

# 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

### **Steroids and tuberculosis meningitis**

Tuberculosis (TB) meningitis is well recognised as a serious condition with a significant mortality, and in survivors a risk of longer-term neurological complications. It has long been believed that these complications are related to dense inflammatory exudate in the basal meninges, interfering with cerebrospinal fluid (CSF) flow, damaging afferent nerves or causing a vasculitis potentially leading to cerebral infarction. It therefore seemed reasonable to give corticosteroids as well as anti-TB drugs, in an attempt to suppress this potentially deleterious inflammatory response.

Steroid treatment in TB meningitis has become standard treatment for decades, but what is the critical evidence for benefit? This has been summarised in a recent *Lancet* editorial,<sup>1</sup> which points out that most past studies have given conflicting results, generally suggesting a benefit from steroids in terms of mortality, but not for long-term outcome in survivors.

Two Cochrane reviews of the literature in 2000 and 2008 confirmed a large benefit in mortality, but considered that there was insufficient data to make firm conclusions on morbidity. This year, a third Cochrane review has been published, which adds two more trials to the meta-analysis.<sup>2</sup> The results confirm the mortality benefit (which is now beyond question), but suggest a slight increase in morbidity.

After these meta-analyses we can conclude that steroids definitely improve mortality in TB meningitis, but their effect on morbidity remains uncertain. Steroids are certainly still indicated in all patients with this serious disease. The generally agreed dose in adults is 0.4 mg/kg/day of dexamethasone or 2.5 mg/kg/day of prednisolone. Treatment is given for four weeks, followed by gradual dose reduction over the next two to four weeks. There is no evidence for one type of steroid being superior to the other.

One final important point is that in the largest trial so far of steroids in TB meningitis,<sup>3</sup> carried out in adolescents and adults, there was a significant improvement in both mortality and morbidity when steroids were used in milder, compared with more severe cases of the disease. This is probably as may be expected, but nevertheless means that early diagnosis and prompt treatment are vitally important.

### **News on yellow fever**

Yellow fever is one of the classic 'antique' tropical

diseases, well known to African doctors as far back as the 19th century. It has generally been thought to be a disease now under control, but recent news from Angola suggests that this is not the case.<sup>4</sup> Cases of yellow fever were first reported in Angola in December 2015, and since then there have been about 3000 cases with 328 deaths – over a 10% mortality. Emergency vaccination campaigns began in February 2016, and the number of new cases has now stabilised. However, a vaccine coverage rate of at least 80% is needed to give real disease control. Worryingly, new cases (though in smaller numbers) have been reported from the neighbouring country Democratic Republic of Congo. There are concerns that spread may occur to other nearby countries such as Zambia and Namibia.

The World Health Organization (WHO) has convened an emergency committee. There has been concern about WHO's supplies of yellow fever vaccine which had become seriously depleted by the Angola outbreak, but these seem to have now been replenished. The emergency committee is also considering the question of vaccine 'dose sparing' to prevent future strains on vaccine supply. This is an area where research on the effectiveness of lower vaccine doses is urgently needed.

By chance a separate but related event has recently occurred which will help with long-term vaccine supplies. The standard system for many years is that yellow fever vaccines need to be repeated every 10 years. However, the number of post-vaccination cases (even beyond 10 years) is very small, and WHO has just advised that a single vaccine is acceptable for lifelong protection, and booster doses are not needed.

### **The benefits of fever?**

An interesting recent report has examined the relationship between the presence or absence of fever in severe infections and subsequent mortality outcome. The study was from Denmark and investigated 2128 adult patients admitted over a two-year period with 'severe infection'.<sup>5</sup> This was defined as infection combined with evidence of dysfunction of at least one organ (eg renal failure, hypoxia etc). Patients were divided by admission core (rectal) temperature, and this was correlated to 30-day mortality. Of the 2128 patients 64 (3.0%) were hypothermic, 1216 (57.1%) normothermic, and 848 (39.9%) febrile. Temperature definitions were <36.0°C hypothermic, 36.0–38.0 normothermic and >38.0 fever. The overall 30-day mortality for the group was 16.1%, but when analysed by temperature an interesting pattern emerged. For hypothermic patients mortality was 37.5%, in normothermic patients it was 18.3%, and it was 11.2% for those with fever.

