How to apply the evidence-based medicine concept to nuclear medicine diagnostic studies — a review

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Abstract

Evidence-based medicine (EBM) is defined as using the best available evidence for managing patients in daily healthcare practice. Although this approach has been applied successfully in many medical fields, it has not been addressed fully in the radiological discipline in general and nuclear medicine in particular. In this review, the concept of EBM has been introduced briefly and four steps of EBM practice have been explained. Asking answerable questions and finding the best evidence that constitutes the first two parts of EBM practice are explained in brief. The next two steps (appraising the available evidence and applying the best evidence) are explained in more detail. Since the bulk of nuclear medicine studies are of a diagnostic nature and most of the daily practice of a nuclear medicine specialist is involved in diagnosis, we have focused on the diagnostic studies. Systematic reviews are also explained to some extent. Appraisals of other kinds of study, such as interventional or prognosis studies, are not included in this review.

Keywords: evidence based medicine, critical appraisal, nuclear medicine

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Introduction

Evidence based medicine (EBM) is a relatively new approach to provide health care by which the best evidence is found for a definite clinical question and is applied in the most efficient way. Although this kind of practice is becoming the standard in patient care, it can be very time consuming and the users of this approach have to be equipped with efficient ways to succeed [1, 2]. However, application of EBM in radiology and allied disciplines (such as nuclear medicine) has not been addressed fully to date [3–6].

In EBM, standard techniques are used for searching the bulk of literature, and appraising the relevant data (regarding the validity and effect size). This property makes the results of the EBM approach reproducible. Reproducibility is the main difference between traditional and evidence based approaches to medical practice [2, 7–8]. Usually EBM practice is divided to 4 steps [7–8], which are shown in Table 1.

In this review these 4 steps are explained with the main focus on the diagnostic studies which constitute the major part of nuclear medicine practice.

Step 1: asking an answerable question

This step is the cornerstone of EBM practice. Asking an answerable question is defined as taking clinical data and converting them into a format to be used in the next steps mentioned above [9].

To achieve this goal, our clinical question has to be divided into several distinct sections:
1 — the specific group the patient belongs to;
2 — the test we want to apply for the diagnosis of the disease;

Table 1. Four steps of evidence based medicine (EBM) practice

| Step I: Asking an answerable question |
| Step II: Searching for the best evidence |
| Step III: Critical appraisal of the evidence |
| Step IV: Applying the evidence to an individual patient |
Step 2: searching for the best evidence

In the growing world of internet and computer science, finding the best evidence is becoming increasingly difficult and time consuming. This is the main obstacle for finding the best evidence in the published medical literature. For example, Ely et al. reported that family physicians asked an average of 3.2 questions in a single sentence. The major parts of this sentence can be underlined for convenience in future searches. The following example would be helpful in this regard.

Assume that you are a Nuclear Medicine specialist, and the pneumonologist of your hospital wants to know if you can help in the differentiation between active and inactive tuberculosis in an adult patient with a history of treated pulmonary tuberculosis (6 months ago), since the results of the sputum culture take several weeks to be ready. The pneumonologist has heard about the application of 99mTc-sestamibi in this clinical situation in a scientific meeting and wants to know if 99mTc-sestamibi can help in this regard, or not. The answerable question for this scenario is shown in Table 2.

As mentioned above, without formulating a PICO question in every distinct clinical scenario, the other steps of EBM practice cannot be completed. It is recommended that adequate time be spent practicing this step [9].

Medical literature resources

Available medical resources for using in EBM practice are evolving very rapidly and not all resources are high in quality. It is recommended that the medical resources be categorized in a hierarchical manner [12]. Original studies are at the bottom of this hierarchy, synthetic literature (systematic reviews) are the next level, the synopses of studies and syntheses are the next, and finally evidence-based information systems (the most comprehensive resource) would be at the top of the hierarchy. This hierarchy is usually called the "4S" which stands for (from bottom to top): "studies", "summaries", "synopses", and "systems". When seeking the best available evidence, the highest-level resource available for the problem should be searched first [9, 12].

