

# Evidence-based medicine in pediatric rheumatology

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## ABSTRACT

*Evidence-based medicine (EBM) has increasingly gained importance over the past two decades. This review defines and discusses EBM in the light of specific issues relating to pediatrics and pediatric rheumatology. The efforts of pediatric rheumatologists to practice and promote EBM are summarized.*

## What is evidence-based medicine?

The philosophical roots of evidence-based medicine (EBM) date back to the mid-19th century in Paris, when Louis, Bichat and Magendie demanded that medical decisions be based on external evidence. Although not new, EBM was effectively promoted by Gordon Guyatt, David Sackett and other physicians at McMaster University (Hamilton, Canada) who revived the idea of EBM. Since then EBM has substantially influenced medical decisions during the last two decades.

EBM can be defined as the conscious, explicit and judicious use of the current best evidence in making decisions about the care of individual patients. The practice of EBM means integrating individual clinical expertise with the best available external evidence. Clinical expertise is the proficiency gained through clinical experience and practice. The best available evidence, which is the clinically most relevant research, may come from the basic sciences in medicine, but mostly it is the result of clinical research involving powerful diagnostic tests, exact prognostic markers, and the safety and efficacy of therapeutic interventions (1).

Sometimes EBM is accused of leading to 'cook book' medicine or of being a vehicle of governmental agencies and health care providers aimed at decreasing health care expenses. Both accusations are wrong. Rather, EBM will avoid the use of inherited practice schemes. It requires an on-going re-consideration of

the clinical decisions made. The aim of EBM is to identify the best treatment strategy in order to guarantee high quality of care. EBM integrates external knowledge, but will never replace clinical expertise and the patient's personal choice. This may or may not raise the costs of the health care system. EBM can help to justify health care expenses, because it provides proof that the therapies rendered are based on the best current evidence and therefore are expected to have the highest yield for the patient (2).

## Why should evidence-based medicine be practiced?

EBM can be practiced by anyone and in any field of medicine. It should be practiced by everybody, because health care professionals can be expected to have access to the best and most up-to-date evidence when recommending an intervention for any given patient predicament (3).

Several debatable assumptions guide traditional medical practice. We start our careers thinking that our knowledge gained in medical school and residency is durable. In the 21st century, with its abundance of information, this assumption is no longer valid: consulting colleagues, reading journals, attending educational meetings and relying on the information provided in textbooks does not suffice to keep us current with all relevant knowledge gained in the field. EBM is patient-centered and thus helps physicians keep their knowledge of the best available care for their patient up-to-date.

Parents and patients are increasingly educated consumers with ready access to both appropriate and inappropriate medical information through the media and Internet. Assessing the literature to support or refute their belief will strengthen the credibility of medical decisions and improve patient compliance with treatment regimens and with follow-up (1).

### How is EBM practiced?

Briefly, a clinical problem is identified. Information relevant to the clinical problem is then selected by a systematic literature search. Once the relevant information has been extracted, its quality has to be assessed by the physician in order to identify the best available evidence. Based on the 'best evidence' from the literature, the patient's preference and the clinical expertise of the EBM practicing physician determines the best treatment strategy for the patient.

A current handbook outlines and discusses the approach to EBM (2). In addition, brief guides to EBM in pediatrics have recently been published (4, 5). The website of the Centre for Evidence-based Medicine in Oxford (UK) (<http://www.cebm.jr2.ox.ac.uk>) also offers information on how to practice EBM. There are several pediatric EBM-websites, such as the website of the Center for Evidence-based Child Health (<http://www.ich.bpmf.ac.uk/ebm/ebm.htm>) and that of Pediatric Evidence-based Medicine (<http://depts.washington.edu/pedebm>).

### Sources for the evidence

The medical databases MEDLINE or EMBASE are available on CD-ROM or via the Internet. EMBASE contains many European publications frequently missed by MEDLINE searches. Among others, the National Institute of Health (USA) offers the PubMed database via the Internet (<http://www.ncbi.nlm.nih.gov/PubMed>) without charge.

