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

Outcome of XDR tuberculosis

No African health workers need to be reminded of what a major problem tuberculosis (TB) is. Globally it is now estimated that at least 5% of cases are multidrug-resistant (MDR), and of these about 5-10% are extensively drug-resistant (XDR). The figures are probably higher in Africa, and certainly are in South Africa. Here, 10% of TB cases in 2008 were MDR, and in 2011 there were 500 confirmed cases of XDR-TB. Currently it is estimated that South Africa has the highest number of XDR cases in the world. XDR is generally defined as MDR disease, with resistance to a fluroquinolone, and either amikacin, capreomycin or kanamycin. An important report has recently been published by a South African group of researchers with extensive experience of XTR-TB. This concerns the long-term outcome of the condition, and results are of considerable concern.[1]

A total of 107 patients with microbiologically confirmed XDR-TB were enrolled between March 2008 and August 2012. Of these, 44 (41%) were HIV positive, and 64% of isolated bacteria were resistant to at least eight drugs. The patients were treated as in-patients for prolonged periods of time, with a median of eight separate drugs. At two years follow-up 49 (46%) had died, and at 5 years the mortality was 78 (73%). Default rates were 7% and 4% at two and five years respectively; and treatment failure rates were 23% and 10%. Mortality was not related to HIV status.

These gloomy figures show the seriousness of XDR-TB. With a near 80% five year mortality, the outcome is worse than most malignant conditions. Also, significant numbers of sputum-positive patients (defaulters or treatment failures) are re-entering the community, and therefore likely to spread the disease.[2] The South African researchers describe the current status of XDR-TB as 'an acute global health crisis', and it is hard to argue with their viewpoint. Urgent and adequately funded research is needed to discover and trial new drugs to treat this fearsome new menace.

Not so neglected NTDs?

A recent Lancet editorial reviews progress in tackling what are now widely known as 'Neglected Tropical Diseases' (NTDs).[3] These conditions include African and South American trypanosomiasis, filariasis, schistosomiasis, trachoma, onchocerciasis, soil-transmitted helminthiasis, leishmaniasis, leprosy and dracunculiasis. A major meeting of NTD stakeholders in London in 2012 made a declaration ('The 2012 London Declaration') to control or eradicate these major 10 NTDs by 2020. In April 2014, a further meeting (this time held in Paris) was convened to review progress in achieving the London Declaration aims.

There has certainly been impressive progress. In 2013 there were an estimated 1.35 billion treatments given for these 10 diseases, a 35% increase since 2011 Drug donations have increased – these were given to 37 countries in 2011 and 55 in 2012. Over 70 countries now have national NTD programmes. Drug company involvement in research and treatment supply has increased, and several academic NTD departments now exist.

This is excellent news. NTDs are clearly no longer 'neglected' in the usual sense of the word. Nevertheless, there is still much work to be done. It is estimated that still only 36% of patients in need of NTD drugs receive them. There seems to be a particular problem with anti-schistosomal drugs, as in 2012 only 31 of 52 countries with endemic schistosomiasis had treatment programmes. Political and social unrest is a problem in some areas - for example the African Horn, Afghanistan and Pakistan - and this can seriously interfere with drug supply. Political will and adequate finances are also continuing problems.

The fight for the 2020 goals must still therefore go on. NTD specialists must also consider how 'control' of the 10 major NTDs is to be defined, as it seems certain that most will not be eradicated by 2020.

Clostridium difficile in Africa

The bacteria Clostridium difficile is a major problem in western countries. It causes a troublesome diarrhoeal disease, often associated with preceding antibiotic use. It was first recognised as 'pseudo-membranous colitis', and was particularly associated with clindamycin therapy; though now the true bacterial cause is known, and it is recognised that a wide variety of antibiotics can act as precipitants. C.difficile diarrhoea can be highly infectious on hospital wards, and in the UK, patients are all cubicle nursed, and usually treated with oral metronidazole. The disease particularly affects the old and debilitated, and can sometimes be fatal, or at least contribute to death.

Up to now there has been little information on C.difficile prevalence in Africa, but a recent study from Zimbabwe has given useful new information.[4] A total of 268 diarrhoeal stool samples from various clinics and hospitals in Harare were cultured, and 23 (8.6%) were positive for C.difficile. The age range of the affected individuals was interesting - 12 were 2 to 10 years old, four were 21 to 30 years old, two were 31 to 40 years old, three were 51 to 60 years old, and two were over 60 years.