The evidence based "systems" include all relevant evidence regarding a clinical problem and are updated on a regular basis to provide the most up to date available evidence. These systems are usually under strict review process. Two of these "systems" are UpToDate (http://www.uptodate.com) and Clinical Evidence (http://www.clinicaleducation.com). They are not freely available online; however, those physicians who have University Athens system subscription can have access to them.

"Synopses" are the next level of medical resources. As the name implies, these are synopses of original studies and systematic reviews. Usually these "synopses" provide structured abstracts of studies that meet the preset criteria, in addition to an accompanying commentary by an expert on the study results. They are usually peer reviewed extensively as well. The "synopses" can be considered as a shortcut to find an answer to a clinical question. Two examples of this level of resources are Evidence Based Nursing and ACP Journal Club. They are not freely available on the net either.

Synthetic literature constitutes the next "S" which is "syntheses". Databases for systematic reviews are in this level. It should be noted that review articles, although very useful, are the opinions of individuals on a topic and can be very misleading since there is no standard method for preparing them. By way of contrast, systematic reviews and meta-analyses are objective reviews, which are more reliable than the review articles. The main characteristics of narrative review articles, systematic reviews, and meta-analyses are depicted in Table 3. The most comprehensive data-

### Table 2. Answerable question for a clinical scenario

<table>
<thead>
<tr>
<th>Patient or problem</th>
<th>Adult patient with a history of treated pulmonary tuberculosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>99mTc-sestamibi scintigraphy</td>
</tr>
<tr>
<td>Comparison</td>
<td>Sputum culture</td>
</tr>
<tr>
<td>Outcome</td>
<td>Differentiation of active from inactive pulmonary tuberculosis</td>
</tr>
<tr>
<td>Question</td>
<td>In an adult patient with a history of treated pulmonary tuberculosis, how sensitive is 99mTc-sestamibi scintigraphy for differentiation of active from inactive pulmonary tuberculosis?</td>
</tr>
</tbody>
</table>

### Table 3. Characteristics of narrative review articles, systematic reviews, and meta-analyses

<table>
<thead>
<tr>
<th>Narrative review articles</th>
<th>Systematic reviews</th>
<th>Meta-analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods to collect and interpret data are subjective</td>
<td>Methods to collect and interpret data are objective</td>
<td>Quantitative. Otherwise the same as systematic review</td>
</tr>
<tr>
<td>Not appraisable</td>
<td>Appraisable</td>
<td></td>
</tr>
<tr>
<td>Replication impossible</td>
<td>Easily replicable</td>
<td></td>
</tr>
</tbody>
</table>
base for systematic reviews is the Cochrane Library (http://www.cochrane.org). This database has a collection of systematic reviews prepared according to its own standards and it provides a list of other systematic reviews in the medical literature. It is not free but it can be accessed through an Athens system subscription.

Individual “studies” are in the bottom of the medical resources hierarchy. Searching for the best evidence in this level is time-consuming and found articles need to be critically appraised. Many databases are available for medical literature. Two of the most commonly used databases are SCOPUS (http://www.scopus.com) and Medline’s Pubmed (http://www.ncbi.nlm.nih.gov/pubmed).

Although there are many medical resources which provide the best available evidence, currently only a few of them address the issues of radiology and nuclear medicine. For the questions regarding interventions and treatment, usually the Cochrane Library should be searched for any systematic review or RCT. If this search does not yield any useful article, Pubmed (or other resources) is recommended. However, when the clinical question is of a diagnostic nature (as is the case for the majority parts of Nuclear Medicine practice), Pubmed is recommended, especially the Clinical Queries option within it [13–14].

A detailed explanation of searching medical databases such as Pubmed is beyond the scope of this review and can be found elsewhere in the literature [9, 14].

