Viewpoint

Over-diagnosis and other crises facing evidence-based medicine

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Introduction

There is a crisis in 'evidence-based medicine' (EBM).[1] Reviewers and meta-analysts have become aware that much of their work may be futile because some investigators only publish selected results that favour their own point of view. Such reviews can only be reliable if there is access to all the raw data or if everyone is compelled to publish 'negative' results too. This is proving difficult and controversial.[2] The latest example is dabigatran, which was hailed as a safe advance that needs no coagulation monitoring. It seems that the reduced frequency of bleeding if there is coagulation monitoring was not reported.[3] There is also widespread uncertainty about the thresholds for treatment. This has been highlighted in the 'over-diagnosis campaign' to address a concern that many patients are subjected to harm without much benefit. Many see the problem as one of vested interest e.g. where those who gain from supplying a treatment will tend to advocate a low threshold for treating whereas those who wish to reduce costs or effort prefer to set high thresholds. The evidence needs to support what is best for the patient and gathered by those who care for them e.g. acute medicine physicians.

What is 'evidence' anyway?

'Evidence' is a group of facts that are made available to interested parties in order to justify or explain an opinion about a prediction and decision (or resolve a difference of opinion). This includes the patent's symptoms, signs and test results in support of each diagnosis and decision as well as published research. If such 'evidence' is to work then all parties must agree how the evidence is to be sought, recorded, interpreted and acted upon. If there is persistent concern despite the availability of the 'evidence' then the conventions of evidence have to be changed. In truth, there has always been an undercurrent of concern about the scope of EBM, so in some ways, things have come to a head.

Improving the conventions to avoid over-treatment

Thresholds for beginning treatment are often based on two standard deviations or some other cut-off. For example patients with 'Diabetic albuminuria' are often treated with an ACE inhibitor or an angiotensin receptor blocker (ARB) to prevent nephropathy if the albumin excretion rate (AER) is between 20 and 200 mcg/min. However, the risk of nephropathy at an AER of 19mcg/min (when no treatment would be given) is little different to the risk at 20 mcg/min (when treatment is given). Also, the risk of nephropathy does not appear to rise from its level at 20mcg/min until the AER is over 40mcg/min (this corresponds to about 30% of patients treated at present).[4] It would be more sensible to estimate the risk of nephropathy at the patient's actual AER value and the proportion benefiting at this level if the patient is treated. The same approach can be taken with other test results e.g. troponin and d-Dimer values.

Avoiding over-diagnosis and under-diagnosis

Over-diagnosis occurs if a patient is labelled with a diagnosis when there is little prospect of that patient benefiting from that diagnosis but being harmed because of unnecessary anxiety or by an unhelpful treatment that causes adverse effects. The diagnostic criteria should be set so that all patients with little prospect of benefiting from any of the treatments directed at the diagnosis are excluded. Perhaps a diagnosis that cannot be excluded should only be confirmed if it can be shown that at least one treatment or advice has a clinically significant probability of helping the patient.

Reasoning by probabilistic elimination

Reasoning by probabilistic elimination plays a central role in medicine. It is used when formulating diagnostic criteria and when working through a differential diagnosis. For example, 'Diabetic albuminuria' depends on at least one of the criteria for diabetes mellitus being present and the AER being 20 to 200mcg/min on two out of three occasions (according to current criteria). However, it must also be shown that it is improbable that the patient has a UTI, congestive cardiac failure, hypertension, some form of nephritis, renal tract stone or tumour or orthostatic proteinuria. If there are no red cells in the urine on dipstick testing then this negative finding occurs commonly in patients with 'ARB preventable nephropathy' but less commonly in those with nephritis, renal tract stone or tumour, making the latter improbable and 'ARB preventable nephropathy' more probable. An overnight collection, a normal BP, no oedema, a normal heart size, a normal urine dipstick and a normal ECG probably eliminates the other conditions causing proteinuria. All these findings suggest that it is more probable that the patient will have 'ARB preventable nephropathy'. This combination of findings currently forms the diagnostic criterion for 'Diabetic albuminuria', so that when they are present

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then this diagnosis is assumed by convention to be 'certain'. However, there would be a case for moving the AER cut-off point up to 40mcg/min.

