Forcefeeding and restraint of Guantanamo Bay hunger strikers

We write regarding the forcefeeding and restraint of Guantanamo Bay detainees currently on hunger strike.[1,2] The World Medical Association specifically prohibits forcefeeding in the Declarations of Tokyo and Malta, to which the American Medical Association is a signatory.

Fundamental to doctors' responsibilities in attending a hunger striker is the recognition that prisoners have a right to refuse treatment. The UK government has respected this right even under very difficult circumstances and allowed Irish hunger strikers to die. Physicians do not have to agree with the prisoner, but they must respect their informed decision. Those breaching such guidelines should be held to account by their professional bodies. John Edmondson (former commander of the hospital at Guantanamo) instigated this practice, and we have seen no evidence that procedures have changed under the current physician in charge, Ronald Sollock.[3]

Edmondson, in a signed affidavit, stated that "the involuntary feeding was authorized through a lawful order of a higher military authority."[4] This defence, which has previously been described as the Nuremberg defence,[5] is not defensible in law. In a reply to an earlier draft of this letter, Edmondson said that he was not forcefeeding but "providing nutritional supplementation on a voluntary basis to detainees who wish to protest their confinement by not taking oral nourishment".

Recently, it was confirmed that health-care staff are screened to ensure that they agree with the policy of forcefeeding before working in Guantanamo Bay.[1] On his departure, Edmondson was awarded a medal for his "inspiring leadership and exemplary performance [which] significantly improved the quality of health care for residents of Guantanamo Bay" and "scored an unprecedented 100% on both the Hospital and the Home Health surveys."[3] The New York Times, however, reports that hunger striking detainees are strapped into restraint chairs in uncomfortably cold isolation cells to force them off their hunger strike.[2]

We urge the US government to ensure that detainees are assessed by independent physicians and that techniques such as forcefeeding and restraint chairs are abandoned forthwith in accordance with internationally agreed standards.

We declare that we have no conflict of interest.

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Clopidogrel and metoprolol in myocardial infarction


AP

In their randomised trial comparing metoprolol with placebo in patients with acute myocardial infarction (Nov 5, p 1622),[1] the COMMIT Collaborative Group specify that evidence of moderate heart failure (Killip class II or III) was not an exclusion criterion. However, stage III of the Killip classification[2] is defined as severe (not moderate) heart failure and comprises patients with frank pulmonary oedema with rales throughout the lung fields. Stage II of the Killip classification[2] also includes patients with pulmonary congestion. According to guidelines by the American College of Cardiology and American Heart Association on the management of patients with ST-elevation myocardial infarction,[3] β blockers should not be given acutely to patients with heart failure evidenced by pulmonary congestion or signs of a low-output state.

It is true that the European guidelines on the diagnosis and treatment of acute heart failure[4] mention that in patients with overt acute heart failure and more than basal pulmonary rales, β blockers should be used cautiously and that among patients in whom ischaemia and tachycardia are present, intravenous metoprolol can be considered. However, most patients included in the COMMIT study did not present with tachycardia, as can be seen from table 1 of the paper. Furthermore, because the aim of the study was not to assess the efficacy of metoprolol in patients with acute myocardial infarction complicated by acute heart failure but in a wide range of patients with acute myocardial infarction, the recommended caution could not have been considered for each patient individually.

In this sense, ethical concerns arise from the randomisation of 9105 patients in Killip II stage and, much more importantly, of 2144 patients in Killip III stage to a β blocker or placebo.

See **Online** for webappendix

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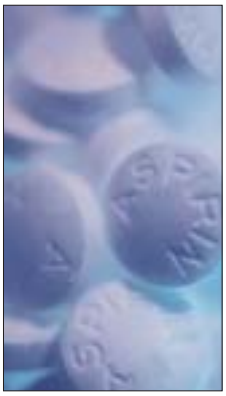

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The COMMIT Collaborative Group[1] report a significant early hazard of cardiogenic shock in patients with ST-elevation myocardial infarction who receive β blockers. The magnitude of benefit due to β blockade (reduction in reinfarction and ventricular fibrillation) was nearly identical to the risk of developing cardiogenic shock. Could the overall lack of benefit be because some patients received β blockers inappropriately?