This very interesting study has a number of implications. First, it shows that septic patients with hypothermia (or even normothermia) are at increased mortality risk, and need especially vigorous therapeutic intervention. Secondly, the results would seem to confirm traditional teaching that fever is an appropriate response to infection aimed at inhibiting the growth and survival of infecting organisms. Finally, this raises the question of whether attempts should be made to modulate fever (for example with antipyretic drugs such as paracetamol) – these results may suggest that fever is to be encouraged.

The really important message is that many patients with serious sepsis do not have fever, and these patients have a particularly poor outcome.

### The Hertoghe sign and leprosy

A recent case report in the *Quarterly Journal of Medicine (QJM)*<sup>6</sup> gives a reminder to tropical doctors of a physical sign in leprosy which most of us learnt many years ago, but have probably rarely if ever seen. This is loss of the lateral third of the eyebrows in lepromatous leprosy. The reported case was of an Italian man who had been a prisoner in Venezuela for 25 years, and on return to Italy had a diffuse rash and peripheral sensory neuropathy, as well as loss of the outer hair of his eyebrows bilaterally. The diagnosis of lepromatous leprosy was confirmed by skin biopsy.

Lateral eyebrow hair loss is known as the Hertoghe sign, or less often 'Queen Anne's sign'. It is said to be common in lepromatous leprosy if it is looked for - and that may be why it is not often reported. Similar appearances can be seen in syphilis, and sometimes advanced hypothyroidism.

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## STDs Review

### Sexually Transmitted Infection testing

Accurate diagnostic tests are key to preventing and controlling infectious diseases, and vital to early treatment. This is especially true for sexually transmitted infections (STIs). Prompt diagnosis and treatment can prevent long-term effects of infection and stop ongoing transmission within communities.<sup>1</sup> In the absence of diagnostic tests, diagnosis relies on syndromic management and clinical judgement. Syndromic management using algorithms based on a patient's presenting symptoms has long been the foundation of STI management in low-resource settings. However, the deficits of syndromic management, including missing asymptomatic infections, lack of antibiotic susceptibility testing, the poor predictive value of syndromic treatment leading to overuse of antibiotics, and limited disease surveillance and partner notification, are cause for concern.<sup>2</sup> Most worrying is that syndromic management continues to be used in many high prevalence HIV countries, despite the clear epidemiological and biological links between STIs and HIV.

While progress is being made developing point-of-care (POC) tests to diagnose STIs, there is still need

for tests that meet the criteria set by the World Health Organization's Sexually Transmitted Diseases Diagnostics Initiative in 2001.<sup>3</sup> The ASSURED acronym defines the qualities needed for rapid tests to be effective in disease prevention: Affordable (the people affected by the disease can afford the test), Sensitive (few false negatives), Specific (few false positives), User-friendly (can be performed by people with minimal training), Rapid (quickly generates results) and Robust (doesn't need to be refrigerated), Equipment-free (easily collected test specimen like urine, saliva), Delivered to those who need it (portable, acceptable to population). By enabling diagnosis and treatment in one visit, POC tests facilitate immediate intervention and prevent continued spread of infections. Immediate results also permit expedited partner therapy (EPT), where patients are provided with treatment or a prescription for their sexual partners. These tests also support opportunities for counseling about risk behaviours, and prevent patient loss to follow-up.

Few POC tests meet all of the ASSURED criteria, and it is important for countries and programmes to determine the most important elements of tests used in the context of local disease prevalences. The sensitivity of a test is very important where rates of HIV and syphilis infections are high, as failing to identify and treat these diseases has serious consequences.<sup>1</sup> Poor specificity may be less important in instances where overtreatment does not carry great risks, as in syphilis. Other factors, such as conditions of use, shelf life, storage temperatures and price, all affect the practicality and feasibility of using diagnostic tests in remote locations.

