This is a pre-copyedited, author-produced PDF of an article accepted for publication in *the Journal of Evaluation in Clinical Practice* following peer review. The definitive publisher-authenticated version Crowther H, Lipworth W, Kerridge I. **2011**. EBM and Epistemological Imperialism: Narrowing the divide between evidence and illness. *Journal of Evaluation in Clinical Practice*. 17(5):868-872 is available online at http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2753.2011.01723.x/full .

EBM and Epistemological Imperialism. Widening the divide between evidence and illness

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Evidence Based Medicine (EBM) is an approach to clinical practice that relies on the use of systematically reviewed published clinical research of high quality. Whilst there is some speculation as to whether a true consensus definition of EBM exists (Loughlin (2008)(1)), a commonly cited explanation "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients' (Sackett et al (1996)(2)). Most approaches to "EBM" incorporate the use of an evidence hierarchy that presupposes that some forms of evidence are better than others (Guyatt and Rennie (2002)(3)), that meta-analyses and randomised controlled trials (RCTs) will guide a better level of care than expert or local knowledge.

Although EBM is pervasive throughout all health literature a number of ethical (Gupta (2009)(4)), epistemological (Loughlin (2008)(1)), and clinical practice critiques (Tobin (2008)(5)) have emerged. Criticisms of EBM on ethical grounds have previously been summarised by Kerridge (2010)(6) and include ; "that the implicit and explicit requirement for RCTs may lead to unnecessary research being done where sufficient evidence already exists;... that methods privileged by EBM, most notably the RCT, are methodologically unable to answer questions related to individual patients;.... that evidence hierarchies are inadequate and misleading;.... that the dataset that EBM draws from is systematically bias[ed],.... that the translation of evidence into practice through clinical practice guidelines and decision aids is both ethically and epistemologically problematic...[and] that evidence is not value-neutral and cannot be easily translated into practice."

The cultural biases implicit within EBM had been noted by Rogers (2004)(7) who when examining the impact of EBM on the socially disadvantaged demonstrated the cultural bias within EBM. The socially disadvantaged are excluded from the production of evidence and consequently "remain disenfranchised from the goods of EBM". Such is the power bestowed upon published research findings that once demonstrated, the imperative to implement management "proven" to be effective is greater than any regard of a community's health priorities or with consideration of "robust justice related reasons" for implementing such an approach. The research is able to answer whether a treatment is effective but EBM fails to help the medical and wider community determine whether such treatment should be pursued.

Such biases within EBM extend beyond that of the socially disadvantaged and the exclusion (or comparative reduction of) other population groups are commented on widely in the literature. The subjects of large RCTs are more likely to be male, less than 65 years old, white and educated. Essentially all main stream A* graded journals invite only manuscripts written in English, and despite a massive increase in biomedical research being undertaken in the 5 BRICS countries (Brazil, Russia, India, China and South Africa), emphasis in clinical practice remains on evidence produced in Northern Europe and North America. Similar commentary with regards to the lower engagement of women with the production of clinical epidemiology is made by Goldenberg (2010)(8). As EBM insists upon the incorporation of such published evidence it implicitly sanctions such biases and consequently is therefore becomes a biased approached to clinical decision making.

The cultural biases with EBM can be considered within a framework including the research agenda, formation of research questions, conduct of trials, translation into practice and access to results.

The research agenda, those areas of health which are considered a priority by those funding research projects is the first cultural bias of EBM. Such the majority of funding for therapeutic trials comes from pharmaceutical companies(9) there exists (sometimes implicitly) a pressure to produce trials that will ultimately be of financial benefit to the company. Such an agenda does not necessarily represent the true health needs of a community (either in the medically developed or non-developed world). Government and research funding bodies who are independent of pharmaceutical funding also have clear, often explicit research agendas. Australia's National Research Priorities 2011(10) (criteria against which funding is considered) identified four key aims for this year: "A healthy start to life", "Ageing well, ageing productively", "Preventive health care…prevent disease through the adoption of healthier lifestyles and diet…" and "Strengthening Australia's social and economic fabric".

Although all very laudable ideas it is clear that the opportunity to produce research with internationally applicable results would be somewhat limited.

The formulation of research questions are usually in line with national research priorities as such these have cultural bias. They are also methodologically biased with an emphasis placed on randomisation and epidemiologic outcomes. Such methods, although privileged by EBM hierarchies, are biased towards the type of questions that can be answered in such a quantitative manner (Kerridge (2010)(6).

