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REVIEW ARTICLE

Evidence-Based Dermatology: A Synopsis

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Abstract. The aim of evidence-based medicine is to support clinical decision making by providing tools for systematically locating, appraising, and applying the best information currently available to improve patient outcomes. This article summarizes the basic steps for practicing evidence-based medicine in the management of cutaneous diseases. Special emphasis is placed on the following 4 major steps in the process: asking a clinical question taking into consideration 4 elements; finding the evidence; critically appraising the evidence; and integrating the new information into clinical expertise and judgment, in order to make the best decision in each clinical setting.

Key words: dermatology, evidence-based medicine, randomized controlled trials, meta-analysis, information management, systematic review.

DERMATOLOGÍA BASADA EN EVIDENCIA: UNA SINOPSIS

Resumen. El objetivo de la medicina basada en la evidencia es entregar herramientas que permiten localizar, evaluar y aplicar la mejor evidencia científica, permitiendo de esta forma apoyar la toma de decisiones clínicas y mejorar el cuidado de nuestros pacientes. Este artículo resume los pasos básicos para la práctica de la medicina basada en evidencia en dermatología, con énfasis en las cuatro etapas fundamentales de este proceso: la formulación de una correcta pregunta clínica, la búsqueda de la información, la evaluación crítica de la información encontrada y la integración de esta información en la experiencia y juicio clínico, con el fin de ayudar a tomar la mejor decisión según cada escenario.

Palabras clave: dermatología, medicina basada en la evidencia, ensayo controlado aleatorizado, metaanálisis, gestión de la información, revisión sistemática.

Background

When routine clinical decision-making is based solely on personal knowledge of pathophysiology and clinical experience, several difficulties and limitations emerge.[1,2]

On the one hand, our understanding of the pathophysiology of skin diseases is evolving constantly as a result of explosive growth in basic research in dermatology. Decisions based on "pathophysiologic reasoning" could therefore change very quickly.[3,4] Likewise, there are many instances in which the biological plausibility of a wide range of interventions used in both dermatology and general medicine has eventually been rejected, or worse, interventions have been shown to be dangerous after clinical trials or meta-analysis of trials.[5-7]

In addition, and without any intention to undervalue personal expertise as an excellent source of knowledge, decision-making that relies on experience alone often amounts to overgeneralization from anecdotal observation, with a tendency to recall scientific evidence in a previously learned form while incorrectly incorporating more significant recent evidence. This is particularly the case when new findings disagree with prior beliefs and experiences.[1-4]

The varying degree of correspondence between conclusions based on a combination of pathophysiologic reasoning and personal clinical experience on the one hand, and the actual clinical effectiveness and safety of many medical interventions on the other, makes it necessary to bring the findings of clinical research fully into the clinical decision-making process. It is also necessary to regularly update one's knowledge of research findings.

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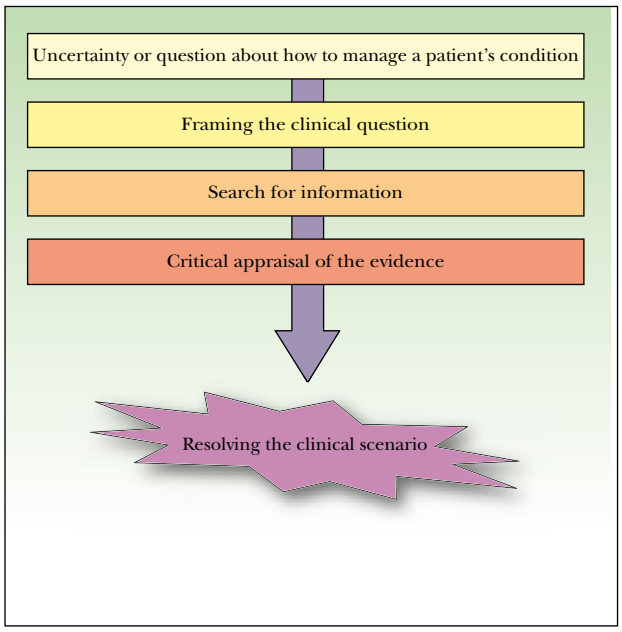

Figure 1. The evidence-based medicine process starts with a patient-driven question about the management of a particular case. Once clinical uncertainty has arisen, the next step is to ask a structured clinical question, followed by a search of the literature and critical analysis of the information found. The process, which ends with resolution of the scenario by applying the evidence and making a decision, is a tool that stands alongside good judgment, clinical expertise, and the values and preferences of the patient.

