, who perform a comprehensive search through the full body of evidence, including systematic reviews, assess studies for quality, consider patient values and preferences, and make specific recommendations for clinical treatment. Guideline developers will publish findings on clinical society websites, or in their journals, eg. as a guideline by the Endocrine Society[11] or the American Heart Association/American Stroke Association.[12] Guidelines should describe how the literature review was conducted and the date, demonstrating a credible process.[13] A resource to find summaries and guidelines is the US National Guideline Clearinghouse (http://www.guideline.gov).[14] Also useful is the guide to using guidelines, offered by Ignacio Neumann et al, in their book chapter "How to Use a Patient Management Recommendation".[15]

Taking the example of a patient with Clostridioides difficile infection a search for guidelines related to CDI finds that the search terms "clostridium" and "society guidelines" in a web browser finds the Infectious Disease Society of America Clostridium Difficile Practice Guidelines.[16] The Association of Medical Microbiology and Infectious Disease Canada treatment practice guidelines for Clostridium difficile infection, are also easily accessible on-line.[17] These two guidelines speak to treatment of initial and recurrent infections, in adult patients, including when and why vancomycin, fidaxomicin or metronidazole are used.

A decision analysis combines the benefits and harms of a treatment option with values and preferences, often represented as a decision tree.[18] The decision tree makes all of the important elements explicit, so they may be discussed. The options and alternatives are laid out, and this can be a tool for discussion of proposed treatment with the patient.

A systematic review is an organized, systematic search and assessment of all of the available evidence on a topic. Systematic reviews are the starting point for clinical guidelines. Ideally a systematic review includes searching for studies that are not published, in order to avoid publication bias. The studies are appraised for confidence in the effect estimates, and a meta-analysis (pooling the estimated effects on each outcome of interest), is included where appropriate.[19] A systematic review saves you the work of searching for individual studies and assessing their trustworthiness.

Murad et al explain that:

> *"the goal of a systematic review and meta-analysis is often to present evidence users (clinicians, patients and policymakers) with best estimates of the effect of an intervention on each patient important outcome. When interpreting and applying the results, you and your patient must balance the desirable and undesirable consequences to decide on the best course of action".*[20]

The systematic review process includes determining the specific criteria for studies that will and will not be part of the review; thorough search of medical databases; bias assessment for each included study; data abstraction from the studies; results summarizing; meta-analysis, with a confidence interval; analysis of heterogeneity of the studies and an attempt to explain discrepancies in effects.[21]

Agoritsas et al provide multiple resources, including the Cochrane Database of Systematic Reviews: https://www.cochranelibrary.com. Once at this site a search box allows the researcher to input terms, eg. "Clostridium difficile antibiotic treatment", or "Clostridium difficile probiotics". Along with the list of reviews, there will be a tab showing "trials", which will tell you if a controlled trial has been done on your topic.

Summaries of clinical evidence are useful for questions about current practice on a specific topic, eg. current recommendations for treating CDI. Summaries of clinical research include UpToDate, DynaMed, or Clinical Evidence. The UpToDate summary on Clostridioides difficile infection gives the date it was last updated and how current the literature review is.[22] Note at the left side of the page there is a link to "society guidelines".

Pre-appraised research is compiled by trained research staff who critically analyze it – selecting from the huge number of published studies, identifying those that meet pre-specified methodologic standards, for therapy or prevention. For example, methodologic guidelines for inclusion in a database may stipulate that a study must have involved random allocation, 80% follow-up rate or better and at least one patient-important outcome. Examples of pre-appraised research are found in databases, such as McMasterPLUS, accessible through BMJ EvidenceUpdates, http://plus.mcmaster.ca/EvidenceUpdates/QuickSearch.aspx.[23]

Non-pre-appraised literature

If there are no guidelines, systematic reviews, or summaries, and database searches for pre-appraised research were fruitless, then look to the non-pre-appraised research. These include PubMed's MEDLINE and EMBASE.[24] The delay between a study being published and it being included in pre-appraised databases means that searching through non-pre-appraised research may yield a study that was published so recently that it has not yet been appraised.