The conduct of research demonstrates a cultural bias with regards to recruitment. It has previously been reported that subjects in trials are most often white men (Keuken et al (2011)(11). Women and ethnic minorities are underrepresented as trial participants and as such the results of such trials cannot easily be extrapolated to these groups (Mastroianni et al (1994) cited Keuken et al (2011)(11)). Whilst this is concerning for philosophical reasons, there are direct pharmacological and physiological implications; some diseases are seen only in particular ethnic groups (ie Sickle Cell Disease) and some drugs are metabolising very differently by some people in different ethnic groups, an example of this the genetic variation in liver enzymes that effect warfarin metabolism clustering in different ethnic groups (Capodanno and Angiolillo (2010)(12).

The translation of research into clinical practice relies on the external validity of the results. If the environment in which the trial has been undertaken is not similar to where you may try to integrate the results into practice the meaningfulness of the results is questionable. This environment might be with regards to the patients included, the local expertise involved in patient care (for example to provision of high quality intensive care or radiology in the trial hospital), infrastructure differences for example the provision of a safe blood supply and the financial appropriateness of the therapy in question.

The access to research results is dependent on access to the internet and either proficiency in reading English or access to translation. This again demonstrates cultural bias.

This bias, evident at all levels of the production and incorporation of clinical research is such that the validity of any evidentiary claims made EBM must be reduced.

This effect is most profound and exaggerated in Haematology where the incorporation of molecular techniques into evidence production is increasing. At the change of the millennia the development of molecular biological knowledge and technique has impacted greatly upon diagnosis, prognosis and targeted therapy. Such an approach has been widely adopted in haematology practice and as such has been at the forefront of technological and management developments. The practice of EBM based haematology exaggerates these biases and provides an elegant illustration in diagnosis and management of Acute Myeloid Leukaemia (AML).

Whilst for the purpose of this paper we have chosen to use AML as the illustrative example, there are a number of different diseases within haematology which could easily have been selected.

AML, until the advent of cytogenetic techniques was previously categorised according to one of eight morphological types dependent on the features identified under simple light microscopy; slide preparation and examination could be undertaken with minimal cost and a diagnosis could be made by anyone with training in morphological examination. The WHO classification of Tumours of Haematopoietic and Lymphoid Tissue now in a 4th edition (12) incorporates genetic abnormalities into a classification using both cytogenetic (the detection of large chromosomal abnormalities) and molecular (the detection of small gene specific abnormalities) techniques, and now recognises more than 20 types of AML (Table 1).

Table 1: WHO classification of Acute Myeloid Leukaemia and related myeloid neoplasms

Acute Myeloid Leukaemia with recurrent cytogenetic abnormalities
AML with t(8:21)(q22;q22); RUNX1-RUNX1T1
AML with inv(16)(p13.1q22) or t(16;16)(p13.2;q22); CBFB-MYH11
AML with t(15;17)(q22;q12); PML-RARA
AML with t(9:11)(p22;q23);MLLT3-MLL
AML with t(6;9)(p23;q34); DEK-NUP214
AML with inv(3)(q21q26.2) or t(3:3)(q21;q26.2); RPN1-EVI1

AML (megakaryoblastic) with t(1;22)(p13;q13); RBM15-MKL1
Provisional entity; AML with mutated NPM1
Provisional entity; AML with mutated CEBPA
Acute myeloid Leukaemia with myelodysplasia-related changes
Therapy-related myeloid neoplasms
Acute myeloid Leukaemia, not otherwise specified
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukaemia
Acute monoblastic/monocytic leukaemia
Acute erythroid leukaemias
Pure erythroid leukaemia
Erythroleukaemia; erythroid/myeloid
Acute megakaryoblastic leukaemia
Acute basophilic leukaemia
Acute panmyelosis with myelofibrosis
Myeloid Sarcoma
Myeloid Proliferations related to Down Syndrome
Transient abnormal myelopoiesis
Myeloid leukaemia associated with Down Syndrome
Blastic plasmacytoid dendritic cell neoplasms

The majority of these disease entities are dependent on the use of complex laboratory techniques, requiring significant technical skill and expensive hardware and consumables. For obvious reasons much of the non-developed world has no access to such techniques.

