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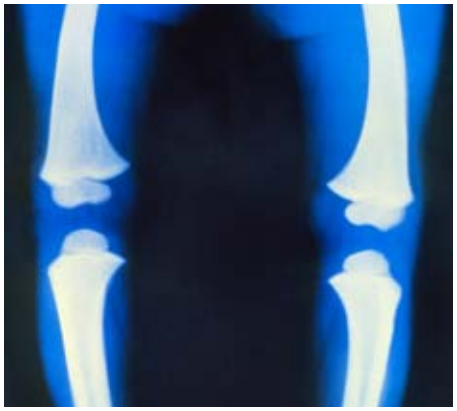
Vitamin D: some perspective please

Health claims are ahead of the evidence

Nicholas C Harvey senior lecturer and honorary consultant rheumatologist
Cyrus Cooper director and professor of rheumatology, MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton SO16 6YD, UK nch@mrc.soton.ac.uk

Vitamin D deficiency has been associated with an ever expanding list of diseases, and with this have come almost tonic-like claims for vitamin D supplementation. In observational studies, low vitamin D status has been associated with increased risk of multiple sclerosis, type 1 and type 2 diabetes, cardiovascular disease, colon cancer, breast cancer, autoimmunity, and allergy.[1] The UK government has advised that all pregnant women, and children under 5 years, should take 400 IU vitamin D daily; a recent news story, however, reported a survey conducted by a charity which suggested that only 26% of pregnant women and 46% of healthcare professionals are aware of these guidelines.[2] The most recent musculoskeletal trend seems to be the attribution of childhood problems such as Blount's disease and slipped femoral epiphyses to vitamin D deficiency and the incorrect conflation of rickets with low serum calcidiol (25-hydroxyvitamin D_3) concentrations.[3] So are health professionals causing ill health through their lack of awareness and advocacy of vitamin D supplementation?

The high profile news coverage and the enthusiastic promotion of the results of observational studies as though they proved causality might lead the undiscriminating observer to think so. We think, however, that some perspective is needed. That vitamin D deficiency may cause childhood rickets is indisputable. Rickets was widespread in the white population during the industrial revolution, but the current increase in rickets and other manifestations of vitamin D deficiency, such as neonatal hypocalcaemic tetany, is seen mostly in the dark skinned population of the United Kingdom. Serum calcidiol concentrations are lower in dark skinned than in white UK populations,[4] independent of latitude. Among Asian women in the south of England median serum calcidiol concentrations were 24.9 nmol/L in summer and 16.9 nmol/L in winter, whereas in white women the corresponding values were 62.5 nmol/L and 39.9 nmol/L. The proportion of women with low concentrations of calcidiol across the year (<40 nmol/L) was 10-49% in white women and



BIOPHOTO ASSOCIATES/SPL

Most relationships with vitamin D are much less clear than rickets

89-91% in Asian women.[4] The marked disparity in the incidence of clinical disease and severity of vitamin D deficiency between ethnic groups in the UK seems to have been overlooked in much lay and scientific reporting. This is not to say that we should ignore moderately low concentrations of vitamin D in up to 49% of the white population; the question is whether it is a health problem.

These differences also beg the question of how to define normality. Studies have reported the serum calcidiol concentration at which parathyroid hormone reaches a plateau to be between 25 nmol/L and 125 nmol/L, making it difficult to deduce a functional definition of vitamin D deficiency.[5] Similar uncertainty surrounds estimates derived using fractures, bone turnover markers, and fractional calcium absorption.[6] A recent postmortem based study found that a substantial proportion of people with serum values less than 25 nmol/L had normal bone histology.[7] These observations suggest that it is difficult to extrapolate from a low serum vitamin D status even to bone disease with any degree of certainty on an individual basis. Indeed, a recent randomised controlled trial suggested that high dose vitamin D supplements might even increase the risk of fracture.[8]

