SED QUIS CUSTODIET IPSOS CUSTODES?

"Who is to guard the guards themselves?" is the translation of this quote from Juvenal’s Satires. It was brought to mind by a thoughtful article by Neville Goodman [1] who asks “who will challenge evidence-based medicine?” Goodman is concerned that EBM is in danger of becoming an unchallengable orthodoxy following its own political agenda.

Tough words, and possibly rightly tough. The underlying theme is that there is an ideological difference of opinion about EBM, and that there is probably no evidence that EBM provides better medical care in total than whatever we choose to call whatever went on before. After all, even EBMers themselves disagree all the time about the rights and wrongs of the technical bits of meta-analysis. EBM seems to be so statistical that you need a brain the size of a small planet even to begin to understand it. And finally, proponents ignore seemingly valid criticisms.

Real world motifs

Most of us live in a real world where these arcane arguments have little value. What we need are tools to help us get the job done best, fastest, and cheapest (probably in that order). We want a sort of holy trinity, involving evidence of effectiveness, value for money, and quality improvement.

Can evidence help us, or should we eschew everything called EBM because it may itself have problems? When EBM was defined [2] it was defined thus: “evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients”.

Nothing wrong in that. Stated in a slightly different way, this is how Goodman’s article also begins. It’s not the use of evidence per se that irritates Goodman, but the special meaning that seems to derive from systematic reviews and meta-analyses, as if they have some magical power.

Layered knowledge

Meta-analyses may not always agree. This issue of Bandolier examines some of those disagreements in cholesterol lowering on page 2. But the upshot is that the meta-analyses generally do agree, and most of those not agreeing had included non-randomised trials — a no-no for therapeutics trials unless that is the only information you have.

So on page 6 we have a meta-analysis of prophylactic antibiotics after basilar skull fracture. Only two of 12 included studies were randomised, and those two were small. So the bulk of the world’s information comes from non-randomised studies. You have to make a decision whether it is the policy for your institution, or for this particular patient, to prescribe prophylactic antibiotics against possible meningitis. There is a balance of benefit and harm to be struck. Do you want this information (because that’s all there is), or none?

Tricky, isn’t it. Using only randomised studies makes sense when there are lots. It may not make sense when there are few or none, especially when they all say much the same thing. Having them in a meta-analysis is better than not knowing that the evidence is there, but doesn’t make using the evidence any easier. It’s the difference between a rule and a tool.

And if you want to try to make a difference in practice, you may have even less evidence than that. Look at the book review for the Promoting Action on Clinical Effectiveness (PACE) programme (page 8). No randomised trials at all – just good examples of how others have done it, plus experience. But that’s evidence too, just a different type, with a different weight, to be used differently.

Sticks and stones

We look at crystal ball evidence relating to falls and hip fractures on pages 2 to 5. Different sorts of evidence, with models of future health care needs – yet another sort of evidence. What we need to do is assess the evidence on risks, try and figure out who is most at risk of a fall or fracture, and try the various ways that have been shown (with various types of evidence) to be effective in preventing falls and fractures.

Continued on page 8/ col 2
META-META-ANALYSIS

To add to the “King Kong versus Godzilla” arguments about whether a single large randomised trial is better than a meta-analysis of smaller trials we now have to add problems of discrepancies of meta-analyses themselves. The study of the value of cholesterol lowering and the effects on coronary heart disease [1] is the first Bandolier has found which looks at the results of different meta-analyses and tries to prise out nuggets of philosophical gold.

Is cholesterol lowering beneficial?

Twenty-three separate meta-analyses were found. Outcomes examined were those of total mortality, cardiovascular mortality and nonfatal cardiovascular disease. As the Table shows, the results of the analyses overwhelmingly supported cholesterol lowering for reduction in nonfatal cardiovascular disease and cardiovascular mortality, but not total mortality.

Garbage in – garbage out?

Of the 23 analyses, eight were not supportive of benefit. Of those eight, three included non-randomised studies, and one didn’t state whether it did or not. None of the 15 studies supportive of benefit included non-randomised studies. So here is one lesson learned again: for treatments, including non-randomised studies has to be justified.

The supportive meta-analyses were also generally better designed. Not only did they include only randomised studies, but had more explicit exclusion criteria that allowed a more direct evaluation of the effects of cholesterol lowering without confounding factors. None of the non-supportive meta-analyses included authors with meta-analytic expertise. An interesting post-hoc observation was that only 4 of 10 analyses in British journals were supportive, compared with 11 of 13 in non-British journals.

