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

Neonatal sepsis

Estimates of the global burden of neonatal sepsis, especially in low- and middle-income countries (LMIC) are scarce. This is owing to a number of reasons including the large proportion of infants born at home, limited facilities for diagnosis and with restricted resources priority is given to treatment of older infants and children.

A retrospective review of hospital-based childhood deaths was undertaken in Malawi, where the under-5-mortality rate is 64/1000 live births. The major causes of death were malaria 26.0%, malnutrition 13.6%, HIV-related illness 9.9%, sepsis 8.9% and perinatal deaths 4.4% (perhaps a third of which may have been due to sepsis).[1] Deaths in the neonatal nursery were excluded. The study demonstrates that in this setting priority for detection and managing neonatal sepsis is dwarfed by the burden of disease in older infants and children.

In a review of 150 newborns clinically suspected of sepsis in Ghana, the median (IQR) gestational age was 38weeks (36-39) and 26 (17.3%) had positive blood cultures. All were resistant to ampicillin.[2]

A prospective study of neonates born in three tertiary care centres in Delhi, India enrolled 13,530 infants of 88,633 live births (15.3%) suspected of sepsis between 2011 and 2014.[3] The total incidence of sepsis was 14.3% and of culture-positive sepsis was 6.2%. Two thirds of the total episodes occurred at or before 72h of life (early onset sepsis, EOS). Multidrug resistance was defined as Gram-negative isolates resistant to three of five antibiotic classes (extended-spectrum cephalosporins, carbapenems, aminoglycosides, fluoroquinolones and piperacillin-tazobactam). Two-thirds of 1005 isolates were Gram-negative and multidrug resistance was detected in 38-82%. Methicillin resistance (MRSA) was found in 61% (85/140) of coagulase-negative staphylococci and 38% (43/114) of S.aureus isolates. Nearly a quarter of deaths were owing to sepsis.

A literature search of antimicrobial resistance in LMIC from 1990-2008 found 10 relevant reports.[4] Resistance against E.coli was as follows: ampicillin 72%, cotrimoxazole 78%, third generation cephalosporins 19% and gentamicin 13%. The first-line antimicrobial agents recommended by WHO for serious infections in young infants is ampicillin and gentamicin.

Most of the detailed research on neonatal sepsis is undertaken in high-income countries (HIC) which have among other tools the benefit of good microbiology services and antimicrobial stewardship, meticulous records and data collection, PCR in addition to optimal practices in obtaining cultures of body fluids, and a range of inflammatory markers. However, the downside is the relatively large proportion of very low birth weight (VLBW) infants requiring often prolonged mechanical ventilation, intravenous and enteral feeding and exposure to multiple invasive devises which are often complicated by systemic fungal infections.

In a report of almost 400,000 live births at academic-based neonatal centres in the USA between 2006 and 2009, there were 389 infants with EOS (0.98 cases per 1000 births) with 43% due to Streptococcus agalactiae (GBS) (0.41 per 1000 live births) and 29% to E.coli (0.28 per 1000 live births).[5] Most infants with GBS infections were full term (73%) and 81% of those with E.coli were preterm. Overall case fatality was 16% and it was inversely related to gestational age: 54% at 22-24w, 30% at 25-28w, 12% at 29-33w and 3% in infants more than 37w gestation. Mortality rates for infants with GBS were 9% and were 33% with E.coli sepsis. However, when adjusted for gestational age, mortality rates were similar. Although GBS is isolated from infants (and their mothers) in LMIC[6] is it is uncommon. This might be partly due to laboratory difficulties in differentiating GBS from other streptococci. Intrapartum antimicrobial prophylaxis administered to GBS-colonised women has reduced the prevalence of early GBS invasive infections and Gram-negative pathogens are now emerging as an increasing cause of EOS.[5]

Low maternal and neonatal vitamin D levels are associated with increased risk of EOS.[7]

In HIC coagulase-negative staphylococci (CONS) are the most common isolates in late-onset sepsis (LOS), followed by S.aureus , a proportion of which are multiresistant (MRSA).[5] However, the prevalence of CONS can be substantially reduced by good infection control measures.[8] Candida spp are now the third most common cause of LOS in LBW infants (<1500g). Apart from prematurity, gastrointestinal colonisation and vascular catheterisation are important risk factors which, if reduced, have the potential for control of fungal transmission.[5]