Furthermore, much of the evidence linking low vitamin D status to non-bone outcomes has been derived from observational studies and is therefore subject to a range of interpretational difficulties (as recognised by the recent Institute of Medicine report). These include reverse causality (disease may cause reduced exposure to sun), confounding (low physical activity may cause low vitamin D, obesity, and increased risk of diabetes), classification bias (vitamin D status defined in terms of diet, not blood concentrations, which correlate poorly with nutritional intake),[9] and differences in assay methods.[10] Most basic science studies use the active form of vitamin D—calcitriol (concentrations of which are tightly regulated in vivo)—and the results of its pharmacological action on end organs is conflated with an effect of supplementation. In addition, reluctance to publish null or negative findings tends to bias the literature in favour of a positive effect. The result is that when the benefits of vitamin D supplementation suggested by such studies have been tested in randomised controlled trials they have often not been confirmed. A good example is chronic soft tissue pain, where observational studies showed an inverse association between serum calcidiol concentration and level of pain, but randomised controlled trials found no benefit from supplementation.[11] Finally, the safety of population strategies incorporating vitamin D supplementation in large numbers of people over long periods of time also needs clarification.

In an age of evidence based medicine, we need to prove the benefit, lack of benefit, or even harm of our interventions. In addition to detailed laboratory based mechanistic studies and research to validate appropriate biomarkers for adequacy, large well designed randomised controlled trials with long term follow-up are urgently needed to clarify the role of vitamin D and the usefulness of supplementation.[12] Only with such investigations will we be able to navigate through the mass of literature, both lay and scientific, that enthusiastically promotes vitamin D as a cure for almost all modern maladies.

Competing interests: Both authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; NCH is lead-principal investigator and CC is chief investigator of the MAVIDOS Maternal Vitamin D Osteoporosis Study, a large ongoing double blind randomised placebo controlled trial of vitamin D supplementation in pregnancy aimed at optimising bone health in offspring.

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- Clinical Review: Clopidogrel in acute coronary syndromes (*BMJ* 2009;338:b1180)
- Research: Ticagrelor versus clopidogrel in patients with acute coronary syndromes intended for non-invasive management (*BMJ* 2011;342:d3527)

Prescribing proton pump inhibitors with clopidogrel

PPIs seem not to cause myocardial infarction in users of dual antiplatelet treatment

Laura Ellyn Targownik associate professor of medicine, section of gastroenterology, Department of Internal Medicine, University of Manitoba, Winnipeg, MB, Canada, R3N 0V6 targowni@cc.umanitoba.ca

STEVE PERCIVAL/SPL

Add a PPI for all patients using dual antiplatelet drugs

In a linked research paper, Douglas and colleagues analysed whether proton pump inhibitors (PPIs) influence the risk of adverse cardiovascular outcomes in users of aspirin and clopidogrel.[1] The use of aspirin and clopidogrel, or dual antiplatelet treatment, is currently the standard of care for the prevention of coronary stent thrombosis.[2] Although use of dual antiplatelet therapy is associated with an increased risk of gastrointestinal haemorrhage,[3] this risk can be greatly reduced through the concomitant use of a PPI.[4] However, clinicians have become worried about using PPIs with dual antiplatelet treatment after the discovery that PPIs may interfere with clopidogrel mediated platelet inhibition through inhibition of the CYP2C19 cytochrome pathway, which is necessary for activation of clopidogrel.[5] In addition, the findings of observational studies suggest that PPIs are associated with an increased risk of adverse cardiac outcomes in users of dual antiplatelet treatment.[6] However, given the inherent biases in observational datasets, it is unclear whether this association is causal. Because a randomised controlled trial of sufficient statistical power is unlikely to be performed to establish definitively whether PPIs interfere with the ability of clopidogrel to reduce the risk of cardiovascular events, new pharmacoepidemiological strategies that mitigate against the effects of any systematic biases must be sought.

Douglas and colleagues performed a series of complementary analyses of data from the United Kingdom General Practice Research Database (UKGPRD) to delineate whether PPIs influence the risk of adverse cardiovascular outcomes in users of dual antiplatelet treatment.[1] The authors first used a standard Cox proportional hazards model to assess the risk of recurrent myocardial infarction in people who did and did not use PPIs who were receiving aspirin and clopidogrel. They found that use of PPIs was associated with a significant risk of myocardial infarction (hazard ratio 1.35, 95% confidence interval 1.26 to 1.45). However, people who are prescribed a PPI are probably at higher underlying risk of myocardial infarction than those who are not given a PPI. For example, obese people may be at higher risk of myocardial infarction and are also more likely to have gastro-oesophageal reflux disease and to take a PPI for this indication. Although a Cox proportional hazards model can control for known confounding variables that may be linked to both PPI use and myocardial infarction, it cannot adjust for the effects of factors that were not measured. In addition, it cannot adjust for the effects of unknown characteristics that may be associated with PPI use and that also increase the risk of myocardial infarction. Thus, residual confounding may lead to the detection of an association between PPI use and myocardial infarction even if no causal association exists.