Elephants and pygmies

Faced with an elephant, half a dozen blindfolded pygmies will each come out with a different description of what it is. And when it comes to knowing the truth, blindfolded pygmies just about sums up where each of us is. The answers may be simple, but it is the questions that are difficult.

So if you want to know the truth about cholesterol lowering, the spread of questions my be as wide as whether cholesterol lowering reduces overall mortality to which cholesterol lowering regimen is best for my particular patient? The way in which information is gathered to provide the knowledge-base to try and answer each of these questions will be different.

So we should praise the fact that so many meta-analyses have been done, not bury meta-analysis because so many have been done. The problem, though, for the busy practitioner, is to have simple tools to hand to make sure that the many clinical decisions made every day are made as correctly as possible. For treatments, those tools will come best from systematic review and meta-analysis. How long before we see then first meta-meta-meta analysis?

Reference:

People are living longer, and the baby-boomers of the late 1940s and early 1950s are well into their “Sanatogen” years. Living longer does not mean sitting quietly in a corner, and the over 50s, over 70s, and even over 80s are travelling more than ever, and are more active then ever. Their health may be at least as good, if not better than ever before.

But age brings some physical deficits, and a downside of all this is that falls are becoming more common, and the risk of injury from falls is increasing. There is evidence that about a third of the over 65s living in the community and half those living in institutions fall every year. These trends, and some projections for the future, come from splendid studies of falls and hip fractures in Finland [1, 2].

**INJURIES FROM FALLS ARE INCREASING IN OLDER ADULTS**

<table>
<thead>
<tr>
<th>Event</th>
<th>Number of meta-analyses</th>
<th>Favours treatment</th>
<th>No difference</th>
<th>Favours control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal cardiovascular disease</td>
<td>12</td>
<td>12</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>15</td>
<td>10</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Total mortality</td>
<td>18</td>
<td>3</td>
<td>14</td>
<td>1</td>
</tr>
</tbody>
</table>

**Study**

Because they do these things well in Scandinavia, and Finland in particular, there is a system which identifies all fall-induced injuries resulting in hospital admission, or death, in the whole Finnish population (about five million) with a high degree of accuracy. A fall was defined as a descent from one metre or more. Only the over-50 population was included, and only hospital admission and not emergency department visits not requiring admission. Injuries included fractures, soft tissue bruises and contusions, and soft tissue wounds and lacerations. Data were available from 1970/1, and were analysed up to 1995 (falls) and 1997 (hips).
Results

From the mid-70s onwards there was a continual year-on-year increase in the number of fall-induced hospital admissions in men and women (Table). The average annual increases were 12% for women and 10% for men. The age-adjusted incidence increased from 494 to 1398 per 100,000 between 1970 and 1995, a 183% increase.

The total number of deaths each year also increased (Table). The average annual increases were 2.4% for women and 4.9% for men. The age-adjusted incidence in fall-induced death was unchanged over most of the time between 1970 and 1995.

The authors projected the trends in this study forward into the next century. Assuming that the linear trend continued to increase, and putting that with the projected increase in the population of over 50s in Finland, the number of fall-induced hospital admissions would peak at about 61,000 fall-induced hospital admissions and 19,000 broken hips in about 2030 – about three times the burden in 1995/7 (Figure).

Implications for the UK

There is every reason to think that these figures for Finland are, if anything, conservative. What would these figures mean if they were applicable to the UK?

The UK population is about 12 times that of Finland, so on a nation-wide basis the burden would be expected to be about 430,000 in 2010 and 730,000 in 2030, of which about 130,000 and 230,000 would be fractured hips. At its peak, and making a simple assumption that each hospital visit would be about three days, this is equivalent to about 15 400-bed hospitals occupied full-time.

The average primary care group (PCG) with 100,000 population has now about 35,000 people aged over 50 years. If the Finnish incidence is approximately that in the UK, that means there are now 420 people admitted to hospital in any one year due to a fall, and 140 will be hip fractures. By 2030 that could rise to 1,200 falls needing a hospital admission, with 400 hip fractures.

These are big figures of public health and resource concern. About 5% of falls result in a fracture, and serious injury in another 5-10%. The severity of injury and incidence increases with age, and the crystal ball here is telling us of major problems to come.

Bandolier 20 reported on a meta-analysis on randomised studies in hospitals and community-dwelling elders in the USA.

Reference:
RISK FACTORS FOR HIP FRACTURE IN WOMEN

One of the most serious consequences of a fall in older persons is a hip fracture. Bandolier has previously highlighted the evidence (issues 25 and 49) that few people who have a fractured hip regain independent living, and the majority either die or have major disability as a consequence. Clearly a situation where more people fall will give rise to more people having a fractured hip.

