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

Diagnosing typhoid fever

The Widal test is one of the oldest diagnostic serological tests, used to confirm a clinical suspicion of typhoid fever. It is still in widespread use for the diagnosis of typhoid, but there have for many years been doubts about its accuracy, compared with the 'gold standard' of positive blood culture. However, although culturing *Salmonella typhi* in the blood is the ideal confirmatory test, not all tropical laboratories have this facility, and a negative blood culture may not always exclude typhoid.

The Widal test detects serological antibodies to lipopolysaccharides on the *Salmonella* bacterium which are either somatic ('O' antigens) or flagella ('H' antigens). Ideally the test should be done on paired sera – an initial sample at presentation, and a second 'convalescent serum' done 7 to 14 days later (assuming the patient survives). Serial dilutions of the serum samples are made, and latex particles impregnated with the O or H antigens are added, and the mixture incubated. If the patient's serum contains antibodies, an agglutination reaction occurs, and the dilution at which this happens is recorded. The result is usually reported as the reciprocal of the dilution at which agglutination takes place; thus if it is at a 1 in 80 dilution, the result would be '80'.

There are a number of potential problems with the Widal test. The reagents need to be stored at low temperature, and there is a lack of standardisation of the antigens. Cross reactivity can occur with other *Salmonella* species, and also false positive results can occur in other infections (such as malaria, meningitis, and tuberculosis).

An interesting new study from the Democratic Republic of Congo (DRC) has examined in detail the accuracy of the Widal test in suspected typhoid.[1] This was prompted by a surprising recent increase in notified cases (118 727 in 2009), with an unexpectedly low mortality rate of only 0.03%. Both these figures suggest an over-diagnosis of typhoid. In view of this, on-site surveys of diagnostic methods were carried out in Kinshasa, DRC; as well as external quality assessments (EQA) of the Widal test, and comparative microbiological blood cultures.

A total of 536 healthcare facilities in Kinshasa province were surveyed. Most (62%) diagnosed typhoid by clinical features and Widal test, though availability of the Widal test was variable. Only 8 (1.5%) centres could perform blood cultures. The external assessment of the Widal test revealed variability of reagents and methods (8 different kits were in use), as well as some cold-chain problems. Paired sera were not frequently tested. These problems frequently led to misleading results – of three samples of sera that were externally checked, the local results were correct in 27%, 66%, and 3% of cases respectively. A blood culture survey of 3820 patients suspected of typhoid fever, showed a positive culture in only 2.4% of cases. Finally, a survey of prescribing doctors and nurse showed widespread trust in the Widal test for the diagnosis of typhoid.

These results confirm over-diagnosis of typhoid in the DRC, largely due to over-reliance on the Widal test. The situation is very likely to be similar in other areas of Africa. Though the Widal test has been in use for over 100 years, it has rarely been critically evaluated, especially in an African 'field' situation. The use of a second 'convalescent' test is ideal, but is of course rarely possible in an African situation. Assuming, therefore, that only one Widal result is available in a patient with suspected typhoid, this useful research from DRC suggests that results must be interpreted carefully.

NCDs – more action needed

It is widely recognised that non-communicable diseases (NCDs) are a major threat (if not **the** major threat) to present and future health. The spectrum of NCDs is wide, but particularly important conditions are:

- diabetes (especially type 2)
- cardiovascular disease
- stroke
- asthma
- chronic obstructive pulmonary disease (COPD)
- hypertension
- epilepsy.

Many of these (notably type 2 diabetes, stroke, hypertension, and cardiovascular disease) greatly increase in prevalence with increased age. Thus, extended life expectancy will necessarily increase the number of patients with NCDs. Global demographic changes include increased life expectancy,[2] and although this is occurring most noticeably and rapidly in developed countries, it is also visible in poor countries including wide parts of Africa.