We experience uncertainty every day when deciding how to reach a diagnosis, evaluate prognosis, and prescribe treatment. In addition, the volume of medical literature is growing exponentially,[8] and there is unfortunately no direct relation between the quantity and quality of published information.[9-11] The dermatology literature, as in other specialties, offers a great deal that is of very uneven quality, a situation that makes it difficult to keep abreast of the best available evidence.

Evidence-based medicine (EBM) proposes a series of heuristics for finding information efficiently, analyzing it critically, and using it appropriately.[4]

What Is EBM?

EBM is defined as "the conscientious, explicit and judicious use of current best evidence" when making clinical decisions about the care of individual patients. Evidence-based dermatology is the application of the principles of EBM to the care of patients with skin diseases.[3,4] The concept that provides the foundation for EBM is the use of current best evidence, derived mainly from clinical trials, in a process that brings that evidence into play alongside clinical expertise and the particular circumstances and preferences of the individual patient.

General Principles of EBM

The practice of EBM unfolds in 4 phases (Figure 1) beginning with a patient-driven question about clinical management and concluding with the application of evidence found in the form of a decision made about that patient.

Framing Answerable Clinical Questions

Awareness of uncertainty and the transformation of doubt into an answerable clinical question is the first step in the practice of EBM.[4]

Questions are generally of 2 types:

1. General questions refer to the features of a disease andcan be answered by consulting such sources as textbooks, class notes, or review articles.
2. Clinical (or action) questions bear a direct relation to decisions concerning a particular patient's condition, whether they involve diagnosis, treatment, or prognosis.

The second type of question cannot usually be answered based on traditional sources of information like textbooks. Other sources, such as studies found in biomedical journals, must be used once they are located with the help of online databases.

Steps in Framing Clinical Questions

1. The first step in formulating a question is to establish which clinical aspect is the object of interest. In other words, one decides whether the issue in a specific situation will be diagnosis, treatment, prevention, or prognosis. Different epidemiologic study designs answer different questions (Figure 2) and their features can be summarized (Figure 3 and Table 1).
2. The second step is to include 4 elements in the phrasing of the question. These elements, which make up the PICO formula, are patient population, intervention, comparator, and outcomes (Figure 2). Table 2 presents a well structured clinical question and a poorly framed one.

Posing a clinical question using this structure is an essential step in the practice of EBM, given that in

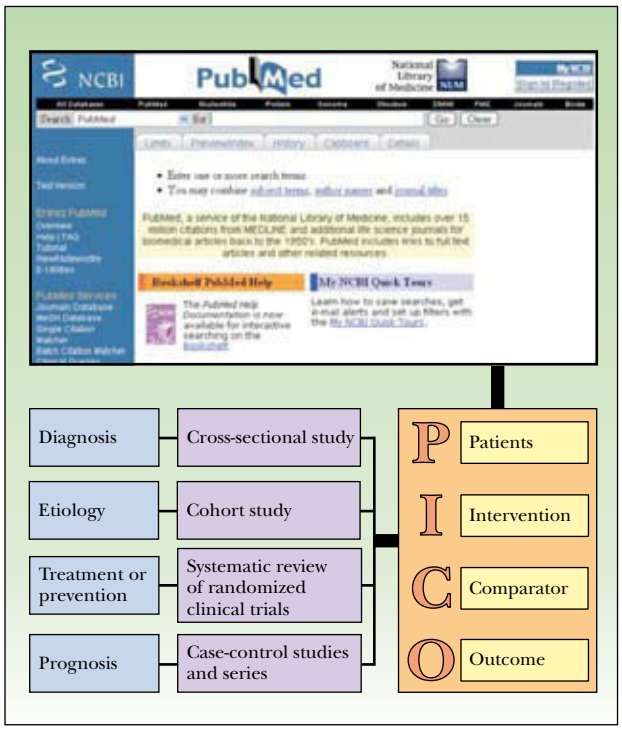

Figure 2. Framing an appropriate clinical question starts with deciding whether it relates to diagnosis, etiology, treatment, or prognosis. This classification narrows the search to a particular type of study. The question will later be divided into 4 parts to help us find the study that answers the question most efficiently. The first 2 or 3 phrases in the question will yield terms to be used in a search engine such as PubMed.

