Clinical Review

Clinical Review identifies issues in the medical literature of interest to clinicians in Africa. Essential references are given at the end of each section

Medicine Review

Relapsing fever revisited

Little attention is paid to relapsing fever, but it remains a significant problem in some areas of the tropics. A recent case report in the journal *Tropical Doctor* reminds us of the condition.[1] The case reported resulted in the patient's death, probably due to a Jarisch–Herxheimer reaction.

Relapsing fever is due to a spirochaetal bacteria of the *Borrelia* species. It can be either louse-borne (LBRF) or 'epidemic', or tick-borne (TBRF) or 'endemic'. LBRF is caused by *Borrelia recurrentis*, but TBRF can be caused by many types of *Borrelia* – perhaps the best known is *Borrelia duttoni*. This organism is named after the British parasitologist from the Liverpool School of Tropical Medicine, John Dutton. On an expedition to The Congo in 1905 he identified the causal organism of TBRF, which was later named after him. Sadly, Dutton died of the very disease he had found the cause of.

Rarely, relapsing fever can be transmitted transplacentally, or by transfusion of infected blood, but insect transmission is by far the most common mode of spread. Both TBRF and LBRF cause a classical intermittent high fever, resolving by crisis, but later returning. Diagnosis is usually made by thick or thin blood films (usually done because malaria is suspected) taken at the time of fever. There is also now a polymerase-chain-reaction (PCR) test which is the most sensitive method of detection. Both types of relapsing fever usually respond well to either tetracyclines or penicillin, though the disease can sometimes be complicated (e.g. myocarditis, meningitis, shock), and fatalities do occur.

A particular feature of relapsing fever is that patients may dramatically deteriorate after the initiation of treatment. This is known as the Jarisch–Herxheimer reaction (JHR), and is due to the rapid release of endotoxins and cytokines from dying bacteria. It may affect up to 50% of cases, and occurs within a few hours of the first dose of antibiotic. It is usually manifested by collapse, agitation, fever, rigors, hypotension tachypnoea, tachycardia, and myalgia. Clinically, it resembles the syndrome of septic shock, but can also be mistaken for an anaphylactic reaction to the antibiotics. Treatment is supportive, with intravenous fluids and oxygen, and antibiotics should be continued. Some recommend steroids to reduce the severity of the JHR, but there is no definite evidence of benefit. Pre-treatment with anti-TNF (tumour necrosis factor) drugs may be helpful, but such therapy is unlikely to be available.

The recently reported case[1] was from northern Tanzania, where TBRF is due to *Borrelia duttoni*. A 19-year-old woman presented with a 2-day history of fever and vomiting. Earlier on the day of admission, she had delivered a healthy baby girl at home. She was thought to have malaria and was given quinine, but blood slides showed no malarial parasites. However, the slides showed large numbers of spirochaetes identified as *B duttoni*. She was given 1 mega-unit of procaine penicillin intramuscularly, and some hours later developed a classic JHR with hypotension (blood pressure 90/20 mmHg), tachycardia (120 per minute) and tachypnoea (60 per minute).

Despite supportive measures, she suffered a cardiac arrest soon after, and could not be resuscitated. The baby developed an unidentified febrile illness soon after, but recovered and no clear diagnosis was made.

Relapsing fever in pregnancy can lead to early labour and it is possible that this patient's delivery was precipitated by her TBRF. Transplacental infection can occur, and it is of interest that the infant developed a febrile illness post-delivery, though the cause was not identified.

Complications of infection, and risk of JHR, are strongly related to the intensity of infection, and the authors recommended the use of the '*Borrelia* index'.[2] This is the ratio of spirochaetes to leucocytes (white blood cells, WBC) seen on the blood film. An index of 1 spirochaete to 3 WBCs (1/3) or less suggests that complications are unlikely. An index up to 9/3 makes minor complications likely, and an index of >10/3 makes severe complications and JHR very likely.