The problem of residual confounding can be rectified by performing a within subject analysis, where subjects function as their own controls, because this eliminates many systematic differences between the two groups. When Douglas and colleagues performed such an analysis on this dataset they found no significant association between PPI use and myocardial infarction (0.75, 0.55 to 1.01) when the incidence rate of myocardial infarction in people taking aspirin and clopidogrel was compared between periods of concomitant PPI use and periods of non-use. The researchers performed similar analyses for other known CYP2C19 inhibitors and found no associations with myocardial infarction in the within person analysis despite finding a significant association between their use and myocardial infarction in the proportional hazards model. They concluded that once residual confounding is minimised no association exists between myocardial infarction and PPI use in people who use dual antiplatelet treatment. These results lend support for the use of PPIs and dual antiplatelet treatment to prevent gastrointestinal haemorrhage.

Although the within person analysis is a useful approach its validity hinges on the assumption that participants' underlying risk of myocardial infarction does not vary over time and that they are no more or less likely to be prescribed PPIs if the risk of myocardial infarction increases. Although PPIs may be given if prodromal symptoms of myocardial infarction are mistaken for reflux or dyspepsia, this would lead to a stronger association between PPI use and myocardial infarction, which was not the case. The results of this analysis also agree with higher quality prospective analyses in which the use of PPIs was not associated with an increase in myocardial infarction in people who used dual antiplatelet drugs. Moreover, although studies have shown that activation of clopidogrel is reduced in patients with lower CYP4530 2C19 activity,[7] current evidence suggests that there is no definite association between low CYP4530 2C19 activity and adverse cardiac outcomes.[8 9]

Because patients with cardiovascular disease are at an especially high risk for morbidity and mortality after an acute gastrointestinal haemorrhage,[10] clinicians should strongly consider prescribing a PPI to all patients who use dual antiplatelet drugs, especially in the presence of additional risk factors for gastrointestinal complications, such as age over 60; concomitant use of non-steroidal anti-inflammatory drugs, other anticoagulants, or corticosteroids; and important medical comorbidities.

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RESEARCH, p 15

An appropriate antibiotic and a short course of plasmapheresis in a selected subset of patients might be an effective strategy

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Watching the detectives: tracking the source of Europe's latest *E coli* outbreak (*BMJ* 2011;342:d3884)

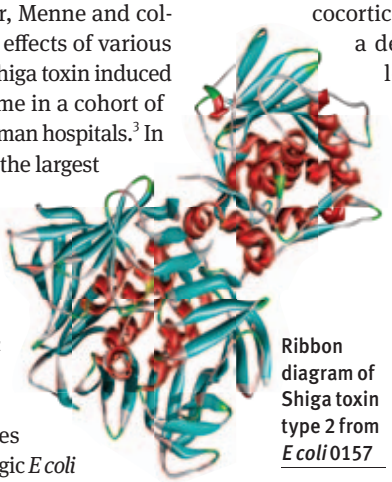
Treating Shiga toxin induced haemolytic uraemic syndrome

Clinical lessons from a recent outbreak of *Escherichia coli* O104:H4 in Germany

Ferruh Artunc associate professor, University Hospital Tuebingen, Department of Medicine IV, Section of Nephrology and Hypertension, 72076 Tuebingen, Germany ferruh.artunc@med.uni-tuebingen.de

Shiga toxin induced haemolytic uraemic syndrome occurs in a minority of patients after infection with enterohaemorrhagic *Escherichia coli* or *Shigella* spp. It is characterised by thrombotic microangiopathy and renal failure, which are attributed to toxic effects of Shiga toxin on systemic and renal microcirculation. The pathogen is commonly part of the intestinal flora of cattle and is transmitted by contaminated food. Worldwide, the most common strain is *E coli* O157:H7, which causes the syndrome mainly in young children.[1] Prognosis is good and treatment is mainly supportive, because no treatment has been proved to be effective and the use of antibiotics or plasmapheresis is controversial.[2]