Agoritsas et al recommend bookmarking the Evidence-based resources that your clinic, hospital or university subscribes to on your electronic devices.[25] A university or medical school librarian is also a great resource. McMaster University Health Science library links to multiple resources about EBM: https://hslmcmaster.libguides.com/c.php?g=306765&p=2044668.

Applicability of Evidence

How does the evidence relate to my patient?

Once you have successfully obtained a guideline, systematic review or found studies through databases, the question of applicability remains. Looking at the inclusion and exclusion criteria of trials, or the sub-group analyses will help determine if your patient could have been included in the trials.

> "The optimal evidence for decision making comes from research that directly compared the interventions in which we are interested, evaluated in the populations in which we are interested, and measured outcomes important to patients. If populations, interventions, and outcomes in studies differ from those of interest, (ie. the patient before us), we lose confidence in estimates of effect."[26]

Dans et al suggest the SCRAP mnemonic to recall five factors that may affect application of results to a specific patient: Sex, Comorbidity, Race/ethnicity, Age and Pathology of the disease. Is the baseline risk your patient faces, similar to that of the patients in the study? Studies often report relative risk reduction (RRR), which is the response of a population as a mean, although biologic and socioeconomic factors may alter the treatment effect.[27] As well, depending on baseline risk, the absolute risk reduction (ARR) for patients will vary. The absolute risk reduction is the difference between the patient's baseline risk of an adverse outcome, and the risk they would have after the intervention.[28]

Finally, Dans et al suggest consideration of whether both patient and clinician can adhere to the treatment, and whether the benefits outweigh the risks and costs? Is the evidence so strong that the usefulness of an intervention is clear? When recommendations are weak, or applicability to the specific patient is limited, decision-making is more complex.

Making decisions with your patient

"*Evidence-based medicine* (EBM) involves conscientiously working with patients to help them resolve (sometimes) or cope with (often) problems related to their physical, mental, and social health."[29] An evidence-based approach involves understanding the patient's "perspectives, priorities, beliefs, expectations, values and goals for health and life", as evidence

alone is not sufficient basis for a treatment decision.[30] Ideally, interactions with patients are bidirectional, allowing the clinician to understand aspects of the patient's life that may affect their use of a treatment or medication. The clinician will also provide information, and support the patient in understanding options.

A shared decision-making approach requires a "high degree of empathy" as patients consider information and may have difficulty coming to, or sticking to a decision.[31] Patients may not raise issues about money or other personal information that are embarrassing if they do not sense empathy in the clinician. Understanding some aspects of the patient's life and potential barriers to implementation of the treatment will contribute to its success. Will your patient with CDI have insurance coverage to pay for vancomycin or fidaxomicin? Is metronidazole going to be much more affordable? Will your patient abstain from alcohol, as would be required while taking metronidazole?

Montori et al explain that time constraints in clinical practice may necessitate differentiating between important vs unimportant or straightforward vs difficult decisions, that will require more in-depth conversation. In patients with multiple comorbidities how will the added treatment affect their quality of life? Is minimizing the burden of treatment a consideration? In situations in which the clinician or patient may require more time to research the question or treatment, Montori et al suggest setting an additional meeting or appointment to reconvene for further discussion.[32]

In Summary

Evidence-based practice requires clinical skills to both find high quality evidence-based resources, and to discuss treatment with patients to ensure a feasible plan. With practice you will become adept at finding the best available evidence. Readers are encouraged to look to Agoritsas et al for further elucidation of search strategies, hierarchies of evidence and additional resources.[33] Understanding the types of resources available and how to find them will help you make informed choices and strengthen your clinical skills.