Diabetes is a particularly high-profile NCD which has perhaps been most clearly associated with population ageing, as well as Westernisation (demographic transition). The type 2 variety has been described as an 'epidemic' or 'pandemic' for some time now,[3] and future prevalence predictions worldwide are massive. Already, the disease consumes at least 10% of the healthcare budgets of most countries – both in Europe and Africa. Respected experts from the USA and Australia have recently described the situation as needing 'urgent attention'.

But where is this urgent action to come from – for diabetes in particular and for NCDs in general? The answer is unfortunately unclear. Despite widespread publicity and acceptance of the NCD problem, no clear worldwide plans or initiatives have emerged. The best

hope may be an integrated primary care approach,[4] but clear leadership (and realistic allocation of resources) is needed. Front-line doctors everywhere understand the huge and increasing burden of NCDs, but it is time that governments, global bodies such as the World Health Organization (WHO) and the United Nations (UN), as well as research funding sources; backed NCD care and research more realistically.

Hepatitis E virus

Most general doctors know very little about hepatitis E virus (HEV), but it is now globally the commonest cause of acute viral hepatitis,[5] and it is common in Africa, although of course diagnostic facilities are not commonly available.

The virus was first discovered in Afghanistan, during the Russian occupation in the 1980s. An unexplained outbreak of hepatitis occurred in a military camp, and the new virus was detected by electron microscopy. Serological tests for diagnosis are now available.

In developing countries, HEV occurs both sporadically and epidemiologically. In Africa, it is usually the HEV-2 strain which is found, and an especially large epidemic occurred recently in Uganda.[6] Infection is usually water-borne, but can be transmitted vertically, or from blood transfusions. Those affected are usually young adults (15–35 years) and for some reason men are more prone to infection.

HEV can be more severe if patients with pre-existing liver disease are infected, though this is more common with HEV-1 and HEV-3 infection. Chronic infection can occur, and also curious neurological complications may be seen – including for example Bell's Palsy or Guillain–Barré Syndrome.

Though anti-viral treatment can be effective, most attacks are self-limiting, and as already mentioned, serological confirmation in Africa is rarely available. However, the infection is now numerically important, and diagnostic facilities are likely to develop and spread over the next few years.

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STI Review

Control of sexually transmitted infections

Unsafe sex ranks in the top five causes of the global burden of disease. The interventions that exist to prevent and control sexually transmitted infections (STIs) operate at different levels. Diagnostic tests, vaccines, and antimicrobial agents can be very effective at the individual level. However, there has been less success in prevention and control at the partnership, sexual network, and population levels. Focusing on three interventions – strengthening partner notification, implementing antenatal syphilis screening, and delivering STI prevention vaccines – has been proposed as a realistic strategy for scaling up STI control.[1]

Partner notification

Notifying partners of possible STIs improves identification of cases, helps prevent reinfection, and can interrupt continued transmission within a larger sexual network. This is most effectively done through index patients referring their partners for treatment. This is often the only realistic, affordable option. However, patients need to be told more than simply to refer their partners for treatment. Randomised trials have shown that patients infected with gonorrhoea or chlamydia who are given infection-specific written information for their partner(s), and/or receive additional counselling, are up to 50% less likely to have repeat infections on follow-up compared with those who received simple partner referral.[1] To facilitate partner notification, healthcare providers need clinical guidelines that include recommendations about appropriate contact periods, advice, follow-up, and protection of patient confidentiality. Expedited partner therapy, which involves patients delivering treatment to their partners, also could be used more effectively, but requires clear diagnostic and treatment protocols.

The use of information technology has the potential to significantly improve many aspects of STI control, especially partner notification.[2] Websites have been set up that provide information on STIs and which allow individuals to contact their partners anonymously through email or short text messages. Information technology is also facilitating STI services through computer-assisted self-interviewing, electronic medical records, decision support software (helping facilitate diagnosis and treatment), computer-based counselling, short text messaging to improve screening and appointment attendance, and web-based STI testing. Clearly, these innovations require reliable technological infrastructure – something not yet widely available in sub-Saharan Africa – but the potential is significant.

