

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

Mapping cholera – past and present

Cholera is an ancient and fearful disease. Its onset is abrupt, and the diarrhoea profuse and watery ('rice water stools'). Abdominal cramps and vomiting can also occur. Severe dehydration and sometimes acidosis may result, sometimes leading to shock and death. With prompt recognition and vigorous fluid replacement, the modern mortality should be low.

The research wing of MSF (Médecins sans Frontières) has produced an interesting report from the 2008–2009 cholera epidemic in Harare, Zimbabwe.¹ They explored 'descriptive spatial analysis' (essentially disease mapping) to identify risk factors and risk locations. The data were drawn from registries at Cholera Treatment Centres (CTCs) and Oral Rehydration Points (ORPs) in Harare and the neighbouring Chitungwiza during the epidemic. Cholera was defined clinically according to MSF guidelines, i.e. during an epidemic a case is any patient with three or more liquid stools and/or vomiting over the preceding 24 hours. The time and location of each case were recorded, and complex statistical methods were used to analyse case clustering, temporal evolution, and the proximity of cases to bus stops, markets, etc. The analysis was aided by digital mapping derived from satellite imagery.

Overall, 19 422 people met the case definition of cholera, with the outbreak lasting 46 weeks. There were marked differences in the concentration of cases in different areas of the city and suburbs. A concentration map was presented in the paper, showing that most cases were in the south-west suburbs of Harare. There was a statistically significant correlation between case occurrences and bus stops and markets. The heavily affected south-west areas were also marked by having higher-density populations, and were low-lying areas of land.

The study very elegantly shows what may be expected during an epidemic of a highly infective water-borne diarrhoeal disease such as cholera. Overcrowded, poor areas with inadequate sanitation and piped water were especially affected. Markets were a risk factor, presumably because vendors frequently prepare and sell food in unhygienic conditions. Bus stops often have small 'mini-markets' nearby, again increasing transition risk.

The message for town planners, public health depart-

ments, and health ministries is clear. Cholera outbreaks will continue as long as overcrowding, inadequate sanitation, and contaminated water supplies continue.

This excellent paper has one small omission in my opinion; it fails to reference the first doctor to clinically map a cholera outbreak, and in 1854, for the first time, prove the water-borne transmission of the disease. This was Dr John Snow, an inquisitive London general practitioner who was practising in south London during the third great cholera epidemic of Great Britain in 1854 (previous outbreaks had been in 1832 and 1849, and the 4th and last was yet to come in 1866).² In those days the cholera vibrio was unknown, and the favoured cause of cholera was 'miasma' or transmission by 'bad smells' emanating from the sewage and effluent which filled the London streets. Snow strongly suspected that this was wrong, and that cholera may be transmitted by drinking infected water. He noted that the area in which he worked had two separate water supplies. One (the Lambeth Company) was drawn from a relatively clear area of the River Thames before it reached London, and the other (the Southwark and Vauxhall Company) was taken from the Thames in central London, where the river received direct sewage. Realising that this was by chance a 'natural experiment', Snow mapped out the cholera cases by water supply, and conclusively showed a close association between the polluted water supply and cholera infection.^{2,3}

John Snow did not have satellite maps of London, as did the MSF researchers, but though their work was over 150 years apart, both came to similar conclusions.

Problems with delivering artemisinin combination therapy (ACT)

Uncomplicated malaria in Africa is best treated currently with artemisinin combination therapy (ACT). This is well accepted and backed by the World Health Organization (WHO). However, access to ACT is still variable, and a recent report from Uganda has assessed the extent of the availability problem, and explored the underlying reasons.⁴

Uganda adopted ACT as primary malaria treatment in 2005, with artemether–lumefantrine (AL) as the first line drug. Standard AL contains 20 mg of artemether and 120 mg of lumefantrine per tablet. It is distributed free in Uganda in four different packages depending on the patient's body weight (5–14 kg, 15–24 kg, 25–34 kg and over 35 kg). The drug is taken twice daily for 3 days.

