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Improving blood safety worldwide

A three-article series on transfusion medicine appears in this week’s issue of the journal. The articles provide an update on the use of red blood cell, platelet, and coagulation factor transfusions in clinical practice. Transfusion medicine is a fast-moving and exciting field of research. But worldwide access to its life-saving interventions is limited to relatively few. In many regions of the developing world access to these treatments is simply not available. And unlike the developed world, where much of the blood goes to the treatment of older patients, a substantial portion of blood in the developing world goes to treat younger patients: infants and children with anaemia due to malaria, for example; victims of trauma; and mothers with blood loss due to childbirth.

On World Blood Donor Day this past June 14, WHO focused on the role that safe blood supply plays in saving the lives of these young women. The theme was "Safe Blood for Safe Motherhood". According to WHO, more than half a million women die every year during pregnancy, 99% of them in the developing world. The most common cause of maternal mortality is haemorrhage during or shortly after delivery, contributing to 34% of maternal deaths in Africa, 31% in Asia, and 21% in Latin America and the Caribbean.

In many cases, blood is not available because effective systems for collection do not exist. To maintain an adequate blood supply, 1–3% of the population needs to be blood donors. But of 172 countries responding to a survey released on World Donor Day by WHO, 80 have failed to achieve that mark with less than 1% of the population donating. 79 of these are in the developing world. The safest blood comes from unpaid donors who donate for altruistic reasons. In this group, the prevalence of HIV, hepatitis infection, and other blood-borne pathogens is lowest. Infection rates are higher among donors who are family members or members of the community, who donate to replace blood used by a patient, a common practice in many regions, and infection rates among paid donors are higher still. According to the WHO survey, the number of countries that have achieved 100% unpaid voluntary donations rose from 39 in 2002, to 50 in 2004, including the Central African Republic, which increased its proportion of voluntary donations from 25%, Egypt from 15%, and Uruguay from 28%.

Progress is also being made in developing effective blood-testing services. Although 41 of 148 countries that supplied the WHO with data reported they were not yet able to meet the WHO’s minimum standard of testing for hepatitis B and C, HIV, and syphilis, ten nations reported they had made that goal: Benin, Burundi, Chile, Democratic Republic of Congo, Ecuador, Guinea-Bissau, Honduras, Mauritania, Uzbekistan, and Democratic Republic of Korea.

Where blood is available, it is often unsafe. WHO recommends that, at a minimum, blood be screened for HIV, hepatitis B, hepatitis C, and syphilis. Of 148 countries that provided WHO data for screening, 41 reported that they were not able to screen all donated blood for one or more of these infections. Of the 40 countries in sub-Saharan Africa, 28 have yet to implement national quality systems needed to assure effective screening of donated blood. WHO estimates that the lack of effective screening results in up to 16 million new infections with hepatitis B, 5 million new infections with hepatitis C, and 160 000 cases of HIV infection every year. Overall, 5% to 10% of HIV infections worldwide are the result of transfusions of contaminated blood or blood products.

To increase access to blood transfusions and to promote blood safety, WHO has for many years worked to help nations adopt an integrated approach for blood safety that has four key elements: establishment of a nationally-coordinated blood transfusion service, collection of blood from exclusively voluntary donors from low-risk populations, testing of all blood for compatibility and transfusion-transmissible infections, and reduction of unnecessary transfusions.

In all these areas, progress is being made, albeit slowly. The safest blood comes from unpaid donors who donate for altruistic reasons. In this group, the prevalence of HIV, hepatitis infection, and other blood-borne pathogens is lowest. Infection rates are higher among donors who are family members or members of the community, who donate to replace blood used by a patient, a common practice in many regions, and infection rates among paid donors are higher still. According to the WHO survey, the number of countries that have achieved 100% unpaid voluntary donations rose from 39 in 2002, to 50 in 2004, including the Central African Republic, which increased its proportion of voluntary donations from 25%, Egypt from 15%, and Uruguay from 28%.

For more on blood transfusion safety see http://www.who.int/bloodsafety/en/
Europe’s clinical trials partnership programme in peril

On July 17, the findings of an independent expert group on the troubled European and Developing Countries Clinical Trials Partnership (EDCTP) programme were released. The review was commissioned by the European Commissioner for Research Janez Potočnik following a very critical European Court of Auditors report in 2005 and ahead of a possible new funding round.

Despite an attempt by EDCTP to gloss over the core message in a highly spun press release, the report makes depressing reading. EDCTP needs to improve substantially if new funding is to be provided, with drastically improved governance and tangible outputs by the end of 2008. Many areas are highlighted as problematic including its complicated co-funding rules, which make it impossible for projects to be initiated by researchers from developing countries and which lead to wasteful duplication in the review process.

Since its initiation in 2003 as a global public-private partnership, EDCTP has had four different executive directors, has only spent a fraction of the possible €600 million, has not developed a clear vision and convincing strategy, and lacks political and public accountability. How realistic, then, is what essentially amounts to going back to the drawing board?

Allyson Pollock, director of the Centre for International Public Health Policy at the University of Edinburgh and a member of the review panel, disagrees with the recommendations of the other members and explains in a separate dissenting chapter, and in speaking to The Lancet, why she thinks that EDCTP is unlikely to meet the objectives laid out. Pollock believes that the serious concerns about political control and accountability cannot be overcome in the present structure and that the best way forward would be to fold EDCTP into European Commission (EC) control. She goes further, though, in her recommendations and urges the EC to work with governments in Africa to provide a coherent and comprehensive north-south partnership research strategy grounded in public-health needs.

These are sensible and welcome suggestions. Only then, will Europe get a step closer to the goal it stated for EDCTP: “To reduce poverty in developing countries by improving the health of the populations.”

MRSA: moving beyond mops and matrons

Last week, figures released by the Health Protection Agency revealed that the number of patients with methicillin-resistant Staphylococcus aureus (MRSA) in England has dropped by 6% since January this year. However, despite this progress, the government’s target to reduce MRSA rates by 50% by 2008 is unlikely to be met.

In England and Wales, the traditional focus of infection control has been on hospital cleanliness. But this “mops and matrons” approach has diverted attention away from some fundamental behavioural and management issues. For example, adherence to hand-cleaning practices rarely exceeds 60% among health-care workers. But evidence shows that increasing the opportunities that health professionals have to clean their hands by placing an alcohol-based handrub beside every hospital bed and encouraging them to carry handrub, substantially improves hand hygiene practices.

In addition, with few new antibiotics in development, strategies that promote good antibiotic prescribing practice are essential. But, according to a report published on July 25 by the Healthcare Commission, only 8% of National Health Service (NHS) trusts provide education and training to relevant staff on antibiotic prescribing and 39% did not provide feedback on antimicrobial prescribing practices. Such staff management issues need to be resolved along with other practical problems that hamper health workers’ ability to prevent infections, such as the lack of single rooms in NHS hospitals to isolate and treat infected patients.

Spurred on by the introduction of mandatory reporting of MRSA in 2001, many trusts intensified their efforts to reduce infections. Last month, the Healthcare Commission said it would undertake a programme of unannounced inspections at 120 trusts over the coming year—its biggest ever set of visits relating to health-care-associated infections. This move is welcome and should put the necessary pressure on trusts to put infection control at the core of hospital care.
Interferon beta in multiple sclerosis: how much BENEFIT?

Despite pivotal trials of the disease-modifying agents interferon beta and glatiramer acetate, worldwide approval by licensing agencies, and a growing trend to treat all patients with early multiple sclerosis, controversy still exists about who and when to treat.1,2

When a person presents to a neurologist for evaluation of a first event (clinically isolated syndrome) suggestive of multiple sclerosis, the treating physician has a daunting task when making a rational therapeutic recommendation. He or she has to assimilate evidence-based medical facts, knowledge of the natural history of the disease, pharmaceutical promotional material, imperfect diagnostic criteria, and the patients’ wishes. Does the evidence support the use of a disease-modifying agent without delay? For patients with limited clinical or radiographic disease dissemination, or when patients are reluctant to begin parenteral treatment, is a watchful waiting or delayed approach inappropriate?

The magnitude of clinical benefit in terms of disability prevention is an important consideration in the therapeutic decisionmaking process, in view of the financial cost, adverse effects, patients’ reluctance to begin long-term parenteral therapy, and the fact that patients with multiple sclerosis might do well for decades without treatment.1,3,4 Trials have focused on accessible outcomes of relapse behaviour and MRI variables of disease activity, and have shown only partial benefit on disability progression over the short term.5,6 Objective interpretation of clinical effect is obscured when statistical analyses in large randomised trials emphasise relative risk reductions and their p values, rather than the magnitude of benefit (eg, numbers needed to treat, absolute risk reductions).

A key issue, for both multiple sclerosis and clinically isolated syndrome, is whether disease-modifying agents have any long-term benefit on accumulation of disability. The CHAMPS,7 ETOMS,8 and BENEFIT (2-year placebo-controlled phase)9 studies showed that treatment with interferon beta reduced the rate of conversion to clinically definite multiple sclerosis within 2 years of clinically isolated syndrome. The benefits, however, were modest. The number of patients needed to treat to prevent one from developing clinically definite multiple sclerosis at 2 years was six (BENEFIT) and at 3 years was seven (CHAMPS). Whether delaying the second attack has any long-term effect on disability remains unclear.7,9

To answer the disability question, we must rely on extension trials which, although imperfect (unblinding of patients and evaluators, drop-outs, and assumptions from missing data), are the best we have.1 In today’s Lancet, Ludwig Kappos and colleagues10 set a new benchmark in the presentation of results from BENEFIT, by providing measures of magnitude of clinical benefit (numbers needed to treat and absolute risk reductions) and subgroup analyses. Additionally, they have sought to address many concerns of previous trials by maintaining blinding for the initial randomisation for both patients and physicians, and had a lower drop-out rate (15% and 10% of interferon and placebo groups, respectively) than did other studies.11

Kappos and colleagues report results of a 3-year follow-up of the BENEFIT trial, and provide data to support their conclusion that “early initiation of treatment with interferon beta-1b prevents the development of confirmed disability” and suggest that delaying treatment has “an effect on later accumulation of disability”.10 At first look, one might surmise that this follow-up at last dispels controversy and provides the practising neurologist with the data needed to support early treatment for all patients with a clinically isolated syndrome and MRI findings suggestive of
Comment

multiple sclerosis (at least two clinically silent lesions on T2-weighted scan). Unfortunately, caution is warranted and the general applicability of the findings to patients with clinically isolated syndrome is uncertain.

Although statistically significant, the benefit of early compared with delayed treatment in terms of disability progression was small. The difference in mean scores on the expanded disability status scale (EDSS) between first event and last follow-up were small in both the delayed treatment (a worsening of 0.15 steps) and the early-treatment groups (an improvement of 0.11 steps). To put this change in context, changes of less than 0.5 steps in EDSS have never been considered a validated outcome for individual patients. Furthermore, most patients in Kappos and colleagues’ study had low EDSS scores (median 1-5, IQR 1-0-2-0), which are associated with lower reproducibility and higher inter-rater variability than higher EDSS scores.

Although the primary outcome in Kappos and colleagues’ follow-up was based on the categorical measure time to confirmed worsening of EDSS by one or more steps, the additional presentation of EDSS data as a mean, whereby the EDSS is treated as a continuous variable even though it is a stepwise non-continuous scale (each step is assigned on the basis of a functional system score and ambulation), raises some concern. Some have argued that non-parametric distribution-free tests (eg, χ² or U tests) would be more appropriate.

When patients in BENEFIT were stratified according to the extent of disability progression (steps of 0-5 or less, 1-2, and more than 2-0 by EDSS) within the 3-year follow-up, the differences for each of the three stratified groups between patients treated early and those whose treatment was delayed were small (2%, 1-0% and 2-8% respectively). Furthermore, 12 patients need to be treated early to avoid one additional patient developing a confirmed EDSS progression, defined as an increase in EDSS score of 1 or more steps.

A finding not to be overlooked in Kappos and colleagues’ follow-up was the lack of a significant benefit of early compared with delayed treatment in patients with limited clinical signs or symptoms (53% of study patients) or limited MRI disease dissemination (29% of study patients with less than nine T2-weighted lesions) at baseline. In the post-hoc subgroup analysis, the limited sample size and the relatively low event rate of “confirmed EDSS progressions” probably affects power for analysis, and the results of the final 5-year BENEFIT analysis will be important.

Kappos and colleagues have set a new standard against which future extension trials will be compared. They present the first evidence that interferon beta-1b treatment has a beneficial effect on accumulation of confirmed disability in patients with a first event suggestive of multiple sclerosis. The results should, however, be interpreted with care because the magnitude of benefit, although statistically significant, is clinically small. This follow-up should not be misconstrued as evidence for a treat-all approach.

Sean J Pittock
Departments of Neurology and Laboratory Medicine and Pathology, Mayo Clinic College of Medicine, Rochester, MN 55901, USA
Pittock.Sean@mayo.edu

I declare that I have no conflict of interest.

Cervical screening by visual inspection with acetic acid

In today’s Lancet, Rengaswamy Sankaranarayanan and colleagues show that visual inspection with acetic acid (VIA) can be an effective and acceptable method of cervical screening in low-resource settings. They found a 25% reduction in cervical cancer incidence and a 35% reduction in mortality compared with the control group. Indeed, they reported earlier than planned (after 7 years rather than 10 years) because the effect was greater than anticipated. Coming from the UK, which has one of the most effective screening programmes in the world, I have always been a little sceptical about enthusiasm for VIA. Perhaps my developed-world viewpoint has made me feel uncomfortable with the concept that VIA is “good enough for them, but not good enough for us”. However, if a VIA programme can be as effective as Sankaranarayanan’s study suggests, I should think about revising my opinion.

From a cytology screening culture in the developed world, it is important to appreciate that the test we consider “good” does not perform well in developing countries, with sensitivity ranging from 44% to 78%. Cytology screening programmes in developing countries are hampered by poor infrastructure (eg, postal and other communication services), lack of quality control for laboratories and cytology reporting, and poor treatment facilities. Furthermore, the lack of education of women often results in low participation. Unfortunately, many of these factors will apply to any type of screening programme. VIA, with treatment at the screening visit, has the potential to avoid many logistic problems, while also being inexpensive.

Sankaranarayanan and colleagues provided intensive and extensive training for the health workers, nurses, and doctors involved. Additionally, continuous quality-control procedures were in place. Both training and quality control need to be stressed, because VIA can give variable results depending on the training of personnel. There is a danger that countries will skimp on training and instigate VIA programmes, which will not give results as good as those that Sankaranarayanan found.

Sankaranarayanan and colleagues’ study shows the difficulty of achieving adequate coverage in screening programmes, because of the 167 women with cervical cancer in the intervention group, 61 (nearly a third) were non-participants. There was a 64% participation rate in the intervention group, despite a prior education programme, which begs the question how likely is a high participation rate in routine practice? Education and engagement of the local communities are crucial factors to ensure high participation, but will the resources and infrastructure for such programmes be available? Without participation rates over 60% (preferably more than 70%) a screening programme is unlikely to be effective.

To circumvent the problems of poor communication facilities, transport, and follow-up, cryotherapy was done on the same day as VIA screening, but followed a colposcopically-directed biopsy, so that a retrospective correlation could be made with histology. The correlation with histology showed that, whereas 9·9% of those screened were VIA-positive, only 6·2% actually had cervical intraepithelial neoplasia (CIN) or cancer. Thus about 27% of women who screened positive were treated unnecessarily. This specificity is high compared with other studies, in which figures as low as 49% have been reported, but generally are around 75%. A comparison with histology on an ongoing basis can be (and was here) used for quality control. However, in most studies, and certainly in real life, colposcopically-directed biopsies are not done before treatment. Sankaranarayanan and colleagues assert that cryotherapy is safe with few complications, which certainly seems to be true in studies by their group. But a systematic review of obstetric outcomes after treatment for CIN did not include cryotherapy, because the reviewers could not find acceptable studies of long-term outcomes with this treatment.

The printed journal includes an image merely for illustration
After cryotherapy, women must abstain from intercourse for a month, or at least use condoms. Doing so might prove difficult in countries where women are often disempowered and men may be reluctant to comply. Indeed, in a South African study, half the women reported that they had had intercourse within a month of treatment and only around half of those used condoms. 6

Additionally, cryotherapy is best suited to the treatment of low-grade disease: cure rates for high-grade lesions range between 71% and 96%.7 Again, in Sankaranarayanan and colleagues’ study, large-loop excision of the transformation zone was available for those lesions considered unsuitable for cryotherapy. But the real world does not always have colposcopic evaluation available and facilities for subsequent large-loop excision. Sankaranarayanan is to be commended that, despite the likely difficulties, long-term follow-up is planned to monitor the longer-term effects and infer potential screening intervals.

A major problem for countries wishing to instigate VIA screening (and for comparison of different studies) is that there are no uniform criteria for doing the procedure, nor for reporting VIA positivity. These points are a substantial drawback, because of the potentially highly subjective nature of the test. Studies are beginning to suggest that the addition of Lugol’s iodine staining improves the sensitivity and specificity of VIA and that such staining is the nature of the test. Studies are beginning to suggest that the addition of Lugol’s iodine staining improves the sensitivity and specificity of VIA and that such staining is easier to learn and use,8 which is intuitively obvious to a colposcopist. In the long term, HPV vaccines will probably offer the greatest hope for cervical cancer prevention in all countries. However, for those without current screening programmes, perhaps VIA, but together with iodine staining, will be the way forward in the near future.

Anne Szarewski
Wolfson Institute of Preventive Medicine, London E1CL 6BQ, UK
anne.szarewski@cancer.org.uk

I have been sponsored to lecture and/or attend conferences by GlaxoSmithKline and Merck Sharpe & Dohme, and consulted for both companies and J&J. I have been involved in studies sponsored by J&J and Digene, and am involved in HPV vaccine trials (GlaxoSmithKline), and biomarker studies (Digene, Norchip, Roche, MPM, Genprobe, Genomica and Abbott). GlaxoSmithKline have commissioned me to write about HPV for health professionals, and I have written in publications for health professionals and for the lay media.


CD4 T-cell responses to combination antiretroviral therapy

Combination antiretroviral therapy (ART) effectively suppresses viral replication, as assessed by the plasma HIV-1 RNA concentration being below the assay’s limit of detection. The CD4 T-cell count increases rapidly in the first few months after starting combination ART, and more gradually thereafter.1 This CD4 increase is accompanied by a striking reduction in morbidity and mortality. Prophylaxis against opportunistic infections can safely be discontinued when the CD4 count increases.1 There is considerable individual variability in CD4 cell responses with older age being a key risk factor for poorer responses,1,3 because of diminishing thymic reserve. CD4 counts increase when a patient is on combination ART at a slower rate in those with suboptimum virological responses,3,4 but continue to increase as long as the viral load is below 10 000 copies per mL.4 Interestingly, the initial increase in CD4 count is the same irrespective of the baseline count.3,5 However, two cohort studies of patients with good virological responses to combination ART (defined as viral loads suppressed to <1000 or <400 copies per mL2,6,7) reported a plateau effect of CD4 responses. Patients who started combination ART with lower CD4 counts had a levelling off of CD4 increases below the normal range after several years.2,5 In today’s Lancet, Amanda Mocroft and colleagues8 examine a larger cohort of patients with a stricter criterion for virological response, a viral load below 50 copies per mL, which is appropriate because this cutoff is the current
standard of care. They followed an innovative approach by only assessing CD4 responses in periods of virological suppression and found that CD4 counts became normal in patients with a baseline CD4 count above 350/µL, with ongoing increases in patients with lower baseline counts, including those with counts above 200/µL for more than 5 years of follow-up. As the authors state: “This finding is consistent with an asymptotic rather than a plateau effect”. The findings are important because they imply that patients maintaining maximum virological suppression on combination ART will eventually achieve normal CD4 counts, even those with low baseline CD4 counts.

How important is it to achieve normalisation of CD4 counts? The development of new AIDS illnesses or death is related to the CD4 count achieved on combination ART, so more is clearly better. But quantitative restoration of CD4 count does not mean that immunity is normal. Pathogen-specific immune responses partly recover, which accounts for the striking reduction in major opportunistic diseases. However, the magnitude of specific immune responses is predicted by the nadir rather than the current CD4 count in patients on combination ART, and patients with higher CD4 nadirs have lower immune responses than do HIV-uninfected controls. Of factors known when combination ART is started, the CD4 count when patients start the treatment is the strongest predictor of survival. Cohort studies of outcomes on combination ART show lower survival with baseline CD4 counts below 200/µL than with 200–350/µL, but minimum or no further survival advantage with baseline CD4 counts above 350/µL, even after correcting for lead-time bias. Thus Mocroft and colleagues’ findings cannot be used to justify starting combination ART in patients with low CD4 counts (<200/µL).

What are the implications of Mocroft and colleagues’ findings for low-income countries, where the majority of patients who need combination ART live? In an analysis of multiple cohorts the CD4 count at the start of combination ART was substantially lower in low-income than in high-income countries (median 108/µL vs 234/µL). The average patient in low-income countries who starts combination ART with advanced disease can now be expected to eventually normalise their CD4 counts, provided maximum virological suppression can be maintained. However, many low-income countries do not offer monitoring of viral load; even when available such monitoring is done infrequently, and the more expensive assays that have detection limits of 50 copies per mL are not widely available. Therefore the ability to confirm maximum virological suppression is limited.

Mocroft and colleagues’ finding that CD4 counts continue to increase on combination ART until normal values are reached, even with low CD4 counts at baseline, is only generalisable to patients on combination ART during periods of maximum virological suppression. A potential weakness is that they included patients with intermittent periods of virological suppression, analysing only those periods when suppression was present, although censoring the analysis at time of first viral rebound or adjusting for the time each patient spent with unsuppressed viraemia did not affect the findings. Loss of virological suppression followed by re-suppression could result in different CD4 responses. Nevertheless, the researchers have shown that at least for patients with ideal responses to combination ART, normalisation of CD4 counts is likely to be achievable across a range of baseline counts.

Gary Maartens, Andrew Boulle
Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa (GM); and School of Public Health & Family Medicine, University of Cape Town, Cape Town, South Africa (AB)
gary.maartens@uct.ac.za

We declare that we have no conflict of interest.
The Lancet’s important series on health and human rights, which starts today, illustrates some of the ways in which the delivery of medical services must answer to human rights principles. It was, after all, the Universal Declaration of Human Rights that endowed every person with a claim to basic health care, which means a right for their lives to be protected from treatable diseases and injuries. That declaration imposes a health-care duty on all states and—to the extent that many states cannot cope—on wealthier nations, individually and through the UN, to come to their aid. This duty is increasingly shouldered by non-governmental organisations, whose personnel, working in zones of war and famine, face ethical dilemmas that must be resolved by recourse to human rights rules. Doctors traditionally bound by ethics of neutrality and confidentiality are increasingly called on to speak out about and against the crime and corruption its members witness. They may be called on to bear witness—to give testimony, even against their own patients. As the world figures out how to do justice to victims of man-made atrocities and natural disasters, the time has come to examine the moral accountability of the medical profession.

Precedents tend to be stark and simple—Josef Mengele experimenting with victims of genocide, army doctors in Chile helping Augusto Pinochet’s torturers to calibrate their electric shock machines, and the like. Direct involvement in human rights abuses is obviously wrong. Nobody criticises the Harley Street doctors who treated Pinochet, although perhaps they should; providing medical succour to a terrorist on the run now entails, under UK law, a legal duty to inform the police, immediately and in detail. The International Committee of the Red Cross (ICRC) notoriously kept quiet about Hitler’s concentrations camps, for fear of being banned from them—a Faustian bargain now regarded as indefensible. Yet it also kept quiet about the torture it found at Abu Ghraib, which allowed its secret reports to be ignored by US authorities until one was leaked to the newspapers. The organisation’s permanent presence at Guantánamo is now exploited by the Bush administration as evidence that there can be no torture in the camp. Yet, if there has been torture, the ICRC fetish for confidentiality would prevent it from telling anyone other than the torturer. How, in these circumstances, can the ICRC provide a safeguard—the role for which it is given (ICRC) notoriously kept quiet about Hitler’s concentrations camps, for fear of being banned from them—a Faustian bargain now regarded as indefensible. Yet it also kept quiet about the torture it found at Abu Ghraib, which allowed its secret reports to be ignored by US authorities until one was leaked to the newspapers. The organisation’s permanent presence at Guantánamo is now exploited by the Bush administration as evidence that there can be no torture in the camp. Yet, if there has been torture, the ICRC fetish for confidentiality would prevent it from telling anyone other than the torturer. 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organisations should avoid knee-jerk commitment to instant reporting (best left to newspapers) and should acknowledge a responsibility to release findings that have been double-checked and, in appropriate cases, peer-reviewed. There have been serious cases of false allegations (eg, the notoriously invented claim that Saddam Hussein’s forces threw babies out of hospital incubators during the invasion of Kuwait), and some non-governmental organisations have left themselves open to the criticism that they have exaggerated allegations against unpopular governments to raise money or membership.

The new international criminal courts which deal with war crimes have developed laws of evidence to protect certain witnesses—notably war correspondents and human-rights monitors—whose compelled testimony could imperil sources or make perpetrators less willing to cooperate. These rules, which generally allow sources’ anonymity and compel testimony only if crucial to the result of the case, need to be adapted to take into account the ethical concerns of doctors, nurses, and aid workers who are also potential witnesses. Patients’ confidentiality is an acknowledged value, but might have to be overridden in the interests of bringing home responsibility for a war crime, whereas medical staff can be compelled to testify, certainly if their evidence is vital to cases involving attacks on hospitals or ambulances.

The articles in this series are particularly welcome for their analysis of the South African cases that have forced drug companies to reduce the price of vital medicines, and of the Indian decisions that infer from the constitutional right to life a right to primary health care and to health insurance. These second-generation rights have often been regarded in developed countries as unjusticiable, or at least as unenforceable against the state, but creative lawyers in South Africa and India have found ways to make them meaningful. Another connection between human rights and health can be discerned in the evidence of the resurgence of diseases long thought to have been eradicated, in states which evince no respect for the civil rights of their citizens. This causal link serves to emphasise the indivisibility as well as the universality of fundamental rights: freedom from avoidable illness is as essential as freedom from discrimination or persecution. That means that medical services must now be delivered within an ethical framework infused by human rights considerations: dilemmas will remain, but they will be more acceptably resolved.

Geoffrey Robertson
Doughty Street Chambers, London WC1N 2PL, UK
g.robertson@doughtystreet.co.uk

I am an appeal judge for the UN War Crimes Court in Sierra Leone.

**Right to the highest attainable standard of health**

The right to the highest attainable standard of health lies at the heart of the health and human rights movement. Of course, this right does not provide magic solutions to complex health issues, any more than do ethics or economics. Nonetheless, the right to health has a crucial constructive role to play. Health policymakers and practitioners who ignore this fundamental human right are failing to use a powerful resource that could help to realise their professional objectives.

At the international level, the right to health was first articulated in the Constitution of the World Health Organization 1946. Subsequently, it was enshrined in several binding international human rights treaties, such as the International Covenant on Economic, Social and Cultural Rights, as well as many national constitutions. However, it remained little more than a slogan for more than 50 years. Not until 2000 did an authoritative understanding of the right emerge—when
the UN Committee on Economic, Social and Cultural Rights, in close collaboration with WHO and many others, adopted General Comment 14.3

This substantive instrument confirms that the right to health not only encompasses access to health care, but also the underlying determinants of health, such as safe water, adequate sanitation, a healthy environment, health-related information, and freedom from discrimination. The right has a preoccupation with disadvantaged groups, participation, and accountability.4 Moreover, it places a responsibility on high-income countries to help developing countries deliver the right to health to their people.5

Although General Comment 14 leaves many questions unanswered, it remains groundbreaking and marks the moment when the right to health ceased to be a slogan and became an important instrument for all health policymakers and practitioners.

As UN Special Rapporteur on the right to the highest attainable standard of health, I try to make the right to health—and General Comment 14—more specific, accessible, practical, and operational. Informed by consultations with a wide range of health workers, my 30 or so reports focus on poverty and discrimination. Some reports look at the right to health in specific countries, such as Sweden, Romania, Mozambique, Peru, and Uganda.6-8 Some focus on special situations, such as Guantánamo Bay and the war in Lebanon and Israel during mid-2006.9,10 Several address broad right-to-health issues, such as maternal mortality, mental disability, access to medicines, sexual and reproductive health rights, and the skills drain of health professionals—a perverse subsidy from the poor to the rich that undermines the right to health of those who live in sending countries. Because the right to health is subject to progressive realisation, one report sets out a human rights-based approach to health indicators, to enable progressive realisation of the right to health to be monitored and measured.11

All these reports and interventions look at issues through the right-to-health lens. In this way, they develop an analytical framework for unpacking the right to health. This framework deepens understanding of complex health issues and helps to identify practical policy and programmatic responses, including measures that are meaningful to disadvantaged communities and individuals.

One of the most pressing challenges is the integration of the right to health in all national and international health-related policies. To achieve this end, the traditional human rights methods and techniques (such as naming and shaming, letter-writing campaigns, taking test cases, and slogans) are not enough. These traditional methods must be supplemented with new techniques and skills, such as indicators, benchmarks, impact assessments, and budgetary analysis. These new methods are now taking shape, reflecting the growing maturity of the health and human rights movement.12

Unfortunately, some commentators seem to be oblivious to these new developments. They still seem to treat the right to health as if it were little more than a bumper sticker or an instrument for tackling torture and, at a pinch, discrimination within health care.

Obviously, the realisation of the right to health depends on enhancement of public health and delivery of medical care by health workers. Equally, the classic traditional objectives of the health professions can benefit from the new dynamic discipline of human rights. Health workers can use the right to health to help them devise equitable policies and programmes that: benefit the most disadvantaged; strengthen health systems; place important health issues higher up national and international agendas; secure better coordination across health-related sectors; raise more funds from treasuries;
leverage more funds from developed to developing countries; and in some countries, improve the terms and conditions of those who work in the health sector.

In short, the right to the highest attainable standard of health is an asset and ally, which is at the disposal of all health workers. Why not grasp and use a resource that not only helps to achieve professional objectives, but also helps to fulfill professional responsibilities.\(^1\(^3\)

Paul Hunt
University of Essex, Colchester, Essex CO4 3SQ, UK

I declare that I have no conflict of interest.


### Epilepsy onscreen: getting it wrong

Cinematic and television portrayal of people with epilepsy has been blamed for the poor understanding of the condition found in a recent survey by Sallie Baxendale and Annette O’Toole at University College London, London, UK.\(^1\) The internet-based survey of over 4600 staff and students and their email contacts suggested that a high proportion of individuals do not know what happens during seizures, and would do potentially dangerous or unnecessary first-aid interventions.

Many respondents thought that foaming at the mouth and violence were characteristics which happened “often” or “always” during a seizure. More worrying was the proportion that could not identify the correct first-aid procedures for during or after seizures. Two-thirds of respondents would immediately call an ambulance on encountering a seizing person, and one-third would even place an object in their mouth in the belief that such an intervention would prevent the patient swallowing their tongue, with the risk that the object might cause choking or damage teeth. Typical first-aid guidelines state that an ambulance is required only if the seizure lasts longer than 5 min, if the person is unconscious for more than 10 min or if there are multiple seizures, and that the seizure should be allowed to occur while ensuring that the person is in no danger from sharp, hard, or otherwise dangerous objects.\(^2\)

A key factor in the survey determining understanding of seizures was familiarity with epilepsy. Seeing an epileptic seizure being managed in public was also shown to improve knowledge of the correct first-aid interventions. Surprisingly, however, witnessing an epileptic seizure did not improve an individual’s knowledge about the physical presentation of seizures.

Are these results specific to epilepsy? Probably not; asking people about other first-aid situations, such as cardiac arrest, might show similar misinformation. Perhaps what Baxendale and O’Toole’s study suggests is that broader and wider-reaching first-aid teaching is required in the UK, especially if first-aid procedures are misrepresented by screenwriters and the mass media.

Rachel L Brown
Somerville College, University of Oxford, Oxford OX2 6HD, UK

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Clinical update: surgical management of rheumatoid hand

Rheumatoid arthritis is often first identified in the upper extremity, with inflammation to the wrist, metacarpophalangeal joints, and proximal interphalangeal joints—this pattern is defined as rheumatoid hand disease. Chronic synovial proliferation damages ligaments, impairs tendon gliding, destroys joints, and causes compressive neuropathy and muscular disuse atrophy. Functional and cosmetic changes in the hand could affect a patient’s employment prospects, lead to loss of independence, and cause social isolation. Preservation of hand function requires the use of medical, physical, and surgical means. Although improved medical treatment has reduced the need for surgery, such surgery is not yet obsolete. There are substantial differences about surgical indications between rheumatologists and hand surgeons. The lack of randomised trials makes any treatment plan a matter of debate, and thus collaborative relationships between specialists, including implementation of appropriate clinical studies, are important to provide the best care.

The goals of surgery are four-fold: relief of pain, restoration of function, prevention of future deformity (usually considered in early disease), and improvement of hand cosmesis. The improvement in the hand’s appearance after surgery is by no means trivial and is often regarded as important for patients’ satisfaction because of the pain-relieving benefits provided by the surgical procedures. Deformity does not always need surgery, but cannot be entirely disregarded. Waiting for severe or end-stage disease will restrict treatment options and reduce final functional outcome. Active rheumatoid disease does not preclude surgical intervention, but lack of response to an adequate medical programme is a prerequisite. Continuing medical management in conjunction with prophylactic surgery could even increase the chance of disease remission. Many drugs, including methotrexate and prednisone, can be continued perioperatively without substantial risk of postoperative surgical complications.

Early in the disease process, the focus of both medical and surgical management should emphasise maintenance of normal structure and function in the hand. Early decompression of the median nerve and flexor tenosynovectomy is recommended when carpal tunnel syndrome impairs grasp, feeling, and proprioception within the hand, which can occur in as many as 80% of patients with rheumatoid arthritis. Compressive neuropathies are often overlooked, because sensory disturbances might be regarded as a minor annoyance compared with other problems. 90% of patients show improvements in median nerve function after surgery, even in those who have had rheumatoid arthritis for longer than 15 years.

Tenosynovitis that limits tendon motion could affect extrinsic extensors and flexors, and intrinsic tendons. Proliferative tenosynovium is characterised by pain, swelling, palpable crepitus, and impaired active movement, and contains increased concentrations of metalloproteinases, collagenases, and cytokines. It may invade and weaken tendons, occasionally causing rupture. Tenosynovectomy prevents rupture in patients at risk. Such procedures are most common dorsally at the wrist, in finger flexor sheaths, and in the carpal tunnel. In one study, 84% of patients were satisfied with the outcome of flexor tenosynovectomy, with recurrent inflammation seen in only 10% of patients over 5 years.

In chronically inflamed joints, the same destructive process distends and damages capsuloligamentous structures, and causes bony erosions and cartilage destruction. When medical management fails to control inflammation, synovectomy reduces joint pain and swelling, and could delay deformity and articular destruction when used in early disease. This process could also obviate the need for more complex surgical intervention and even circumvent the need for other treatments. At surgery, mild joint-deformity can be corrected without joint replacement.

In a multicentre study, synovectomy did not prevent recurrence or produce radiographic improvement beyond 5 years. However, a subsequent randomised study of 48 patients showed a positive effect of synovectomy in patients refractory to medical management. As a primary endpoint of the study, patients in the surgical treatment group showed a significant reduction in the number of swollen and painful joints. This improvement in pain was also accompanied by a significant improvement in erythrocyte sedimentation rate and concentration of C-reactive protein. More than 40% of surgically treated patients remained in remission in 3-year follow-up, during which articular damage did not progress.
With disease progression, synovitis eventually leads to joint instability and destructive arthritis. The wrist rests in radial deviation, with ulnar translocation and supination of the carpus. These changes are seen in 70% of patients 3 years after disease onset.12–14 Dorsal subluxation of the ulnar head also occurs, affecting forearm rotation and causing many ruptures of the digital extensor tendon, which is called the caput ulnae syndrome (figure 1).14 Wrist deformity can be corrected and extensor rupture prevented with early intervention, including ulnar head resection, wrist extensor tendon rebalancing, and tenosynovectomy.12 When radiocarpal arthritis is present, early intervention remains possible. Preservation of the midcarpal joint enables radiolunate arthrodesis to realign the carpus, while maintaining a functional arc of wrist motion. In advanced cases, surgical options might need to be restricted to wrist arthrodesis and tendon transfers. A study of 25 patients followed up for 13 years after limited wrist fusion, resection of the distal ulna, and extensor tenosynovectomy showed resolution of symptoms in 22 patients. Grip strength and forearm rotation were greatly improved. The midcarpal joint space remained preserved in 16 of the 25 wrists. Overall, carpal arthrodesis is one of the few surgical procedures that consistently reduces pain and improves hand function in patients with rheumatoid arthritis.