Antenatal syphilis screening

Antenatal syphilis is at least as important a cause of foetal and perinatal mortality as HIV infection. While many countries have antenatal syphilis screening policies, the implementation of programmes is problematic. In some areas with high syphilis prevalence, like Africa, many women do not receive any antenatal care, or do so after 20 weeks gestation. It is estimated that fewer than one in eight women receives syphilis testing at any time during pregnancy.[3] While rapid syphilis tests have been available for many years, effective antenatal screening depends on several factors. In addition to point-of-care tests and antibiotics, screening depends on early antenatal clinic attendance, decentralisation and same-day

treatment, partner notification and treatment, third trimester retesting, and strengthening of health services to provides supplies, training and monitoring.[1]

Studies show the benefits of multiple point-of-care testing of pregnant women. A study in Uganda and Zambia found that integrating rapid syphilis testing with existing prevention of mother-to-child transmission of HIV programmes increases screening and treatment of syphilis.[3] The introduction of rapid syphilis testing also led to improved laboratory quality assurance systems, training of health workers on congenital syphilis prevention, quality assurance and point-of-care testing, and supply chains. Integrating the supply chains reduced days of stock-out of HIV test kits, and did not negatively affect HIV services. A study in rural India found that triple testing of pregnant women for HIV, syphilis, and hepatitis B infection was both feasible and acceptable to women.[4]

The World Health Organization has formed a partnership with the London School of Hygiene and Tropical Medicine, the Bill and Melinda Gates Foundation, Save the Children, and the US Centers for Disease Control and Prevention to raise awareness of the need to eliminate congenital syphilis and provide support for prevention and treatment. Within Africa, WHO, the Mozambique National Health Institute (INS), and Health Alliance International (HAI) are jointly conducting a study in central Mozambique to quantify the burden of congenital syphilis, evaluate the effectiveness of syphilis treatment administered at different times during pregnancy, and characterise women not screened for syphilis in pregnancy. As of May 2012, over 3000 women have been enrolled in the first 2 months of the study.[5]

Vaccines against STIs

Vaccines can protect individuals, and, if delivered as part of a comprehensive programme, can have benefits at the population level.[1] Currently, there are effective vaccines available against hepatitis B, which can lead to liver cancer, and against human papilloma virus (HPV), which is associated with precancerous lesions of the cervix. The WHO has recommended universal hepatitis B vaccination of infants (the only strategy that can eliminate sexual transmission of hepatitis B) since 1992 and is now included in the immunisation protocols of 162 countries. Chronic infection has been reduced in those countries. HPV vaccine is recommended for girls aged 11 to 14, but reaching these girls, especially those not in school, is difficult. The vaccine is new and expensive, which has limited its adoption. However, studies are beginning to show other benefits of HPV vaccination. A study from Costa Rica of the vaccine Cervarix, which prevents cervical disease caused by HPV types 16 and 18, found that it is protective against anal HPV infection in women as well.[6] While anal cancer is very rare, women are twice as likely as men to develop the disease, and women with cervical neoplasia are at greater risk for anal HPV infection. Until HPV vaccination is included in national childhood vaccination protocols, it will have limited impact.

Syndromic management

While syndromic management remains one of the most cost-effective and successful ways to manage bacterial STIs in Africa, several factors challenge its success.[7] Most significantly, syndromic management has little impact on asymptomatic infections. Disease surveillance and periodic revision of protocols, as necessary, are crucial. In some cases protocols can be simplified. A study of bacterial vaginosis clinical diagnosis in India determined that using two clinical criteria, especially high pH (>4.5) and amine odour tests, was as accurate as use of the standard Amsel criteria.[8] More widespread use of rapid point-of-care tests for syphilis could supplement syndromic management, and similar tests are needed to detect gonorrhoea and chlamydial infections. The increase of antibiotic-resistant gonorrhoea in Africa is of significant concern.

