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

Uncommon stroke syndromes

Hypertension affects about one-quarter of the world's population, and is common in Africa – particularly among urban, diabetic, and obese populations. Its major complication is stroke – or cerebrovascular accident (CVA). Classical hemiplegic stroke syndromes, due to anterior circulation ischaemia or infarction, are well known. The less common posterior or brain-stem stroke syndromes are not as well recognised, but a useful recent review outlines their major presentations.[1]

- **Lateral medullary syndrome of Wallenberg.** This has also been known as 'PICA' or posterior inferior cerebellar artery syndrome. It is the commonest brain-stem stroke, and classically leads to ipsilateral cerebellar weakness and inco-ordination, with contralateral sensory signs – the typical 'dissociated anaesthesia' (loss of pain and temperature sensation with preservation of touch and other sensory modalities). Dysarthria, Homer's syndrome, and lower cranial nerve palsies can also occur.
- **Lateral pontine syndrome.** This is also known as AICA (anterior inferior cerebellar artery) syndrome. There are ipsilateral cerebellar signs, and often V, VII and VIII nerve lesions. Vomiting, ataxia, and nystagmus can also occur.
- **Medial medullary syndrome of Dejerine.** This is actually a paramedial infarct of the medulla, and can cause bilateral weakness, upbeat nystagmus, and hypo-ventilation, with a poor prognosis.
- **Superior cerebellar artery syndrome**. This causes ipsilateral cerebellar symptoms and signs, as well as dysarthria ('pseudobulbar' speech) and sometimes contralateral dissociated anaesthesia. Nausea and vomiting also often occurs.
- **Ventral pontine ('Locked in') syndrome.** Here, there is extensive pontine infarction, with preservation of the supranuclear ocular pathways. Patients are quadriplegic, but have preserved eye movements. Most other cranial nerve function is lost, but the patients are conscious and hearing is either preserved or later recovers. Communication is therefore only possible by eye movements, hence the name 'locked in'.
- **Ondine's syndrome ('Ondine's curse').** Here, diffuse brain-stem ischaemia interferes with the control of automatic respiration. Ventilation is normal when the patient is awake, but there is complete failure when asleep – usually requiring assisted ventilation. It is a very rare, but naturally dramatic, stroke syndrome.

All of the above are not easy to diagnose, but in areas where stroke is common, they will all occasionally occur. Doctors need to be aware of the possibility of uncommon stroke syndromes in any patient with acute neurological deficit which does not fit with a standard hemiplegic CVA.

Amoebic liver abscess and aspiration

A recent edition of the journal *Tropical Doctor* contained a very useful article on the subject of aspiration of amoebic liver abscesses.[2] The authors, and the patients studied, were from India, but the results are highly relevant to African medical practice. Generally accepted teaching is that metronidazole therapy is sufficient for the vast majority of amoebic liver abscesses. Aspiration should be considered if the abscess is likely to rupture, if metronidazole treatment fails, or if the abscess is very large. But what constitutes 'large'? Most agree that abscesses less than 5 cm in diameter can be medically treated, and those over 10 cm may need aspiration. Uncertainty exists with abscesses between 5 and 10 cm in diameter.

The Indian workers carried out a randomised prospective trial which involved 57 adults with newly presenting solitary right lobe abscesses of 5–10 cm diameter. The patients were randomised to either metronidazole alone (n = 29) or metronidazole plus ultrasound-guided abscess aspiration (n = 28). There were no deaths in either group, and no significant differences in treatment failure, complications, and duration of hospitalisation. The aspiration group had resolution of pain and fever a little sooner than the non-aspiration group, but this was not statistically significant.

This is a very useful study, confirming common African experience that metronidazole alone is, in the majority of cases, quite sufficient for amoebic liver abscess therapy. Assuming ultrasound is available, aspiration can be considered only in abscesses over 10 cm in diameter (unless there are other clinical indications).

Finally, the results of this study also raise an interesting question. Should a similar trial be conducted on abscesses over 10 cm in diameter – a size that may indicate aspiration? We will probably never know the answer to this question, as collecting sufficient numbers of abscesses of this diameter may be difficult.

We should continue to be grateful for metronidazole in the treament of invasive amoebiasis. As a medical student in Kenya in 1970, I can remember chloroquine with emetine as standard treatment – toxic and relatively ineffective. Within a few years metronidazole was standard treatment, and countless lives have been saved over the ensuing decades.

Burning feet syndrome

A recently published historical review has looked at 'Burning feet syndrome',[3] an old tropical syndrome of painful neuropathy which has modern counterparts. The condition refers to painful neuropathic dysaesthesia of the feet and lower legs, often coming on relatively quickly in conditions of poverty and poor nutrition. The pain is often described as 'tingling', 'shooting', or 'burning' (hence the syndrome's name), and is typically worse at night. Outbreaks have been described in the past in poorly nourished West Indian plantation workers (1887), inmates of Zomba Jail in Nyasaland (1911), and

Chinese migrants to Malaya (1940). Perhaps the best descriptions were made among Allied prisoners of the Japanese (1942–1945), particularly in those labouring on the Thai-Burma ('Death') Railway.