In a linked research paper, Menne and colleagues present data on the effects of various treatments on the course of Shiga toxin induced haemolytic uraemic syndrome in a cohort of 298 patients treated at 23 German hospitals.[3] In 2011, Germany experienced the largest reported outbreak of Shiga toxin induced haemolytic uraemic syndrome, which affected 855 of the 3842 people who had been infected with enterohaemorrhagic *E coli* from contaminated fenugreek sprouts.[4] Analyses of isolates from stool samples showed that enterohaemorrhagic *E coli* O104:H4 was the causative strain.[5] This unusual and aggressive strain carried virulence factors typical of Shiga toxin-producing enterohaemorrhagic *E coli* as well as extended spectrum β-lactamase,[5] and it led to severe haemolytic uraemic syndrome in a large proportion of mainly adult patients. The clinical features of the syndrome commonly included dialysis dependent acute kidney injury or involvement of the central nervous system, which needed treatment in intensive care with mechanical ventilation.



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Ribbon diagram of Shiga toxin type 2 from *E coli* O157

In their retrospective in depth analysis, Menne and colleagues analysed various treatment strategies.[3] These included supportive treatment, plasmapheresis, and treatment with antibiotics or eculizumab, an antibody that blocks the terminal complement cascade and was reported to be effective in children with refractory Shiga toxin induced haemolytic uraemic syndrome during the outbreak.[6] Patient outcomes were compared in different subgroups. These included patients treated with or without the following: plasmapheresis (251 *v* 47 patients), antibiotics (52 *v* 246), eculizumab on top of plasmapheresis (67 *v* 65), and glucocorticoids given at the beginning of plasmapheresis (174 *v* 77).

Overall, 53.7% of patients required dialysis, 12.4% had seizures, and 18.1% were mechanically ventilated. Despite the high morbidity, mortality was low at 4%, and all but three patients recovered kidney function at six months. The authors found no clear benefit of plasmapheresis or eculizumab, whereas glucocorticoids were associated with a delayed recovery of platelet count and creatinine concentration. However, the syndrome was more severe in patients who received plasmapheresis or eculizumab, which introduced substantial indication bias to the data analysis. Surprisingly, antibiotics were the most effective treatment. Antibiotics were associated with significantly reduced neurological morbidity, no overall mortality, no need for abdominal surgery, and a shorter duration of enterohaemorrhagic *E coli* excretion. This is surprising because an earlier study found that antibiotics were associated with an increased risk of developing the syndrome, and this was explained by increased release of Shiga toxin.[7] In the current outbreak, patients received a combination of meropenem, ciprofloxacin, and rifaximin, with the addition of azithromycin when eculizumab was started. An in vitro study found that, among other antibiotics, meropenem, rifaximin, and azithromycin downregulated the release and expression of Shiga toxin, whereas ciprofloxacin had a stimulatory effect.[8]

Although the largest yet, the current study cannot draw a line under the controversy about the efficacy of plasmapheresis in Shiga toxin induced haemolyticuraemic syndrome.[2]

Patients with severe disease were treated with plasma exchange and they were compared with patients with milder self limiting disease. In a small case series of patients from the same outbreak, positive effects of plasmapheresis were reported.[9 10] Plasmapheresis might interfere with complement dysregulation and reduce the excessive activation of the alternative pathway of complement that is induced by Shiga toxin,[11 12] as reflected by low concentrations of C3 in patients treated with plasmapheresis.[10] The current study suggests that many patients with mild to moderate haemolytic uraemic syndrome can be managed without plasmapheresis, but the possibility that a subgroup with severe disease still benefits from this treatment cannot be excluded. The effects of eculizumab are difficult to evaluate because patients were treated with the antibody on top of plasmapheresis, through which large amounts may have been eliminated, and they also received azithromycin. Furthermore, the analysis excluded data on another 97 patients who were treated with eculizumab in an industry sponsored trial. Overall, the data show that eculizumab seems to have no clear benefit when used on top of plasmapheresis or in refractory states.

As with many retrospective studies, Menne and colleagues' results can be used only to generate new hypotheses that should be investigated in a randomised trial. However, their data show that an appropriate antibiotic and a short course of plasmapheresis in a selected subset of patients might be an effective strategy for the treatment of severe Shiga toxin induced haemolytic uraemic syndrome.