### Point-of-care testing for *Chlamydia trachomatis* and *Neisseria gonorrhoea*

While nucleic acid amplification tests (NAATs) remain the gold standard for diagnosing *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoea* (NG), their cost, reliance on laboratory infrastructure and time required to obtain results limit their application in resource-poor contexts. However, one newer NAAT test, the Cepheid GeneXpert assay, can detect DNA of CT and NG from vaginal and endocervical swabs, and from female and male urine samples.<sup>4,5</sup> The test has shown high sensitivity (97.4–98.7%) and specificity (99.4–99.9%) in urogenital specimens. The GeneXpert test relies on a cartridge-based NAAT assay platform and an automated sample preparation and extraction process, which makes the test fairly simple to use. The test does not require electricity (a freezer, computer, vortexer) and a trained technician, but does not have to be laboratory-based. The hands-on test time is about five minutes, with results available in about 90 minutes. Another study evaluated field use of the GeneXpert test in a trachoma (ocular chlamydia infection) endemic community in Tanzania.<sup>6</sup> The study compared the GeneXpert test with the Roche AmpliCor CT test, testing 144 duplicate eye swabs from children aged 0–9 years. One hundred percent (100%) of the samples found to be negative by AmpliCor were also negative by GeneXpert, and 95% of the samples positive by GeneXpert were also positive by AmpliCor.

GeneXpert tests for tuberculosis are already being

used in many African countries, including South Africa. Adding the combined CT/NG GeneXpert test to the existing infrastructure would be straightforward. GeneXpert is also introducing an assay for *Trichomonas vaginalis* (TV). In the future, individual assays may be replaced by multiplex arrays to test for several infections at one time.<sup>3</sup>

Another new POC test for CT, the Atlas Genetics Velox™, relies on an electrochemical detection method. It has demonstrated clinical sensitivity of 98.1% and specificity of 98.0%. The technology uses an integrated fluidic card for sample processing and reagent handling and incorporates a novel technique for detection of proprietary ferrocene electrochemical labels and utilises a low-cost reader instrument.<sup>4</sup> Another technology for POC CT testing is the microwave accelerated metal enhanced fluorescence (MAMEF) assay. The MAMEF assay can detect approximately 10 inclusion-forming units/ml of CT in less than nine minutes, including DNA extraction and detection. Using a plasmid-based assay on archived clinical samples, sensitivity and specificity were 82.2% (37/45) and 92.9% (197/212), respectively.<sup>4</sup>

### Point-of-care testing for *Trichomonas vaginalis*

The OSOM TV *Trichomonas* Rapid Test for *Trichomonas vaginalis* (TV) also shows promise as a POC test. It is an ICT capillary flow (dipstick) assay that detects TV membrane proteins, with an additional internal control. It requires five steps to complete, with results in 10 minutes. An early study compared the sensitivity and specificity of OSOM, wet mount and culture performed on vaginal swabs from 449 sexually active women.<sup>4</sup> The overall prevalence of TV was 23.4% by a gold standard of either positive wet mount or positive culture. For the vaginal swabs, OSOM displayed 83.3 and 98.8% sensitivity and specificity, respectively, and it performed better than wet preparation. In another comparison with wet preparation, culture and a NAAT assay, the OSOM performed very well with a sensitivity and specificity of 90 and 100%, respectively in 330 sexually active females aged 14–21 years. The prevalence of trichomoniasis in this population was 18.5% (61/330); the sensitivity of wet preparation ranged from 50 to 54% and for culture was 75%. In symptomatic women, the sensitivity of OSOM was 92.5% and for the NAAT, 97.5%.

There is also an Atlas Genetics TV test using electrochemical detection being developed. The assay features novel electrochemical end point detection, with a multi-copy region of the TV genome as a target. In a preliminary performance study, 90 clinical vaginal swab samples were used to verify the performance of the prototype assay, demonstrating a sensitivity and specificity of 95.5% (42/44) and 95.7% (44/46), respectively.<sup>4</sup>

The costs of these tests and their availability within sub-Saharan Africa – both crucial determinants of use – are not currently known. However, as more tests are developed, the costs to manufacture, distribute and use the tests will decline, making them more available.<sup>7</sup>

### Other technologies

Technology is making laboratories portable and miniature. These ‘labs-on-a-chip’ make use of microfluidics and nanofluidics – the manipulation of the flow of small

quantities of fluid in micrometer or smaller channels. Nanosensors are able to analyze these small amounts of fluid to detect down to single molecules. Even simple paper chips that test a drop of blood or urine (similar to do-it-yourself pregnancy kits) are being developed.<sup>8</sup>

Mobile phones are also being used to communicate and analyse results. A study in Rwanda used a smart-phone attachment to test whole blood drawn via finger prick from 96 female patients seeking care at prevention of mother-to-child HIV transmission clinics or voluntary counseling and testing centres.<sup>9</sup> The dongle performed a triplexed immunoassay not currently available in a single test format: HIV antibody, treponemal-specific antibody for syphilis, and nontreponemal antibody for active syphilis infection. Health care workers obtained diagnostic results in 15 minutes with sensitivity of 92 to 100% and specificity of 79 to 100%, consistent with current clinical algorithms. Patient preference for the dongle was 97% compared to laboratory-based tests, and most appreciated the convenience of obtaining quick results with a single fingerprick. The authors conclude that combining microfluidics with recent advances in consumer electronics can make certain laboratory-based diagnostics accessible to almost any population with access to smartphones.

