ABSTRACT
Nowadays, Medical practice is largely based on the best available evidence. However, the evidence may not always be readily available and clinician and/or other health allied professionals may need to learn how to search for it. This article gives highlights on the very vast and growing subject of evidence based medicine (EBM), followed by a practical application of searching for it in the real life, in a situation when the available evidence is limited.

Keywords:
Evidence based medicine; Evidence based practice; PICO; Testicular adrenal rest tumours; Congenital adrenal hyperplasia; Glucocorticoids.

INTRODUCTION
There is a gap between what is known in Medicine and what is done by the health care providers. A main reason is the fact that these providers rapidly found themselves encountered by an influx of a huge variety of new information, ranging from the irrelevant to the very important and they need to cope with this. To close the gap, evidence-based decision making gradually emerged as a solution to integrate the best research evidence with clinical expertise and patient values. The concept of evidence based medicine (EBM) and ideas attributed to it, such as evidence-based guidelines, care paths, questions and solutions, have now become part of daily clinical life, and the health care professionals increasingly become familiar with it.

In 1996, Dr. David Sackett defined EBM as “the
conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients” [1,2]. This definition, put forward by one of the pioneers of EBM [3], has since been adopted by major international organizations, including the Cochrane Collaboration and the Centre for EBM in Oxford, UK. Subsequently, Sackett et al [4], in 2000, redefined EBM as “the integration of best available evidence, clinical expertise and patient preferences and values”. This simpler, current definition gives equal emphasis to: 1) the patient’s situation, 2) the patient’s goals, values and wishes, 3) the best available research evidence, and 4) the clinical expertise of the practitioner.

EBM helps assessing the level of evidence available to inform the etiology, diagnosis, management and prognosis of patients from illness as well as the implications on health economics. This includes both the evidence to use or not to use a particular diagnostic tool or therapy for a particular patient, and helps clinicians to predict whether a treatment will do more good than harm [5].

Because EBM is used in other allied health specialties, such as dentistry, nursing, occupational health and psychology, some prefer to use evidence based practice (EBP) or evidence-based health care (EBHC) terminologies, to broaden its application to other allied health care professionals.

In the past, experience of physicians or other health care workers to make clinical decisions has dominated. In the current information era, this approach would be suboptimal. Nowadays, we need to integrate the 3 components of EBP together to make clinical decisions about patients’ health. These are: clinical expertise, patient values, and the best research evidence. Clinical expertise refers to the clinician’s cumulative experience, education and clinical skills. The patients bring forward their own personal expectations and unique concerns and values. The best evidence is usually found in clinically relevant research in which a sound methodology has been used [6]. In most of the cases, a sound clinical experience would be in agreement with evidence available from research. Though in few scenarios, further critical analysis should be conducted in order to validate research findings and evaluate the strength of the evidence available from it. One of the few classic examples which reflect some limitations of research as a source of evidence is when the answer from it is “There is no evidence of …” depending on the power of the study. Therefore, it is sensibly agreed in the EBM field that an “absence of evidence” is not always an “evidence of absence”.

EBM has evolved from clinical epidemiology and therefore they share the same ground of methodology [7]. Clinical epidemiology aims to bridge the gap between clinical practice and public health using population health sciences to inform clinical practice. In the same context, EBM has transformed medical practice using scientific methods applied on population sciences to inform clinical decision making. Therefore, the results of population-based research form the foundation of EBM, which aims to use the experience gained from research literature on a population of patients to guide decision making in individual cases.

Generally speaking, there are three dimensions of EBM, which are interdependent:

1. Treating individual patients based on the best available evidence from primary research.
2. Using a systematic review of medical literature to evaluate the best studies on specific topics. This can be through a journal club, or can be processed through some designed computer programmes. Most of clinical practice guidelines; especially consensus guidelines from worldwide specialist groups; use this method and provide us with a summary of already evaluated best available evidence.
3. Continuously educate health professionals to
use EBM efficiently and popularize it amongst public, patients, communities and educational institutes.