The Ugandan research project examined patterns of malaria treatment at health centres in two separate districts – Bushyeni (in south-west Uganda, population 731 392) and Iganga (in eastern Uganda, population 540 939). Clinical staff, laboratory staff, health officials, and patients were interviewed using a structured questionnaire.

The survey firstly revealed that many clinical posts were unfilled, and that laboratory facilities were scarce. Only 9% of patients studied had a malarial blood film checked (possibly partly because patients were charged for the test), and interestingly, of those tested, only 15% were positive.

All health centres had management guidelines using

AL displayed in consultation rooms. The diagnosis of malaria was made clinically in 88% of health centres, but over 50% did not have a thermometer available. Only 47% of centres had AL in stock for all weight categories, and many of these had experienced recent shortages. Alternatives to AL were also often poorly supplied. When new supplies of drugs arrived at health centres, the news often spread around the community, and attendances increased.

Of the patients diagnosed with malaria, many (57%) had received some treatment beforehand. This was often from private pharmacies, and in 60% of cases was chloroquine monotherapy. At the health centre, only 58% of patients were treated with AL, and 28% were given chloroquine alone.

A number of problems were identified underlying these difficulties. Drug supply to clinics was erratic, and central release of funds for drug purchase was sometimes delayed. Lack of laboratory support led to over-treatment, with further pressure on drug supplies. Even when AL was available, it was not always used, particularly when chloroquine was in stock. Lack of adherence to guidelines was a particular problem in the private sector.

The authors of this important report (which is likely to be applicable to many or most African countries) made several recommendations. Central funding for ACT needs to be adequate and secure, and lines of distribution improved. Laboratory diagnostics (or 'rapid diagnostic' techniques) need to be more widely available. Health Centre clinical staff should have regular educational sessions to ensure national guideline adherence, and this should extend to the private sector. Finally the researchers recommend a phased withdrawal of ineffective anti-malarial drugs, notably chloroquine.

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immunosuppression often suffer with several skin diseases concurrently. The atypical presentation, severity, and clinical spectrum of skin diseases seen in some patients may alert the physician to underlying immunosuppression and the need for HIV testing. Therefore, the skin can be an excellent marker of internal disease and a window to underlying immunosuppressive states. So common is skin disease in association with HIV infection that it has become a widespread belief amongst laypersons in many parts of Africa that those suffering with severe or intractable skin disease may be infected with HIV. This of course is not true for all skin diseases. Certainly, recurrent, severe or atypical herpes zoster, extensive seborrhoeic dermatitis or molluscum contagiosum, and recalcitrant viral warts indicate HIV testing. Some skin diseases such as Kaposi's sarcoma (KS), papular pruritic eruption (PPE) or eosinophilic folliculitis are more specific for HIV infection. And some skin diseases can be indicative of the patient's immune status as they characteristically manifest at certain CD4 counts: chronic herpes simplex infection, eosinophilic folliculitis and molluscum contagiosum occur with advanced immunosuppression whereas herpes zoster is a good example of early HIV-related skin disease. Infectious and inflammatory skin diseases are more common with HIV infection but the incidence of drug reactions and cancer is also increased with HIV immunosuppression.¹

The widespread implementation of anti-retroviral therapy (ART) has led to a significant reduction in the prevalence and severity of HIV immunosuppression-related skin diseases, particularly opportunistic infections. ART has also improved the responses of many HIV-related skin diseases to standard therapies whereas previously they were refractory to treatment. However, skin disease is still common in HIV-infected patients receiving ART but these patients suffer with a different spectrum of dermatological disorders: this includes an increase in acute drug reactions, long-term side effects associated with anti-retrovirals (ARVs), an increased risk of acquiring some skin cancers, and skin disease associated with the phenomenon commonly described as immune reconstitution syndrome (IRS).²