The main message of this useful report is to remind doctors in Africa of this important infection, and when it is diagnosed, to watch the patient very carefully after antibiotic treatment is started in case of the Jarisch–Herxheimer reaction.

Problems with polio

As a highly vaccine-preventable infection, poliomyelitis (polio) has for many years been on the agenda of the World Health Organization (WHO) as an eradicable disease. Over the last decade or so, remarkable progress has been made, led not just by WHO, but also by UNICEF and the Rotary Foundation. Polio cases are now a small fraction of the numbers 10 to 15 years ago, and only three countries are now regarded as 'polio-endemic' – Afghanistan, Nigeria, and Pakistan. In 2013, there were only about 100 cases reported from these countries, and recently the GPEI (Global Polio Eradication Initiative) set a deadline of the year 2018 for total polio eradication.[3] One of the several strategies for achieving this aim is the continued replacement of oral polio vaccine, to eliminate the rare occurrence of vaccine-related polio.

But though eradication remains possible, worrying political issues have emerged which may interfere with this aim. Polio has re-emerged in the Horn of Africa, and suspected cases are being reported from Syria. In the African Horn, earlier this year, there were 174 cases in Somalia, 14 in Kenya, 6 in Ethiopia, and 3 in South Sudan. In Somalia, political groups have prevented

access to polio vaccines and spread false rumours about adverse effects. Worryingly, after a continuous 22-year presence, Médicins San Frontières (MSF) has now withdrawn from Somalia, because of danger to its health workers.

Even in the three polio-endemic countries, with well-established prevention and eradication programmes, there are problems. In Pakistan, there have been well-publicised attacks on polio workers, and rumours have been spread that the vaccine is aimed at sterilising Muslims. All of this demonstrates the difficult and often fragile interface between medicine and politics. There is no question that polio can be eradicated from the world, but as with many medical advances, it requires the political will to do so.

Acute bronchitis – dogma disputed!

It is always refreshing to see medical research cast doubt on accepted principles of medicine. A recent report in the *British Medical Journal* appears to disprove the standard approach to the treatment of acute bronchitis. Traditional and time-honoured teaching is that a recent onset cough with no sputum or with white sputum, usually indicates acute bronchitis of viral origin. If, however sputum is present and it is discoloured (usually green), then that is taken to indicate a bacterial cause, and antibiotics are given.

Researchers from Spain have, however, conducted a randomised controlled trial (RCT) in adult patients with uncomplicated acute bronchitis with discoloured sputum, which suggests that antibiotics are not effective.[4] Of 416 patients recruited, 137 were randomised to antibiotic treatment (coamoxiclav 625 mg tds (three times a day), 136 to ibuprofen (600 mg tds), and 143 to placebo. Neither of the active treatments reduced the period of time to resolution of cough, compared with placebo. Adverse events were significantly more likely in those treated with antibiotics (12%) compared with those treated with either ibuprofen (5%) or placebo (3%).

So should this study change our standard practice? The answer is probably yes, but it must be emphasised that this study was of *uncomplicated* bronchitispati ents. Any patient with cough and discoloured sputum who has 'red flag' symptoms or signs may need antibiotics. These may include, for example, a patient who is particularly unwell, has pre-existing chest problems (e.g. chronic obstructive pulmonary disease (COPD), or asthma), or has lateralising signs on auscultation. Such patients may also require chest radiography to exclude a pneumonic illness.

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Paediatrics Review

New WHO guidelines for management of severe acute malnutrition

Severe acute malnutrition (SAM) and lesser degrees of malnutrition are associated with abject poverty, chronic food insecurity, and high levels of infectious diseases, especially diarrhoea, respiratory infections and HIV infection. Rates increase during acute food insecurity owing to famine and displacement associated with armed conflict. Severe oedematous malnutrition is now mainly seen in sub-Saharan Africa.

