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Review Article

Evidence Based Medicine Series
Part 4. WHY SOME GOOD STUDIES WITH CLINICALLY IMPORTANT RESULTS CANNOT BE APPLIED TO OUR PATIENTS

NM Lai, *MRCP, MRCPCH* School of Medicine and Health Sciences, Monash University Malaysia.

Address for correspondence: Dr Lai Nai Ming, Senior Lecturer in Paediatrics, School of Medicine and Health Sciences, Monash University Malaysia, JKR 1235, Bukit Azah, 80100 Johor Bahru, Johor, Malaysia. Tel: +607-2190600, Fax : +607-2190601,
Email: lainm123@yahoo.co.uk

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INTRODUCTION

One major misconception towards EBM practitioners is that they push to adopt all valid and clinically important evidence without having a second thought. Such assumptions stem from an incomplete understanding of the definition of EBM.[1,2] A crucial step in EBM is the assessment on whether the evidence fits our population and individual patients, hence whether adopting such evidence is possible or appropriate. Ignoring this step would in fact undo our hard work in the preceding steps of EBM.

We have previously covered the assessment of internal validity and clinical importance. These aspects of critical appraisal, although important, may be seen as tedious and time-consuming by the busy clinicians.[3,4] The good news is that they may already have been done by others on our behalf. Many clinical studies are critically appraised soon after they appear by people who are skilled in this area. Referring to those pre-appraised resources is one way to save our work and reduce uncertainties on the value of a clinical study. However, certain steps in the practice of EBM require our own efforts at all times. These include asking answerable, relevant clinical questions, as covered previously, and deciding the applicability of the evidence, as we aim to cover here.

Alongside the major disease characteristics, biological, cultural and personal variations may be responsible for differences in responses to a medical intervention.[5,6] We have to take into account such variations in deciding whether to apply the evidence. We do not want to patronize our patients with a treatment that is proven in a different population, a therapeutic regime that is not feasible in our setting, or a treatment against his values and preferences. We use some examples to illustrate these issues in more detail, as follows.[7]

1. Differences in patient characteristics

Example: Male circumcision and HIV

In an article published in Lancet in 2007,[8] Bailey et al assessed whether circumcision for young males reduced the risk of HIV infection. They conducted a randomized controlled trial on men aged 18 to 24, comparing circumcision against a controlled group where circumcision was delayed. They showed that the circumcised group was significantly less likely to acquire HIV compared to uncircumcised group, relative risk: 0.47 (95% CI: 0.28 to 0.78). This is clearly a clinically important reduction in risk. So, should we routinely circumcise all males in Malaysia to reduce their risks of HIV infection? How do we make sense of the study in the Malaysian context?

Comments

There are key differences between the setting of the study and the local setting in Malaysia. The prevalence of HIV in man in Kenya is 4%,[9] while in Malaysia, HIV prevalence in adults is around 0.5%.[10] Although gender-specific figures in Malaysia are not available, it is obvious that HIV has a much lower prevalence in Malaysia compared to Kenya. As the prevalence of the target condition is lower, male circumcision, if adopted here, would not have achieved the same degree of reduction in risk as demonstrated in the study. Besides, the characteristics of the at-risk group are different. In Africa, HIV is predominantly transmitted sexually, while in Malaysia, intravenous drug users make up of a major proportion of the at-risk group. One would imagine that circumcision does not affect the risk of this group.

Next, if circumcision is recommended, non-Muslim males in this country may not accept the procedure. This issue of patient value and preference is detailed under the subsequent heading.

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Other major population characteristics to be considered when deciding applicability of a study include age groups, sex, disease classification, severity and co-morbidities. A quick way of cross-checking our patients' characteristics against that of the study participants is to look at the study exclusion criteria, and make sure that our patients do not fall under these criteria.

2. Non-feasibility of the treatment or diagnostic plan.

Example: ECMO and neonatal respiratory failure

In a Cochrane systematic review that includes four randomized controlled trials,[11] Extracorporeal Membrane Oxygenation (ECMO) is shown to have substantial benefits in reducing death for newborn infants with severe respiratory failure, relative risk for mortality: 0.44 (95% CI: 0.31 to 0.61).