Risk and reasons

While risk factors for hip fracture is a complex area, there is a review [1] giving a good overview of the problems, and beginning to outline the basis of a strategy for tackling future increases in the size of the problem. The factors in hip fracture risk are many – some related to the skeleton, others related to the risk of falling, and some more complex factors intermediate between both (Figure 1 and Table 1).

While this review brings in a number of different studies to highlight each particular risk factor, the key study is a large examination of risk factors in 9,500 white women in the USA [2]. This examined women of at least 65 years and followed them every four months for a mean of over four years.

A searching statistical analysis identified the key factors, out of many, which were associated with increased risk of hip fracture (Table 2). These were combined with the bone density at the heel to demonstrate just how some women could be identified at being particularly at risk. Fifteen percent of women had at least five risk factors, and had an incidence of hip fracture of 19 per 1000 woman years – or about a 2% risk every year. The 47% of women with two or fewer risk factors had a risk of 1 per 1000 woman years – or

Table 1: Risk factors for hip fracture in women

<table>
<thead>
<tr>
<th>Skeletal related risk factors</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral neck geometry</td>
<td>Longer hip axis (trochanter to pelvic rim) increases risk of fractured neck of femur</td>
</tr>
<tr>
<td>Microarchitecture</td>
<td>Bone strength is associated with increased risk, and can be measured with broadband ultrasound attenuation. Risk increased about 7-fold in women above versus below median heel ultrasound measures</td>
</tr>
<tr>
<td>Mineral structure</td>
<td>Fluoride may increase bone strength</td>
</tr>
<tr>
<td>Bone turnover</td>
<td>Biochemical markers of increased bone turnover may be related to increased risk</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fall related risk factors</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuromuscular function</td>
<td>Inability to rise from chair unaided five times, or on feet for fewer than 4 hours a day, inability to heel-to-toe walk all associated with increased risk</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>Poor mental health is a risk factor</td>
</tr>
<tr>
<td>Medications and drugs</td>
<td>Sedative use, long-acting benzodiazepines increase risk. Caffeine consumption increases risk</td>
</tr>
<tr>
<td>Fall mechanics</td>
<td>Fall on side highly increases risk</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complex risk factors</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Most hip fractures occur after 75 years</td>
</tr>
<tr>
<td>Genetic background</td>
<td>Maternal hip fracture increases risk. Some genetic markers are being studied which might be useful predictors of increased risk</td>
</tr>
<tr>
<td>Body size</td>
<td>Being tall at a young age, being thin, or losing more than 10% of body weight since age 25 all increase the risk, while gaining weight may reduce risk</td>
</tr>
<tr>
<td>Physical activity</td>
<td>High levels of physical activity, especially walking, are associated with reduced risk of fracture</td>
</tr>
</tbody>
</table>
about 0.1% a year. When combined with bone density the risks were increased even further with those with the lowest bone density (Figure 2).

So what can we do?

It comes down to preventing hip fractures and preventing falls. For hip fractures the targets for interventions are shown in Figure 3. For people with skeletal problems, there are a number of therapeutic interventions – from bisphosphonates, hormone replacement therapy, to the use of hip protectors, though exercise may be of importance also. The key is to identify those people most at risk.

There is a Cochrane review of interventions to reduce the incidence of falling in the elderly [3]. This showed, on a limited number of trials with about 500 patients, that exercise alone or in conjunction with a health education programme were ineffective in protecting against falling. There was some evidence that interventions targeting multiple identified risk factors in individual patients might be effective.

Another important area to examine is that of prescribed drugs. What appears to be the first of a series of drugs and falls in over 60s [4] identifies many classes of psychotropic drugs as having an association with falls in non-randomised studies. Though frustratingly without any data other than odds ratios and relative risks, it reported that falls were common. For instance, in seven prospective studies of community-dwelling older people the annual incidence of falls ranged between 29% and 52%, and in two long-term studies looking at psychotropics the incidence of falls over six months was 58%.

We know that many drugs – antihypertensives, for instance, may have dizziness as an adverse effect. It is likely that many of the medicines prescribed for older people for very good reasons may contribute to falls – an additional source of harm.

So no simple answer, but much food for thought. Bandolier would love to know of any practical studies which have set out to reduce falls in older people at particularly high risk, apart from that in Bandolier 20. A recent report [5] suggests that screening for fall-related risk factors need take only about five minutes. These, though, are for women. Falls and hip fractures in men could do with some more attention to derive risk factors for them, also.