Chronic synovitis in metacarpophalangeal joints can damage the restraining collateral ligaments and the sagittal band, which balances extrinsic extensor and intrinsic tendon forces. The result is metacarpophalangeal ulnar deviation and palmar subluxation, with ulnar subluxation of the extensor mechanism. Loss of the joint extension takes place, causing a functional problem with grasp and release. More extensive destruction and irreducible deformity to the joint requires joint replacement. Silicone implants function as spacers after resection arthroplasty (figure 2). When enveloped in capsule and scar tissue, these implants provide stability and reliable pain relief.15 Active metacarpophalangeal motion and digit alignment improve initially. Over time, implants can fracture, in association with recurrent deformity and loss of motion. Of 381 patients with metacarpophalangeal arthroplasty, 83% and 63% still have their implanted joints intact at 10 and 17 years, respectively.16 Crossed intrinsic transfer, soft-tissue rebalancing, and wrist realignment with partial or total wrist-fusion have all been associated with improved implant survival.16,17 Patients’ satisfaction with metacarpophalangeal arthroplasty has been linked to functional improvements and to cosmetic improvements of the hand.16,18

New metacarpophalangeal-implant designs with improved fixation methods, new materials, and unconstrained anatomical articular-surface components could improve long-term results of arthroplasty. A recent review19 of these newer joint designs used in patients with osteoarthritis noted a 40% improvement in grip strength and pinch strength, with only two of 19 patients noting joint pain at 1 year postoperatively. Joint stability in these designs depends on soft tissues, including functioning collateral ligaments, which means that implantation must occur before advanced deformity occurs. The early results with this new generation of implants are encouraging. Randomised trials will be needed to study acceptance over established silicone-implant designs.20
At the interphalangeal joints, swan-neck and boutonnière deformities often develop, and become rigid over time (figure 3). Angular deformities also occur, especially in the thumb. Wrist deviation and metacarpophalangeal ulnar-drift affect proximal interphalangeal position, and could need correction before proximal interphalangeal surgery. The swan neck deformity is particularly disabling. Timely intervention is desirable to correct early swan-neck deformities, because rigid deformities usually need arthrodesis in a compromised position to provide the best function. Early correction of swan-neck deformities often consists of tenodesis procedures that restrict function, leading to development of swan-neck deformities.

Successful management of the rheumatoid hand needs a collaborative effort from rheumatologists, surgeons, therapists, and patients. Such working relationships should allow optimum preservation of function over time. Future advances benefiting patients will be facilitated by therapists, and patients. Such working relationships should allow optimum preservation of function over time. Future advances benefiting patients will be facilitated by therapists, and patients.

We declare that we have no conflict of interest.

Human rights abuses threaten health in Burma

Decades of neglect, civil war, and corruption have rendered Burma’s health system incapable of responding to infectious diseases and other health risks. And, as the country closes its doors to more and more aid agencies, the situation only looks set to worsen. Rhona MacDonald reports.

At the end of June, the International Committee of the Red Cross (ICRC)—in a rare departure from its usually confidential stance—publicly denounced the repeated violations of international humanitarian law committed against civilians and detainees by the military government in Burma (Myanmar). The use of detainees as porters for the armed forces and many acts of violence committed against civilians living in conflict affected areas along the Thai-Burma border, are among the long list of abuses committed by the government.

In a press statement on June 29, Jakob Kellenberger, the president of the ICRC said “The ICRC has repeatedly drawn attention to these abuses but the authorities have failed to put a stop to them...The continuing deadlock with the authorities has led the ICRC to take the exceptional step of making its concerns public”.

Between 1999 and 2005, the ICRC visited hundreds of detainees in more than 70 prisons and labour camps to assess their living conditions and treatment. On the basis of the ICRC’s recommendations, and with its support, the detaining authorities worked to improve the water supply, accommodation, and provision of health care available to detainees. This development led to measurable progress: by 2005, the mortality rate of detainees had dropped by 50%, even though it still remained twice as high as within the general population. But, since late 2005, the ICRC has not been able to visit any places of detention and the humanitarian situation seems to be deteriorating.

Carla Haddad, spokesperson for the ICRC at its headquarters in Geneva, told The Lancet more about the situation. “Since 2005, the government of Myanmar has imposed increasingly severe restrictions on ICRC activities, making it impossible for the organisation to continue visits to thousands of detainees in line with its usual working procedures, which include carrying out private interviews with detainees. This has also prevented the ICRC from conducting independent field visits to conflict affected areas and from delivering aid to civilians according to strictly humanitarian, neutral, and apolitical criteria”. Haddad added that “the ICRC’s activities have therefore been drastically scaled down to a few limited projects in the field of physical rehabilitation for amputees and mine victims”.

The military government, which has ruled the country since 1962, has severely restricted the movement of international aid agencies and non-governmental organisations (NGOs) with the result that some have had to leave the country despite its many health problems.

Almost 90% of Burma’s 52 million population are at risk of malaria, and the country has one of the highest rates of tuberculosis in the world with nearly 97,000 cases detected every year. There are 25,000 estimated new infections of HIV every year, with significant spreading of the disease in young people and high-risk groups. A third of children are chronically malnourished, 15% of the population is food insecure, and the under-5 mortality rate is 106 per 1000 compared with 21 per 1000 in neighbouring Thailand.

Yet the military government spends less than US$1 per person on health and education every year—national expenditures in health and education are 3% and 10%, respectively. The military, including an army of over 450,000 soldiers, receives 40% of the budget, even though Burma has been at peace with its neighbouring countries for decades.

According to a recent report by researchers from the Human Rights Center of the University of California at Berkeley and Johns Hopkins Bloomberg School of Public Health, the Burmese military is destroying medical supplies intended for civilian populations and detaining and killing...
The military government has ruled Burma by force for over 40 years

needed to help displaced people hiding in the jungles and conflict zones of Burma, many of whom have infectious diseases.

The UK’s Department for International Development—as one of only four donors based in Burma—is in a leading position to scale up the assistance given to displaced people and refugees. Shahid Malik, the UK Minister for International Development told The Lancet “The British Government is committed to addressing the dreadful levels of poverty in Burma, which is why the UK has been playing a leading role in establishing programmes to provide health services in the country”.

The UK, Australia, the European Commission, the Netherlands, Norway, and Sweden have set up the Three Diseases Fund (known as the 3D Fund), to help fight tuberculosis, malaria, and HIV/AIDS in Burma as part of a $100 million joint-donor programme set up in response to the Global Fund to Fight AIDS, Tuberculosis and Malaria having to pull out of Burma in 2005 due to the restrictions imposed by the Burmese Government. The aim of the 3D Fund is to target those most at risk of being infected by each of the three diseases, with a particular focus on those who have little or no access to public-health services.

Although the authors of the joint University of California, Berkeley, and Johns Hopkins report acknowledge that large infusions of foreign aid directed at the health sector can potentially lessen the burden of infectious diseases in Burma, they also caution that it could have unintended consequences. “This is tricky terrain”, said Stover. “There is always the danger that foreign aid aimed at one specific disease can divert health professionals and their institutions from addressing other serious health problems, and can also provide national authorities with a ready excuse for decreasing even further their paltry expenditures in health.”

Stover and his team are now planning to map what all the various organisations are doing in Burma and its borders and then hold subregional training seminars. “There is no time to wait for international agencies to do something. We need to act now”, he said.

Stover also believes in a soft and hard approach. “International humanitarian aid needs to reach those most in need, but there also has to be continued pressure on the Burmese Government to increase its spending on health, lift the travel restrictions it has imposed on aid and development organisations, and increase the amount of cross border assistance to internally displaced people”, he said.

Stover thinks that it is vital to get China on board for progress to be made, especially now that some Chinese health professionals are concerned with the rates of infectious diseases at the Chinese border with Burma.

In his press statement, the ICRC’s president reminded all states party to the Geneva Conventions of their obligation, under article 1, to respect and ensure respect of the Conventions. Haddad explains what this should mean in practice: “In their bilateral talks with the government of Myanmar, states should urge the government of Myanmar to respect international humanitarian law”.

Meanwhile the continuing behaviour and actions of the armed forces are contributing to a climate of constant fear in the population and have forced many people to leave their homes and join the ranks of the internally displaced, or flee abroad. And, according to the Reuters news agency, Thailand has now closed its doors to new refugees, making their future increasingly uncertain. As Haddad says, the ICRC “are concerned about the lack of provision of basic services to civilians living along the Thai-Myanmar border where no humanitarian organisation has access today”.

Rhona MacDonald
How important is neutrality to humanitarian aid agencies?

As western governments wage “humanitarian wars”, maintaining neutrality in providing aid seems increasingly difficult for non-governmental agencies. Priya Shetty investigates the challenges that Médecins Sans Frontières faces in trying to keep its work free of political agenda.

Vanessa van Schoor recollects the time she was travelling in a Médecins Sans Frontières (MSF) land cruiser in Sharia, south Darfur, when the jeep was flagged down by African Union peacekeepers, who had confused the vehicle for one of their own. For van Schoor, head of MSF’s Darfur mission until 2006, this incident epitomises the growing confusion in distinguishing between military and humanitarian actors in conflict regions—a mix-up that can have fatal consequences for aid workers.

The link between military and relief agencies was so deeply felt, says van Schoor, that in 2005, tribal militia in west Darfur threatened MSF that if UN peacekeepers entered the war-torn area, “we would be considered part of that western front, and a jihad would begin”.

But this was not the first time MSF had been threatened because of perceived links with US forces. In August, 2004, MSF withdrew from Afghanistan after five of its staff were murdered. The increasingly visible links between aid agencies and coalition forces were blamed for the violence. A Taliban spokesperson claimed responsibility for the murders of the MSF Afghanistan workers saying “Organisations like Médecins Sans Frontières work for American interests and are therefore targets for us”.

Not only are military forces increasingly and openly co-opting humanitarian efforts in “hearts and minds” missions, but also several aid agencies have been accused of either willingly collaborating with coalition forces or doing little to disassociate themselves from them—their stance being that it does not matter how political their actions are as long they provide help to those who need it.

But MSF, which views independence from political or religious ideology as a cornerstone of its work, believes it does matter, and 35 years after it was founded, the organisation’s ability to provide independent medical aid to strife-ridden regions is being severely threatened by the lack of distance between military and relief forces.

Western governments had already begun in the 1990s to place humanitarian goals centre stage in military efforts, says Nicolas de Torrente, head of MSF-USA. But it was after Sept 11, 2001, that the ability of humanitarian organisations to remain politically neutral was destroyed. Bush’s us-or-against-us doctrine “denies the possibility of neutrality by simply vanishing it away. It defines the two sides of the conflict—‘terrorism’ versus ‘freedom’ and ‘civilisation’”, said Oxfam’s policy adviser on Iraq, Jo Nickolls.

When former US Secretary of State Colin Powell described non-governmental organisations (NGOs) as “force multipliers”, and former UK Prime Minister Tony Blair called for the need for a “military-humanitarian coalition” these views served only to increase the perception that all western NGOs are merely extensions of foreign policy, says MSF’s UK director Jean-Michel Piedagnel.

MSF does not solely blame the military for the blurring of agendas. Although several MSF staff did not want to name any specific NGO, they said that some aid agencies’ actions—travelling with military escorts, advising military troops on where to deploy, or calling for military intervention in certain conflict areas—are confusing the situation further.

Why does MSF value independence so strongly? The values of neutrality and independence have an “operational value”, says de Torrente. “They help us gain access and reduce security risks enabling us to deliver much needed assistance in volatile and sensitive environments.”

Neutrality, along with independence and impartiality, was a key founding principle of MSF. The agency was created in 1971 by a group of French doctors, some from the ICRC, who challenged the ICRC’s mandate that neutrality meant keeping silent.

On acceptance of the 1999 Nobel Peace Prize, MSF’s then president James Orbinski said “silence has long been confused with neutrality...we are not sure that words can save lives, but we know that silence can certainly kill”.

One of the organisation’s most political activities has been its Campaign for Access to Essential Medicines, which was launched in 1999 to give people in the developing world access to medicines for diseases—such as HIV/AIDS, tuberculosis, and malaria—that are routinely available in western countries. Despite MSF’s reluctance to solve problems—its mandate being to speak out and force governments to act...
to take action—those involved in the campaign say the organisation felt it could not stand by and do nothing.

The campaign proved to be not only high-profile but also highly successful—the pressure applied to governments and pharmaceutical companies helped to bring down the price of antiretrovirals for developing countries from US$10 000 per year to less than $300. But the organisation struggled to reconcile the overtly political tone of the access campaign with its traditionally neutral stance. Mary Moran, now head of the Pharmaceutical Research and Development Policy Project in Sydney, Australia, joined MSF to help set up the campaign. She recalls the fierce debate within MSF over whether the campaign was in line with the agency’s principles. "It never went smoothly within MSF, there were moves to shut the campaign down; it was always under pressure to stay small", she says.

Oxfam, among others, felt compelled to speak out against Iraq war because of the effect it would have on civilians to which MSF workers were killed in 2003. Its spokesperson Michael Bailey says "we thought that the consequences for the civilian population would be sufficiently grave, and outweigh the benefits of the military intervention".

But MSF founder Rony Brauman has questioned the merit of such antiwar statements. "Nobody thought to ask these NGOs on what information or strategic analysis they based their assertions, nor what instrument Oxfam and others used to measure the intensity of a humanitarian crisis caused by bombing in comparison to the crisis produced by Saddam Hussein's dictatorship", he said.

For several agencies, remaining non-political in the current highly charged political climate is unrealistic. Paul O’Brien, ex-advocacy coordinator in Afghanistan for aid agency CARE, disagrees with de Torrente’s calls for humanitarian aid agencies to remain non-political. Writing in the Harvard Human Rights Journal in 2004, he says that, post 9/11, “politics are too important to be left to politicians. The fiction of humanitarian neutrality… can no longer be relied upon for all humanitarians in highly politicized contexts such as Afghanistan and Iraq. In such environments, politicized humanitarianism is both right and realistic”.

Financial independence is key to operational and political independence says de Torrente; more than 80% of MSF’s annual budget—about $500 million—comes from private donors as unrestricted funds (ie, not tied to any crisis or country). Although NGOs who accept funding from governments should not be branded as sell-outs, says Bailey, Oxfam would refuse funding that might subject it to political control. It does not take money from USAID, for example, because of the perception of the US government’s greater demands—compared with European Union countries—for political allegiance from the aid agencies that it funds. This difference has also led some to speculate whether US NGOs value neutrality less than their European counterparts.

For Abby Stoddard, at the Center on International Cooperation, a research and advocacy organisation based in the USA, such differences are philosophical rather than practical. “Both US and European NGOs can and do operate independently of the great power governments on the ground, even those who receive large shares of their funding from them.” But ultimately, she says, “people in dire need tend not to care where the aid comes from as long as it comes”.

As for the future, MSF’s sole focus is getting aid to those who need it most. Despite concerns over a lack of humanitarian space in Iraq, it re-entered the fray, setting up a new mission in Amman last August. Whether it will return to the heart of conflict is uncertain. “We will continue exploring possibilities”, says MSF’s International Council president Christophe Fournier. Afghanistan is still a no-go area until judicial processes surrounding the killing of the MSF workers have been resolved. But returning to the country is high on the agency’s agenda, says Vickie Hawkins, head of operations for MSF Afghanistan in 2004.

Adhering to its core principles of neutrality, impartiality, and independence is a daily battle, says Piedagnel. “We are continually asking ourselves whether we are compromising, and if we are, is it acceptable?” The wider NGO community might benefit from a reminder of these principles, suggests Bailey, “some of the ideals of humanitarianism need to be re-argued and re-fought”.

Priya Shetty
I was recently incensed by an editorial in The Economist that dismissed all social and economic rights, like many other readers I wrote in, querying their stance, and enquiring if The Economist had ever heard of the United Nations’ Universal Declaration of Rights. The response I got from one of the editors left me stunned: “I am of course aware that economic and social rights feature in the UN declaration on human rights and elsewhere. The ‘right’ to a job, education, health, etc sounds superficially attractive, but in practice it is either pernicious or meaningless.” He continued, “It would be more honest if the defenders of these economic, social, and cultural rights would come straight out and say that they believe that socialism is the answer, and campaign for it, rather than dressing up their demands for more state intervention in the legalistic language of rights.”

So what is the best response to such human rights “denialists”? Writer, mathematician, epidemiologist, and human rights activist, Théodore MacDonald gives us many of the answers in The Global Human Right to Health: Dream or Possibility? It is perhaps a reflection of the breadth of experience and expertise of the author that he takes you on a rapid, but well researched, journey through many of the issues involved in human rights. He explains the historical background of the UN, and its related agencies—the World Trade Organisation, the International Monetary Fund, The World Bank, and WHO—before discussing the human rights involved in each of the Millennium Development Goals, such as access to clean water. He details the inequalities in global wealth distribution and the role of transnational corporations in thwarting human rights. He uses a wealth of data and evidence from many different sources to make his case with conviction and clarity. His message is clear. We must find and evaluate alternatives to neoliberalism or there is no hope of ever achieving the human right to equity in health. MacDonald outlines neoliberalism’s fatal flaw; “Like any competition, it produces winners (and that is its attraction), but it must also produce losers, and they are as integral a part of the system as the winners. We cannot merely say that the losers are a blip on the system and that fine-tuning the whole apparatus will gradually fade them out of the picture. Without the losers, the system wouldn’t work.”

And when losing means poverty and degradation, it is easy to see how neoliberalism might lose its attraction for those not fortunate enough to be winners. Indeed, the World Bank has estimated that between 1993 and 2003, globalisation created 200 million new poor people.

So what alternatives does MacDonald offer? He proposes that some radical changes towards internationalism are needed, including a global finance system, and believes that the only existing body that has any hope of making the right to global equity in health a reality is the UN. But the UN itself would have to change almost beyond all recognition to take up this role. As the author succinctly puts it: “The UN is constituted to protect the rights of nations, but not the rights of people.”

At present, the UN is a complicated conundrum of contradictions. How can it protect and support human rights while simultaneously running agencies that sustain the violation of these rights? In Health, Human Rights and the United Nations: Inconsistent Aims and Inherent Contradictions? MacDonald deals with this very question. The UN’s many internal problems and frequent inconsistencies in its decisions and actions are the inevitable result of the incongruity of its current make up, which reflects history rather than the 21st-century world. The current UN reforms may deal with some of the more peripheral issues, but in MacDonald’s opinion the planned reforms will not tackle the root of the UN’s problems. These fundamental problems contribute to its paralysis and powerlessness to do anything apart from observe the many human rights abuses perpetrated by some governments. For example, like many, I am frustrated by the UN’s inaction in the face of despicable atrocities such as that currently taking place in Darfur. So I am left wondering what on earth is the point of having the UN if it lacks the ability to intervene in such appalling situations?

With impressive attention to detail and use of contemporary information—much of it gathered from non-governmental organisations (NGOs)—MacDonald studies the past and present human rights situation in Darfur, Liberia, Burma, and the Occupied Palestinian Territories. His analysis of this series of UN disasters helps shed light on the reasons for the organisation’s present passivity.

The Darfur crisis raises the issue of the UN’s inability to sustain its stewardship of the Universal Declaration of Human Rights. For example, in 2005 when it became obvious that the UN was not going to intervene effectively, either by trade sanctions or otherwise, the National Security officials in Darfur suddenly became much more resistant to the UN Mission. As for Burma, in 2005 Paulo Sergio Pinheiro, the UN Special
Rhona MacDonald, vented his frustrations to the General Assembly: “the Government of Myanmar (Burma) has not invited me to visit the country since November, 2003...which I deeply regret.” He then went on to detail the widespread and systematic violations of human rights in Burma and the consistent failure of the government to protect its citizens. However, the latest UN attempt to censure Burma was vetoed by China who is the biggest importer of natural resources from Burma and so would have a lot to lose if sanctions were imposed. Liberia also has a long history of human rights abuses, including recruiting child soldiers and sexual exploitation of female refugees. According to reports from several NGOs, which MacDonald documents, the UN Mission in Liberia does not take sexual exploitation seriously, with some UN employees reported as saying that “Liberian women choose to be prostitutes”. And where do you even begin to start with the Occupied Palestinian Territories? MacDonald writes: “Since Israel’s 1967 occupation of the West bank, Gaza and East Jerusalem, there has been almost unanimous international consensus on how to resolve the crisis—an international conference based on international law and UN resolutions. However, Israel disagreed, and this was backed by the US.” He then discusses the repeated failures of the UN in this complex and highly political humanitarian disaster.

After this depressing analysis that showcases the persistent failures of the UN to protect human rights, MacDonald discusses some possible ways forward. He describes the UN as a possible “village policeman” in the “global village” but argues: “if the UN is to be a successful ‘village policeman’ for the world though, it has to find some way of separating its advocacy and mediator roles.” He suggests doing away with the current veto system that is a convenient vehicle to best serve the political interests of the “Big Five”—the USA, Russia, China, the UK, and France—and proposes an alternative: “General Assembly members should be elected by ballot all the adult suffrage that they will represent. If a smaller subgroup with veto powers is felt (by the General Assembly members) to be useful, then they should be elected regularly by the General Assembly. Permanent veto power is unacceptable. This would effectively guarantee that the economically powerful countries will not always wield their power.”

MacDonald acknowledges that overcoming the tendency of member states to make decisions on the basis of narrow national interests rather than global needs remains a difficult obstacle. However, he believes that the remediation of this problem lies with the political determination of each state, recommending that powerful states like the G8 would have to lead the way. But if progress on the nuclear non-proliferation treaty and the agreement to give 0.7% of their gross national income to tackle the MDGs in poor countries is anything to go by, the G8 has so far set an appalling example.

So who can save the UN? MacDonald discusses the potential merits of the current UN Secretary General Ban Ki-Moon to lead the UN in a more positive direction, before pointing the finger directly at us—citizens of the global village. MacDonald holds great faith in the power of people, believing that the reforms he has proposed are best made by the determination of citizens to elect politicians most suited for the task. He is also optimistic about the ability of people to change the world. His books are educational, journalistic, and inspiring and are aimed at “ordinary people”. He believes that if such people know what is being done in their name, as he has outlined in his books, they will stand up, make a noise, and start asking awkward questions. I am also an optimist who believes in the power of people to change the world, but I wish I had more faith in our desire to do so. Both of these books highlight that there is no excuse for inaction in the face of the human rights abuses taking place under the UN’s watch. After all, complacency equals complicity.

Rhona MacDonald
rhona.macdonald@lancet.com
Paul Hunt is a human rights lawyer who decided, about 15 years ago, that he needed to expand the traditional boundaries of his calling. While working in Africa, he saw that there was a whole human rights dimension that was being largely unaddressed. “I made a conscious shift as an academic and something of an activist as well. Africa was a turning point, when I appreciated very well how crucial economic, social, and cultural rights were, including the right to health.” Hunt was ahead of his time, and if the world is now catching up, he must take some of the credit. Since 2002, he has been UN Special Rapporteur on the right of everyone to the highest attainable standard of physical and mental health, which has now involved him in groundbreaking human rights struggles. His job, created by the UN Commission on Human Rights, is to inform, advise, and support countries in the understanding of health as a human right and, inevitably, it also means that he will blow the whistle. There are things that he can say but the UN secretariat cannot. “I push boundaries, but I stay within my mandate”, he says. “If I fail to do that, I will be in trouble with the Human Rights Council.”

He was, for instance, appalled by the camps for displaced people in northern Uganda during 2005. “What shocked me was the UN’s neglect of that issue and those people for 18 years. At the press conference I held on leaving Uganda, I was very critical of the UN.” His words, and the efforts of others too, he says, seem to have had some effect on the UN’s work in the region. “I think it’s my job to speak within my mandate, but robustly, boldly and independently”, he says. Naturally, that gets him into trouble. In 2004, one of his first reports was on sexual and reproductive health rights. “I was concerned that progress made at Cairo in the 1990s and Beijing was being rolled back. I thought it was important to say these were integral rights to the right to the highest attainable standard of health.” His report was criticised by the USA, Saudi Arabia, Cuba, Pakistan, and Egypt. His later work on the detainees of Guantanamo Bay was less controversial, “We said close it. That was achievable. “Since then it has become commonplace.” When Hunt and his colleagues reported on the conflict between Lebanon and Israel last year, there was far more trouble—their report “was criticised by just about everybody”, he says.

So did the Israel/Lebanon report achieve anything? That’s hard to know, in his work, Hunt says. The report struggled with the issue of cluster bombs and was forced to conclude they were not unlawful under international law. But it said they should be unlawful. “Since then there is the beginning of a move to outlaw cluster bombs. Our report was probably one contribution to the groundswell against these appalling weapons.” Hunt recognises that results are difficult to achieve. He tells how his son, Rob, was once asked by a friend, “What does your Dad do?” within Hunt’s hearing, “to which Rob replied, somewhat weakly, ‘he travels around the world doing good’. There was then a nicely timed pause and deep sigh, ‘but it never works’. Sometimes it feels like Rob was right, but then I hear that, say, a government is changing a law or policy and maybe one of my interventions had a bearing on this change of heart.”

Hunt has always had a desire to change the world. He read law at Cambridge University with the intention of using it as a tool to help bring social justice to impoverished and deprived people. Following civil and criminal litigation, he went to Gaza and the West Bank to help a fledgling human rights organisation, returning to the UK to work with the National Council for Civil Liberties, now Liberty. After the formative experience in the Gambia with the African Centre for Democracy and Human Rights Studies, he moved to New Zealand and was nominated to the UN Committee on Economic, Social and Cultural Rights and then to the newly created post of Special Rapporteur in 2002. A professor of law and a member of the Human Rights Centre of Essex University, UK, he is also an adjunct professor of law at Waikato University, New Zealand.

Adriaan van Es, founder of the Netherlands-based International Federation of Health and Human Rights Organisations, says Hunt has helped put health as a human right on the map. “I think that he has contributed greatly to establishing and elaborating a real picture of what the right to health means”. He adds that Hunt “is quite outspoken. He refrains from being too confrontational but in his diplomatic language you can read a lot of outspoken lines and positions on a lot of subjects. Nobody questions the right to a fair trial and he has helped develop an understanding that there should be an equal entitlement to a functioning health-care system as a core right within a state.”

Last year, Hunt gave a speech to the General Assembly on maternal mortality which, he says, “was as punchy as I can be within the rules both spoken and unspoken”. The human rights community, he said, “should take up the issue just as vigorously as it does extrajudicial executions, arbitrary detentions, and prisoners of conscience”. Then he produced figures to show how much more common maternal deaths are than all these other injustices. Of his job, he says, “It’s a wonderful thing to do. Utterly impossible of course. The UN does not provide me with sufficient resources to monitor the right to the highest attainable standard of health in Essex, never mind the UK, Europe, and the world. But I do my best.”

Sarah Boseley
sarah.boseley@guardian.co.uk
Dame Anne Laura McLaren

Developmental biologist and geneticist who influenced the science and ethics of reproduction and embryology. She was born in London on April 26, 1927, and died in a motor vehicle accident on July 7, 2007, aged 80 years.

Anne McLaren was one the UK's most respected scientists, with a career that spanned five decades and encompassed fundamental discoveries in embryology, genetics, and reproduction. But according to her own characteristically modest explanation, she only went into science because the university entrance exam for English literature involved too much reading. In an interview published shortly before her death, McLaren said “I looked at all the papers and biology was easiest—you didn’t have to read so much, you could swat it all up from textbooks, as opposed to reading novels and poems.” It’s certainly true that McLaren rarely allowed literature to distract from science or her family, remembers Elizabeth Simpson, from Imperial College London. Simpson and McLaren met in 1970 at a party at the house of immunologist Peter Medawar. “My baby daughter was asleep in a carrycot in a quiet part of the house, and from our first conversation it was clear that Anne was very enthusiastic about babies, both human and murine!”

McLaren once said she was interested in “everything involved in getting from one generation to the next”, a phrase that serves as an elegant summary of her prodigious career, which began in the early 1950s at University College London. There, she and her husband Donald Michie (who died in the same accident as McLaren) began studying differences in the number of lumbar vertebrae in inbred mice. The questions they wanted to answer about the role of the uterine environment required better techniques for superovulation and embryo transfer, says Robin Lovell-Badge, from the National Institute for Medical Research in London, UK. “The techniques they developed then are still used by people all over the place”, he said. Later that decade, McLaren moved to the Royal Veterinary College in London, where she and John Biggers showed that early mouse embryos could be grown outside the uterus, and still develop to term once returned to the uterus. It was work that would help pave the way for the arrival of in-vitro fertilisation for human beings in the 1970s.

McLaren’s degree in zoology was earned at Lady Margaret Hall, Oxford University, and over the following decades she made a large number of important contributions to reproductive biology. “She did significant things throughout her life”, says Simpson. “There have been at least half a dozen really seminal things.” For example, she undertook important work on chimeras and germ cells during the 1960s and 1970s, as well as leading the Medical Research Council’s Mammalian Development Unit, created around her in 1982 to catalyse research into mouse genetics, embryology, and reproductive biology. In 1984, McLaren and Simpson revolutionised our understanding of the male-determining gene on the Y chromosome, disproving the prevailing theory that the H-Y transplantation antigen was the Y-dependent testis inducer.

As a mentor to other scientists, McLaren had an extraordinary capacity for calm and pragmatic advice, remembers Jim Smith, Chairman of the UK’s Wellcome Trust/Cancer Research UK Gurdon Institute. Her insights were never routine, adds Lewis Wolpert, who lived across the road from McLaren for some time. “If you wanted advice on anything, she would consider it and give you the most original response”, he said. Beyond the laboratory, McLaren immersed herself in public debates over the social and ethical implications of human reproduction. She was a member of the Warnock Committee that had an important role in the passing of the 1990 Human Fertilisation and Embryology Act, and served for a decade on the regulatory body that it established, the Human Fertilisation and Embryology Authority. From 1991 to 1996, McLaren was Foreign Secretary of the Royal Society, the first woman officer of the society. She officially retired in 1992, but continued researching primordial germ cells at the Gurdon Institute, and was still publishing papers last year. She received many awards, including the Royal Medal of the Royal Society and the Japan Prize, and was made a Dame in 1993.

Stephen Pincock
stephenpincock@gmail.com
Acute lung injury and acute respiratory distress syndrome

In their Review on acute lung injury and the acute respiratory distress syndrome (May 5, p 1553),1 Arthur Wheeler and Gordon Bernard attribute pulmonary oedema in acute lung injury to increased vascular permeability with leakage of oedema fluid into the lungs, and state that no specific treatment is available. They do not mention that a reduction of alveolar fluid clearance is equally important.

Mortality in patients with acute lung injury is strongly associated with reduced pulmonary fluid clearance.2 Improvement has been achieved by use of β agonists, which act on alveolar sodium and chloride transport, generating the osmotic gradient that removes water from the alveolar airspace. An increase in chloride channel function by β agonists was shown in children with pulmonary oedema related to meningococcal septicaemia.3 Wheeler and Bernard claim that β agonists do not improve outcome in patients with acute lung injury. However, a double-blind randomised controlled trial has shown that intravenous salbutamol significantly decreases lung water and plateau intravenous salbutamol significantly decreases lung water and plateau intravenous salbutamol significantly decreases lung water and plateau

In panel 1 of their Review,1 Arthur Wheeler and Gordon Bernard list the causes of acute lung injury. Among drug-related causes, only overdoses of salicylates and narcotics are cited. Yet the list of drug-related causes is extensive.2 Non-cardiogenic pulmonary oedema has been seen in relation to hydrochlorothiazide, antineoplastic agents, tocolytic medications, and several other drugs.3,4 Gemcitabine, amiodarone, nitrofurantoin, catarabine, and infliximab have been implicated as possible causes of acute respiratory distress syndrome.2,3 The exact mechanism of pulmonary toxicity has not been elucidated for most drugs.

Acute lung injury and acute respiratory distress syndrome are common clinical manifestations of drug-induced lung injury.1 The possibility of such must be kept in mind, and systematically evoked, particularly if the cause of lung injury is not evident. Diagnosis is based on a history of drug exposure with a temporal relation between the introduction of the drug and the onset of symptoms, and on exclusion of other causes of acute lung injury. Clinical management is based on timely withdrawal of the offending drug and supportive measures. Symptoms resolve quickly, although fatalities have been reported with some drugs. Corticosteroids might be necessary in some cases.2

Use of potentially harmful drugs (ie, acute-lung-injury inducers) in patients with acute respiratory distress syndrome warrants caution and awareness. Indeed, many researchers suggest the avoidance of amiodarone for treatment of supraventricular and ventricular arrhythmias in case of severe respiratory failure, and after thoracic or non-thoracic surgery.1 We declare that we have no conflict of interest.

*Chaker Ben Salem, Houssem Hmouda, Kamel Bouraoui
chaker_doc@yahoo.fr

Département de Pharmacologie Clinique, Faculté de Médecine de Sousse, Avenue Mohamed Karoui, 4002 Sousse, Tunisia (CBS, KB); and Medical Intensive Care Unit, Sahhlou University Hospital, Sousse, Tunisia (HH)


Arthur Wheeler and Gordon Bernard,1 in their excellent Review on acute lung injury and acute respiratory distress syndrome, comment that there is a paucity of data to guide selection of formula for administering enteral nutritional support to such patients. Two recently published randomised controlled trials3,4 have shed new light on the issue of enriching enteral diets with eicosapentaenoic acid, γ-linolenic acid, and antioxidants. In the first study,2 Singer and colleagues showed significant improvement in gas exchange variables and respiratory mechanics, and a shorter duration of mechanical ventilation, in patients with acute respiratory distress syndrome who received enteral nutritional support enriched with eicosapentaenoic acid and γ-linolenic acid. In the second trial, Pontes-Arruda

Michael Eisenhut
michael_eisenhut@yahoo.com

Luton and Dunstable Hospital NHS Foundation Trust, Lewsey Road, Luton LU4 0DZ, UK

Correspondence
and colleagues showed an absolute reduction in 28-day mortality of 19.4% (67.3% vs 47.9%; p=0.037) in the group that received enteral feeds enriched with eicosapentaenoic acid, γ-linolenic acid, and antioxidants. This group also had significant improvements in oxygenation status, a higher number of ventilator-free days and days out of intensive care, and fewer new organ dysfunctions.3

These beneficial effects of immunonutrition possibly result from reduced production of proinflammatory eicosanoids and cytokines, caused by alteration of the availability of arachidonic acid in tissue and immune-cell phospholipids.4 This reduction serves to attenuate the severity of pulmonary inflammation and thus the increase in alveolar-capillary membrane permeability. The relatively low cost of enriched enteral nutritional support, as well as the safety with which it can be given, makes immunonutrition a promising new frontier in the management of patients with acute lung injury and acute respiratory distress syndrome.

I declare that I have no conflict of interest.

Navneet Singh
navneetchd@yahoo.com

Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Sector 12, Chandigarh 160012, India


The Review by Arthur Wheeler and Gordon Bernard1 provides an incomplete picture of recent publications on prolonged glucocorticoid treatment in acute respiratory distress syndrome.

Several randomised trials have been published on prolonged glucocorticoid treatment (for 7 days or more) in early acute lung injury,2 early acute respiratory distress syndrome,3 and unresolving acute respiratory distress syndrome.4 These trials consistently report that prolonged glucocorticoid treatment is associated with significant improvement in PaO2/FiO2,4 and a significant reduction in markers of systemic inflammation,2–4 bronchoalveolar lavage neutrophilia,4 duration of mechanical ventilation,2–4 and stay in intensive care.2–4

The effect of glucocorticoids on the duration of mechanical ventilation is far greater than that seen with the recommended low tidal volume ventilation.2 The absolute reduction in mortality (13%) is also greater than the 9% reduction seen with low tidal volume ventilation.2 Most importantly, the mortality benefits of glucocorticoid therapy are more significant when treatment is started before day 14 of acute respiratory distress syndrome.14 No other treatment in acute respiratory distress syndrome has shown a similar level of improvement in biological and physiological variables and survival.

Additionally, glucocorticoid treatment has a strong benefit/risk ratio when it is applied in conjunction with measures shown to reduce morbidity associated with glucocorticoids.3 These measures include intensive infection surveillance, avoidance of paralytic agents, and avoidance of rebound inflammation with premature discontinuation of treatment that might lead to physiological deterioration and reintubation.1

Correct use of this inexpensive and highly effective anti-inflammatory therapy saves lives.

We declare that we have no conflict of interest.

‘G Umberto Meduri, Paul E Marik, Stephen M Pastores, Djillali Annane umeduri@utmem.edu

University of Tennessee Health Science Center, Division of Pulmonary, Critical Care, and Sleep Medicine, 956 Court Avenue, Room H316, Memphis, TN 38163, USA (GUM); Thomas Jefferson University, Philadelphia, PA, USA (PEM); Memorial Sloan-Kettering Cancer Center, New York, NY, USA (SMP); and Université de Versailles Saint-Quentin-en-Yvelines, Garches, France (DA)


Authors’ reply

We agree with Michael Eisenhut that, along with numerous other actions, β agonists increase fluid clearance from the lung, although we are unaware of data to suggest that fluid clearance is “equally important” to the processes favouring oedema formation. Although β agonists have been shown to improve physiological variables, and in uncontrolled studies are associated with improved clinical outcomes, improvements in important clinical outcomes (eg, survival or ventilator time) in placebo-controlled trials remain unproven. However, the US National Heart Lung and Blood Institute Acute Respiratory Distress Syndrome (NHBLI ARDS) Network investigators find this idea sufficiently promising that we are poised to launch the very placebo-controlled trial of β agonists in acute lung injury that Eisenhut believes is warranted.

Chaker Ben Salem and colleagues correctly write that several drugs can...
cause acute lung injury, and we believe clinicians should carefully consider all possible causes. The references Salem provides nicely summarise the topic. Unfortunately, space limitations precluded presentation of an extensive list of drug-induced causes and we thought it important to emphasise that, numerically, pneumonia, severe sepsis, and aspiration lead the list of causes.

