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

Family medicine and primary care

Indications for tonsillectomy

When I moved last year to a new position in a different province of South Africa, I noticed that there seemed to be a high tonsillectomy rate in primary and secondary care. In the previous areas where I have worked, we rarely did such procedures but here I found that there is a weekly tonsillectomy list in the theatres of a number of the small hospitals I visited. I had assumed this to be a local problem. However on a recent trip I was in discussion with a general surgeon from Kenya who talked about the problem of surgical trainees going to rural hospitals and performing procedures that they should not necessarily be doing, with tonsillectomies being included in that list.

Following what I saw, I found an article published last year that looked at the issue of rates of tonsillectomy.[1] The authors found that it is a commonly performed procedure internationally but that there is wide variation in rates (190 - 850/100,000 people ≤19 years of age). They therefore carried out the study to look at the rate in the private health sector in South Africa with regional variations and compare this to international rates. The authors found that the rate was more than double the highest reported national tonsillectomy rate (1,755/100,000 in 2013) and varied regionally within the country. There is no evidence of an increased burden of disease that relates to this. The authors conclude that the variation is due to differences in training and clinical practice, and thus is to some extent a cultural issue amongst medical practitioners. They argue for the development of evidence-based locally relevant indications for tonsillectomy to guide clinical practice.

An article published in the *American Journal of Otolaryngology* earlier this year from Egypt looked at the management of recurrent tonsillitis in children.[2] They compared two antibiotic regimens namely azithromycin and Benzathine penicillin and found these to be equally effective in the reduction of recurrence to each other but also similar to the results obtained with tonsillectomy. A Cochrane review on tonsillectomy versus nonsurgical treatment for chronic or recurrent acute, tonsillitis indicated that there is a small reduction in the number of episodes of sore throat in children in the first year after surgery compared to nonsurgical treatment.[3] The authors note the two studies show there was no significant difference in quality of life outcomes and one study showed no difference in analgesic consumption. In terms of adults there is insufficient evidence on the effectiveness of tonsillectomy. They note that potential benefits of surgery should be weighed against the risks which are not insignificant. In summary it seems that they may be some indications for tonsillectomy in children with chronic and recurrent tonsillitis but tonsillectomy for tonsillitis is difficult to justify in adults.

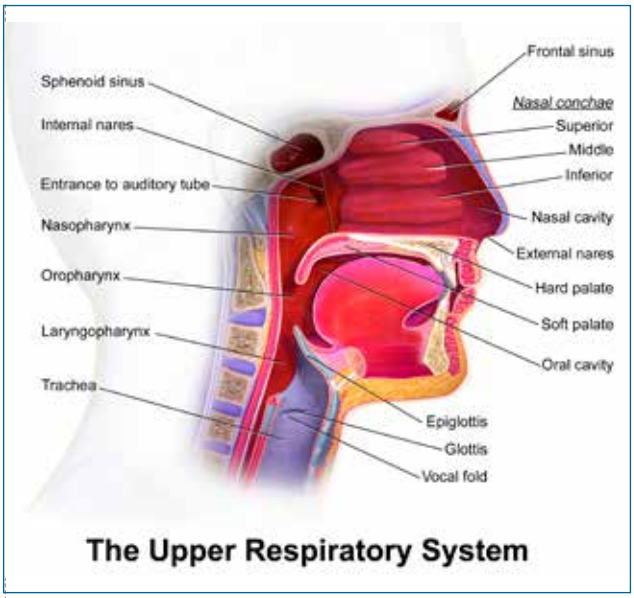
A review paper published last year on indications for tonsillectomy noted that clinical guidelines often include peritonsillar abscess, but suggested that on the basis of evidence, tonsillectomy as first-line treatment is not indicated and should be limited to patients with recurrences, complications or a history of recurrent tonsillitis.[4] Further the author states that tonsillectomy compares to antibiotic therapy and thus because of the considerable post-operative morbidity there needs to be clear indications around the number of episodes required to justify tonsillectomy as opposed to any other treatment. Once again, the need for appropriate, local, evidence-based guidelines is clear.