**Full-text articles: how to get them**

Many Nuclear Medicine journals are freely available online. The Iranian Journal of Nuclear Medicine, the Hellenic Journal of Nuclear Medicine, Nuclear Medicine Review, Nuklearmedizin, the Quarterly Journal of Nuclear Medicine and Molecular Imaging, the Annals of Nuclear Medicine (not the recent issues), the Journal of Nuclear Medicine (not the recent issues), and the Journal of Nuclear Medicine Technology (not the recent issues) are among such freely accessible journals. For those physicians who have a university Athens system subscription, most of the other journals are also freely available. This is also true for the Cochrane Library and its systematic reviews.

**Step 3: critical appraisal**

Not all published articles are of high quality regarding the level of evidence. Critical appraisal is the process of evaluating individual studies to determine the level of evidence, which is an easy and efficient way to do this task.

**Levels of evidence**

The Oxford Centre for Evidence Based Medicine provides a free online table of levels of evidence (Table 4) [15]. With the guide of these tables, we can assign a level of evidence to each article in order to select the highest quality studies. By this strategy, there would be no need to read all articles regarding a clinical question. Many poor quality articles can be omitted in this step.

For each study, several questions have to be answered in order to assign a level of evidence. Several free appraisal sheets are available online for this purpose [16, 17]. These sheets contain two main parts:

1 — questions regarding the validity which can be found in the materials and methods section.

2 — the effect size or strength of the study, which is presented in the results section. The first section is the main part to be used for assigning the level of evidence [18].

**Question 1: What was the spectrum of patients who underwent the test in question?**

Whole spectrum of target disease should be covered in the study considering the severity and temporality (mild and severe disease, acute and chronic disease). Randomization would ensure avoiding selection bias. The characteristics of the patients (such as gender, age, ethnicity, etc) should be considered to assure that all of whom have undergone both the diagnostic test and the reference standard; or a clinical decision rule not validated.

**Table 4. Oxford centre for evidence-based medicine levels of evidence for diagnosis studies (reproduced with permission)**

<table>
<thead>
<tr>
<th>Level</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>SR (with homogeneity*) of Level 1 diagnostic studies; CDR† with 1b studies from different clinical centres</td>
</tr>
<tr>
<td>1b</td>
<td>Validating** cohort study with good†† reference standards; or CDR† tested within one clinical centre; Independent blind comparison of an appropriate spectrum of consecutive patients, all of whom have undergone both the diagnostic test and the reference standard</td>
</tr>
<tr>
<td>1c</td>
<td>Absolute SpPins and SnNouts†††</td>
</tr>
<tr>
<td>2a</td>
<td>SR (with homogeneity*) of level &gt; 2 diagnostic studies</td>
</tr>
<tr>
<td>2b</td>
<td>Exploratory** cohort study with good†† reference standards; CDR† after derivation, or validated only on split-sample§ or databases; Independent blind comparison but either in non-consecutive patients or confined to a narrow spectrum of study patients (or both), all of whom have undergone both the diagnostic test and the reference standard; or a clinical decision rule not validated</td>
</tr>
<tr>
<td>3a</td>
<td>SR (with homogeneity*) of 3b and better studies</td>
</tr>
<tr>
<td>3b</td>
<td>Non-consecutive study; or without consistently applied reference standards</td>
</tr>
<tr>
<td>4</td>
<td>Case-control study, poor or non-independent reference standard</td>
</tr>
<tr>
<td>5</td>
<td>Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”</td>
</tr>
</tbody>
</table>

By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a † at the end of their designated level. **Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using regression analysis) to find which factors are “significant”. § Clinical decision rule. (These are algorithms or scoring systems which lead to a prognostic estimation or a diagnostic category). †† Good reference standards are independent of the test, and are applied blindly or objectively, applied to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the test is included in the reference, or where the “testing” affects the reference) implies a level 4 study. ††† An “Absolute SpPin” is a diagnostic finding, the Specificity of which is so high that a Positive result rules-in the diagnosis, an “Absolute SnNout” is a diagnostic finding, the Sensitivity of which is so high that a Negative result rules-out the diagnosis; Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into “derivation” and “validation” samples.
the study is applicable to the patients on whom the test is going to be used [16, 19]. The eligibility criteria should also be defined meticulously [19].