We strongly agree with Navneet Singh that the studies by Gadek, Pontes-Arruda, and Singer form a solid foundation to justify doing a large randomised placebo-controlled trial in which omega-3 fatty acids and antioxidants are studied with survival and days ventilator-free as endpoints. In fact, the NHLBI ARDS Network has designed such a trial that will be starting imminently.

Gianfranco Meduri and colleagues’ letter highlights the persistent controversy about the use of corticosteroids in acute lung injury. No single adequately powered study in which patients with acute lung injury are treated and analysed as randomised (i.e., intention-to-treat design) has ever shown a survival benefit for corticosteroids. We question the validity of combining studies of heterogeneous populations and varied treatments to draw further conclusions on this question.

We agree that oxygenation or experimental markers of inflammation might be improved, as they are for other investigational therapies (e.g., nitric oxide), and perhaps that patients can be temporarily removed from ventilation more rapidly. However, we are unaware of data to support the existence of the concept of “rebound inflammation”.

Like Meduri and colleagues, we wish corticosteroids offered a survival advantage, but we were simply unable to confirm such a positive effect on overall outcome in the ARDS Network trial, which is by far the largest to date to address this question.1

**WHO guidelines for treatment of severe pneumonia**

We welcome the publication by Lisa McNally and colleagues (April 28, p 1440),1 which provides vitally important information on the causes of pneumonia in a population of HIV-exposed children in sub-Saharan Africa. However, we believe that McNally and colleagues’ conclusion that the WHO guidelines are inadequate for all children younger than 1 year, irrespective of HIV prevalence, is ill-founded. Several characteristics of the population in McNally and colleagues’ study limit the generalisability of the findings. Unlike the circumstances at the study’s referral centre in Durban, South Africa, WHO’s pneumonia guidelines provide guidance on the management of acute respiratory infections in facilities with limited diagnostic capabilities.2 They are also meant to assist first-level workers in the identification of sick or very sick patients for referral and more intense management.

Other factors that detract from the generalisability of the findings are the inclusion of a high proportion with very severe disease (71%) and clinical cyanosis (55%), late presentation of disease at enrolment (median 4–5 days), a very high rate of HIV infection or exposure (68% positive, 11% exposed), high previous use of antibiotics (39%), and young median age (4–8 months).

Taken together, we believe that these characteristics of the study population identify a highly specialised group of children from whom conclusions about the microbial causes of pneumonia are limited. Furthermore, these data are not sufficient to conclude that (a) the same range of agents causes pneumonia in areas of low or moderate HIV prevalence, or that (b) the WHO recommendations for empirical treatment of pneumonia in infants should be changed at this time.

SQ, MW, and OLD are employed by the Department of Adolescent Health and Development, World Health Organization. *Shamim Qazi, Martin Weber, Olivia Lawe-Davies, Donald M Thea qazis@who.int

Department of Adolescent Health and Development, World Health Organization, 1211 Geneva 22, Switzerland (SQ, MW, OLD); and School of Public Health, Boston University, Boston, MA, USA (DMT)


**Authors’ reply**

Shamim Qazi and colleagues challenge our conclusion, arguing that our patient population was highly specialised and therefore not representative. We disagree. The HIV epidemic has critically stretched health-care resources in endemic areas, resulting in admission of only the sickest children.1 Although King Edward Hospital, where our study was done, is a referral centre, children were included in our study only if they fulfilled WHO criteria and

APW and GRB are investigators in the US National Institutes of Health NHLBI ARDS Network.

gordon.bernard@vanderbilt.edu

Vanderbilt University School of Medicine, Nashville, TN 37232, USA


Correspondence
were referred directly from primary care. South Africa has implemented the WHO Integrated Management of Childhood Illness guidelines. Children therefore receive a dose of parenteral antimicrobials before referral for secondary-level care, partly explaining why 39% of children in our study had urinary antimicrobial activity.

We have compared the characteristics of our study children with those published for children enrolled in similar studies in areas with varying HIV prevalence (table). Graham and colleagues described children admitted to hospital with pneumonia in Blantyre, Malawi—an area of high HIV prevalence. The duration of symptoms, age of children enrolled, and previous antibiotic use were similar to those in our study. Although data are limited, the characteristics of children in our study are also broadly similar to those reported in other paediatric pneumonia studies from medium-prevalence and high-prevalence HIV-endemic areas.

Shamim Qazi and Donald Thea have themselves called for a change in first-line WHO therapy in areas of high HIV prevalence, with which we agree. We too recognise the need for studies like ours to be done in areas with moderate or low HIV prevalence. In the meantime, reappraisal of empirical antimicrobial therapy in highly HIV-infected communities is urgently needed.

LM joined GSK Biologicals after the study ended and has GSK shares. GSK had no involvement in the study design or funding.

The important study by Lisa McNally and colleagues challenges the validity of the WHO recommendations for empirical antibiotic treatment of HIV-infected children with pneumonia. It is, however, important to recognise the limited options for improving these recommendations, given the complexity of the causes of pneumonia among children for whom treatment fails.

In particular, changes of antibiotic regimen alone would be unlikely to improve treatment failure in children infected with respiratory viruses (33%). Some of the pneumonias caused by both pneumococci and respiratory viruses might, however, be preventable by vaccination with pneumococcal conjugate vaccines. Additionally, the identification of *Pneumocystis jirovecii* as the most significant pathogen in infants with treatment failure, despite empirical treatment as recommended by WHO, confirms the limited success of treating HIV-infected children with severe *P. jirovecii* pneumonia.

The higher prevalence (15%) of *Mycobacterium tuberculosis* in this study than in three other studies (8% each), might be related to a greater sensitivity of methods used for sample collection and an increasing burden of tuberculosis. Nevertheless, the observation that *M. tuberculosis* was identified in 21.8% of children with treatment failure perhaps merits most attention. Of particular noteworthiness is that all the studies focused on children with an acute illness, challenging the numerous clinical algorithms used for making a clinical diagnosis of pulmonary tuberculosis and the notion that this disorder rarely presents acutely.

The management of childhood pulmonary tuberculosis deserves greater priority and is the one issue that can and should be addressed more urgently. We believe tuberculosis should be included in both diagnostic and therapeutic algorithms for acute childhood pneumonia in areas with high HIV and tuberculosis prevalence.

### Table: Comparison of patients’ characteristics between pneumonia studies in HIV-endemic areas

<table>
<thead>
<tr>
<th>Site</th>
<th>McNally</th>
<th>Madhi</th>
<th>Bakeera-Kitaka</th>
<th>Graham</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of children</td>
<td>Durban, South Africa</td>
<td>358</td>
<td>1215</td>
<td>121</td>
</tr>
<tr>
<td>Proportion with HIV</td>
<td>68%</td>
<td>45%</td>
<td>36%</td>
<td>62%</td>
</tr>
<tr>
<td>Mean age (months)</td>
<td>5</td>
<td>9 (8)*</td>
<td>9 (13)†</td>
<td>5</td>
</tr>
<tr>
<td>Median SP0₂</td>
<td>88%</td>
<td>NR</td>
<td>79 (84)†</td>
<td>60 (86) [89]†</td>
</tr>
<tr>
<td>Median days cough</td>
<td>5</td>
<td>NR</td>
<td>NR</td>
<td>5 (3) [3]†</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>67</td>
<td>NR</td>
<td>72 (71)†</td>
<td>80 (80) [72]†</td>
</tr>
<tr>
<td>Previous antibiotic use</td>
<td>39%</td>
<td>NR</td>
<td>NR</td>
<td>53%</td>
</tr>
<tr>
<td>Mortality</td>
<td>15%</td>
<td>7%</td>
<td>24%</td>
<td>22%</td>
</tr>
</tbody>
</table>

NR=not recorded in publication. Different papers use IQR or range and therefore only medians or means are quoted. *HIV-infected (HIV-uninfected); †Children with *P. jirovecii* pneumonia (children without *P. jirovecii* pneumonia); ‡Children with *P. jirovecii* pneumonia (children with bacteraemic pneumonia) [other children].

The higher prevalence (15%) of *Mycobacterium tuberculosis* in this study than in three other studies (8% each), might be related to a greater sensitivity of methods used for sample collection and an increasing burden of tuberculosis. Nevertheless, the observation that *M. tuberculosis* was identified in 21.8% of children with treatment failure perhaps merits most attention. Of particular noteworthiness is that all the studies focused on children with an acute illness, challenging the numerous clinical algorithms used for making a clinical diagnosis of pulmonary tuberculosis and the notion that this disorder rarely presents acutely.

The management of childhood pulmonary tuberculosis deserves greater priority and is the one issue that can and should be addressed more urgently. We believe tuberculosis should be included in both diagnostic and therapeutic algorithms for acute childhood pneumonia in areas with high HIV and tuberculosis prevalence.
Tunelled pleural catheters in malignant pleural effusion

In a Comment on the safety of talc for pleurodesis in patients with malignant pleural effusions (May 5, p 1494), 1 Yossef Aelony suggests that treatment of this disorder with indwelling tunelled pleural catheters can shorten survival. Our work is quoted in support of this remark, 2 but we believe that our data have not been correctly interpreted.

Although the goal of treatment with tunelled pleural catheters is symptom control and not pleurodesis, a substantial number of patients do achieve “spontaneous” pleurodesis, which simplifies care of these patients. This event requires lung re-expansion as well as time, occurring at a median of 59 days after catheter placement in our experience. 1 As such, we believe that patients with short life expectancy do not spontaneously pleurodese as often as patients who have a longer life expectancy, mostly because they do not live long enough to reach this endpoint.

Our data can in no way be used to infer that tunelled pleural catheter treatment and the associated lack of spontaneous pleurodesis is the cause of shortened survival. In fact, the lack of a negative effect of tunelled pleural catheter treatment on survival has been well documented in a randomised controlled trial in which the technique was compared with doxycycline pleurodesis: survival rates were identical between the two groups. 3

I declare that I have no conflict of interest.

Alain Tremblay
atremlay@ucalgary.ca
Division of Respiratory Medicine, University of Calgary, Calgary, Alberta T2N 4N1, Canada

Our data can in no way be used to infer that tunelled pleural catheter treatment and the associated lack of spontaneous pleurodesis is the cause of shortened survival. In fact, the lack of a negative effect of tunelled pleural catheter treatment on survival has been well documented in a randomised controlled trial in which the technique was compared with doxycycline pleurodesis: survival rates were identical between the two groups. 3

I declare that I have no conflict of interest.

Yossef Aelony
y.aelony@cox.net
Harbor-UCLA Medical Center, Torrance, CA 90502, USA


Author’s reply

Alain Tremblay correctly indicates that the fact that the patients in his study who did not spontaneously pleurodese died sooner than those who pleurodese does not prove that pleurodesis failure and continued drainage of protein-rich or lymphocyte-rich fluids were the cause of their shortened life.

What are the arguments favouring talc pleurodesis over tunelled pleural catheter drainage? First, pleurodese patients live longer. 1 Second, many physicians believe that continued loss of protein and lymphocytes through a chest tube could impair host defences against a tumour. Third, it has been suggested that, since malignant pleural mesothelioma is paucivascular, effective pleurodesis could deprive this neoplasm of important pleural fluid nutrients. 2 And fourth, talc could function as a specific tumour suppressant. 3 Permanent suppression of the effusion and talc tumour suppression could explain why talc poudrage—which is more effective than most pleural sclerosants—might be associated with longer survival in malignant pleural mesothelioma. 4

Tremblay’s reference 3 shows that a relatively inferior form of pleurodesis—doxycycline instillation—was associated with the same survival as the tunelled catheter. However, doxycycline failed to create pleurodesis in 32%; 21% recurred with effusion after discharge. So this study only compares catheter drainage with a relatively ineffective pleurodesis. Thoracoscopic talc poudrage done by experienced pulmonologists is associated with 80–90% long-term success. 5

My personal belief is that a randomised study comparing the tunelled catheter with thoracoscopic talc poudrage is needed to properly respond to Tremblay’s letter. The endpoints should include total costs of medical and hospital care over the lives of the patients, quality of life assessment, and the length of survival.

I declare that I have no conflict of interest.
Other experience from Singapore

Simon Shorvon (June 2, p 1835),1 by quoting from an earlier newspaper article, appears to be urging UK doctors to avoid accepting posts in Singapore. I disagree with this advice, which I assume is coloured by his own unfortunate experiences in that country.

I have recently returned from a 4-year stint of continuous full-time employment as a senior consultant physician by the Ministry of Health Singapore at Singapore General Hospital and later at the National Skin Centre, and also as clinical professor at the National University of Singapore.

My own experience of the Ministry of Health, its administrators, and the Singapore Medical Association has been uniformly very positive. Singapore health authorities are invariably scrupulously fair employers and they are accommodating to “expat” employees almost to a fault. Throughout my period of work there, I never heard anyone complain of unfair treatment.

Singapore is short of doctors, and it will be some years before the country can meet its own needs. Until then, given the increasing burden of ill health due to an ageing and expanding population, reliance will have to be placed on attracting expatriate doctors. UK medical training and qualifications are held in high esteem in Singapore, and the profession is structured closely on the UK model. Recruits from the UK will meet with abundant good will and, although in return they will be expected to work hard, they can be assured of a professionally enriching experience.

I declare that I have no conflict of interest.

Malcolm W Greaves
mwatsong@hotmail.com
St Johns Institute of Dermatology, St Thomas’ Hospital, London SE1 7EH, UK

Imre Loefler

Clare Kapp’s Obituary of Imre Loefler (May 12, p 1596),1 at for him the young age of 77 years, hints at his splendid presence and influence over two generations of students and all others who came into contact with him.

I was lucky enough to be a visiting final year student on his surgical firm in his last months as head of surgery at the university teaching hospital Lusaka, Zambia, before his move to Nairobi. Towards the end of a memorable ward round, which included a 17-year-old girl whose leg had been amputated by an angry hippo and a 12-year-old with a huge mandibular swelling (a Burkitt’s lymphoma that all but melted after one dose of cyclophosphamide the next day), I was asked what I would suggest for a postoperative patient with a (slight) cough. I ventured a chest radiograph. Loefler pounced amiably: “Cruickshank, is that going to change your management? Never do a test that is unlikely to change it, least of all in our setting here”.

Ever since, I’ve tried to implement that simple lesson which wealthier countries’ medical practice has long lost. His legacy as a teacher was to generate critical thinking long before we institutionalised evidence-based practice.

I declare that I have no conflict of interest.

Kennedy Cruickshank
clinep@manchester.ac.uk
Division of Cardiovascular and Endocrine Sciences, Core Technology Facility, University of Manchester, Manchester M13 9NT, UK

Effect of early versus delayed interferon beta-1b treatment on disability after a first clinical event suggestive of multiple sclerosis: a 3-year follow-up analysis of the BENEFIT study

Ludwig Kappos, Mark S Freedman, Chris H Polman, Gilles Edan, Hans-Peter Hartung, David H Miller, Xavier Montalbán, Frederik Barkhof, Ernst-Wilhelm Radü, Lars Bauer, Susanne Dahms,* Vivian Lanius, Christoph Pohl,† Rupert Sandbrink,‡ for the BENEFIT Study Group

Summary

Background Several controlled studies provide evidence that treatment with interferon beta in patients with a first event suggestive of multiple sclerosis (MS) delays conversion to clinically definite MS (CDMS). Our aim was to determine whether early initiation of treatment with interferon beta prevents development of confirmed disability in MS.

Methods In the initial placebo-controlled phase of the double-blinded BENEFIT study, patients with a first event suggestive of MS and a minimum of two clinically silent lesions in MRI were randomised to receive either interferon beta-1b 250 µg (n=292) or placebo (n=176) subcutaneously every other day for 2 years, or until diagnosis of CDMS. Patients were then eligible to enter the follow-up phase with open-label interferon beta-1b. In the current prospectively planned analysis 3 years after randomisation, the effects of early interferon beta-1b treatment were compared with those of delayed treatment initiated after diagnosis of CDMS or after 2 years on the study. The primary outcomes of this ITT analysis were time to diagnosis of CDMS, time to confirmed expanded disability status scale (EDSS) progression, and score on a patient-reported functional assessment scale (FAMS-TOI). This trial is registered with ClinicalTrials.gov, number NCT00185211.

Findings Of the 468 patients originally randomised, 418 (89%) entered the follow-up phase: 392 (84%) completed 3 years' post-randomisation follow-up. After 3 years, 99 (37%) patients in the early group developed CDMS compared with 85 (51%) patients in the delayed treatment group. Early treatment reduced the risk of CDMS by 41% (hazard ratio 0.59, 95% CI 0.44–0.80; p=0.0011; absolute risk reduction 14%) compared with delayed treatment. Over 3 years, 42 (16%) patients in the early group and 40 (24%) in the delayed group had confirmed EDSS progression; early treatment reduced the risk for progression of disability by 40% compared with delayed treatment (0.60, 0.39–0.92; p=0.022; absolute risk reduction 8%). The FAMS-TOI score was high and stable in both groups over the 3-year period (p=0.31).

Interpretation Our data suggest that early initiation of treatment with interferon beta-1b prevents the development of confirmed disability, supporting its use after the first manifestation of relapsing-remitting MS.

Introduction Three multicentre, placebo-controlled studies have shown that treatment of patients with a first episode of neurological symptoms (also called clinically isolated syndrome) highly suggestive of multiple sclerosis (MS) with interferon beta delays conversion to clinically definite MS (CDMS). Furthermore, neuropathological findings suggest the potential for immunomodulatory treatment of MS to have a greater effect early in the disease course, by early inhibition of the cascade of events that leads to irreversible axonal damage and disability. However, until now, there has been no controlled evidence showing that treatment with interferon beta initiated early after the first event has an effect on the development of confirmed disability as compared with delayed treatment. The Betaferon/Betaseron in Newly Emerging multiple sclerosis For Initial Treatment (BENEFIT) study, assessing interferon beta-1b in patients with a first event suggestive of MS, was designed to address this issue. Here, we present the results of the preplanned 3-year analysis of BENEFIT.

Methods Patients and procedures The BENEFIT study consisted of a placebo-controlled phase and a follow-up phase. The 2-year double-blinded, placebo-controlled phase, which was completed in 2005, assessed the safety, tolerability, and efficacy of interferon beta-1b 250 µg (8 MIU) subcutaneously every other day in patients with a first event suggestive of MS. Eligible patients had experienced a first neurological event suggestive of MS and had at least two clinically silent lesions on a T2-weighted brain magnetic resonance imaging (MRI) scan. Within 60 days of the onset of the first clinical event, and after providing written informed consent, patients were randomly assigned, in a 5:3 ratio, to interferon beta-1b 250 µg or placebo subcutaneously every other day. Patients completed the placebo-controlled phase when CDMS was diagnosed by use of modified Poser criteria, or after 2 years. Patients who completed the placebo-controlled phase were eligible to enter the follow-up phase and, after

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*Dr Dahms died in July, 2007
†Contributed equally to the study
‡Members listed at end of report
University Hospital, Basel, Switzerland (Prof L Kappos MD, Prof E-W Radü MD); Ottawa Hospital-General Campus, Ottawa, Canada (Prof M S Freedman MD); Vrije Universiteit Medical Center, Amsterdam, Netherlands (Prof C H Polman MD, Prof F Barkhof MD); Centre Hospitalier Universitaire, Rennes, France (Prof G Edan MD); Heinrich-Heine-Universität, Düsseldorf, Germany (Prof H-P Hartung MD); National Hospital for Neurology and Neurosurgery, London, UK (Prof D H Miller MD); Hospital Vall d’Hebron, Barcelona, Spain (Prof X Montalbán MD); Bayer Schering Pharma AG, Berlin, Germany (L Bauer MD, S Dahms PhD, V Lanus MD, C Pohl MD, R Sandbrink MD); and University Hospital Bonn, Germany (C Pohl)

Correspondence to: Professor Ludwig Kappos, Neurology and Department of Research, University Hospital, Petersgraben 4, 4031 Basel, Switzerland lkappos@uhbs.ch


Articles
renewing their written informed consent, were offered interferon beta-1b 250 μg subcutaneously every other day for up to 5 years from randomisation. Every effort was made to obtain full follow-up assessments of all patients, including those who did not opt for interferon beta-1b treatment. Patients and investigators were kept blinded to the original treatment allocation throughout the trial. Accordingly, at the beginning of the follow-up phase, interferon beta-1b was titrated in all patients, whether they had been on placebo or interferon beta-1b. However, 13 patients were unblinded: 12 placebo patients did not develop any clinical or MRI activity for 2 years and were informed accordingly after a recommendation from the study’s independent advisory board; the treatment code of one further patient was unblinded by the investigator due to a serious adverse event.

In the follow-up phase, regular visits were scheduled every 6 months. A specially trained physician, not involved in the patient’s care and without access to their files, did standardised neurological assessments with the expanded disability status scale (EDSS). EDSS scores range from 0 to 10, with higher scores indicating more severe disease. Relapses were assessed and defined in accordance with established guidelines and the diagnosis of CDMS was confirmed by a central committee masked to treatment allocation. Additional assessments (all blinded) were: brain MRI scans every 12 months (assessed by the MRI Analysis Centre, Amsterdam) and the multiple sclerosis functional composite (MSFC) score every 6 months. Of note, MRI scans were more frequently obtained during the placebo-controlled phase of the trial (in total, there were up to seven scans post-screening for both study phases until year 3). Patient-reported outcomes were obtained every 12 months, by use of the functional assessment of MS (FAMS) instrument, the EuroQol-5 Dimensional Questionnaire (EQ-5D), and the visual analogue scale (VAS). Neutralising antibodies were measured every 6 months with the MxA assay (cutoff value for neutralising activity was defined as 1:20).

Statistical analysis
The statistical analysis plan was finalised before the database of the placebo-controlled phase was locked in June, 2005. The prespecified intention-to-treat (ITT) analysis set consisted of all randomised patients who received at least one dose of the study drug of the placebo-controlled phase after randomisation. The patient group initially randomised to interferon beta-1b (the early treatment group) was compared with the group initially randomised to placebo with the option of starting with interferon beta-1b after CDMS or after 2 years (the delayed treatment group).

After discussion with regulatory authorities, two analyses of the integrated data set after completion of years 3 and 5 were planned. A nominal two-sided significance level of 0.0253 (with Šidák’s adjustment for multiple comparisons) was assigned to the analyses of the primary endpoints at both time points, thus allowing for an overall type 1 error probability of 0.05. All data obtained up to the 3-year visit were used here for the 3-year analysis.

Three prespecified primary efficacy measures were tested in a sequential, conditional approach: time to CDMS was tested first, followed by time to confirmed EDSS progression (not previously tested in the placebo-controlled phase), and the FAMS-trial outcome index (FAMS-TOI) score (range of scores 0 [worst] to 148 [best]).

EDSS progression was defined as an increase in the EDSS score by 1-0 or more step compared with the lowest score obtained during the screening period (ie, at screening or at baseline visit); this progression had to be confirmed after 6 months. In the main analysis of this outcome, EDSS values obtained at unscheduled visits were not taken into account, since they largely represent relapse-associated changes in neurological symptoms, which do not necessarily imply permanent deficits. Sensitivity analyses were done, one that included unscheduled visits, two that both excluded unscheduled visits and, additionally, visits within 30 or 90 days after the onset of a relapse, one which took the EDSS obtained at the baseline visit (not the lowest of screening and baseline as in the main analysis) as the reference value, and one counting only EDSS progressions sustained until the last visit within the 3-year period. In a further sensitivity analysis, patient’s who discontinued the study prematurely without confirmed progression were counted as having progressed, or as progression-free.

The effect of early versus delayed treatment on time to confirmed EDSS progression (main analysis) was also assessed post-hoc in subgroups of patients stratified by clinical presentation (monofocal vs multifocal) and MRI findings indicating subclinical disease dissemination (≥9 T2 lesions) or infl ammatory activity (presence vs absence of gadolinium-enhanced lesions) at the time of the first event.

Prespecified secondary clinical outcome measures included: time to MS as defined by the McDonald criteria; annualised relapse rate; risk for recurrent relapses; neurological status as measured by MSFC score; and health-related quality of life as rated with EQ-5D and VAS. Secondary outcomes obtained by brain MRI included: cumulative number of newly active lesions (new T2 or new gadolinium-enhanced lesions); change in lesion burden (on T1-weighted and T2-weighted images); and change in brain volume as measured by a modified version of the Structural Image Evaluation using Normalisation of Atrophy (SIENA) program. p values for secondary outcomes were not corrected for multiple testing. In a post-hoc analysis, annualised relapse rates in the first, second, and third years were also calculated separately.
For time-to-event outcomes, differences between the early and delayed treatment groups were analysed by the log-rank test (primary analysis) and by adjusted Cox proportional hazards regression. As prespecified, covariates considered in Cox regressions for time to CDMS and time to McDonald MS were steroid use during the first clinical event, onset of disease (monofocal vs multifocal), age at screening, sex, and number of T2 lesions and gadolinium-enhanced lesions at screening; time to confirmed EDSS progression was adjusted (as preplanned) for T2-lesion volume at screening.

The treatment effect on the annualised relapse rate was assessed by a generalised linear Poisson regression model (covariates considered were steroids, onset of disease, and T2 lesions).

Treatment effects on patient-reported outcomes and MRI efficacy variables were analysed by non-parametric and on MSFC score by parametric analysis of covariance, with corresponding parameters from baseline (for patient-reported outcomes) or screening (for MRI) assessments as covariates. The frequencies of adverse events and the number of individuals above and below
the threshold of neutralising antibody activity were analysed with descriptive statistics. Apart from the primary outcomes, all other statistical analyses were not adjusted for multiple testing.

Statistical analyses were done with SAS version 9.1.3. This trial is registered with ClinicalTrials.gov, number NCT00185211.

Role of the funding source

The members of the steering committee and the study sponsors designed the study. The authors had access to all the data, participated in the analysis and interpretation of data, and were members of the publication committee. LK, representing the study’s steering committee, had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. 418 (89%) of the 468 patients who had started placebo-controlled treatment chose to enter the follow-up phase; 378 of these individuals opted for follow-up treatment with interferon beta-1b 250 µg subcutaneously every other day. 392 (84%) completed 3 years’ follow-up; 343 of those who had opted for further treatment were still on interferon beta-1b at this time. The median exposure time to interferon beta-1b over the 3-year period was 1080 days (IQR 854–1093) for the early treatment group and 364 days (175–679) for the delayed treatment group.

The two randomised groups of the double-blind study were much the same in terms of demographics and clinical and MRI characteristics (table 1). There were no substantial differences of key baseline characteristics and CDMS or McDonald MS conversion rates between patients of the two randomised groups who did not enter the follow-up study, suggesting that enrolment in the follow-up phase was not biased by selective dropouts (data not shown).

In the early treatment group, the risk of confirmed EDSS progression (main analysis; excluding unscheduled visits) was reduced by 40% over a 3-year period (figure 2 and table 2). The number needed to treat early to avoid one additional confirmed EDSS progression was 11·9.

When unscheduled visits were included in the analysis, a similar reduction of the risk for confirmed EDSS progression was found in favour of early treatment (table 2). Sensitivity analyses of time to confirmed EDSS progression, which excluded visits within 30 or 90 days of the onset of a relapse, or only counting EDSS...

<table>
<thead>
<tr>
<th>Placebo-controlled phase</th>
<th>Follow-up phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon beta-1b</td>
<td>Placebo</td>
</tr>
<tr>
<td>(n=292)</td>
<td>(n=157)</td>
</tr>
<tr>
<td>Sex (female)</td>
<td></td>
</tr>
<tr>
<td>207 (71%)</td>
<td>124 (71%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>30 (24·0–37·5)</td>
<td>30 (25·0–36·0)</td>
</tr>
<tr>
<td>Monofocal disease onset</td>
<td></td>
</tr>
<tr>
<td>153 (52%)</td>
<td>93 (53%)</td>
</tr>
<tr>
<td>Steroid use (yes)</td>
<td></td>
</tr>
<tr>
<td>209 (72%)</td>
<td>123 (70%)</td>
</tr>
<tr>
<td>Number of T2 lesions</td>
<td></td>
</tr>
<tr>
<td>17 (7·0–39·5)</td>
<td>17 (8·0–37·0)</td>
</tr>
<tr>
<td>Number of Gd-enhanced lesions</td>
<td></td>
</tr>
<tr>
<td>0 (0·0–1·0)</td>
<td>0 (0·0–1·0)</td>
</tr>
<tr>
<td>EDSS score at baseline</td>
<td></td>
</tr>
<tr>
<td>1·5 (1·0–2·0)</td>
<td>1·5 (1·0–2·0)</td>
</tr>
</tbody>
</table>

Table 1: Screening characteristics of participants in the placebo-controlled and follow-up phases of BENEFIT
progression if sustained until month 36 further support the results of the main analysis (table 2).

When a patient’s premature study discontinuation was counted as progression, the log-rank test for time to confirmed EDSS progression yielded a p value of 0·1011. If these patients were counted as progression free the log-rank test yielded a p value of 0·0172 (0·59, 0·38–0·91; p=0·017). The number of confirmed EDSS progressions up to year 3 was low compared with the number of patients who were lost to follow-up without confirmed EDSS progression (68 patients).

Analysis of unconfirmed EDSS scores by visits showed that somewhat fewer patients in the early treatment group had an increase in EDSS score from their first event to the last clinical visit within the 3-year period than did those in the delayed group (change of EDSS scores by 0·5 step or less: 233 [80%] patients in the early group vs 205 [70%] patients in the delayed group; EDSS increase by 1·0–2·0 steps: 42 [14%] vs 36 [12%]; EDSS increase by >2·0 steps: 10 [3%] vs 13 [4%]). At the year 3 visit, most patients were still in the low-to-medium range of the EDSS scale (median 1·5, range 0·0–7·5). Mean EDSS scores tended to increase over time in the delayed treatment group (mean score 1·41 [SD 1·24] vs 1·05 [1·21] at year 3) while remaining stable or better in the early treatment group (mean score 1·52 [0·85] vs 1·58 [1·11] at year 3) providing more support to confirmed EDSS progressions (up to day 1080).

Post-hoc analysis of the treatment effect in subgroups defined by disease characteristics at the time of the first event suggestive of MS showed that early treatment with interferon beta-1b reduced the risk for confirmed EDSS progression in each of the groups (table 4). Treatment effects seemed to be lower, and were not significant, in patients with less clinical or MRI disease dissemination. The magnitude of the treatment effect was largely comparable in patients with or without gadolinium-enhanced lesions in the screening MRI.

In the early treatment group, the risk for CDMS was reduced by 41% over a 3-year period (table 2). The number needed to treat early to avoid one additional conversion to CDMS was 7·1. Differences in favour of early interferon beta-1b treatment were also found for time to McDonald MS (table 2) and annualised relapse rate over

## Table 2: Effect of early vs delayed interferon beta-1b on occurrence of clinically definite MS, MS according to the McDonald criteria, and confirmed EDSS progression

<table>
<thead>
<tr>
<th></th>
<th>Number of patients with event (up to day 1080)</th>
<th>Risk (Kaplan-Meier estimates up to day 1080)</th>
<th>Hazard ratio (95% CI)</th>
<th>p value (log-rank test)</th>
<th>Absolute risk reduction (day 1080)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early treatment (n=292)</td>
<td>Delayed treatment (n=176)</td>
<td>Early treatment (n=292)</td>
<td>Delayed treatment (n=176)</td>
<td></td>
</tr>
<tr>
<td>CDMS</td>
<td>99 (34%)</td>
<td>85 (48%)</td>
<td>37%</td>
<td>51%</td>
<td>0·59 (0·44–0·80)</td>
</tr>
<tr>
<td>McDonald MS</td>
<td>205 (70%)</td>
<td>146 (83%)</td>
<td>74%</td>
<td>85%</td>
<td>0·54 (0·44–0·68)</td>
</tr>
<tr>
<td>EDSS progression</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excluding unscheduled visits (main analysis)*</td>
<td>42 (14%)</td>
<td>40 (23%)</td>
<td>16%</td>
<td>24%</td>
<td>0·60 (0·39–0·92)</td>
</tr>
<tr>
<td>Including unscheduled visits*</td>
<td>45 (15%)</td>
<td>42 (24%)</td>
<td>17%</td>
<td>25%</td>
<td>0·61 (0·40–0·93)</td>
</tr>
<tr>
<td>Sensitivity analyses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unscheduled visits and visits 90 days after relapse excluded*</td>
<td>38 (13%)</td>
<td>36 (20%)</td>
<td>14%</td>
<td>22%</td>
<td>0·60 (0·38–0·95)</td>
</tr>
<tr>
<td>Unscheduled visits excluded, baseline EDSS as reference†</td>
<td>36 (12%)</td>
<td>37 (21%)</td>
<td>14%</td>
<td>22%</td>
<td>0·54 (0·32–0·91)</td>
</tr>
<tr>
<td>Unscheduled visits excluded, sustained up to last clinical visit within 3 years*</td>
<td>28 (10%)</td>
<td>27 (15%)</td>
<td>10%</td>
<td>16%</td>
<td>0·61 (0·36–1·03)</td>
</tr>
</tbody>
</table>

*Defined as an increase in the EDSS score by ≥1·0 step compared with the lowest score obtained during the screening period (ie, at the screening or at the baseline visit). EDSS progression was defined as an increase in the EDSS score by ≥1·0 step compared with the lowest score obtained during the screening period to first score relevant for EDSS confirmation.

## Table 3: Change in functional system scores in patients with confirmed EDSS progression (up to day 1080)

<table>
<thead>
<tr>
<th>Function</th>
<th>Early treatment (n=42)</th>
<th>Delayed treatment (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual functions</td>
<td>8 (19%)</td>
<td>12 (30%)</td>
</tr>
<tr>
<td>Brainstem functions</td>
<td>11 (26%)</td>
<td>7 (18%)</td>
</tr>
<tr>
<td>Pyramidal functions</td>
<td>21 (50%)</td>
<td>14 (35%)</td>
</tr>
<tr>
<td>Cerebellar functions</td>
<td>13 (31%)</td>
<td>12 (30%)</td>
</tr>
<tr>
<td>Sensory functions</td>
<td>24 (57%)</td>
<td>17 (43%)</td>
</tr>
<tr>
<td>Bladder and bowel functions</td>
<td>9 (21%)</td>
<td>10 (25%)</td>
</tr>
<tr>
<td>Cerebral functions</td>
<td>17 (40%)</td>
<td>16 (40%)</td>
</tr>
</tbody>
</table>

Data are n (%) of patients with increase in functional system(s) from lowest score obtained during the screening period to first score relevant for EDSS confirmation.

*An increase in EDSS score by ≥1·0 step compared with the lowest score obtained during the screening period (ie, at the screening or the baseline visit).
3 years (figure 3). Post-hoc analyses of the annualised relapse rates within the first, second, and third year after the first event showed the most marked differences between the early and delayed treatment groups in the first year (figure 3).

Throughout the 3 years of observation, most patients in both groups had high and stable scores on the FAMS-TOI (p=0.31 for group difference at 3 years; data not shown). Scores on the EQ-5D rating scale decreased in the delayed group, and improved in the early group (p=0.016 at 3 years; data not shown). The compound MSFC score improved over the 3 years in most patients and no significant difference was found between treatment groups (p=0.408; data not shown). In the cognitive subtest of MSFC (the paced auditory serial addition test), patients in the early treatment group had better results than did those in the delayed group (p=0.011 at 3 years). In the subtests of upper (nine-hole peg test, p=0.118) and lower (25-foot walk, p=0.792) extremity function, results did not differ significantly between treatment groups.

Fewer newly active lesions developed in the early treatment group over 3 years than in the delayed treatment group (p<0.0001; data not shown). T2-lesion volume in both groups decreased from screening to year 3 in most patients. This decrease was more pronounced in the early treatment group; however, the difference between the groups was not statistically significant (p=0.070; data not shown). There were only minor changes over time and there were no differences between groups when the volume of T1-hypointense lesions (p=0.89) and the brain volume (p=0.15) at 3 years were compared with those of the screening MRI (data not shown).

The frequency of adverse events was within the known safety and tolerability profile of interferon beta-1b, and did not differ from those reported at the end of the placebo-controlled phase. In the cognitive subtest of MSFC (the paced auditory serial addition test), patients in the early treatment group had better results than did those in the delayed group (p=0.011 at 3 years). In the subtests of upper (nine-hole peg test, p=0.118) and lower (25-foot walk, p=0.792) extremity function, results did not differ significantly between treatment groups.

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The frequency of adverse events was within the known safety and tolerability profile of interferon beta-1b, and did not differ from those reported at the end of the placebo-controlled phase. The most common adverse events in the study period were flu-like symptoms (391 events in 49% of all patients; 144 [49%] patients in the early group and 68 [39%] patients in the delayed group). The most frequent abnormal laboratory findings were leucopenia (65 [22%] patients in the early group vs 22 [13%] in the delayed group) and raised alanine aminotransferase concentrations (46 [16%] patients in the early group vs 12 [7%] in the delayed group). During the follow-up phase more patients in the delayed treatment group prematurely stopped interferon beta-1b due to adverse events (18 [12%] in the delayed group vs six [2%] in the early group).