There are new technologies being developed, such as duplex antigen/antibody tests for use with STI syndromic management, and rapid lateral flow tests that can be used on oral fluids instead of blood for detection of HIV, syphilis, and hepatitis B and C.[9] There are mechanical test result readers that can accurately interpret test results, as well as communicate with a central database documenting results and tracking supplies. Simple isothermal nucleic acid amplification tests can detect bacterial and viral STIs within 15–60 minutes using equipment that can be powered by battery or solar energy. New specific nucleic acid amplification testing devices for tuberculosis will soon be able to test for chlamydia and gonorrhoea. New technology is not a panacea, however. In addition to the issues of cost, quality control, and implementation, in many countries STI services are not accessible to many high-risk groups, including commercial sex worker and MSM (men who have sex with men) populations.

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Paediatrics Review

Reduction in postnatal HIV infection and mortality in infants

For pregnant HIV-positive women in low-income countries who are offered and co-operate with antenatal and postnatal HIV prophylaxis, HIV infection of their infants can be reduced to less than 2%. Now, the main emphasis is prevention of HIV infection through breast milk which may account for up to 40% of HIV infection in infants in sub-Saharan Africa.[1]

The Mma Bana Study in Botswana, undertaken between 2006 and 2008, assigned 560 HIV-positive pregnant women with CD4 cell counts >200/µL to receive abacavir+azidothymidine (AZT)+lamivudine (3TC) or lopinavir/ritonavir+AZT+3TC from 26 to 34 weeks gestation to weaning at 6 months postpartum.[2] One hundred and seventy (170) women with CD4 counts<200 /µL or AIDS received nevirapine (NVP)+AZT+3TC (observational group). Newborn infants received single dose (sd) NVP+AZT for 4 weeks. Virological suppression (<400 copies per ml) was 92–96% in the three groups at delivery and 92–95% through exclusive breastfeeding (BF) to 6 months. At 6 months, 8 of 709 infants (1.1%) were HIV infected, 6 were infected *in utero* and 2 during BF. All HAART (highly active antiretroviral therapy) regimens from pregnancy to 6 months postpartum resulted in high rates of virological suppression.

Between 2005 and 2008 the Kesho Bora Study Group recruited 824 pregnant women at 28 to 36 weeks' gestation with WHO stage 1–3 HIV infection and CD4 cells 200–500/µL in five sites in Burkino Faso, Kenya, and South Africa.[3] They received: (a) AZT+3TC+lopinavir/ritonavir until cessation of BF to a maximum of 6.5 months postpartum, or (b) AZT+NVP through delivery. In December 2006, AZT+3TC for 1 week postpartum was added. All infants received sd NVP at birth and from December 2006, AZT for 1 week after birth. At 6 weeks, the cumulative rate of HIV transmission was 3.3% in Group a compared with 5.0% in Group b, and at 12 months 5.4% in Group a and 9.5% in Group b (p=0.029). Cumulative rate of HIV transmission or death at 12 months was 10.2% in Group (a) compared with 16% in Group b (p=0.017). In mothers who intended to BF the cumulative rate of HIV infection at 12 months was 5.6% in Group a)and 10.7 in Group b (p=0.02). Triple therapy during pregnancy and BF was superior to AZT+NVP in reducing HIV transmission.

The Six Week Extended Dose Nevirapine (SWEN) trial undertaken in Ethiopia, India, and Uganda initially compared, (a) extended dose NVP through 6 weeks, with b sd NVP in BF infants.[4] The most recent report describes endpoints through 12 months. HIV transmission was 8.9% in Group (a) compared with 10.4% in Group b, which was not significant. However, mortality at 12 months was half in Group a (risk ratio :0.53, 95% CI 0.32-0.85). The impact in Group a)was highest for infants of mothers with CD4 counts >350/µL. It was concluded that for populations with limited access to HAART, NVP during BF increased HIV-free survival especially for less immunosuppressed mothers.