The key to diagnosis of neonatal sepsis is the ability to repeat blood and CSF cultures and indices of inflammation. Up to a third of VLBW infants may have meningitis but no signs of systemic sepsis.[9] Inflammatory indices include total leucocyte count (WBC) and differential, ratio of immature/total neutrophil ratio (I/T),[10] C-reactive protein (CRP),[11] ESR and procalcitonin levels.[12] WBC should be estimated after 4h of age and due to the varying levels during the first 12h of life serial measurements are more informative than a single one. CRP requires hepatic synthesis after the onset of infection and thus serial measurements, if possible in combination with other acute phase reactants and markers such as procalcitonin and interleukins levels (e.g. 6 and 8), are required. Procalcitonin levels may also be used in decisions to reduce antibiotic therapy in neonates suspected of EOS.[12]

In LMIC it is estimated that rates of neonatal sepsis in the community are up to 170/1000 live births when

clinically diagnosed and 5.5/1000 live births when diagnosed by blood culture.[13] In many regions of LMIC the majority of births take place at home or in first-level health facilities, and even if sepsis is diagnosed, access to hospital may be constrained for a number of reasons, including availability of transport. It is essential that management of neonatal sepsis should commence in the community with adequate training of health workers and availability of appropriate antibiotics. In the hospital environment it is not known (nor may never be known) how many infants with neonatal sepsis die because of the very serious increasing evidence of multidrug resistance to first and second (and even third) line antimicrobials. There must be increased awareness of the risk of sepsis, especially EOS, and regular availability of inflammatory markers, e.g. WBC and differential and CRP. Stewardship of antimicrobials has to begin in both the community and health facilities.

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STIs

Syndromic management of STIs

Syndromic management of sexually transmitted diseases based on a patient's symptoms remains an important, low-cost tool for diagnosing and treating infections in many low resource settings worldwide. The accuracy of these syndromic approaches, however, often depends on how well the syndromic protocol corresponds with the prevalence of infections and levels of antibiotic resistance in the local population. National protocols must be regularly updated to reflect these evolving factors, and health care providers must receive training on the revised protocols. While syndromic management can be very effective, there are many situations where it performs poorly.

A systematic review of syndromic management of vaginal discharge culled through 2,845 studies and evaluated 16 of these which used the WHO Vaginal Discharge Flowchart[1] and found the diagnostic flowcharts performed poorly at identifying cervical infections (*Neisseria gonorrhoeae* and *Chlamydia trachomatis*).[2] The four flowcharts had sensitivity (among those with infection, what percent test positive) of 27.37%. The flowcharts were more successful at identifying vaginal infections (Bacterial vaginosis and *Trichomas vaginalis*). Based on these findings, the authors conclude the vaginal discharge flowcharts should focus on management of vaginal infections, and they could be used an intermediate approach for cervical infections among sex workers. Another systematic review of abnormal vaginal discharge flowcharts assessed 36 studies and 99 flowcharts.[3] Summary sensitivities for WHO flowcharts ranged from 41.2 to 43.6%, and for locally adapted flowcharts from 39.5 to 74.8%. Overall the flowcharts were found to be poor diagnostic tools, with many women receiving unnecessary treatment and many women with cervical infections were not detected.

A study in Zimbabwe assessed the aetiology of symptomatic vaginal discharge and the adequacy of the current syndromic management guidelines.[4] Of the 200 symptomatic women in the study, 146 had an aetiology detected, including bacterial vaginosis (24.7%), *N. gonorrhoeae* (24.0%), yeast infection (20.7%), *T. vaginalis* (19.0%), *C. trachomatis* (14.0%), and *M. genitalium* (7.0%). The syndromic management protocol covered 115 (57.5%) of the women who had gonorrhoea, chlamydia, *M. genitalium* or bacterial vaginosis, while 85 women (42.5%) received treatment without a diagnosis.

Syndromic management is more successful among men presenting with urethral discharge. Men presenting with urethral discharge in Zimbabwe are treated with a single intramuscular dose of kanamycin or ceftriaxone in combination with a week's course of oral doxycycline. A study of 200 men with urethral discharge in Zimbabwe found 163 (81.5%) had one or more pathogens, including *N. gonorrhoeae* (73.5%), *C. trachomatis* (22.5%), *T. vaginalis* (4.0%) and *M. genitalium* (3.5%) (5). Among these men, 60% had one infection, 20% had two infections, and 1% had three infections. The current syndromic management and treatment protocols are adequate, but ongoing monitoring for gonococcal resistance is needed.

