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Views & Reviews: Courage is treating patients with Ebola (*BMJ* 2014;349:g4987)

Ebola and other viral haemorrhagic fevers

Be prepared, with new guidance featuring old and well established principles

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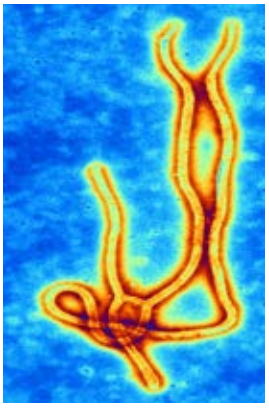
The ongoing Ebola outbreak in West Africa is the largest and most complicated that the world has ever seen. Since it was first identified in the forested regions of south eastern Guinea in March,[1] it has spread to Liberia, Sierra Leone, and Nigeria and has now been declared a "public health emergency of international concern" by the World Health Organization.[2]

Ebola virus is one of a group of zoonotic viruses that can cause severe disease in humans.[3-5] They are of particular public health importance because of their ability to spread to carers and healthcare workers, the often high case fatality rate, difficulties in their rapid recognition, and the lack of effective specific treatments.[3-6]



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Be prepared

The current epidemic is caused by the Zaire strain of Ebola virus, which has a mortality of 50-90% in endemic settings. No licensed cure or vaccine is available, although research is in progress to develop these and two American healthcare workers are reported to have received an experimental monoclonal antibody preparation.[7] The keys to case management are early recognition and isolation of cases, use of personal protective equipment, and the provision of supportive medical care to reduce mortality.[2 6]

Guidance on management of viral haemorrhagic fever was developed for UK healthcare professionals after a laboratory acquired case of Ebola infection,[8] and imported cases of Lassa fever. The guidance was revised by the Advisory Committee on Dangerous Pathogens in 2012 and updated last month.[9 10] Similar guidelines are available in the United States[4] and European countries,[11] and they differ in emphasis from those developed for use in resource poor settings.[6] Guidance and information for the British public are also available in a range of reliable internet resources including NHS Choices.[12-14]

Imported cases of viral haemorrhagic fever in the UK are rare and patients are often healthcare workers, military personnel, or others who work in rural environments.[15] These diseases differ from infections such as influenza or severe acute respiratory syndrome because they are usually transmitted by direct contact with blood or other body secretions rather than being airborne. Also, patients with viral haemorrhagic fever are not infectious until they develop symptoms. The likelihood of epidemic transmission in Western settings, including to fellow travellers on airplanes, is therefore low.

The initial clinical presentation is non-specific, so viral haemorrhagic fever should be considered in any patient with a fever or history of fever in the previous 24 hours who has returned from an endemic area in the past 21 days (the longest incubation period). Most febrile travellers returning from endemic areas will have other infections, such as malaria, which also need rapid diagnosis and management.[16] Unfortunately, a travel history is rarely elicited in most day to day consultations, leading to delays in diagnosis and in the isolation of patients at risk.[17-19]

The updated guidance includes flow diagrams, tables, and appendices that offer advice on the assessment of exposure risk, management of patients, and all aspects of infection control. It links to the UK's Imported Fever Service,[20] which can provide case specific advice on risk assessment and rapid diagnostic testing to augment advice from local infection specialists.

The guidance recommends that patients identified as having a possible viral haemorrhagic fever should be isolated until the results of specific investigations are obtained from reference laboratories, which may take up to 24 hours. It is important not to delay diagnosis and treatment of more common diseases, such as malaria or typhoid, during this period. In the past this has been a problem outside specialist centres,[21] owing to safety concerns associated with performing otherwise routine blood tests in patients with a suspected viral haemorrhagic fever. The updated guidance is welcome because it acknowledges that it is safe to perform these tests locally to support clinical management while awaiting the results of specific diagnostic tests.