**STEPS OF EBM**

EBM has passed through milestones of developments. In 1992, five steps of EBM were first described [8], followed by the experience of constellation of experts who attended a conference of Evidence-Based Health Care Teachers and Developers in 2003, which was summarized into five steps of EBM and was published in 2005 [9]. The following 6 steps which evolved from the 2005 steps of EBM are currently in use:

The 5 ‘A’s’
- **Assess**: A problem or clinical question arise from the patient care.
- **Ask**: sensible and focused question or questions derived from the case. They are usually composed of 2 types: background and foreground questions, the PICO method (Patient, Intervention, Comparison, and Outcome) is usually used to formulate the foreground question.
- **Acquire**: evidence from literature which requires a good, systematic and skilful search
- **Appraise**: the acquired evidence, which also requires good appraising skills.
- **Apply**: the evidence you assessed on patient’s management after integration with patient’s expectations and needs or at least empower the patients with evidence to help those making decisions about their own health.

To complete the cycle, some advice evaluating your performance at the end of the process as a self reflection which will form the 6th “A”:
- **Analyse**: the effect of your exercise and evaluate your performance (weaknesses and strengths).

**PICO APPROACH**

PICO is a mnemonic to help remembering the key components of a well focused foreground question. It consists of:
- **P** = Patient or problem
  Identify your patient and/or clinical problem around who/which the questions to be answered are focused.
- **I** = Intervention, prognostic factor, or exposure
  Which main intervention, prognostic factor, or exposure are you considering? (Order an investigation, order a medical treatment or surgery). What will influence the prognosis? What are the factors to which the patient might be exposed that can increase risks?
- **C** = Comparison
  If a comparator is available, using an alternative to compare with your intervention (diagnostic tool or therapeutic intervention) is usually useful to encourage the search and evaluation of evidence and provides the clinician as well as the patient with treatment options.
- **O** = Outcomes
  It depends on what you are trying to achieve for the patient. Palliative or curative? Relieve or reduction of symptoms? Accurately diagnose or rule out a diagnosis (with a test of reasonable sensitivity and specificity)?

The following is an example of how a background and foreground questions can be formulated (on a teenager presenting with a goitre which turned out to be Grave’s disease):

<table>
<thead>
<tr>
<th>Root and verb</th>
<th>Disorder / test, etc</th>
</tr>
</thead>
<tbody>
<tr>
<td>What causes ...</td>
<td>Goitre in adolescents</td>
</tr>
<tr>
<td>How should we treat ...</td>
<td>Grave’s disease</td>
</tr>
</tbody>
</table>
ASSESS: Synopsis of an endocrine case presentation

I recently dealt with a 16-year-old young man who was followed in an endocrine clinic for congenital adrenal hyperplasia (CAH). Apart from his testicles, he did not have other palpable masses in his scrotum. However, ultrasonad and MRI tests showed bilateral testicular adrenal rest tumours (TART) which were occupying 1/3 of each of his testicles and they were located near the epididymis on each side. He claimed that he was compliant with his steroid replacement therapy which was at a high dose (hydrocortisone 23 mg/m²/day). However, his serum androgen levels were found to be strikingly high (17OHP > 3000 ng/dL and androstenedione was 35 ng/dL). Simultaneously, this patient also has other ongoing gastrointestinal symptoms and is currently investigated for a possible inflammatory bowel disease (IBD). I postulated a theory that this could possibly result in pooling of his steroid doses to treat the inflammatory process. The patient and his mother were understandably very concerned about his testicular masses and would like to know about TART and the options of management including surgery.