Meta-analysis data on randomized clinical trials (RCTs) is summarized in the database of the Cochrane Collaboration (<http://hiru.mcmaster.ca/cochrane/default.htm>). The Cochrane Library also offers access to databases of other relevant secondary reviewers of the international literature. In 1997 a 'Child Health Field' was organized within the Cochrane Collaboration to help promote EBM in pediatrics.

Multiple peer-reviewed pediatric and rheumatology journals are published online and thus make the availability of the most recent medical literature easy. There are many other sources of information and websites that provide fast access to medical knowledge.

To be both comprehensive and exhaus-

tive in a literature search, the databases MEDLINE, EMBASE and that of the Cochrane Clinical Trial Registry should be used as sources of information (5). Optimal search strategies to identify studies pertaining to treatment, diagnosis, and prognosis have been developed (6). Large amounts of information that may be useful for answering the clinical problem are often identified.

### Searching for the best evidence

The more difficult and critical task of an EBM practicing physician is to critically appraise the suitable literature, which will then provide the 'best evidence'. The most useful and up-to-date series of guides to the reader of clinical reports has appeared in the *Journal of the American Medical Association (JAMA)* during the last several years (7). This series of *Users' Guides to the Medical Literature* (8-33) offers succinct guidelines to assess the evidence provided by different types of publications. Practical everyday examples are used to illustrate how to evaluate the results of a study and weigh the quality of the evidence provided.

Although the *Users' Guides to the Medical Literature* also include articles to judge the results of clinical trials, more detailed guides are available. Chalmers *et al.* (34) offer a complete guide to the assessment of clinical trials that has been in use for many years, and is probably one of the most comprehensive reviews on this topic (7). In the 1980's the *New England Journal of Medicine* recommended that contributing authors follow the suggestions of derSimonian *et al.* (35) when preparing reports of clinical trials.

In 1985 a group of medical journal editors, clinical epidemiologists and statisticians developed a consensus statement about how randomized controlled trials should be reported - the Consolidated Standards of Reporting Trials, or CONSORT statement (36). This statement contains 21 items that deal mainly with issues concerning reporting methods, results and the discussion of the findings. It identifies a graphic display of allocation and status of patients throughout the trial. Thus it provides an excellent template on which to formulate or judge the report of a clinical trial.

Because not every epidemiological study deals with patients, judging the quality of an epidemiological investigation requires an approach similar to, but separate from, judging clinical investigations. The suggestions offered by Walker (37) provide a compact guide to reporting the results of an epidemiological study and can be used for judging a report.

### Continuously applying the best evidence in clinical practice

Once the best evidence is identified, clinical judgement and the patient's preferences will interact and lead to a clinical decision reflecting the current knowledge from the literature. EBM requires the commitment to continuous self-directed learning and is likely to be accompanied by a change in the traditionally used sources of information. Because EBM is aimed towards improved patient care and outcome, its decisions have to be continuously monitored for their validity in the individual case. Thus it is necessary to be vigilant and to reassess clinical decisions, even if they were initially based on the best available evidence. This is because the evidence may change or because the necessary evidence, applicable to your patient, was initially not available. For instance, the evidence in the literature may not have been obtained from children or might have been based on short-term follow-up data. Thus the results in a pediatric patient with long-term follow-up may be different from that observed in the adult population or when using information obtained from short-term studies.

### Evidence-based medicine in pediatrics and its caveats

#### *Randomized clinical trials*

It is generally accepted that there is a hierarchy of evidence with physician opinion at the bottom and RCTs at the top and other form of evidence, such as observational studies, in between. Traditionally data from RCTs are thought to provide the highest quality of evidence, because a true medical experiment is performed which attempts to control for external influences in order to answer the proposed study question. EBM in adults relies heavily on the results of RCTs. In adults, 82% of clinical

decisions can be supported by RCTs or convincing non-experimental evidence, but only 50% of pediatric practice is similarly supported. Preventive therapies, such as immunizations, and medication prescribing, have the best supporting evidence and anticipatory guidance the weakest (38). Neonatology is probably the pediatric subspecialty that practices EBM the best in that 92% of all clinical decisions made are adequately supported by evidence from the literature (39).