Acute drug reactions with ART

Adverse drug reactions are more common and more severe with HIV infection and the risk of developing them is increased with advancing immunodeficiency. The most common clinical presentations are exanthema (maculopapular rash) followed by urticaria. The prevalence of life-threatening drug reactions such as Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) is also significantly higher with HIV infection. A high incidence of bullous fixed drug eruptions with mucocutaneous involvement has also been described in African populations in association with HIV. However, the incidence of acute drug reactions appears to be even higher in HIV-infected patients after they are started on ART, one study reporting an increase from 8% to 20%.² Drug reactions are often immunologically mediated and this increased incidence may be a consequence of improved immune responses after ART initiation. In addition, polypharmacy and altered

Dermatology Review

What impact has ART had on HIV-related skin diseases?

HIV infection has myriad manifestations. Skin diseases are one of the commonest and earliest manifestations and occur at all stages of HIV infection, their incidence and severity increasing with advancing immunosuppression. Furthermore, patients with advanced HIV

drug metabolism in HIV-infected patients increases the risk of drug interactions. Furthermore, the drugs used for the prophylaxis and treatment of opportunistic infections such as sulfonamides, aminopenicillins and anti-tuberculous drugs are often incriminated, and ARVs themselves are a frequent cause of drug reactions. ARV-related drug reactions generally occur soon after ARV initiation but are usually reversible or treatable. They are commonest with the non-nucleoside reverse transcriptase inhibitors (NNRTIs) nevirapine and efavirenz. The incidence of nevirapine-induced rash ranges from 9% to 32% and its frequency increases with dose increase. It usually occurs within the first 6 weeks of commencing treatment when patients require close monitoring. The rash can range from a mild exanthema to SJS. SJS requires prompt recognition and permanent discontinuation of the drug.³

Long-term adverse effects of ART

ARVs are also associated with long-term mucocutaneous effects such as pigmentary changes, lipodystrophy syndrome, and the retinoid effects of protease inhibitors.³ These appearance-related adverse effects are important because they can lead to decreased adherence and regimen failure.

ARVs can cause metabolic abnormalities leading to changes in fat distribution known as the HIV lipodystrophy syndrome: there is either an accumulation or loss of fat, which can occur together and is usually visibly evident 3 to 24 months after commencing ARVs. Lipoatrophy affects the face, buttocks, and limbs with preservation of muscle mass. It is most commonly associated with the drugs zidovudine and stavudine and it is reported to affect 30% of patients receiving stavudine after 2 years of treatment.⁴ Lipohypertrophy affects the dorsocervical fat pad, the submandibular region, the breasts and abdomen and is strongly associated with protease inhibitors. Lipodystrophy can be managed by changing ARVs: this is more effective for lipoatrophy than lipohypertrophy but any positive effects may take several years. Facial lipoatrophy is particularly cosmetically disfiguring and stigmatising and consequently stavudine is being phased out of ART regimens when possible.

ART-associated mucocutaneous and nail pigmentation occur more commonly in patients with darker skin colours and therefore can be a particular problem in African populations. Zidovudine is commonly incriminated. However, these pigmentary side-effects are usually dose dependent and reversible with dose reduction or drug withdrawal.

Protease inhibitors, particularly indinavir, can produce retinoid-like side-effects such as alopecia, xerosis, cheilitis or paronychia. These can cause discomfort which if significant may lead to ART discontinuation. Approximately 30% of patients receiving indinavir develop two or more of these retinoid-like side-effects which occur early during treatment but resolve when indinavir is stopped.³

Skin cancers after ART

The significant increase in life expectancy associated

with ART has increased the risk of HIV-infected patients acquiring malignancies. Although ARVs are protective of AIDS-defining malignancy such as KS they have had no impact on the incidence of non-AIDS-defining skin cancers such as basal cell carcinomas (BCCs), squamous cell carcinomas (SCCs), and melanomas, which in contrast has increased in HIV-infected patients on ART. However, this has been the case in white-skinned populations and these skin cancers do not appear to be a significant problem in darker-skinned African populations. The exception is anogenital SCCs: co-infection with oncogenic human papilloma virus (HPV) types has significantly increased the risk of developing anogenital SCCs in HIV-infected patients with HPV-related disease such as condylomata acuminata, irrespective of skin colour. Therefore, clinicians should have a low index of suspicion for investigating for anogenital SCC in HIV-infected patients with any signs of anogenital skin disease as ART does not appear to be protective of anogenital SCCs despite the general improvement in cutaneous warts after ART initiation.⁵