Unfortunately no information was available on recent antibiotic usage, or other co-morbidities (in particular HIV/AIDS infection). Nevertheless, if nearly 10% of diarrhoea in sub-Saharan Africa is potentially due to C.difficile, then adequate testing for this organism is vital, with appropriate therapy and measures to stop cross-infection.

Raising awareness of acute HIV infection

The illness of acute HIV-1 infection has been well recognised for many years. Sometimes called 'seroconversion syndrome', it occurs about two weeks after viral transmission. It is characterised by fever, myalgia, headache and sometimes rash. At this stage the patient is highly infectious. Not surprisingly, acute HIV infection may closely resemble an attack of malaria, but new work from East Africa shows that the diagnosis is often not considered.[5,6] The research showed that HIV testing was only done in 16% of young (18-29 years) adults presenting with fever. Yet acute HIV infection is probably as common as malaria in this age range.

The authors of the report point out that guidelines for investigating and treating fever in sub-Saharan Africa tend to concentrate too much on malaria. HIV testing should be considered in all young adults presenting with fever, especially if they are sexually active and the malarial slide is negative. Anti-retroviral therapy at this stage would not only improve patient outcome, but would also reduce HIV transmission in general.

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STIs Review

Syndromic management

Sexually transmitted infections (STIs) continue to be a significant health burden, especially in low- and middle-income countries. The World Health Organization (WHO) estimates that almost half a billion cases of curable STIs (gonorrhoea, chlamydia, syphilis, trichomoniasis) occur every year, a number virtually unchanged in the past decade.[1] In addition, at least 536 million people are infected with incurable herpes simplex virus, and an estimated 291 million women have human papillomavirus (HPV) infection at any point in time. There are many cost-effective tools for prevention and treatment of STIs, but their application in resource limited settings has been inadequate. Syndromic management has long been the go-to diagnostic tool in the absence of laboratory services. This clinical approach can be very effective for assessing urethral discharge, but is notoriously poor when applied to other syndromes, such as vaginal discharge, and fails to identify asymptomatic infections. An assessment of syndromic management of STIs as part of the Kisumu Incidence Cohort Study found syndromic management to be insufficient.[2] The Kisumu study was an observational prospective cohort study to estimate the incidence of HIV seroconversion. Many studies of syndromic management take place within STI clinics, where clients have already self-selected for STI diagnosis and treatment. This study took place within a research context, where all participants were asked about STI signs and symptoms, and assessed how well syndromic and laboratory aetiological diagnoses matched. In this group, syndromic management missed the majority of STI infections. Overall, 10.8% of participants were diagnosed with an STI through syndromic management, while 32.2% had an STI confirmed with laboratory testing. Herpes simplex virus type 2 was the most prevalent STI. The study also compared responses of participants to clinician-administered computer-based personal interviews with participant self-administered computer-based interviews. Participants were more likely to report symptoms of STIs in the self-administered interviews, a finding that might improve syndromic management in some situations. Another study in Kisumu compared self-reporting of STI symptoms with clinician-initiated questions.[3] HIV-infected women attending an HIV clinic were asked if they had any current health complaints. After their routine visit, the women were interviewed specifically about abnormal vaginal discharge and received a speculum exam. The study found that the 13 women who self-reported STI-related symptoms in their routine visit did not have laboratory-confirmed disease (testing for N. gonorrhoeae, C. trachomatis and T. vaginalis). Of the 41 women who tested positive for an STI, 78% (32/41) reported no symptoms at all and 31% (10/32) would have been diagnosed with an STI-based on clinical exam. This study indicates that having clinicians ask women about any vaginal complaints, and/or a speculum examination can significantly improve diagnosis of STIs in this population.