References:


Figure 3: Targets for reducing hip fracture rates in women

<table>
<thead>
<tr>
<th>Skeletal targets</th>
<th>Fall related targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates</td>
<td>Oestrogens</td>
</tr>
<tr>
<td>Calcium</td>
<td>SERMs</td>
</tr>
<tr>
<td></td>
<td>Tibolone</td>
</tr>
<tr>
<td></td>
<td>Vitamin D</td>
</tr>
<tr>
<td></td>
<td>Hip protectors</td>
</tr>
<tr>
<td></td>
<td>Increased activity?</td>
</tr>
</tbody>
</table>
PROPHYLACTIC ANTIBIOTICS DO NOT PROTECT AGAINST MENINGITIS IN PATIENTS WITH BASILAR SKULL FRACTURE

With a basilar skull fracture there is potential for exposure to pathogens from the respiratory tract or ear, and thus an increased risk of meningitis. There may also be leakage of the cerebrospinal fluid which could facilitate this. The logic therefore is to give antibiotics prophylactically to prevent meningitis. That this is not an effective strategy is implied by a new meta-analysis [1].

Study

The review sought out published studies on the use of prophylactic antibiotics for prevention of meningitis after basilar skull fractures, but using only MEDLINE. They found 14 studies, two of which had no extractable data. Of the other 12, nine were retrospective, one a combined retrospective and prospective study, and two were prospective and randomised. Three studies were in children. A wide variety of different antibiotics were used, were started within 72 hours of hospital admission and continued for between three days to one week after CSF leakage resolved.

Results

In the 12 studies (1,241 patients) in which there was extractable data on cases of meningitis, 5.3% (38/719) of those given antibiotics had meningitis, compared with 7.1% (37/522) of those who did not have prophylactic antibiotics (Figure). The odds ratio was 0.88 (95% CI 0.54 to 1.42). The two randomised studies had only 95 patients, and there were two cases of meningitis in the control group, and none in the treated group. Sub-group analyses showed no significant differences for patients with skull fracture and CSF leakage, or in children.

Comment

This is one of those really difficult reviews, and it is worth using it as a tutorial as to how we might evaluate evidence:

♦ The review itself can be criticised, perhaps, for not trying harder to find other trials by searching other databases, including the Cochrane Library, a repository of over 200,000 controlled trials.
♦ The data in the review can be criticised because only two of the 12 studies were prospective and randomised (and they were small).
♦ The results of the data included showed no statistically significant benefit for antibiotics. Yet the meningitis rate was almost 2% lower with antibiotics than without. The NNT was 55, with a confidence interval from 22 to –106. In other words, although the confidence interval included antibiotics having a greater risk of meningitis, much of its range was in the area where antibiotics did actually benefit, including benefit in 1 in 22 patients.
♦ There was no analysis of adverse effects from antibiotics. We had no information which might have balanced small benefits against additional harm.

What we are left with is the uncertain estimate that a percent or so of meningitis cases following basilar skull fractures may be prevented by prophylactic use of antibiotics. But we don't know which antibiotic might be best, nor how long antibiotics should be given. We do know that the ultra-large clinical trial needed to resolve the uncertainty will probably never be done, so in the meantime we have to manage as best we can.

Reference:
METHADONE MAINTENANCE INTERVENTIONS

Methadone has been around as a morphine-like opioid for about 50 years, and since the 1960s has been used as a type of legal opioid substitution therapy. This is a difficult area, and the question perennially seems to be “why bother?”. A systematic review has sought to try and answer this difficult question.

**Study**

A thorough search strategy sought out papers examining people with a diagnosis of opiate-dependent substance abuse without any concurrent psychiatric diagnosis. Experimental designs in which methadone maintenance was compared to control – heroin-dependent individuals not on methadone maintenance, and those having a pre-post design. Outcomes were illicit opiate use (by drug analysis and self-reporting), HIV risk behaviour, and various assessments of criminal behaviour.

Eleven studies were found, and it was demonstrated that different trial designs made no difference to outcomes. The results were presented in a highly statistical way, but they did display sufficient results to show the percentage of patients in the methadone maintenance programmes who decreased risk behaviours, and to compute a notional number needed to treat. These are shown in the Figure.

For instance, illicit opiate use was reduced by 67% by methadone maintenance, with a NNT of 2.9. For drug-related criminal behaviour, 85% would be expected to reduce this, with a NNT of 1.4.