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**Table 4:** Treatment effect of early vs delayed interferon beta-1b on confirmed EDSS progression in subgroups of patients with different clinical/MRI characteristics at the time of the first event

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Early Treatment</th>
<th>Delayed Treatment</th>
<th>Early Treatment Risk</th>
<th>Delayed Treatment Risk</th>
<th>Hazard Ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monofocal* at first event suggestive of MS (n=246)</td>
<td>26/19</td>
<td>19/26</td>
<td>19%</td>
<td>24%</td>
<td>0.75 (0.42–1.34)</td>
<td>0.320</td>
</tr>
<tr>
<td>Multifocal† at first event suggestive of MS (n=222)</td>
<td>16/19</td>
<td>19/22</td>
<td>12%</td>
<td>24%</td>
<td>0.47 (0.24–0.90)</td>
<td>0.024</td>
</tr>
<tr>
<td>≤9 T2 lesions at screening MRI (n=138)</td>
<td>13/10</td>
<td>10/14</td>
<td>17%</td>
<td>20%</td>
<td>0.78 (0.34–1.78)</td>
<td>0.553</td>
</tr>
<tr>
<td>≥9 T2 lesions at screening MRI (n=330)</td>
<td>29/30</td>
<td>30/24</td>
<td>15%</td>
<td>26%</td>
<td>0.55 (0.33–0.91)</td>
<td>0.020</td>
</tr>
<tr>
<td>No gadolinium-enhanced lesion at screening MRI (n=266)</td>
<td>19/21</td>
<td>21/25</td>
<td>13%</td>
<td>21%</td>
<td>0.55 (0.30–0.93)</td>
<td>0.063</td>
</tr>
<tr>
<td>≥1 gadolinium-enhanced lesion at screening MRI (n=198)</td>
<td>19/23</td>
<td>23/19</td>
<td>19%</td>
<td>29%</td>
<td>0.63 (0.34–1.16)</td>
<td>0.139</td>
</tr>
</tbody>
</table>

*pSigns and symptoms at the first event indicate one lesion in the CNS. †Signs and symptoms at the first event indicate at least two anatomically separate lesions in the CNS. ‡Unscheduled visits excluded.

---

**Figure 3:** Annualised relapse rate estimates over the 3-year follow-up period

Error bars are 95% CI. p values refer to Poisson regression analysis. The proportion of patients exposed to interferon beta-1b in subsequent years of the study was as follows (early/delayed treatment group): first year 100%/28%, second year 94%/48%, third year 87%/88%.
Neutralising activity (defined as a titre ≥20 NU/mL) was detected at least once in 88 of 277 (32%) patients in the early treatment group and in 34 of 173 (20%) patients in the delayed treatment group; of these, 41 (47%) patients in the early group and eight (24%) of those in the delayed treatment group had converted to negative status by 36 months. Neutralising activity had no effect on either relapse-related or disability-related outcomes (data not shown).

Discussion

We found a beneficial effect of early treatment with interferon beta-1b (250 µg, every other day, subcutaneously) on 6-month confirmed EDSS progression 3 years after the first event suggestive of MS, indicating that a delay of such treatment by, essentially, just one event, even at this early stage of the disease, has an effect on later accumulation of disability. Even though most patients in both groups remained at a low level of disability 3 years after the initial event, the delay in accumulation of disability with early treatment seen here is clinically relevant.

Relapsing-remitting MS presents with a first neurological attack and most patients recover fully from their initial symptoms within a short period of time. Recent evidence, however, suggests that subclinical damage persists and is frequently progressive, although its functional consequences are still being compensated by existing redundant connections and reorganisation of neuronal networks. Over time, most patients with a first event suggestive of MS and additional clinically silent MRI lesions develop relapsing-remitting MS and have a substantial risk for progressive disease and severe disability later on. An effective immunomodulatory treatment initiated early after the presenting symptoms of MS would be expected not only to delay a second demyelinating event but also to prevent or delay permanent disability.

The need for methodologically sound follow-up studies of placebo-controlled trials in a chronic disease such as MS has been emphasised repeatedly. Previous studies have shown a beneficial effect of early treatment on the risk of conversion to CDMS, but they were too brief and not prospectively designed to capture any effect on disability. For example, in an open-label, investigator-initiated 5-year follow-up of one of these studies, nearly 50% of the original population was lost to follow-up and no effect of early versus delayed treatment with interferon beta-1a (30 µg, once weekly intramuscularly) on confirmed progression was found. Therefore, we made major efforts to address these issues by strictly applying the ITT principle, keeping the original treatment allocations masked, retaining the same standards of assessments, and by prospective planning of the statistical analysis. The value of EDSS as an outcome measure was supported by a study by Rio and colleagues, which provided evidence that a confirmed increase by one step on the EDSS is an important negative predictor of permanent and severe disability 5 years later.

Our findings are in line with those of an extension of a pivotal study for interferon beta-1a. In this study, patients with established relapsing-remitting MS initially randomised to placebo were offered active treatment with interferon beta-1a (22 or 44 µg subcutaneously, three times a week) after completing 24 months on study. In a post-hoc analysis 4 years after the start, time to EDSS progression (confirmed after 3 months) was longer in those patients who had been initially randomised to the 44 µg dose than in those in the crossover group (p=0.047).

Changes in the EDSS scores in a relapsing-remitting MS population, even if confirmed after 6 months, could reflect continuing relapse-associated temporary changes, rather than permanent disability. The annualised relapse rates in the early and delayed treatment groups were very similar in the second year and nearly identical in the third, most probably due to the increasing exposure to interferon beta-1b in the delayed group. This finding suggests that the differential effect of early treatment on disability seen in the third year after the initial event is not due to a direct effect of relapses at the time of the last assessments. In support of this argument, sensitivity analyses excluding EDSS values obtained at visits up to 90 days after a relapse confirmed the robustness of the effect of early interferon beta-1b treatment on time to confirmed EDSS progression.

To better define patients who might benefit more or less from early treatment initiation, we did analyses in subgroups with different levels of disease activity at first presentation. The smaller sample size in each of the dichotomised groups and the low rate of confirmed EDSS progressions limit the interpretation of this approach. Interestingly, the effect of early versus delayed interferon beta-1b treatment is different from that previously reported on time to CDMS as described in the analysis of the placebo-controlled phase of the BENEFIT study. Here, multifocal initial presentation and higher lesion load seem to define subgroups of patients who benefit more from early treatment initiation (while occurrence of contrast-enhanced lesions had no effect); by contrast, in the earlier analysis, the treatment effect of interferon beta-1b on the risk of CDMS seemed to be more pronounced in patients with monofocal disease or lower T2-lesion counts at baseline.

The longer observation period provided by the planned 5-year analysis of this trial, should allow for more events of confirmed disability progression to occur, and could provide more informative evidence on prognostic indicators of treatment response. The MSFC score did not detect any relevant deterioration of neurological function in either of the treatment groups during the observation period. This occurrence is somewhat surprising, since the aim of...
MSFC was to improve on sensitivity to change as compared with EDSS and other pre-existing measures of neurological deficits. Nevertheless, a low sensitivity for change has also been described by others, and could indicate that this measure is not equally suitable for all MS subpopulations. Specifically, the MSFC score was developed with data from patients with established MS and not clinically isolated syndrome. As a composite instrument, MSFC captures three domains of neurological function, which are affected in nearly all patients in later stages of MS (ambulation, dexterity of upper extremities, and attention/short-term memory) but are less frequently affected in patients with earlier-stage disease, where symptoms such as visual or sensory deficits are frequently found in isolation. These symptoms are not all captured by MSFC, but do affect EDSS scores. Of note, improvements in the cognitive subtest of MSFC after 3 years were more pronounced in patients receiving early treatment. Given the exploratory nature of these analyses of a single study, the relevance of this finding needs further confirmation.

In patients with relapsing-remitting MS, interferon beta-1b has previously been shown to have a profound effect on the development of new inflammatory lesions as shown by cerebral MRI. For patients with a first event suggestive of MS, this effect was confirmed in the placebo-controlled part of the BENEFIT study and preserved over 3 years, despite increasing exposure to interferon beta-1b in the initial placebo group. Since patients had to enter our study soon after the onset of neurological symptoms of the first event, pretreatment MRI frequently depicted active inflammation that is subject to spontaneous remission. Only a few of our patients had an increase in overall T2-lesion or T1-lesion volumes during the 3 years of observation, and overall changes in brain volume seemed to be low compared with findings reported for established MS.

Contributors
LK was responsible for the central CDMS confirmation during the study. CHP and FB were responsible for the central eligibility assessment during the study. LK, MSF, CH, GE, HPH, DHM, XM, FB, LB, SD, CP, and RS were actively involved in drafting and amending the study protocol, reviewed the statistical analysis, and actively contributed to the writing and reviewing of the submitted manuscript. FB was responsible for the central MRI analysis (apart from brain volume analysis) of the study. EWR was responsible for the central MRI brain volume analysis of the study. SD and VL were responsible for biometric analyses in the study. SD and VL were responsible for the central MRI brain volume analysis of the study. EWR was responsible for the central CDMS confirmation during the study. LK was responsible for the central CDMS confirmation during the study. CHP and FB were responsible for the central eligibility assessment during the study. LK, MSF, CH, GE, HPH, DHM, XM, FB, LB, SD, CP, and RS were actively involved in drafting and amending the study protocol, reviewed the statistical analysis, and actively contributed to the writing and reviewing of the submitted manuscript. FB was responsible for the central MRI analysis (apart from brain volume analysis) of the study. EWR was responsible for the central MRI brain volume analysis of the study. SD and VL were responsible for biometric analyses in the study.

The BENEFIT Study Group
Principal investigators—Austria: S Strasser-Fuchs, Graz; T Berger, Innsbruck; K Vass, Vienna. Belgium: C Sindic, Brussels; B Dubois, Leuven; D Dive, Liège; J Debruyne, Ghent. Canada: I. Metz, Calgary; G Rice, London (ON); P Duquette, Y Lapierre, Montreal; M Freedman, Ottawa; A Traboulsee, Vancouver; P O’Connor, Toronto.
Czech Republic: P Stourač, Brno; R Taláž, Hradec Králové; O Zapletalová, Ostrava; I Kovářová, E Medová, Prague; J Fiedler, Plzen.
Denmark: J Frederiksen, Glostrup. France: B Brochet, Bordeaux; T Moreau, Dijon; P Vemersch, Lille; J Pelletier, Marseille; G Edan, Rennes; M Clanet, Toulouse; P Clavelou, Clermont Ferrand; C Lebrun-Frenay, Nice; O Gout, Paris. Finland: M Kallela, Helsinki; T Pirttilä, Kuopio; J Riusuainen, Turku; K Koivisto, Seinäjoki; M Reunanen, Oulu; I Elovära, Tampere. Germany: A Vrilinger, H Altenkínch, Berlin; K Wessel, Braunschweig; H-P Hartung, W Steinke, Düsseldorf; H Kölmel, Erfurt; P Oschmann, Giessen; R Dierm, Göttingen; A Dressel, Greifswald; F Hoffmann, Halle/Saale; K Baum, Hennigsdorf; S Jung, Homburg/Saar; P Heteret, D Reske, Cologne; M Sailer, Magdeburg; J Köhler, Mainz; N Sommer, Marburg; R Hohlfeld, Munich; K-H Henn, Offenbach; A Steinerbrecher, Regensburg; H Tumani, Ulm; R Gold, P Reinhardt, Würzburg; R Komoly, G Gács, G Jakab, Budapest; I Csiba, Debrecen; L Vécsei, Szeged. Israel: A Miller, Haifa; D Karussis, Jerusalem; J Chapman, Tel-Hashomer. Italy: A Ghezzi, Gallarate; G Comi, Milan; P Gallo, Padua; V Così, Pavia; I Darelli, Turin. Netherlands: B Anten, Sittard; L Visser, Tilburg. Norway: K-M Myhr, Bergen. Poland: A Szczaździcki, Kraków; K Szemraj, Łódź; Z Stelmasiak, Łódź; R Podemski, Wrocław; Z Maciejek, Bydgoszcz. Portugal: S Sega-Jazbec, Ljubljana. Spain: X Montalbán, T Arbizu, A Saiz, Barcelona; J Bárbara, Barakaldo; AR Arrojo, Madrid; O Fernández, Málaga; G Izquierdo, Sevilla; B Casanova, Valencia. Sweden: J Lycke, Möln达尔. Switzerland: I Kappos, Basel; H Mattle, Bern; K Beer, St Gallen. UK: R Coleman, Aberdeen; J Chataway, London; J O’Riordan, Dundee; S Howell, Sheffield.
Eligibility review committee—C H Polman, F Barkhof, F Uitdehaage, CDMS confirmation committee—I. Kappos, A de Vera, S Wu.
Central MRI analysis—F Barkhof, E-W Radiu.

Conflict of interest statement
LK discloses that the University Hospital Basel has received research support from Bayer Schering, Biogen Idec, GlaxoSmithKline, Merck Serono, Novartis Pharmaceuticals, Sanofi-Aventis, Teva Pharmaceuticals, and Wyeth Pharmaceuticals. LK has been principal investigator, member, or chair of steering committees or advisory boards in MS clinical trials sponsored by Abbott Laboratories, Bayer, Bayhill, Berlex, Biogen Idec, Boehringer-Ingelheim, Bristol-Myers Squibb, Centocor, Eisai, Genzyme, GlaxoSmithKline, Immune Response, Medicinova, Neurocrine, Novartis Pharmaceuticals, Sanofi-Aventis, Bayer Schering, Merck Serono, Roche, Teva Pharmaceuticals, UCBB Pharma, and Wyeth, and has received lecture fees from one or more of these companies. Payments and consultancy fees have been exclusively used for the support of research activities. MSF is a consultant/advisory board member for Bayer Schering Pharma, GlaxoSmithKline, Merck Serono, Novartis Pharmaceuticals, and Teva Neuroscience. CHP has received consulting fees from Biogen Idec, Bayer Schering Pharma AG, Teva Pharmaceuticals, Merck Serono, Novartis Pharmaceuticals, GlaxoSmithKline, UCB, AstraZeneca, Roche, and Antisense Therapeutics; lecture fees from Biogen Idec, Bayer Schering Pharma AG, Novartis, and Teva Pharmaceuticals; and grant support from Biogen Idec, Bayer Schering Pharma, GlaxoSmithKline, Novartis Pharmaceuticals, Merck Serono, Wyeth, and Teva Pharmaceuticals. GE received personal compensation for serving on an advisory board and for speaking from Bayer Schering Pharma AG. HPH has received honoraria and consultancy fees from, and participated as an investigator in phase 2 and 3 trials for, Biogen Idec, Bayer Vital, Bayer Schering, Merck Serono, and Teva Pharmaceuticals. He has also received research grant support from Biogen Idec. DM has received grant support from Biogen Idec, Elian, Bayer Schering, and GlaxoSmithKline for MRI analyses in clinical trials, as well as honoraria for advisory or consultancy work, lectures, and related travel expenses from Aventis, Biogen Idec, Bristol Myers Squibb, GlaxoSmithKline, Bayer Schering, Merck Serono, UCB Pharma, and
Wyeth. XM has received honoraria for consultation and speaking from Serono, Bayer Schering Pharma AG, Biogen Idec, Sanofi-Aventis, Teva, and Novartis. FB received consultancy fees from Bayer Schering Pharma for doing the central MRI analysis in the BENEFIT study. EWR received grant support from Biogen Idec, Bayer Schering, Novartis, Sanofi-Aventis, and GlaxoSmithKline for assessment of multicentre MS studies. Payments for advisory board and steering committee membership, as well as speaker honoraria by the above mentioned companies to EWR were exclusively used for research projects at the Department of Neuroradiology. LB, SD, VL, CP, and RS are salaried employees of Bayer Schering Pharma AG.

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References
Effect of visual screening on cervical cancer incidence and mortality in Tamil Nadu, India: a cluster-randomised trial

Rengaswamy Sankaranarayanan, Pulikkottil Okkuru Esmy, Rajamanickam Rajkumar, Richard Muvonge, Rajaraman Swaminathan, Sivanandam Shanthakumari, Jean-Marie Fayette, Jacob Cherian

Summary

Background Cervical cancer is the most common cancer among women in developing countries. We assessed the effect of screening using visual inspection with 4% acetic acid (VIA) on cervical cancer incidence and mortality in a cluster randomised controlled trial in India.

Methods Of the 114 study clusters in Dindigul district, India, 57 were randomised to one round of VIA by trained nurses, and 57 to a control group. Healthy women aged 30 to 59 years were eligible for the study. Screen-positive women had colposcopy, directed biopsies, and, where appropriate, cryotherapy by nurses during the screening visit. Those with larger precancerous lesions or invasive cancers were referred for appropriate investigations and treatment. Cervical cancer incidence and mortality in the study groups were analysed and compared using Cox regression taking the cluster design into account, and analysis was by intention to treat. The primary outcome measures were cervical cancer incidence and mortality.

Results Of the 49311 eligible women in the intervention group, 31343 (63·6%) were screened during 2000–03; 30958 control women received the standard care. Of the 3088 (9·9%) screened positive, 3052 had colposcopy, and 2539 directed biopsy. Of the 1874 women with precancerous lesions in the intervention group, 72% received treatment. In the intervention group, 274430 person years, 167 cervical cancer cases, and 83 cervical cancer deaths were accrued compared with 178781 person-years, 158 cases, and 92 deaths and in the control group during 2000–06 (incidence hazard ratio 0·75 [95% CI 0·55–0·95] and mortality hazard ratio 0·65 [0·47–0·89]).

Interpretation VIA screening, in the presence of good training and sustained quality assurance, is an effective method to prevent cervical cancer in developing countries.

Introduction Cervical cancer is the most common cancer among women in many developing countries, where 85% of the estimated 493 000 new cases and 273 000 deaths in 2002 occurred worldwide.1 Although population-based cervical cytology screening has resulted in a substantial reduction in cervical cancer burden in developed countries, lack of screening or inefficient cytology screening programmes contribute to the high risk seen in sub-Saharan Africa, south and southeast Asia, Oceania, Central and South America, and the Caribbean.2–4

The difficulties in organising cytology screening in developing countries have prompted the assessment of alternative methods like visual inspection with 3–5% acetic acid (VIA) for prevention of cervical cancer. In several studies, VIA had an acceptable sensitivity in detecting cervical intraepithelial neoplasia (CIN).4–11 Although model-based studies suggest that low-intensity, single-round of VIA screening once a lifetime is a cost effective method to reduce disease burden,12–17 whether it can achieve a significant reduction in cervical cancer incidence and mortality in real programme settings is unclear. The Christian Fellowship Community Health Centre, India, and the International Agency for Research on Cancer (IARC) of WHO, France, jointly did a cluster randomised trial to assess the efficacy of VIA screening to reduce cervical cancer incidence and mortality in a high-risk population in India.18 The results, after 7 years from the beginning of the screening, in terms of reduction in cervical cancer incidence and mortality are described in this paper.

Methods Design

The study design and methods of this trial were described in detail in a baseline paper.16 Clusters (panchayaths or municipal units) were first assigned numbers, and a statistician in IARC, not involved in the project, randomly assigned these numbers into two groups using computer-generated random numbers. Of the 114 clusters in seven subdistricts of the Dindigul district randomly chosen for the study, 57 were randomised to each group. The two groups were then randomly assigned either to an intervention group, to receive a single round of VIA screening by trained nurses, or to a control group to receive existing care. No matching of clusters was done. Women in one control group cluster were not enumerated from the beginning of the screening, in terms of reduction in cervical cancer incidence and mortality are described in this paper.
The study protocol was reviewed and approved by the institutional scientific and ethics review committees of the Christian Fellowship Community Health Centre and IARC.

**Participants and procedures**

Eligible participants were apparently healthy women aged 30–59 years with an intact uterus, no past history of cervical cancer, and were living in the study clusters. Female health workers visited households and interviewed the eligible women for sociodemographic and reproductive variables after explaining the study and obtaining written informed consent. All eligible women were educated about prevention, early detection, and treatment of cervical cancer. Those women in the 57 intervention group clusters were personally invited for VIA screening and were given a card indicating the date, time, and place of screening. Eligible women in the 56 control group clusters were not offered screening, but were advised on how to access prevention services by educating them on cervix cancer control by screening, signs and symptoms of cervical cancer, early diagnosis, treatment, and where screening and early diagnosis or treatment services were available (both in government or voluntary and private sectors), and were encouraged to use such health-care facilities.

A group of female health workers—non-medical high-school or university graduates—were trained to enumerate households, and to identify and interview eligible women. Eight registered nurses did a 3-week training course, using IARC manuals to develop skills in doing VIA, colposcopy, cryotherapy, directing biopsies, discussing results, treatment, follow-up care, and in referring women with precancerous lesions unsuitable for cryotherapy and invasive cancer cases for excisional treatment and cancer-directed therapy. Three doctors were trained to supervise nurses and to do the loop electrosurgical excision procedure (LEEP).

Screening clinics, supervised by a doctor, took place in the villages. The nurse examined the cervix with naked eye using a speculum and a bright halogen focus lamp after applying 4% acetic acid. VIA result was reported 1 min after the application as per the criteria described in the IARC manual. VIA was negative when no acetowhite lesions or ill-defined, scattered, or geographic acetowhite areas away from the squamocolumnar junction were detected. VIA was positive when dense, opaque, well-defined acetowhite lesions touching the squamocolumnar junction or cervical growths turning acetowhite were seen. Test results were explained to the women, and the low likelihood of their currently having cancer or precancerous lesions, although no screening test is 100% accurate, was explained to women who were VIA-negative.

Nurses counselled women who were VIA-positive and offered immediate colposcopy, directed biopsy for those with colposcopic abnormalities, followed by cryotherapy during the same screening visit, when appropriate. A colposcopic impression was made in terms of normal, benign findings (eg, ectropion, cervicitis, polyp), low-grade or high-grade precancerous lesion, and invasive cancer as described in the IARC manual. The colposcopy findings were explained to the women, and punch biopsies were directed from the abnormal areas. Those with colposcopic impression of low-grade or high-grade lesions were offered immediate cryotherapy after the directed biopsy when all the following criteria were met: the lesion involved less than three quadrants of the transformation zone with no extension into the cervical canal or vaginal walls; the entire lesion could be covered by the cryoprobe; the squamocolumnar junction was fully visible; and there was no suspicion of invasive cancer. Cryotherapy was done by double-freeze technique (3-min freeze; 5-min thaw; 3-min freeze) without local anaesthesia. Women with lesions not eligible for cryotherapy were referred to the Christian Fellowship Community Health Centre for LEEP. Treated women were advised to report back if they had any side-effects after treatment. They were advised on homecare (precautions to be taken at home) to avoid infection of the wound, delay in healing, and other side-effects, and were advised to come for clinical follow-up after 1 year to assess regression of lesions. Those with suspected invasive cancer were referred for investigations and treatment.

Biopsy specimens were processed in the screening project pathology laboratory and the slides were reported.

![Figure 1: Trial profile of all eligible women](image-url)
on by the pathologists at the PSG Institute of Medical Sciences and Research, Coimbatore, India.

Provider competency was maintained by medical supervision in the field, monitoring screen-positive rates, correlation between colposcopy and histology findings, positive predictive values for any grade of CIN, and by refresher courses. Internal and external quality control measures were in place for colposcopy and pathology.16

The following process measures were used to monitor study inputs: participation for screening, diagnosis and treatment, screen-positivity, and positive predictive value of VIA for CIN and cervical cancer.16

The primary outcome measures were cervical cancer incidence and mortality, and a post-hoc analysis was used to assess these measures in specific 10-year age-groups. Secondary outcome measures included stage distribution (stipulated in the protocol) according to the FIGO staging system.19 Outcome data were collected by the staff of the Dindigul district cancer registry, independently constituted for the accrual of cancer incidence and mortality data in the district, and who were not part of the core investigators in the trial. The registry staff were masked to whether the woman belonged to the study cohort and to which group the cases belonged.

The registry staff actively obtained data for cervical cancer cases and other cancer sites, staging, and treatment of cases from the entire Dindigul district (2 million people, 6267 km²) including the areas both covered by and not covered by the study, by use of case-finding methods recommended by IARC and the International Association of Cancer Registries for cancer registration in developing countries.20 Registry staff systematically visited 64 data sources in Dindigul and nine surrounding districts where cancer patients from the Dindigul district were likely to be diagnosed or treated, and actively abstracted information from case-records. They visited the municipal death registration offices, death registers at churches and mosques and collected data for all deaths. They also visited households to collect additional information, and project health workers visited households every year to collect information on deaths and migration. Carcinoma in-situ cases were classified as CIN 3. The cancer cases were coded by the ICD-O 2nd edition codes21 and cause of death was coded using ICD-10 by the registry staff.22

The cause of death in each cervical cancer case in the district was assessed on a case-by-case basis by the cancer registry staff, who did not know the assignment of each woman, by considering information from hospital records, death certificates, by house visits, and project health workers visited households every year to collect information on deaths and migration. Carcinoma in-situ cases were classified as CIN 3. The cancer cases were coded by the ICD-O 2nd edition codes21 and cause of death was coded using ICD-10 by the registry staff.22

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interviewing relatives and friends. Hence, a team of personnel different from the trial investigators identified the cause of death.

The registered cervix cancer cases and deaths were then classified as belonging to the intervention or control clusters, or to areas not involved in the study, by matching with the study database on a case-by-case basis by the registry staff, screening project staff, and trial investigators.

Prevalent cancer cases which were diagnosed when screening began were excluded from analysis. We classified cases of cervical cancer in the intervention group as screen-detected (diagnosed after a positive VIA), detected by symptoms in screen-negatives (diagnosed after a negative VIA), among those treated for CIN, and among non-participants.

**Statistical analysis**

Data were entered into an ACCESS database and analysed using the STATA 9.2 software package. Analysis was by intention-to-treat, ie, all eligible women in the clusters randomised were considered irrespective of their participation in the interview or screening. Since this trial used a cluster design, analysis of household and individual characteristics was done using the cluster as the unit of analysis. Comparison of cluster proportions or means of household and individual characteristics between the two study groups was done using the Wilcoxon rank-sum test. Multivariate analysis of cancer incidence and mortality endpoints was done using Cox proportional hazards regression, taking into account cluster design and adjusting for age, education, marital status, and parity, using intention to treat analysis.

Participation in screening and treatment, screen-positivity, and stage distribution were calculated as proportions. For calculation of incidence rates in all eligible women, the number of person-years in the intervention and control groups was calculated from the date of study entry of the woman to date of diagnosis, death, migration, or last follow-up visit. For mortality rates, the number of person-years was calculated from the date of study entry of the woman to date of death, migration, or last follow-up visit. The earliest date of entry was January, 2000, and the latest date of exit was December, 2006.

This study was planned to have an 80% power at the 5% significance level to detect a 50% reduction in cumulative mortality rate from cervical cancer within 10 years of enrolment between the intervention and control groups. The death rate from cervical cancer in women 30–59 years of age was assumed to be around 20 per 100,000 women, on the basis of data from urban areas in India. This assumption was made because of the lack of reliable data for cancer mortality in rural areas of India. We assumed that a cluster with an average of 600 women will provide about 4900 person-years of observation after 10 years (assuming a dropout rate of 25%). With the effect of the intra-cluster correlation, we assumed a coefficient of variation of 0.3, ie, the true rates of death from cervical cancer would vary between 8 and 32 per 100,000 women in the control group. This leads to a design effect of 1.08 and we thus had to

![Figure 2: (A) Participation in screening; (B) Screen-positivity, cervical intraepithelial neoplasia (CIN) grade 1 (CIN 1) detection rate; and (C) CIN 2–3 and cervical cancer detection rates by 5-year age-groups](image)

**Table 3: Stage of disease by study group and detection mode**

<table>
<thead>
<tr>
<th>Detection mode</th>
<th>Screen positive</th>
<th>Screen negative</th>
<th>Screen positive CINs and later diagnosed with cancer</th>
<th>Not screened</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control 1A</td>
<td>1 (0·6)</td>
<td>18 (10·8)</td>
<td>17 (25·3)</td>
<td>1 (10·0)</td>
</tr>
<tr>
<td>Control 1B</td>
<td>15 (9·5)</td>
<td>15 (9·0)</td>
<td>4 (6·0)</td>
<td>4 (13·8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 (6·0)</td>
<td>4 (13·8)</td>
<td>3 (10·0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 (13·8)</td>
<td>4 (6·5)</td>
</tr>
<tr>
<td>Intervention 2+</td>
<td>98 (62·0)</td>
<td>105 (62·9)</td>
<td>45 (67·2)</td>
<td>19 (65·5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>19 (65·5)</td>
<td>6 (60·0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6 (60·0)</td>
<td>35 (57·4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>44 (27·0)</td>
<td>29 (17·3)</td>
<td>1 (1·5)</td>
<td>6 (20·7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 (1·5)</td>
<td>24 (36·1)</td>
</tr>
<tr>
<td>Total</td>
<td>158 (100·0)</td>
<td>167 (100·0)</td>
<td>67 (100·0)</td>
<td>29 (100·0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>29 (100·0)</td>
<td>10 (100·0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 (100·0)</td>
<td>61 (100·0)</td>
</tr>
</tbody>
</table>

Data are number of individuals (n [%]): CIN=cervical intraepithelial neoplasia.
randomise at least 52 clusters in each study group.” However, the observed mortality rate in the control population during the study was much higher than assumed, which enabled us to observe a significant effect on cancer rate and mortality 7 years from the beginning of the study, rather than waiting for 10 years, as predicted in the power calculations.

Role of the funding source
The funding source of the study had no role in study design, data collection, analysis, interpretation or writing of the report. The corresponding author had full access to all the study data and final responsibility for submission for publication.

Results
Figure 1 shows the flow of study clusters and eligible women throughout the trial. All 49 311 eligible women in the intervention and the 30 958 in the control groups were interviewed. The study groups were well balanced for distribution of religion, occupation, income, and menopause, but some differences were observed for age, education, marital status, and parity (table 1). Only two of the eligible women had ever had previous cervical screening.

Enumeration of households and eligible women started in October, 1999, and screening started in January, 2000. Screening was mostly completed by April, 2003, although some additional women were enumerated and screened subsequently. Of the 49 311 eligible women in the intervention group, 31 343 (63.6%) were VIA positive; 3052 (98.8%) had colposcopy, and 2539 (82.2%) had directed biopsy (table 2). CIN 1 was diagnosed in 1656 (5.3%) women, CIN 2–3 in 218 (0.7%), and 67 (0.2%) were screen-detected cervical cancers (table 2).

Screen-positive and CIN detection rates declined as age increased; women aged 30–39 years at screening had higher rates of CIN, whereas older women had a higher frequency of cancer (table 2, figure 2). The positive predictive value of VIA to detect CIN 2–3 lesions and cancer was 9.2% (285 of 3088). Cryotherapy, LEEP, or conisation was done on 1172 (70.8%) women with CIN 1.

Cancer was 9.2% (285 of 3088). Cryotherapy, LEEP, or conisation was done on 1172 (70.8%) women with CIN 1. The positive predictive value of VIA to detect CIN 2–3 lesions and cancer was 9.2% (285 of 3088). Cryotherapy, LEEP, or conisation was done on 1172 (70.8%) women with CIN 1.

The intervention group had lower cervical cancer incidence and mortality rates than the control group. Overall and age-specific hazard ratios for incidence of all cervical cancers, of cancers at stage II or worse, and death from cervical cancer, adjusted for age, education, marital status, parity, and the cluster design are given in table 5. Overall, the intervention group had a significant 25% reduction in cervical cancer incidence (hazard ratio 0.75 [95% CI 0.55–0.95]) and a significant 35% reduction in cervical cancer mortality (hazard ratio 0.65 [0.47–0.89]) compared with the control group. For cervical cancer incidence, the reduction in the adjusted hazard ratio was greatest in the 30–39-year age-group (0.62 [0.40–0.96]). There was no evidence of significant heterogeneity on the incidence hazard ratio outcomes.

Table 4: Incidence of and mortality from cervical cancer by study group

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Control</th>
<th>Intervention</th>
<th>ASR/100 000†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Person-years</td>
<td>Crude rate (95%CI)/100 000*</td>
</tr>
<tr>
<td>Cervical cancer incidence</td>
<td>158</td>
<td>178 394</td>
<td>88.6 (74.9–105.3)</td>
</tr>
<tr>
<td>Incidence of stage II or worse cancers</td>
<td>98</td>
<td>178 394</td>
<td>54.9 (44.5–68.4)</td>
</tr>
<tr>
<td>Cervical cancer death</td>
<td>92</td>
<td>178 781</td>
<td>51.5 (42.0–63.6)</td>
</tr>
</tbody>
</table>

ASR=age standardised rate. *Only cluster design adjusted for; rates are per 100 000 women person-years. †Standardised using world standard population; rates are per 100 000 women person-years.
across the three age-groups, both for cervical cancer incidence (p=0.63) and stage II or worse cancers (p=0.36). Similarly for cervical cancer mortality, the hazard ratio was reduced most in the 30–39 age-group (0.34 [0.18–0.66]) followed by that in the 40–49 age-group (0.55 [0.31–1.00]). There was evidence of significant heterogeneity on the hazard ratios for cervical cancer mortality across the three age-groups (p=0.045).

Discussion

Successful screening leads to reduction in cervical cancer incidence by detection and treatment of CIN. Strategies involving cytology screening and multiple visits for diagnosis and treatment are impractical in low-resourced and most medium-resourced developing countries. We show that cervical cancer burden can be reduced by a single round of VIA screening. Our findings indicate that VIA is a simple, feasible, and effective method to prevent cervical cancer and death among deprived populations in developing and developed countries, and also emphasise that high quality training of providers, continuous quality assurance, and monitoring are crucial for the success of VIA screening programmes.

We need to consider some of the methodological aspects of our study and the discrepancies between the preliminary results included in our baseline paper.##

### Table 5: Overall and age-specific hazard ratio for incidence for all cervical cancers, cancers at stage II or worse, and for cervical cancer deaths

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Overall Hazard ratio (95% CI)</th>
<th>Age group (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>30–39</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hazard ratio (95% CI)</td>
</tr>
<tr>
<td>Intervention group (crude hazard ratios)*</td>
<td></td>
<td>0.67 (0.52–0.85)</td>
</tr>
<tr>
<td>Cervical cancer incidence</td>
<td></td>
<td>0.68 (0.50–0.91)</td>
</tr>
<tr>
<td>Incidence of stage II or worse cancers</td>
<td></td>
<td>0.59 (0.43–0.80)</td>
</tr>
<tr>
<td>Cervical cancer death</td>
<td></td>
<td>0.75 (0.59–0.95)</td>
</tr>
<tr>
<td>Intervention group (adjusted hazard ratios)†</td>
<td></td>
<td>0.76 (0.57–1.02)</td>
</tr>
<tr>
<td>Cervical cancer incidence</td>
<td></td>
<td>0.65 (0.47–0.89)</td>
</tr>
<tr>
<td>Incidence of stage II or worse cancers</td>
<td></td>
<td>0.76 (0.57–1.02)</td>
</tr>
<tr>
<td>Cervical cancer death</td>
<td></td>
<td>0.75 (0.59–0.95)</td>
</tr>
</tbody>
</table>

Hazard ratio=1.00 for all members of control group. *Adjusted only for the cluster design. †Overall ratios adjusted for age, education, marital status, parity, and cluster design, and age-specific ratios adjusted for education, marital status, parity, and cluster design.
Articles

(mainly intended to describe the study design) and the current results. The differences between the number of eligible, screened, and screen-positive women in the two reports are due to additional enumeration and screening done after that baseline paper was submitted. In this paper we describe the number of women from whom a biopsy was taken and the number of CIN cases in screen-positive women only, whereas the baseline paper also included biopsies and CIN cases among some screen-negative women (treated with cryotherapy for benign conditions such as large ectropion or severe cervicitis and had a routine biopsy before cryotherapy).

We undertook this study in Dindigul district, India, because of the high-risk of cervical cancer and the availability of diagnostic and treatment facilities. Village clusters were randomised to keep contamination between study groups to a minimum, and randomisation was done before household surveys and individual interviews. The imbalances between the study groups for some of the variables are due to randomisation of clusters before enumeration and knowledge of eligible women characteristics. For this reason all the differing variables have been adjusted for in the analysis. We had more women in the intervention group than in the control group because some intervention clusters had relatively large populations, some women moved into the intervention clusters from elsewhere during the screening years (2000–03), and some women missed enumeration at the beginning because of their unavailability at that time and the refusal of one control cluster to be enumerated. This imbalance would not affect the results and conclusions drawn from the study since the analysis has been done as a randomised trial. This observation is further exemplified by the fact that if we restrict our analysis to the 34803 eligible women in the intervention and 30770 eligible women in the control group identified by the initial single enumeration in the year 2000, the intervention group had a 30% reduction in cervical cancer incidence (hazard ratio 0·70 [95% CI 0·53–0·92]); a 27% reduction in the incidence of stage II or advanced cancers (0·73 [0·53–0·99]) and a 42% reduction in cervical cancer mortality (0·58 [0·41–0·82]) compared with the control group. Thus, the results for enumerated women in 2000, before screening was initiated, are similar to those for all enumerated women in the intervention (49311 eligible women) and control groups (30958 eligible women) that we have presented in this paper; the results by age-groups, cumulative cervical cancer incidence rate, stage II or worse cancer incidence rate, cumulative cervical mortality over time and all cause mortality (544.8 in the control and 477.2 per 100 000 in the intervention group; hazard ratio 0·87 [95% CI 0·78–0·97]) were also similar.