To be fully effective the new guidance must be supported by the training of medical, nursing, and laboratory staff in risk assessment, universal precautions, and the use of personal protective equipment. Follow-up of contacts of cases is essential for infection containment. In the event that a patient tests positive, specialist care is available in the UK through the high level isolation unit, based at the Royal Free Hospital in London. The unit can provide advice on safe care for high risk patients and safe transfer, as well as taking over the management of seriously ill patients in the tailor made facility. The UK has specially equipped ambulances and trained staff to accomplish such transfers when needed.

Travel history is crucial

The risk of a traveller acquiring a viral haemorrhagic fever and importing it to the UK is very small but must be considered. The key message for healthcare professionals is to take a travel history from all patients with fever and perform a more specific risk assessment for patients returning from areas endemic for these diseases, according to the recently updated guidance. All frontline hospital doctors and managers should also make sure that they can answer "yes" to the following questions: have you considered that someone with viral haemorrhagic fever could present to your facility? Do you have a local protocol? If so, can you and your staff find it? And, lastly, have you adequately trained your staff in the use of personal protective equipment? If not, now is the time to do so.

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The cost of drugs is a consideration. Patients with adrenal insufficiency are often young and will require lifelong replacement treatment

Glucocorticoid replacement

Pending further studies of new agents, the old treatments are still the best

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Steroids are among the most commonly prescribed drugs. Synthetic glucocorticoids such as prednisolone and dexamethasone are commonly used as anti-inflammatory or immunosuppressive agents in supra-physiological doses and have longer half lives than the naturally occurring hydrocortisone.

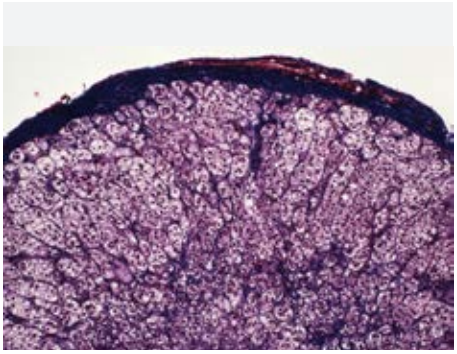
Patients with primary adrenal insufficiency require replacement of both mineralocorticoid, in the form of fludrocortisone, and glucocorticoid. All healthcare professionals should know how to manage patients with hypocortisolaemia, some of whom will be at risk of life threatening adrenal crises.[1]

In the United Kingdom, hydrocortisone is the most commonly prescribed glucocorticoid for replacement therapy in both primary and secondary hypocortisolaemia. Other glucocorticoids are more often used for other conditions. Dexamethasone is the most potent and is mainly used in intracranial and oncological conditions. Prednisolone is the standard treatment for most inflammatory conditions. Prednisone is also available as a delayed release preparation and is converted to active prednisolone by first pass metabolism in the liver.

In healthy humans, cortisol is secreted from the adrenal glands in a distinct circadian rhythm, with peak levels in the early morning, dropping to undetectable levels during the night.[2 3] Hydrocortisone replacement therapy is tailored to mimic this diurnal pattern. Hence, conventional treatment with hydrocortisone for hypocortisolaemia is generally divided into three daily doses, with a larger proportion of the total dose taken in the morning.

In 2012 an oral modified release formulation of hydrocortisone, Plenadren, was licensed in the UK. What are its advantages?

The basis for the licensing decision was a single non-blinded crossover trial of 64 patients.[4] In the trial, participants were randomised to receive either a single daily dose of modified release hydrocortisone or a standard immediate release formulation in three divided doses



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Source of the problem

for 12 weeks, followed by a switch to the other formulation for a further 12 weeks. The study showed that patients taking the once daily formulation had a lower body weight, blood pressure, and glycated haemoglobin concentration at 12 weeks compared with those taking conventional doses of hydrocortisone. This was unsurprising, however, as the doses of hydrocortisone were not comparable: the 24 hour cortisol exposure was lower with the modified release formulation than with the standard doses. Lower hydrocortisone doses than the 20-30 mg daily usually prescribed may therefore result in similar benefits to those seen with the modified release formulation at a fraction of the cost.