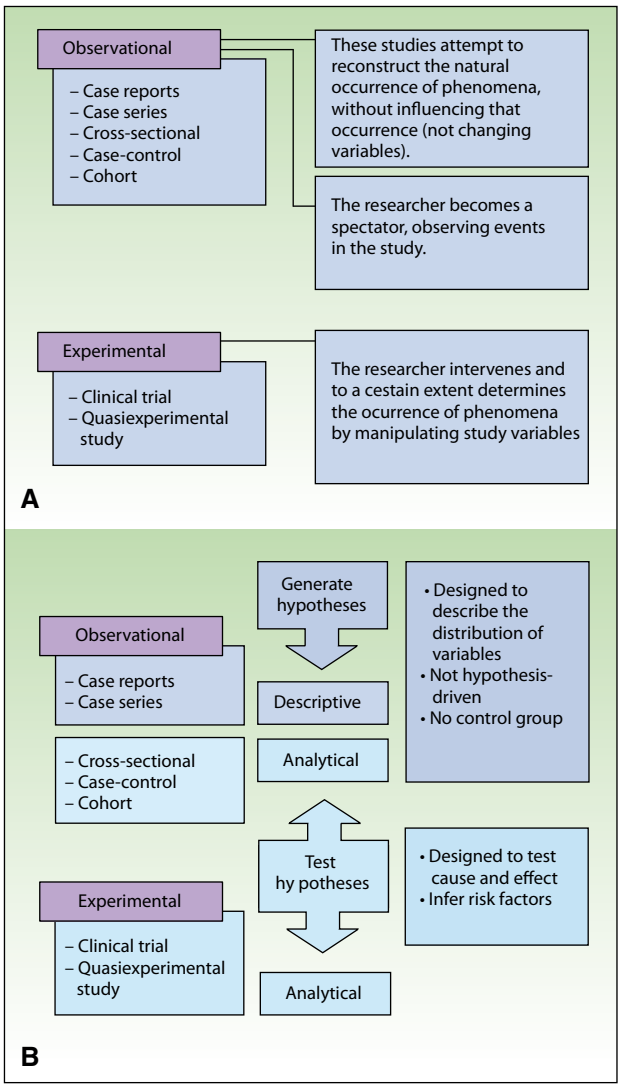

Figure 3. A. Epidemiologic studies may be either experimental or observational. In experimental studies, a group of patients is exposed to an intervention. If assignment to an intervention has not been randomized, the study is termed quasiexperimental. When an experimental design is not viable, observational studies are designed to simulate the experiment that cannot be performed.
B. Observational studies are classified according to whether they include statistical analysis or not. All experimental studies include such analysis.

addition to focusing and clarifying our uncertainty it also usually allows us find relevant articles by taking the first 2 or 3 words of the question and introducing them into database search engines such as those provided through PubMed.[12]

Efficient Searching of the Literature

In recent years we have witnessed revolutionary changes in the manner in which information is generated, disseminated, and used.[13-15] Since the introduction of Internet vehicles for communicating medical information, printed books, journals, and indexes have been replaced by electronic platforms and we now search online for information to support our decisions.

A veritable explosion of information sources have been made available online, but while it is true that access has increased, the search has also become more difficult to the point that the experience is often frustrating and exhausting.[16,17]

Given that all published information is not of equal value, a hierarchy of evidence has been established based on study design and reflecting the relationship between quality and the likelihood of bias. Designs that produce information with a lower risk of bias are ranked first in a ladder of evidence that reflects the hierarchy. In the study of treatment, systematic reviews of clinical trials provide the first level of evidence and are followed by individual clinical trials (Figure 4).

Table 1. Main Features of Epidemiologic Studies

Observational studies without statistical analysis
- Describe a patient or series of patients with a similar diagnosis
- Are useful for generating new hypotheses, but for evaluating the presence of a statistical association, their great limitation is the absence of a control group

Observational studies with statistical analysis

Prevalence or cross-sectional studies
- Investigate exposure and disease in all subjects simultaneously
- Cannot determine the time sequence of events because of the simultaneous study of those events
- Are called studies of the diagnostic cutoff point when the researcher compares a test with a gold standard

Case-control studies
- Follow a group of patients and compare them with a healthy control group
- Evaluate 1 or more disease-related factors, comparing frequency of exposure to disease and other factors between cases and controls
- Measure the odds ratio to quantify the association between risk and disease
- Incidence cannot be calculated in this design

Cohort studies
- Identify individuals in terms of the absence or presence of exposure to a certain factor
- Follow individuals that are disease-free at baseline to observe the frequency of appearance of a studied event over a period of time
- Allow incidence to be calculated

Experimental studies: clinical trials
- Allow the notion of cause to be addressed more directly
- Ideally have the following characteristics:
  1. A design that compares 1 or more experimental groups to 1 or more control groups
  2. Randomization of individuals to the groups

Synthesis of information: systematic reviews
- Are distinguishable from narrative reviews or "updates"
- Are structured and follow a protocol to systematically analyze current evidence related to a specific problem
- Are based on a literature search of a variety of sources, such as databases, manual searching, and direct contact with experts, among others
- Include studies according to assessment of quality
- Provide a more complete, less biased overview of the state of the question on a particular topic
- May summarize with a single effect measure, in an approach known as meta-analysis, providing certain conditions are met

Searching online banks of previously appraised research increases our chances of finding higher-quality evidence quickly. Such resources contain information that has already been subjected to critical analysis in accordance with the principles of EBM, thereby providing high-quality support for decision-making without our having to analyze the validity of study design on our own.