There is also growing use of mobile phone cameras as optical imaging devices.<sup>10</sup> Low cost, portable multi-wavelength fluorescence plate readers have been developed, especially to detect microbial toxins, and low cytometry has been used to detect very low cell concentrations. New approaches, like image stacking, use of lasers and streak imaging, have been developed to improve the sensitivity of these readers.

A study in California, US, was able to read and count single-molecule DNA and RNA using a camera phone.<sup>11</sup> By selecting amplification-indicator dyes that are within the spectral sensitivity of standard camera phones, the study was able to read sequence-specific single nucleic acid molecules in nanolitre volumes. When used with devices that integrate sample preparation and nucleic acid amplification, this approach will increase the affordability and distribution of diagnostic tests.

Another study created a portable biochemical analysis platform using a consumer-class quadcopter drone.<sup>12</sup> Managing disease outbreaks in remote areas often relies on inefficient and time-consuming channels for sample collection, diagnosis and action. To address these obstacles, the study authors removed the drone’s propellers and attached 3D-printed centrifuges to extract nucleic acid from samples. Convective thermocycling, powered by an external battery, enabled the polymerase chain reaction (PCR) with a single heater using a standard five volt USB source that powers mobile devices. The results are read via time-resolved fluorescence detection and amplification by a mobile phone camera and analysis app. And all this at a cost of less than \$US50! Using this drone technology could significantly reduce the time between sample collection and analysis in remote areas.

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## Paediatrics Review

### Maintenance intravenous fluids for children: time for action in low- and middle-income countries

For many decades maintenance fluid volumes for hospitalised children have been based on the formula by Holliday and Segar which was calculated from caloric expenditure, viz, 100ml/kg/day for the first 10 kg body weight, 50 ml/kg for the next 10 kg and 20 ml for each kg thereafter. The composition was commonly a hypotonic solution, e.g. sodium chloride 0.18% (Na 30 mmol/L, CL 30 mmol/L) with 4% dextrose.<sup>1</sup>

As explained in a recent editorial in Paediatrics and International Child Health by Trevor Duke, this for formula is inappropriate for sick children with infectious diseases, e.g. pneumonia, bronchiolitis, and sepsis, and intracranial disorders, also for surgical and post-anaesthesia patients, where antidiuretic hormone levels are commonly increased (SIADH). This may be complicated by impaired renal function, increased capillary permeability affecting the brain, lungs and soft tissues resulting in poor lung compliance and hypoproteinaemia.<sup>2</sup> In children with pneumonia<sup>3</sup> and bacterial meningitis<sup>4</sup> over a third may have hyponatraemia on admission and in bronchiolitis from 33%<sup>5</sup> to 80%.<sup>6</sup>

There have been a number of randomised controlled trials (RCTs) comparing hypotonic with isotonic maintenance fluids in regard to occurrence of hyponatraemia

but very few from low- and middle-income countries (LMICs). There has been one from India<sup>7</sup> and a recent one from Mexico.<sup>8</sup> Many of the studies have relatively small numbers of study participants and heterogeneous groups comprising children admitted to medical wards, and intensive care units (ICU), or undergoing surgery.

There have been three meta-analyses on the subject each comprising 10 RCTs and each analysing around 900 study participants and all were published in 2014.<sup>9–11</sup> All three meta-analyses concluded that hypotonic maintenance fluids increased the risk of hyponatraemia. There was insignificant risk of hypernatraemia in the isotonic groups. However, there was a predominance of patients from surgical or ICU settings and results generally applied only to the first 24 hours of admission.<sup>11</sup>