Since the publication of the World Health Organization (WHO) guidelines for management of severe malnutrition in 1999[1] there have been a number of developments, particularly expansion of care in the community using ready-to-use therapeutic foods (RUTF) and the increasing availability of antiretroviral drugs (ARVs). There are increasing demands for revision of the WHO 1999 guidelines particularly on subjects such as management of persistent diarrhoea and enteropathy, dehydration and shock, infections and choice of antibiotics, HIV-infected children and infants <6 months of age.[2–4] However, randomised controlled trials on most aspects of SAM are few, which limits the ability to produce firm guidelines.[5] A summary of the main subjects in the new guidelines[6] is outlined below.

Criteria for admission to a programme for management of SAM for infants 6–59 months are: mid-upper arm circumference (MUAC) <115 mm or weight-for height/length (wt/ht) <–3 Z-score using the 2006 WHO growth standards,[7] or bilateral oedema. Wt/ht percent of standard is no longer advised. In addition, admission may be necessary for patients with disability, social issues, or difficult access to care. The decision regarding inpatient (IP) or outpatient (OP) care depends on medical complications and appetite. Children who have appetite and are clinically well are treated as OP in Community-based Therapeutic Care (CTC). Those with medical complications, severe oedema (+++) or poor appetite, or presenting with one or more of the IMCI (Integrated Management of Childhood Illness) danger signs, should be admitted to IP care. The decision to transfer from IP to CTC depends on appetite and clinical condition, not anthropometric outcome. Criteria for discharge from CTC are: wt/ht ≥–2 Z score or MUAC ≥125 mm and no oedema for at least 2 weeks. Because MUAC criteria of <115 mm for admission may not detect up to 75% of children with wt/ht <–3 Z-score, the same method of measurement on admission should be used for decision regarding discharge. Periodic follow-up is important to monitor progress and avoid relapse.

Patients with uncomplicated SAM treated in CTC should receive a course of oral antibiotic such as amoxicillin but undernourished children who do not have SAM should not routinely receive antibiotics. Children admitted with complications and/or signs of infection or who are lethargic and sickly should receive parenteral antibiotics. However, because of increasing rates of resistance to second-line antibiotics, e.g. chloramphenicol, gentamicin and cephalosporins, the choice of antibiotics will depend on local sensitivity patterns and

requires further research.

Patients should receive approximately 5000 IU vitamin A daily either as part of therapeutic foods or a multi-micronutrient formulation. If they are receiving commercially available F-75, F-100 or RUTF or foods made up locally, which comply with WHO specifications (and thus contain adequate vitamin A), they do not require high-dose vitamin A. There is concern regarding adverse effects of combined high-dose plus daily low-dose supplementation with vitamin A. A high-dose vitamin A regime is still advised for clinical signs of vitamin A deficiency, recent measles, and severe diarrhoea or shigellosis.

Most RUTF are lipid-based pastes combining milk powder, electrolytes, and micronutrients and have the same nutrient value as F-100 with the addition of 10–14 mg/100 g of iron. RUTF have now replaced F-100 for nutritional rehabilitation in a number of centres. During administration of RUTF the patient is offered safe drinking water to take at will. Carbohydrate-rich feeds may sometimes cause osmotic diarrhoea in SAM patients many of whom may have villous atrophy. However, RUTF does not increase the incidence of, or worsen, diarrhoea, and is not harmful or less effective than F-100 in children with SAM who have diarrhoea. Nonetheless, close monitoring of pulse and respiration rates are important in view of the possibility of refeeding syndrome with RUTF and F-100. The transition phase from F-75 to rehabilitation with RUTF (or F-100) should proceed over 2–3 days. If the patient does not take the prescribed volume of RUTF then top-up feeds should be given with F-75. Children with SAM who are receiving F-75, F-100, or RUTF should not be given additional zinc as there is adequate amounts in these therapeutic feeds.