**Comment**

This is a very difficult study to follow. It does not give much information on trial design, and, for instance, gives only information on those people who stayed in the studies for six to 12 months and we are not given drop-out rates. The results may be applicable only to those opiate-dependent individuals who both seek treatment and remain in treatment. What we have here, though, is an important benchmark against which future treatments, like intravenous anasthetic withdrawal, could be compared, and proper studies designed.

Reference:

**Figure**: The percentage of individuals seeking treatment and remaining in a methadone maintenance programme who would demonstrate a reduction in various types of behaviour. Numbers at the end of the bars are the computed numbers needed to treat for one individual to benefit with treatment who would not benefit without treatment.
CARE

One of the most exciting new developments in e-medical research is that on the Clinical Assessment of the Reliability of the Examination, which is a collaborative study of the accuracy and precision of the clinical examination. If you want to know all about it, it’s Internet address is http://www.carestudy.com/.

The all-too-common study of the accuracy and precision of the clinical examination comprises four experts examining 40 patients, the latter selected to confirm the biases and reputations of the former. The pioneering work of the US-Canadian Co-operative Research Group on the Clinical Exam reversed this trend, but even it has faced formidable problems in participation rates and patient numbers.

A group of Canadians currently working at the NHS R&D Centre for Evidence-Based Medicine in Oxford are trying to solve the problems of both numbers and clinical applicability by catalysing the execution of large (>100 clinicians enrolling >1000 patients), simple (<2 minutes per patient and <15 patients per participating clinician), fast (<2 weeks, with automatic data entry via the Internet) studies of the accuracy and precision of specific elements of the history and physical examination. Their initial efforts led to >160 clinicians from 20 countries joining CARE.

CARE works like this:

♦ Anybody, at any stage of training or experience, can join the enterprise just by signing up for it. The only pre-requisites are an interest in the clinical examination, ACCESS TO THE INTERNET (for that’s how we’ll do our work), and well-developed sense of humour.

♦ Individuals in the collaboration nominate symptoms and signs they’d like to validate (or debunk!) and broadcast them to the membership.

♦ Members who share an interest in this same topic come together electronically as Investigators, and proceed to design and debug the protocol and offer it to the entire collaboration.

♦ The membership-at-large vote with their precious time, enrolling just a few patients each and reporting their results electronically.

♦ Analyses are shared, PowerPoint summaries posted, and papers published (with authorship by the Investigators, on behalf of CARE, and acknowledging every member who entered the requisite number of patients).

The first study is now undergoing data analysis and has evaluated the validity of a 2-minute examination in ruling-in/out chronic obstructive airways disease. Nominations for other studies are flooding in. Membership already is over 165, but the target is at least 1000 colleagues around the world. The objectives are good science, better examinations, and lots of fun. The people running the show are Sharon Straus, Finlay McAlister, and David Sackett.

Use the address above to get in touch, or follow their progress in adding science to the art of diagnosis.

Book Review


This is a book that should be on the shelf of everyone at director level in a health service. It’s journey to the shelf should be via well-thumbed pages and a split spine showing that it has been read and the contents digested. It is a synopsis of the 16 projects in the Promoting Action on Clinical Effectiveness (PACE) programme, which itself grew out of GRIP projects (see Bandolier 1,3,4 and 8).

The key message is that promoting effectiveness is a messy process requiring facilitation, flexibility and the ability to coax and cajole to drive the work forward. It also takes time, may be expensive on the steep part of the learning curve, and needs some lateral thinking, but can be highly rewarding. Examples given are just terrific – pointing out some of the often complicated ways that have to be used to make progress. But once you’ve read about them, you too have learned the hard lessons. So you too can get stuck in, knowing how to do it.

Pulling the lessons together – identifying the bricks in the wall of progress – is also accomplished, with simple lessons of how to survive and thrive in the complicated systems we call the NHS. Any NHS executive who hasn’t read this book is not doing his/her job, because clinical effectiveness is the core of what the NHS is all about.

Ultimate agreement

This is not to dismiss Goodman’s criticisms. Bandolier agrees with most of them. In the Oxford Dictionary “cartel” is described as “a combination of business firms to control production, marketing, etc. and avoid competing with one another”. There is a suspicion that there is an EBM cartel, which likes things its way, and where disagreement is suppressed. That would be bad if it were true. It is only by trying to do things differently that we learn that the rocks of yesteryear are the sands of today. More meta-analysis, and more disagreement, but with a constructive motif is what we need. And there’s nothing wrong, and everything right, with a great big dollop of criticism, plus a regular changing (or checking) of the guards.

Reference: