

ISSUES IN MEDICINE Prevention of infective endocarditis in developing countries – justifiable caution?

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The internationally accepted practice of prescribing prophylactic antibiotics to individuals at risk of infective endocarditis has come under scrutiny. There are no published high-quality randomised controlled trials of the intervention, but new insights have emerged. Bacteraemic episodes are common following simple activities such

as brushing teeth. Endocarditis following procedures is extremely rare, and systematic reviews of the evidence for prophylactic antibiotics have failed to demonstrate efficacy.

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In both Europe and the USA, guideline bodies have limited their indications for endocarditis prophylaxis. The UK has taken the bolder step of not recommending it at all, but clinicians are appropriately cautious in changing long-established practice. South Africa has a high burden of rheumatic heart disease and HIV, and inappropriate restrictions could have major consequences. However, in areas of high prevalence, it is equally concerning to continue with a practice that may have little benefit and some potential harm.

The CRASH trial¹ demonstrated that corticosteroid use in head injury was associated with increased mortality. It was estimated that 10 000 patients might have died over the previous few decades because of this intervention.² Clinicians had reasoned that although there was no clear evidence of benefit, short-term use seemed unlikely to cause harm. This trial serves as a sobering reminder of the fallibility of intuitive assumptions of benefit based on biological plausibility and weak evidence.

Recently, many guidelines on infective endocarditis (IE) prophylaxis have been revised. The National Institute of Health and Clinical Excellence (NICE) guideline from the UK does not recommend antibiotic prophylaxis in patients with predisposing cardiac conditions undergoing dental and non-dental interventional procedures.³ Other guidelines still recommend prophylaxis when the consequences of developing IE are expected to be most severe, or in patients at highest risk.⁴ These recommendations are based on differing interpretations and weighting of the same limited body of evidence.

The evidence

Dental and endoscopic procedures may cause transient bacteraemia.⁵ IE is sometimes preceded by an interventional procedure, and antibiotics given before such procedures reduce the frequency of positive blood cultures.⁶ Although their validity has been questioned,

antibiotics reduce the frequency of episodes of IE in some animal models.⁷

Bacteraemia detectable by blood culture may occur after more than 20% of toothbrushing episodes,⁸ with even higher frequencies in individuals with suboptimal dental hygiene.⁹ IE can develop despite prophylaxis.¹⁰ Extractions are often performed because of dental sepsis, and it is conceivable that the underlying condition produces more cumulative bacteraemic episodes than the treating intervention.¹¹

A 2004 Cochrane review, and a 2008 update,¹² failed to identify any blinded randomised controlled trials (RCTs) on IE prophylaxis but found 4 case control studies. Two studies^{13,14} were felt to be biased as information on antibiotic use was unavailable for more than 20% of the case patients. A third study included very low-risk patients.¹⁵ The remaining case control study¹⁶ did not support a protective effect of antibiotic use, and even pooling this with the two studies excluded because of bias did not show benefit.

Agha *et al.*¹⁷ pooled all 4 case control studies, regardless of their drawbacks, to derive a non-significant odds ratio (OR) of 0.46 (95% confidence interval (CI) 0.2 - 1.1). Although the effect size is large, benefit was again unproven.

The NICE economic model

The OR of 0.46 from the Agha model was used in the NICE economic model¹⁸ to provide an estimated 50% relative risk reduction. Most modelling of the cost-effectiveness of new medications would stop here. If efficacy – the denominator – is not demonstrated to exclude a null effect, then the cost-effectiveness ratio is undefined.

The risk of an individual with a predisposing cardiac condition developing IE after a procedure was set at 4.1 per million interventions. This rate appears to be derived from a calculation in a previous economic model¹⁹ that specifically addressed patients with mitral valve prolapse, and calculated its estimates based on work from the 1970s. In natural frequencies, the base case estimate of 4.1 per million is the same as 1 in 250 000, increasing to at most 1 in 10 000 for patients with prosthetic valves.

The probability of fatal anaphylaxis after oral amoxicillin was set at zero (no harm) in the model base case.

A multi-national study²⁰ (Hungary, Spain, India and Sweden) reported 6 (95% CI 2.4 - 15) cases of anaphylaxis per 100 000 individuals treated with oral amoxicillin. Mortality rates for amoxicillin-associated anaphylaxis are poorly defined, with concerns about under-reporting.²¹ For anaphylaxis in general, mortality is estimated to be less than 1%.²² Assuming amoxicillin-associated anaphylaxis is no different to other aetiologies, fatal anaphylaxis

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after oral amoxicillin might be expected in less than one in a million patients. An earlier cost-effectiveness study used a figure of 0.9 per million.²³

Model results – NICE

In the NICE base case analysis, 21 cases of IE would be prevented for every 10 million patients given prophylaxis in the presence of a predisposing cardiac condition. To prevent one death from IE, one would need to treat 2.5 million people. Using the same model, if ongoing prophylaxis of 50% efficacy is continued for a lifetime (mean of 1.5 dental procedures per year), the NICE group estimated a mean quality adjusted life year (QALY) accrual per person of 50 minutes over a 50-year time horizon. The cost per QALY was £204 000, which is well above the conventional NICE cut-off of £30 000 per QALY. The model was able to demonstrate cost-effectiveness for patients at high risk (e.g. those with prosthetic valves) but even then only using generous risk assumptions.