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Endgames: Opportunistic chlamydia screening in a general practice consultation (*BMJ* 2011;343:d5108)

Screening for *Chlamydia trachomatis*

Screening may not be the best next step

Berit Andersen head of Department of Public Health Programmes, Randers Regional Hospital, 8390 Randers NØ, Denmark berand@rm.dk
Frede Olesen professor of general practice, Research Unit for General Practice, Aarhus University, 8000 Århus C, Denmark

Population based screening for asymptomatic *Chlamydia trachomatis* infection has been postulated since the introduction of nucleic amplification techniques that enable testing on non-invasive samples.[1] Screening also seems logical because the infection is common and curable and asymptomatic, and symptomatic infections are thought to be important causes of pelvic inflammatory disease and other complications of the female reproductive system.[2]

In the linked cluster randomised trial with a stepped wedge design, van den Broek and colleagues report on the effectiveness of screening in more than 300 000 Dutch men and women.[3] The study provides important new information on the feasibility of screening. The results are disappointing and suggest that the strategy should be reconsidered. Over the course of three rounds of screening the participation rate fell from 16.1% to 9.5%. In addition, 4.2% of participants were *C trachomatis* positive at the first invitation and there was only a non-significant decrease to 4.0% after the third invitation. The low participation rate was not expected, as an earlier study with one round of a similar intervention in the Netherlands had a participation rate of 41%.[4] The results did not support the planned national roll-out of the programme. These findings highlight the importance of conducting feasibility and effectiveness studies for future screening interventions to test how things turn out in "everyday life."

Mass media campaigns may be doing a disservice to patients by maintaining the view that testing for *C trachomatis* in asymptomatic people is more important than reducing unsafe sex

This study measured both infection control and prevention of pelvic inflammatory disease, but only 20% of tested women answered the question about pelvic inflammatory disease. The overall prevalence of pelvic inflammatory disease was 1.9%, and this did not change during the study period. This incidence in the population is low compared with earlier expectations, but it corresponds to the background incidence in the recently published POPI (Prevention of Pelvic Inflammatory Disease) trial.[5]

What should be the next step from a population perspective? At least two directions are possible. One is to continue efforts to improve screening interventions—for example, by introducing selective screening and improving both the participation rate and the evaluation of effectiveness. This strategy is supported by the current study, because the estimated prevalence in the population declined only in South Limburg, where a selective procedure was introduced.

Alternatively, before screening is considered it might be useful to review important questions in the light of the most recent knowledge. For example, it might be useful to review the strength of the evidence that asymptomatic lower genital *C trachomatis* infections are likely to ascend and cause pelvic inflammatory disease and reproductive complications, and the evidence that regular testing and treatment of asymptomatic women can change the progress and spread of the infection. Might the pathology of the infection have changed?

The evidence that *C trachomatis* infections are associated with pelvic inflammatory disease is based on two randomised trials that were performed more than 10 years ago.[6 7] Systematic and structured reviews have questioned the total body of evidence that supports screening for chlamydia,[8 9] as well as the evidence to support an increased risk of infertility after a *C trachomatis* infection.[10 11] Recently, the randomised POPI trial showed only a non-significant reduction in pelvic inflammatory disease in a screened population compared with an unscreened population, partly as a result of a lower incidence of inflammatory disease (1.9%) in the background population than previously reported.[5] The POPI trial also found that most cases of pelvic inflammatory disease were in women who are negative for *C trachomatis* at baseline.

It would therefore be prudent to await more evidence for efficacy and effectiveness before implementing new large population based screening initiatives for chlamydia. We will, however, still see patients with infection in our clinics. Good practice in the consultation room demands appropriate case finding when infection is suspected and that detected infections are treated and partner notification carried out to reduce reinfection. These procedures should be provided along with good individual and population based information about safe sex and the prevention of sexually transmitted diseases and their associated complications. Doctors and mass media campaigns may be doing a disservice to patients by maintaining the view that testing for *C trachomatis* in asymptomatic people is more important than reducing the risk of unsafe sex.