As outlined above, the practice of EBM in pediatrics should be of the utmost priority. And yet, RCTs providing the necessary evidence are not always available. The reasons for this phenomenon are numerous. The special vulnerability of children has to be considered. There are substantial developmental and biologic changes in childhood and therefore study results valid for one age group may be irrelevant for another age group. Accordingly, either very large studies or multiple smaller studies have to be conducted to accommodate the increased variability among pediatric patients. Small sample sizes are a particular problem for rare childhood diseases, such as those seen in pediatric rheumatology clinics. At times parents are required to act as proxies for their children. The use of parents instead of patients as the reporters of symptoms creates an additional potential source for errors in the results, which must be taken into account when planning pediatric studies.

Many of these issues are irrelevant when diseases in adult patients are investigated. Therefore, the methodological approach in adult studies is quite different from that necessary in pediatrics. Given the special features of pediatric medicine, RCTs are difficult to perform or in some instances even impossible or unethical. RCTs are also quite costly and therefore not always performed for financial reasons. The great majority of studies are supported by drug companies and therefore are mainly geared towards testing the safety and efficacy of newly developed medications (3). Given the vested interest of the pharmaceutical industry, RCTs will be supported more often for drug trials rather than for trials aimed at studying other clinically impor-

tant issues such as physical therapy and psychosocial interventions.

Even when evidence is available in the form of RCTs, it should not be forgotten that RCTs may have their pitfalls and will not automatically provide high-quality evidence (40).

#### *Observational studies*

Studies in which the investigator does not proscribe any experimental maneuver on the study subjects are referred to as observational studies. They include cohort studies, case control studies or case series. Observational studies are not *a priori* inferior to RCTs in providing evidence (3, 41, 42). They are important because they convey 'real world' information about patient management. The everyday clinical management of patients is obviously different than that of patients recruited for RCTs (41). Obtaining 'real world' information is not easy in pediatric rheumatology, where diseases are chronic and therapeutic success is multi-factorial. While RCTs are generally conducted over time periods that rarely exceed one year, with intense monitoring and carefully selected patients, observational studies typically follow larger groups of patients in a "real world" setting, over a long period of time.

Health care costs are rising and, not surprisingly, policy makers demand that the submission of new drug applications to regulatory agencies be accompanied by evaluations of their economic benefits (41). Data from observational studies are required to make economical judgements about the use of drugs and other treatment modalities (41). Economic benefit analyses require long-term follow-up data, which are generally not available from RCTs. Although we need observational studies to guide our decisions, the comparison of results from these studies is often difficult or impossible. They use different definitions for establishing the diagnosis, for the different types of interventions, or differ in the ways that they measure outcome.

#### *Primary evidence may be biased*

When appraising the evidence we must remember that the primary evidence in the literature could be biased. This may

simply occur because studies with positive results are preferentially published over those demonstrating a negative result (publication bias). For instance, if a medication was found to be ineffective for a particular disease on several occasions, these results may remain unpublished, particularly if the agent being tested is new and not a standard therapy. If the same medication is found to be somewhat effective in a few other studies - and these positive studies are then published - the false impression may arise that the medication under investigation is beneficial, although in reality it is not. A good example of this phenomenon is the use of D-penicillamine, which was felt to be effective for the treatment of chronic arthritis until it was demonstrated that this medication was not superior to placebo (43,44).

#### *The self-evidence paradoxon*

A peculiarity that is often encountered in pediatric rheumatology is the so-called 'self-evidence paradoxon' (45). The evidence published on the efficacy of very powerful treatments is sometimes sparse. For instance, physiotherapy is one of the mainstays of treatment in pediatric rheumatology. Yet the published evidence on the effectiveness of physiotherapy is scant. Thus sometimes we have to accept that, while the formal quality of evidence is low, the likelihood of an intervention to be beneficial is high. Therefore when practicing EBM, one cannot simply conclude that the lack of evidence is equal to the ineffectiveness of a treatment intervention.

#### *Summarized evidence: Systematic reviews, metaanalyses, decision analyses and guidelines*

EBM promotes the condensation of evidence in systematic reviews, meta-analyses and practice guidelines. Summarizing the best evidence begins with rigorous systematic attempts to locate and assess all relevant studies on a given topic. If this does not occur or the included primary evidence is biased, then systematic reviews or metaanalyses may actually exaggerate the already existing bias in the literature.

Metaanalyses condense previously obtained evidence, taking into considera-

tion differences in clinical settings and the quality of the provided information. This summarized evidence can then conveniently be used for clinical decisions. One example is the metaanalysis on the comparative efficacy and safety of advanced drug therapy in children with JRA [now: juvenile idiopathic arthritis (JIA)] (46). The methodological shortcomings of metaanalyses are frequently due to the incomplete consideration of all the available studies. Difficulties also result from the comparison of studies whose patient populations have different characteristics or when there is variation in the outcome measures used (42). In addition, the rules used to assess the quality of the studies included are a potential source of bias in metaanalyses. It has been shown that differences in these inclusion rules for studies can result in different final conclusions drawn from metaanalyses (47).

Decision analysis is another tool frequently used to summarize and combine evidence. The aim of decision analyses is to identify the best treatment strategy for a clinical problem, considering the benefits and risk associated with it. Using Bayesian algebra, information derived from the literature is combined and restructured in order to create a model of the clinical problem encountered in daily practice. For example, the use of a fixed combination of misoprostol and diclofenac or diclofenac alone in adult arthritis was recently evaluated for its cost effectiveness using decision analyses (48, 49). Another example is the use of decision analysis to evaluate the need for anticoagulation in antiphospholipid positive patients, considering the possible risks of recurrent thromboses and anticoagulation complications (50).

Clinical guidelines are EBM tools that facilitate decision making with regard to problems commonly encountered in clinical practice. One example of clinical guidelines already used and generally accepted in practice is the 'Guidelines of the American Academy of Pediatrics for Ophthalmological Examinations in Children with Juvenile Rheumatoid Arthritis' (51). In contrast, guidelines for the screening of eye complications following the use of antimalarials are still being discussed (52, 53).

### How evidence-based medicine is currently practiced in pediatric rheumatology

Pediatric rheumatologists constitute a small group of pediatric subspecialists who take care of children with chronic musculoskeletal diseases. Generally, there are no disease-specific laboratory tests or clinical features upon which a diagnosis for our patients can be easily based. We are still trying to understand the etiology of rheumatologic diseases, and current therapies do not cure but only provide symptomatic relief. The medications used are often associated with significant, long-term side effects.

Given this quite difficult situation, EBM has a long tradition in pediatric rheumatology. Both national and international collaborations allow investigations of rare rheumatologic diseases. They provide the basis for studying sufficiently large patient populations to allow valid conclusions to be drawn. Research in outcome measures facilitates the generation of high-quality evidence. Thus, the pediatric rheumatology community is already practicing and actively promoting EBM in many ways.

#### *Classifications and disease measures*

Early on classification criteria were introduced for children then diagnosed with chronic juvenile arthritis (JCA) or juvenile rheumatoid arthritis (JRA) (54, 55). Recently, these classification criteria were unified based on newly gained scientific insights (56). Different subgroups of juvenile idiopathic arthritis (JIA) were formed to categorize patients for studies on prognosis and treatment. This will facilitate the international comparison of study results.

Preliminary criteria for the definition of improvement in patients with JRA (JIA) have been established (57, 58). They are now being used in trials to evaluate the efficacy of new medications and are a mainstay for the comparison of treatment regimens in pediatric rheumatology. One of the measures included in these preliminary criteria of improvement is the Childhood Health Assessment Questionnaire (CHAQ, 59). The CHAQ is one of the most frequently used measures of physical function in children with musculoskeletal diseases (60, 61). The CHAQ

has good inter- and intra-observer reliability and construct validity (62-64).

The Health Assessment Questionnaire (HAQ, 65) developed for adults served as a template for the subsequent development of the CHAQ. Thus, the pediatric rheumatology community benefited from research performed on adult rheumatology patients. Similarly, the different disease activity indices developed and validated for adult systemic lupus erythematosus (SLE) (66-79) were found to be sensitive to clinical change and could be applied in childhood-onset SLE (cSLE) (70, 71). These indices can now be used with confidence to measure disease activity in cSLE patients, and to stratify cSLE patients in future studies based on disease activity scores. The Systemic Lupus Erythematosus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR-DI) was developed for adult SLE to measure permanent damage. The SLICC/ACR-DI also has construct and content validity when used in cSLE (72, 73). Therefore it can be used to quantify permanent disease damage in these patients.

Although there are other well-validated disease-specific and generic outcome measures available for use in adult rheumatology patients (74-76), not all of them can be easily applied to children. Unlike cSLE, some childhood-onset rheumatic diseases are distinctly different from those observed in adults. Therefore a new disease activity and damage scale has been developed and validated for juvenile idiopathic inflammatory myositis, which is quite different from adult myositis (77). Similarly, measurement of the health-related quality of life (HRQL) in children will be different from that in adults. Children have different priorities and needs in life compared to adults and any HRQL measure must consider the extensive developmental changes observed in pediatric patients (78-80). Therefore new disease-specific HRQL measures for children were introduced and are still being tested (81, 82).

#### *Multicenter and multinational collaborations*

The Pediatric Rheumatology Collaborative Study Group (PRCSG) founded in

1973, and the Pediatric Rheumatology International Trial Organization (PRINTO) founded during the last decade, have promoted the organization and conduction of international trials and collaborative studies. Prior to the creation of the PRCSG there were virtually no RCTs in pediatric rheumatology (83). One of the most recently published RCTs tested the safety and efficacy of etanercept in children (84). A multicenter, multi-national approach (US and Canada) was taken to recruit a sufficient number of patients within a short period of time. Using this approach, etanercept has become rapidly available for use in children.

Other multi-nation activities to evaluate the effectiveness and safety of medications used for the treatment of JIA include the observational study on the use of Neoral/Sandimmune. Several multinational registries have been established, such as the registry of patients with systemic sclerosis (85), of patients with connective tissue diseases (86), or the sibpair registry (US and Canada). The latter effectively promotes genetic studies of JIA.

### How could we do better?

#### *Outcome measures - the backbone of EBM*

It is apparent that good outcome measures are essential for practicing EBM. Rheumatologists treating adults have long recognized this and coordinated their efforts by establishing the OMERACT (Outcome Measures in Rheumatoid Arthritis Clinical Trials) meetings. Well-validated and universally accepted outcome measures in pediatric rheumatology are crucial. They will facilitate the conduction of RCTs and make the combination and comparison of observational studies easier. This will provide a solid base of evidence for the effective practice of EBM.

In addition, outcome measures are essential for future research in the fields of genomics and pharmacogenomics. Valid outcome measures are required to correlate the influence of different genes on the course and the severity of a disease and its responsiveness to drug therapy. If a gene is investigated for its influence on the response to certain drugs, valid outcome measures have to be in

place. Without good outcome measures, efforts to identify disease-relevant genetic loci will be futile.

#### *More outcome measures: Flare criteria*

Studies in JIA will benefit from the development of valid flare criteria. This will help to define treatment failures and to identify important clinical change in disease activity. Flare criteria have been recently proposed for adult SLE (87), but have not yet been validated for use in cSLE.

#### *More outcome measures: Radiographic outcome measures*

During the OMERACT IV meeting (Cancun, 1998), different radiographic outcome measures for adult chronic arthritides (88, 89) were assessed for their measurement properties. The reliability, construct validity, and sensitivity to change of different radiographic indices were evaluated and compared (90). Similarly, radiographic standards for children with chronic arthritis are required. This will facilitate the measurement of the long-term side effects of the different treatment approaches considering joint structure, growth disturbances and the final height of pediatric patients.

#### *Further validation of functional outcome measures*

Functional outcome measures such as the CHAQ (59) are now commonly used in studies and in daily clinical practice. Although the CHAQ is widely used it is unclear whether it is really superior to other functional indices (60, 61). It has been suggested that the CHAQ may not be sensitive to clinically important change in patients with pauciarticular JCA (JIA) (91). The measurement properties of the CHAQ will require further investigation with regard to the possible influence of age, gender or ethnicity on the CHAQ scores. It is still unknown what constitutes a minimal clinically important difference in the functional status of a patient and whether doctors, patients, and their parents really rate the physical health in the same way.

#### *More outcome measures: Health-related quality of life (HRQL)*

Medical treatments in pediatric rheumatology should also be assessed with regard to the impact that they have on the HRQL of our patients. The assessment of physical function alone does not suffice. For instance, the well-known and undoubtedly important change in the energy level of children treated with tumor necrosis factor antagonists is not accounted for in the CHAQ scores. In contrast, HRQL measures will reflect such a change in the general well-being of the patients.

The term HRQL is conceptualized as a patient's perception of the impact of disease and treatment on a variety of aspects of life, including physical (functional) health, mental health, and social dimensions (domains). The HRQL can be measured in a non-preference based or preference-based approach. Non-preference based HRQL weighs the different domains according to the importance estimated by the developer of the HRQL scale. Such instruments are meant to measure the value which society places on a certain health state. In contrast, preference-based HRQL reflects the individual perception of personal health.

The importance of HRQL for treatment decisions has been recognized and pursued in adult patients for many years, but research in pediatrics lags far behind. Unlike in adults, the measurement of preference-based HRQL has not been well established in pediatrics (92, 93). It has been shown that the commonly used measures of preference-based HRQL for adults are not suitable for use in children. These methods, when used in children, have different measurement properties than would be expected on the basis of previous studies in adults (94). In addition, parents are not useful proxy reporters of the preference-based HRQL of their children.

The measurement of non-preference based HRQL is necessary to perform cost-effectiveness analyses of health interventions for health policy decisions and the allocation of health funds. Cost-effectiveness analyses are gaining increasing importance in pediatrics. For some health interventions, measurement of the preference-based HRQL is more suitable - for example, when a patient is asked to decide between treatment regi-

mens of similar efficacy but with a different spectrum of side effects. Quality-adjusted life years (QALY) are often used in economic analyses. The measurement of QALYs is based on the measurement of preference-based HRQL.

#### *Uniform reporting of results of statistical analyses*

With the increased implementation of EBM and the availability of user-friendly statistical programs, many different strategies to analyze data are now being described in the medical literature. They include different types of regression analyses, Monte Carlo simulations or Bootstrap analyses. Often the results of these analyses are difficult to compare, because different coefficients are reported or the confidence intervals for the estimates are not provided. The interpretation of study results would be facilitated if a universally accepted reporting scheme for the different types of analyses was used. This would also provide a good basis for future metaanalyses and sample size calculations.

#### *Practice guidelines*

The practice of EBM in the clinical setting is greatly facilitated by the development and implementation of practice guidelines. The success of such guidelines in other fields of pediatric medicine has been demonstrated, although their ultimate effectiveness depends on both the available body of evidence and effective strategies for rapid dissemination of the recommendations made (95). Historically these guidelines have relied on consensus and expert opinion. Currently, most guidelines use an EBM approach.

Useful guidelines for pediatric rheumatologists remain to be developed, in particular guidelines for the use of immunization, for the initiation and monitoring of newly developed biological agents, for the monitoring and treatment of osteoporosis, and for the use of growth hormones.

#### *Where do we go from here?*

Practicing EBM is like driving in the dark, you cannot see beyond the headlights, but you can complete the whole journey. Quality is more important than

quantity when it comes to evidence. There is a need for further research to broaden and improve the available evidence in pediatric rheumatology. Taken together, the field of pediatric rheumatology has made quite impressive steps towards forming a knowledge base upon which EBM can be practiced. Continuing efforts to practice EBM have and will lead to further improvement in the standard of care.

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