Comments
Despite the magnitude of its benefits, ECMO is currently not available in Malaysia.

Example: Procalcitonin and bacterial infections

In a randomized-controlled trial published in the Archives of Internal Medicine in 2008,[12] Briel et al examined the use of procalcitonin level as a guide to determine the need for antibiotics for patients presented with symptoms of acute respiratory infections. They found that with procalcitonin-guided therapy, there was a 72% reduction in the prescription of antibiotics (95% CI: 66% to 78%), with no significant difference in the days of restricted activities and symptom persistence or exacerbation.

Comments
Procalcitonin is a relatively new tool to assess the presence and severity of acute bacterial infections. Despite its proven benefits, this test is not yet widely available in Malaysia.

Under the heading of feasibility, other issues to consider include the cost and local capacity to monitor and follow-up patients as required.

3. Patient-important outcomes not being the focus.

In the study above on procalcitonin and bacterial infections, we note a major reduction in the use of antibiotics. Although clinically important, the strategy benefits the health system more than the individual patients directly. In Malaysia, such guided therapeutic strategy may currently only be adopted mostly in the private setting, where patients bear the cost of the test. Patients may argue that since there is no difference in the outcomes that matter to them directly, like symptom persistence and days of restricted activities, it is not worth paying for the test. Many will rather have the antibiotics, which probably cost less.

4. Patient's values and preferences.

Example: Surfactant for respiratory distress in preterm infants: Poractant versus beractant

We quote here two randomised controlled trials comparing different preparations of natural surfactant: poractant (porcine) and beractant (bovine) on the respiratory outcomes of preterm infants. The trials show that infants receiving poractant had significantly less oxygen requirements at 6[13]and 48 hours[14] after birth respectively. In one trial, infants less than 32 weeks of gestation who received poractant had a lower mortality rate up to 36 post-conceptional age compared to those receiving beractant (3% versus 11%, p = 0.03)[13]. The second trial showed that infants who received poractant had lower incidence of patent ductus arteriosus compared to those receiving beractant (17% versus 45%, p = 0.02).

Comments
Surfactant and antenatal corticosteroid have been the cornerstones of neonatal care.[15] Different preparations of surfactant are available, from synthetic to animal-derived. Collectively, animal-derived surfactants have been shown to be superior to synthetic surfactant.[16,17] Among the animal-derived surfactants, poractant and beractant are the most commonly used. Poractant has a much smaller volume of administration (around 1 ml/kg) compared to beractant (around 4 ml/kg), and studies above suggest that poractant may be the better choice for the highlighted outcomes. However, Muslim patients may prefer beractant as poractant is derived from pork extract, and most Malaysian hospitals use only beractant.

Example and comments: chemotherapy for advanced cancer

The benefits of chemotherapy for cancer have long been established.[18-20] However, for patients with advanced cancer, the reduced benefits have to be weighed against the unpleasant side effects, in a patient who is already debilitated by the disease. Some patients are willing to cope with such side effects in the hope to survive, while others prefer to have a better quality of life that is free from side effects of chemotherapy in what they see as the terminal stage of their disease.

Patient's values and preferences is a complicated issue that must be considered with sensitivity and respect. They may be driven by culture, religion or personal values, and involves considerations on the potential changes the care plans have in their lifestyles, and their ability to cope with

these changes. These issues may only be clear after a cordial patient-physician consultation. The responsibility of a physician is to provide truthful information and involve patients in the decision-making process.[6]

Final note

Evidence based medicine starts and ends with our patients. From asking clinical questions to assessing the applicability of the evidence, keeping the patient's interests in sight will provide the whole EBM process a meaningful anchor.

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Research Digest

Text messaging is as effective as telephone reminder in reducing non-attendance in patient with chronic disease

Liew SM, Tong SF, Lee VKM, *et al.* Text messaging reminders to reduce non-attendance in chronic disease follow-up: a clinical trial. *Br J Gen Pract.* 2009;59:916-20.

Affiliation of first author: Department of Primary Care Medicine, University of Malaya

931 subjects with chronic disease were randomised to receive either text messaging reminder, telephone reminder or no reminder for their follow-up appointment. Both reminder methods were more effective than no reminder in reducing non-attendance. Text messaging reminder is almost as good as telephone reminder.