Children with SAM presenting with some or severe dehydration but who are not shocked should be rehydrated slowly, either orally or by nasogastric tube with oral rehydration solution (ORS) at 5–10 ml/kg/h up to a maximum of 12 hours. ORS may be ReSoMal (45 mmol/L sodium and 40 mmol/L potassium) or half-strength WHO low-osmolarity ORS (full strength contains 75 mmol/L sodium) with added potassium and glucose. These solutions are not suitable for patients with cholera or profuse watery diarrhoea.

Intravenous (IV) fluids are indicated in SAM when there is circulatory collapse caused by severe dehydration or septic shock and the child is lethargic or unconscious (excluding cardiogenic shock). Septic shock should be considered when there are signs of dehydration but no history of watery diarrhoea, in children with hypothermia or hypoglycaemia, and children with both oedema and signs of dehydration. The rate of IV fluids should be 15 ml/kg/h and suggested fluids include half-strength Darrow's solution + 5% dextrose or Ringer lactate + 5% dextrose. If these are unavailable 0.45% saline + 5% dextrose should be used. If there is no improvement after 1 hour a blood transfusion of 10 ml/kg, should be given over 3 hours.

There are many questions regarding the above suggested regimens:

- What are the most appropriate fluid strategies for SAM patients with severe dehydration and shock, e.g. type, volume, and rate of fluid administration.
- What are the most appropriate methods for monitoring hydration status.
- How can the types of shock – hypovolaemic, septic, and cardiogenic – be differentiated.

Many HIV-infected infants and children present with severe wasting and stunting, and persistent or chronic diarrhoea. Mortality for HIV-infected children with SAM treated in CTC (30%) and nutritional rehabilitation units (31%) is similar.[8] They are three times more likely to die during rehabilitation than uninfected patients. The cause of wasting is complex and includes altered glucose and lipid metabolism, malabsorption, micronutrient deficiency, co-infections, higher rates of food insecurity, and poverty and poor care owing to illness or death of their mother. The main factor affecting outcomes is availability of ARVs and standard of medical care. Management is similar to that of HIV-uninfected children. There are several on-going studies on the pharmokinetics of ARVs in HIV-infected children. Suboptimal dosing is not found when drugs are based on weight band tables compared with using calculations of surface area. ART should be commenced as soon as possible after stabilisation and treatment of sepsis as indicated by return of appetite and resolution of oedema (if present).

The main reason for SAM in infants <6 months of age is suboptimal feeding practices, especially breastfeeding. Many infants may have been low birth weight and have persistent diarrhoea and recurrent sepsis. Mortality is often higher than older children with SAM and there should be a low threshold for admission for IP care and observation. The main priority is establishing or re-establishing exclusive breastfeeding. If an infant is not breast fed, support should be given to the mother or female caregiver to re-lactate or if not possible, to encourage wet nursing (provided, of course, that the person is HIV negative). Supplementary feeds should be considered. For SAM without oedema, these could include expressed breast milk, commercial infant formula, F-75 or diluted F-100. For infants with oedema, infant formula or F-75 should be given as a supplement to breast milk. Infants should not be given undiluted F-100 owing to the high renal solute load and risk of hypernatraemic dehydration. Weight gain should be monitored using WHO growth velocity standards or, in practice, should be >5 g/kg/d for at least 3 consecutive days.

The recommendations in this guideline are planned to be reviewed in 2020 and guidelines revised if necessary.

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AIDS Review

2013 WHO Consolidated guidelines on the use of ARV drugs

The main event of last year was the launch in June of the 2013 World Health Organization's (WHO) *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection*,[1] and this was accompanied by a commentary outlining the 'what, why and how' of the guidance.[2] Since the 2010 guidelines, there have been a series of landmark studies (outlined in previous AIDS updates in *Africa Health*) demonstrating the benefit of early antiretroviral treatment (ART) for prevention of HIV transmission and reduction of individual morbidity and mortality. As the benefits of ART for HIV treatment and prevention have become clearer, HIV programme managers have been faced with a broadening array of options for the use of ARV drugs and require advice about their use at the clinical, operational, and programmatic levels. In response to these needs, WHO updated and combined all its ARV-related guidance into one consolidated guidelines document, which adopts a continuum of care approach from the diagnosis of HIV to the sustained use of ARV drugs and provides clinical, operational, and programmatic guidance.