We used an unscreened control group, because there are no organised screening programmes in India. A single visit approach was used to maximise participation of screen-positive women for diagnosis and cryotherapy. Since death registration is likely to be incomplete in rural India, we took additional measures such as collecting data from death registers in churches, mosques, and by annual house visits in villages, as well as active cancer registration in the entire district to ensure accuracy and completeness of outcome assessment. Misclassification of cause of death is unlikely because of the low risk of endometrial cancer in rural India, and almost all cancer patients there die of cancers affecting them in view of the advanced stages at presentation.

We saw a significant decline in disease burden earlier than predicted by power calculations, within 7 years from the beginning and 3·5 years from the completion of screening, due to the higher than assumed cervical cancer mortality rate (assumed in the light of lack of reliable cancer mortality data in rural India and in the study area) observed in our study population. We plan to continue the follow-up of study population for cervical cancer incidence and mortality for several years to have information on long-term effect of the single intervention and to infer on screening intervals based on the extent of shrinkage of mortality reduction following single intervention. Overestimation of the effect of VIA is unlikely in view of the blinded assessment of outcomes in our study. The lower effect of VIA in older women seems to be due to the migration of transformation zone into the endocervical canal and the lower participation in these age-groups.

The convincing and important decline in cervical cancer incidence and mortality as well as all cause mortality should alleviate any concern that our trial results were reported and interpreted too early. The decline in cervical cancer burden was observed within 5–7 years from initiation, or achieving good coverage, of screening programmes in Nordic countries, Canada, and the UK.

In England, the programme was reorganised in 1988, more than 70% coverage was achieved by 1990, and cervical cancer incidence fell by 35% during 5 consecutive years thereafter. Cervical cancer is an important cause of death in our study population as evidenced by the fact that it accounted for 11% of deaths in the control group and all-cause mortality in the intervention group was significantly reduced possibly due to both prevention of cervical cancer by VIA screening and health care interaction (eg, correction of anaemia and blood pressure measurements) through the intervention. The progress of our study was regularly reviewed by the IARC Scientific Council and the decision to publish was taken after their review of results in November, 2006.

VIA has been shown to be a simple, affordable, safe, acceptable, and accurate test. It has acceptable sensitivity and specificity in the range of 56–77% and 64–86%, respectively, to detect high-grade CIN in several studies involving a wide range of test providers after competency based training. The real-time results after VIA enables a single visit approach linking diagnosis and treatment with testing.
We investigated the effects of visual screening on cervical cancer incidence and mortality by age-groups in view of the inability of visual screening to assess the endocervical canal into which the transformation zone moves with advancing age (menopause), and when the frequency of CIN also declines. This study will help to establish the optimum age range for providing visual screening, which is important in the context of developing countries where repeated screening rounds are not feasible because of organisational and resource constraints. The greatest reduction in hazard ratios were observed for the 30–39 year age-group, which makes biological sense, since the transformation zone where cervical neoplasia occur is fully exposed on the ectocervix in young women, enabling VIA to detect the abnormalities. In modelling studies, even a low-intensity, once in a lifetime screening for women between 30–45 years has been shown to reduce cervical cancer burden by 30%. In a modelling study, a single-visit VIA screening at the age of 35 years reduced the lifetime risk of cancer by between 25% and 36% and cost less than US$500 per year of life saved. Our results indicate that VIA is a suitable screening test for women aged 30–39 years and for premenopausal women. We are assessing cost-effectiveness data and quality of life in our study and these will be reported separately.

In a randomised trial in South Africa, VIA followed by cryotherapy resulted in a 37% and 46% lower prevalence of CIN 2–3 lesions at 6 and 12 months, respectively, compared with a control group who received delayed assessment at 6 months. Our findings on incidence and mortality reduction following VIA are consistent with the results in the modelling and South African study. However, we should note that cryotherapy for women testing positive for human papillomavirus (HPV) resulted in much higher declines in the prevalence of CIN 2–3 lesions at 6 and 12 months (77% and 74%, respectively) compared with the control group in the South African study. HPV testing is certainly more objective and reproducible than VIA and does not depend on the visibility of the transformation zone; it is less demanding in terms of training and quality assurance, but it needs sophisticated equipment and the current costs are prohibitive for use in developing countries. A simple, affordable, rapid (results within 3 h), user-friendly, and accurate HPV test suitable for use in low-resourced countries is currently being validated and will be available soon. The possible replacement of a highly provider-dependent and subjective test like VIA with the new HPV test is an exciting option to avoid the variation and subjectivity in test interpretation and to minimise efforts required in training, sustaining skills, and quality assurance. However, this simple test replacement alone will not automatically ensure success and further improve mortality reduction unless the crucial programmatic steps on coverage, good quality treatment, follow-up, and monitoring are ensured, as we have shown in our study.

Although HPV vaccination is a promising control option, it will take several decades to establish its effect on cervical cancer burden and the vaccine costs are currently prohibitive. Timely implementation of an affordable and effective screening strategy in developing countries is thus crucial, while waiting for further improvements in HPV testing, vaccine technology, costs, and its widespread use.

Our findings can readily be generalised to other regions of India and developing countries given the prevailing similar risks and conditions as in our study population. The convincing reduction in disease burden and the feasibility justify the routine use of single round of VIA screening both in clinical and public health settings for cervical cancer prevention in developing countries. Routine teaching of VIA for medical students, nurses, health workers, and doctors will facilitate wide diffusion in clinical and community settings. Service delivery for VIA-positive women could involve colposcopic triage and biopsy where sufficient capacity exists; in regions with limited capacity, a single-visit strategy involving cryotherapy without colposcopy or biopsy can be considered. We believe that VIA screening, supported by sustained training and quality inputs, should be established in routine health services in India in view of the high burden of disease (120 000 new cases and 80 000 deaths a year) and other high-risk developing countries and deprived populations. This will help in establishing an infrastructure for screening which can easily adapt to further developments in affordable, rapid and accurate HPV testing technology.

**Contributors**

R Sankar had the initial idea and was responsible for the conception and study design, monitoring, supervision, acquisition, analysis, and interpretation of the data, and provided training of project staff. POE participated in the conception and design of the study, and in the monitoring, supervision, acquisition, analysis, and interpretation of the data, and provided staff training and clinical services and responsible for the overall supervision of the project since 2005. RR participated in the conception and design of the study, and in the monitoring, acquisition, analysis, and interpretation of the data, and provided staff training and clinical services and responsible for the overall supervision of the project during 2000–04. RM participated in the analysis and interpretation of the data and sample size calculations. R Swami participated in the conception and design of the study, and in the acquisition, analysis, and interpretation of the data and is responsible for cancer registration. JMF participated in the analysis and interpretation of the data. SS participated in the in the acquisition, analysis, and interpretation of the data, and the interpretation and reporting of histopathology. JC participated in the conception and design of the study, and in the monitoring, supervision, acquisition, analysis, and interpretation of the data, and provided clinical services.

**Conflict of interest statement**

We declare that we have no conflict of interest.

**Acknowledgments**

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Clinical Medicine, University of Oxford, Oxford, UK) for his support and assistance in the design and the monitoring of the study; Lucien Frappart (Hôpital E Herriot, Lyon, France), Sudha S Sundar (Cheltenham General Hospital, Cheltenham, UK), Somanathan Thara and Ramani Wesley (Regional Cancer Centre, Trivandrum, India) for their assistance in training of staff and quality assurance; Eric Lucas (Screening Group, IARC) for his assistance in data management; and Evelyn Bayle (Screening Group, IARC) for her help in preparing this manuscript.

References


Normalisation of CD4 counts in patients with HIV-1 infection and maximum virological suppression who are taking combination antiretroviral therapy: an observational cohort study

A Mocroft, A N Phillips, J Gatell, B Ledergerber, M Fisher, N Clumeck, M Losso, A Lazzarin, G Fatkenheuer, J D Lundgren for the EuroSIDA study group

Summary

Background Combination antiretroviral therapy (cART) has been shown to reduce mortality and morbidity in patients with HIV. As viral replication falls, the CD4 count increases, but whether the CD4 count returns to the level seen in HIV-negative people is unknown. We aimed to assess whether the CD4 count for patients with maximum virological suppression (viral load <50 copies per mL) continues to increase with long-term cART to reach levels seen in HIV-negative populations.

Methods We compared increases in CD4 counts in 1835 antiretroviral-naive patients who started cART from EuroSIDA, a pan-European observational cohort study. Rate of increase in CD4 count (per year) occurring between pairs of consecutive viral loads below 50 copies per mL was estimated using generalised linear models, accounting for multiple measurements for individual patients.

Findings The median CD4 count at starting cART was 204 cells per μL (IQR 85–330). The greatest mean yearly increase in CD4 count of 100 cells per μL was seen in the year after starting cART. Significant, but lower, yearly increases in CD4 count, around 50 cells per μL, were seen even at 5 years after starting cART in patients whose current CD4 count was less than 500 cells per μL. The only groups without significant increases in CD4 count were those where cART had been taken for more than 5 years with a current CD4 count of more than 500 cells per μL, (current mean CD4 count 774 cells per μL; 95% CI 764–783). Patients starting cART with low CD4 counts (<200 cells per μL) had significant rises in CD4 counts even after 5 years of cART.

Interpretation Normalisation of CD4 counts in HIV-infected patients for all infected individuals might be achievable if viral suppression with cART can be maintained for a sufficiently long period of time.

Introduction

Combination antiretroviral therapy (cART) has been shown to reduce mortality and morbidity in patients with HIV.1 The goal of cART, according to current treatment guidelines, is to reduce HIV viral replication to below the limit of detection.2 As viral replication falls, the CD4 count increases.3-4 The initial increase is rapid and usually lasts 3–6 months, followed by a phase of slower CD4 count increases.5 The factors that determine CD4 count responses are partly known and are thought to depend on both the host and the virus, and there is substantial variation in CD4 count recovery.6 In patients with virological suppression (HIV-RNA viral load <1000 copies per mL), older age, a longer duration of HIV infection, and lower CD4 counts at starting cART were predictors for maintaining lower CD4 counts.6 In the Swiss HIV Cohort Study,7 a third of patients were incomplete responders, and only half continued to have CD4 count increases. The remainder were described as reaching a CD4 plateau, with no further increases in CD4 count. This finding led to the conclusion that not all patients might eventually respond to cART by achieving a CD4 count in the normal range.

Several factors have been investigated to establish the relation with CD4 count recovery, including viral pathogenicity, host factors, or co-infection with hepatitis B or C.5,8,9 The most consistent finding, however, is that patients who start cART with lower CD4 counts need longer treatment to achieve CD4 counts in the normal range.10 There has been little research to date on CD4 count increases in analyses restricted to patients with maximum virological suppression (viral load <50 copies per mL). Previous work from the EuroSIDA study11 assessed the increases in CD4 count in patients with maximum virological suppression, and found some differences according to cART regimen in use, but this previous study did not specifically address long term CD4 count increases and when or at what level CD4 counts were no longer increasing. The objectives of our study were therefore to describe the relation between duration of treatment, CD4 count at the start of cART, current CD4 count, and CD4 count increases in antiretroviral-naive patients starting cART who achieve maximum virological suppression.

Methods

Patients

EuroSIDA is a prospective, European study of 14262 patients with HIV-1 infection in 92 centres across Europe.
Articles

(last data collection and the date of starting and stopping each antiretroviral drug. Data for hepatitis B and C antibody status were recorded in 1997 at the inception of cohort III and for patients still under follow-up from cohorts I–II, similarly at the recruitment of cohort IV, and every year thereafter. Hepatitis B and C serological markers were assessed with commercial ELISAs.)

Members of the coordinating office visited all centres to ensure correct patient selection, and that accurate data were provided, by checking the information against case notes for all reported clinical events and a random sample of 10% of all other patients.

Statistical methods

All antiretroviral naive patients from EuroSIDA with at least two consecutive viral loads of less than 50 copies per mL were eligible for inclusion. Patients were required to have a CD4 count measured in the 6 months before starting cART and distinct CD4 counts measured within at most 4 weeks (either side) of each viral load measure (95% of CD4 counts were measured on the same date as viral load measurements). cART was defined as exactly two nucleosides or nucleotides plus a single protease inhibitor, ritonavir boosted protease inhibitor, a non-nucleoside reverse transcriptase inhibitor (NNRTI), or abacavir.

Baseline (for descriptive purposes) was defined as the first of two consecutive viral loads of less than 50 copies per mL after starting cART. The first viral load measurement was used because that was the time point from which patients were included, conditional on there being a consecutive viral load of less than 50 copies per mL. The change in CD4 count occurring between each pair of consecutive viral loads of less than 50 copies per mL was calculated and standardised for the time between measurements to give the yearly change in CD4 count. Thus a patient with four consecutive viral loads of less than 50 copies per mL would contribute data from three viral-load pairs: change in CD4 between first and second viral load, second and third, and third and fourth. Pairs of viral-load measurements were excluded if any change (start or stop) in antiretrovirals had been made between the measurements.

Generalised linear models, using a normal distribution and an identity link function, with adjustments for repeated measurements (since each patient could be included any number of times depending on their viral load, CD4, and cART history) were used to describe CD4 count changes stratified by time since starting cART, CD4 count at starting cART, and current CD4 count. These stratifications were decided a priori in order to investigate the relations between key variables. Where patients had multiple viral loads recorded within a 4-week period, the maximum viral load was used for analyses; similarly, patients with multiple CD4 counts measured within a 4-week period had the median of these values used.

| Characteristics at baseline of 1835 antiretroviral naive patients starting cART with two or more consecutive viral loads of less than 50 copies per mL | | |
|---|---|---|---|
| **All patients** | **CD4 count at baseline (cells per µL)** | ≤350 | 351–500 | >500 |
| **Sex** | | | | |
| Men | 1444 (78.7) | 581 (37.8) | 351 (77.3) | 512 (80.1) |
| Women | 391 (21.3) | 161 (21.7) | 103 (22.7) | 127 (19.9) |
| **Race** | | | | |
| White | 1577 (85.9) | 626 (40.4) | 381 (83.9) | 570 (89.2) |
| Other | 258 (14.1) | 116 (15.6) | 73 (16.1) | 69 (10.8) |
| **Exposure group** | | | | |
| Homosexual | 888 (48.4) | 321 (44.6) | 215 (47.4) | 342 (53.5) |
| Intravenous drug user | 288 (15.7) | 130 (27.3) | 70 (15.4) | 88 (13.8) |
| Heterosexual | 520 (28.3) | 215 (41.9) | 139 (30.6) | 166 (30.6) |
| Other | 139 (7.6) | 66 (8.9) | 30 (6.6) | 43 (6.7) |
| **Region** | | | | |
| South/Argentina | 458 (25.0) | 161 (21.7) | 103 (22.7) | 194 (30.4) |
| Central | 440 (24.0) | 154 (20.8) | 112 (24.7) | 174 (27.2) |
| North | 620 (33.8) | 297 (40.0) | 159 (35.0) | 164 (25.7) |
| East | 317 (17.3) | 130 (20.8) | 80 (17.6) | 107 (16.7) |
| **Previous AIDS diagnosis** | | | | |
| Negative | 1049 (57.2) | 403 (54.3) | 268 (59.0) | 378 (59.2) |
| Positive | 274 (14.9) | 123 (16.6) | 72 (15.9) | 79 (12.4) |
| Unknown | 512 (27.9) | 216 (29.1) | 114 (25.1) | 182 (28.5) |
| **Hepatitis C antibody status** | | | | |
| Negative | 1357 (74.0) | 551 (74.3) | 326 (71.8) | 480 (75.1) |
| Positive | 78 (4.3) | 35 (4.7) | 26 (5.7) | 17 (2.7) |
| Unknown | 400 (21.7) | 156 (21.0) | 80 (17.6) | 107 (16.7) |
| **Age, median (IQR)** | 39.2 (33.4–46.3) | | | |
| Month/year when baseline data recorded, median (IQR) | 10/01 (9/99–11/03) | | | |
| Nadir CD4, median (IQR) (cells per µL) | 170 (70–282) | | | |
| Peak viral load, median (IQR) (log₁₀, copies per mL) | 4.97 (4.40–5.44) | | | |

Data are N (%) unless otherwise stated. *Baseline was arbitrarily defined as the date of the first of two consecutive viral loads of less than 50 copies per mL. †Hepatitis C RNA or hepatitis B DNA was not routinely measured and it is unknown if patients were chronically infected.
In multivariable models, adjustments were made for factors previously shown to be associated with change in CD4 count in patients with a viral load of less than 50 copies per mL; age, time since cART initiation, change in CD4 since cART initiation, nucleoside pair (zidovudine-lamivudine, lamivudine-stavudine, stavudine-didanosine, tenofovir plus one nucleoside, abacavir plus one nucleoside, or any other combination of two nucleosides), and third drug (single protease inhibitor, ritonavir boosted protease inhibitor, NNRTI, or abacavir). The CD4 count previous to the pair used to calculate changes in CD4 counts was included in multivariable models to avoid regression to the mean and problems of overfitting. An additional adjustment was made for time between starting cART and initial virological suppression (<50 copies per mL).

All analyses were done using SAS (Statistical Analysis Software, version 8.2, Cary, NC, USA).

Role of the funding source
The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had full responsibility for the decision to submit for publication.

Results
There were 3365 antiretroviral-naive patients who started cART in the EuroSIDA study; of these, 2598 had at least one viral load measured with a lower limit of detection of 50 copies per mL, and 2000 had a pair of consecutive viral load measurements of less than 50 copies per mL included in analyses, representing 6503 (47·1%) viral load pairs in patients taking a protease inhibitor-based regimen, 5660 (41·0%) in patients taking a NNRTI-based regimen, and 1646 (11·9%) in patients taking a triple-nucleoside regimen containing abacavir. Zidovudine-lamivudine was the most commonly used nucleoside pair (61·5%), followed by stavudine-lamivudine (15·3%).

Table 2 shows the unadjusted rate of increase in CD4 count (per year) stratified by current count (ie, the CD4 count measured before each viral load pair). For example, there were 1353 viral load pairs where the current CD4 count was 200 cells per μL or less. In these patients, the mean rate of increase in CD4 (per year) with viral load below 50 copies per mL was 74 cells per μL (95% CI 58–91), whereas the mean current CD4 count was 137 cells per μL (134–139). Notably, the only group that did not have significant increases in CD4 count were those patients with a current count of more than 700 cells per μL, where the mean yearly change in CD4 was 18 cells per μL (–6 to 43). The current mean CD4 count in these patients was 922 cells per μL (914–930).

A multivariable model adjusted for nucleoside pair, cART regimen, age, change in CD4 count since starting cART, time since starting cART, and time to initial virological suppression, showed little evidence of no further increases in CD4 count at higher current CD4 count levels (figure I). For current CD4 counts of less than 700 cells per μL, there was a 40–60 cells per μL CD4 count rise per year with a viral load of less than 50 copies per mL. There was a lower, but still significantly increasing, yearly change in CD4 counts in patients with a current CD4 count of more than 700 cells per μL.
24 cells per μL; 95% CI 1–46, p=0·047). Adjusting for other variables, such as hepatitis B or C co-infection, exposure group, ethnic origin, or time spent with a viral load of less than 50 copies per mL did not alter these findings and were not related to rate of CD4 count change. Additionally, in the multivariable model, there was no interaction between the rate of increase in CD4 count (per year) and age (p=0·61), change in CD4 since starting cART (p=0·88), peak viral load (p=0·22), CD4 count at starting cART (p=0·38), or between current CD4 count and duration of cART (p=0·60).

This analysis was then stratified both by current CD4 count and years since starting cART (figure 2). The greatest increases in CD4 count were seen in the year after starting cART (around 100 cells per μL), irrespective of the CD4 count at starting cART. Significant, but lower, increases in CD4 count (about 50 cells per μL per year) were seen up to 5 years after starting cART in patients whose current CD4 count was below 500 cells per μL. The only group without significant increases in yearly CD4 count was patients who had taken cART for more than 5 years with a current count of more than 500 cells per μL. The current mean CD4 count in this patient group was 774 cells per μL (95% CI 764–783), whereas in the first year of cART the current mean CD4 count was 658 cells per μL (640–676), in years 1–3 was 710 cells per μL (700–720), and in years 3–5 was 747 cells per μL (737–756). Similar results were seen after adjustment for nucleoside backbone, cART regimen started, age, and change in CD4 count since starting cART.

Additional analyses were done to investigate both the sensitivity and potential sources of bias in these findings. Analyses were repeated with stratification by CD4 count at starting cART, rather than current CD4 count, and the adjusted mean changes are shown in table 3. Of the patients with maximum virological suppression, those who started cART with CD4 counts of less than 200 cells per μL continued to have significant increases in CD4 count 5 years after starting cART. In this analysis, the only group without significant increases in CD4 count were those who started cART with a CD4 count of more than 350 cells per μL and had been taking cART for more than 3 years. A further sensitivity analysis censored patients on stopping cART, because patients with treatment interruptions and subsequent virological suppression might have higher rates of CD4 count change. Only a small proportion of the patients included in this analysis underwent a treatment interruption (less than 5%) and hence the results were entirely consistent with those shown above (data not shown). Similarly, ten viral load pairs were included from patients treated with interleukin-2 (0–076), and exclusion of these data did not alter our findings. Finally, various transformations of the change in CD4 count were investigated to assess the sensitivity of the generalised linear model to variability in the data. We also repeated analyses using alternative methods, including mixed
models and binomial regression, modelling whether there was an increase in CD4 in different strata, rather than modelling the absolute change in CD4. All sensitivity analyses gave consistent results to those reported above.

Discussion

This study of CD4 count increases in antiretroviral-naive HIV-infected patients starting cART and who subsequently achieve maximum viral suppression has found little evidence of a plateau effect. Most patients continued to have significant rises in CD4 count, even at more than 5 years after cART initiation, whereas significant, but smaller, increases were seen in patients who started cART with low CD4 counts. Normalisation of CD4 counts in HIV-infected patients for all infected individuals was seen in patients starting cART with a CD4 count of more than 350 cells per μL and might be achieved in patients starting cART with lower CD4 counts if viral suppression can be maintained for a sufficiently long period of time.

Pre-infection CD4 counts were not known and we cannot to say whether the counts returned to this level. With sufficient duration of virological suppression, CD4 levels in patients starting cART with CD4 counts in excess of 350 cells per μL were approaching levels seen in HIV negative patients, of around 800 cells per μL.13–15 The rates of CD4 count increases seen after the first year of cART were consistent with those seen in HIV-negative patients after chemotherapy.16 Although patients who started cART with low CD4 counts continued to have significant rises in cell count, the absolute current level of CD4 count, roughly 500 cells per μL, was consistently lower than patients who started cART with higher counts. The rate of CD4 count increase diminished with increasing time since starting cART in patients starting cART with lower CD4 counts. This finding is consistent with an asymptotic rather than a plateau effect, whereby patients continue to have significant but progressively smaller increases in CD4 counts. Longer follow-up in this patient group is required to investigate whether CD4 counts in this group can reach the levels seen in patients starting cART with higher CD4 counts. Additionally, there is some evidence to suggest that functional immune reconstitution is incomplete in patients starting cART with lower CD4 counts.16

The increase in CD4 cell count will result in a corresponding reduction on the risk of opportunistic diseases or death associated with HIV, as the CD4 count, rather than viral load, remains one of the strongest markers of clinical disease progression.14,15 The risk has been shown to decrease as CD4 count increases,1,15 although there remain a small number of patients who develop opportunistic infections at higher than expected CD4 counts.16 Whether or not there will be a residual increased risk of clinical progression in patients after CD4 counts return to above 500 cells per μL or the levels seen in uninfected patients is unknown. Research from the SMART study group would suggest that the lowest rates of HIV-disease progression, liver-related events, or non-AIDS defining malignancies would be seen in patients who continue to take cART with virological suppression.17

Previous studies considering the occurrence of a plateau in CD4 counts have addressed a range of questions using a various methods in both antiretroviral-naive and experienced patients with variable viral suppression.5,12–14 In 2001, Tarwater and colleagues15 found no further increases in CD4 count after 2–3·5 years of cART in 314 HIV-infected patients from the MACS study, most whom were treatment-experienced. In 20 patients with moderately advanced disease enrolled in the ACTG 375 study, most changes in CD4 count took place within the first year of treatment, and there were no significant increases in CD4 count in the second or third year of therapy.16 Data from a larger patient group from the Swiss HIV Cohort Study17 describe CD4 count increases up to 4 years after starting cART. There was some evidence of a plateau, and around 40% of patients achieved a CD4 count of more than 500 cells per μL after starting cART. However, the subgroup of patients who remained on cART continued to have CD4 count increases at 4 years after starting treatment. In two further studies of patients with virological suppression,12,15 there was evidence of significant increases in CD4 counts at 3–4 years after starting cART, but there were limited data beyond this time to show whether further CD4 count increases would be seen. A more recent paper reported a return to near-normal levels in CD4 count among patients starting cART with a CD4 count less than 350 cells per μL, consistent with our findings, but unlike our results, found no significant increases in CD4 counts after 4 years of cART, irrespective of the level of immunodeficiency at starting cART.18

Crucially, this study differs in several ways from those previously published. We have used different methods to estimate CD4 count changes, taking advantage of the serial measurements in CD4 count and viral load recorded over time. This method means that all changes in CD4 count while a patient had maximum viral suppression were included in analyses, greatly increasing power of this study. Alternative statistical methods and sensitivity analyses showed consistent results. Patients in this study had extensive follow-up while viral load was below 50 copies per mL, had maximum virological suppression, and the analysis focused on their current CD4 count. This method indicates the current level of immunodeficiency, taking into account changes that have occurred to date. Other studies have had shorter follow-up, or have used higher limits of detection for viraemia.10,12,15–17

There are several points which should be considered. We excluded around half the antiretroviral-naive patients starting cART because of either incomplete virological suppression or because they did not satisfy the precise inclusion criteria, which were chosen a priori to determine CD4 count increases under optimum
antiretroviral treatment. This means that our findings are only generalisable to patients who have an optimum response to cART and should therefore be regarded as a best-case scenario. Up to 30% of patients starting cART will not achieve viral suppression and the CD4 counts in these patients will not increase to the same extent.24,29,30 Many cART regimens are associated with both long term and short term toxicities,2,31,32 treatment interruptions are common,33–35 and viral load might not always be maintained at such a low level. This study includes patients with long term follow-up after starting cART, and half of the patients started cART before 2000. Since that time, there has been a change in the antiretrovirals available and the way they are combined,36,37 which has led to an improvement over the best-case scenario. Up to 30% of patients starting cART using contemporary regimens would be more likely to have sustained maximum suppression of viraemia, and therefore the potential to achieve a CD4 count in the range seen in HIV-negative individuals. We chose an arbitrary baseline for our analyses, and this is clearly different to the baseline as defined in clinical trials. CD4 count changes most rapidly during the first few months of treatment with cART.3 As a consequence, in this study the observed change in CD4 count after some years of cART might be more similar to the changes observed in earlier years when compared with clinical trials. Finally, the patients included in our study were predominantly of white ethnic origin and the extent to which the results will be generalisable to patients from different ethnic origins is unclear.

In conclusion, we have shown that most patients with HIV who can maintain viral load at less than 50 copies per mL continue to have significant rises in CD4 counts, even after protracted exposure to combination therapy. Patients who started cART with a CD4 cell count of more than 350 cells per μL had CD4 cell counts approaching the level seen in HIV-negative individuals after more than 3 years of cART and had no further significant rises in CD4 counts.

References

18 Coakley EPG, Samore MH, Gillis JM, Hughes MD, Hammer SM. The values of quantitative serum HIV-1 RNA levels and CD4 cell counts for predicting survival time among HIV-positive individuals with CD4 counts of <50 x 10^6 cells/l. AIDS 2000; 14: 1147–53.


A 56-year-old female smoker with diabetes mellitus, hypercholesterolaemia, and obesity was admitted to the intensive care unit with septic shock, caused by a urinary-tract infection. She was treated with high doses of norepinephrine: up to 1·4 μg/kg/min. She developed severe abdominal pain. Abdominal radiography, with the patient supine, showed severe dilatation of the colon, and air in much of the colonic wall—ie, pneumatosis coli. After colectomy, histological examination of the colon showed widespread ischaemic colitis.

Figure: Air forming a thin line in the colonic wall
The pelvis can be seen in the background.
Every year, about 75 million units of blood are collected worldwide. Red blood cell (RBC) transfusion is one of the few treatments that adequately restore tissue oxygenation when oxygen demand exceeds supply. Although the respiratory function of blood has been studied intensively, the trigger for RBC transfusion remains controversial, and doctors rely primarily on clinical experience. Laboratory assays that indicate failing tissue oxygenation would be ideal to guide the need for transfusion, but none has proved easy, reproducible, and sensitive to regional tissue hypoxia. The clinical importance of the RBCs storage lesion (ie, the time-dependent metabolic, biochemical, and molecular changes that stored blood cells undergo) is poorly understood. RBCs can be filtered, washed, frozen, or irradiated for specific indications. Donor screening and testing have dramatically reduced infectious risks in the developed world, but infection remains a major hazard in developing countries, where 13 million units of blood are not tested for HIV or hepatitis viruses. Pathogen inactivation techniques are in clinical trials for RBCs, but none is available for use. Despite serious immunological and non-immunological complications, RBC transfusion holds a therapeutic index that exceeds that of many common medications.

Introduction

After the first successful human blood transfusions in the 17th century, James Blundell, the English obstetrician who undertook some of the early procedures, cautioned that blood transfusion should be reserved for emergencies.1 Half of Blundell’s first ten transfusion recipients died. One can only wonder how many of his patients might have been saved by appropriate transfusion, how many benefited from the small increments in oxygen-carrying capacity they received, and how many succumbed to transfusion-related complications.

Modern transfusion began with the identification of the major blood groups in 1901 and subsequent use of the agglutination technique for compatibility testing in 1907.2 The development of anticoagulant-preservative solutions led to the establishment of World War I blood depots in British Casualty Clearing Stations.3 The quality of these early red blood cell (RBC) components was not well documented, but by all accounts, war-time transfusions saved lives.4 Clinicians now have an array of RBC components, and the physiology of oxygen delivery has been researched extensively. However, the decision to begin blood transfusion remains controversial.

Whole blood and RBCs

Whole blood (450–500 mL per unit) is collected for refrigerated storage into plastic packs with pre-measured anticoagulant-preservative.1 The volume, preservative, haemoglobin content (usually >50 g), and storage interval or “shelf life” differ according to national criteria.5,6 Plasma proteins and other cells in RBCs preserve differently—for example, platelets and granulocytes in refrigerated blood lose biological function within 48 h. In practice, whole blood is rarely available and used infrequently for situations such as massive bleeding where red cells, volume, and plasma factors are all needed.

Red blood cell units (RBCs, packed red cells) are prepared by removing plasma from whole blood, often replacing it with an additive solution for improved cell viability during extended storage. These blood additives have proved safe—even for neonates, although little is known about their use in critically ill premature infants requiring massive transfusion.6 RBC volumes range between 200 mL and 350 mL and the haematocrit from 55% to 80%. One unit of RBCs transfused to an adult should in theory raise the haemoglobin concentration by 1 g/dL.7 In practice, the effect is more variable, with a lower rise in haemoglobin concentration in patients with splenomegaly and renal insufficiency. The effect is also dependent on the patient’s height and weight, the haemoglobin content of the unit, and the age of the cells.8,9 Similarly, although transfusion of 8–10 mL/kg of RBCs is expected to increase haemoglobin by 3 g/dL in an infant, the effect might be smaller in practice.10

Fresh or stored cells: the storage lesion

Erythrocytes age more rapidly during refrigeration than they do in the body.11 The gold standard for red cell viability is the survival of 75% of injected radiolabelled cells at 24 h—an arbitrary standard that permits a quarter of transfused erythrocytes to be non-viable. Time-dependent

Search strategy and selection criteria

We identified reports by searching Medline (1960–2006) with the following MeSH subject headings: “erythrocyte transfusion”, “blood component transfusion”, “blood transfusion”, and “erythrocytes/ transplantation”. The terms were combined using the Boolean operator “OR” since the MeSH term “erythrocyte transfusion” was previously indexed in Medline as “blood component transfusion” (1992–93), “blood transfusion” (1969–92), and “erythrocytes/transplantation” (1968–92). Search results were restricted to include only English language papers. We searched the PubMed database with the keywords “red cells”, “transfusion”, and “transfusion reaction”. Articles were selected on the basis of the best available evidence for each topic.
Table 1: Indications for modifications of red-cell components

<table>
<thead>
<tr>
<th>Technique</th>
<th>Purpose</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukoreduction</td>
<td>Reduction of febrile non-haemolytic</td>
<td>Patients who have had an episode of FNHTR; as an alternative to donor units tested negative for CMV, neonates, and transplant patients</td>
<td>Not effective for prevention of transfusion-associated graft-versus-host disease</td>
</tr>
<tr>
<td></td>
<td>transfusion reactions (FNHTR);</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>reduction of cytomegalovirus (CMV)</td>
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<td></td>
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<tr>
<td></td>
<td>transmission (CMV-safe); and reduction of HLA alloimmunisation</td>
<td></td>
<td></td>
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<tr>
<td>Irradiation</td>
<td>Prevention of transfusion-associated</td>
<td>Recipients of allogeneic hematopoietic transplants; transfusion to blood relatives; patients on immunosuppressive regimens; congenital immunodeficiencies; malignancies; in utero transfusion, and premature infants</td>
<td>Does not reduce infectious risks or prevent FNHTR; unnecessary for aplastic anaemia or HIV-infected patients in the absence of other indications for irradiation</td>
</tr>
<tr>
<td></td>
<td>graft-versus-host disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Washing</td>
<td>Prevent allergic reactions; decrease</td>
<td>Recurrent severe allergic reactions (not responsive to premedication with antihistamines); IgA or haptoglobin-deficient patients when component from deficient donor is not available; recipients at risk from hyperkalaemia: newborns; and intrauterine transfusions</td>
<td>Washing results in a 15–20% loss of red cells; and not equivalent to leukoreduction</td>
</tr>
<tr>
<td></td>
<td>risk of hyperkalaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume-reduction</td>
<td>Reduction of volume to reduce</td>
<td>Patients who have plasma volume expansion; normovolaemic chronic anaemia; thalassemia major; sickle-cell disease; congestive heart failure; and children, the elderly, and others susceptible to volume overload</td>
<td>Not equivalent to washing for prevention of allergic reactions</td>
</tr>
<tr>
<td></td>
<td>circulatory overload</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Freezing</td>
<td>Long-term storage of autologous or</td>
<td>Patients with rare blood phenotypes or multiple alloantibodies</td>
<td>Might not be feasible for RBCs with abnormalities such as haemoglobin S or hereditary spherocytosis; not equivalent to leukoreduction (might remove &gt;95% of WBCs); depending on the method of freezing used, the post-thaw shelf-life might be 24 h or 2 weeks; thaw-wash process is lengthy—this component is not suited to emergency supply of multiple units</td>
</tr>
<tr>
<td></td>
<td>rare allogeneic blood phenotypes, and</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>strategic blood deposits</td>
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</table>

Changes in RBC quality and quantity are commonly referred to as the storage lesion. In storage, adenosine triphosphate (ATP) declines with time, resulting in changes in red-cell shape, and decline in membrane lipid content and cell rigidity. Other changes also occur in storage: cells metabolise the glucose in the preservative solution, lactate is produced, pH starts to fall, potassium increases in the suspending medium, free haemoglobin and iron are released from haemolysed red cells, and membrane lipid is shed in the form of vesicles. The organic phosphate that binds to deoxyhaemoglobin and facilitates oxygen delivery, 2,3-diphosphoglycerate (DPG), becomes undetectable by week 1 of RBC storage. After transfusion of DPG-depleted cells, haemoglobin affinity for oxygen rises significantly. These observations have raised concerns that stored RBCs might not deliver sufficient oxygen to critically ill patients. However, the clinical impact of DPG loss has been difficult to show, perhaps because DPG is regenerated in vivo and nearly restored within a day of transfusion.

A few observational studies suggest that the storage lesion could be responsible for transfusion-associated complications such as immunosuppression and multiple organ failure syndrome. However, these reports suffer from the limitations of retrospective analyses. In animal studies, plasma from stored red cells caused vasoconstriction and lung injury. One study of critically ill patients reported a fall in gastric mucosal pH, an indicator of splanchnic hypoxia, after transfusion of RBCs stored for more than 15 days, but a later study failed to confirm these findings. In one study, RBCs stored for 3 weeks were as effective as fresh cells (3–5 h old) in reversing the neurocognitive deficit of acute anaemia. With the exception of massive or exchange transfusion for neonates, where excess potassium in stored RBCs can be toxic, little clinical evidence exists to support the notion that fresh RBCs (ie, taken fewer than 7 days before transfusion) is better than stored blood.

**RBC compatibility, and modifications to RBCs**

Compatibility testing is designed to ensure that the patient receives the intended units of RBCs and that transfusion will be effective with minimum risk of an adverse reaction. The process includes ABO and Rh typing of donor and recipient, testing recipient serum for clinically important alloantibodies, and crossmatching donor red cells with recipient serum by a technique that detects serological incompatibility. Many laboratories now use computer
software instead of the serological crossmatch method. Since most fatal reactions are caused by incompatibilities in the ABO system, ABO typing alone can provide safe blood in an emergency. For the most urgent cases, group O Rh-negative (or “universal donor”) blood is issued, and compatibility testing is completed after the fact. RBCs can be modified by filtration, washing, irradiation and cryopreservation for special indications (table 1).