The SHOCK trial investigators[2] have drawn attention to the existence of a subset of patients with acute myocardial infarction who have systemic hypoperfusion (as manifested by cold extremities and oliguria) while maintaining arterial blood pressures above the threshold set for diagnosing shock (by compensatory increase in systemic vascular resistance). These patients went on to require inotropic or mechanical circulatory support and had a high mortality (43%), leading these investigators to refer to the condition as "pre-shock". In the absence of stringent criteria to exclude compensated systemic hypoperfusion (systolic blood pressure <100 mm Hg was the only relevant exclusion criterion in COMMIT), it is likely that such patients would have entered the COMMIT study. The negative inotropic effect of metoprolol therapy would have tipped the balance towards manifest systemic hypoperfusion and cardiogenic shock. Patients in Killip class III would also have experienced similar adverse consequences.

Further, the COMMIT group state that they were able to give doses of intravenous metoprolol similar to that in the MIAMI study. That study[3] randomised only 22% of eligible patients, and therefore represents a low-risk population. However, because of its pragmatic design, the COMMIT study encompasses a much wider spectrum of risk. Presumably, high doses of β blockers in an unselected population of patients with myocardial infarction will cause more adverse effects than in a low-risk population. This indiscriminate use, combined with the postulated sensitivity of Chinese people to β blockers, could have contributed to the net lack of benefit.

The emphasis should therefore be on the prudent use of β blockers in stable patients immediately after an acute myocardial infarction, rather than on a blanket ban on all immediate post-myocardial-infarction use.

I declare that I have no conflict of interest.

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In the first of their two large randomised trials (Nov 5, p 1607),[1] the COMMIT Collaborative Group address the early introduction of clopidogrel as well as aspirin antiplatelet therapy in acute myocardial infarction. Of particular relevance to us is the risk of bleeding with these interventions. The investigators showed a non-significant difference between clopidogrel and placebo in both fatal non-cerebral and transfused non-fatal bleeds. But they were unable to give a further breakdown of the underlying cause of these events (notably gastrointestinal bleeds). Furthermore, inclusion criteria for this trial were determined on a local basis, and although active bleeding was classified as high risk, there is no mention of past medical history of ulcer disease or the like.

Evidence regarding the proposed combination of these agents is sparse at best. In the MATCH study,[2] aspirin and clopidogrel led to more bleeding than clopidogrel alone. In an aspirin-induced gastrointestinal secondary prevention setting, Chan and colleagues[3] showed that the combination of aspirin and a proton-pump inhibitor (PPI) was associated with a significantly lower incidence of bleeds than clopidogrel alone (0·7% *vs* 8·6%, p=0·001). Another study comparing both therapies individually with PPI cover revealed that both had a similar bleed profile.[4]

There are no established guidelines in this area, but PPIs have been tried and tested in the longer term and would seem to be the agents of choice.[5] Obviously, this is a topic that requires further research. Pragmatically approaching the problem in a real-life setting, we would strongly advocate that our cardiology colleagues have a low threshold for prescription of such medications if there are concerns, especially acutely, but also later on. In gastrointestinal bleeding, prevention is clearly better than cure.

We declare that we have no conflict of interest.

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Authors' reply

Given wide variation in the use of early β-blocker therapy for acute myocardial infarction,[1] the entry criteria for COMMIT were determined chiefly by the "uncertainty principle": that is, patients were eligible only if their responsible doctors were substantially uncertain as to whether the treatment was clearly indicated or clearly contraindicated.[2] This approach has the practical advantage of excluding all patients in whom there were considered (for whatever reasons) to be clear contraindications to the study treatments, while still allowing the balance of benefits and risks to be assessed in a wide range of settings where uncertainty persisted (such as among patients at higher risk than those typically studied in previous trials[3,4]).

Overall, the control incidence of cardiogenic shock after randomisation was only about 4% in COMMIT, chiefly because patients at high risk of developing shock were generally excluded by their doctors. The intravenous then oral metoprolol regimen studied was carefully titrated, and doctors were free to alter the treatment as required for each particular patient. Ganesan Karthikeyan suggests that the lack of net benefit with early metoprolol therapy might be due to poor tolerability among ethnic Chinese. But, although this possibility is widely discussed, there is no good evidence for it. Although a small pharmacodynamic study indicated that Chinese individuals may require lower β-blocker doses,[5] titration of the intravenous metoprolol in COMMIT resulted in doses very similar to those given in the previous MIAMI trial among Caucasians. For example, all three intravenous metoprolol injections were received by 94% of COMMIT patients in the low-risk subset defined to correspond to the MIAMI entry criteria (Killip I, systolic blood pressure >105 mm Hg and heart rate >65 bpm) compared with 95% among such patients in MIAMI.[2,4] Compliance with the oral metoprolol regimen in COMMIT was also about the same as with the similar oral regimen in MIAMI.