Although Plenadren has been marketed as a convenient once daily formulation and patients prefer a once daily formulation to multiple daily doses, adherence did not differ between the two formulations. Neither did quality of life scores.[4] The cost of drugs is a consideration. Patients with adrenal insufficiency are often young and will require lifelong replacement treatment. Currently, Plenadren costs almost four times as much as standard hydrocortisone (£224 (€283; $380) compared with £60.70 for 28 tablets (20 mg)).[5]

If slow release formulations bring advantages then glucocorticoids with longer half lives offer possible alternatives in the treatment of hypocortisolaemia. Prednisolone has an ideal half life, allowing once daily treatment,[6] and patients with adrenal insufficiency derive the same subjective benefit from equivalent doses of prednisolone and hydrocortisone.[7] Prednisolone costs £1.31 for 28 tablets at the 5 mg dose; data on overtreatment with once daily prednisolone remain inconclusive.[8-10]

Prednisone, an inactive drug precursor converted to active prednisolone in the liver, offers no obvious added benefit to prednisolone, and the modified release preparation is expensive. Soluble prednisolone is also available, but at £39.93 for 28 tablets at the 5 mg dose[5] is about 40 times more expensive than standard prednisolone tablets. Dexamethasone is less commonly used because of its longer duration of action.

We now need long term randomised clinical trials looking at the efficacy and side effects of the available glucocorticoids in the management of hypocortisolaemia. A further study comparing truly equivalent doses of hydrocortisone, prednisolone, and modified release hydrocortisone is required.

Current formulations of hydrocortisone do not fully replicate the normal circadian rhythm of cortisol.[11] Several centres measure levels of cortisol in patients who are taking hydrocortisone and use these data to titrate dose and timing of treatment. As a result some patients follow three times daily regimens while others (presumably slower metabolisers) have twice daily dosing. Other centres do not measure levels but treat patients empirically.

Prednisolone rules, for the moment

Centres that titrate doses will want to measure levels of prednisolone, and assays are being developed to enable this. At present, however, there is no evidence of any difference between the three replacement options, so it is logical to use the most cost effective, which is prednisolone. Plenadren is the least cost effective and hence has no current place in the treatment of adrenal insufficiency. Hydrocortisone was the most cost effective option until 2008, when its price increased 60-fold,[12] but prednisolone should now be the first line option for glucocorticoid replacement therapy.

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- Practice: How effective is tranexamic acid for acute gastrointestinal bleeding? (*BMJ* 2014;348:g1421)
- Observations: Tranexamic acid in trauma: we need stronger global health policy (*BMJ* 2013;347:f4593)
- Research: Effect of tranexamic acid on mortality in patients with traumatic bleeding (*BMJ* 2012;345:e5839)
- Research: Effect of tranexamic acid on surgical bleeding (*BMJ* 2012;344:e3054)

Tranexamic acid for surgical bleeding

Uncertainty over vascular occlusive events warrants an adequately powered RCT

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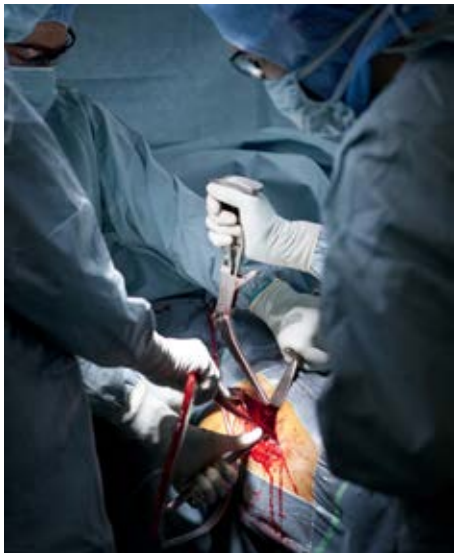
Joint replacement accounts for a large share of the 230 million major operations carried out each year worldwide. Each year in England and Wales alone there are about 180 000 hip and knee replacements.[1] Bleeding is an important complication, and many patients require a blood transfusion. One strategy to reduce surgical bleeding is to use the antifibrinolytic drug tranexamic acid.

