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.

Paediatrics Review

CPAP and high-flow nasal cannula oxygen therapy for treatment of hypoxic respiratory disorders

In 1971 Gregory and co-workers described the treatment of 20 severely ill newborns with Respiratory Distress Syndrome (RDS) (18 intubated and two in a pressure chamber around the head) with continuous positive airway pressure (CPAP). As CPAP was increased arterial oxygen tension rose and minute ventilation decreased. There was little effect on arterial CO\textsubscript{2} tension, pH or lung compliance. The apparatus comprised an oxygen/air gas mix, an anaesthetic bag with spiget to control the escape of gas, a water bottle to control the pressure, and a pressure gauge. Sixteen of the infants survived. This simple CPAP system was welcomed as mechanical ventilators in the early days of paediatric mechanical ventilation (MV) were not easy to use. However, as improved ventilators with a CPAP mode became available there was less need for this simple CPAP delivery system. But this system would have been ideal for low resource countries, except for the difficulty in obtaining air cylinders. Thus it took over 20 years for an appropriate CPAP system to be designed in a developing country at Sultan Qaboos University, Oman, using a Beneventiste valve and nasal prongs. The arrival of surfactant for management of RDS in high-income countries has also made a difference to outcome, but it is not available in many low-income countries.

Since then, there have been a number of studies demonstrating the benefits of CPAP for newborns with respiratory disorders, viz lower rates of failed treatment and reduced mortality, reduced requirement for MV, and lower failure rates for bubble CPAP (bCPAP) than ventilator CPAP. For very low-birth weight infants there is improved short-term survival. A study of neonates > 1000g in Malawi compared bCPAP with standard care and found that a 27% improvement in survival, including those with infants complicated by sepsis.

CPAP is produced by exhalation against a constant opening pressure, which produces a positive end expiratory pressure (PEEP). Physiologically CPAP maintains lung volume during expiration, decreases atelectasis (alveolar and lung segmental collapse), improves oxygenation, and reduces respiratory fatigue.

The advantage of bCPAP is that it can be set up and run by nurses. There is a risk of pneumothorax and possibly retinopathy of prematurity if care is not taken regarding oxygen concentration. If the gas is not adequately humidified there may be drying of the nasal mucosa, bleeding and nasal obstruction, and in ill-fitting nasal prongs may cause nasal septum damage.

The systems for CPAP and high-flow nasal cannula (HFNC) oxygen therapy have recently been comprehensively reviewed by Trevor Duke. The principles are as follows: oxygen and air need to be mixed by a gas generator or blender and the gas must be humidified, but an oxygen concentrator, which can produce 5–10 L/min is an alternative, and the gas (taken from the atmosphere) will have a degree of humidification. The gas is delivered to the infant by nasal prongs, which must have low resistance and fit well. The expiratory limb of the circuit is immersed in a bottle filled with water to a level which provides the appropriate CPAP pressure (cm H\textsubscript{2}O). The term ‘bubble’ CPAP is used as the water bottle is the only exit for the gas and thus bubbles furiously (as opposed to Gregory’s system). HFNC is an alternative form of CPAP (although the CPAP level cannot be measured). High gas flow of up to 2 L/kg/min is administered through nasal prongs. The gas must be humidified and pure oxygen should not be given to preterm infants because of the risk of retinopathy. There is a risk of pneumothorax, which possibly could be higher in asthma.

Recently, the use of CPAP in developing countries has been widened to include children with acute respiratory distress associated with pneumonia, sepsis, dengue shock syndrome, and malaria.

A randomised controlled trial was undertaken at the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B), Dhaka in children under five years with severe pneumonia (WHO definition) and hypoxaemia (SpO\textsubscript{2} < 90% in room air). The value of bCPAP (5 L/min commencing at a CPAP level of 5 cm H\textsubscript{2}O and increasing up to 10 cm H\textsubscript{2}O), standard low-flow nasal cannula (LFNC) (2 L/min) or HFNC (2 L/min, maximum 12 L/min) were compared. The bCPAP system was constructed locally using nasal prongs and the gas flow was provided by an oxygen concentrator. The HFNC system also used nasal prongs and the LFNC system was delivery from oxygen cylinders with a nasal catheter. Primary outcome was treatment failure after more than one hour of treatment (i.e., clinical failure, and requirement for intubation and MV).