Many of these resources are free and they are usually current. We will now describe in general terms the resources most useful for dermatologists, given their design, simple search interface, and high standards applied to the information they retrieve. Table 3 summarizes web-based portals that give access to these resources.

Collections of Systematic Reviews and Groups That Assess New Health-Care Interventions

The Cochrane Collaboration is an outstanding example of a nonprofit group that produces high-quality systematic reviews of research on treatment, prevention, and rehabilitation in all specialties and makes them available online. The Cochrane Skin Group is among the 50 collaborations currently working on projects.[18,19] This group's website presently lists around 30 published systematic reviews, along with a number of protocols and titles of future reviews. The list continues to grow. The Database of Abstracts of Reviews of Effects (DARE) provides critical appraisals of systematic reviews listed in the main biomedical databases. This group publishes a structured summary, with critical comments, of methodologically valid systematic reviews.

Secondary Publications

Secondary publications are those in which groups of experts review important, well-designed studies. The reports contain a structured summary and critical analysis.

Books Applying the Evidence-Based Approach: BMJ Clinical Evidence, UpToDate *and* Evidence Based Dermatology

BMJ Clinical Evidence, which addresses the treatment of common health problems and is updated every 6 months, has covered around 200 diseases to date. A section on skin disorders contains information on the management of a variety of conditions: acne, tinea pedis, fungal toenail infections, atopic dermatitis, cellulitis, erysipelas, psoriasis, scabies, lice infestation, herpes labialis, skin cancer, wrinkles, vitiligo, warts, and seborrheic dermatitis.[20]

UpToDate covers a wide-ranging list of diseases in all specialties and is being added to on a regular basis. Although the search process and analysis has been less rigorous than that of *BMJ Clinical Evidence*, after February 2006 a system for grading evidence found for each topic was incorporated.

Finally, *Evidence Based Dermatology* includes information on the management of a wide range of skin diseases and

Table 2. Summary of Definitions Used When Posing Answerable Clinical Questions, With an Example of a Well-Formulated Question and a Poor Question

	Patient	*Intervention*	*Comparison*	Outcome
Definitions	Establish the characteristics of the patient about whom the question is asked.	Specify the issue (treatment, prognostic factor, or diagnostic test) to be analyzed.	Specify the comparator (placebo, another treatment, another diagnostic procedure).	State the effect (outcome) we are looking for.
Well-designed clinical question	In a 70-year-old man with nodular basal cell carcinoma on the nasal dorsum…	... is photodynamic therapy with methyl aminolevulinate more effective than...	... surgery...	... in reducing the 5-year recurrence rate?
Poorly-designed clinical question	How should basal cell carcinoma be treated?			

includes guidelines, based on systematic reviews and clinical trials.

Evidence-Based Clinical Practice Guidelines

Evidence-based clinical practice guidelines recommend ways to manage a health-care problem, starting with diagnosis and going on to discuss treatment and prognosis.

Critically Appraised Topics

Critically appraised topics are reports of critical analysis of the literature on a particular clinical scenario.

Metasearch Engines: Tripdatabase and SUMsearch

Metasearch engines are tools that bring together information from several databases. Information might come from collections of critical appraisals or it might be extracted from primary source indexes. Examples of sources are PubMed, the Cochrane Library, DARE, and collections of clinical practice guidelines. These engines therefore retrieve a mix of material that has been previously subject to critical appraisal along with studies that have not yet been evaluated.

Although available appraisals have increased in number considerably, there is still a dearth of such information, particularly in dermatology. Therefore, as the diverse clinical questions we pose about our patients cannot yet be answered in this way, we must often use unfiltered indexes such as those accessed through PubMed. The information in these primary sources has not been subjected to critical appraisal; consequently, the reader must evaluate the quality of a study's design before incorporating its results into the decision-making process. Epidemiologic designs that occupy higher positions in the evidence ladder should be preferred.