REFERENCES

1 Agoritsas T, Vandvik PO, Neumann I, Rochwerg B, Jaeschke R, Hayward R, Guyatt G, McKibbon KA. "Finding Current Best Evidence",
in Guyatt G, Rennie D, Meade MO, Cook, DJ, eds. *User's Guides to the Medical Literature: a Manual for Evidence-based Clinical Practice.* New York: McGraw Hill Education, 2015: 29-49.
2 Guyatt G, Jaeschke R, Wilson M, Montori VM, Richardson WS, "What is Evidence-based Medicine?" in Guyatt G, Rennie D, Meade MO, Cook, DJ, eds. *User's Guides to the Medical Literature: a Manual for Evidence-based Clinical Practice.* New York: McGraw Hill Education, 2015: 7-14.
3 Guyatt et al, ibid., p. 8.
4 Agoritsas et al, ibid.
5 Guyatt G, Meade MO, Agoritsas T, Richardson WS, Jaeschke R. "What is the Question?" in Guyatt G, Rennie D, Meade MO, Cook, DJ, eds. *User's Guides to the Medical Literature: a Manual for Evidence-based Clinical Practice.* New York: McGraw Hill Education, 2015: 19-28.
6 Schunemann HJ, Wiercioch W, Exteandia I, Falavigna M, Santesso N, Mustafa R, Vetresca M, Brignardello-Peterson R, Laisaar K, Kowalski S, Baldeh T, Zhang Y, Raid U, Neumann I, Norris SL, Thornton J, Harbour R, Treweek S, Guyatt G, Alonso-Coello P, Reinap M, Brozek J, Oxman A, Akl EA. "Guidelines 2.0: systematic development of a comprehensive checklist for a successful guideline enterprise", *The Canadian Medical Association Journal*, February 18, 2014, 186 (3): E123-142.