Interestingly, the paper includes original descriptions of 54 Far East POWs (prisoners of war) with burning feet (described by one of the authors – a POW army doctor at the time) collected between 1942 and 1943. The symptoms were very typical, and often appeared precipitated by an acute infection such as malaria or dysentery, though there was always a background of severe malnutrition. Uniquely, this study recorded physical signs, and interestingly only 20% had signs of sensory loss. These outbreaks were almost certainly nutritional in origin, probably related to B vitamin deficiency. Deficiencies of nicotinic acid, thiamine, pyridoxine, and riboflavin have all been implicated, and it may be that multiple deficiencies contribute to the syndrome.

Nowadays, 'burning feet' is seen most commonly in diabetes, where the description is virtually identical with the syndrome of painful diabetic sensory neuropathy. Here the origin is of course metabolic rather than nutritional, but the end result of disabling dysaesthetic nocturnal pain is the same. Some patients with other causes of sensory neuropathy may occasionally also present with a 'burning feet' syndrome – including with alcohol-related neuropathy, and HIV infection.

This interesting report demonstrates that apparently 'lost' tropical syndromes from the past can have strikingly similar modern counterparts, albeit of different aetiology.

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STI Review

Surveillance

The World Health Organization (WHO) estimates that a million people acquire a sexually transmitted infection (STI), including HIV, every day. There are more than 30 bacterial, viral, and parasitic pathogens responsible for these infections. Each year, almost 500 million curable STIs occur, including those due to *Treponema pallidum* (syphilis), *Neisseria gonorrhoeae*, *Chlamydia trachomatis,* and *Trichomonas vaginalis*. The largest disease burden is found in sub-Saharan Africa, Latin America, and the Caribbean, followed by the Western Pacific Region. Millions of viral STI infections also occur annually, attributed mainly to HIV, herpes simplex viruses (HSVs), human papillomaviruses, and hepatitis B virus.

WHO has updated its guidelines for surveillance of STIs.[1] The epidemiology of STIs, including HIV, has changed and new technologies have altered how infections can be monitored. The new guidelines build on the earlier 1999 edition. The document offers ministries of health and other health policy makers a framework for implementing STI surveillance systems that generate consistent and reliable data. It focuses on the timely collection, analysis, and use of data to understand the disease burden and use of services. For example, controlling genital ulcerative disease, including syphilis, requires high quality data to guide programmes.

The guidelines include updated information on the prevalence of specific STIs and their distribution. It also explains surveillance systems and their components, along with STI assessment and monitoring. Determining which STIs should be under surveillance can be aided by focusing on the aetiology of an STI, and syndromes. The guidelines cover syndromic management, and the role of laboratories. Although there are now more rapid diagnostic tests available, laboratories are necessary for accurate surveillance of diseases and microbial resistance. Finally, the document discusses the dissemination and communication of surveillance results, along with evaluation of surveillance systems.

Laboratory testing

WHO has also updated its manual on laboratory diagnosis of STIs.[2] Edited by global experts in STI research, this update of the 1999 manual explains the principles of laboratory tests in the context of screening and diagnostic approaches. It also updates antimicrobial susceptibility testing. As mentioned in the new guidelines for STI surveillance cited above, this manual explains the advances in diagnostic testing, including nucleic acid amplification and rapid point-of-care tests. There are several reasons for STI testing, including surveillance, validation of syndromic management algorithms, quality assurance, diagnosis of persons with signs and symptoms of possible STI, screening of asymptomatic at-risk persons, and antimicrobial susceptibility testing. The reason for the test may affect the choice of test. This revised version includes new chapters on a number of topics, including diagnostic techniques for *Mycoplasma genitalium* and laboratory quality management. There is excellent, detailed information provided in separate chapters on each disease, which includes specimen collection, transport, and laboratory testing. Annexes focus on equipment, tests, media, reagents, and stains. While the primary audience for this manual is microbiologists and medical technologists, it is extremely useful to all those working in STI prevention and treatment, including programme administrators and medical staff. The information provided can help national programmes identify and procure the appropriate diagnostic tests for local settings.