A narrow spectrum of recruited patients would place a study in level 2 of evidence. For example, in a study by Ahmadhosseini et al., the application of 99mTc-MIBI in pulmonary tuberculosis diagnosis was evaluated [20]. A rapid review of the abstract of this article shows that a narrow spectrum of patients entered the study (only patients with active or inactive treated tuberculosis). A good spectrum of patients in this study would be all patients with respiratory symptoms that are indicative of tuberculosis.

Question 2: Was the reference standard the best available test?

The reference standard is the test used in a study to establish the diagnosis of the studied disease. Special care is needed to select the best available test for this purpose. Sputum culture for pulmonary tuberculosis and pulmonary angiography for pulmonary embolism are two examples in this regard. Sometimes, follow up instead of reference standard is used to find out if the patient has the disease or not. In this case, the period of follow up should be long enough considering the nature of the disease [16, 19]. In some clinical scenarios, there is no single best reference standard, and a combination of clinical findings and paraclinical tests should be used. For example, this strategy should be used for the diagnosis of recurrent lymphoma lesions [21]. A poor reference standard would place a study in level 4 of evidence.

For example, in a study by Fallahi et al. the value of 99mTc-MIBI for diagnosis of multiple myeloma lesions was evaluated. The reference standard in this study was a combination of clinical and paraclinical tests, which seems to be the best available reference standard [22].

An example of poor reference standard would be the detection rate of sentinel lymph node by lymphoscintigraphy instead of using axillary lymph node dissection (ALND) [23].

Question 3: Were the reference standard and the index test applied to all patients in the study regardless of the index test results?

The reference standard test should be used for all patients (regardless of index test results). The most common flaw in the diagnosis studies is failure to meet this criteria [18]. This would place a study in the level 3 of the evidence.

For example, in a study by Kostakoglu et al. [24] on 67Ga diagnostic efficacy for diagnosis of active lymphoma in the residual masses after treatment of lymphoma, the authors obtained a sensitivity of 96% and a specificity of 80%. However, the gold standard of the study (biopsy) was not performed for all patients. Apparently, the positive result of 67Ga was the main decision-maker for the application of biopsy in this study.

The period between reference standard and index test has to be considered since it should be short enough to assure that the target disease did not change between the reference standard and the index test [17]. For example, the time between a pulmonary embolism event and pulmonary angiography should not be too long, since the thrombolysis process can interfere in the diagnosis of pulmonary embolism.

Question 4: Was the comparison between the index test and reference standard blind and independent?

The interpreters of the index and reference standard tests should be blind to the results of each test in order to avoid expectation bias [19], which can place a study in level 4 of evidence.

Question 5: Were the index test and reference standard explained fully in the article?

Reliable duplication of the results of each study depends on this question. For example, the type of collimator, the type of gamma camera, etc. should be mentioned in the study.

The above-mentioned questions are very important to assign a level of evidence to each article. Many articles (with low validity) can be omitted at this point and not reviewed further. The remaining questions evaluate the results of the study.

Question 6: What were the results of the study?

For diagnostic tests, sensitivity, specificity, and positive and negative predictive values (PPV and NPV) should be considered and can usually be found in the results section of studies. Figure 1 shows a 2 × 2 chart for a dichotomous test. The definitions can be found in Table 5.

When the results of a test are of multilevel or continuous nature (such as gated SPECT indices), the cut-off value of the index test is the main determinant of the sensitivity and specificity. In these situations, there is a negative correlation between sensitivity and specificity. This is the basis of receiver operating characteristic (ROC) analysis. The ROC curve shows the sensitivity and specificity for different cut-off points of the test results. It is very important to con-

Reference standard

<table>
<thead>
<tr>
<th>Index test positive</th>
<th>Reference standard positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positive (a)</td>
<td>False positive (b)</td>
</tr>
<tr>
<td>Index test negative</td>
<td>False negative (c)</td>
</tr>
</tbody>
</table>

Figure 1. 2 × 2 chart for a test with dichotomous results.