Another analysis from the Zimbabwe STI Etiology Study assessed how well the syndromic protocols for genital ulcer disease (GUD) performed (6). Of the 200 men and women in the study, 38.5% were positive for Herpes simplex virus (HSV), 16% positive for *T. pallidum* (syphilis), 1% positive for Lymphogranuloma venereum (LGV)-associated strains of C. trachomatis,

and 49% had no infection. For all GUD patients, HIV positivity was 52.2%, with higher rates among women (59.8 % vs. 45.2% among men) and among patients with HSV (68.6% vs. 41.8%). There was a high rate of chlamydia and gonorrhoea comorbidity (31% of women and 23.5% of men). However, 63% of women and men with coinfections (17% of all patients with GUD in this study) did not have vaginal or urethral discharge, and would have not received treatment under syndromic protocols. Future guidelines should address these coinfections.

A study in South Africa highlights the risks of missed STI infections. Two-hundred and ninety-eight HIV-seronegative females, ages 16-22, from Soweto and Cape Town were tested for STIs and bacterial vaginosis (BV).[7] The study found rates of BV (46.6%) and HPV (66.8%) were high in both communities. Rates of infection with *C. trachomatis* and *N. gonorrhoeae* were more than twice as high in Cape Town than in Soweto (chlamydia: 42% vs. 18%; gonorrhoeae 11% vs. 5%). Only 24% of the adolescents with vaginal discharge-causing STIs or BV were symptomatic. In this group, syndromic management of vaginal discharge had a sensitivity of 23% and specificity (among those without infection, what percent test negative) of 85% for diagnosing a discharge-causing STI or BV. More than 70% of the young women in this study with treatable STIs that could enhance HIV risk would have been missed by syndromic management alone.

Point of care testing

One of the best ways to improve on syndromic management of STIs is to use point of care (POC) tests to confirm infection and enable effective treatment in one visit. Fortunately, there are many highly sensitive and specific tests now available to test for *C. trachomatis*, *N. gonorrhoeae*, and *T. vaginalis* and the technologies are changing rapidly. A systematic review of 33 research studies on POC tests for these pathogens found at least one test for each infection with sensitivity and specificity ≥90%.[8] There is need for more research on the acceptability, feasibility, cost, and sensitivity and specificity among populations not considered to be at risk, including pregnant women.

The December 2017 Supplement to the journal *Sexually Transmitted Infections* focuses on POC testing for STIs and includes reviews of the performance of POC tests for dual tests for HIV and syphilis, urogenital gonococcal infections, urogenital *Chlamydia trachomatis*, *Trichomonas vaginalis*, and human papillomavirus.[9] It also includes reports on the evaluation of POC tests for syphilis in Brazil, and among men who have sex with men in Verona, Italy; on the acceptability and feasibility of scale-up of dual HIV/syphilis testing in Malawi; and POC tests that combine diagnostics with antimicrobial resistance prediction for *N. gonorrhoeae* and *M. genitalium*.

Recognising the importance of POC testing in the overall strategy to address the impact of STIs on global health, the World Health Organization Department of Reproductive Health and Research convened a group of experts in 2014 and 2015 to develop protocols for independent evaluation of promising POC tests, to investigate implementing these core protocols in select countries, and to develop a roadmap for the development of new POC tests.[10] While there are many diagnostic products in the pipeline, there is need to help these along by setting up evaluation sites, harmonising regulatory processes, and modelling cost-effectiveness.

STI challenges

The journal *Lancet Infectious Diseases* published a comprehensive Commission on STIs in July 2017 which discusses recent advances in STIs and promotes debate on the education, control, treatment, and diagnosis of STIs.[11] Based on input from international experts, the Commission identified five areas where there have been significant advances, new problems have emerged, or the epidemiology of infections has changed. These areas are: future directions of the control of chlamydia, treatment of gonorrhoea in the face of increasing antimicrobial resistance, cause of bacterial vaginosis and implications for treatment, challenges in the diagnosis and control of STIs in low- and middle-income countries, and how the medical interventions to address HIV infection might affect other STIs. Three other challenges of importance, but not included in the Commission are also discussed: the control of *M. genitalium*; the burden of syphilis, with a focus on China; and what improvements in the management of STIs should be implemented at the health system level.