Respiratory function of RBCs
Few clinical signs or symptoms reliably predict early tissue hypoxia, and not many physicians will wait for hypotension, oliguria, or impaired consciousness before starting treatment. Assays that indicate failing tissue oxygenation during acute blood loss or chronic anaemia should guide transfusion need. In practice, however, none has proved easy, reproducible, or sensitive to regional tissue hypoxia. Oxygen delivery from the lungs to the tissues takes place in a complex system in which the erythrocyte functions as the primary intermediary, and compensatory mechanisms overlap. The molecular mechanisms responsible for regulation of microvascular blood flow to meet local tissue oxygen demand are the least well understood component of this system.

The respiratory function of red cells, tissue oxygen requirements, and red cell oxygen transport and delivery have been well described. Haemoglobin binds oxygen cooperatively so that small changes in oxygen tension result in large amounts of oxygen being taken up from the lungs or released to the tissues. The oxygen-haemoglobin dissociation curve shows the relation between the oxygen saturation of haemoglobin and oxygen tension (figure 1). Oxygen uptake and release are affected by local tissue pH and carbon dioxide concentration as well as by DPG binding. The steep portion of the curve indicates that oxygen tension is well preserved even if oxygen-haemoglobin saturation falls precipitously. This results in the continued delivery of oxygen to the tissues despite progressively lower levels of saturation. Shifts in the P50, the partial pressure at which haemoglobin is 50% saturated, compensate for changes in oxygen tension in the pulmonary alveoli or at the tissue level.

Principles of oxygen transport
Acute loss of about 20% of blood volume elicits compensatory increases in heart rate and cardiac output, as well as a rise in vasoactive hormones, redistribution of blood flow, and influx of extravascular fluid to the intravascular compartment. Acute blood loss is managed initially by restoring volume to avoid haemorrhagic shock. Infusions and fluid shifts result in an abrupt decrease in haemoglobin. As haemoglobin falls, compensatory mechanisms reach their limits in the different organ systems. These mechanisms are also less effective in people who are ill or elderly.

Oxygen is transported while bound to haemoglobin, and is dissolved in plasma. The solubility of oxygen in plasma is low and transport by diffusion is inefficient. Arterial oxygen content (CaO₂) is calculated according to the panel. In non-anaemic patients with a haemoglobin of 14 g/dL and breathing room air, most oxygen is haemoglobin-bound; only 2% is dissolved in the plasma. By contrast, in a severely anaemic patient with a haemoglobin of 5 g/dL and breathing 100% oxygen, 20% of oxygen is dissolved in the plasma. The panel shows equations for the calculation of oxygen delivery (DO₂), which is the product of cardiac output and CaO₂; oxygen consumption (VO₂), the product of cardiac output and the arterial-venous difference in oxygen content; and the relation between oxygen consumption, cardiac output, haemoglobin, and oxygen extraction.

A decrease in the haemoglobin concentration does not necessarily result in reduced DO₂ because cardiac output usually increases. A second global compensatory mechanism involves increasing oxygen extraction, which lowers venous oxygen saturation and partial pressure. With these two mechanisms, normovolaemic patients can tolerate haemoglobin concentrations as low as 5 g/dL without a reduction in VO₂ or signs of impaired oxygenation (figure 2). In addition, at low haemoglobin concentrations, blood flow is redistributed to maintain oxygenation of heart, and brain, and other key organs and tissues.

Panel: Oxygen delivery and consumption

CaO₂=\((Hb\times1.34+SaO₂)+(PaO₂\times0.003)\)

DO₂=cardiac output×CaO₂

VO₂=cardiac output×(CaO₂−CvO₂)

VO₂=cardiac output×[(Hb\times1.34+\((SaO₂−SvO₂)+(PaO₂−PvO₂)\times0.003)]
Physiological adaptation to progressive normovolaemic anaemia

Progressive anaemia results in reduction of blood viscosity, which favours venous return to the heart and facilitates ejection of stroke volume. In addition, normovolaemic anaemia increases sympathetic stimulation of the heart, which contributes to the increase of cardiac output during anaemia. In anaesthetised patients, the increase in cardiac output results almost exclusively from an increase in stroke volume, while in conscious individuals, heart rate increases as well. The increase in cardiac output is greater in awake patients than in those who are anaesthetised. An increase in heart rate in an anaesthetised patient should be interpreted as evidence of hypovolaemia rather than as compensation for acute development of anaemia. DO2 decreases during progressive normovolaemic anaemia despite an increase in cardiac output. However, oxygen extraction also increases and thus VO2 remains constant in awake patients, even at haemoglobin of 5 g/dL. Both awake and anaesthetised patients tolerate progressive anaemia well. Awake patients compensate primarily by boosting cardiac output, whereas anaesthetised patients also increase oxygen extraction.

The limits of compensation

One approach to deciding when to transfuse RBCs compares oxygen delivery with oxygen consumption and defines a “critical haemoglobin concentration”—the point at which compensatory mechanisms for anaemia have been maximised and further reduction in haemoglobin would result in compromised cellular metabolism.

As haematocrit falls, oxygen consumption remains unchanged until a critical DO2 (COxCaO2) is reached where cardiac output and extraction compensation can increase no further and oxygen consumption begins to drop. VO2 is limited by demand above critical DO2, and limited by supply below it (figure 2). Patients are in serious danger of organ failure if DO2 drops below this critical value.

The critical haemoglobin threshold is similar in healthy animals of different species (figure 2). In healthy humans, the critical haemoglobin is unknown but certainly below 5 g/dL. With normovolemic anaemia, cognitive and memory functions may be impaired before effects on the global circulation appear. Acutely decreasing the haemoglobin to 5 g/dL in healthy volunteers results in no signs of circulatory insufficiency. Cognitive function, however, starts to decline reversibly at 6 g/dL; at 5 g/dL immediate and delayed memory are impaired. This subtle dysfunction reverses immediately with transfusion to raise haemoglobin to 7 g/dL or on breathing oxygen. Whereas studies of anaesthetised animals and healthy volunteers define a critical hemoglobin concentration, these studies include no margin of safety for patients with significant medical debility whose compensatory mechanisms might be further compromised by medications, sepsis, trauma or other disorders.

Moderate isovolemic haemodilution is well-tolerated in elderly patients (aged 65–88 years) with no known cardiac disease. Elderly patients can tolerate a reduction in haemoglobin to 9 g/dL and maintain VO2 by increasing cardiac output and oxygen extraction as effectively as younger people. Autologous blood was re-transfused at a lower haematocrit of 7–7 g/dL and at a haemoglobin <7 g/dL in nine of 20 patients. No signs of circulatory instability or myocardial ischemia were noted. In addition, in patients undergoing coronary artery bypass surgery, compensatory mechanisms were largely independent of age. In a retrospective chart review, the haemodynamic response to a blood transfusion after cardiovascular surgery was not affected by age.

Correction of anaemia in uraemic patients is associated with an improvement in haemostasis, and the acute removal of two units of RBCs results in an increase in the bleeding time. By contrast, the effect of acute anaemia on blood coagulation in the perioperative and trauma setting is less clear. For trauma and surgery, a haemoglobin of 7–8 g/dL may represent a reasonable balance between limiting RBCs transfusion and compromising blood coagulation.
**Indications for RBC transfusion**

Despite extensive physiological data, indications for RBCs transfusion are controversial. Before the 1980s, most perioperative transfusion protocols used the “10/30 rule,” which held that haemoglobin must exceed 10 g/dL and haematocrit should be higher than 30% before operation.69 This recommendation, intended for high-risk anaesthesia patients, was later applied to all transfusion settings, acute or chronic, and became synonymous with the single haemoglobin value 10 g/dL, at which transfusion is indicated. Similarly, the term “transfusion trigger,” coined to describe factors that motivate physicians to order blood, has become equated with critical haemoglobin value.68,69 An “optimal” haematocrit has been calculated, and experimental data suggest that 35% represents the best combination of cardiac output and haematocrit in healthy animals and humans.70 But patients are rarely healthy. One value, however convenient, is unlikely to prove optimal for all conditions.70

RBC transfusion is administered most often to surgical and intensive care patients.71–73 Most studies assessing transfusion thresholds are non-randomised cohort studies, the results of which should be interpreted cautiously; obtaining unbiased results is probably impossible. Observational studies suffer from uncontrolled confounding because blood transfusion is itself an independent marker of disease severity. How many patients need transfusion but are not given it is not known, but studies of diverse patient groups such as children with malaria, people who refuse transfusion for religious reasons, trauma patients, and elderly patients with acute myocardial infarction suggest that the number could be high.74–78

**Transfusion during intensive care**

The Transfusion Requirement in Critical Care (TRICC) is the largest and most widely cited clinical trial evaluating RBC transfusion thresholds.74 The TRICC investigators randomly allocated 838 adults with haemoglobin lower than 9 g/dL to two transfusion groups.75 The “liberal” transfusion group received enough blood to maintain haemoglobin at 10–12 g/dL. The “restrictive” group received blood when the haemoglobin fell below 7 g/dL to maintain the haemoglobin at 7–9 g/dL. The primary outcome was 30-day mortality (table 2).

30-day mortality was 23·3% in the group with higher maintained haemoglobin concentrations and 18·7% in the other (p=0.10). There were no significant differences between groups in long-term mortality, infections, or days on ventilator.76 However, the group with lower haemoglobin had a lower rate of myocardial infarction and congestive heart failure than the higher haemoglobin group. A large observational study recorded similar results.77

This year, results were published of a trial in children in the intensive care unit. The researchers compared a 7 g/dL threshold on the rate of multiple organ dysfunction with a 9–5 g/dL threshold.78 As with the TRICC trial, outcomes were much the same in patients allocated to liberal transfusion threshold and restrictive transfusion, and was associated with a 44% drop in the number of red-cell transfusions. These combined findings suggest that many patients in intensive care units are receiving more RBCs than is necessary, although it is unclear how these findings apply to other clinical settings.

**Perioperative RBC transfusion**

Careful preoperative preparation for elective surgery and use of other blood management techniques reduce the need for allogeneic blood transfusion. Undiagnosed anaemia might be detected first during preadmission testing and is common in the elderly.80,81 The lower the preoperative haemoglobin concentration, the more likely that a patient will be transfused in the perioperative period. Unsuspected anaemia before elective surgery should prompt a diagnostic evaluation and, if possible, correction of the underlying cause.

**Autologous transfusion**

With preoperative autologous RBC donation, patients donate up to several units of blood before surgery and then receive their own stored blood during or after operation. The underlying assumption is that transfusing a patient’s own blood carries a reduced risk of infectious and immunological complications, and that the patient regenerates some of the blood stored, resulting in less allogeneic transfusion. Meta-analysis of clinical trials confirms a 40% reduction of allogeneic blood transfusion.82 However, autologous pre-donation is associated with a 30% increase in the need for transfusion (whether allogeneic or autologous), with 80% of patients needing to be given at least one unit of blood.

Other problems with pre-donation autologous storage include the risk of an adverse event during donation, accidental administration of the wrong unit, and the risk of bacterial contamination at least as high as that with allogeneic blood.83 In addition, the patient still receives stored blood with low DPG levels and other changes due to storage. Studies of autologous transfusion have used different transfusion protocols, which makes comparisons of reduction in allogeneic transfusion problematic.

Acute normovolaemic haemodilution involves the removal of a large volume of blood at the start of inducing
anesthesia, and replacing this volume with crystalloid. The blood is re-infused after the surgical procedure is completed, and haemostasis is established. A meta-analysis of 42 trials recorded that the frequency of a patient receiving allogeneic transfusion was not lower than that of patients receiving usual care, although patients who did receive a transfusion used 1–2 fewer units of blood.36 Cell salvage involves re-infusion of blood shed during a surgical procedure. Meta-analysis of clinical trials indicates that cell salvage reduces allogeneic blood transfusion exposure.37 Whereas no significant adverse effects have been shown in clinical trials, the average reduction in transfusion needed tends to be small.38 Cell salvage is most effective in surgical procedures associated with very large blood loss volume.92,93

**Allogeneic transfusion**

Clinical trials evaluating allogeneic transfusions in surgical patients provide little guidance for transfusion practice because most are small104–106 or include healthy patients with low frequency of adverse outcomes.107 Two large observational studies of RBC transfusion in surgical patients reached opposing conclusions. A study in 8787 hip-fracture patients that investigated the association between postoperative transfusion, and mortality and morbidity found neither harm nor benefit from postoperative transfusion at haemoglobin triggers of higher than 10 g/dL or lower than 8·0 g/dL.108 By contrast, a study in 2202 patients undergoing coronary artery bypass surgery reported more frequent postoperative infarcts in patients with higher postoperative haematocrit than in those with an intermediate or low haematocrit.109 The proportion of transfused patients in the groups was similar.

**Patients with cardiovascular disease**

In healthy patients, coronary blood flow increases greatly during acute anaemia to compensate for the decrease in CaO₂. Cardiovascular disease could increase the risk from anaemia because of restricted oxygen delivery to the myocardium.110–112 This concern is supported by results from a study3 in surgical patients who refuse blood transfusion for religious reasons—irrespective of haemoglobin concentration, patients with cardiovascular disease had a greater risk of dying than those without it. Two small studies found higher cardiovascular events in patients with haematocrit less than 28%.75,108 In other studies, however, patients with severe coronary artery disease tolerated acute reductions of haemoglobin to 10 g/dL or 8–9 g/dL.113 In a study of patients undergoing surgery for hip fracture, the association of transfusion and mortality did not differ between the 3783 patients with cardiovascular disease and the 5004 patients with no disease.114

A sub-group analysis of the TRICC trial noted that a restrictive RBCs transfusion strategy seemed safe in most critically ill patients with cardiovascular disease, with the possible exception of patients with acute myocardial infarcts and unstable angina.115

Three large observational studies have investigated the association between transfusion and outcome in patients with acute myocardial infarction or acute coronary syndrome. Each study reached a different conclusion. In an analysis of US Medicare billing data, the association between haematocrit at admission to hospital and death was assessed in 78 000 patients with acute myocardial infarction.77 In those with a haematocrit lower than 33%, transfusion was associated with a reduction in mortality. In a study of bleeding patients enrolled in three clinical trials of thrombolytic therapy in acute coronary syndrome, transfusion was associated with increased risk of death and acute myocardial infarction or death.112 A third study of acute coronary syndrome recorded different results in patients with ST-segment elevated myocardial infarction and non ST-segment myocardial infarction. Blood transfusion was associated with reduced risk of cardiovascular death in the former, but an increased risk of adverse outcome in the latter.113

Compromised myocardial contractility might limit the tolerance of acute anaemia, at least in animals, although there are few clinical data to support this. In one group of patients with severe coronary artery disease and a left ventricular ejection fraction between 26% and 83%, there was no correlation between low ejection fraction and inability to increase cardiac output.116 In dogs, regional contractile dysfunction induced by haemodilution is reversible with minimal RBC transfusion.117

**Chronic anaemia**

In chronic anaemia, increased cardiac output, an increase in red cell DPG, and redistribution of blood flow compensate for the reduced capacity of the blood to carry oxygen.118–120 Cardiac output is inversely related to haemoglobin. The symptoms of anaemia include fatigue, weakness, dizziness, and reduced exercise tolerance. Transfusion is not usually indicated for these symptoms unless the haemoglobin is so low that the patient cannot function until specific treatment reverses the anaemia.121,122 Rapid respiration and shortness of breath are signs of oxygen deficit and evidence of cardiac decompensation. Progression to changes in mental activity and muscle cramps indicates severe oxygen deprivation that presages coma and death. For children with severe anaemia related to malaria, RBC transfusion saves lives.74 Eight (89%) of nine children with haemoglobin lower than 4 g/dL who were not transfused died, whereas 50 (80%) of 65 who received RBCs survived. Patients vary in their ability to tolerate different levels of anaemia. Those with angina or severe congestive heart failure precipitated by anaemia should be transfused.

The goal of RBC transfusion for congenital anaemia is to maintain normal growth, development, and quality of life, while minimising the adverse effects of recurrent transfusion. For patients with thalassaemia major, modest transfusion to a level of 9–10 g/dL will prevent signs and symptoms of anaemia, and suppress uncontrolled erythropoiesis with its accompanying irreversible bone
deformities. For patients with sickle-cell disease, transfusion to a concentration of 10 g/dL is as effective as more aggressive regimens in preventing complications of surgery. Chronic transfusion reduces stroke by 90% in children at high risk, and should be maintained indefinitely. Only anecdotal data exist to support the use of RBC transfusion for patients with other complications of sickle-cell disease. Chronic transfusion did not reduce the complications of pregnancy in women with the disease.

Patients with sickle-cell disease on chronic transfusion regimens might benefit from extended typing of their red cells, which can reduce the alloimmunisation rate and the frequency of haemolytic transfusion reactions.

**Adverse events associated with RBC transfusion**

Transfusion safety involves both the quality of the RBC component and the integrity of the transfusion process from donor collection through administration of the blood. Although the safety of RBC transfusion has improved dramatically during the past 50 years, major risks remain (table 3). Some adverse events such as acute haemolysis occur after only a few millilitres of blood are transfused, while others, such as transfusional haemosiderosis and variant Creutzfeldt-Jakob disease (vCJD) may not become apparent for years. No method has been licensed for inactivation of pathogens in RBCs.

**Immune-mediated reactions**

The frequency of acute haemolytic reactions has changed little in the past quarter of a century and is calculated at 1 in 18 000 with mortality between 1 in 600 000 and 1 in 18 000 000 per unit transfused. Accidental transfusion of ABO-incompatible RBCs remains a leading cause of fatal transfusion reactions. The rate of mislabelled and miscollected samples for the transfusion service has been code identified to improve patient identification. Some hospitals have addressed administration errors by restricting RBC transfusions in the emergency room and surgical suites to type O, while others have investigated electronic bar code identification to improve patient identification.

Acute haemolysis results in the rapid intravascular destruction of red cells. The severity of the clinical syndrome probably represents the degree of complement activation and activation of cytokines, and can include fever, back pain, flushing, anxiety, hypotension, and chest pain. Pulmonary haemolysis, progression to renal failure, and coagulopathy are danger signs. Non-immune haemolysis from RBCs that are overheated, accidentally frozen, or mixed with hypotonic solutions before infusion can mimic incompatible transfusion. Treatment in all cases should be supportive.

Alloimmunisation from red-cell transfusions occurs at a rate of about 1% per unit transfused. The incidence depends on genetic factors, dose and frequency, the immunogenicity of the antigen, and the degree of immunosuppression. Delayed haemolytic reactions caused by RBCs alloantibodies occur in 1 in 4000–6000 units of red cells transfused. Most of these reactions are either not apparent or are clinically mild and detected by slight jaundice, low-grade fever, and a drop in haemoglobin that occurs a week or two after transfusion. However, lethal intravascular haemolysis has been reported.

Recipient immune response to the leucocytes, and less often cytokines in red-cell transfusions, result in the chill-fever reactions commonly referred to as “febrile non-haemolytic transfusion reactions” (FNHTR). FNHTR are common, but under-reported. A prospective study of HIV-infected patients who received 3864 red cell units during 1745 transfusion episodes documented the frequency of fever as 16·8%. Fever associated with transfusion was recorded about four times as often as the hospital attending staff reported it using a voluntary transfusion reaction form. 3·1% of recipients had a fever elevation exceeding 2ºC. Severe reactions are characterised by flushing within 5 min of the start of transfusion, followed by a temperature spike and rigors about 60 min later. Whereas these reactions are often classified as unimportant by attending staff, they are of great concern to the patient and result in delays in transfusion and costs for evaluation. Red cells can be leuko-reduced to reduce FNHTR.

A related, but far more severe pulmonary reaction (transfusion-related acute lung injury [TRALI]) has been associated with leucocyte antibodies in donor blood. The typical reaction is characterised by chills, fever, a non-productive cough, dyspnoea, cyanosis, and hypotension or hypertension occurring within 1–2 h of transfusion. Characteristic radiographic findings include bilateral pulmonary infiltrates, numerous, predominantly perihilar opacities, and infiltration of the lower lung fields without

### Table 3: Estimated risks in transfusion per unit transfused in the USA

<table>
<thead>
<tr>
<th>Condition</th>
<th>Estimated Risk</th>
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<tbody>
<tr>
<td>Febrile reaction</td>
<td>1 in 300</td>
</tr>
<tr>
<td>Urticaria or other cutaneous reaction</td>
<td>1 in 50–100</td>
</tr>
<tr>
<td>RBC alloimmunisation</td>
<td>1 in 100</td>
</tr>
<tr>
<td>Mistransfusion</td>
<td>1 in 14 000–19 000</td>
</tr>
<tr>
<td>Haemolytic reaction</td>
<td>1 in 6 000</td>
</tr>
<tr>
<td>Fatal haemolysis</td>
<td>1 in 1 000 000</td>
</tr>
<tr>
<td>TRALI</td>
<td>1 in 5 000</td>
</tr>
<tr>
<td>HIV 1 and HIV2</td>
<td>1 in 2 000 000–3 000 000</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>1 in 100 000–200 000</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>1 in 1 000 000–1 in 2 000 000</td>
</tr>
<tr>
<td>HTLV I and II</td>
<td>1 in 64 000</td>
</tr>
<tr>
<td>Bacterial contamination</td>
<td>1 in 5 000 000</td>
</tr>
<tr>
<td>Malaria</td>
<td>1 in 4 000 000</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>1 in 20 000–50 000</td>
</tr>
<tr>
<td>GVHD</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Immunomodulation</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
cardiac enlargement or engorgement of the vessels. Unlike pulmonary oedema associated with circulatory overload, central venous pressure and pulmonary wedge pressure are not raised in TRALI. Some 15% of cases present with mild-to-moderate hypotension, typically unresponsive to fluid challenge, and another 15% present with hypertension.142 The true rate is unknown, but in the USA, TRALI has been estimated to occur once in every 5000 transfusions.143

Mild anaphylactoid allergic reactions such as urticaria occur during 3% of transfusions.144 In a retrospective analysis of 1613 transfusion reactions, allergic reactions accounted for 17%, but of these only 7% were severe, accounting for 1·7% of all transfusion reactions. Allergic reactions occurred with a frequency of 1 in 4124 blood components and 1 in 2338 transfusion episodes.145 By contrast, IgE-mediated anaphylactic reactions following transfusion occur in about 1 in 20,000–47,000 transfusions.146 These reactions have been attributed historically to anti-IgA occurring in IgA-deficient patients, although antibodies to other proteins such as haptoglobin may prove more important.147 Reactions can be avoided by administering RBCs drawn from IgA-deficient donors.148 Whereas the frequency and severity of urticaria can be reduced by antihistamines, no evidence supports pretreatment with steroids, antipyretics, or other medications for any other allergic reaction.

When T-lymphocytes in RBC transfusions engraft in an immunosuppressed recipient, a highly lethal disorder known as transfusion-associated graft-versus-host-disease (TA-GvHD) frequently results.149 Whereas early reports suggested that TA-GvHD was confined to immunocompromised patients and transfusions between first-degree relatives, immunocompetent patients are clearly at risk.150 Freshly collected blood predisposes to the disease, which usually occurs 4–30 days after transfusion. In the most severe form of the syndrome, involving multiple organ systems, mortality is high.151 To avoid the risk of GvHD from blood transfusion, the transfused components must be irradiated to inactivate donor lymphocytes.152,153 Frozen deglycerolised RBCs have been used for premature infants and intrauterine transfusion without evidence of TA-GvHD.

Numerous alterations in circulating immune cells have been reported in patients transfused with allogeneic blood, some persisting for months or longer. The question has been whether these observations represent laboratory curiosities, or whether they reflect a clinically-relevant alteration in recipient immune status, transfusion-related immune modulation (TRIM). The seminal observation that transfusion before renal transplantation improved the survival of cadaver-derived renal allografts suggested that allogeneic RBCs transfusion has a tolerising effect.154 The role of perioperative blood transfusion in the recurrence of surgically excised tumors and in increasing the risk of postoperative infection has been disputed for decades.155–158 Several trials suggest leukoreduced RBCs result in fewer postoperative infections and substantial reductions in morbidity and mortality.159,160 Based on the sum of evidence, TRIM seems likely to be added to the list of unintended effects of allogeneic blood transfusion. The magnitude, importance, causative agents, and patient groups at particular risk have yet to be defined.161

**Non-immune reactions**

Transfusion-associated circulatory overload is neither acknowledged nor reported often enough. Over 7 years, 1 in 3168 patients transfused with RBCs at the Mayo Clinic reportedly had circulatory overload. After a bedside consultation service was introduced, the frequency of reports rose to 1 in 708 patients, the increase undoubtedly related to improved awareness.162 A separate retrospective analysis in 385 elderly patients who had had orthopaedic surgery detected a volume overload rate of about 1%.163 Hypotensive reactions severe enough to require circulatory support have been recorded when Bradykinin and angiotensin generated when blood components are exposed to the charged surfaces of leukoreduction filters.164–166 Filters from several different manufacturers have been implicated. In a study of patients undergoing heart transplantation, 24 episodes of hypotension were noted in 30 patients who received blood components filtered at the bedside.167 11 of these were receiving angiotensin-converting enzyme (ACE) inhibitors.

Transfusion-related iron overload is a particular risk to chronically transfused patients, and the major cause of death in individuals with thalassaemia.168,169 About 1 mg of iron is contained in each millilitre of RBCs or about 200 mg of iron in each unit of RBCs. Each year of transfusion adds 5–8 g of iron to body stores of chronically transfused patients, accumulating in the skin, heart, liver, and endocrine organs. Iron-related endocrine dysfunction—growth retardation, diabetes, hypothyroidism, and hypogonadism—are irreversible. Two-thirds of patients die from iron-related cardiac disease.170 Onset of organ dysfunction is variable and not directly related to the degree of iron overload.171 Subclinical cardiac abnormalities can occur when total body iron reaches as low as 20 g.172 Iron chelation therapy must be instituted early and aggressively for patients requiring repeated RBC transfusion.173

**Future directions**

Several developments promise to revolutionise RBC transfusion. The genes encoding the major blood group antigens have been cloned, and differences in DNA sequence have been associated with erythrocyte surface antigen expression. Molecular technology has already been used to determine fetal Rh blood group in the maternal circulation. Using a microarray chip format, rapid screening for single-nucleotide polymorphisms (SNPs) in blood group coding sequences has been accomplished and suggests that a new generation of fully automated DNA analysers could replace agglutination for blood typing, for selecting the best donors for patients with multiple
alloantibodies, and even for improved compatibility testing. Integrated microchip arrays or nanotechnology are being developed to enhance rapid screening of donated blood for any number of infectious agents.

Better understanding of microcirculatory control and sensitive measures of tissue hypoxia promises to provide a more objective basis for initiating, continuing, or discontinuing RBC transfusion. To circumvent RBC compatibility problems, methods to remove and mask blood group antigens are being investigated. Large-scale ex-vivo production of mature human erythrocytes from haematopoietic stem cells has been achieved. Whereas creating tens of millions of RBCs seems improbable, the technology might be useful for rare donor units. Finally, creating tens of millions of RBCs seems improbable, the ex-vivo production of mature human erythrocytes from continuing RBC transfusion. To circumvent RBC more objective basis for initiating, continuing, or discontinuing RBC transfusion. A new formula for blood transfusion volume in the critically ill. Arch Dis Child 2005; 90: 724–28.


Klein HG. Getting older is not necessarily getting better. Anesthesiology 2003: 98: 807–08.


Transfusion Medicine 2

Platelet transfusions

David F Stroncek, Paolo Rebulla

Ever since platelet transfusions were shown to reduce mortality from haemorrhage in patients with acute leukaemia in the 1950s, the use of this therapy has steadily grown to become an essential part of the treatment of cancer, haematological malignancies, marrow failure, and haematopoietic stem cell transplantation. Today, more than 1·5 million platelet products are transfused in the USA each year, 2·9 million products in Europe. However, platelet transfusion can transmit infections and trigger serious immune reactions and they can be rendered ineffective by alloimmunisation. There are several types of platelet components and all can be modified to reduce the chances of many of the complications of platelet transfusion. Transfusion practices, including indications for transfusion, dose of platelets transfused, and methods of treating alloimmunised recipients vary between countries, and even within countries. We review commonly used platelet components, product modifications, transfusion practices, and adverse consequences of platelet transfusions.

Introduction
Platelet transfusions were shown to reduce mortality from haemorrhage in patients with acute leukaemia in the 1950s, and the use of the therapy has steadily grown since then. The procedure has become an essential part of the treatment of cancer, haematological malignancies, marrow failure, and haematopoietic stem cell transplantation. Despite the procedure’s medical importance, it can trigger serious side-effects, and modifying platelet components to reduce potential complications is vital.

More than 1·5 million components of platelets are transfused each year in the USA and 2·9 million in Europe. Three different platelet preparations are used in the two regions; we review the main features of each preparation, and highlight clinically relevant differences. We also discuss the most important biochemical indices of platelet quality during storage, as well as technical and operational issues related to the collection and production of platelets.

Technological advances
A key step in the development of methods for preparing platelet products—often called platelet concentrates or components—for transfusions was the change from glass collection bottles to disposable multiple plastic bag sets that are still used for the collection of the standard unit of 450–500 mL of whole blood. The change from glass bottles to disposable plastic bag sets for the collection of blood made it possible to collect and prepare platelets within a closed system. This not only greatly reduced the risk of bacterial contamination but also facilitated the implementation of a simple, two-step differential centrifugation platelet preparation protocol. The first step in this protocol involves centrifuging whole blood at a slow speed—a soft-spin—that sediments the red and white cells and concentrates most platelets in the supernatant plasma, also called the platelet-rich plasma (PRP). In the second step, the PRP is centrifuged at a higher speed—a hard-spin—which sediments the platelets. The supernatant or platelet-free-plasma is removed and the sedimented platelets are re-suspended in 50–70 mL of plasma. Despite its simplicity, an important limiting step of this method is the need to pool several platelet concentrates to achieve an appropriate platelet dose for most adults (300–600×10⁹ platelets, which corresponds to 4–8 concentrates).

A second important advancement was the development in the 1970s of blood-cell separators that allowed the selective collection of large numbers of platelets in pre-defined volumes of donor plasma, using a procedure termed apheresis. Although this procedure is more expensive than PRP centrifugation, it carries the inherent advantages of automation and of decreasing the number of donors to which a recipient is exposed, and thus the recipient’s risk of acquiring a transfusion-transmitted infectious disease.

In the same decade, investigators began removing leucocyte-rich and platelet-rich buffy coats from red-cell concentrates, to use the white cells for interferon production in the pre-recombinant technology era and to reduce leucocyte-related transfusion side effects. The regular use of this procedure yielded large numbers of routinely produced buffy coats, which in turn led to the development of a novel whole-blood procedure for the preparation of platelet concentrates, named the buffy coat method.

Search strategy and selection criteria
We searched PubMed for English-language articles with the keywords “platelet”, “platelet transfusion”, “platelet refractoriness”, “alloimmunization”, and “platelet components” published between 1960 and 2006. Priority was given to prospective clinical studies published in journals with a high impact factor.
Both the buffy coat and PRP procedures use a two-step differential centrifugation process, but the sequence of the steps for the buffy coat method is reversed; its first step is a hard-spin of whole blood that leads to the sedimentation of all cells, including platelets. The platelets and leucocytes sediment on top of the red cells forming the buffy coat. Four to eight buffy coats of the same ABO/Rh group are collected, pooled, and diluted in autologous plasma or in a crystalloid solution. The pooled buffy coats are centrifuged (soft-spin) and the platelet-rich supernatant is retained as the platelet concentrate while the sedimented red and white cells are discarded (figure 1). An important feature of the buffy coat method is the ability to select the optimal platelet storage additive solution as the diluent, thus decreasing side-effects from the infusion of large volumes of plasma, and improving platelet metabolism during storage. Studies have shown that PRP platelet concentrates can be easily adapted to incorporate an additive solution and pooled storage, and support the long-standing evidence that pooled storage is not detrimental to platelet quality.12

It has long been a principle of blood component production that they should contain as few white cells as possible, since leucocytes increase the risk of untoward complications. Because removal of white cells by post-storage filtration does not remove biologically active substances released by white cells during storage13, leucocyte reduction is now achieved by pre-storage filtration of platelet concentrates or by apheresis protocols which use size and density differences between platelets and white cells to remove white cells during platelet collection.14–16

Although the in-vivo and in-vitro properties and effectiveness of buffy coat, PRP, and apheresis platelets are similar,17–20 the USA and Europe have different standards on the platelet concentrates (table 1). A multicentre analysis of blood components prepared by both methods summarises the composition of these products.22 Routine haematology cell counters, however, which are frequently used for quality assurance of blood components, are not specifically designed nor calibrated for this purpose. Thus, such data in scientific reports should be interpreted carefully.

Storage and transportation
Lack of oxygen is detrimental to platelet metabolism, so manufacturers of platelet storage bags have developed special plastic containers with volume-to-surface ratios that allow sufficient gas exchange between the internal volume and the external ambient air.11,12 Moreover, current standards require that stored platelets are continually gently agitated to prevent the platelet sedimentation that makes oxygen inaccessible to a proportion of platelets.

The complex platelet subcellular anatomy suffers at temperatures below 18°C. These temperatures damage micro-canaliculur structures and induce the clustering of platelet receptors. These clustered receptors are easily recognised by macrophages, which rapidly remove the previously “chilled” platelets from the circulation.25 Galactosylation can prevent the clearance of platelets chilled for 2 h,26 but has no effect when platelets have been stored for 48 h or longer.27 The standard temperature for platelets storage is 20–24°C but this is associated with an increased risk of bacterial growth in the small fraction of platelet concentrates that harbour microbes in the suspension media.28

Although it is common to try to maintain platelets in agitated suspension during transportation, recent studies have challenged the need for this requirement, particularly for products with low platelet concentrations.
It is possible that less stringent, more practical, agitation rules will be developed if conclusive supporting evidence is obtained.

**Platelet quality**

Determination of pH is a simple laboratory procedure that has been traditionally used to determine the quality of platelets in vitro. Many standards quote a “safe” pH range, which is allegedly associated with good in-vivo recovery and function. But several studies have challenged the validity of this approach because of the weak correlation between in-vitro pH and post-transfusion in-vivo function.

An even simpler test to determine quality is “swirling”. “Swirling” is a visual effect caused by defraction when platelets are manually re-suspended and held up to a strong light (figure 2). The presence of swirling indicates the suspension contains high-quality, discoid platelets. Swirling provides a reasonable correlation with in-vivo data. An important advantage of the swirling test is that it can not only be done in a laboratory setting such as a blood bank, but also immediately before transfusion in the clinic, on the ward, or at the bedside. Training staff to perform this test is simple, since the visual image produced by 1-day old platelets (usually showing very good swirling) can be easily compared with that of expired platelets stored in a refrigerator for several hours. Old platelets do not show any swirling since their morphology changes from discoid to spherical, a shape that does not diffract light.

**Detecting bacteria in platelets**

Several methods have been used to screen for contaminated platelets, including microscopic examination of gram stains of platelets, measurement of glucose levels and pH, and swirling, but these methods are insensitive (table 2). Point-of-transfusion bacteria detection systems involving solid-phase laser cytometry and dielectrophoresis are available in Europe, but the assays require at least 30 mins and are technically demanding, making this technology impractical in some settings.

In 2003, some US blood centres began to use automated liquid media cultures capable of detecting very low levels of bacteria. Testing is usually done 24 h or more after platelets collection to allow any contaminating bacteria to grow and increase the sensitivity of the assay. Another system involves the sterile removal of 2–3 mL of platelets 1 or more days after collection, and measurement of oxygen levels after incubating for 24 hours at 35°C. A fall in oxygen tension indicates the presence of bacteria. These methods have reduced, but not eliminated, the risk of bacterial contamination.

**Indications for transfusion**

**Transfusion trigger**

Traditionally, platelets were administered prophylactically when a patient’s platelet count fell below 20 000 platelets per µL. This practice was challenged in 1991 when Gmür and colleagues reported their 10-year transfusion study in 103 leukaemic patients. Stable patients were transfused prophylactically at a count of 5000 platelets per µL or less; patients with fresh minor haemorrhage or body temperature higher than 38°C were transfused at 6000–10 000 platelets per µL.
those with coagulopathy or heparin therapy, or both, and before bone-marrow biopsy or lumbar puncture were transfused at 11,000–20,000 platelets per µL; and patients with major bleeding complications or about to undergo minor surgical procedures were transfused at counts of >20,000 platelets per µL. That Gmür and colleagues recorded evidence of only three fatal haemorrhages suggested that the traditional transfusion trigger of 20,000 platelets per µL could be safely decreased to 10,000 platelets per µL in stable patients with cancer or blood disorders. Since then, several other prospective and retrospective studies have confirmed these findings. A transfusion trigger of 10,000 platelets per µL is now widely recommended, and widely adopted in clinical practice.

It is important to point out that the patient’s platelet count is just one element that needs to be considered. The cornerstone of platelet transfusion therapy is careful monitoring of the patient for the early detection of signs and symptoms of increased haemorrhagic risk and, when appropriate, increasing the transfusion threshold. Factors that indicate the patient is at increased risk of bleeding include raised body temperature, rapid decrease in platelet count, and sepsis. If a prophylactic transfusion trigger of 10,000 platelets per µL is used for stable patients, the clinical automated cell counter used to monitor the platelet count must have the power to detect very low platelet counts.