The key clinical recommendations are as follows.

1. The CD4 count threshold for initiating ART is raised to 500 cells/mm^3 or less for adults, adolescents, and children 5 years or older, while prioritising those with advanced HIV disease and those with CD4 cell counts <350 cells/mm^3.
2. Life-long ART is recommended to pregnant and breastfeeding women with HIV, regardless of CD4 testing and who live in countries with generalised epidemics. This approach (Option B+) was first proposed and implemented in Malawi over 2 years ago, and offers important programmatic and clinical benefits.[3] Using data collected through routine programme supervision, Malawi has shown that Option B+ is well accepted with a 750% increase in the number of pregnant and breastfeeding women starting ART compared with the number starting before this approach was implemented, and with a 12-month retention rate of nearly 80%.[4]
3. ART should be initiated in the following individuals regardless of WHO clinical stage or CD4 cell count: persons with HIV-associated TB (this is unchanged since 2010); persons with HIV and hepatitis B with evidence of severe chronic liver disease; partners with HIV in serodiscordant couples; and children below 5 years of age.
4. A first-line ART regimen of a once daily, fixed-dose combination of tenofovir–lamivudine–efavirenz or tenofovir–emtricitabine–efavirenz is to be used across all populations of children (3 years and older), adolescents, adults, and pregnant women. In children less than 3 years of age, a lopinavir-based regimen is recommended as first-line ART, regardless of exposure to non-nucleoside reverse transcriptase inhibitors. The recommendations for second-line ART in 2013 remain the same as 2010, with heat-stable fixed-dose combinations and atazanavir/ritonavir and lopinavir/ritonavir being the preferred protease inhibitor options.
5. Viral load testing is the preferred approach to monitoring ART response.

Operational recommendations focus on task shifting, decentralisation, integration, promotion of adherence to medication, and retention on therapy.[1,2] Modelling studies predict that implementation of the 2013 guidelines compared with using the 2010 guidelines would prevent 3.5 million new HIV infections and 3 million HIV/AIDS deaths by 2025, but this would cost 10% more than the US$22–24 billion budget needed annually for a full HIV response.

Epidemiology of HIV/AIDS and scale-up of antiretroviral therapy

The latest figures on the HIV/AIDS epidemic and the scale-up of ART in 2012 are provided through the 2013 UNAIDS report[5] and the 2013 WHO/UNICEF/UNAIDS report.[6] By the end of 2012, there were an estimated 35.3 (32.2–38.8) million people living globally with HIV, an increase from previous years as more people are receiving life-saving ART. Adults constitute 32.1 million and children under the age of 15 years 3.3 million of the global total. In 2012, 2.3 (1.9–2.7) million people were newly infected with HIV and 1.6 (1.4–1.9) million people died from HIV/AIDS, both of these numbers being down from previous years.

Sub-Saharan Africa continues to bear the brunt of this epidemic with 25 million adults and children (71% of global total) living with HIV, 1.6 million new HIV infections (70% of global total), and 1.2 million deaths (75% of global total). Of children estimated to be living with HIV, 2.9 million (88%) live in sub-Saharan Africa, with 88% of new HIV infections and 90% of deaths in children occurring in this region. There is considerable variation in the severity of epidemics on the continent, with southern Africa still the most severely affected region, and South Africa's epidemic continuing to be the largest in the world.

By the end of 2012, there were 9.7 million people from low- and middle-income countries on ART, representing 61% of all those who were eligible under the 2010 WHO HIV treatment guidelines, but representing only 34% of the 28.3 million people eligible for ART in 2013. However, with the global progress made in ART scale-up, it is likely that the international community will reach the UN target of providing ART to 15 million people by 2015.