But, despite the care with which patients were selected and treatment was used in COMMIT, allocation to metoprolol produced a highly significant increase in the incidence of cardiogenic shock, and the proportional increase was similar (about 30%) across many different types of patient studied (see table 6 of the original report[2]), including those presenting without heart failure or hypotension. As discussed at length in our report (and in agreement with Karthikeyan), the COMMIT results indicate that the hazards of immediate β-blocker therapy after acute myocardial infarction outweigh the benefits in patients at high risk of developing shock. Much of this excess of cardiogenic shock with metoprolol occurred during the first day or so after admission, whereas the reduction in reinfarction and ventricular fibrillation emerged more gradually. So, a policy of delaying the initiation of β-blocker therapy until patients are haemodynamically stable may well avoid much of the hazard while retaining much of the benefit. (By contrast with the suggestion by Javier Borja and colleagues, however, the absolute excess risk of cardiogenic shock produced by immediate treatment was particularly large among patients presenting with tachycardia.)

No specific information was recorded in COMMIT about the risks of gastrointestinal bleeding, although patients with a recent history of gastric ulcer were generally excluded, especially if fibrinolytic therapy was to be given. There was, however, no evidence that the addition of clopidogrel to aspirin for an average of about 2 weeks after acute myocardial infarction produced any material increase in the incidence of any particular type of serious bleed. Even so, as suggested by Neeraj Bhala and Jaspal Taggar, it may well be worth considering the addition of a proton pump inhibitor to prevent gastrointestinal bleeding in patients who are to receive prolonged antiplatelet therapy for the prevention of heart attacks and strokes.

The Clinical Trial Service Unit has a staff policy of not accepting honoraria or other payments from the pharmaceutical industry, except for the reimbursement of costs to participate in scientific meetings. JX, LJ, and LL have accepted honoraria from the pharmaceutical industry for lecturing in China.

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AP

Harm reduction for sex workers

We commend *The Lancet* for publishing Michael Rekart's Review of harm reduction as it relates to sex work (Dec 17, p 2123).[1] The real and varied harms that sex workers face are well known, and Rekart outlines a realistic approach to their mitigation. Positioning sex workers themselves at the centre of the response makes sense and is well supported by evidence.

For all its strengths as a review of interventions that can benefit sex workers, the paper actually understates their potential contribution to public health. Two examples where comprehensive interventions have had a broad effect are worth highlighting. Both address structural conditions of commercial sex, tackling many of the important issues raised in this paper. Thailand's 100% Condom Use Programme not only resulted in individual benefits—enabling sex workers to demand condom use and access care for sexually transmitted infections (STIs)—but also had a large-scale public-heath effect.[2] Rates of curable STIs fell by more than 95% during the 1990s, and HIV prevalence declined in most population groups (except drug users who were not reached by interventions). By 2002, an estimated 5·7 million HIV infections had been averted, among sex workers and their clients, of course, but also far larger numbers among people at lower risk.[3] Similar results were also seen to a varying degree when this approach was adopted in other Asian countries, including Cambodia, Burma, China, and Mongolia.

A different approach was taken around the same time in the Sonagachi district of Kolkata, India.[4] Beginning with peer interventions and clinical STI services, a community empowerment model was progressively developed to take on a range of health and social harms faced by sex workers. Today, HIV prevalence remains low in Kolkata compared with other Indian cities. More than 60 000 sex workers participate throughout the state of West Bengal, savings and credit schemes have reduced dependency on sex work, and self-regulatory boards effectively address a range of abuses from trafficking to child prostitution.

Both of these examples illustrate the potential of well designed and well implemented structural interventions to reduce harm. Both involve multiple components, including outreach and peer interventions, barrier protection, and good clinical services to reduce STI burden and address sex workers' other needs. Both have had measurable public-health effects.