In the UK, scripts for prophylactic antibiotics for IE fell sharply after release of the NICE recommendations, without a significant alteration in IE incidence.²⁴ In the tangled terminology of non-inferiority studies, this early review excluded a rise in incidence of more than 9.3%, which was less than the pre-set value of 15% (determined by background data fluctuations). An alternative explanation for the unchanged rate might be that high-risk patients in the UK continue to be prescribed antibiotics despite the new recommendations.²⁵

Variations in international guidelines

The French IE prophylaxis guideline of 2002²⁶ was followed by a British Antimicrobial Society report in 2006,²⁷ and the American Heart Association guideline of 2007.⁴ In 2008, NICE²⁸ suggested the practice be suspended completely. In 2009, the European Society of Cardiology still recommended prophylaxis for high-risk individuals in line with the AHA guidelines.²⁹

A further variation arose in the Australasian guidelines,³⁰ where prophylaxis was still recommended in 'Indigenous Australians' with rheumatic heart disease, based on expert opinion that the condition was more severe in this group.

The published debate

There is now almost a decade's worth of lively commentary following common themes that can be grouped according to shortcuts and pitfalls in our thinking (the taxonomy of heuristics and biases):^{31,32}

- 1. Denial of any evidence** – statements suggesting that in the absence of RCTs, decision making is essentially arbitrary. In one instance, there was outright refusal even to read the evidence.³³ Evidence-based medicine (EBM) advocates using the best available evidence, but acknowledges that sometimes only observational studies are available.
- 2. Causal schema bias** – a tendency to be more comfortable with explanations incorporating a causal narrative (bacteraemia causes IE; antibiotics reduce bacteraemia; therefore antibiotics reduce endocarditis). This 'coherent' explanation is appealing to many clinicians.³⁴
- 3. Group think** – adopting beliefs shared by a group. A shared and strongly endorsed guideline gains credibility.³⁵
- 4. Fundamental attribution error** – ignoring alternative explanations for endocarditis after an intervention.³⁶
- 5. Honouring sunk costs** – because we have 'always' done this, it may be worth continuing to invest in the strategy.³⁷
- 6. Availability heuristic** – vivid cases override balanced recollection (we remember the active sportsperson who developed an

IE-associated stroke after a tooth extraction,³⁸ but fail to recall the many other patients who didn't).

7. Ad hominem arguments – disparaging the individual presenting the argument.³⁹

8. Risk aversion and asymmetrical value assignments (valuing potential losses higher than gains) – potential gains from limiting the overuse of antibiotics and avoiding anaphylaxis are seen to be less tangible than the potential occurrence of an avoidable episode of IE.⁴⁰

Practical belief revision

Coherence-correspondence models of thinking may explain some of the resistance to paradigm shifts described by Kuhn.⁴¹ Coherence emphasises the existence of a logical explanatory narrative whereas correspondence focuses more on empiric observation, with greater tolerance for gaps in understanding. Both models have led to important advances in medicine.⁴² Of 124 articles in one journal in 2009, 13% were considered 'reversals' – new higher quality trials that contradicted current practice.⁴³ Initial adoption on the basis of physiological principles (coherence) rather than sound evidence was a common theme among the reversals.

One cognitive crutch recognises the limited half-life of medical truth.⁴⁴⁻⁴⁷ We might change our learning mindset, which from medical school days has always been acquisitive (What new things did I learn today?) to include the countervailing question (What mistaken belief have I relinquished today?).

Shifting between the coherence and correspondence models may also be of value. In the current example, paying attention to the cracks in the smooth narrative of biological plausibility can be punctuated by a review of the (very limited!) numeric information.

Local applicability

When international guidelines looking at the same body of evidence make differing recommendations, it becomes particularly important to achieve local clarity. It may be reasonable to argue that developing countries in Africa lack the resources to re-explore the evidence and develop their own guidelines, although adaptation of international guidelines may be feasible.⁴⁸⁻⁵⁰ Such adaptations should acknowledge local factors, e.g. the high prevalence of rheumatic heart disease and HIV, and potentially greater IE severity owing to late presentation and differing causes of valvular damage. However, these factors affect policy effectiveness rather than efficacy. If IE prophylaxis works, then a policy of using it will benefit more individuals in areas of high prevalence and severity; if it doesn't work, and is being given to many people, there is potential for more harm.

Future directions

Further debate culminating in a consensus position on IE prophylaxis in developing countries would be helpful. Prophylaxis has modest – if any – value, but a trial six times the size of CRASH would be needed to establish clearly whether it does more good than harm. It seems unnecessary to retain the traditional recommendations when NICE, AHA and ESC have already revised their stance, but changing established belief takes time. A pragmatic approach might be to emphasise both good dental hygiene and early recognition and treatment of established endocarditis, and to de-emphasise reliance on an intervention of uncertain benefit.

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