7 Alons-Coello P, Oxman AD, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, Trewe S, Mustafa RA, Vandvik PO, Meerpohl J, Guyatt GH, Schunemann HJ. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well-informed healthcare choices. *The British Medical Journal* 2016: 353; i2089.
8 Murad MH, Montori VM, Ioannidis JPA, Neumann I, Hatala R, Meade MO, Devereaux PJ, Wyer P, Guyatt G. "Understanding and Applying the Results of a Systematic Review and Meta-Analysis", in Guyatt G, Rennie D, Meade MO, Cook, DJ, eds. *User's Guides to the Medical Literature: a Manual for Evidence-based Clinical Practice.* New York: McGraw Hill Education, 2015: 471-489.
9 Murad et al, ibid, p. 476.
10 Murad et al, ibid. p. 481.
11 Endocrine Society, Clinical Practice Guidelines. Available from: https://www.endocrine.org/guidelines-and-clinical-practice/clinical-practice-guidelines, accessed Jan. 2, 2019
12 American Heart Association/American Stroke Association. 2018 Cholesterol Clinical Practice Guidelines. Available from: https://www.ahajournals.org/guidelines/cholesterol, accessed Jan. 2, 2019
13 Neumann I et al, ibid.
14 Agoritsas et al, ibid.
15 Neumann I, AKl EA, Vandvik PO, Agortisas T, Alonso-Coello P, Rind DM, Santesso N, Alexander PE, Mustafa RA, Prasad K, Bates SM, Schunemann HJ, Guyatt G. "How to Use a Patient Management Recommendation: Clinical Practice Guidelines and Decision Analyses" in Guyatt G, Rennie D, Meade MO, Cook, DJ, eds. *User's Guides to the Medical Literature: a Manual for Evidence-based Clinical Practice.* New York: McGraw Hill Education, 2015: 531-543.
16 Infectious Diseases Society of America, "Clostridium Difficile" clinical practice guideline, Clinical Infectious Diseases, March 19, 2018, 66 (7): E1-48. Available from https://www.idsociety.org/practice-guideline/clostridium-difficile/. Accessed Jan 3, 2019.
17 Loo VG, Davis I, Embil J, Evans GE, Hota S, Lee C, Lee TC, Longtin Y, Loule T, Moayyedi P, Poutanen S, Simor AE, Steiner T, Thanpi N, Valiquette L. "Association of Medical Microbiology and Infectious Disease Canada Treatment Practice Guidelines for Clostridium Difficile Infection". *Journal of the Association of Medical Microbiology and Infectious Disease Canada*, 2018, 3.2. Available from: https://www.ammi.ca/Content/AMMI%20Canada%20treatment%20practice%20guidelines%20for%20Clostridium%20difficile%20infection.pdf, accessed Jan. 4, 2019
18 Neumann I, AKl EA, Vandvik PO, Agortisas T, Alonso-Coello P, Rind DM, Santesso N, Alexander PE, Mustafa RA, Prasad K, Bates SM, Schunemann HJ, Guyatt G. "How to Use a Patient Management Recommendation: Clinical Practice Guidelines and Decision Analyses" in Guyatt G, Rennie D, Meade MO, Cook, DJ, eds. *User's Guides to the Medical Literature: a Manual for Evidence-based Clinical Practice.* New York: McGraw Hill Education, 2015: 531-543.
19 Agoritsas et al., ibid.
20 Murad MH, Montori VM, Ioannidis JPA, Neumann I, Hatala R, Meade MO, Devereaux PJ, Wyer P, Guyatt G. "Understanding and Applying the Results of a Systematic Review and Meta-Analysis", in Guyatt G, Rennie D, Meade MO, Cook, DJ, eds. *User's Guides to the Medical Literature: a Manual for Evidence-based Clinical Practice.* New York: McGraw Hill Education, 2015: 471-489. (quote from p. 475).
21 Murad MH, Jaeschke R, Devereaux PJ, Prasad K, Carrasco-Labra A, Apritsas T, Cook DJ, Guyatt G. "The Process of a Systematic Review and Meta-analysis", in Guyatt G, Rennie D, Meade MO, Cook, DJ, eds. *User's Guides to the Medical Literature: a Manual for Evidence-based Clinical Practice.* New York: McGraw Hill Education, 2015: 459-469.
22 Kelly CP, Lamont JT, Bakken JS. "Clostridioides (formerly Clostridium) difficile infection in adults: treatment and prevention. Last updated October 15, 2018. https://www.uptodate.com/contents/clostridioides-formerly-clostridium-difficile-infection-in-adults-treatment-and-prevention
23 Agoritsas et al, ibid. p 39.
24 Agoritsas et al, ibid. p 39.
25 Agoritsas et al. ibid.
26 Murad MH, Montori VM, et al, ibid. p. 483.
27 Dans AL, Dans LF, Agortisas T, Guyatt G, "Applying Results to Individual Patients", in Guyatt G, Rennie D, Meade MO, Cook, DJ, eds. *User's Guides to the Medical Literature: a Manual for Evidence-based Clinical Practice.* New York: McGraw Hill Education, 2015: 235-247.

28 Dans et al, ibid., p.244.
29 Guyatt G, Jaeschke R, Wilson M, Montori VM, Richardson WS, "What is Evidence-based Medicine?" in Guyatt G, Rennie D, Meade MO, Cook, DJ, eds. *User's Guides to the Medical Literature: a Manual for Evidence-based Clinical Practice.* New York: McGraw Hill Education, 2015: 7-14.
30 Montori V, Elwyn G, Devereaux PJ, Straus SE, Haynes RB, Guyatt G, "Decision-making and the Patient", in Guyatt G, Rennie D, Meade MO, Cook, DJ, eds. *User's Guides to the Medical Literature: a Manual for Evidence-based Clinical Practice.* New York: McGraw Hill Education, 2015:547-559.
31 Montori et al, ibid, p. 553.
32 Montori et al, ibid., p. 557.
33 Agoritsas et al, ibid.