Vaccines

There are more than 30 bacterial, viral and parasitic pathogens classified as STIs. Many of these infections can be cured, but antibiotic resistance, especially against N. gonorrhoeae, is a growing problem. There are currently only two STI vaccines, against hepatitis B and human papillomavirus. There is now renewed interest in pushing forward the development of new STI vaccines. In 2010, the Decade of Vaccines was initiated, and in 2012, the 194 member states of the WHO approved a Global Vaccine Action Plan. This plan is a roadmap for stakeholders, such as governments, health professionals, academics, manufacturers, global agencies, civil society, the media, and the private sector, to follow in improving immunisation worldwide.[4]

In April 2013, the WHO convened a technical consultation on STI vaccines. These experts focused on the development of new vaccines against five STIs: HSV-2, chlamydia, gonorrhoea, trichomoniasis and syphilis. Participants discussed the current knowledge base and status of vaccines, critical knowledge gaps, and next steps for accelerating vaccine development and availability. A special issue of the journal Vaccine, co-edited by the WHO and the U.S. National Institute of Allergy and Infectious Diseases, captures much of the technical information discussed at the consultation and is an excellent resource.[5] While the obstacles are many,

there is reason to be hopeful that vaccines can make an impact on STI morbidity and mortality. Experience with the hepatitis B and HPV vaccines demonstrates that with investment in science, a thorough analysis of the public health need and potential global markets, and with strong political leadership, STI vaccines can have an impact.[6,7]

HPV, cervical cancer and genital warts

It was not until 1992 that scientists discovered that HPV was the cause of cervical cancer. More than 100 HPV types have been identified, and it is now known that HPV types 16 and 18 are associated with 70% of invasive cervical cancers. The highest incidence of cervical cancer is in sub-Saharan Africa, and the disease is the most common cause of cancer deaths among women in the region. HPV types 6 and 11 are responsible for 90% of genital warts (condyloma acuminata). While considered benign, genital warts can be difficult to treat and often recur.

The prevalence of HPV among women with normal cervical cytology is an average of 24% in sub-Saharan Africa, higher than rates found in more developed countries.[8] The highest incidences of HPV infection and cervical cancer are found in Eastern and Western Africa. HIV infection increases the incidence and prevalence of all HPV-related diseases. Given the aging of the population, concomitant HIV infections and lack of preventive services, the already significant incidence and mortality due to HPV is expected to grow over the next two decades in Africa.

There are now two effective vaccines that can protect against certain HPV types. The bivalent vaccine, Cervarix™, protects against types 16 and 18. The quadrivalent vaccine, Gardisil™, protects against types 6, 11, 16 and 18. Both are given in a three-dose schedule over six months and are very effective. Studies show that among women who have not been infected with HPV prior to vaccination, the quadrivalent vaccine is nearly 100% protective again genital warts caused by types 6 and 11, and 83% effective against all genital warts.[9]

Following the establishment of national HPV vaccine programmes in Australia, Sweden, Denmark and the US, the number of genital wart cases in these countries has fallen. Australia began vaccinating women aged 12-27 years in 2007. In 2008, the proportion of women under age 28 with genital warts declined by 25%.[8] Five years later, there were no warts diagnosed in vaccinated women, and warts were rare among men and women under age 21, suggesting that the reproductive rate of the virus had fallen below one. Such a rapid response is largely due to the high vaccination coverage rate in Australia (over 70%), and the data shows what a significant and swift impact HPV vaccination can have within a population.

Effective HPV vaccination programmes depend on vaccinating those at risk prior to infection with HPV. This means fully vaccinating young girls ages 9-13 before the initiation of any sexual activity which could infect them with HPV. To help make this a reality in many parts of the world, the Global Alliance for Vaccines and Immunisations (GAVI) has negotiated a reduced price of US$4.50/dose for the HPV quadrivalent vaccine (it costs up to US$120/dose in more developed countries), and has begun pilot HPV vaccination programmes in many countries.[10] By December 2013, 20 countries had qualified for GAVI assistance in introducing HPV vaccine programmes in Africa, and demonstration projects have begun in Kenya, Ghana, Madagascar, Malawi, Niger Sierra Leone and Tanzania.

A modelling study of the cost-effectiveness of HPV vaccination found that vaccination of 58 million 12-year-old girls in the 179 countries studied would prevent 690 000 cases of cervical cancer and 420 000 deaths, mostly in low- and middle-income countries, at a cost of US$4 billion.[11] The authors conclude that HPV vaccination is cost-effective in 87% of the countries studied and is very cost effective in low-income countries with the highest vaccine-preventable burden of cervical cancer, but these countries also are least likely to have country-level HPV vaccine programmes.