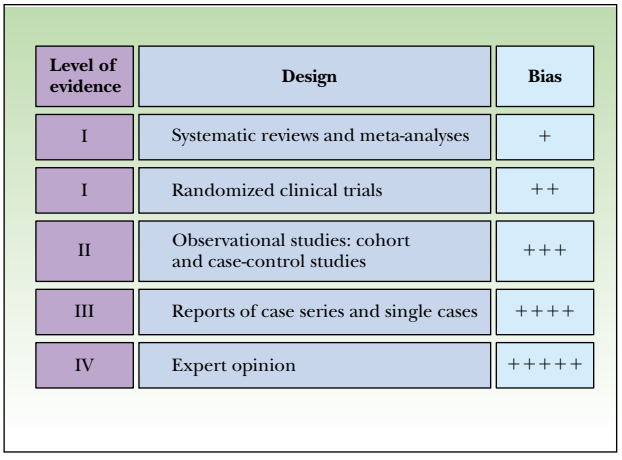

Figure 4. Levels of evidence in the literature on therapy. The highest rung on the ladder of evidence is occupied by systematic reviews. On the lowest rung are reviews based on expert opinion. This hierarchy is based on considering which designs are likely to produce the least bias.

Searching for Primary Sources on PubMed

Unlike collections of critical appraisals of research, primary-source search portals like PubMed retrieve inconceivably large amounts of information from databases. A properly framed question, using the PICO formulation,

Table 3. Summary of Online Resources Described

Sources of previously appraised information	
Collections of systematic reviews, databases, and websites of groups that evaluate health interventions	
– Cochrane Library	http://www.cochrane.org
– Cochrane access via Bireme	http://cochrane.bireme.br
– Cochrane via Cochrane Plus Library	http://www.update-software.com/Clibplus/ClibPlus.asp
– Cochrane Skin Group	http://www.nottingham.ac.uk/~muzd
– CRD database	http://www.york.ac.uk/inst/crd/crddatabases.htm
Secondary information sources	
– *ACP Journal Club*	http://www.acpjc.org
– *Evidence Based Medicine*	http://ebm.bmjjournals.com
– *Bandolier*	http://www.jr2.ox.ac.uk/bandolier
– *EBD section on Archives of Dermatology*	http://www.archderm.com
Books based on the principles of EBM	
– *Evidence Based Dermatology*	http://www.blackwellpublishing.com/medicine/bmj/dermatology
– *BMJ Clinical Evidence*	http://www.clinicalevidence.com
– *UpToDate*	http://www.uptodate.com
Clinical practice guidelines	
– UK National Electronic Library for Health Guidelines Finder	http://rms.nelh.nhs.uk/guidelinesfinder
– US National Guideline Clearing House	http://www.guideline.gov
– Guidelines International Network	http://www.g-i-n.net
– British Association of Dermatology	http://www.bad.org.uk/healthcare/guidelines
– American Academy of Dermatology	http://www.aad.org/professionals/guidelines
Critically appraised topics	
– BestBets	http://www.bestbets.org
– The CAT Bank	http://www.minervation.com
– Dermatoscopio	http://www.dermatoscopio.cl
– EBDerm	http://ebderm.org
– CAT Crawler	http://www.bii.a-star.edu.sg
Metasearch engines	
– Tripdatabase	http://www.tripdatabase.com
– SUMsearch	http://sumsearch.uthscsa.edu
Primary information sources	
– PubMed	http://www.pubmed.com

Abbreviation: EBM, evidence-based medicine.

becomes much more important when using such sources. A variety of tools for helping clinicians find high-quality information more efficiently through PubMed have been developed in recent years.[21]

A very useful way to improve information retrieval is to use medical subject headings (MeSH), which are standardized terms for describing the content of articles in the PubMed-searched databases in a way that shows their relationship to other articles. MeSH are assigned to all articles, so that including them among the search terms will mean that the process is faster and more effective (Figure 5).

Another useful PubMed tool is the clinical queries interface[22,23] (Figure 5). This resource focuses searches in accordance with the type of clinical question, in other words, whether it is about etiology, therapy, diagnosis, or prognosis. Searches may also be made either sensitive or specific, the second strategy being the one that is usually most useful for retrieving the most relevant information as quickly as possible. Searches performed with the clinical