The most recent RCT, comprising the largest number of participants studied from one site (n641), was undertaken at the Royal Children's Hospital, Melbourne, Australia.<sup>12</sup> Eligible participants were children aged three months to 18 years requiring IV maintenance fluids. Three-hundred and nineteen (319) received Plasma-lyte148 (Na140) (comprising in mmol/L: Na 140, Cl 98, K 5, Mg 1.5, acetate 27, gluconate 23 and glucose 50 g/l), and 322 received 0.45% sodium chloride with 5% glucose (Na77). The study continued for 72 hours or until the patient was receiving <50% of standard maintenance rate. Hyponatraemia was defined as serum sodium <135 mmol/L with a decrease of at least 3 mmol/l compared with baseline measurement. The study fluid was stopped early if sodium decreased to <130 or increased to >150 mmol/L. Half of the patients had undergone a surgical operation immediately before or during the treatment period and there were similar proportions in the elective and emergency surgery groups. Mean (SD) serum sodium on admission in the Na140 group was 137.8 (3.1), range 131–148 and in the Na77 group, 138.2 (3.1), range 131–147.

Fewer Na140 patients (12, 3.8%) developed hyponatraemia than those in the Na77 group (35, 10.9%), (p=0.001). Hypernatraemia developed in 14 (4.4 %) Na140 patients and 18 (5.6 %) Na77 patients, and seizures in 1 (0.3%) and 7 (2%) patients, respectively. However, all patients with seizures had a known seizure disorder. The greatest risk of hyponatraemia was in the first six hours in both groups, and the Na140 group had a very small risk of hyponatraemia beyond the first day of treatment compared to a continuous risk for the Na77 group. Of the 18 patients admitted to ICU 5 (46 %) of 11 patients in the Na77 group had hyponatraemia compared to 1 (14.1 %) of the Na140 group.

This large RCT confirms the finding of previous trials and demonstrates that children administered isotonic maintenance solutions have lower risk of hyponatraemia compared to those receiving hypotonic solutions.

Some countries, i.e. UK and Canada have issued patent safety alert warnings regarding the risks of using hypotonic fluids for maintenance therapy and Duke advises that the World Health Organization (WHO) should now also proceed to issue a patent safety alert which will encourage Ministries of Health and hospitals in LMICs to remove stocks of fluids with very low sodium concentration.<sup>2</sup>

For IV maintenance fluid therapy WHO recommends

Ringer's lactate with glucose (contains in mmol/L: Na 130, Cl 109, lactate 28, K 4, and Ca 5). (Hartmann's solution has an almost identical composition) or 0.9% normal saline with glucose (sodium and chloride 150 mmol/L) or half normal saline (0.45%, sodium and chloride 77mmol/L) with glucose.<sup>13</sup> However, in the meta-analysis by Foster et al, a subgroup analysis of hypotonic fluids comprising 0.45% sodium chloride with glucose demonstrated a relative risk of hyponatraemia of 2.42 (95% CI 1.32-4.45).<sup>10</sup> Also the fluid chosen for the hypotonic arm of McNab et al's study was 0.45% sodium chloride in 5% glucose.<sup>12</sup> Although many of the RCTs reviewed used 0.9% saline and 5% glucose as the isotonic fluid there is concern that the high chloride level could cause hyperchloraemic metabolic acidosis. Thus, because of this concern, ideally Ringer's lactate (or Hartmann's solution) or plasma-lyte148 are the optimal maintenance solutions.<sup>2,14</sup> However, presently the risk is theoretical and 9% saline is cheaper than the above two solutions. Until there is clear evidence that 0.9% saline is a real risk for hyperchloraemic acidosis there is no reason not to use it in LMICs.

Duke's article details fluid rates, volumes and composition for maintenance fluids for sick children and outlines important issues regarding monitoring for the duration of IV fluids.<sup>2</sup>

Further trials are required on the management of maintenance fluids for infants <3 months of age and fluids in general for children with severe malnutrition. For young infants there is concern that isotonic maintenance fluids could cause hypernatraemia. The metabolism in children who reach the stage of severe malnutrition is very complex. There is increased total body sodium despite hyponatraemia of the extra cellular space as well as hypoproteinaemia. One reason for the hyponatraemia may relate to intracellular leakage of sodium.<sup>15</sup> Considerable research effort is now required to work out both the optimal fluid and volume for the treatment of hypovolaemia and shock and provision of safe maintenance fluids for severely malnourished children.

It is now time for action on provision of safe maintenance fluids for sick children and those who are undergoing surgery especially in LMICs.

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# Africa HEALTH

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