Most vaccination campaigns focus on young girls because they are most at risk from HPV infection, and it is thought to be most cost effective. If vaccination coverage among young girls is over 50%, it is expected that the entire population will experience herd immunity. While the overall burden of HPV-associated disease is highest among women, recent studies highlight that HPV infection is also common in men and boys. HPV infection in men is associated with anal, oropharyngeal and penile cancers. A systematic review and meta-analysis of HPV infection in men in sub-Saharan Africa found a pooled prevalence of any HPV was 78.2% among HIV-positive men, and 49.4% among HIV-negative men.[12] A study of HPV types found in cancerous and pre-cancerous penile lesions among men in South Africa found a high variety of HPV types.[13] Of the 51 samples analysed, HPV types 11 and 16 had similar incidences. In pre-cancerous lesions, HPV 11 was most frequent (80%), followed by HPV 31 and 16 (25% each) and several other types. In cancerous lesions, HPV 16 was most common (62.9%), followed by HPV 11 (34.3%), and several others. Several lesions showed from two to six HPV types in one lesion. These results indicate that young boys in South Africa, who may be exposed to many HPV types as young as age 10, could benefit from vaccination.

Research continues on HPV vaccines, and a nine-valent vaccine which covers types 6, 11, 16, 18, 31, 33, 45, 52, and 58 is in clinical trials. The effectiveness of using two doses of the current vaccines instead of three is also being examined. Despite the challenges of logistics and cost, it is clear that high coverage HPV vaccination programmes can have a significant impact on health and are worth the investment.

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Paediatrics Review

Vitamin D deficiency and rickets – a worldwide disorder

Rickets, generally considered a disease of toddlers, can have long-term effects, including obstructed labour and reduced bone size and mass in adulthood.[1] Vitamin D deficiency (VDD) during peak periods of growth, e.g. term infants, the first two years (6-24 months) of life and puberty, is the main cause of rickets and VDD during pregnancy is an important factor in the early manifestation in infants. There is no clear threshold of vitamin D (VD) level below, which rickets will develop as the level of calcium intake is also important.[1] In Nigerian children exposed to adequate sunlight, hypocalcaemia is the major factor in the cause of rickets.[2,3] However, in African children where dietary calcium levels are low, a higher level of VD may be required to maintain normal bone metabolism.[4] A recent case control study of 67 Indian children with nutrition rickets and 68 age, and sex-matched healthy controls found significantly lower levels of calcium and higher dietary phytate levels in ricketic infants, but no significant difference in the 25 hydroxy vitamin D (25OHD) levels between the two groups.[5] In children with borderline low 25OHD, the dietary calcium level may be crucial in the development of rickets and both are important in treatment. Thus, rickets exists along a spectrum between isolated VDD to isolated calcium deficiency, with perhaps other environmental and in some cases genetic factors also involved.[2]

Aetiology

Vitamin D_2 (ergocalciferol), obtained from the diet or vitamin D_3 (cholecalciferol), the form synthesised in skin and found in cod liver oil are hydroxylated to 25OHD (calcidiol) in the liver.[1] This is excreted by the proximal renal tubules where it undergoes 1-hydroxylation to 1,25dihydro vitamin D (1,25$(OH)_2$D) (Calcitriol). Its main function is increasing calcium absorption from the gut. Failure to absorb calcium stimulates release of parathyroid hormone, which results in loss of phosphate by the kidneys. Absence of phosphate at the growth plate and failure of mineralisation of osteoid results in rickets. However, in rickets of prematurity which usually occurs in infants born before 28 weeks the cause is deficiency of phosphate and other minerals rather than VDD.

VDD in term infants in the first few weeks of life is due to maternal VDD and commonly presents with hypocalcaemic convulsions. Rarely it presents as cardiomyopthy. In the period 2000-2006, 16 infants (three weeks - eight months old) were admitted to paediatric cardiac units in south east England with cardiomyopathy associated with hypocalcaemia and low VD levels; six had cardiac arrest and two died.[6] All were from ethnic minorities and all had been breast fed. Similar cases have been reported from India.[7]

Maternal 25OHD crosses the placenta and undergoes placental conversion to 1,25$(OH)_2$D and at birth 25OHD concentration in cord blood closely correlates with maternal levels.[8] Unless the mother is on a near pharmacological dose of VD, e.g. 100µg per day (4000 IU. 1µg =40 IU) breast milk will contain very low levels of VD (<1.5 µg/L).[1] The daily requirement for young infants is 10 µg/day. Infants born to replete mothers who are exclusively breast fed will be VDD after eight weeks.[8]