There are many other examples of interventions that have reduced direct work-related harms faced by sex workers.[5] Although the differences between such interventions are many, all have found ways to reach sex workers with relevant, effective services and, increasingly, to involve and empower them as part of the solution. Direct health interventions can greatly reduce morbidity and have frequently served as an impetus for broader social change. WHO and partners are exploring new approaches to scale up interventions that reduce the incidence of HIV while supporting marginalised populations such as sex workers to improve their lives.

We declare that we have no conflict of interest.

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Zinc supplementation in children with HIV-1 infection

We welcome the publication of Raziya Bobat and colleagues' randomised trial of zinc supplementation in HIV-1-infected South African children (Nov 26, p 1862);[1] it adds much to a neglected area of nutritional research. However, we feel their conclusion that zinc supplementation should be used as an adjunct therapy for children with HIV-1 infection is not entirely justified by the data.

The study was principally designed and powered as a safety study, with the aim of excluding an increase in viral load in the zinc group (specified as the primary endpoint). Although efficacy was suggested by a significant reduction in the proportion of clinic visits caused by watery diarrhoea (frequency of new diarrhoea episodes was not reported) and a modest advantage in bodyweight (not sustained) in the zinc supplementation group, these outcomes were apparently not specified a-priori as secondary endpoints and should be interpreted with caution in view of the multiple analyses done.

There was no significant reduction in viral load, no increase in percentage CD4 count, no decrease in frequency of opportunistic infections, and no decrease in overall mortality; these are the normal outcome variables by which the efficacy of HIV treatments are judged. Larger clinical-endpoint studies are required to confirm the preliminary efficacy findings of this study.

Furthermore, the trial was done in children who were not receiving antiretroviral therapy (ART), although, as Bobat and colleagues point out, 40% would have been eligible for such treat-

ment. ART is known to result in major improvements in morbidity and mortality, and some observational data suggest that it might also reduce zinc deficiency, possibly obviating the need for specific supplementation.[2] Whether zinc supplementation provides any additional benefit over and above that of ART is uncertain.

No trial has been done in children, but our randomised controlled trial of zinc supplementation in adults taking ART showed no benefits with respect to immune response to tuberculosis, CD4 counts, and viral load.[3] Even though malnutrition (in the form of low bodyweight) remains an important prognostic factor in patients starting ART,[4] the advantages of specific macronutrient and micronutrient supplementation regimens must be proven in large-scale randomised controlled trials in patients taking ART before they can be recommended as routine adjunctive therapy.

Although Bobat and colleagues' study showed that zinc supplementation was safe, the recommendation to use zinc treatment in HIV-1 infected children might not be so innocuous. In many underdeveloped countries where access to ART is not yet widespread, limited financial resources, infrastructure, and trained manpower represent major barriers to scale-up and implementation of ART programmes. Diversion of such resources to deliver interventions for HIV-1-infected children that are unproven and undeniably less effective than ART might prove counter-productive.

We declare that we have no conflict of interest.

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Authors' reply

Our study was principally designed to assess the safety of zinc supplementation for children with HIV-1 infection, but its effect on morbidity (particularly diarrhoea and respiratory tract infections) and mortality were explicit secondary outcomes.

Although the study was not powered to detect small differences in morbidity and mortality between the two groups, we saw a significant reduction in episodes of diarrhoea, and strong trends in the reduction of respiratory tract infections and mortality (two deaths in the zinc supplementation group and seven in the placebo group). We believe that this finding provides evidence of the efficacy of zinc supplementation for children infected with HIV-1. However, our conclusion that zinc supplementation should be used as an adjunct therapy for children with HIV-1 infection was not solely based on these findings, but on the substantial evidence that zinc supplementation reduces morbidity from diarrhoea and respiratory-tract infections in children not infected with HIV-1.[1–4]

The benefits of zinc supplementation for HIV-1-infected children should not be judged by reductions in HIV-1 viral load or increases in CD4 counts. Given the effectiveness of zinc supplementation in HIV-1-uninfected children, the benefits of zinc supplementation in infected children are probably mediated by other mechanisms. The absence of any beneficial effect of zinc supplements on HIV-1 viral load or CD4 counts in HIV-1-infected adults receiving antiretroviral therapy is not germane to the assessment of the effectiveness of zinc supplementation in reducing morbidity and mortality in children.

Antiretroviral therapy was not available in South Africa at the time of our study. The effectiveness of zinc in reducing morbidity in HIV-1-infected children might be diminished in those receiving antiretroviral therapy, but its effectiveness in uninfected children suggests zinc supplements may provide additional benefit.