Two hundred and twenty five (225) eligible children were recruited: bCPAP (79), LFNC (67) and HFNC (79). Treatment failure rates were as follows: bCPAP 5 (6%), LFNC 16 (24%) and HFNC 10 (13%); bCPAP vs. LFNC (p=0.0026) and bCPAP vs. HFNC (p=0.175). 23 (10%) patients died, viz bCPAP 3 (4%), LFNC 10 (15%) and HFNC 10 (13%). Children who received bCPAP had a significantly lower death rate than those receiving LFNC (p=0.022).

The study demonstrated that bCPAP improved outcome of patients with severe pneumonia and hypoxia, however the trial was stopped early on the advice of the data and safety monitoring board because of the higher failure rate in the LFNC than the bCPAP group, which reduced the certainty of the results. Also the study was interrupted because the oxygen concentrator had a temporary failure to deliver sufficient rate of gas flow, which was considered to be due to ‘machine fatigue’.

The early cessation of the trial was examined in an annotation which concluded that firm conclusions cannot
be drawn because the trial was stopped too early, and the decision was based on incorrect statistical procedures.16

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References

Dermatology Review

Scabies: a neglected tropical disease with significant public health implications

Aetiology and epidemiology

Scabies is an important communicable disease that was added to the World Health Organization’s (WHO’s) list of neglected tropical diseases (NTDs) in 2013. It is a skin disease caused by infestation by the ubiquitous mite Sarcoptes scabiei var. hominis. It is known to affect 300 million people annually.1 It is prevalent globally and it particularly afflicts those of low socio-economic status and those living in over-crowded conditions.

Outbreaks of scabies in institutions and refugee camps are common. The highest incidences of scabies occur in tropical countries with rates of up to 25%.2 Indigenous communities in the South Pacific and northern Australia have reported rates as high as 50%. Children in resource-limited regions of the world are the most susceptible. In some communities up to 70% of infants are affected in their first year of life.3

Scabies transmission occurs through direct and prolonged contact, and possibly through sharing contaminated clothing or bedding. It causes intense itching, which is worse during the night. Therefore it can severely affect sleep and quality of life. Chronic scratching of the skin leads to a rash with excoriations, which compromises the barrier function of the skin. This poses a risk of secondary bacterial infections. Scabies places a considerable economic burden on individuals and communities in both costs of treatment as well as loss of working days.

Diagnosis and clinical presentation

There is no accurate means of diagnosing scabies. A presumptive diagnosis is usually made on the basis of clinical signs and a history of contact with other scabies cases. Identification of the mite or eggs via microscopic examination of skin scrapings from an affected area of the skin does not always yield a positive result as patients usually carry low numbers of mites. Adhesive tape stripping as an alternative to skin scrapings may produce a higher yield of mites. Dermoscopy can be useful but requires training and experience. These tests are not always feasible in resource-limited regions.

A clinical diagnosis of scabies can be challenging as it can mimic other skin lesions, in particular eczema or impetigo. In highly endemic regions or where there is a known outbreak of scabies, the clinical diagnosis becomes easier as the index of suspicion for scabies is higher. The initial lesions of scabies are ‘scabies burrows’, which consist of a serpiginous or linear track of erythematous or brownish papules. These develop after a female mite penetrates the skin in order to lay its eggs. Scabies burrows are commonly located in the inter-digital finger web and toe web spaces, but can occur on any part of the body. They are not always apparent and are easily missed as they can be obscured by a local inflammatory response. More widespread skin lesions of scabies develop as an immunological inflammatory response to the mite. These lesions can look eczematous, pustular, vesicular and rarely bullous (Figure 1). Common areas of involvement include the wrists, elbows, natal cleft, axillae, and around the nipples (Figure 2). In men, genital lesions are common and in young children, the palms, soles, head, and neck region may be affected.

A first infestation of scabies causes pruritus 2–8 weeks after acquiring the infestation. Pruritus occurs as a consequence of a hypersensitivity response to scabies mite and initially may not be associated with any skin lesions. During the initial asymptomatic period, individuals with scabies are still infectious. If re-infestation occurs, the symptoms and signs of scabies appear much sooner as the individual is already sensitized.