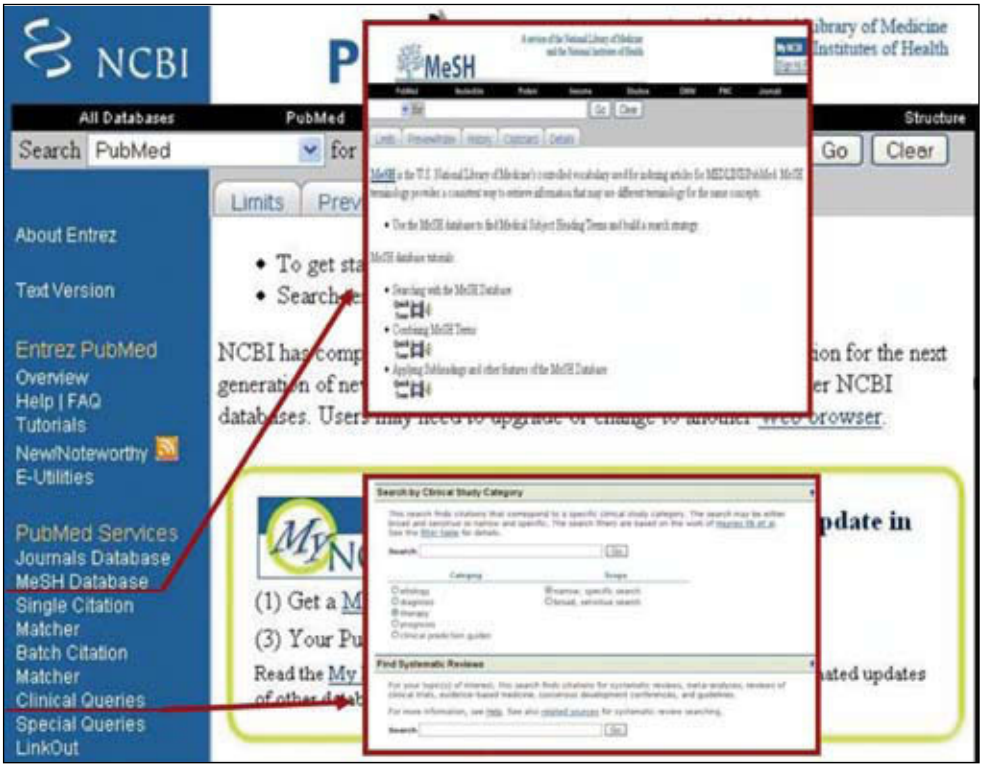

Figure 5. The Medical Subject Headings browser and the Clinical Queries interface are two of the most useful tools available on the PubMed search portal.

queries tool tend to be of greater clinical relevance than those performed using the main PubMed interface.

Analyzing Information Critically

Evaluation of Quality

If the information that answers our question is available in a collection of critical appraisals, the study discussed has been evaluated in a general way already. We will only need to assess the magnitude of clinical effect before incorporating the new information to our decision-making. When primary sources, such as those found directly through PubMed are used, however, their quality must be analyzed critically before we decide to implement the findings. A summary of the most important aspects to assess in studies related to therapy and diagnosis are shown in Table 4.[24-29]

Assessing the Magnitude of Effect

Clinical trials. The results of clinical trials may be presented in a variety of ways, affecting the impression physicians form of the magnitude of effect.[30] Thus, depending on what effect measure is chosen, a treatment might seem to have greater or lesser impact even though the measures express the same effect size.[30]

The Medical Subject Headings browser and the Clinical Queries interface are 2 of the most useful tools available on the PubMed search portal. It is important to emphasize that absolute measures are affected by baseline risk (risk subjects have before treatment in the control or placebo group). Absolute risk can therefore be extrapolated to a specific clinical scenario only insofar as the underlying risk of an individual is similar to that of the subjects in the trial. Measures of relative risk, on the other hand, remain constant across different clinical scenarios, regardless of underlying risk.[30,31]

Studies of diagnostic tests. Correct diagnosis is the first step toward appropriate management of a patient's condition. A medical history and physical examination give rise to suspicion of a particular diagnosis. Such clinical intuition (which we call pretest probability) will be insufficient in some scenarios for either ruling out or confirming a specific diagnosis. Tests must be performed to move the process toward posttest probability, which will allow us to take decisions.

Each test has intrinsic sensitivity and specificity, regardless of the prevalence of the disease in the study population. However, these intrinsic characteristics are not helpful for decision-making in routine practice given that they only provide information about the likelihood of obtaining a positive or negative result in terms of whether

Table 4. Essential Features to Critically Evaluate in Clinical Trials and Studies of Diagnostic Procedures: Design Flaws Are Directly Related to the Likelihood of Bias, Which Will Affect Study Quality and Applicability to Clinical Practice