There is negligible VD synthesis during winter months at latitudes greater than 35° in the northern hemisphere and the 32° latitude in the southern hemisphere.[4] Increased concentration of melanin in the skin reduces the ability of ultraviolet B (290-315 nm range) to convert 7-dehydrocholesterol to previtamin D.[1] Thus, dark skinned people require more prolonged sunlight exposure than those light skinned to obtain equivalent amounts VD. Recommended sunshine exposure in the UK for white children and adults is 15 minutes of unshaded noon-time exposure, three times per week, with 35% skin surface exposed. However, studies using simulated sunlight exposure have demonstrated that South Asian adults in the UK require more than threefold longer exposure to produce comparative amounts of 25OHD to white adults.[9] In the Middle East and other Islamic regions, where cultural and religious customs dictate the type of clothing for women and adolescent girls, the entire body may be covered apart from the face and hands. Throughout the world the youth of today now spend much of their time outside school hours indoors watching television or working with computers.

Decreased atmospheric pollution in industrialised countries since the 1950s due to clean-air legislation is likely to be one of the factors in the decrease in incidence of VDD at least in the white skinned population. There is some evidence that the increase in air pollution in large urban conurbations in low- and middle-income countries is also a factor in the increased incidence of VDD, such as in India[10] and elsewhere.

In high-income countries the increased incidence of rickets is mainly in recent immigrants with pigmented skin.[1]

Genetic disorders such as vitamin D receptor (VDR) gene polymorphism may also be a factor in the aetiology of rickets in Asians, especially Chinese populations.[11]

Definitions of vitamin D deficiency

Measurement of VD is difficult and complex, and thus is unlikely to be available in many non-research laboratories in low-income countries. Also, there is no clear agreement on cut-off levels for defining deficiency. A vitamin level required for optimal growth may differ from that required to prevent rickets.[1] The following are commonly used definitions: severe deficiency < 27.5 nmol/L; deficiency 27.5-50 nmol/L; and insufficiency 50-75nmol/L.

The incidence and prevalence of rickets is difficult to estimate and rates will change with socioeconomic development. The more studies of 25OHD undertaken in the childhood population the more likely will be the finding of subclinical and pre-rackitic VDD.[12] The geographical distribution of rickets has been recently reviewed.[2,13]

Prevention

Prevention of rickets comprises public awareness and public health efforts to promote the importance of adequate sun exposure and VD intake through diet and supplementation. However, in societies where children and adolescent women are not exposed to adequate sunshine for cultural reasons, the former alone is unlikely to succeed. Also, in some western countries because of concerns about skin cancer, excessive restriction of sun exposure and use of high factor sun cream may reduce endogenous production of VD.

Presently, regimens for VD supplementation in high-income countries are principally aimed at people living in high latitudes in northern Europe and Canada, and immigrants with skin pigmentation. However, regimens and doses differ between countries.

The UK Department of Health advice is as follows:[1] All pregnant and breastfeeding women should receive daily supplements of VD. However, the usefulness and safety of VD supplementation during pregnancy is not established in rigorous randomised trials.[14] If the mother is not taking supplements throughout pregnancy, her infant may need to commence VD drops from one month of age. Otherwise the infant should start supplementation at six months and continue until five years of age. Pre-term infants are at particular risk. Most formula milk, breakfast cereals and margarines are fortified with VD. In the UK, fortification of chapatti flour aimed at the Asian community is effective in raising VD levels, but is not universally used.[1]

In low- and middle-income countries, where VD supplementation of foods are not routine, each region needs to establish a practical regimen for VD supplementation depending on variables such as latitude, cultural attitudes regarding exposure to sun light, women's clothing and socioeconomic status. In countries where poor children have inadequate VD intake, dietary calcium supplementation may also be necessary.[5] Advice regarding eating VD-rich foods (fish liver oils, fatty fish, mushrooms, egg yolks and liver) is unlikely to succeed in poor societies.

In Turkey, where VDD rickets was endemic, especially in the eastern part, nationwide free VD supplementation was effective in virtually eradicating rickets.[15]

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See page 53 for questions about this article