Crusted scabies is a rare form of scabies and infected individuals are often immunocompromised or...
debilitated. Afflicted individuals are hyper-infested with thousands of mites compared with only 5–15 mites in a person with the classical common form of scabies. Crusted scabies also has distinct clinical features and presents with greyish, scaly, hyperkeratotic plaques. A diagnosis of crusted scabies is not always considered as pruritus is not a prominent feature and is sometimes absent altogether. However, microscopic examination of skin scrapings should easily identify the mite. Prior to the introduction of oral ivermectin, crusted scabies was associated with a 5-year mortality rate of up to 50%, usually from secondary bacterial sepsis.

Complications of scabies

In the Tropics and resource-limited regions scabies is often complicated by secondary bacterial infections of the skin with group A *Streptococcus pyogenes* and *Staphylococcus aureus* manifesting as impetigo, and soft tissue infections such as abscesses or cellulitis. These skin infections predispose to more serious invasive infections and post-infective complications that are associated with significant morbidity and mortality. Infection of the skin can seed to bone and joints (osteomyelitis and septic arthritis), or internal organs and heart valves (infective endocarditis), or can progress to more severe deep tissue infection (pyomyositis and necrotising fasciitis). Infection of the blood stream can lead to generalised sepsis and toxin-mediated disease, including toxic shock syndrome. A well-recognised post-infective complication of scabies is acute post-streptococcal glomerulonephritis (APSGN), which typically presents 1–2 weeks after streptococcal infection. Outbreaks of APSGN have been linked to outbreaks of scabies. APSGN can contribute to the development of chronic kidney disease and subsequent renal failure in adulthood.

Scabies complicated by streptococcal skin infection has also been linked to acute rheumatic fever as countries with high rates of rheumatic heart disease also have high rates of scabies and impetigo, but low rates of streptococcal pharyngitis.

**Treatment**

The index case of scabies, as well as all household contacts, should be treated at the same time to prevent re-infestation. Treatment should also be given to all sexual contacts and any person who has had prolonged direct skin-to-skin contact with the index case in the preceding month. There are several topical treatments for scabies, but they are associated with varying degrees of efficacy, tolerability, and adverse effects. They all require patients to have access to washing facilities as treatment is applied all over the body for up to 24 hours before being washed off. The efficacy of topical treatments is higher if they are reapplied after one to two weeks because of the life cycle of the mite. Bedding, clothing, and towels used in the previous three days by the index case and all contacts should be decontaminated by either washing in hot water or sealing in a plastic for at least 72 hours in order to destroy any scabies mites, as they are not able to survive for more than 2–3 days away from human skin. The use of insecticide sprays and fumigants is not recommended. A high degree of treatment compliance amongst the index cases as well as contacts is required as otherwise there is a significant risk of re-infestation.

Of the topical treatments, 5% permethrin (1% permethrin used to treat head lice should not be used to treat scabies) is the most effective, is easy to use, and is recommended for treating infants as well. Permethrin is well tolerated, has low toxicity, is poorly absorbed by the skin, and is rapidly metabolised. However, it is expensive and not readily available in many endemic regions. Other topical treatments for scabies include crotamiton (10%), benzyl benzoate (6.25–25%), mala...

Figure 1. Pustular lesions of scabies.

Figure 2. Severely excoriated lesions of scabies affecting the wrist flexors, elbow extensors and natal cleft.
programme of scabies through mass drug therapy of oral ivermectin have already successfully demonstrated reduced scabies prevalence from 25% to 1% with concomitant reductions in secondary bacterial infection and renal disease. The mission of the recently formed ‘International Alliance for the Control of Scabies’ (IACS) is to advance the agenda for the control of scabies.

In conclusion, there are several challenges to managing the global disease burden of scabies. These include the need to develop specific diagnostic tests for scabies, as presently diagnosis is only possible through clinical recognition, to develop new treatments for scabies with high efficacy but good tolerability, and to implement integrated programmes to control the disease.