Non-traditional STIs

There are more than 30 recognised sexually transmitted infections worldwide, including those transmitted primarily by sexual contact and those that can be transmitted sexually, but whose primary mode of transmission is by food, vector or droplet.[12] The latter types of non-traditional STIs pose significant challenges to health care providers. One study looked at shigellosis and *N. meningitidis*, two infections that have recently emerged as sexually transmissible.[13] Shigellosis is a diarrhoeal disease caused by the species of bacterium *Shigella*. Once most common in children and international travellers, in the 1970s the infection grew more common among men who have sex with men (MSM) in the United States. Sexual transmission of *Shigella* likely occurs during oral-anal or digital-anal sex. Routine case reporting for *Shigella* does not include information about sexual practices, but rising rates of *Shigella* among men in the US and England between 2004 and 2015, while rates declined among women and children, indicate *Shigella* is re-emerging as an STI among MSM. Some *Shigella* strains are showing multidrug resistance internationally among MSM.

N. meningitidis is the bacterium that causes invasive meningococcal disease (IMD). It is spread primarily by droplet and infects the respiratory mucosa. About 5-10% of healthy adults are nasopharyngeal carriers, and the bacterium has also been isolated in men with urethritis. *N. meningitidis* in the human urogenital tract could be the result of oral-genital sexual contact, and the bacterium is genetically adapted to the urogenital tract. More recently there have been outbreaks of IMD among MSM in Europe, Canada and the US. It is not clear what the primary mode of transmission is between MSM.

Two other viruses have been newly recognised as being sexually transmissible. In the Ebola virus outbreak

in West Africa in 2013, there were more than 28,000 confirmed cases and more than 11,000 deaths. Follow-up of cases among individuals not in close proximity to those infected led to the confirmation of Ebola virus in semen. While this had been confirmed in prior outbreaks of Ebola, in this outbreak, Ebola was found to persist in male semen 565 days after the onset of symptoms. Although the risk of transmission from semen is thought to be small, the number of male Ebola survivors made flare-ups a concern even as the epidemic declined. It is thought female-to-male transmission of Ebola is inefficient, but possible.

The large outbreak of Zika virus in Latin America and the Caribbean in 2015-2016 drew global attention in part because of its association with microencephaly. While the primary mode of transmission is through the bite of the *Ades spp*. mosquito, sexual transmission of Zika has been confirmed since 2008. An estimated 80% of Zika infections are asymptomatic, creating a huge reservoir of virus.[14] Case reports from 13 countries now document probable sexual transmission, via oral, anal and vaginal sex, to partners of travellers returning from endemic areas. Like Ebola, Zika virus persists in the body. The maximum time the Zika virus has been confirmed to survive in genital fluids is 188 days in semen by reverse transcriptase PCR (RT-PCR), 69 days in semen by culture, 3 days in vaginal fluid by RT-PCR, and 11 days in cervical mucus by RT-PCR. These non-traditional STIs offer lessons for the future detection, prevention and control of other re-emerging and newly recognized STIs.

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Pharmacy

Falsified Medicines

I have written before about counterfeit medicines, and there is now more international interest. Europe is introducing on Saturday 9 February 2019, the Falsified Medicines Directive (FMD). Falsified is defined as contains no active ingredient, the wrong active ingredient or the wrong amount of the correct active ingredient. It does not include medicines that contain the correct amount of the active ingredient, but are labelled as a different brand.

The system will work be each individual container (pack or bottle) printed with a 2-D barcode identifying each pack (representing a 20 digit number). The *Pharmaceutical Journal*[1] describes the process as identifying each pack at the point of dispensing, then decommissioning (removing from the active database). The system ensures that the manufacturer also adds a tamper-proof seal to each container.

If a pack has a bar-code that doesn't match the manufacturer's information, or a duplicate barcode dispensing the pack is prohibited.

The cost of the system is funded by the manufacturers, but there are concerns that it would take longer to dispense the medicines, and that training is required.

This system appears to be the European solution similar to two systems reported by the BBC in 2016 (www.bbc.co.uk/news/business-37470667). Both the mPedigree and the Sproxil system use a scratch-off label with a number that is sent by SMS and the database confirms if the pack is genuine.

All these systems have a unique pack identifier. If they are implemented on a larger scale they should reduce the amount of counterfeit medicines on sale.

Pregnancy and Breast Feeding

Some of the more difficult enquiries concern the use of medicines in pregnancy and breast feeding. For many medicines there is no good information, and no one source provides sufficient details for all patients.

Recently the BNF (British National Formulary) has re-designed the layout in order to make it easier to read electronically. There used to be appendices about pregnancy and breast feeding; now the information is within each monograph. The information in the BNF is accurate, however it errs on the side of caution, and the information is not always useful for the immediate care of patients.

The BNF is available as an App for iPhone and Android, and online at www.medicinescomplete.com, however access may be restricted in some countries.