ASK: clinical question

To answer the question about options of management and evaluate the available evidence as well as their

Table 2- Foreground question (PICO)

<table>
<thead>
<tr>
<th>Patient /problem</th>
<th>Intervention / exposure</th>
<th>Comparison</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>In a 14 -year-old girl with a relapse of Graves’ disease</td>
<td>Would radioactive iodine therapy</td>
<td>Compared to carbimazole</td>
<td>More likely lead to euthyroid status 10 years later?</td>
</tr>
</tbody>
</table>

Table 3- Background questions

<table>
<thead>
<tr>
<th>Root and Verb</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>What causes …</td>
<td>TART</td>
</tr>
<tr>
<td>What are the consequences of</td>
<td>TART</td>
</tr>
<tr>
<td>How can we treat</td>
<td>TART</td>
</tr>
</tbody>
</table>

TART- testicular adrenal rest tumour

Table 4- Foreground question

<table>
<thead>
<tr>
<th>Patient /problem</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>In a patient with CAH who developed TART</td>
<td>Intensifying glucocorticoid (GC) therapy (Medical treatment)</td>
<td>compared to testis sparing surgery</td>
<td>results in regression of TART, and surgery is not superior to medical management</td>
</tr>
</tbody>
</table>

CAH- congenital adrenal hyperplasia, GC- glucocorticoids; TART- testicular adrenal rest tumour.

http://www.sudanjp.org
suitability for my patient, I put forward 3 backgrounds and 1 foreground questions as below:
The question has been formulated this way because:
I would like to know about the best option of management I can offer, or suggest for my patient, supported by the up to date evidence (evidence based), and also because I anticipated that this is likely to be the most important question in the patient’s mind, to be answered (patient expectations). In fact, this is a reasonably rare condition in paediatric endocrinology, so it is my first experience to deal with such a clinical problem in a patient (clinician expertise).

**ACQUIRE: Searching available evidence**
I used the following search strategies to find answers for my questions:

Internet searches: www.library.qmul.ac.uk, to which I have access, using a web search engine called: Metalib, which helped me to search on: congenital adrenal hyperplasia* and testicular adrenal rest tumour* from the most commonly used database including Cochrane collaboration, PubMed as well as the web of knowledge. I managed to scrutinise my search into 14 papers in Metalib when I used “TART in CAH” for my search. This included a clinical practice guideline on CAH in general (secondary study).

I have also briefly looked at results from search engines including: www.intute.ac.uk and www.evidence.nhs.uk but the results were too many to look at, and I therefore, matched them with the list on my first search in Metalib.

There were no results from the Cochrane database to answer the foreground question. I therefore went straightaway to PubMed where I confirmed the list I obtained from the search in Metalib by looking at the accompanying citations and similar articles after accessing the abstracts of the relevant papers. This helped me to identify 1 -2 more papers as well. Two of these papers were review articles. I looked at the references in one of these reviews to find out more relevant papers. I could not access one of these 2 reviews in full but was able to look at the abstract. From looking at the reference list in one of the reviews, I have found useful clinical practice guidelines on the assessment, diagnosis and management as well as follow up for CAH from the Endocrine Society.

To have access for the full text of the identified relevant articles from the above list, after going through the abstracts, I have used combination of search: using “Article search” through Sfx service from QMU library and PubMed Medline for original research papers: www.ncbi.nlm.nih.gov/entrez/query.fcgi?tool=igbqmulib.

**APPRAISE: Evaluating the available evidence**
Appraising the evidence would include that: the design and conduct of a study are free from bias or not. i.e randomisation, concealment of allocation, blinding, loss to follow up and the analysis if it was an intention to treat analysis (ITT). This will illustrate the level of evidence according to the hierarchy of evidence. However, there may be limitation to this approach depending on what is available from searching the literature. Though, this, in itself, may raise the attention that more solid evidence will need to be generated to answer a particular clinical question when the available evidence is limited.

I will mainly appraise here a review article and comment on a paragraph on the guidelines as the most valuable available evidence I found in the management of TART in CAH:

- A review article in a high impact journal (Secondary Study):
- Clinical Practice Guidelines from a group of CAH
experts in the Endocrine Society (Secondary study):


I think the review article addressed an important clinical question. In adult patients with CAH the presence of TART is an important cause of gonadal dysfunction and infertility. The concerns about the development of this problem start from adolescence, possibly because of the additional LH stimulation effect on the growth of TART. In the last decade several papers have focused on the origin and pathogenesis of these tumours. In the review paper the authors reviewed the embryological, histological, biochemical and clinical features of TART and discussed the treatment options. The research questions in this article were:

• Evaluation of the natural history of TART and validation of the proposed classification.
• Early detection methods for TART.
• Role of angiotensin II (AII) and luteinizing hormone (LH) as growth-promoting factors.
• Medical and surgical treatment options.