Essential characteristics of a well-designed clinical trial
1. Detailed descriptions of inclusion and exclusion criteria, interventions, comparisons, patient characteristics at baseline, calculation of sample size and statistical power
2. Random assignment of subjects to groups along with adequate masking of the randomization procedure
3. Single- or multiple-blinding of those involved in the study
4. Full reporting of losses to follow-up in each group and the reasons for such withdrawals
5. Analysis of data on an intention-to-treat basis
Essential characteristics of a well-designed diagnostic study
1. Independent, blind comparison of the studied diagnostic test with a gold standard
2. Inclusion of a range of patients that is sufficient to reflect clinical practice
3. Performance of the gold standard test independently of the studied test
4. Clear description of how the studied diagnostic test was applied. There should be a full account of patient preparation before the test, staff training in procedures (technique, possible side effects) and interpretation of results
Essential characteristics of a well-designed systematic reviewa
1. Addresses a clinical problem that can be expressed as a specific question in which the patients, interventions, comparators, and outcomes have a common underlying biological and pathophysiologic basis
2. Inclusion of original research papers that are appropriate for the clinical question that has been posed. Randomized clinical trials should be included if treatment efficacy is being evaluated, cross-sectional studies if diagnostic tests are the object of interest, and cohort or case-control studies if prognosis is the focus
3. Broad search of the literature on electronic databases, manual search of reference lists, and contact with experts and pharmaceutical companies to locate unpublished studies or those presented only at seminars, conferences or as doctoral theses
4. Ideally, no restriction on language of publication
5. Appraisal of research design quality based on objective criteria. Ideally, there will be 2 independent appraisers.
6. Heterogeneity of results between studies should have been tested before data meta-analysis. If the heterogeneity test is statistically significant, the meta-analysis loses validity

the patient actually has the disease or not. When we order tests, however, we have no knowledge of the true diagnosis.

Positive or negative predictive values do provide an indication of the likelihood that a patient is healthy or not. However, because they are highly dependent on prevalence (or pretest probability), these values also have limited usefulness in clinical practice, since the pretest probability will be different for each patient.

The maximum likelihood ratio test tells us how much more likely it is that a patient is healthy or not based on positive or negative findings of a diagnostic test. Unaffected by prevalence, this value remains constant in different clinical scenarios.

Figures 6 and 7 show how to calculate relevant measures in clinical trials of treatment and diagnostic procedures, respectively.[25,32,33]

Precision of measures. All measures analyzed represent a point estimate of that effect; however, if one repeated a study a hundred times, the results would be similar, but not necessarily the same. A confidence interval (CI) is the range within which the point estimate will lie most of the times a study is repeated.[30]

The 95% CI is the one used most often. It means that if we repeated a study a hundred times, the results would fall within the stated interval about 95 times. When results are given with narrow intervals, precision is greater than when intervals are large. A CI that overlaps a value of 1 in the case of relative measures or 0 in the case of absolute measures may indicate either that an intervention is ineffective or that the sample size was too small to demonstrate an effect.

Summarizing and Storing Results

Critically Appraised Topics

Critically appraised topics are records of answers to clinical questions that have been structured in accordance with the principles of EBM.[34] Such documents have 2 purposes: on the one hand they provide a personal record of answers we have found, and on the other they allow us to share this information with colleagues who might eventually need answers to the same questions. The format used for these records are ideal for presenting and summarizing clinical sessions and to demonstrate the practice of EBM to colleagues who are just getting started.

The basic format is as follows:

1. Title that sums up the content
2. The clinical question
3. The search strategy used
4. The reference to the study used to answer the question
5. Summary of results
6. Comment on the research methods used in the study, the importance of the results, and how they should be applied in clinical practice
7. References to studies cited in writing the comment

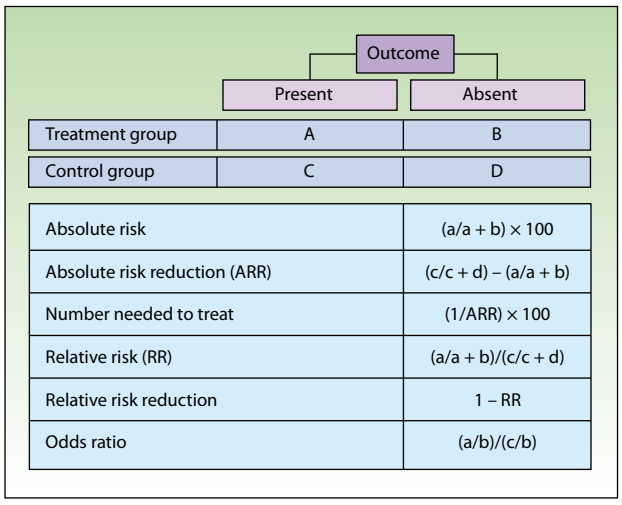

Figure 6. Summary of effect measures used in interventional studies.

Various websites collect reports of critically appraised topics. Among the best-known are *Archives of Dermatology*[35] and the portal Ebderm,[36] which provides a list of topics treated in this way.