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References

Epidemiology of HIV/AIDS and the scale-up of antiretroviral therapy
The estimated numbers on the HIV/AIDS epidemic and the scale-up of antiretroviral therapy (ART) in 2014 are provided by UNAIDS. By December 2014, there were an estimated 36.9 (34.3–41.4) million people living with HIV/AIDS globally. Adults constituted 34.3 (31.8–38.5) million and children under the age of 15 years constituted 2.6 (2.4–2.8) million of the global total.1 In 2014, 2.0 (1.9–2.2) million people were newly infected with HIV and 1.2 (980 000–1.6) million people died from HIV/AIDS, both of these estimates being slightly lower than the previous year.

Sub-Saharan Africa continues to bear the brunt of this epidemic with 25.8 (24.0–28.7) million adults and children (70% of global total) living with HIV, 1.4 (1.2–1.5) million new HIV infections (70% of global total) and 790 000 (670 000–990 000) deaths (66% of global total).1 Of children living with HIV, an estimated 2.3 million (88%) resided in sub-Saharan Africa, with 86% of new HIV infections and 87% of deaths in children occurring in this region. There is considerable varia-
tion in the severity of epidemics on the continent, with southern Africa still being the most severely affected, and the epidemic in South Africa continuing to be the largest in the world.

By the end of 2014, there were 14.9 million people globally receiving ART, representing 40% of people living with HIV. By mid-2015 this number had reached 15.8 million. In sub-Saharan Africa there has been excellent progress, especially in the eastern and southern regions of the continent, with 10.7 million people on ART by the end of 2014, representing 41% of all people living with HIV, and by mid-2015 this number had reached over 11 million. South Africa’s ART programme remains the largest in the world with 3.1 million on ART by the end of 2014. Scale-up, however, in sub-Saharan Africa is uneven. Some countries (Zimbabwe, Zambia, Malawi, Kenya, Uganda, Ethiopia, Swaziland, and Namibia) have 50% or higher coverage, some such as the Democratic Republic of Congo, Nigeria, and Cameroon are at 20% coverage while others are much lower with South Sudan at 6% and Madagascar at 2%. In Africa particularly, men who are eligible for ART are less likely to start or be retained on ART compared with women. Additionally, sex workers, people who inject drugs, transgender people, men who have sex with men and prisoners all face multiple barriers that deny them the benefits of HIV treatment and care services.

**When to start ART**

In the last decade, the recommended threshold for starting ART in HIV-infected people has gradually changed from <200 cells/μL in 2003 to <350 cells/μL in 2010, and to <500 cells/μL in 2013. During this time, arguments have emerged to support an even earlier start of ART to prevent the development of important non-communicable and communicable diseases, and to considerably reduce the risk of HIV transmission. The evidence to support individual benefits of early initiation of ART at CD4 cell counts ≥500/μL had previously come from observational studies, but 2015 saw the publication of two seminal studies (INSIGHT START and TEMPRANO) that have had a significant influence on policy.

The INSIGHT START trial was a multicentre randomised study in 35 countries amongst 4685 patients to determine benefits and risks of initiating ART immediately in asymptomatic HIV-positive patients with CD4 counts > 500 cells/μL, compared with deferred initiation until the CD4 count had decreased to 350 cells/μL. Early ART initiation was associated with a 57% reduction in the risk of death, a serious AIDS-related event or a serious non-AIDS-related event. TEMPRANO was a multicentre, individual-randomised, 2-by-2 factorial design superiority trial conducted in Abidjan, Côte d’Ivoire, on 2056 patients with a CD4 cell count of <800 cells/μL, and meeting no criteria for starting ART according to the most recent WHO guidelines at enrolment. Four groups were allocated to either immediate start of ART or deferred ART until the World Health Organization (WHO) criteria for starting ART were met, and each group was also randomised to isoniazid preventive therapy for 6-months or placebo. Early ART initiation was associated with a 44% lower risk of death or severe HIV-related illness compared with ART initiated, according to prevailing WHO criteria at the time, with isoniazid preventive therapy adding significantly to the individual benefit.