Tranexamic acid inhibits clot breakdown by reducing the binding of plasminogen to fibrin. A recent systematic review and meta-analysis of randomised controlled trials showed that tranexamic acid reduces surgical bleeding and blood transfusion by about one third.[2] However, the effect of the antifibrinolytic on the risk of vascular occlusive events remains uncertain. Perioperative myocardial infarction often goes undetected as many patients do not experience ischaemic symptoms.[3] Nevertheless, an increased cardiac troponin level, a sensitive marker of myocardial injury, is common after major surgery and is associated with appreciable morbidity and mortality.[4]

In a linked article, the effort by Poeran and colleagues to resolve the uncertainty about the effect of tranexamic acid on vascular occlusive events is therefore welcomed.[5] In a retrospective cohort study the authors compared the outcomes of 20 051 patients who received tranexamic acid during hip or knee arthroplasty with 852 365 patients who did not, using data from 510 US hospitals. They found that tranexamic acid reduces blood transfusion with no increase in vascular occlusive events, even after adjusting for patient characteristics and comorbidities.

Can we now conclude that tranexamic acid is safe for routine use in joint replacement surgery? Giving a drug that reduces blood clot breakdown to patients at increased risk of vascular occlusive events must surely be based on reliable evidence. Although any increase or decrease in risk is likely to be moderate, because of the hundreds of thousands of older adults who undergo joint replacement surgery each year even a moderate effect could be important.

Reliable assessment of moderate effects requires strict control of random error and bias.[6] Does the study by Poeran and colleagues fulfil these criteria?



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By reducing surgical bleeding, tranexamic acid might reduce the perioperative tachycardia that increases myocardial oxygen demand

Control of random error means big studies with large numbers of outcome events, and with over 872 000 patients Poeran and colleagues' study is certainly big. However, rigorous control of bias means proper randomisation and here the study falls short. As the authors acknowledge, unmeasured or residual confounding is a large threat to validity that can be dealt with only by randomisation. The authors' defence that trials have limited "generalizability to more general populations" confuses statistical and scientific inference. Whereas statistical inference, the process of using sample information to make inferences about the population from which it was drawn, is helped by having a representative sample, scientific inference involves making valid conclusions about biology.[7]

Insights from unrepresentative patients

Valuable insights into the effects of drugs can be obtained even from patients who are unrepresentative of those in whom the drug will be used. The finding of the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH-2) trial that tranexamic acid reduces death from bleeding in adults with trauma was generalised to children, with an adult dose recommended in children over 12 years and a weight related dose for younger children, even though this age group was explicitly excluded from the trial.[8] But is there any good biological reason why tranexamic acid would work in a 20 year old and not in a 12 year old? Generalisability is not "established" by data from "actual everyday practice" but depends on valid information about treatment effects and informed judgment about the factors that may be relevant to the drug's mechanism of action.[7]

Treatments that reduce bleeding often increase the risk of thrombosis. According to the summary of product characteristics,[9] tranexamic acid is contraindicated in patients with a history of arterial or venous thrombosis. However, in the CRASH-2 trial there were fewer vascular occlusive deaths associated with tranexamic acid and a statistically significant reduction in fatal and non-fatal myocardial infarction.[10] The pathogenesis of perioperative myocardial infarction includes an imbalance in myocardial oxygen supply and demand, rupture of coronary artery plaque, and platelet activation.

By reducing surgical bleeding, tranexamic acid might reduce the perioperative tachycardia that increases myocardial oxygen demand and prevent the decrease in haemoglobin level responsible for reduced myocardial oxygen supply.[11] Furthermore, plasmin is a potent mediator of inflammation and by inhibiting plasmin production, tranexamic acid might reduce the inflammatory response thought to contribute to rupture of coronary artery plaque.[11]

If tranexamic acid reduces rather than increases the risk of myocardial infarction in patients requiring surgery, it could be a highly cost effective way to improve surgical safety.[11] The large reduction in the risk of myocardial infarction reported by Poeran and colleagues is consistent with this hypothesis. Although it would be premature to recommend the routine use of tranexamic acid in general and orthopaedic surgery, it is surely time to resolve this uncertainty in an adequately powered randomised controlled trial.