Another web-based tool available free online—CatMaker—allows a clinician to quickly and easily compile a list of appraised topics.[37]

Applying Evidence to a Patient's Case

Once evidence has been located and appraised, it remains to incorporate it into clinical decision-making in the scenario that gave rise to the question. This is one of the most difficult parts of the EBM process. In carrying out this step, we will need to assess how similar the patient is to those included in the study that was appraised in order to know if our patient will experience the same benefits and has a similar level of risk of adverse effects. It is important to decide whether or not age, sex, disease stage or type in the study subjects, and the particular interventions studied, among other factors, allow us to generalize the results to a concrete clinical situation.

It is also necessary to judge whether the results of the study have real clinical consequences, in other words whether we can expect a clinically significant change after applying the intervention. Also needed is a consideration of all potential side effects of the intervention.

Finally, the patient's wishes and beliefs must be taken into consideration, along with cost and available resources in the light of the clinician's experience and judgment.

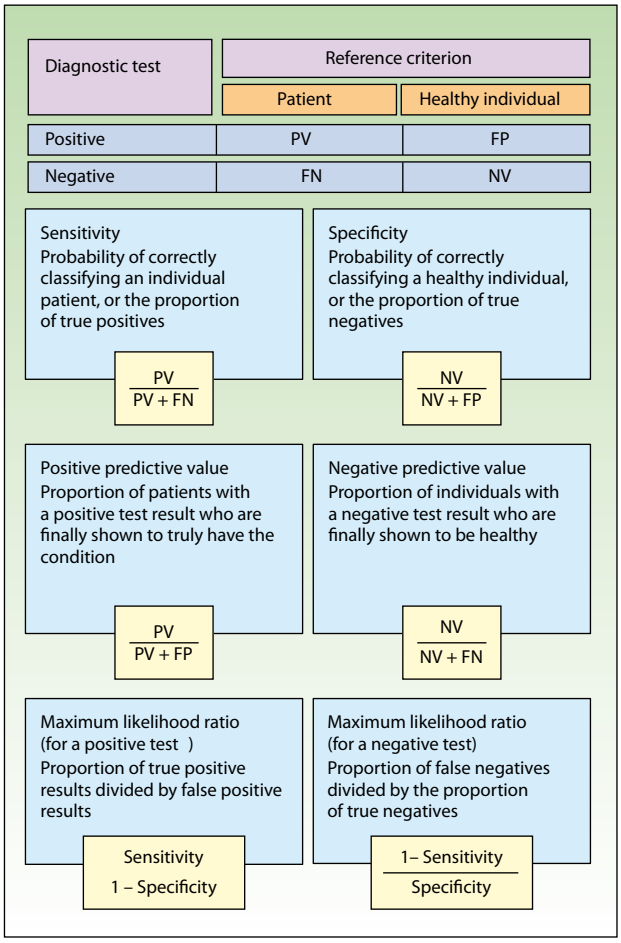

Figure 7. Summary of measures used in studies of the utility of diagnostic tests. PV indicates positive values; FP, false positives; FN, false negatives; NV, negative values.

Limitations of EBM

Although the practice of EBM and instruction in the method is present in many hospitals and universities, this approach has certain limitations that have given rise to strong criticism. Some of the charges that have been directed against EBM are as follows:

1. The available literature often fails to help a clinician make decisions about specific cases, particularly in specialties like dermatology, usually because published information is of poor quality or nonexistent. However, as discussed above, the solution lies in classifying the literature according to levels of evidence, taking into consideration information from the highest quality study available in the first instance, or by bringing our own experience or that of more expert colleagues into the picture.

2. The EBM paradigm places emphasis on randomized clinical trials and systematic reviews, and few of these are available in dermatology, particularly in relation to rare conditions. This does not rule out a place for EBM in our practice, however. On the one hand, this approach gives us the tools we need to select the highest quality information available even if there are no randomized trials or systematic reviews. On the other, given the explosive increase in the numbers of such studies and reviews in recent years, it is only a question of time before they can resolve most of our clinical questions.
3. Lack of resources or consideration of the patient's wishes will often mean that the best-available evidence cannot be applied. Looking again at the definition of EBM, however, this is not a defect of the method per se. Rather, it is a product of the fact that decisions are not based on evidence alone, but require the integration of many factors (evidence, clinical judgment, circumstances) related to an individual's case.

We feel that many of the limitations attributed to EBM are put forth as a result of poor understanding of the approach's definition and practice. It is to be expected that the situation will improve in the coming years and that many more practitioners will come to know and use this valuable tool.

Conflicts of Interest

The authors declare no conflicts of interest.

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