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RESEARCH, p 14

Implementation of the early warning score requires a thoughtful pilot phase

A national early warning score for acutely ill patients

A new standard should help identify patients in need of critical care

Ann McGinley consultant nurse, Critical Care Outreach Service, Royal London Hospital, Barts Health NHS Trust, London UK
Rupert M Pearse clinical reader, Barts and the London School of Medicine and Dentistry, Queen Marys, University of London EC1M 6BQ, UK
r.pearse@qmul.ac.uk

National early warning score	Clinical risk
0	Low
Aggregate 1-3	
Red score (individual scoring 3)	Medium
Aggregate 5-6	
Aggregate ≥7	High

The critical care unit, which clusters patients with life threatening illness in a single location, is now a familiar concept. It offers patients the best chance of survival through optimum technology and the concentration of clinical skills and experience. As critical care has developed, it has repeatedly been noted that poor outcomes commonly result from a failure to promptly recognise and treat patients who become acutely ill on a standard hospital ward. As part of a long term strategy to tackle this problem, the Royal College of Physicians has launched a national early warning score.[1] This is a welcome development that may be good news for patients. However, it is worth highlighting potential pitfalls.

Patients die not from their disease but from the disordered physiology caused by the disease. The early warning score uses this concept to identify patients at risk. Points are allocated according to basic clinical observations including pulse rate, respiratory rate, blood pressure, oxygen saturation, and level of consciousness. The higher the score the more likely it is that the patient is developing a critical illness (figure). A high score prompts healthcare staff to request a detailed clinical assessment, which should result in early and effective treatment. In the United Kingdom, most hospitals already use a locally developed early warning score. In many cases, such tools were derived in response to a national review of critical care services, which set out a strategy to provide an integrated system-wide approach to the care of critically ill patients.[2] This review emphasised that adequate care should be provided to all patients regardless of their location within the hospital, and it ushered in the concept of "critical care without walls." An early warning score system must be linked to an effective clinical response. Nurse led critical care outreach teams are common in UK hospitals, although in other countries a physician often leads the medical emergency team.

The effectiveness of the twin concepts of early warning scores and critical care without walls has been debated. An institutional level response of this type obliges clinicians to adopt a new system that is not entirely of their choosing. An increase in workload for critical care staff as they take responsibility for patients throughout the hospital may seriously affect the provision of care within critical care units. Some commentators have expressed concern about the limited evidence to justify critical care outreach services.[3] The evidence base is indeed inconsistent: early positive studies provided grade C evidence, which has not been confirmed by more robust research.[4-6] Nonetheless, the impact of the "failure to rescue" critically ill patients in the ward environment is undeniable.[7] Critical care outreach does not seem to have been widely implemented internationally, but in the UK at least, this system seems here to stay.[8]

It is increasingly clear that tackling variations in quality of care improves patient outcomes. One of the strengths of the NHS in the UK is the ability to implement top down strategies to provide a consistent standard of patient care where definitive evidence may never be forthcoming. The rapid and complete implementation of the World Health Organization safer surgery checklist is just one example.[9] If the critical care outreach concept is to be developed further, it makes sense to implement the national early warning score in the same way. Staff who move between hospitals will then find a similar approach to patient monitoring and a similar response to the deteriorating patient in each location. Institutions where critical care outreach is not fully developed will seek to raise standards to the national level and will probably come under pressure to do so. The opportunity for general practitioners and pre-hospital care staff to use the early warning score could create a simple common language to describe the severity of acute illness.

It is essential to achieve a careful balance between national standards and local priorities, however, because a good idea that is badly implemented can have a negative effect. Patient groups characterised by abnormal physiology, such as those with end stage renal failure or recovering from brain injury, may present particular difficulties. Implementation of the early warning score requires a thoughtful pilot phase, which should include a validation of the trigger thresholds that activate a response. Wider implementation will require adequate staff training and a sensitive approach when restructuring established systems that already work well. Meanwhile, frontline NHS staff must work positively to ensure the new system is effective. Only then can we establish whether a national early warning score is good news for patients.

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Ensuring open access for publicly funded research

The right way to mix green and gold approaches

Peter Suber director of Harvard Open Access Project, Berkman Center for Internet and Society, Cambridge, MA 02138, USA psuber@law.harvard.edu

On 16 July 2012, three major announcements transformed open access policy in the United Kingdom. The Research Councils UK (RCUK) announced a stronger version of the open access policy it originally adopted in 2006.[1 2] The UK minister of universities and science announced that the government had accepted most of the recent open access recommendations from the Working Group on Expanding Access to Published Research Findings that he appointed last September (informally called the Finch group after its convener, Janet Finch).[3-5] Finally, the Higher Education Funding Council for England (HEFCE) announced plans to require open access to research submitted to the next Research Excellence Framework in 2014.[6]