Because it is a review article (overview), rather than a systematic review, they did not have methods section to explain their search process of reviewing databases. However, I found all the papers which I identified from my search in their references (72 papers), reflecting their thorough search in literature. Most, or all, of the reference papers were case controlled, case reports or lab based (in mice), but there were no controlled blinded trials or cohort studies. There was limitation in the numbers of patients who participated, especially with surgical interventions (7 – 8 per study) reflecting the rarity of the condition. There were contradicting results in literature with regards to the response to intensification of glucocorticoid (GC) therapy (controlling ACTH level) and optimizing mineralocorticoid (MC) therapy (controlling the effect of AII on TART). This was initially interpreted as: steroid responsive or unresponsive TART but there were no sensible reasoning been mentioned for this unresponsiveness. In this review the authors proposed a new five-stage classification of TART, based on sonographic, clinical and biochemical parameters that may lead to a better follow up and treatment of patients with TART.

TART stages 2 and 3 may be successfully treated by increasing the dose of GC. Intensifying GC therapy may lead to reduction of the tumour size by suppression of ACTH secretion [10]. However, some studies report failure of intensified GC treatment; serious side-effects after longstanding treatment and it may only lead to temporary improvement of the obstruction because tumour growth may start again after lowering the GC dose, and therefore some patients will not accept this treatment option [10-15]. Nevertheless, optimizing GC medication, especially in patients with poor hormonal control, is important to determine whether tumour growth is reversible (stage 3).

In stage 4, increasing the dose of GC is probably no longer effective in decreasing tumour size, but removal of the tumour may prevent further testicular damage. Because of the benign character of the tumours, testis-sparing surgery has been proposed for the treatment of TART. Walker et al [15] performed testis-sparing surgery in three CAH patients. Postoperatively, there was good vascular flow and no recurrence of the tumour. Tiryaki et al [16] reported two CAH patients with steroid-unresponsive testicular tumours, who were also treated by testis-sparing surgery. In neither study was information about pituitary–gonadal function before and after surgery reported. In a recent study by the authors of the review article, they showed that in patients with longstanding TART (stage 5); gonadal dysfunction did not improve; suggesting irreversible damage to the surrounding
Testicular tissue [17]. Furthermore, additional damage from surgery could not be excluded.

ES Guidelines (By topic specialist group):
Consensus Process and Validity: Consensus was guided by systematic reviews of evidence and discussions. The guidelines were reviewed and approved sequentially by The Endocrine Society’s CGS and Clinical Affairs Core Committee, members responding to a web posting, and The Endocrine Society Council. At each stage, the Task Force incorporated changes in response to written comments.

TARTs increase with age in CAH, impairing fertility. The prevalence of these tumours varies between 0 and 94%, depending on the study population [18-20]. Undetected adrenal rest tumours may obstruct the somniferous tubules, causing secondary gonadal dysfunction and infertility. When tumours are unresponsive to steroid therapy, surgical intervention by a testis-sparing procedure with cryopreservation of the semen may be needed, because fertility is uncertain.

**Conclusion and APPLY**
Answering background and foreground questions:
- TART is the most important cause of infertility in male CAH patients.
- The incidence of TART in adult CAH patients (16 years and above), detected by ultrasound as the method of choice, is high (up to 94%).
- TART are not malignant, but longstanding TART can result in irreversible damage to testicular tissue.
- TART have histological and functional features of adrenocortical tissue, and growth can be stimulated by elevated ACTH concentrations.
- Intensifying GC therapy (which will suppress high ACTH levels = the main stimulant to the growth of adrenal rest cells with which the patients were born) is the first step in the treatment of TART; before testis sparing surgery is considered.

Testicular biopsies are advised to evaluate the quality of the surrounding testicular parenchyma before surgery.
- In this stage the only indication for surgery is the relief of pain and discomfort caused by TART. Therefore, mainly in longstanding TART with signs of gonadal dysfunction, testicular biopsies are advised to evaluate the quality of the surrounding testicular parenchyma before surgery is considered.
- Because AII may also stimulate tumour growth the mineralocorticoid treatment has to be optimized.
- As long as medical and surgical treatments of TART are far from perfect, patients should be informed about the negative effects of TART on fertility and cryopreservation of semen should be offered as soon as possible. Because adrenal rest cells are already present in the embryological period it is clear that prevention of TART is not possible.
- In our patient: Looking back in the performed imaging, his TART is likely to be at stage 3, maximum 4, though accurate classification may require a surgical biopsy. I explained the different options of management for the patient and his mother. When we did 17OH and cortisol (pre doses) profile for him, he had a poor control in the morning. We changed him to oral prednisolone which is a long acting steroid and 5 times more potent than HC in its action. Bearing in mind the possibility of an associated IBD, prednisolone might have been a better option for him anyway especially that there were no further concerns about his growth which had completed. If IBD is ruled out by GI scope, dexamethazone which is even more potent can be an option but only for short duration as it is known of serious side effects especially on the bone if used for longer durations. Nevertheless, it may be more helpful in terms of regression of his TART. We also had
a discussion about semen cryopreservation. The prednisolone was prescribed as 10 mg in two divided doses of 5 mg, to improve opposing the ACTH early morning peak effect with the evening dose and to avoid gastric side effects with a high evening dose as he was already on proton pump inhibitor (PPI) for chronic gastritis.

**Analyse: the effect (Strengths and weaknesses of this approach)**

- This includes the effect on the patient management and the effect on whoever searched for the evidence in terms of his/her clinical practice and decision making.
- The patient did not have IBD in GI scope. He had an excellent response to oral Prednisolone in terms of TART and GI symptoms. The patient and his mother were delighted of the news that his TART regressed to only 0.8 mm tumour size on each side in a follow up USS for his testes after 6 months of switching to prednisolone. This supports the limited evidence in literature, I found in my search, and, therefore, the detailed information of this case may well be separately published as a case report in peer review journal to inform the literature evidence. Overall, the patient was very pleased with the GI scope result and the regression of his TART. However, to this end, he, and his mother, started to be more concerned about fertility. This may generate another clinical question about TART and its management that requires a careful search using EBM strategy.
- I found that using this approach is very useful in managing my patients. The advantages are many but in general, it gave me confidence that I treat my patients according to the best available evidence. I found this very ethical and highly professional. In addition, this is exactly how I like to be treated myself if I were the patient, so I feel it is fair enough on my patients. On the other hand, in some occasions this may be exhausting when you search for evidence on rare conditions or when there are contradicting data in the literature. However, again the inspiring side of this process is that it opens the door for more conclusive research to find out more perfect answers for remaining questions. For example in this case: probably, in the future, new types of GC – such as slow-release hydrocortisone or selective ACTH inhibitors – may help to suppress ACTH more effectively without the risk of adverse events. Further studies in childhood are required to investigate whether surgery in stages 2, 3 and 4 may prevent irreversible damage to the testes. Hopefully, in order to prevent damage of residual testicular parenchyma, introduction of new surgical techniques may facilitate the surgical treatment of the tumours at an early stage, i.e. in childhood.

**ACKNOWLEDGEMENT**

The author would like to acknowledge Dr Yaser Adi, Senior Researcher, Sheikh Bahamdan’s Research Chair for EBHC-KT, College of Medicine, King Saud University, for his kind review and comments on this article. I would also like to thank the patient, and his mother, for their kind agreement of their clinical case to be published and used in these learning activities.
REFERENCES