Ratios of sensitivities

It is the ratios of two sensitivities that were used in the above reasoning by probabilistic elimination to make some diagnoses or benefit from a treatment more probable and others less probable. The details of this reasoning are given in the Oxford Handbook of Clinical Diagnosis.[5] However, EBM currently assesses diagnostic tests using the likelihood ratio based on the 'sensitivity' divided by 'one minus the specificity'. 'Specificity' is useful when arriving at cut-off points for population screening but only has a limited role in day to day clinical reasoning. EBM should use ratios of sensitivities instead, like experienced diagnosticians.

Evidence-based summaries

The complete evidence for a patient's diagnosis and decision in an acute medical unit must also specify that patient's personal evidence in the form of the symptoms, signs and test results that support each diagnosis and treatment (see table 1). This is the justification trainees are asked to provide by consultants on post-take ward rounds and teaching them to put this in writing could provide many benefits. They can be provided with guidelines as to what they should include as evidence in such summaries and use these to write discharge summaries more quickly and with improved content. This evidence-based summary can also be shown to the patient or supporters who can then ask deeper questions about the harms and benefits before accepting or continuing a treatment.[6] It helps those who take over care to understand quickly what has been done already and why, thus improving continuity of care, the lack of which is a big worry.[7] It could also be used as a basis for each AMU to collect data to verify independently the reliability of licensing studies and for gathering more information (with appropriate funding support) to refine diagnostic and treatment criteria for the benefit of patients and their doctor's ability to help them.

Table 1. An evidence-based summary

Mr A B aged 55 retired policeman
PC: Central chest pain for 40 minutes

Positive finding summary:
Central chest pain for 40 minutes with jaw discomfort, sweating, and nausea. PMH of hypertension and type 2 diabetes mellitus. BP 138/84 on admission. ECG: T wave inversion S2, AvF, V4, and V5. BM 7.6mmol/l.

Evidence-based assessment and plan

1. ***?Unstable angina ?Non-ST elevated myocardial infarction (NSTEMI)***
   Outline evidence: central chest pain for 40 minutes with jaw discomfort, sweating and nausea, resolved on admission. ECG: T wave inversion S2, AvF, V4 and V5.

Other active diagnoses

2. ***Essential hypertension well controlled***
   Outline evidence: BP 138/84 on admission when taking bendroflumethiazide and irbesartan. U& E normal, CXR normal.
3. ***Type 2 diabetes mellitus well controlled***
   Outline evidence: Latest HbA1c 8.1% 6 months ago on biochem data base. BM = 7.6mmol/l on admission on metformin.
4. ***Diabetic microalbuminuria***
   Outline evidence: mean of 3 AERs = 103mcg/min 6 months ago on biochem data base, now on irbesartan.

Plan:

a. First Troponin I awaited, for 2nd troponin after 3 hours (for differential diagnosis 1)
b. Aspirin 300mg stat (for differential diagnosis 1)
c. Start Bisoprolol 5mg od (for differential diagnosis 1)
d. Start GTN spray PRN (for differential diagnosis 1)
e. Continue bendroflumethiazide 2.5mg od (for diagnosis 2)
f. Continue Irbesartan 300mg od (for diagnoses 2 and 4)
g. Continue metformin 500mg bd (for diagnosis 3)

Conclusion

The most obvious 'evidence' in AMU is the patient's symptoms, signs and test results that support each diagnosis and decision. A clear summary of this evidence in writing has a major potential for good. It would also support a fresh approach to gathering reliable research evidence to support the diagnostic reasoning and decisions of experienced consultants, their trainees and students.

Declaration of competing interests

Nothing to declare.

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