A FUNDAMENTAL OBJECTIVE of medical research (indeed any scientific research) is advancing knowledge. The act of discovery, of learning something new and leaving a mark in the understanding of medicine, is what motivates many investigators. Implicit to this concept of discovery is defining what is already known. Much as there cannot be light without darkness, one cannot identify what is new without defining what is already known.

Introduction

A requirement of any academic endeavor, therefore, is to map what is *currently* known using the available evidence. (Note: The adverb "currently" warrants emphasis, as there is uncertainty in all that is "known," and new evidence, or reappraisal of established evidence, may update the "current" state of knowledge.) The importance of this step is embedded in the very word "investigate," whose origins include the Latin for "footprint" or "track"—thus, before treading a new path, an investigator must start by examining the footprints left by the investigators who have come before.

This chapter provides a framework for making use of available evidence and describing the different types of evidence, where and how to find it, and finally how to approach and apply the evidence when examining a research question.

Defining Medical Evidence

What is being referred to when talking about medical evidence? In broadest terms, medical evidence is the mass of data derived from systematic observation, experimentation, and clinical experience, that informs an understanding of the field of Medicine and is used to guide decisions in the health sciences. In transfusion medicine, this evidence ranges from basic science (such as cellular biology and animal models) to clinical studies.

Professionals in academic health sciences often refer to medical evidence as "the literature." This term gives the vague impression that the totality of medical evidence is stored in a single repository that can be easily accessed for consultation. In reality, "the literature" is amorphous, distributed across many sources, and it is currently impossible to point to one place (physical, digital, or otherwise) where "the literature" exists.

The Internet has drastically improved the accessibility of medical evidence, with several databases of published experience accessible online. It is much easier to now access formal, peer-reviewed journals where medical research is published, but also nontraditional platforms (the so-called grey literature) for medical evidence. Using a well-structured search strategy, an investigator can access much of the relevant medical evidence for a given topic, although it is impossible for an individual researcher to access *all* the relevant medical evidence for a given topic, partly due to the volume and breadth of academic production, partly because not all knowledge is published or publicly available.

Primary, Secondary, and Tertiary Sources

Medical evidence can be classified according to its originality and proximity to the source of information. Primary sources, as implied by the name, are as close as one can get to the observed results of experiments. This type of evidence is empirical, obtained from direct observation of experiments and includes original research activities (experiments or clinical studies) that provide hypotheses, generate data, and result in conclusions inferred from the data. Primary medical evidence is found mainly as articles in scientific journals or conference abstracts but can also be found in the aforementioned grey literature [eg, graduate theses, internal research reports, publicly accessible databases such as the Serious Hazards of Transufion (SHOT) scheme in the United Kingdom, and patents].

Secondary medical evidence is inferential and could not exist without the primary sources. This category of medical evidence includes work that lists, summarizes, compares, combines, or reanalyzes primary data to describe the present state of discipline-specific evidence and draw conclusions. Secondary evidence will cite primary evidence directly and includes narrative review articles, systematic reviews, meta-analyses, practice guidelines, newsletters, compiled data, and article indexes. This category often provides new insights or discovery through reinterpretation, reanalysis, or synthesis of primary evidence across individual studies.

Tertiary medical evidence is the distillation of primary and secondary evidence and provides a succinct summary of the knowledge in a discipline. Encyclopedias (eg, Wikipedia), textbook chapters, and fact books represent tertiary medical evidence.

Importance of Using Available Evidence

As in any field of study, the existing evidence in the health sciences should be consulted as a first step in any research project. This consultation allows investigators to identify gaps in clinical knowledge and specify which questions merit further investigation. Review of the available evidence informs judgments to be made about the relative importance of a question. Not every research question needs to be original or never-before evaluated. In fact, reproducibility is an important aspect of theory formation. However, certain questions have enough high-quality evidence behind them that the question can be considered "answered," and academic pursuits are thus better made in other directions.

Occasionally, what has been accepted as "scientific fact" is based on shaky evidence, and this is revealed only through thorough review of the available evidence. Making use of the available evidence improves the efficiency of research and optimizes the relevance of the research question.

Finding (Relevant) Medical Evidence

As noted earlier, there is, unfortunately, no single location that a researcher can peruse and capture all the relevant existing evidence. However, the vast majority of primary and secondary evidence is available online and indexed in at least one of the major abstract and indexing databases. Well-populated and easily searchable databases that focus on the health sciences include PubMed/MEDLINE, Embase, and the Cochrane Library (see Online Resources listing at the end of this chapter). Web of Science and Scopus include publications from the medical literature but are very broad (covering many disciplines across natural sciences, social sciences, the arts, and humanities).

There is considerable overlap across these databases (with the exception of Cochrane Library, which focuses on systematic reviews and meta-analyses), and whether or not multiple databases need to be searched depends on the circumstances. For an investigator completing a preliminary background literature review to better define the current landscape, a search of one or two databases may suffice, but for an investigator completing a systematic review on a specific topic, searches in all the major databases should be completed (often as a starting point). Librarians with experience in searching the medical literature can be consulted to ensure the search strategy is as complete as possible.

Tertiary evidence (textbooks, encyclopedia entries) is less easily found on these indexing databases. Search engines such as Google Scholar can be useful for identifying tertiary sources of evidence (in addition to primary and secondary ones).

As in many other fields, the use of artificial intelligence is being developed to facilitate the identification of the available online medical evidence (eg, SciSpace) and have the potential to transform current search methods as these technologies improve. Although these tools will likely make literature searches more efficient, the limited transparency with which these technologies operate is a current limitation.