A therapeutic platelet transfusion strategy is also being investigated by several groups of researchers. In this approach, stable patients are given platelets only for clinically relevant bleeding. This strategy was judged safe in a study of autologous peripheral blood stem-cell transplant patients, and preliminary results from a multiple-centre randomised study support this finding.

### Patients undergoing surgery

The threshold for prophylactic platelet transfusions is generally higher for surgery patients. For most procedures, a platelet count of >50,000 platelets per µL is considered adequate. In CNS procedures, however, the threshold is >100,000 platelets per µL. Patients with normal preoperative platelet counts might need platelet transfusion if surgical blood loss is great and large quantities of erythrocytes are transfused. Platelet counts fall during surgery because of haemodilution, but the quantity of blood loss that leads to thrombocytopenia varies greatly between patients.

### Exceptions

Transfusion triggers and indications differ for some patients and clinical conditions and these exceptions are thoroughly reviewed elsewhere. However, it is worth noting transfusion practices for patients undergoing cardiopulmonary bypass (CPB) surgery, those with thrombotic thrombocytopenic purpura (TTP), heparin-induced thrombocytopenia (HIT), and immune thrombocytopenic purpura (ITP), and for neonates.

CPB is associated with a reduction in platelet counts because of haemodilution and transient platelet function impairment. In the past, CPB patients were routinely transfused with platelets during or after the procedure, but prospective randomised studies have shown this to be ineffective, suggesting that prophylactic platelet transfusion is inappropriate in this setting.

Thrombocytopenic neonates are at increased risk for intracranial haemorrhage; although the threshold for prophylactic transfusions is higher as a result, there is no consensus on the number. A threshold of 30,000 platelets per µL for prophylactic transfusions has been recommended by some, with a threshold of 50,000 platelets per µL for neonates at increased risk of bleeding—especially those weighing less than 1000 g.

Since neonates are at risk for cytomegalovirus (CMV) disease, transfusion-associated graft-versus-host disease, and volume overload, platelets transfused to neonates should be CMV-safe, gamma-irradiated and, in some cases, volume-reduced.

Several clinicians have reported sudden clinical deterioration and death immediately after transfusion of platelets to TTP patients. However, such patients undergoing plasma exchange therapy have received platelet transfusion without adverse effects. Until more data are available, it seems prudent to avoid platelet transfusions in TTP patients unless they are at serious risk of bleeding. Patients with HIT are at risk for arterial and venous thrombosis, and platelet transfusion is not recommended.

Platelet transfusion can be effective in ITP patients, but it is generally reserved for life-threatening bleeding.

### Transfusing platelets

#### Transfusion dose

The optimum platelet dose has not yet been defined, and is controversial. The general consensus is that therapeutic transfusions should increase the transfusion recipient’s platelet count to a level that provides adequate...
use platelet counts measured at 60 mins and 18–24 h after the transfusion. For the convenience of the recipient and clinical care staff, platelet counts are often measured 10 minutes after the transfusion rather than after 60 minutes. In practice, platelet counts are measured once at either 10 or 60 min after transfusion.76

One method is to compare the difference in platelet counts before and after transfusion—the absolute platelet count increment (API)77 (table 3). Since the API depends on the quantity of platelets in the transfused product and the patient's size, it is difficult to set an API criteria for an effective transfusion. The corrected count increment and percent platelet count increment make adjustments for the dose of platelets transfused. When platelet count increments are low, the patient is considered to be refractory to transfusions (table 3).

Whole-blood measurements of platelet function before and after transfusion have also been used to assess the effectiveness of platelet transfusions.82 Measures of clinical bleeding are sometimes used in clinical trials that compare the effectiveness of various platelet components.83

Refactoriness to transfusion

Refractoriness to platelet transfusions is most likely to be due to non-immune factors, although immune factors can sometimes be responsible. In refractory patients with cancer or haematological diseases, non-immune factors are present in 72–88% and HLA antibodies in 25–39%.84–86

Non-immune factors associated with decreased post-transfusion platelet count increments include clinical conditions such as splenomegaly and drugs such as vancomycin.87–91 (panel).

Platelets express HLA-A, HLA-B, and human platelet antigens (HPA). There is a strong association between the presence of HLA antibodies in the transfusion recipient and platelet refractoriness, but the relation between platelet-specific antibodies and refractoriness is weaker.88,90 Before the widespread use of leucocyte-reduced blood components to prevent alloimmunisation, 45–70% of chronically transfused patients developed antibodies to HLA class I antigens.85–90 Chronically transfused patients become alloimmunised to platelet-specific antigens less commonly. The proportion

Table 3: Methods used to assess the effectiveness of platelet transfusions

<table>
<thead>
<tr>
<th>Calculation</th>
<th>Criteria for an adequate response*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute platelet increment (API)</td>
<td>10–60 min post-transfusion</td>
</tr>
<tr>
<td>Corrected count increment (CCI)</td>
<td>18–24 h post-transfusion</td>
</tr>
<tr>
<td>Percent platelet increment (PPI)</td>
<td>NA</td>
</tr>
<tr>
<td>(Post-transfusion minus pre-transfusion platelet counts)</td>
<td>NA</td>
</tr>
<tr>
<td>(patient’s body surface area/number of platelets transfused)</td>
<td>&gt;4500 platelets per m²</td>
</tr>
<tr>
<td>(patient’s body surface area/number of platelets transfused)</td>
<td>&gt;2500 platelets per m²</td>
</tr>
<tr>
<td>(observed/expected platelet count increment)</td>
<td>&gt;20%</td>
</tr>
<tr>
<td>(observed/expected platelet count increment)</td>
<td>&gt;10%</td>
</tr>
</tbody>
</table>

Adapted from references 43, 78, and 79. NA=not available. *Generally, two or three consecutive transfusions must be ineffective before a patient is considered refractory to platelet transfusions; some centres require the transfusion of fresh ABO-compatible platelets for assessing platelet refractoriness since count increments can be lower for older or ABO-incompatible platelets.†The expected change in platelet counts is a value based on the number of platelets transfused and the recipient’s blood volume.
of patients with antibodies to platelet-specific antigens varies, but ranges from 2% to 17%.84,86,94,96,97 Platelets also express blood group A and B antigens,98 and ABO-compatible platelets are usually transfused. However, when platelet inventories are low or when platelets from HLA-matched donors are required, ABO-incompatible platelets might be transfused. Repeated transfusions of ABO-incompatible platelets could increase the titres of the recipient’s anti-A and anti-B, and lead to a fall in post-transfusion platelet count increments by about 30%.81

Preventing alloimmunisation
Removal of contaminating leucocytes from erythrocyte and platelet components prevents alloimmunisation.94,99 The treatment of platelets with ultraviolet B irradiation is also effective at preventing alloimmunisation,94 but this method is not widely used. While these methods are highly effective, alloimmunisation remains an important impediment to effective transfusion. Antibodies to HLA class I antigens can be found in 14% of women who have had one or two pregnancies, and in 26% who have had three or more pregnancies.100 Although in some countries, all blood components are leucocyte-reduced, in many countries leucocyte-reduced blood products are either unavailable or are only used in some cases.

Transfusing alloimmunised patients
Two main strategies have been used to transfuse alloimmunised patients: matching donor-recipient HLA antigens and crossmatching platelets. HLA-matching involves identifying the HLA type of the recipient and transfusing platelets from donors with matched antigens.101 HLA matching requires the availability of large numbers of HLA-typed donors. A registry of about 18 000–25 000 HLA-typed people is needed to provide at least five HLA-A and HLA-B matched donors for 80% of white patients.102 Since maintaining a registry of this size is expensive and difficult, alloimmunised patients are often transfused with platelets from donors that are only partially matched.101 Systems have been developed to match donor and recipient by assigning HLA-A and HLA-B antigens with shared public epitopes to clusters called cross-reactive groups (CREGs). When non-matched platelets are to be transfused, the donor is selected so that the antigens of donor and recipient belong to the same CREG. When one or two mismatches of HLA-A or HLA-B antigens in CREGs is permitted, a pool of 1000–3000 donors will meet the transfusion needs of most white patients.103 However, transfusion with platelets from partially matched donors is not as effective as that with all four antigens matching.93,104

Another approach to finding HLA-compatible donors is the selection of donors with “acceptable” antigen mismatches. Patient plasma is tested against a panel of screening cells from several people; HLA-A and HLA-B antigens on the screening cells that give negative reactions are considered acceptable. The alloimmunised patient is transfused with platelets from donors expressing HLA-A and HLA-B identical or acceptable antigens.

A molecular-based computer algorithm called HLA-Matchmaker can be used to find HLA compatible platelet donors.105,106 This algorithm is based on the principle that short three-aminoacid sequences or triplets, characterise polymorphic sites of the HLA molecules, and are the critical components of allo-sensitising epitopes. The selected HLA alleles will be compatible since they do not contain any epitope absent in the recipient. A retrospective study107 has shown that platelets selected with this algorithm result in higher post-transfusion count rises than those selected using traditional HLA matching strategies.

A commonly used alternative to HLA-matched platelets is the transfusion of crossmatch-compatible platelets.72,80,108 Crossmatching tests plasma from an alloimmunised patient against platelets available for transfusion or aliquots of platelets from potential donors that have been frozen or refrigerated.109

Panel: Factors associated with refractoriness to platelet transfusions or reduced post-transfusion platelet responses

<table>
<thead>
<tr>
<th>Factors associated with refractoriness to platelet transfusions or reduced post-transfusion platelet responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-immune factors</td>
</tr>
<tr>
<td>Clinical factors</td>
</tr>
<tr>
<td>Splenomegaly92–95</td>
</tr>
<tr>
<td>Infection93,94</td>
</tr>
<tr>
<td>Fever93,95</td>
</tr>
<tr>
<td>Bleeding93</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation93,95</td>
</tr>
<tr>
<td>Drugs</td>
</tr>
<tr>
<td>Amphotericin92–95</td>
</tr>
<tr>
<td>Vancomycin93,95</td>
</tr>
<tr>
<td>Ciprofloxacin98</td>
</tr>
<tr>
<td>Heparin99</td>
</tr>
<tr>
<td>Patient factors</td>
</tr>
<tr>
<td>Sex (male)92,95</td>
</tr>
<tr>
<td>Increased weight92,93</td>
</tr>
<tr>
<td>Increased height92,93</td>
</tr>
<tr>
<td>Previous pregnancies90</td>
</tr>
<tr>
<td>Previous transfusions90</td>
</tr>
<tr>
<td>Immune factors</td>
</tr>
<tr>
<td>Antibodies</td>
</tr>
<tr>
<td>HLA89,90</td>
</tr>
<tr>
<td>Platelet-specific89</td>
</tr>
<tr>
<td>Erythrocyte81,90</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Platelet product</td>
</tr>
<tr>
<td>Age90</td>
</tr>
</tbody>
</table>
HLA-specific and platelet-specific antibodies in the patient’s plasma react with platelets expressing incompatible antigens. Only platelet components that are compatible are transfused. Several methods have been used to crossmatch patient samples including commercial kits and automated systems. HLA-matched and crossmatch-compatible platelets are equally effective. The decision over which to use depends mostly on the resources available. Since providing HLA-matched platelets requires the recruitment of specific donors, such platelets can only be obtained by apheresis. For crossmatching, apheresis, buffy coat, or the PRP method can be used.

For highly alloimmunised patients and those with rare HLA types, finding compatible platelets can be difficult. Several immune-modulatory therapies have been used to try to overcome alloimmune platelet refractoriness: intravenous immune globulin, cyclosporin A, vinblastine, staphylococcal protein A, removal of HLA antigens with citric acid. Despite anecdotal positive outcomes, these strategies are usually not successful or practical.

Adverse effects
Platelets, like most blood products, can transmit blood-borne pathogens including HIV, hepatitis B virus (HBV), hepatitis C virus (HCV), and CMV. Testing of donors for HIV, HBV, and HCV, and preventing people at risk of infection with these viruses from donating blood has greatly reduced the incidence of transmission of these agents by transfusion. However, infections still occur as do other complications (table 4).

Infectious complications

Cytomegalovirus
CMV resides in peripheral blood leucocytes, and infection can cause serious morbidity in immune-compromised patients. The transfusion of platelets from CMV-seronegative donors is effective in preventing infection. However, because less than 50% of blood donors are CMV-seronegative, it is not always possible to provide CMV-seronegative platelets. The transfusion of leucocyte-reduced blood components can also prevent infection, and leucocyte-reduced platelets are widely used when CMV-safe blood is required. However, one analysis suggests that CMV-seronegative components might be slightly more effective at preventing virus transmission.

Bacterial contamination
Since platelets can be stored at 20–24°C for up to 5 days in Canada, Europe, Korea, and the USA, bacterial levels in contaminated platelets can become very high. Bacteria usually enter the platelet concentrate by the blood-collection needle entering the vein through skin that has been ineffectively disinfected. Rarely, platelets are contaminated as a result of donor bacteraemia from asymptomatic infections or occult colon cancer. Although bacterial contamination affects a small proportion of platelet concentrates (about 1 in 3000 units), it is often fatal, particularly in immuno-compromised patients with cancer or blood disorders.

The risk of severe transfusion reactions because of bacterial contamination increases with longer storage periods, and platelet storage is limited to 3 days in Japan. However, platelet quality can be maintained beyond 5 days, and some US centres are extending the maximum storage time to 7 days for platelets that have been tested for bacteria with an automated culture system 24 h after collection.

Pathogen inactivation
Systems are now available to reduce the levels of microbes in platelets. One system, Intercept, that is being used in Europe but is not available elsewhere, involves crosslinking pathogen DNA and RNA by adding a psoralen, S-59, and exposing the platelets to ultraviolet light. This and other systems under development inactivate viruses, bacteria, and parasites.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious</td>
<td></td>
</tr>
<tr>
<td>AIDS</td>
<td>HIV-infected donor</td>
</tr>
<tr>
<td></td>
<td>Donor screening and testing</td>
</tr>
<tr>
<td></td>
<td>Pathogen inactivation</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Hepatitis B or hepatitis C virus</td>
</tr>
<tr>
<td></td>
<td>infected donor</td>
</tr>
<tr>
<td></td>
<td>Donor screening and testing</td>
</tr>
<tr>
<td></td>
<td>Pathogen inactivation</td>
</tr>
<tr>
<td>CMV disease</td>
<td>CMV-infected donor</td>
</tr>
<tr>
<td></td>
<td>Donor testing</td>
</tr>
<tr>
<td></td>
<td>Leucocyte reduction</td>
</tr>
<tr>
<td></td>
<td>Pathogen inactivation</td>
</tr>
<tr>
<td>Sepsis or septic shock</td>
<td>Contamination from the platelet</td>
</tr>
<tr>
<td></td>
<td>donor’s skin or from an occult or</td>
</tr>
<tr>
<td></td>
<td>asymptomatic donor</td>
</tr>
<tr>
<td></td>
<td>Bacteriaemia</td>
</tr>
<tr>
<td></td>
<td>Culture product 24 or more hours after collection</td>
</tr>
<tr>
<td></td>
<td>Test for bacteria shortly before transfusion</td>
</tr>
<tr>
<td></td>
<td>Pathogen inactivation</td>
</tr>
</tbody>
</table>

| Immunological          |                                     |
|------------------------|                                     |
| Alloimmunisation        | Leucocytes in platelets              |
|                        | Leucocyte reduction                  |
|                        | UVB irradiation                      |
| Febrile reactions       | HLA antibodies in transfusion        |
|                        | recipient and IL-1β and IL-6 in      |
|                        | platelets                            |
|                        | Leucocyte reduction                  |
|                        | UVB irradiation                      |
| TRALI                  | Leucocyte antibodies, bioactive      |
|                        | lipids, or CD40L in platelets        |
|                        | Exclude donors with leucocyte        |
|                        | antibodies                            |
| Anaphylaxis            | Antibodies in patients reacting with  |
|                        | IgA, haptoglobin, antibodies, or     |
|                        | other plasma antigens                |
|                        | IgA-deficient platelet donors        |
|                        | Washed platelets                     |
| GVHD                   | Engraftment of donor leucocytes in    |
|                        | an immunosuppressed recipient        |
|                        | Gamma irradiation of platelets (25 GY)| |
|                        | Possibly pathogen inactivation       |
| RHD alloimmunisation    | Transfusion of platelets from        |
|                        | RH-D-positive donors to RH-D-negative|
|                        | recipients                            |
|                        | Administer RH immune globulin within |
|                        | 48 h of transfusion                  |
| Haemolysis             | Anti-A and anti-B in donor’s plasma  |
|                        | Exclude donors with high titres of   |
|                        | anti-A or anti-B                     |
| Hypotension            | Generation of bradykinin by the      |
|                        | bedside filtration of platelets in a |
|                        | patient taking angiotensin-          |
|                        | converting enzyme (ACE) inhibitors   |
|                        | Pre-storage or in laboratory         |
|                        | leucocyte reduction                  |

Table 4: Adverse consequences of platelet transfusions

the treatment of platelets with the Intercept system results in the loss of some platelets,\textsuperscript{126} the quality of the remaining platelets is the same as control platelets.\textsuperscript{127} Pathogen-inactivation systems have the advantage of protecting transfusion recipients from pathogens known to cause clinically important infections, and the potential to protect recipients from emerging pathogens. In addition to the loss of platelets, pathogen inactivation procedures are limited by the possible exposure of blood-processing personnel and the recipient to toxic substances, possible environmental contamination, and added cost to the final product.\textsuperscript{127}

**Non-infectious complications**

**Febrile transfusion reactions**

Patients with HLA antibodies often have febrile reactions after transfusion of leukocyte-rich platelets,\textsuperscript{126} which can be prevented by transfusing leukocyte-reduced platelets. Soluble cytokines in platelet components can also cause febrile reactions. Immediately after collection, soluble cytokine levels are very low, but during room temperature storage of leukocyte-rich platelets, the levels of cytokines IL-1β and IL-6 rise.\textsuperscript{126} The transfusion of platelet products with elevated concentrations of IL-1β and IL-6 is associated with fever, chills, rigours, and nausea.\textsuperscript{126} Increased cytokine levels and transfusion reactions can be prevented by removing leucocytes during or immediately after collection.\textsuperscript{128,129}

**Rh alloimmunisation**

Although platelet products contain small quantities of erythrocytes, almost always less than 1 mL, the transfusion of platelets from RhD-positive donors to RhD-negative recipients can result in RhD alloimmunisation.\textsuperscript{122,123} This is particularly problematic for women of childbearing age or younger since fetal or newborn children of women with anti-D are at risk of haemolytic disease. The administration of anti-D immunoglobulin within 48 h of the transfusion of RhD-positive platelets prevents alloimmunisation.\textsuperscript{124} One dose can prevent alloimmunisation from multiple incompatible platelet transfusions.\textsuperscript{135}

**Graft-versus-host disease**

The transfusion of platelets to patients with congenital immune diseases and those undergoing immuno-suppressive therapy can result in lethal graft-versus-host disease (GVHD).\textsuperscript{126,127} GVHD can be prevented by irradiating blood components with gamma rays or x-rays at 25 Gy—high enough to prevent lymphocyte proliferation.\textsuperscript{128,129} Since the threshold of the quantity of transfused lymphocytes that can cause GVHD is unknown, even leukocyte-reduced platelets are irradiated. Pathogen-inactivation techniques that target nucleic acids have the potential to inactivate lymphocytes in treated platelets and prevent GVHD.\textsuperscript{127}

**Transfusion-related acute lung injury**

The transfusion of plasma containing blood products can cause severe pulmonary reactions known as transfusion-related acute lung injury (TRALI).\textsuperscript{126} About 1 in 1500 to 1 in 10 000 transfusions cause TRALI, and 5–15% of these reactions are fatal.\textsuperscript{134,135} TRALI is now the leading cause of transfusion related deaths.\textsuperscript{125} The causes of the injury are controversial, but the transfusion of neutrophil-specific antibodies, HLA antibodies, the bioactive lipid lysophosphatidylcholine, and soluble CD40 ligand have been implicated.\textsuperscript{135–137}

The UK is attempting to transfuse only fresh frozen plasma collected from men since plasma from men is much less likely to contain leukocyte antibodies than would plasma from women. Transfusing plasma only from men reduces the proportion of products that contain leukocyte antibodies, and thus reduce the incidence of TRALI.\textsuperscript{136} However, this is not always possible and it is less practical to collect platelets only from men. Platelets stored in additive solutions are less likely to cause transfusion reactions than those stored in plasma;\textsuperscript{136} it is also possible that platelets stored in additive solution are less likely to cause TRALI, but this has not yet been investigated.

<table>
<thead>
<tr>
<th>Issue</th>
<th>Controversy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet product</td>
<td>Are there any clinical differences between buffy-coat, PRP, and apheresis platelets?</td>
</tr>
<tr>
<td>Measurement of platelet quality</td>
<td>What in-vivo or in-vitro indices correlate best with the effectiveness of transfused platelets?</td>
</tr>
<tr>
<td>Leucocyte reduction</td>
<td>Should some or all platelets be leucocyte-reduced?</td>
</tr>
<tr>
<td>Pathogen inactivation</td>
<td>Should all platelets be treated to inactivate viruses and bacteria?</td>
</tr>
<tr>
<td>Transfusion in oncology and haematology patients</td>
<td>Should platelets be transfused prophylactically or therapeutically?</td>
</tr>
<tr>
<td>Dose of platelets transfused</td>
<td>Should the dose be increased, decreased, or left unchanged?</td>
</tr>
<tr>
<td>Transfusing refractory patients</td>
<td>Which method is best, HLA matching or crossmatching? If HLA matching is used, how should compatible platelets be selected?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Issue</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donors</td>
<td>Most, but not all nations forbid the payment of blood donors\textsuperscript{124}</td>
</tr>
<tr>
<td>Blood procurement</td>
<td>Many European countries and Canada have national blood procurement organisations, but in other European countries and in the USA, blood is collected by hospitals or private organisations\textsuperscript{125}</td>
</tr>
<tr>
<td>Type of platelets transfused</td>
<td>The buffy-coat method is used to produce platelets from whole blood in Europe and Canada, but the PRP method is used in the USA\textsuperscript{125}</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Development</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stealth platelets</td>
<td>Removal of HLA antigens for transfusion to alloimmunised patients\textsuperscript{122}</td>
</tr>
<tr>
<td>Extended platelet storage</td>
<td>Extended liquid room temperature storage of platelets found not to be contaminated with bacteria\textsuperscript{126}</td>
</tr>
<tr>
<td>Lyophilised platelets</td>
<td>Freeze-dried platelets for prolonged storage\textsuperscript{126}</td>
</tr>
</tbody>
</table>

Table 5: Controversies in the collection and manufacture of platelet products and transfusion

Table 6: International differences in the collection and manufacture of platelet products and transfusion

Table 7: Latest developments in the collection and manufacture of platelet products and transfusion
Other immune reactions

Transfusions can cause a wide variety of allergic reactions. The most serious are anaphylactic reactions—antibodies to IgA in patients who lack IgA are the most common cause.107 Patients with anti-IgA antibodies should be given washed platelets or platelets collected from IgA-deficient donors.108 Rarely, platelet transfusions can cause mild haemolysis because of the transfusion of anti-A or anti-B109 or hypotensive reactions due to bradykinin when using bedside leucocyte reduction filters.110 (table 4).

Differences in guidelines and practices

In the developing world, platelet transfusions are either available on a limited basis or not at all and, in general, national policies and regulations on platelet collection, processing, and transfusion do not exist. Whereas platelets are routinely transfused in the developed world, several issues related to platelets and their transfusion are still controversial.

The optimal indications for transfusion, platelet transfusion dose, and methods to transfuse refractory patients are still unknown. Moreover, the platelet preparation technologies used to overcome transfusion complications and adverse effects differ between countries because of differences in the availability of resources, the general organisational framework of blood procurement, national policies, and national regulations. A comparison of regulations in 17 European countries identified many basic differences, including the exclusion of remunerated donors and the absence of regulations on the use of blood products.111 We summarise key controversies and international differences in tables 5 and 6. Differences between countries limit progress toward identifying the best transfusion practices and, in some cases, prevent the provision of the optimum platelet product. Platelet production technology continues to evolve (table 7), but it is likely that even though new platelet products might be developed, it will be many years before they are available in all countries. More unified national regulations and policies are needed.

Conclusion

Platelet transfusions are an important therapy, and their use will probably continue to increase. Although transfusion practices are variable and in some cases the best practices are not fully known, greater harmonisation of national policies and regulations might promote the use of optimum platelet products and development of the best transfusion policies.

Conflict of interest statement

DFS has no conflict of interest. PR has been an advisory board member for Cerus Corporation and a consultant for Navigant Biotechnology.

Acknowledgments

This review is dedicated to the memory of Scott Murphy (1936–2006) for his pioneering work and numerous contributions over four decades to platelet preservation and platelet transfusion therapy.

References


Transfusion Medicine 3

Coagulation factor concentrates: past, present, and future

Nigel S Key, Claude Negrier

Clotting factor transfusions are vital for people with diseases such as haemophilia. In the 1970s and 1980s, transfusions with pooled plasma led to a devastatingly high number of recipients becoming infected with blood-borne pathogens such as HIV and hepatitis C. This epidemic triggered the development of virus-free factor concentrates through a combination of improved donor selection and screening, effective virucidal technologies, and recombinant protein expression biotechnology. There is now a wide range of recombinant factor concentrates, and an impressive safety record with respect to pathogen transmission. However, remaining therapeutic challenges include the potential threat of transmission of prions and other pathogens, the formation of inhibitory alloantibodies, and the international disparity that exists in product availability due to differences in licensure status as well as prohibitively high costs. In the future, it is likely that bioengineered recombinant proteins that have been modified to enhance pharmacokinetic properties or reduce immunogenicity, or both, will be used increasingly in clinical practice.

Introduction

Inherited clotting factor deficiencies are rare, with prevalences between 1 in 10 000 to 1 in 10 000 000. Acquired factor deficiency states, however, are common, and are seen in many pathological conditions. Fresh-frozen plasma (FFP) and cryoprecipitate have traditionally been the mainstays of treatment for inherited coagulopathies. Their use is falling because of concerns over blood-borne pathogen transmission, but the products are still useful when no specific fractionated product is available (eg, factor V deficiency), and in complex acquired coagulopathies characterised by deficiencies of multiple clotting factors (eg, in bleeding from disseminated intravascular coagulation [DIC] or liver disease). Cryoprecipitate is enriched in cryoprotein factor VIII (FVIII), Von Willebrand factor (VWF), FXIII, fibronectin, and fibrinogen. Where available, a pathogen-inactivated form of FFP is recommended.1 However, no similarly treated cryoprecipitate products are available.

Plasma that is fractionated to generate clotting factor concentrates falls into two categories: recovered plasma from whole blood donations (generally uncompensated) through licensed blood banks, and source plasma collected by apheresis, generally using paid donors. The range and specifics of viral testing of individual donors varies internationally, especially since many serological tests are gradually being replaced by direct viral genomic detection using nucleic acid testing. Typically, frozen source plasma is first fractionated into cryoprecipitate by slow thawing. The “cryopaste” can then be used to manufacture FVIII concentrates by, for example, precipitation, gel permeation, or ion exchange chromatography, or by affinity chromatography using immobilised monoclonal antibodies. Cryo-poor plasma (plasma from which the cryoprecipitate has been removed can be further processed to prothrombin complex or other single factor concentrates, or both.

During the late 1970s and early 1980s, the pooling of plasma from 2000 or more donors in clotting factor concentrates (with no virucidal steps) led to an international disaster, in which a large number of haemophilic patients became infected by blood-borne viruses, particularly HIV and hepatitis C. An estimated 9300 haemophiliacs in the USA (almost half the total number) were infected by HIV, and the proportion of those infected by hepatitis C was probably closer to 80%. As a result of this, virucidal methods—most commonly a combination of solvent detergent exposure, nanofiltration, or exposure to heat either as a lyophilised product (“dry heat”) or in the aqueous phase (“pasteurisation”)—were introduced to inactivate infectious particles. However, despite the excellent safety record of these techniques in preventing transmission of lipid-enveloped viruses since the mid 1980s, non lipid-enveloped pathogens such as parvovirus B19 could survive the process and be transmissible.14 In addition, concerns remain regarding the possible transmission of prions by clotting factors, although no documented cases have been reported.15

Internationally, there is considerable variation in the availability and licensed indications for many products. Both plasma-derived and recombinant FVIII and FIX have been widely available for several years. Other
Figure: Historical scheme of FVIII and FIX concentrate development

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<tbody>
<tr>
<td>Subfraction I–O</td>
<td>Late</td>
<td>Late</td>
<td>Early</td>
<td>Early</td>
<td>Early</td>
<td>Early</td>
</tr>
<tr>
<td>Cryo-precipitates</td>
<td>Mid</td>
<td>Mid</td>
<td>Mid</td>
<td>Mid</td>
<td>Mid</td>
<td>Mid</td>
</tr>
<tr>
<td>Low-purity pdFVIII</td>
<td>Heat treatment of pdFVIII</td>
<td>Heat-treated concentrates widely available</td>
<td>Immunoadsorption, treating with solvent or detergent, ion exchange</td>
<td>HIV/HCV screening</td>
<td>Qualification of donors, inventory hold, nucleus and testing, nanofiltration</td>
<td></td>
</tr>
<tr>
<td>Intermediate-purity concentrates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-purity concentrates</td>
<td>Heat treatment of pdFVIII</td>
<td>Heat-treated concentrates widely available</td>
<td>Immunoadsorption, treating with solvent or detergent, ion exchange</td>
<td>HIV/HCV screening</td>
<td>Qualification of donors, inventory hold, nucleus and testing, nanofiltration</td>
<td></td>
</tr>
<tr>
<td>rFVIII available</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rFIX available</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

As a general rule, one unit of FVII, FVIII, FXI, FXIII, or VWF per kg body weight will raise the respective factor activity in the recipient’s plasma by 1.5–2.0 IU/dL (1.5–2.0%), whereas the expected recovery for FIX is 0.7–1.4 IU/dL/U/kg infused.

As transmission of blood-borne pathogens has decreased, the development of inhibitory antibodies to the transfused clotting factor has become the most serious treatment complication, with a cumulative incidence up to 30% in previously untreated patients with severe haemophilia A with first-generation12–15 and second-generation rFVIII.8 Although the risk of developing inhibitory antibodies is partly determined by the specific underlying mutation and severity of the deficiency, concerns remain about the relative immunogenicity of various types of concentrate. In Europe, the development of inhibitory antibodies in low risk patients after introduction of modified plasma-derived FVIII (pdFVIII) concentrates have been reported in two well documented case series reports.16,17 A 2006 retrospective (albeit non-randomised) study from France continues to raise the question that pdFVIII might be less likely to lead to inhibitor development than rFVIII.18

**FVIII concentrates**

Satisfactory management of haemophilia only became possible with the development of plasma-derived clotting factors concentrates in the late 1960s.19,20 In the subsequent two decades, FVIII and FIX concentrates were produced exclusively from human plasma. Plasma from multiple donors was pooled, but this practice was a major contributor to the transmission of blood-borne infectious agents such hepatitis B, hepatitis C21–23 and HIV.24–26 The subsequent evolution of coagulation-factor replacement therapy focused on maximising viral safety through the widespread implementation of donor selection and screening tests and of chromatographic purification and viral inactivation steps (figure).

In the early 1980s, the cloning and sequencing of FVIII initiated the development of rFVIII.27–28 Human rFVIII can only be produced using mammalian cell-culture systems (Chinese hamster ovary cells or baby hamster kidney cells) due to the complex glycosylation and other post-translational modifications required for its full cofactor activity. Scale-up of production and purification processes led to the commercial production of the first full-sequence length rFVIII products—a major biotechnological achievement. In addition, culture media, which used to contain human and animal-derived proteins, now contain chemically synthesised or genetically engineered molecules instead. The purification process removes impurities derived from the medium and cultured cells, and concentrates the rFVIII molecule through various chromatographic steps. All currently available rFVIII products are purified using immunoadsorption chromatography using a murine monoclonal antibody directed against human FVIII.
Although viral transmission has never been recorded with any rFVIII product, a theoretical risk of transmitting a human-derived infectious agent still remains in the first-generation products, in which human and animal proteins were not completely eliminated from the production process. In addition, emerging non-viral pathogens such as the prion responsible for variant Creutzfeldt-Jakob disease (vCJD) must be considered, and reducing the risks of pathogen transmission continues to be a high priority for the haemophilia community.

Recombinant FVIII products have excellent haemostatic efficacy in both previously untreated and treated haemophilia A patients. Since the manufacture of rFVIII is not limited by plasma availability, the improved supply of FVIII in developed countries has contributed to increased application of prophylactic treatment regimens and subsequent improvement of functional outcomes.

**FIX concentrates and prothrombin complex concentrates**

FFP or plasma derivatives (prothrombin complex concentrates [PCCs]; otherwise known as intermediate purity FIX concentrates) were used as the source of FIX in haemophilia B. Prepared either by Cohn fractionation or calcium adsorption of plasma, PCCs were first introduced in the early 1970s (figure). These agents are enriched in prothrombin and factors VII, IX, and X, and also contain trace amounts of factors VIII, VIIa and IXa. However, the specific content of each clotting factor, particularly VII, varies by concentrate. The anticoagulant vitamin K-dependent factors protein C and protein S are also present at variable concentrations.

Thrombotic events, including venous thromboembolism and DIC, as well as microvascular thrombosis and myocardial infarction have been reported with the use of PCCs. These complications seem to occur especially, but not exclusively, with the use of frequent or high dose (>200 U/kg/day) administration. Particular concern for a raised risk of thrombotic complications and DIC has been expressed with regard to patients with severe liver disease, possibly because of their failure to adequately clear activated clotting factors from the circulation. Consequently, measures to reduce the thrombogenicity of these concentrates were taken by the manufacturers that included the addition of heparin, and antithrombin or protein C, or both.

About 15 PCCs are marketed worldwide. Vial potency labeling and dosing recommendations for PCCs are based on IU's of FIX. One IU of FIX corresponds to the activity of FIX in 1 ml of fresh normal human plasma.

The use of PCCs in haemophilia B fell after the introduction of high purity pdFIX (and subsequently rFIX) products in the 1990s. By contrast with PCCs, infusion of these high-purity FIX products did not lead to any significant activation of the coagulation system, confirming that a component other than FIX is responsible for the thrombogenicity of PCCs in haemophilia B. Evidence suggests that it could be excess prothrombin, rather than the content of activated factors VII, IX, or X in these concentrates that is primarily responsible for thromboembolic complications.

PCCs remain a useful treatment for other inherited and acquired coagulation factor deficiency states, for example, in the prevention or treatment of bleeding in inherited factor X or II (prothrombin) deficiency. The use of PCCs as an alternative to FFP has also been reported in some complex acquired bleeding disorders, including dilutional coagulopathy from massive transfusion, bleeding after cardio-pulmonary bypass surgery, and the coagulopathy of acute fulminant and chronic liver failure. However, there are few reports of all these situations, and neither the risk-benefit profiles nor the optimal dosing regimens have been established.

The human FIX gene was cloned in the early 1980s, which led to the expression of human rFIX in CHO cells. Recombinant FIX (Nonacog alfa, Wyeth, PA, USA) is structurally and functionally similar to pdFIX, although minor differences in the post-translational sulfation and phosphorylation of rFIX have been associated with about 30% lower in vivo recovery, especially in children ≤15 years of age. International clinical trials have demonstrated the efficacy and safety of rFIX for the treatment of haemorrhages as well as in prophylactic and surgical settings in previously treated patients (PTPs) and in previously untreated patients (PUPs) with haemophilia B.

### The bypassing agents: FEIBA and recombinant factor VIIa (rFVIIa)

The need for therapies to control bleeding in haemophilia patients affected by high titre inhibitors to FVIII or FIX—that is, to “bypass” the FVIII/IX complex in coagulation—led to a number of early clinical trials exploring the efficacy and safety of PCCs (table 1). In the 1970s, the first activated PCCs were developed. These

<table>
<thead>
<tr>
<th>Study groups</th>
<th>Doses (n)</th>
<th>Total patients (n)</th>
<th>Response rate* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980</td>
<td>Konyne</td>
<td>1</td>
<td>157</td>
</tr>
<tr>
<td></td>
<td>Proplex</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1981</td>
<td>FEIBA</td>
<td>1 or 2</td>
<td>150</td>
</tr>
<tr>
<td></td>
<td>Prothromblex</td>
<td>1 or 2</td>
<td></td>
</tr>
<tr>
<td>1983</td>
<td>Autoplex</td>
<td>1</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>Proplex</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>FEIBA-VH</td>
<td>1</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>rFVIIa</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

*Generally assessed by subjective judgment at 6 h post-infusion. †P<0.05.

Table 1: Randomised clinical trials of bypassing agents (prothrombin complex concentrates (PCC), activated PCCs, and rFVIIa) in the treatment of mild to moderate bleeds in haemophilia complicated by an inhibitor.
products were manipulated ex vivo to increase the content of activated clotting factors, especially FVIIa. At present, only one product, FEIBA (an acronym for Factor Eight Inhibitor Bypassing Activity) VH anti-inhibitor coagulant complex (Baxter Bioscience, Vienna, Austria) is available for this indication.