Rapid tests

Rapid diagnostic tests (RDTs) can facilitate diagnosing STIs in the absence of laboratory services. However, it is important to distinguish between rapid tests and point-of-care (POC) tests. Rapid tests generally have been defined as tests that give a result in <30 minutes. POC tests, on the other hand, are defined as tests that are simple and can be performed at all healthcare settings, especially at primary healthcare settings, with minimal training and little or no equipment. For example, Gram stained microscopy, wet prep, pH, the amine or Whiff test, and the rapid plasma reagin (RPR) or Venereal Diseases Research Laboratory (VDRL) tests are considered

rapid tests and can provide immediate results to guide treatment. However, some of these tests depend on electricity to operate equipment such as a centrifuge or microscope, which means they cannot be used at POC settings without electricity. As the WHO laboratory manual explains, this is the case for the RPR test for syphilis. While it can be performed in less than 10 minutes, testing is often batched which prevents its use for immediate individual testing and treatment. In addition, the RPR reagent requires refrigeration, a centrifuge is needed to separate serum from whole blood, and a rotator is required for mixing the reaction. Hence the RPR, in spite of its name, is neither used as a rapid test nor could it be considered a POC test as it cannot be performed in settings where there is no electricity.

POC tests offer quick results and same-visit treatment. Such tests can increase screening, improve the accuracy of syndromic management and reduce loss to follow-up. A recent study in South Africa affirms that syndromic STI diagnosis that depends on vaginal discharge is often a poor predictor of laboratory-diagnosed infection.[3] Women at high risk for STI infection, but HIV-uninfected, were followed for 24 months. Symptoms of STIs were recorded and laboratory testing for STI pathogens was conducted every 6 months. Only 12.3% (25 of 204 women) who had a laboratory-diagnosed, discharge-causing STI had clinically evident discharge. In this setting, almost 88% of STIs in this group of high-risk women would have been left untreated in a syndromic management setting. Effective POC testing would greatly improve diagnosis in this context.

An online survey of 256 STI experts and professionals (STI-related international conference attendees and US STD clinicians) found that *Chlamydia trachomatis* is the top priority for a new POC test, followed by a test for early HIV seroconversion and a syphilis POC test that identifies current infection.[4] The most important attribute of any POC test was a sensitivity of 90–99%, followed by a cost of no more than US$20. The time frame required was identified as a major barrier to current use of POC STI tests.

The field of rapid tests changes quickly. There are now rapid POC treponemal (syphilis) tests that are highly sensitive (85–99%) and specific (93–100%). They can be used with whole blood obtained by finger pricks, stored at room temperature for up to 18 months, require minimal training, and yield results in 15–20 minutes; but they cannot differentiate between current and past infection. Accurate immunochromatographic assays for HIV, hepatitis C and syphilis now allow self-testing.[5] However, rapid tests for gonococcal, chlamydial, and trichomonas infections are still relatively expensive, technically more difficult to perform, and of lower sensitivity, so are not yet available in low-resource settings.[6] As the technology of rapid tests improves, the opportunities for testing will greatly improve care, partner services, and surveillance.

However, as global experience with preventing and treating maternal syphilis shows, the existence of effective POC tests is not sufficient to prevent illness. It has been summarised that the prioritisation of global health initiatives depends on leadership, communication, political contexts, and issues such as disease severity, availability of effective interventions, and existence of credible indicators of disease.[7] There are clear data showing that maternal syphilis is common (more common than HIV in pregnant women), easily tested, and effectively treated in pregnancy. Therefore, the problem is largely the lack of political will to address the issue. Given the infrastructure and resources focused on HIV, and the fact that maternal syphilis greatly increases the risk of mother-to-child HIV transmission, WHO recently updated its congenital syphilis strategy to combine the prevention of mother-to-child transmission of HIV with syphilis prevention. Part of this joint focus involves the development of a dual rapid test for syphilis and HIV. The experience of this combined approach to HIV–maternal syphilis prevention and treatment will be informative to other STI programmes. It is important that health systems be poised to take advantage of new diagnostic technologies with appropriate political, social and economic support.[8]

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Paediatrics Review

Vitamin A supplementation for infants and children

World Health Organization (WHO) data on the prevalence of vitamin A (Vit A) deficiency in the period 1995–2005 in 64 countries found that globally 7.8% of pregnant women had night blindness and 15.3% deficient serum retinol concentrations (<0.70 µmol/l, subclinical Vit A deficiency).[1] Severe deficiency is <0.35 µmol/l. Maternal night blindness is associated with increased frequency of low birthweight and infant mortality. However, trials of Vit A supplementation of women in pregnancy have not demonstrated significant benefit for their infants.[1] This might depend on the woman's current Vit A status.

Global data for children over 5 years from 99 countries found that 0.9% had night blindness and 33.3% subclinical deficiency.[1] The highest prevalence was in

Africa, 2.1% and 41.6%, respectively, and southeast Asia. The incidence of xeropthalmia has declined, probably because of Vit A supplementation programmes.