Skin disease associated with immune reconstitution syndrome

ARVs can indirectly cause skin disease via inflammatory reactions to microbial and other antigens which occur during immune reconstitution when there is a suppression of the viral load and an increase in the CD4 count. This phenomenon is known as Immune Reconstitution Syndrome (IRS) and is associated with a paradoxical clinical worsening of a known condition or the appearance of a new condition. Estimates suggest that IRS affects 15–25% of adults commenced on ART and it usually occurs within 3 months but can occur up to two years after ART initiation. The skin is the most commonly affected organ accounting for 52–78% of all IRS-associated conditions. A low CD4 count has been identified as a risk factor for IRS events including dermatological events. A large number of skin diseases have been associated with IRS, both infective and non-infective, which may present clinically in an atypical or refractory manner. Mucocutaneous herpes simplex and herpes zoster are the most common IRS-associated dermatological events. Although both molluscum contagiosum and mucocutaneous warts resolve with ART, they can also occur as an IRS phenomenon but with continuing immune restoration they may clear without treatment.^{6–8} Despite a considerable decline in the incidence and mortality rate of HIV-associated KS since the implementation of ART, IRS-associated KS is well-recognised: KS may arise de novo, there may be a relapse of previous disease or a flare-up with enlargement of pre-existing lesions. Although ART is usually successfully continued with regression of KS, some patients do require chemotherapy or radiotherapy. IRS-associated dermatological conditions are rarely severe enough to require discontinuation of ART and can usually be managed with conventional treatment as IRS resolves.⁹

Conclusion

ARVs have had a considerable impact in reducing the burden of skin disease in HIV-infected individuals with

a significant decline in opportunistic and infectious skin diseases in particular. However, they are associated with a range of both short- and long-term effects on the skin. These need to be correctly diagnosed and clearly distinguished as some drug reactions may require immediate withdrawal of ART whereas IRS-related dermatological events can usually be managed without ART interruption. In addition, adherence to ART may be considerably improved if patients understand that some ART-associated skin diseases, such as IRS events, are easily treated or improve with continued ART.

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Clinical Quiz Answers

(See page 72)

Part one

1. (c) and (d). You need to take this story very seriously: headache and constipation are not signs of anxiety in children, not are they the result of bullying. You need to know whether or not the involuntary enuresis has a hidden cause, such as urinary infection or diabetes.

Part two

2. (d). Secondary nocturnal enuresis may well be a serious sign of illness in children, usually not related to anxiety. You must investigate further, and never assume that bedwetting is psychological.

Part three

3. (d) and (e). Answers (a), (b), and (c) are dangerous mistakes to make, as failure to diagnose childhood diabetes (or urinary infection) can lead to loss of life. Any delay in diagnosis of diabetes may lead to ketoacidosis supervening, with its threat of rapid deterioration to death. Most diabetes deaths are caused by cerebral oedema, which is commonest when diabetic ketoacidosis occurs at the start of the illness.

Part four

4. (c) Children newly diagnosed with diabetes need immediate care from a multidisciplinary team that will organise the multiple insulin injections, manage the family's education, and deal with all the practical problems that arise in the care of the child with diabetes. It is not a task to be started in a GP environment.

Part five

5. (a), (b), (c), (d), and (e). All these statements are correct. We should be vigilant and alert to the possibility of diabetes in any child whose behaviour has changed recently, and be wary of assuming that the mother's explanation (in this case bullying at school) is relevant. Missing the onset of diabetes in children, sadly, may result in loss of life.