It should be noted that the classification of the AML is not one made for intellectual interest alone but has a very significant impact on management and prognosis. Numerous molecular abnormalities have been identified as impacting on prognosis subdividing AML into “good”, “intermediate” and “poor” risk. “Good” risk AML includes “AML with inv 16” and “AML with t(8:21)”, these two disease entities have a significantly better prognosis than many other types of AML and as such are treated differently. Unlike for standard risk or poor risk AML in whom early SCT in first remission is recommended, the good risk patients are treated with chemotherapy alone (Wahlin (2009)(13). One other AML fits into the category

of “good risk”, AML with t(15:17) which interestingly appears to be a markedly different disease to other types of Myeloid Leukaemia. This form of AML is treated with medications (all trans retinoic acid and arsensic trioxide) aimed at maturing the leukaemic cells rather than primarily destroying cells (cytotoxic) unlike all other forms. Whilst there are some morphological characteristics (visible using a simple light microscope) the actual diagnosis of this subtype is entirely dependent on confirming the characteristic genetic abnormality and results in some 80% long term survival(14) compared with 60% 4 year survival for the other good risk types(13).

Further studies examining smaller molecular abnormalities have revealed an impact on prognosis. Mutations in exon 12 of the nucleophosmin (NPM1) gene are the most frequent abnormality in AN with normal cytogenetics (previously classed with “intermediate” risk AML) seen in up to 60%(15) of patients and nnow confers a good prognosis for those originally classed as intermediate risk. This is compared with those patient in whom an internal tandem duplication mutation of FLT3 with a normal karyotype who are now reclassified from an intermediate risk disease to one of high risk and consequent poor prognosis.

As more molecular abnormalities are identified as having an influence on prognosis, studies are making recommendations for such grave differences in management as whether or not to proceed to a bone marrow transplant when the patient achieves a remission based on the detection of a single mutation.

With the advent of more and more published studies on the effect that these molecular abnormalities have on prognosis and management, comes the realisation that lack of access to the techniques required to make the classification results not only in a significant disadvantage in making the diagnosis but the suggestion that we are now dealing with entirely different disease entities. Those experiencing AML in Africa are unable to have the same diagnosis as those in Australia.

The disadvantages experienced by AML patients in the non-developed world extend beyond that of diagnosis to the availability of appropriate therapies. Even prior to the most recent classifications of AML the mainstay of treatment relied on the use of combination infusional combined chemotherapy protocols. For such an approach to work not only does one require access to these medications (at not inconsiderable cost) but also to high level supportive care in the form of safe and easily available blood products (such as red cell concentrates and platelets) for transfusion, broad spectrum intravenous antibiotics for the management of febrile neutropenia and access to high levels of nursing and medical expertise. In our centre the cost of drugs alone to provide induction and consolidation chemotherapy to a patient with standard risk AML is in the order of AU$ 23,160 (this is based on non-subsidised figures and does not include the costs of additional medications such as intravenous antibiotics or GCSF). This is clearly not available in a large proportion of the world. As the role of bone marrow transplant (stem cell transplant) became more apparent the use of SCT when a patient had achieved a first remission became recommended for patients who were considered high risk became incorporated throughout the developed world. Once again the criteria for risk are based on advanced genetic testing and are not easily available. In Australia the average cost of a SCT from a sibling is $114,000

for an adults and $227,286 for a child for the first 3 months of care (Gordon et al (2009)(16). The resources required, both absolute financial cost as well as medical expertise are prohibitive for such an approach in most of the world. As each new gene abnormality is detected targeted therapies such as FLT3 inhibitors are incorporated into therapeutic trials. Those experiencing AML in Africa are unable to have the same treatment as those in Australia.

There is, of course, little in the way of published evidence in the management of AML in communities without access to such diagnostic and management approaches. When the majority of RCTs incorporating medical therapies are sponsored by pharmaceutical companies, the impetus to perform studies that utilise the few diagnostic and management techniques available is negligible. Those few studies using patients in countries such as this are performed not to identify the "best evidence based" approach for the management of AML in these communities but as a means of increasing subject numbers or reducing trial costs and as such produce a meaningless evidence base for the care of these patients off trial.

Let us pause for a moment and consider this patient in Africa; they are unable to have a disease classification, we are unable to use published evidence to help prognosticate for them and we are unable to provide the same treatment for them. Consequently we can no longer, by any stretch of the imagination, claim that the African and Australian patients have the **same disease.** Whilst the use of published evidence (and therefore EBM) is impractical with regards to cost and accessibility, it is perhaps more alarmingly, **meaningless** for the African patient.