For those interested not only in the evidence that has been published, but also what evidence can be anticipated, clinical trial registries provide descriptions of registered studies. Popular registries include ClinicalTrials.gov, the International Clinical Trials Registry Platform (ICTRP), the ISRCTN Registry (The UK's Clinical Study Registry), and the European Union Clinical Trials Register (EU-CTR) (see Online Resources listing).

Formulating a Search Using Boolean Operators

Regardless of the database used, the most complete and relevant search results will be obtained by formulating the research question as close to the "PICO" format as possible (population, intervention, comparison, outcome; similar to PICOT, discussed in Chapter 2), searching each PICO category individually, and combining the individual searches using the Boolean operator "AND."

Boolean operators are words used in database searches to refine and improve search results. The three main operators are *AND*, *OR*, and *NOT*. These operators allow terms to be combined or excluded to reduce irrelevant results and make searches more effective.

For example, if one is interested in identifying what has been published related to the use of whole blood in the management of maternal hemorrhage, the following are the steps to take:

Step 1: Frame the research question in PICO format.

Research question: Does whole blood transfusion improve maternal hemorrhage outcomes compared to component therapy?

Step 2: Identify PICO elements.

P (Popluation): Obstetric patients
I (Intervention): Transfusion of whole blood
C (Comparison): Conventional component therapy
O (Outcome): Maternal mortality

Step 3: Construct a Boolean search query.

("obstetric patients" OR "pregnancy") AND
("whole blood transfusion") AND
("component therapy" OR "standard transfusion") AND
("maternal mortality" OR "survival")

These results will be more complete than if a single search is conducted for "whole blood transfusion in obstetrics."

PubMed uses "MeSH" terms (Medical Subject Headings thesaurus), which is a controlled vocabulary used to index articles. The use of MeSH improves the accuracy of literature searches by standardizing terminology and organizing topics into a content hierarchy. MeSH terms can be used to refine search strategies, by limiting searches to subsets within a MeSH category, or including categories from higher up the MeSH hierarchy. Searching for a term in the PubMed MeSH Browser will provide the MeSH terms that it maps to, which can be used to improve the search.

Each database has particularities to its search functions and optimal search strategy, and a detailed description of search strategies is beyond the scope of this chapter. The time spent developing familiarity with one of the major databases is well worth it in the long run, as it will make searches more efficient and complete.

Filtering and Appraising the Evidence

After completing a search of the published literature, the list of identified publications needs to be reviewed and nonpertinent publications filtered out. A good search will return more articles than are directly relevant to the area of interest. If the list of publications is dauntingly large, the search strategy may need adjustment. The search windows for the main health sciences databases include features that facilitate abstract review, such as the ability for the user to save selected abstracts to a collection for future reference.

Once the task of filtering articles for content-relevance is complete, each abstract requires careful review and evaluation. Not all evidence is "good" or useful evidence, nor is all published evidence given equal weight. Well-designed searches will identify studies offering evidence of varying degrees of quality. Several factors then need to be considered when evaluating each publication, including whether the study has been peer-reviewed, where it falls in the hierarchy of evidence, and how it stands up to critical appraisal.

Peer-Reviewed vs Non-Peer-Reviewed Evidence

Peer review is an important part of the scientific method, addressing subjectivity and bias that is inherent to human observation and interpretation. The peer-review process acts as quality control for manuscripts being considered for publication. Through this process, several (typically 2 to 3) individuals with relevant expertise will assess the research methods, interpretation, originality, and significance before publication.

Although peer-review can feel tedious and discouraging to investigators, it is this process that generates credibility in the published evidence and distinguishes "the literature" from opinions found in health magazines, personal blogs, trade journals, and textbooks. Lack of peer review does not, in and of itself, discredit evidence, but non-peer-reviewed evidence should carry significantly less weight than peer-reviewed evidence.

It is intuitive/obvious that a blog post or health magazine column is not peer reviewed. Some sources are less obviously non-peer-reviewed, including textbooks, conference posters and oral abstracts, and so-called preprints (the server medRxiv is a commonly used platform dedicated to preprint articles that have not undergone peer review, but some journals that publish predominantly peer-reviewed content will accept preprints). Again, the lack of peer review does not mean the work is necessarily flawed or without merit, but the lack of peer review necessitates that this evidence be considered distinct from peer-reviewed work.

Hierarchy of Medical Evidence

An important step in using existing medical evidence is evaluating its quality. For example, an investigator interested in studying the use of prothrombin concentrate in the reversal of oral direct anti-Xa inhibitors might be discouraged after a search returns a large volume of evidence on the topic. Hope should not be lost until this evidence is further evaluated. Many topics in the health sciences have much published about them with very few (if any) studies offering a high level and/or quality of evidence.

What is meant by "level of evidence"? Although there is no universally agreed-upon system for comparing all types of evidence, a generally accepted hierarchy is used to rank the primary and secondary medical evidence for clinical application. These rankings are based on the study design used to generate the evidence. The hierarchy is summarized in Table 4-1.

Within this hierarchy, animal studies and translational research are considered the lowest level of evidence, followed by case reports and case series, observational cohort studies, and randomized controlled trials (RCTs). Systematic reviews and meta-analyses are considered the highest level of evidence.

It may be counterintuitive that meta-analyses and systematic reviews are considered a higher level of evidence than RCTs. The former often include RCTs, and so represent an aggregate of multiple individual trials, enhancing the level of evidence provided. Careful review of the studies included in a systematic review or meta-analysis is required, as the secondary evidence will only be as good as the individual primary studies it includes.

Table 4-1. Hierarchy of Medical Evidence

Level	Study Types
1. High	Meta-analyses Systematic reviews
2. Moderate	Randomized controlled trials (RCTs)
3. Low	Observational cohort studies Case-control studies
4. Very low	Case series Case reports
5. Lowest	Animal models Translational research Mechanistic studies