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- Editorial: *The BMJ*'s own patient journey (*BMJ* 2014;348:g3726)
- Analysis: Collecting data on patient experience is not enough: they must be used to improve care (*BMJ* 2014;348:g2225)

Assembling the evidence for patient centred care

National Voices has provided a promising series of narrative reviews

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The initiative encourages patient advocacy groups to use systematic reviews as part of their recommendations for service users and policy makers

National Voices, a health and care charity coalition, has launched "a new set of take-away resources which set out the best ways to engage people and make person centred care happen." These narrative reviews synthesise the evidence from five domains—promoting prevention; improving information and understanding; enhancing experience; supporting self management; and supporting shared decision making. Based on evidence from nearly 800 systematic reviews, they take the form of "simple guide" booklets that can be downloaded from the National Voices website (www.nationalvoices.org.uk/evidence).

With the overarching aim of providing evidence to "support commissioners and providers to access, understand and make use of the best evidence for various approaches to involving people in their health and healthcare," these resources have achieved what they set out to do. The evidence in each of the five domains is summarised into "key themes" for patients, professionals, and organisations, and the evidence covers improvements in knowledge, experience, health service use and cost, and health outcomes. Thus the resources provide a valuable summary across multiple types of interventions. Of added value is the well referenced section that supports the recommendations and highlights interventions where the evidence base is strong.

Like all summaries of evidence, the recommendations are only as good as the evidence that has been synthesised. Relatively little evidence exists on improving health outcomes. For example, the summary table on promoting prevention has nine "improvement initiatives," which include interventions such as opportunistic advice, self help programmes and websites, and mass media campaigns. The authors conclude that such initiatives may improve process measures and intermediate health outcomes such as smoking and alcohol consumption, as well as other health behaviours. Another limitation is that the evidence base largely comprises studies with short durations of follow-up. It is therefore hard to know whether interventions have a sustained influence over time or whether their effects become attenuated, particularly in the absence of continuing interventions.

Other issues arise also. It is difficult to determine effect sizes because little quantifiable data are presented, either in relative or absolute terms. The quality of evidence in relation to observational or experimental studies is not made sufficiently clear, so the likelihood of bias is difficult to judge. Lastly, some of the domains seem to overlap—for example, "improving information and understanding" for patients and "supporting shared decision-making" have much in common.

Complex challenges

These shortcomings are almost inevitable, when many of the interventions are multifaceted, are aimed at patients and professionals simultaneously, and are intended to influence the process of care that health professionals provide and the outcome of care that patients experience as a consequence. Rather than being a criticism of the authors' approach, it is an acknowledgment of how challenging it is to summarise complex evidence into a neat digestible format.

Who should read these recommendations? The reviews are relevant to a broad range of constituencies that are concerned with health. These include policymakers who need to commission cost effective services with an established evidence base; funding organisations that need to be targeting areas where the evidence base is incomplete or poor; patient advocacy and service user groups that need to recommend effective and cost effective interventions to their members; and educational organisations at undergraduate and postgraduate level that need to direct students to these reviews as important summaries of the current evidence base on person centred care.

The National Voices' initiative democratises evidence and encourages patient advocacy groups to consider and use systematic reviews of research as part of their recommendations for service users and health policy makers. The next iteration of reviews might provide more digestible formats and quantifiable recommendations that include the trade offs that patients may want to discuss with their healthcare providers.

The initiative also highlights the importance of involving patients in setting research agendas and priorities. For example, little evidence exists on patients' views, experiences, and preferences regarding interventions for chronic pelvic pain.[1] Our goal should be the sharing and prioritising of research topics that engage patients, clinicians, and researchers, and that have arisen from a systematic assessment of existing evidence.[2 3]

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