For these reasons EBM now creates an epistemological and ontological crisis for medicine. We can no longer classify or understand, what is fundamentally perhaps the same disease process in our African and Australian patient, in the same way, our "knowing" is different. This disparity of knowing is the direct result of EBM and the creation of a two tiered approach to what was although biologically likely to have been the same disease, can no longer be thought of as such. Whether we classify this bias as cultural, geographical or financial we are left with a grossly biased approach to health care that is meaningless to more than 90% of the world and serves to widen the disparity in health outcomes in the medically non-developed world.

There are a number of ways in which this cultural bias could be overcome. Firstly the impossibility of the incorporation of **current** published evidence must be acknowledged, a transparency with regards to the idea that evidential "standards do not operate outside of the social context" (Goldenberg (2010)(8)) must be pursued. By doing this, the pressure to implement the management described in such studies is reduced and allows for the consideration of other justice related factors in clinical care as outlined by Rogers (2004)(7). Secondly the biases of biomedical journals toward the publication of research from the geographical North needs to be overcome to not only reduce the effects of socio-economic factors on study outcomes but also to allow for physiological ethnic differences in treatment effects to be reviewed. The development of institutional or clinician partnerships between countries of varying wealth and expertise will allow for an increase in the applicability of current evidence. By either providing assistance in developing local diagnostic techniques or

by providing a satellite diagnostic centre we would be able to once again begin to understand the disease of patient from both countries in the same way. Either the production of locally relevant research utilising pragmatically available therapies or consideration of current research within a locally feasible framework may allow for a treatment approach that benefits local patients and results in some positive outcomes.

References

1. Loughlin M. Reason, reality and objectivity--shared dogmas and distortions in the way both 'scientistic' and 'postmodern' commentators frame the EBM debate. J Eval Clin Pract. 2008 Oct;14(5):665-71.
2. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. 1996. Clin Orthop Relat Res. 2007 Feb;455:3-5.
3. Guyatt GHaR, D. Users' guides to the medical literature. JAMA. 1993; 270(17):2096-7.
4. Gupta M. Ethics and evidence in psychiatric practice. Perspect Biol Med. 2009;52(2):276-88.
5. Tobin MJ. Counterpoint: evidence-based medicine lacks a sound scientific base. Chest, .133(5):1071-4.
6. Kerridge I. , Ethics and EBM: acknowledging bias, accepting difference and embracing politics. . J Eval Clin Pract. 2010;16(2):365-73.
7. Rogers WA. Evidence based medicine and justice: a framework for looking at the impact of EBM upon vulnerable or disadvantaged groups. J Med Ethics. 2004 Apr;30(2):141-5.
8. Goldenberg MJ. Perspectives on evidence-based healthcare for women. J Womens Health (Larchmt). 2010 Jul;19(7):1235-8.
9. Dorman P, Counsell, C., Sandercock, P. Reports of randomized trials in acute stroke, 1955 to 1995:what proportions were commercially sponsored? Stroke. 1999;30:1995-8.
10. Government A. The National Research Priorities and their Associated Priority Goals. [cited 2011 4/3/11]; Available from: http://www.dest.gov.au/NR/rdonlyres/AF4621AA-9F10-4752-A26F-580EDFC644F2/2846/goals.pdf.
11. Keuken D, Bindels, P., Klazinga, N. and Haafkens, J. A systematic approach for uptake of evidence on sex-specific issues in guidelines - a pilot study. Journal of Evaluation in Clinical Practice. 2010;Epub ahead of print.
12. Capodanno DaA, D. Impact of race and gender on antithrombotic therapy. Thrombosis and Haemostasis. 2010;104:471-84.
13. Wahlin A, Billstrom R, Bjor O, Ahlgren T, Hedenus M, Hoglund M, et al. Results of risk-adapted therapy in acute myeloid leukaemia. A long-term population-based follow-up study. Eur J Haematol. 2009 Aug;83(2):99-107.

14. Lo-Coco F, Ammatuna E, Montesinos P, Sanz MA. Acute promyelocytic leukemia: recent advances in diagnosis and management. Semin Oncol. 2008 Aug;35(4):401-9.

15. Rau R, Brown P. Nucleophosmin (NPM1) mutations in adult and childhood acute myeloid leukaemia: towards definition of a new leukaemia entity. Hematol Oncol. 2009 Dec;27(4):171-81.

16. Gordon R, Thompson, C., Cardan, J, Ecksening, G. Rosten, C. A costing study of blood and marrow transplantation services in NSW. Final report. : Centre of Health Services Development, University of Wollongong2009.