These announcements signal a massive shift towards open access for publicly funded research in the UK, which is extremely good for researchers and taxpayers. The question is whether the new approaches take full advantage of strategies developed over the past two decades for providing open access quickly and inexpensively. The most contentious issue is the balance between "green" and "gold" open access (box).[7]

The new RCUK policy requires open access for all RCUK funded research, starting next April, with a preference for gold over green. When authors publish in an open access journal, or a journal with an open access option, the journal must provide immediate open access to the published version under a CC-BY licence (box). When open access journals levy article processing charges, the RCUK is willing to pay them through block grants to universities. When authors publish in a journal without an open access option, their peer reviewed manuscript must become open access through a repository within six months of publication, or 12 months in the social sciences and humanities, under a CC-BY-NC licence (box).

The Finch group displays an even clearer preference for gold open access. The group recommends green open access only for theses and dissertations, grey literature, data, and preservation.

The Finch group expects the full transition to open access to cost £50m (€64m; $78.5) to £60m a year, of which £38m a year would cover article processing charges. The rest would cover green open access infrastructure ("largely already… built"[9]) and renewed licences for journals that are not open access.

Green open access is less expensive than gold. It can easily accommodate the full research output of a university, funding agency, or nation. Green open access can be mandated today and gold cannot. Because Only about 30% of the world's peer reviewed journals are open access; a policy requiring authors to publish in open access journals would limit choice. That could change if enough journals convert to using open access options. But gold open access isn't there yet.

Gold open access has separate advantages. Open access journals perform their own peer review, whereas open access repositories distribute articles that are peer reviewed elsewhere. Open access journals can generate revenue and even surpluses or profits. Such journals obtain permission to make their articles open access simply by making it a condition of publication. Open access repositories face a higher but surmountable hurdle here. They get their permissions contingently from rights holders who support open access, or systematically from open access policies at funding agencies and universities that secure permissions from authors before those authors sign publishing agreements.

The RCUK and Finch groups, like most supporters of open access internationally, prefer immediate open access and open licences to delayed open access and all rights reserved copyrights. The RCUK and Finch group ultimately prefer gold to green because they want these benefits now, not later, because UK funders are willing to pay for them, because publishers want revenue beyond subscriptions for providing them, and because publishers had a major role in the policy deliberations.

The RCUK and Finch group take good advantage of the virtues of gold. The problem is that they fail to take good advantage of the virtues of green. The Wellcome Trust shows how to do the job better. The Wellcome Trust requires green open access for peer reviewed manuscripts arising from research that it has funded. If authors publish in open access journals with article processing charges, then the trust pays those fees and requires immediate open access under an open licence (soon to be CC-BY).[10] Like the RCUK and Finch group, the Wellcome Trust mixes green and gold, but it harnesses the power of green open access to assure open access for its full research output. A rapidly growing number of funding agencies and universities from around the world take the same step for the same reasons to assure free online access to research. That is a major advantage over the high access prices now shackling research, and that is the point. If we want to shorten embargoes and increase reuse rights, and we do, then we can take further steps, either by strengthening our green policies or paying for gold. What matters first is to use the tools we have to drive open access for the benefit of researchers and taxpayers.

To do that on a global scale, every research funding agency, public or private, and every university, should require green open access for new peer reviewed research articles by their grantees and faculty. Institutions should take that step before adding new incentives or new funding for gold.

A bill now before the US Congress, the Federal Research Public Access Act (FRPAA),[11] would take that first green step for all the major funding agencies in the US federal government, expanding on the successful green open access mandate at the National Institutes of Health. On 17 July 2012, the day after the three big announcements in the UK, the European Commission announced a new open access policy for the European Union and recommended open access policies for member states.[12 13] It is too early to tell how the European policies will balance green and gold. But the worldwide momentum for open access means that the UK needn't worry that it might be acting alone and making its own research freely available while continuing to pay for research from the rest of the world.

Definitions

Green open access: Delivered by repositories
Gold open access: Delivered by journals
CC-BY licence: Allows any kind of reuse provided the user makes proper attribution
CC-BY-NC licence: Similar to a CC-BY licence except that it does not allow commercial use[8]

Provenance and peer review: Commissioned; not externally peer reviewed.

References are in the version on bmj.com.

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