These two trials have helped to determine new WHO policy about when to start ART. WHO guidance was launched on 30th September 2015, recommending that ART be initiated in everyone living with HIV at any CD4 count, and that daily oral pre-exposure prophylaxis be offered to anyone at substantial risk of HIV infection as part of a combination prevention approach. These recommendations will form part of the revised consolidated guidelines on the use of ARV drugs to treat and prevent HIV infection, which will be published by WHO in 2016, and they in turn will facilitate the achievement of UNAIDS Fast-Track targets for 2020.

**Optimising ART regimens**

The increased impetus for scaling up ART that will now happen as a consequence of new WHO guidance depends crucially on an acceptable first-line ART regimen. Almost all countries in the world now use tenofovir-lamivudine (emtricitabine) - efavirenz which is safe, well-tolerated, non-toxic, effective and taken as a single pill once a day. Further work is helping to optimise this regimen. First, a 96-week follow-up of ENCORE1 assessed durability and safety of efavirenz 400 mg daily compared with the standard dose of 600 mg daily. The lower dose had similar efficacy in suppressing viral load compared with the standard dose viral and was associated with a decrease in adverse effects. More work needs to be done in this area in pregnant women and in patients on rifampicin-based anti-tuberculosis (TB) treatment before the 400 mg dose can be recommended as standard practice, but a lower dose would mean better tolerance and potentially lower drug costs.

Second, a novel tenofovir prodrug (tenofovir alafenamide) results in four times higher intracellular concentrations of the active metabolite compared with tenofovir disoproxil fumarate, which is the standard formulation used in first-line regimens. This prodrug thus allows for lower doses which are associated in turn with lower plasma concentrations, and the possibility of reduced renal and bone toxicity. Two controlled, double-blind studies showed that tenofovir alafenamide (10 mg) was associated with significantly smaller mean serum creatinine increases, significantly less proteinuria and significantly smaller decreases in bone mineral density compared with the standard tenofovir disoproxil fumarate (300 mg). These findings should pave the way for ART regimens designed for lifelong use, maximum adherence, and minimum toxic effects.

**HIV-associated tuberculosis**

TB remains an important cause of death in HIV-infected persons, especially in Africa. Of the 1.2 million HIV-related deaths in 2014, 390,000 were due to TB. A systematic review of 36 studies (20 from sub-Saharan Africa) reporting on 3237 autopsies in HIV-infected patients provided useful insight into the true burden of TB at death. Globally, TB was found at autopsy in 40% of adults and 4.5% of children, with adult prevalence being 63% in South Asia, 43% in sub-Saharan Africa, and 27% in the Americas. Where TB was found at post-mortem
it was considered the cause of death in 91% of cases. Overall, TB had remained undiagnosed at death in 46% of patients. The findings confirm the importance of TB as a cause of HIV/AIDS mortality and highlight the critical need to improve prevention, simple and rapid diagnosis, and effective treatment of HIV-associated TB.

In this regard, the use of Xpert MTB/RIF in concentrated urine specimens was found in South Africa to be a useful addition to the TB diagnostic armamentarium. Amongst 427 HIV-infected acute adult medical admissions who were not receiving anti-TB treatment and whose median CD4 cell count was 149 cells/μL, a microbiological diagnosis of TB using an array of different tests was found in 139 (33%) patients. The number (%) of TB cases diagnosed from urine Xpert MTB/RIF was 82 (59%) using concentrated centrifuged urine compared with only 39 (28%) using sputum, reflecting the small number and proportion of patients able to produce sputum in the first 24 hours. Combined urine and sputum Xpert MTB/RIF results gave the greatest diagnostic yield of 108 (78%) TB cases. Such ‘out of the box’ thinking and action will be required to meet the ambitious targets agreed upon in the End TB strategy.

Moving ahead from Millennium Development Goals to Sustainable Development Goals

As this paper goes to press, the Millennium Development Goals (MDGs) which were conceived in 2000 will have expired. MDG6 which aimed to halt and reverse the spread of HIV and the incidence of TB by 2015 was achieved. The new era of Sustainable Development Goals (SDGs) now starts and with SDG 3.3, the international community has committed to ending the epidemics of AIDS and TB by 2030. This bold and ambitious agenda deserves widespread support but will require concerted action on the ground to implement and scale-up activities that really have an impact.

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