Table 5. Definitions of the characteristics of the test shown in Figure 1

<table>
<thead>
<tr>
<th>Characteristic of the test</th>
<th>Definition</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>How good is this test at detecting people with the disease?</td>
<td>a/(a + c)</td>
</tr>
<tr>
<td>Specificity</td>
<td>How good is this test at correctly excluding people without the disease?</td>
<td>d/(b + d)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>What is the probability that a person with a positive test has the disease?</td>
<td>a/(a + b)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>What is the probability that a person with a negative test does not have the disease?</td>
<td>d/(c + d)</td>
</tr>
<tr>
<td>Accuracy</td>
<td>What proportion of all tests yielded the correct result?</td>
<td>(a + d)/(a + b + c + d)</td>
</tr>
</tbody>
</table>
sider the area under the curve in ROC analysis. If this area equals 0.5, the test is of no use. When this area approaches unity, the performance of the test increases (Figure 2).

Sensitivity and specificity are inherent properties of a test and are constant no matter what the prevalence of the disease in the tested population. In contrast, predictive values [both negative (NPV) and positive (PPV)] are dependent on the prevalence of the disease in the population. This is the cornerstone of the Bayes’ Theorem, which is discussed further at the end of this article [5–6, 25].

Question 7: Were the confidence intervals mentioned for the test results?

In addition to p-values, sensitivity, and specificity, other important values should be mentioned for sufficient interpretation. The P-value is only a probability that an outcome has occurred by chance. It is definitely not a substitute for effect size. To appreciate the effect size of a study, the confidence intervals are very useful. A wide confidence interval range indicates a small sample size [26]. For example, the sensitivity of a test can be 80% in two different studies; however, the confidence intervals for this sensitivity can be 70–90% and 40–97%, respectively. The first study provides better evidence in this regard. Online calculators are freely available for confidence interval calculation [27].

A full explanation of this issue is beyond the scope of this article, but an excellent book written by Cohen addresses this issue in detail [28].

Step 4: applying the evidence to a particular patient

As mentioned before, the predictive values of a test are dependent on the prevalence of a disease in a society. This prevalence is usually called pre-test probability. The post-test probability is the refined probability of a disease when both pre-test probability and test results are considered together. For this purpose, likelihood ratios (LRs) are used, which are defined in Table 6. For a given pre-test probability (prevalence), pre-test odds can also be calculated.

\[
\text{PRE-TEST ODDS} = \frac{\text{PRE-TEST PROBABILITY}}{1 - \text{PRE-TEST PROBABILITY}}
\]

These ratios (odds and likelihood ratios) can be combined together by multiplication [18]. No matter how many test are used to refine a probability, this method can be applied as follows:

\[
\text{POST-TEST ODDS} = \frac{\text{PRE-TEST ODDS} \times \text{LR of test } 1 \times \text{LR of test } 2 \times \text{LR of test } 3 \ldots}{1}
\]

Finally, the post-test probability of the disease can be calculated from the calculated odds:

\[
\text{POST-TEST PROBABILITY} = \frac{\text{POST-TEST ODDS}}{1 + \text{POST-TEST ODDS}}
\]

The concept of pre and post-test probability is shown in Figure 2 in another way.

Usually a threshold is set for the probability of each disease for treatment, above which treatment is justified. For example, this threshold for malignant bone tumours is very high (the diagnosis of malignant bone tumours should be almost definite (near 100%) to justify treatment). This is also the case for pulmonary embolism: the probability of the presence of pulmonary embolism should be more than 80% (high probability) to begin treatment.

The main application of a para-clinical test is refining the pre-test probability for a particular patient. If the post-test probability becomes higher than the treatment threshold, the treatment of the disease is justified and vice versa (Figure 3).

Other important issues to be addressed

For implementing the best found evidence in everyday practice, cultural and religious issues should be considered. Some tests and procedures may not be culturally acceptable (no matter how good the performance is), and before requesting a test this important fact should be born in mind.
Economical issues are another important aspect to be considered. With limited budget for health care, many expensive procedures and tests should not be ordered. This is beyond the scope of this review, but you can find a more detailed explanation elsewhere in the literature [29].

References