The vial potency labelling is in arbitrary units of FVIII inhibitor bypassing units, where one unit of FEIBA-VH shortens the activated partial thromboplastin time (aPTT) of high-titre FVIII reference plasma to 50% of the blank value. The drug’s mechanism of action is now believed to be dependent on its content of prothrombin and FXa. Empirically, FEIBA is administered at doses of 50–75 units/kg every 8–12 h, with a recommended maximum daily dose of 200 units/kg. Three early-1980s prospective randomised clinical trials on the early treatment of acute haemarthrosis established the efficacy and safety of PCCs and factor VIII inhibitor bypassing fraction.

Notably however, the response rate, judged subjectively by joint pain resolution, was only 50–60% at 6 h after the first infusion (with significantly higher rates of response for the drug compared with a non-activated PCC), compared to a placebo response rate of 25% (see table 1). These response rates at 6 h are significantly lower than would be expected when using FVIII to treat acute haemarthrosis in haemophilia A uncomplicated by an inhibitor. With repeated dosing over longer periods however, the efficacy rate for FEIBA in the management of acute bleeding events is substantially higher, generally more than 85%.

While partial correction of the prolonged aPTT is typical in haemophilia patients treated with FEIBA, this parameter does not represent a clinically useful laboratory monitoring strategy. Two studies in the past few years have assessed alternatives, including thromboelastography and thrombin generation profiles (“endogenous thrombin potential”) in whole blood and plasma, respectively.

Recombinant factor VIIa (rFVIIa; Eptacog alfa [activated], Novo Nordisk, Bagsvaerd, Denmark) is almost structurally identical to native FVIIa. This agent is widely licensed for the management of bleeding in haemophilia A or B complicated by inhibitory antibodies (at doses of 90–120 µg/kg) and for inherited FVII deficiency (at a dose of 15–30 µg/kg), and in Europe for bleeding in Glanzmann’s thrombasthenia with refractoriness to platelet transfusions due to antibodies to GP Ib/IIa or HLA. In the haemophiliacs, high dose rFVIIa is believed to act by producing a “thrombin burst” on the surface of activated platelets by proteolytic activation of factors IX and X (and ultimately prothrombin) in the absence of tissue factor.

Although some data have suggested increased efficacy with even higher doses of rFVIIa (usually 270 µg/kg) in haemophilia-related bleeding, supportive data from prospective randomised clinical trials have thus far only shown equivalence. Like FEIBA, the haemostatic efficacy rates for rFVIIa vary depending when after administration it is judged; indeed, a recent multi-national randomised cross-over clinical trial (FENOC54) demonstrated equivalence of a 85 U/kg dose of factor VIII inhibitor bypassing fraction and two 105 µg/kg doses of rFVIIa. Response to both was judged to be “effective” in about 80% of cases at 6 h (table 1). Regardless of the indication, administration of rFVIIa invariably results in shortening of the prothrombin time, although this does not correlate with haemostatic efficacy. As with factor VIII inhibitor bypassing fraction, a validated method for monitoring rFVIIa is an area of active investigation. The precise indications for the use of bypassing agents in haemophilia, as well as their relative merits and drawbacks have been reviewed elsewhere.

**Von Willebrand factor concentrates**

Until 2001, cryoprecipitate was the therapeutic mainstay for bleeding in VWD. In 2001, because of concerns for the potential transmission of blood-borne pathogens, the use of pdFVIII products enriched in VWF was recommended for the treatment of bleeding or prophylaxis before surgery in certain sub-types of VWD. Factor concentrates are generally recommended for most patients with type 2 variants (qualitative defects) of VWD, and both severe type 1 and type 3 variants (partial quantitative and severe quantitative deficiencies of VWF, respectively). Most remaining patients with milder variants of type 1 VWD respond well to intravenous, subcutaneous, or intranasal desmopressin (1-deamino-8-D-arginine vasopressin; DDAVP). Although FVIII synthesis is not defective in VWD, its half-life is severely reduced when VWF, its natural carrier and stabiliser to which it is non-covalently bound in plasma, is deficient. Satisfactory haemostasis in VWD is dependent on achieving adequate plasma levels of both VWF (mediating primary haemostasis) and FVIII (responsible for fibrin formation in secondary haemostasis). As a rule, haemostasis is satisfactory when the ristocetin cofactor activity (VWF:RCo)—a measure of VWF activity—is more than 0.6 IU/ml (60% of normal). In the absence of an rVWF concentrate, most products are intermediate purity pdFVIII concentrates that also contain VWF, and thus may be used in the treatment of either haemophilia A or VWD. The only exception is Wilfactin (LFB, Lille, France), a plasma-derived product that is considered to be a highly purified VWF-containing concentrate, although it is only available in a few European markets. Although administration of this product to a patient with severe type 1 or type 3 VWD quickly corrects the plasma deficiency of VWF, there is a delay of 6–12 h before endogenous FVIII activity is restored to haemostatic levels. Thus, protocols in which highly purified VWF is used to control active bleeding generally recommend a single supplemental dose of high purity FVIII concentrate at the onset of therapy.
Table 2 shows that the ratio of VWF:RCo to FVIII activity (FVIII:c) is extremely variable among the available products. Qualitatively, there is also significant variation in the degree of preservation of the larger VWF multimers required for platelet adhesion to sub-endothelial collagen, although the clinical relevance of this finding is unknown.74

Fibrinogen concentrates

A fibrinogenemic patients can develop life-threatening bleeding symptoms that can usually be controlled by fibrinogen replacement or cryoprecipitate substitution therapy.75 A few virally inactivated plasma-derived concentrates are available in some countries for the treatment of inherited fibrinogenemia and hypofibrinogenemia such as Clottagen (LFB, France) and Haemocomplettan P (ZLB Behring, Germany). Effective long-term secondary prophylaxis with administration of fibrinogen concentrates every 7–14 days, particularly after CNS bleeds, has been described,76,77 although the minimal protective level is not well defined. Fibrinogen concentrates have also been used with some success in acquired disorders including haemodilution from massive post-partum bleeding,78 although no firm evidence regarding efficacy and safety, is available.

Factor VII concentrates

There is a poor correlation between FVII levels and the risk of bleeding in FVII-deficient patients.79 Replacement therapy has traditionally been achieved using FFP, “four factor” (FVII-enriched) PCCs, or virally inactivated pDFVII concentrates. In the latter category, three such products are available, although none are marketed in the USA. Well-designed clinical studies documenting haemostatic levels of FVII activity in all situations are lacking, although empirically, a target trough activity of at least 10–15 IU/dL (10–15%) is usually recommended.80 Recombinant FVIIa is now widely used in these patients.81 Development of alloantibodies against exogenous FVII is a rare complication.82

Factor XI concentrates

FXI deficiency has a variable clinical phenotype with a lack of a clear association between bleeding and FXI coagulant activity.85 Bleeding can be excessive after surgery or trauma. While FFP is the only available therapy in the USA, two others, FXI concentrate (Bioproducts Laboratory, Elstree, UK) and Hemoleven (LFB, France), which undergo two viral inactivation steps, are available elsewhere. Retrospective analyses of their use in Europe and Canada have shown them to be safe and effective, although there is a potential for thrombotic complications.86,87 In both products, heparin and antithrombin are added in an attempt to minimise this risk.

Factor XIII concentrates

FXIII circulates as a tetrameric protein consisting of two A and two B subunits. FXIII concentrates have been produced from both human plasma and placenta. However, placental FXIII concentrates are no longer available, and the FXIII-A2B2 heterotetramer (Fibrogammin P, ZLB Behring, Germany) is the only plasma-derived concentrate on the market. It has been administered for treatment and prophylaxis of patients with FXIII deficiency.88 This concentrate is approved in several markets including Japan and a number of EU countries, but in the USA, only FFP and cryoprecipitate are available for use in FXIII deficiency. The recommended prophylactic doses of 10–35 IU/kg can be administered every 4–6 weeks because of its half-life of 5–11 days. Development of alloantibodies against exogenous FXIII is extremely rare, although very problematic when it does happen.89

A new recombinant FXIII-A2 (rFXIII-A2) homodimer containing no human or mammalian products in the culture medium has been manufactured in Saccharomyces cerevisiae. The rFXIII-A2 homodimers are able to associate in plasma with endogenous FXIII-B

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Approximate VWF:RCo/FVIII:c ratio</th>
<th>Half life of VWF:RCo</th>
<th>VWF:RCo recovery (IU/dL/4IU/kg injected)</th>
<th>Viral inactivation method</th>
<th>Licence status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alphanate71</td>
<td>0·6:1</td>
<td>7·1 h</td>
<td>2·5</td>
<td>SD, then dry heat at 80°C for 72 h</td>
<td>Licensed in Italy, the UK, and the USA</td>
</tr>
<tr>
<td>Wilate72</td>
<td>1·0:1</td>
<td>17·1 h</td>
<td>1·5</td>
<td>SD, then dry heat at 100°C for 72 h</td>
<td>Limited European licensure</td>
</tr>
<tr>
<td>Humate-P/Haemate-P72</td>
<td>2·4:1</td>
<td>10·3 h</td>
<td>1·9</td>
<td>Pasteurisation at 60°C for 10 h</td>
<td>Licensed in North America and Europe</td>
</tr>
<tr>
<td>Wilfactin (formerly Facteur Willebrand-LFB)73</td>
<td>&gt;10:1</td>
<td>12 h</td>
<td>2·1</td>
<td>SD, then 35 nm nanofiltration, followed by dry heat at 80°C for 72 h</td>
<td>Limited European licensure</td>
</tr>
</tbody>
</table>

SD=treated with solvent detergent.

Table 2: Some concentrates for the treatment of Von Willebrand disease
subunits to form the stable heterotetramer FXIII-A2B2. The safety, pharmacokinetics, and immunogenicity of rFXIII-A2 have been studied in healthy volunteers in a phase 1 clinical trial. This study shows that rFXIII-A2, when combined with endogenous FXIII-B subunits, has a half-life similar to that of native FXIII. No serious adverse events or evidence of antibody formation to yeast or rFXIII have been detected, suggesting that rFXIII represents a safe and effective alternative to pdFXIII in patients with FXIII-A2 deficiency.

FXIII concentrate could also be useful in patients with acquired FXIII deficiency, including after cardiac bypass surgery, stem-cell transplantation and graft-versus-host disease, and inflammatory bowel disease, though the precise benefit of treatment requires further investigation.

**Off-label use of rFVIIa**

During the past decade, there has been considerable interest in the off-label use of rFVIIa in a variety of acquired medical and surgical haemorrhagic disorders in patients without inherited coagulopathies. The benefit of rFVIIa compared with placebo was shown in retropubic prostatectomy, in which it reduced blood loss and red cell transfusion requirements, and in spontaneous (non-warfarin-related) intracerebral haemorrhage in which it reduced haematoma size and neurological disability. However, prospective RCTs in trauma, orthotopic liver transplantation, partial hepatectomy, and major pelvic surgery all failed to show efficacy. A summary of adverse events reported to the US Food and Drug Administration included 185 thromboembolic arterial and venous events, most of which occurred after the off-label use of rFVIIa. This report highlights the need to assess safety as well as efficacy in prospective RCTs of rFVIIa, and to assess the risk-benefit when using rFVIIa for off-label indications.

**Clotting factor concentrates in reversing therapeutic anticoagulation**

Bleeding from warfarin sodium (4-hydroxycoumarin)-induced over-anticoagulation is a common cause of morbidity and mortality. The most severe bleeding complication is intracerebral haemorrhage, which has a mortality of at least 50% when urgent reversal of excessive anticoagulation is needed in a patient who is actively bleeding, the standard of care in many countries continues to be the administration of FFP and vitamin K. This approach is limited by the time delay involved in thawing plasma, the risks (albeit low) for viral transmission and transfusion-associated lung injury (TRALI), and the potential for fluid overload from the large volume of plasma required. These concerns have prompted an examination of the role of PCCs and rFVIIa as alternative approaches to urgent warfarin reversal.

On the basis of studies showing that PCCs reverse warfarin coagulopathy more rapidly and completely than the standard dose of FFP (10–15 mL/kg), several expert consensus panels have recommended the use of PCCs. A single dose of 30 U/kg or lower seems to be enough to reverse even the most over-anticoagulated patients, with a very low thrombotic risk.

These recommendations have not been widely adopted, especially in North America, possibly because of limited licensing for this indication (only for a few products, and only in Europe), or because of lingering perceptions regarding the thrombotic risk associated with these products in haemophilia; however, this is a very different situation with respect to dosing levels and frequency. There is an urgent need for randomised clinical trials correlating clinical outcomes of PCC or rFVIIa vs FFP with correction of INR values in patients with warfarin-induced haemorrhage.

The development of alternative anticoagulants to standard unfractionated heparin and warfarin continues to be an active area of pre-clinical and clinical development. These agents are generally targeted inhibitors of specific procoagulants, most commonly factor Xa and/or thrombin. While many of these agents possess desirable pharmacological properties such as a more predictable dose-response relationship and greater convenience, they are universally lacking in a specific antidote for reversal in the event of bleeding. Some evidence exists that rFVIIa is capable of partially restoring intravascular thrombin generation in healthy volunteers treated with the pentasaccharide inhibitors of factor Xa. However, clinical evidence for its efficacy is so far limited to case reports.

**Clotting factor concentrates in inherited and acquired thrombotic disorders**

**Antithrombin concentrates**

Hereditary antithrombin deficiency is associated with a significant risk of venous thromboembolism, and patients with this disorder frequently require long-term anticoagulation. Discontinuation of anticoagulation for childbirth or surgery can carry a substantial thrombotic risk, and replacement with antithrombin concentrate has been proposed in these situations.

Plasma-derived antithrombin is marketed in many countries, and the various production processes contain at least one viral inactivation step. A new recombinant human antithrombin concentrate (Atryn, GTC Biotherapeutics, Framingham, MA, USA) produced in the milk of transgenic goats was investigated in a pilot study in which five patients with hereditary antithrombin deficiency underwent six surgical procedures. No thrombotic or bleeding complications occurred. Despite differences in glycosylation (eg, oligomannose structures) with recombinant human antithrombin that probably account for its altered pharmacokinetics, this product was recently approved in the EU for the prophylaxis of venous thromboembolism in surgery in patients with congenital AT deficiency.
The use of antithrombin concentrates in acquired deficiency states is disputed. Despite preliminary encouraging results, a pivotal phase III randomised controlled clinical trial of antithrombin concentrate failed to show a beneficial effect on 28-day mortality in adults with severe sepsis. However, a recent post-hoc analysis of this trial showed a significant reduction in mortality in septic patients with overt DIC treated with high-dose antithrombin concentrate in the absence of heparin. In neonatal respiratory distress syndrome, intracranial haemorrhage, or sepsis, treatment of acquired AT deficiency could improve outcomes, but definitive evidence is lacking. In children with acute lymphoblastic leukaemia and acquired antithrombin deficiency associated with the use of L-asparaginase, the group treated with antithrombin concentrate showed a trend to efficacy and safety (incidence of thrombosis 28% [95% CI 10–46%], compared to 37% [95% CI 24–49%] in the non treated arm).

**Protein C and activated protein C concentrates**

In patients with severe (homozygous) inherited protein C deficiency, including neonates, replacement therapy with human plasma-derived protein C is effective, especially for treating cutaneous thrombosis (purpura fulminans) and preventing thrombosis in high-risk situations. In patients with moderate (heterozygous) deficiency, a short-course of human protein C prophylaxis may reduce the frequency of thrombosis in high-risk situations. This drug has also been used for long-term prophylaxis, in inherited homozygous protein C deficiency. Severe sepsis is associated with rapid depletion of protein C and blunted endogenous protein C activation. Protein C concentrates have been reported to improve outcomes in meningococcal sepsis. The activated form of human protein C (hAPC) possesses anticoagulant, profibrinolytic, and anti-inflammatory properties. A landmark phase III study in adults with severe sepsis showed that treatment with recombinant hAPC (rhAPC; drotrecogin alfa [activated]) was associated with a 6–1% absolute reduction in 28-day mortality compared with placebo.

However, in a second randomised clinical trial, no efficacy of rhAPC was seen in patients with severe sepsis at a lower risk of death. An increased incidence of serious bleeding complications was seen in rhAPC-treated patients. Furthermore, a large randomised, placebo-controlled trial with rhAPC in paediatric sepsis was stopped early because of lack of efficacy. Further clinical trials are needed to establish efficacy of rhAPC in the treatment of patients with severe sepsis.

**The future**

The routine production of coagulation factors by recombinant technology, and the disappointingly slow progress of gene replacement therapy for single gene disorders such as haemophilia, has prompted the development of bioengineered products that have been mutated to overcome their therapeutic limitations. The proteins of interest are usually modified to enhance their pharmacokinetic properties or reduce immunogenicity. Already, mutant forms of rFVIIAs with enhanced activity are under pre-clinical development, and encouraging phase I/II studies confirming the extended protection from bleeding afforded by the weekly infusion of FVIII bound to synthetic polyethylene glycol (PEG)-coated liposomes have been reported. Various pre-clinical approaches have supported the potential therapeutic value of FVIII modified to enhance its circulating half-life by other means (such as polysialylation), or mutated to enhance its resistance to degradation or clearance. B-domain deleted recombinant porcine FVIII molecule is undergoing clinical trials for the treatment of patients with congenital or acquired haemophilia whose inhibitors are only partially cross-reactive to porcine FVIII.

Another unique approach under development for haemophilia B is a synthetic protein comprising FIX fused with the Fc region of IgG to extend the half-life of FIX. A growing trend that is also likely to follow the development of new recombinant clotting factors is their experimental use in acquired deficiency states. However, cost remains a significant limitation of all these technologies. The disparity in the availability of coagulation factor concentrates worldwide is illustrated by the case of haemophilia, where it is estimated that more than 75% of the world’s patients with haemophilia receive either inadequate or no treatment whatsoever. It can only be hoped that the development of transgenic technologies increases the availability and markedly reduces the cost of factor concentrates in the future.

**References**


Casper K, Kipnis SA. Hepatitis and clotting-factor concentrates. JAMA 1972a; 221: 510.


Health and Human Rights 1

History, principles, and practice of health and human rights

Sofia Gruskin, Edward J Mills, Daniel Tarantola

Individuals and populations suffer violations of their rights that affect health and wellbeing. Health professionals have a part to play in reduction and prevention of these violations and ensuring that health-related policies and practices promote rights. This needs efforts in terms of advocacy, application of legal standards, and public-health programming. We discuss the changing views of human rights in the context of the HIV/AIDS epidemic and propose further development of the right to health by increased practice, evidence, and action.

Introduction

Blatant violation of human rights affecting the health of both individuals and populations continues. Examples include the torture of detainees in Abu-Ghraib prison in Iraq;7 systematic rapes and murders in the Balkans,8 Chechnya,9 and Darfur;10 physician involvement in torture,4 botched executions;7 inhumane experimentation;3 and questionable interrogation techniques in the so-called war on terror.11,12 Such violations of human rights can be engineered by or endorsed by governments, institutions of power, and individuals. These deplorable violations exist alongside more subtle activities that also have severe and longlasting effects on health and human rights such as absence of basic health-care systems;11 policies keeping medicines unaffordable;12 and tolerance of discrimination against groups such as injecting drug users,13 people with mental-health disorders,14–16 illegal immigrants,8 or homeless people.7 The continuing and foreseeable absence of access to effective care for most people living with most diseases in poor countries can also be viewed as a violation of human rights.17 Therefore human rights should be imperative in delivery of care and implementation of public-health programmes.

Three main relations between health and human rights exist: the positive and negative effects on health of promotion, neglect, or violation of human rights; the effect of health on the delivery of human rights; and the effects of public-health policies and programmes on human rights.18 Despite the advances in the study and advocacy of health and human rights we still do not fully understand the nature of these relationships, how they interact, or their value to medicine and public-health practice. In this article we address the public health aspects of these relations, and highlight where further research and action are needed.

A brief history of health and human rights

Since the Nuremberg trials and the creation of the UN more than 50 years ago, interest in the association between health and human rights has grown. Until the beginning of the AIDS epidemic in the 1980s and the end of the Cold War, these two issues evolved along parallel but distinctly separate tracks,20 perhaps as a consequence of the state-centric (ie, greater political concern for general state and public interests than for specific individuals or communities) view of the world that prevailed in the second half of the 20th century. However, governments have a responsibility both to deliver essential health and social services, and to enable people and their families to achieve better health by respecting human rights.

In the past 20 years, the HIV/AIDS pandemic and reproductive and sexual health concerns have been instrumental in clarifying the ways that health and rights connect. These issues encompass law and policymaking, and have established the roles and boundaries of responsibility held by state and non-state stakeholders for the conditions that constrain or enable health and for delivery of health and related services.21 The first worldwide public-health strategy to explicitly engage with human rights concerns took place in the late 1980s, when Jonathan Mann directed the Global Program on AIDS at WHO.22 Although this strategy was partly motivated by moral outrage at abuses suffered by people living with HIV, the inclusion of human rights was primarily because evidence was emerging that showed that discrimination was driving people away from prevention and care programmes.23
Panel: The right to health in international law

The right to the highest attainable standard of health—often referred to as the right to health—is most prominently connected to the ICESCR.43 It stipulates that:

The states parties to the present covenant recognise the right of everyone to the enjoyment of the highest attainable standard of physical and mental health. The steps to be taken by the states parties to the present covenant to achieve the full realisation of this right shall include those necessary for:

(a) the provision for the reduction of the stillbirth rate and of infant mortality and for the healthy development of the child;
(b) the improvement of all aspects of environmental and industrial hygiene;
(c) the prevention, treatment, and control of epidemic, endemic, occupational, and other diseases;
(d) the creation of conditions which would assure to all medical service and medical attention in the event of sickness.

Elimination of such discrimination was expected to encourage people not only to fully exert their rights, but also to come forward for voluntary counselling, testing, and treatment of opportunistic infections. Uptake of these services would in turn help them safeguard their dignity, improve their health and wellbeing, and motivate them to adopt behaviours that would restrict further spread of infection. That this strategy—upholding human-rights principles—was set forth by WHO, an inter-governmental organisation with responsibilities for promotion of rights conferred by the UN Charter, placed it in the realm of international law.24 As a result, governments and intergovernmental organisations were made publicly accountable for their public-health and human-rights actions (or inactions). Since the 1980s, responses to the HIV pandemic have drawn attention to the rights of the most vulnerable people and societies, and the need to prevent discrimination in both law and practice.25

A series of international conferences held by the UN, beginning in the early 1990s, further solidified the dual obligations of governments to the health and human rights of their people.21 These conferences brought together emotions and values, but also the experiences of local, national, and international practitioners (physicians, nurses, and other health workers), advocates, and policymakers. The 1997 Program for Reform, designed by Kofi Annan, then UN Secretary-General, highlighted the promotion of human rights as a core activity of the UN, which was another important step in moving issues of health and human rights from rhetoric to implementation, action, and accountability.21

Almost all development agencies, organisations and UN programmes,27 albeit to varying degrees of success, now pay attention to human rights in their work in health. Additionally, many governments are beginning to integrate their human rights obligations into their health-related activities, both in high-income and low-income countries.29 In addition to members of affected populations, medical practitioners have also contributed to bringing human rights into health through their advocacy and practice.20 Nonetheless, integration of human rights in health efforts clearly still has a long way to go.

Human rights and health policy

The links between human rights and health are best understood by referring to the preface to the WHO constitution, which states that health is the “state of complete physical, mental, and social wellbeing and not merely the absence of disease or infirmity” and “the highest attainable level of health is the fundamental right of every human being.”31 Governments are therefore responsible for enabling their populations to achieve better health through respecting, protecting, and fulfilling rights (ie, not violating rights, preventing rights violations, and creating policies, structures, and resources that promote and enforce rights).32 This responsibility extends beyond the provision of essential health services to tackling the determinants of health such as, provision of adequate education, housing, food, and favourable working conditions. These items are both human rights themselves and are necessary for health.33–35 The relation of people with their environment is complex and the fulfilment—or absence—of human rights and their effects on the main determinants of health needs much investigation.

Human rights encompass civil, political, economic, social, and cultural rights. These rights are cast in international law, through many treaties and declarations, beginning with the UN Universal Declaration of Human Rights in 1948.35–41 These documents highlight the importance of promotion and protection of human rights as a prerequisite to health and wellbeing. Although one can devote attention and resources to one specific right, or to a category of closely connected rights, all rights are interdependent and interrelated.42 and as a result individuals rarely suffer neglect or violation of one right in isolation.

Economic, social, and cultural rights, such as education and food, are relevant to health, as are such civil and political rights as those relating to life, autonomy, information, free movement, association, equality, and participation. Recognition of the legal and political obligations that connect economic, social, and cultural rights, as well as civil and political rights, continues to grow. The right to the highest attainable standard of health therefore builds on, but is by no means limited to, Article 12 of the UN International Covenant on Economic, Social, and Cultural Rights43 (ICESCR; panel). It transcends almost every other right.
Although the right to health forms the legal basis for much of the present work in health and human rights, if written today it would probably place greater emphasis on health rather than sickness and on health systems rather than provision of medical care. Addressing the effects of discrimination, gender-related or otherwise, on health and delivery of services is well covered by other rights, again showing how human rights are intertwined.

The legal obligation of states to respect health-related rights is only one part of the picture, because rights are also used to guide policies and programmes for health and wellbeing. They enable a broad response to health and development by national and international stakeholders with responsibilities that reach beyond the health sector. Thus, although international treaties, enriched by declarations and related documents, have legal implications, they importantly can also inform the development of policies and programmes in all states, whether or not a state has signed to be legally bound by the relevant treaty.

Applying human rights to health

The idea of health and human rights as a subject of study is fairly new, and we need to recognise the different ways in which advances in health and human rights can be achieved. Human rights feature in many different ways in the health work of international non-governmental organisations, governments, civil society groups, and individuals. These ways can be broadly categorised as advocacy, application of legal standards, and programming (including service delivery). Some stakeholders use one approach; others use a combination in their work. We use HIV/AIDS as the main example to show the effectiveness of these approaches, although examples in reproductive health, mental health, disability, neglected diseases, or other serious health issues could effectively serve as illustrations.

Development of new treatments and the investment of substantial and increasing resources to offer these treatments to people living with HIV have resulted in access to treatment and care for some people. These people gain substantial duration and quality of life, allowing them to participate actively in political, civil, economic, social, and cultural activities. By contrast, despite global initiatives to increase access in resource-poor places, progress has been slow and remains below expectations.

Advocacy and bearing witness

The model of health and human rights is often used in campaigns for changes in health-related policy and practice. Early campaigns as a response to some governments’ complacency in dealing with AIDS illustrated the success of this approach and set a precedent for health campaigns around the world. The focus of activism is often on recognition and exposure of governmental obligations, establishing the amount of government action or inaction that contributes to existing violations, looking at how a government deals or does not deal with identified problems, and recommending solutions.

Since the turn of the century, the pharmaceutical industry has lowered the price of antiretroviral drugs in low-income countries to less than ten percent of their cost in 2000, mainly because of pressure framed around the right to access treatment, exercised on them by non-governmental organisations, the mass media among others. Although this development brought opportunities for greater access to antiretroviral drugs, national and international work is still needed for these drugs to reach the people who need them, especially those living in low-income and middle-income countries. The most recent international agreements to provide universal access, the human rights obligations of states to make such services available, and the obligations of wealthy countries to engage in international assistance and cooperation puts additional obligations on wealthy countries to help poor ones to achieve these goals. These obligations can be used as an effective advocacy strategy.

Médecins Sans Frontières and Médecins Du Monde have both shown the important parts that individual health practitioners can play in international crises. These groups were founded on the premise that health practitioners and the communities sponsoring them have an international duty to maintain health, especially that of disadvantaged people living in regions affected by warfare or natural disasters. Such principles have grown to include the response to HIV/AIDS and situations of chronic extreme poverty. These organisations were born of civil society in the late 1960s, inspired by the belief that clinicians, other health professionals, and volunteers could improve the health of poor and vulnerable people whose governments were failing to do so, either by design or incapacity.

Although not initially intended as the launch of a health and human rights movement, the emergence and growing influence of these groups and those that have followed, has drawn attention to the universal value of health and the duty of care providers, other humanitarian workers, and the international community to intervene when human rights are ignored. A recurring dilemma confronting these organisations is whether sustainable health action should be associated with documentation and denouncements of witnessed human rights violations, as these activities could both limit their ability to provide health services to the populations they serve, and jeopardise the safety of their workers. Of note, the international appeals from non-governmental organisations and some relief agencies, in such situations as that of the Great Lakes area in Africa in the 1990s, in which a late and weak international response resulted in greater chaos and many casualties that could have been prevented.
The printed journal includes an image merely for illustration.

Doctor from Médecins Sans Frontières examining a child in Darfur—aid agencies such as Médecins Sans Frontières have an important role where human rights violations take place.

Application of legal standards
In a strictly legal sense, applying human rights to health means using internationally accepted and nationally agreed upon norms, standards, and accountability mechanisms within health-care systems and in the work of national and international health, economic, and developmental policymakers. Legal mechanisms can sometimes also provide channels of redress for individuals whose rights have been violated in the context of public-health interventions. In South Africa and several Latin American countries, the human rights provisions of national constitutions (eg, the rights to life, to health, and to benefit from scientific progress) have been interpreted to enable claims for access to antiretroviral medicines. In Latin America, individuals supported by non-governmental organisations, have undertaken 13 successful lawsuits to date against their governments for access to antiretroviral drugs. In fact, in Argentina, one such success resulted in assurances of provision of care for 15000 people. Treatment Action Campaign in South Africa used the courts to ensure that the government was ordered to provide programmes in public clinics for reduction of mother-to-child transmission of HIV. Although these efforts have resulted in positive changes in the law, advocacy is still needed to move these obligations into practice; thus emphasising how advocacy, and application of the law are interrelated.

Rights in delivery of care and programming
Even though many organisations describe their approach to health as rights-based, we have no one definition of what this entails. All such organisations seem generally concerned with ensuring that vulnerable populations are provided with the services that they need, but in practice these organisations have used different approaches to the incorporation of rights into different stages of the programming cycle; from situation analysis, to planning, implementation, monitoring, and assessment. The core components of rights-based approaches include: examining the laws and policies under which programmes take place; systematically integrating core human rights principles such as participation, non-discrimination, transparency, and accountability into policy and programme responses; and focusing on key elements of the right to health—availability, accessibility, acceptability, and quality when defining standards for provision of services.

HIV testing serves as a useful example to illustrate the link between health and rights in programming. Although voluntary HIV testing has been advocated by international agencies since the start of the pandemic and is seen in many national laws and policies, the requirement for testing to be voluntary has recently been debated. The present argument is that people knowing their HIV status is more important than whether they voluntarily seek testing, because they will be able to accurately inform their partners of their HIV status, modify their behaviours, and seek treatment if available. Consequently, an approach known as routine provider-initiated HIV testing is becoming increasingly common in health-care settings—an approach that, without careful guidance, can consist largely of assuming that patients agree to be tested unless they express objection and opt out of taking the test. UNAIDS and WHO have released guidance to support the adaption of national policies to account for this new trend.

This seemingly well-intended approach will need careful monitoring and assessment to ascertain whether HIV tests are being routinely offered or routinely imposed, and whether in either case, the individual has informed choice and power to opt in or opt out of being tested. Future work in this areas needs evidence, rather than ideology, to establish whether these conditions help people access HIV care services, and maintain contact with such services. Attention to principles of rights such as non-discrimination, participation of affected communities, and accountability for potential positive and negative effects of adopting routine HIV testing could help to measure its effectiveness in terms of both rights and health. When a government (most recently China and Lesotho—and both with the support of WHO) decides to screen an entire section of the population for HIV with disregard for domestic law, human rights principles, and international norms while providing little access to care for those testing positive, we face a complex challenge. How regard for human rights translates into policy formulation, programming, and service delivery continues to be debated.

A rights-based approach to programming needs interventions to be implemented in ways that improve health, and that efforts to reach national and international targets, for example, in relation to the numbers of people...
on treatment, do not result in the neglect or violation of human rights. Although application of human rights will not establish if priority should be given to prevention or treatment, consideration of human rights will ensure that attention is given not only to the outcomes of health interventions, but also to the ways they are implemented. For example, an increase in uptake of HIV-testing services could be due to an increase in the availability of high-quality voluntary counselling and testing services, but on the other hand it could also be due to the introduction of mandatory testing for certain population groups. Although both interventions would seem to lead to the same short-term outcome, without regard for the reasons behind the increase in HIV testing the problems of any strategy will not be seen, which could threaten both human rights and public health in the long term.

Concerns for the future

Government roles and responsibilities are increasingly delegated to non-state actors (eg, biomedical research institutions, health insurance companies, health management organisations, the pharmaceutical industry, and care providers) whose accountability is defined poorly and monitored inadequately. No objective measures are available of the commitment and capacity of governments to ensure that actions taken by the private sector and other players, including civil society, are informed by and comply with human rights. Likewise, as the discipline of health and human rights grows, its relevance and effectiveness will depend partly on the ability to understand cultural constraints. Even when countries commit to respect for human rights, health workers need to be educated about how to incorporate human-rights principles into their work, and this should be done equally at schools of medicine, schools of public health, and nursing schools. We expect that as the number of health professionals involved with human rights increases, the practice of health and human rights will also develop.

Steps forward

Attention to human rights can be a way to enhance the value and effects of health work by health policymakers, programme developers, health practitioners, and students. Nonetheless, three topics urgently need that further work. The first is the development of adequate monitoring instruments that measure both health and human rights concerns; the second is building evidence of the effects of application of the health and human rights frameworks to health practice; and the third is the creation of a research agenda to advance our understanding of the associations between health and human rights.

Because health and human rights is a new subject, so too are the ways to measure whether a clinical scenario or public-health decision is ultimately successful in upholding human rights. Efforts are needed to assess the effectiveness of existing methods of assessment and indicators of human rights concerns, and the extent to which these indicators need to be changed. Eventually we will know how the incorporation of human rights can effect the effectiveness of policies and programmes. We need to gain such knowledge quickly to allow us to develop an evidence base that shows the value of attention to rights for health as well as the negative effects on health of both grievous and subtle human rights violations. Until such a time, efforts to systematically review and collate existing information about the effects of human rights on health should be recognised as an urgent need.

Public-health efforts that consider human rights are more likely to be effective than those that neglect or violate rights. Integration of human rights in international health systems is increasingly driven by the recognition that the respect, protection, and fulfillment of human, civil, political, economic, social, and cultural rights, is necessary—not because they are the binding legal obligations of governments, but because they are essential for improvement of the health status of individuals and populations. We need to strengthen and build upon the available information and education about human rights ideas and processes. We also need to share information and cooperate with those working on health and those working on human rights. This cooperation might need institutional change and capacity building within governmental systems, international organisations, civil society stakeholders, and individuals. Increased understanding of human rights is not only of value in itself, but also provides those involved in health planning and care with the necessary means to create conditions that enable people to achieve optimum health.

Conflict of interest statement

We declare that we have no conflict of interest.

References


67 Parry J. China’s pragmatic approach to AIDS. *Bull World Health Organ* 2006; 84: 261–62.


A swollen, red scar

Marenza Leo, Aldo Pinchera, Emilio Fiore, Elisa Giustarini, Claudio Giani

In April, 2006, a 55-year-old woman was referred to our department with redness, swelling, and severe pain at the front of the neck, below the cricoid cartilage. Her symptoms had started a few months previously, and had gradually worsened since. In 1982, the patient had been diagnosed with a euthyroid multinodular goitre; one nodule had compressed her trachea, so she had undergone a partial thyroidectomy. She had been prescribed thyroxine ever since. She had no other medical history of note. The patient’s previous thyroid disorder, anterior neck pain, and swelling led to a provisional diagnosis, on referral, of acute thyroiditis.

Physical examination showed that the swelling and redness were largely confined to the scar left by the previous partial thyroidectomy (figure). The thyroid was enlarged; a 30 mm nodule was detected in the right lobe. Cytological examination of the nodule showed that it was a thyroid adenoma; there was no evidence of inflammation. Blood tests—including a full blood count, routine biochemistry tests, thyroid function tests, and inflammatory markers—gave entirely normal results. Ultrasonography and CT of the neck showed nothing of note, other than the scar. A biopsy of the scar was done. Histopathological examination of the sample showed non-caseating granulomas, consisting of epithelioid cells, multinucleated Langhans’ giant cells, and a rim of lymphocytes. These findings were diagnostic of sarcoidosis. Chest radiography showed bilateral enlargement of the hilar lymph nodes; CT of the chest confirmed this finding, and showed peripheral pulmonary infiltrates. The results of lung function tests were normal; a Mantoux test was negative. A gallium-67 total body scan showed increased uptake of the tracer, in the regions of the neck scar and the hilar lymph nodes. However, serum concentrations of angiotensin-converting enzyme and lysozyme were normal. Moreover, the patient’s lung function was normal—and there was no evidence of uveitis, hypercalcaemia, or neurological or cardiac manifestations of sarcoidosis. We therefore decided not to prescribe steroid treatment. Nonetheless, the redness and swelling of the scar decreased strikingly over the next 3 months. Chest radiography showed that the bilateral hilar lymphadenopathy had also undergone partial spontaneous remission.

Sarcoidosis is a multi-system disease of unknown cause. Skin manifestations have been reported in 20–35% of cases. The best known skin manifestations of sarcoidosis are probably erythema nodosum and lupus pernio. By contrast, scar sarcoidosis is rare, occurring in 2% of patients with sarcoidosis. Scar sarcoidosis can occur after physical trauma, including an injection or a tattoo; it can also be the first manifestation of more widespread disease.

References