In sub-Saharan Africa there has been notable prog-

ress with 7.5 million people on ART by the end of 2012. Eastern and Southern Africa have done especially well, contributing 6.4 million people on ART to this pool: South Africa's ART programme is the largest in the world with about 2.2 million people on ART. Widespread ART coverage has led to reductions in incidence, morbidity, and mortality from HIV/AIDS in the region. A study in rural South Africa showed that life expectancy in 2003 (the year before ART became available in the public sector) was 49.2 years: by 2011, adult life expectancy had increased to 60.5 years, an 11.3 year gain.[7] Based on standard monetary valuation of life, the survival benefits of ART in this rural community far outweighed the cost of providing ART.

HIV infection as a chronic disease

While ART suppresses viral replication, preserves immune function, and prevents many AIDS-related diseases and complications, it does not fully restore health. HIV-infected persons on ART are at risk of developing several non-AIDS disorders that include cardiovascular disease, cancer, renal and liver disease, osteoporosis, and neuro-cognitive disease.[8] These complications are likely to emerge as a major problem as the present generation of relatively young adults begins to age.

There are several reasons for an excess of these non-AIDS diseases. First, HIV-infected persons have an increased prevalence of traditional risk factors for non-communicable diseases such as smoking, alcohol, and substance abuse. Second, adverse effects of ARV drugs contribute to these complications, although with the newer generation of drugs there is reduced toxicity. Third, in ART-treated adults there is chronic activation of the innate immune system with excessive production of inflammatory markers that in turn are associated with an increased risk of atherosclerosis, coronary artery inflammation, and all-cause mortality. Markers of hypercoagulation are also increased in HIV-infected persons on ART and these are associated with systemic clotting, tissue damage, and disease progression. HIV-mediated breakdown of the integrity of the gut mucosa and chronic translocation of gut microbial products into the systemic circulation all contribute to this chronic inflammatory state. Statins and other anti-inflammatory drugs such as chloroquine, aspirin, and COX-2 inhibitors are all being evaluated for their role in reducing this inflammation. With sub-Saharan Africa being the epicentre of the HIV/AIDS epidemic, healthcare systems will need to transition in the next few years from acute care service provision to a service provision that also focuses on chronic care and an ageing population.

A cure for AIDS

The success of ART has led some to consider whether a cure for AIDS might be possible. Although ART causes a complete or near-complete inhibition of HIV replication, the virus persists in long-lived infected resting T cells which contain integrated, transcriptionally latent HIV-DNA, and these serve as a reservoir for on-going infection.[9] Cure in HIV/AIDS is usually defined as *sterilising* (all latent HIV-infected cells are eliminated) or *functional* (latent HIV persists but viraema is very low or absent without the use of ART). The only reported case of a sterilising cure is the Berlin patient, an HIV-infected man who was given a bone marrow transplant from a naturally HIV-resistant donor for acute myeloid leukaemia.[9] While an interesting observation, an invasive intervention such as bone marrow transplantation could never at present be widely implemented, and so the focus has been on the possibility of a functional cure.

The first report of a functional cure is that of an infant born to an HIV-infected woman who received ART within 30 hours of birth (The Mississippi baby), with the child having undetectable viraemia after ART was discontinued at the age of 18 months.[10] Currently, there is incomplete understanding about what cured the infant, but it is possible that very early treatment might prevent formation of latent reservoirs for HIV, at least in an infant with an immature immune system. For the majority of persons who already have established chronic infection, one way forward is the use of the chromatin-modifying drug 'vorinostat', which activates transcription, increases HIV-RNA production in resting T-cells, and hence converts these latently infected cells into active virus-producing cells which can be killed through a host-immune response.[8,9] Other promising approaches to clearing this reservoir of infected resting T cells are gradually being moved into the clinic as the global effort to identify a cure for AIDS continues.

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Africa HEALTH CPD Challenge
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