We do not believe that the provision of zinc supplements would divert resources from treatment with antiretroviral therapy. The cost of zinc supplementation is a small fraction of the cost of antiretroviral drugs. Zinc supplements cost about US$0·01 per dose, and both daily and weekly supplementation have been shown to be effective in HIV-1-uninfected children.[4]

Most HIV-1-infected children still do not have access to antiretroviral therapy, and not all of those with access are eligible for treatment. Zinc supplementation could provide a cost-effective means to reduce morbidity and mortality of HIV-1-infected and uninfected children in resource-poor settings, and could be made available to many more HIV-1-infected children in a shorter period of time than antiretroviral therapy.

We declare that we have no conflict of interest.

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Still Pictures

Zinc and iron supplementation trials in Nepal and Tanzania

The results of the trials designed to assess the effect of iron supplementation on morbidity and mortality in young children in Tanzania and Nepal (Jan 14, pp 133 and 144)[1,2] confirm that iron supplementation is effective in reducing iron deficiency and anaemia. However, one of the trials[1] also shows that there are situations in which iron supplementation might be associated with increased risk of death or severe morbidity leading to hospital admission. This increased risk is attributed mainly to malaria and other severe infectious diseases, but the results of a substudy within that trial suggest that the risk might not be distributed uniformly across the whole sample of children.

As soon as these results were known, WHO convened an expert meeting to review critically the data available from both trials and to assess their possible public-health implications. The main conclusions of that meeting are presented here.

The experts recognised the scientific importance of the results of these trials for policymakers. Nevertheless, they suggested that caution be exercised in changing policy on the basis of a single set of observations. In light of the findings and until WHO recommendations are possibly revised, in regions with a high prevalence of malaria and other infections, they advised that iron and folic acid supplementation for young children be targeted to those who are iron deficient. Every effort should also be made to combine iron supplementation with effective treatment and control of malaria and other severe infectious and parasitic disease.

They also emphasised that these findings should be regarded as specific to iron and folic acid supplementation of young children in regions of the world where malaria transmission is intense and severe infectious disease prevalence is high. The conclusions should not be extrapolated to fortification or food-based approaches for delivering iron.

These results show that additional research and assessment of existing programmes is needed urgently to develop the most effective strategies for controlling iron deficiency and anaemia in regions where malaria transmission is intense and the prevalence of infection high. Other important research issues include: determining the dose of an iron supplement that is both safe and effective, the optimum duration of supplementation, the mode of iron delivery, the pathophysiological basis for the increase in adverse events among iron-sufficient children who are exposed to malaria and infectious diseases, and an assessment of possible interactions between iron and other micronutrients, especially zinc. Finally, it will be necessary to examine more critically the possibility that iron supplementation could affect the course of other potentially fatal infectious disorders such as HIV/AIDS and tuberculosis.

The important message of these trials is that, although iron supplementation is effective in combating iron deficiency, a better understanding of the potential risks and benefits of different levels and modes of delivery in some environments is required. Although iron deficiency is frequently the main factor contributing to anaemia, the control of anaemia requires a multisectorial approach that, through integrated interventions, addresses the various factors that have a significant role in a given community.

We thank Olivier Fontaine for his contribution to this letter. We declare that we have no conflict of interest.

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2 Tielsch JM, Khatry S, Stoltzfus R, et al. Effect of routine prophylactic supplementation with iron and folic acid on preschool child mortality in southern Nepal: community-based, cluster-randomised, placebo-controlled trial. *Lancet* 2006; **367:** 144–52.

Department of Error

Le Guenno B, Formentry P, Wyers M, Gounon P, Walker F, Boesch C. Isolation and partial characterisation of a new strain of Ebola virus. Lancet *1995;* ***345:*** *1271–74*—In this Article (May 20, 1995), the second author's surname should be "Formenty".

Patel HC, Bouamra O, Woodford M, King AT, Yates DW, Lecky FE, on behalf of the Trauma Audit and Research Network. Trends in head injury outcome from 1989 to 2003 and the effect of neurosurgical care: an observational study. Lancet *2005;* ***366:*** *1538–44*—In this Article (Oct 29), the fifth sentence of the seventh paragraph (p 1542) should read: "However, up to 55% of patients with severe head injury have non-surgical injuries, for which mortality is similar to that of surgical lesions."