The recent phase 3 report of the randomised, double-blind, placebo-controlled HPTN (HIV Prevention Trials Network) 046 trial assessed the benefit of extension of once-daily NVP in infants exposed to HIV during exclusive BF.[5] The mothers were recruited from antenatal clinics in South Africa, Tanzania, Uganda, and Zimbabwe and had had standard PMTCT (Preventing Mother-to-Child Transmission) care. Following receipt of NVP from birth to 6 weeks, infants without HIV infection within 21 days of randomisation received: a extended NVP (n 769) or b placebo (n 753) until 6 months or BF ceased. The study was undertaken in the period 2008–2010. In Group a 1.1% of infants developed HIV infection, compared with 2.4% in Group b, equating to 54% reduction in transmission (p=0.049); 16% of Group a and 15% of Group b had serious adverse events but overall mortality rates did not differ between the two groups. Most infant deaths occurred after 6 months and cessation of BF. At randomisation, one-third of mothers were on HAART but this did not differ between the two groups. Extended NVP demonstrated no additional benefit compared with 6 week NVP in infants born to women receiving HAART. This supports current WHO recommendations of only 6 week infant prophylaxis for mothers who are on HAART. Further evidence of the value of NVP prophylaxis during 6 month exclusive BF period was provided by the trial, especially for women with CD4 counts >350/µL.

The Breastfeeding, Anteretrovirals, and Nutrition (BAN) study was undertaken in Lilongwe, Malawi and was reported in 2010[6] and 2012.[7] Women who had been pregnant for 30 weeks or less with a CD4 count of ≥250/µL were recruited between 2004 and 2010. All women in labour received sd NVP and AZT+3TC for 7 days. They were assigned to three groups: (a) mothers (n=849)– AZT+3TC+NVP for 28 weeks (in 2005/2006 NVP was replaced by a protease inhibitor; (b) infants (n=852)– NVP for 28 weeks. Mothers were advised to BF exclusively for 24 weeks and then wean their infants between 24 and 28 weeks. All treatment stopped after mothers reported cessation of BF or at 28 weeks. Mother–infant pairs in Group c, the control group (n=668), received no treatment after 7 days postpartum. However, in 2008 the control group was stopped because of a significantly high HIV transmission rate. Self-reported exclusive BF was high up to 24 weeks in all groups (88–98%). Between 2 and 48 weeks, 93 infants became HIV-infected, 28 (30%) after completion of intervention at 28 weeks and 14 over 6 weeks after reported cessation of BF. How the latter infants became infected is not clear. Cumulative risk of HIV transmission was significantly higher in the control group (7%) compared with Group a (4%) and b (4%). Adverse events, e.g. diarrhoea, malaria, growth faltering, TB, and death, all occurred significantly more frequently after 28 weeks (all unrelated to group). This study demonstrated that both infant and maternal HIV prophylaxis is effective in reducing HIV transmission. As morbidity and mortality increases after cessation of BF after 28 weeks, it was concluded that continued BF with prophylaxis should improve infant survival.

Two other studies of HIV uninfected infants born to HIV-positive mothers undertaken in Lusaka, Zambia[8]

and the PEPI-Malawi trial[9] have also demonstrated increased morbidity and mortality in infants weaned early from BF.

The above studies, some of which are only recently published, would have influenced WHO in their 2010 publication on HIV and Infant Feeding which advises that uninfected infants born to HIV-positive mothers should breast feed for up to 12 months and infants should be weaned only if a safe alternative is available.[10] Unless the mother is on HAART for her own health, HIV infant prophylaxis will need to be continued until it is considered safe to wean the infant. New clinical trials are in progress assessing longer infant HIV prophylaxis. These include daily infant 3TC or lopinavir/ritonavir during BF to age 10 months (NCT 00640263) and NVP up to 18 months of age (NCT 01061151).[11]

Eligibility for HAART for pregnant women depends on a CD4 count ≤350/μL. However, in Malawi HIV prophylaxis coverage is presently only 35% and CD4 counts are generally not available in small laboratories.[12] It is planned to increase coverage and offer HAART to *all* HIV-positive pregnant women *for life* and because of the prevalence of AZT-associated side effects, especially anaemia, to replace it in triple therapy with a protease inhibitor. This may be the way forward in other countriesl too, which would obviate the need for prolonged infant HIV prophylaxis, encourage longer BF, and improve maternal and infant survival.[1,13]

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