Hear Disease in Pregnancy and Breast Feeding

According to some sources, cardiovascular disease has overtaken infectious and insect-mediated disease in some parts of Sub-Saharan Africa,[2] and that cardiac disease (including pre-eclampsia) carry a very high mortality rate in pregnancy. The BMJ (*British Medical Journal*) published a review of cardiac medicines in pregnancy and breast feeding[3] with specific reference to pregnancy in women with congenital heart disease, although much of the information is useful to cardiac disease in general. The article includes a chart of the safety of many cardiac medicines in both pregnancy and breast feeding.[4] The key points of the article relate to pre-conception advice:

- Offer woman of childbearing age with cardiovascular disease counselling and risk stratification before conception
- Counselling is best made available within the paediatric cardiology transition service
- Offer the woman appropriate contraceptive advice
- In women contemplating pregnancy, change cardiovascular medications to those which can be used in pregnancy, and emphasise the importance of close monitoring
- In women not contemplating pregnancy, ensure effective discussion on contraception and early pregnancy termination

The article includes a table derived from the WHO[5] of the relative risks to the mother and infant of the various categories of cardiac disease in the mother.

Class I carries almost no risk, class IV including pulmonary arterial hypertension carries a severe risk of mortality to the mother.

The drugs considered to be safe both in pregnancy and breast feeding are:

- Beta-blockers: labetalol and bisoprolol
- Calcium channel blockers: nifedipine and atenolol
- Platelet inhibitors: low dose aspirin
- Anti-arrhythmic drugs: procainamide and flecainide
- Diuretics: furosemide and hydrochlorothiazide.

Drugs contraindicated in pregnancy are: ACE (angiotensin converting enzyme inhibitors, e.g., captopril), angiotensin receptor blockers (e.g., candesartan), spironolactone.

The chart is especially useful to prescribers and will be a standard reference where I currently work.

Drug Errors

The Policy Research Unit in Economic Evaluation of Health & Care Interventions (EEPRU) has issued a major report of drug administration errors.[6] Error rates reported are up to 90%, but some reports have errors as low as 0.2%. A presentation at the East of England Global Health Conference2 gave medication omission rates of 20%, which was not altered by applied interventions.

Most interventions (72%) are reported to cause no harm to the patient although some can cause death, mainly in elderly patients.

The most significant cause of death (up to 50% of total deaths) from adverse drug reactions (drug side effects) is gastro-intestinal (GI) bleeding cause by NSAIDS (non-steroidal anti-inflammatory drugs, e.g., ibuprofen, diclofenac), anticoagulants (e.g., warfarin), and anti-platelet drugs (including aspirin, and clopidogrel).

The risk of errors was highest in children, patients with renal (kidney) failure, and the elderly. Up to 7% of hospital admissions in the UK are due to side effects of medicines, about two-thirds of these could have been prevented. Prescribing errors varied between care settings. Errors in primary health care (General practice) were about 5%; in secondary care (Hospitals) about 1%; in care homes (mainly for the elderly) about 40%. Administration errors accounted for about 40%, and dispensing errors 16% of the errors. Adverse drug reactions and drug errors cost the NHS in England almost £100 million. Overall 2% of drug errors cause serious harm to patients, but 70% cause minimal harm to patients.

There are interventions that can be made to reduce errors in medication include alerts on high risk drugs. A systematic review identified 12 drug groups that account for 80% of hospital admissions that are medication-related and preventable. Three groups of drugs that are responsible for over a third of these admissions; anticoagulants, antiplatelets and non-steroidal anti-inflammatory drugs (which all cause gastrointestinal bleeding). An important implication from this study is that reducing hazardous prescribing in general practice associated with specific groups of drug could prevent the majority of medication-related hospital admissions.

An article in the *European Journal of Hospital Pharmacy*[7] looked at dispensing errors in the use of trade-names (rather than generic names, although some errors were caused by generic name confusion) for dispensing. The most common error overall was dispensing the wrong amount of drug, but over 40% or errors involved dispensing the wrong drug, and 9% involved the wrong strength of the drug. The overall incidence of dispensing errors was give as 0.02%.

Overall the conclusions could be that there is no substitute for reading and understanding the label on the medication.

Medicines Information for All

A poster presentation[8] at the East of England Global Health Conference looked at the worldwide accessibility of information on medications. The research found that most information was received from the pharmaceutical industry. The amount of research on the subject was minimal (fewer than 50 articles), and that further research was needed.

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