There is limited information on the value of supplementation of neonates with Vit A. Seven randomised controlled trials (RCTs) of supplementation of term infants in developing countries were analysed.[2] Data from three studies demonstrated a statistically significant effect on risk of mortality at 6 months of age in the Vit A groups (95% confidence interval (CI) 0.68–0.99). Due to limited data on this age group for cause-specific mortality and morbidity, Vit A deficiency, anaemia and adverse effects, there is presently no policy on supplementation. Four trials involving 100 000 infants are ongoing which hopefully will answer these questions.

There is considerable information on supplementation of children aged between 6 months and 5 years. It is estimated that 2.3% of total deaths of children in this age group are caused by Vit A deficiency.[1] In a recent systematic review and meta-analysis of RCTs of Vit A supplementation of children aged between 6 months and 5 years, 43 trials with about 215 633 children were included.[3] Seventeen trials comprising 194 483 children reported a 24% reduction in all-cause mortality (risk ratio (RR): 0.76, 95% CI 0.69–0.83). Seven trials reported a 28% reduction in mortality associated with diarrhoea. Vit A supplementation was associated with reduced incidence of diarrhoea, measles, prevalence of night blindness, and xerophthalmia. It was concluded that further RCTs in this age group are not required.

In 2011, WHO revised guidelines for administration of Vit A to children aged between 6 months and 5 years and reviewed the evidence for adverse effects.[4] There was strong evidence for reduction in all-cause mortality but for all other critical outcomes evidence is moderate to low. Available evidence for outcome in HIV-positive children was moderate for all-cause mortality. Vit A capsules are well tolerated with an incidence of side-effects reported in 3.7% – headache, nausea, vomiting and diarrhoea, mostly disappearing within 24 hours of administration. It is estimated that a dose of Vit A every 4 to 6 months, when stored in the liver and mobilised as required over an extended period of time, is adequate. The exact interval between doses depends on Vit A content of the diet and rate of utilisation in the body.

The value of regular supplementation of children aged between 6 months and 5 years with Vit A seemed settled until a recent publication of the Deworming and Enhanced Vitamin A supplementation (DEVTA) trial in rural Uttar Pradesh, north India.[5] The trial involved 2 million pre-school children overall (1 million at any one time) which is larger than all other similar trials combined. The primary aim was to assess the effect of a standard periodic treatment regimen on overall mortality between 1 and 6 years of age. The trial has attracted controversy for a number of reasons. Firstly, the trial was completed in 2006 and results were presented at a meeting in Turkey in 2007 and were reviewed at a meeting in Oxford in 2008, following which it underwent detailed re-analysis. Yet it was not published until 2013. Secondly, the results differ from most other similar trials.

It was a cluster-randomised trial in a defined catchment area of 8338 state-staffed anganwadi child care centres (anganwadi means courtyard). Groups of four neighbouring blocks (clusters) were randomised to: (a) retinol capsules, 200 000 IU, 6 monthly; (b) albendazole, 400 mg tablets every 6 months; (c) both; (d) neither (open control), usual care, no placebo. Over the 5 years of the study, eleven 6-monthly mass treatment days for all children aged between 6 months and 6 years were undertaken. In the second half of the study one centre per block was randomly selected and visited unannounced by a study team 1 to 5 months after any trial Vit A administration to sample blood retinol levels.

Overall compliancy was estimated to be around 86%. Mean plasma retinol concentration was 0.72 µmol/l (SE 0.01) in the Vit A group vs. 0.62 µmol/l (SE0.01) in controls, which was an increase of 16% in Vit A level ($p<0.00001$). The prevalence of severe deficiency (<0.35 µmol/l) was halved (6% vs. 13%), as was the prevalence of Bitot's spots (1.4% vs. 3.5%). Deaths per AWC were 3.01 vs. 3.15, with a mortality ratio of 0.95, 95% CI 0.89-1.03 ($p=0.22$). Absolute risk of death was 2.5% vs. 2.6% for Vit A and control groups, respectively. There was no significant difference in effect for age, sex, cause of death, diarrhoea, or measles.

The authors acknowledge that the mortality reduction in this study is not as great as previous trials (20–30%) but it is not zero! Based on their study they suggest that where Vit A deficiency is widespread but xerophthalmia is rare, reduction of child mortality due to Vit A supplementation should be around 5–15%, i.e. a quarter of that in previous studies.

Results of the albendazole trial found that in children 1–6 years, the risk of dying was 2.5% in the albendazole group vs. 2.6% in controls.[6] The authors conclude that where worm infestation in pre-school children is light there is little effect of regular deworming on mortality.

The comment on the DEVTA Vit A trial calculated that the estimated reduction in mortality was 4% (95% CI 11% reduction to 3% increase).[7] In the correspondence some of the letters were highly critical of the study but these criticisms were strongly refuted by the authors.[8] In the long run, this study, although very large, is unlikely to influence vitamin A supplementary programmes in the near future.

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