Upper respiratory tract infections

It is not only the tonsillectomy that is overused in treating tonsillitis but more broadly antibiotics in the treatment of sore throats and other respiratory tract infections. One does not have to look far in both the scientific and the lay press to find articles about the level of abuse of antibiotics and the dangers brought about by this ongoing problem, especially increasing resistance and the rise of superbugs. A recent CPD article in South African Family Practice about the management of colds and flu[5] is worth reading, because I have noted that many colleagues use the two terms interchangeably as if they are the same illness. The authors make the important point that the common cold and flu are two very different viruses with similar symptoms but there is no place for antibiotic usage in either. In fact despite the widespread use of antibiotics for these conditions, justified by physicians on the basis of shortening the length of the illness or preventing superinfection, they note that there is no clinical evidence suggesting that antibiotic use can alter the course of the disease or prevent secondary infection. Treatment of course should be symptomatic.

It is clear that there are many respiratory tract infections are over treated with antibiotics, despite the fact that most are viral in origin.[6] The World Health Organization (WHO) has called for the development of national action plans in regard to overprescribing. Just this month, an article in the Medical Journal of Australia has advocated for a national strategy to reduce overprescribing in general practice.[7] The WHO indicates that antibiotics are prescribed in 45.9% of patient encounters in Africa, as opposed to a reference value of less than 30%.[8]

Given the problem of the overuse of antibiotics in upper respiratory tract infections, one proposed strategy is that of delayed antibiotics: instead of prescribing antibiotics when the patient presents, if the patient is assessed to have a respiratory tract infection they can



The Upper Respiratory System

be given symptomatic treatment and advice, and asked to return if they are not improving or there is any deterioration the condition. In some health systems prescriptions can be given with instructions to the patient that they wait for two days before deciding whether to fill the prescription. An updated Cochrane review published earlier this year looked at the effects on clinical outcomes and other factors of delayed prescription of antibiotics in respiratory tract infections.[9] They found that for many clinical outcomes either strategy produced the same results. While they were some better patient satisfaction with delayed antibiotics there was not as great a reduction in antibiotic use as there is with not using it at all. Basically the conclusion is that when clinicians feel it is safe not to prescribe antibiotics immediately for people with respiratory infections no antibiotics with advice to return if symptoms do not resolve is likely to result in the least use of antibiotics while still maintaining patient satisfaction and clinical outcomes; where clinicians are not confident to do, delayed antibiotic use is a strategy that is acceptable.

Clinicians often respond that patients or their parents demand antibiotics. A study reported in the annals of family medicine looked at the attitudes of parents towards the use of antibiotics in acute respiratory tract infections with children.[10] They noted the fact that parents have misguided beliefs about the role and value of antibiotics and overestimate their benefits. The authors highlight the need for improved communication and shared decision-making around antibiotic use. The above-mentioned Cochrane review on delayed prescribing suggests that patient satisfaction can be maintained with appropriate explanation.

Another Cochrane review published this year addresses the issue of worldwide health threat of antibiotic resistance by looking at effects of interventions aimed at influencing clinician antibiotic prescribing behaviour for acute respiratory tract infections.[11] They found evidence that point of care C-reactive protein testing, shared decision-making and procalcitonin-guided management reduce antibiotic prescribing. (In February, 2017, the US Food and Drug Administration approved the use of procalcitonin, a blood infection marker, to guide antibiotic therapy in patients with acute respiratory infections.)[12] They note however that most research was undertaken in high countries. Given the widespread abuse of antibiotics in Africa, it is critical that we develop locally relevant strategies for addressing the problem. The use of Centor's criteria, an old approach recently re-evaluated, may provide a more practical approach that could be incorporated into our primary care.[13]

Ultimately it is important that we as clinicians need the recent call in Lancet Infectious Diseases that 'all health-care providers who prescribe antibiotics need to take ownership, engage in stewardship, and understand the societal burden of inappropriate antibiotic use.'[14, p.e56.]

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AIDS

The epidemiology of the HIV/AIDS epidemic and the scale up of antiretroviral therapy (ART) in 2016 was described by the joint United Nations Programme on HIV/AIDS (UNAIDS).[1,2] By December 2016, there were an estimated 36.7 (30.8–42.9) million people living with HIV/AIDS (PLHIV) globally, of whom 94% were adults and 6% were children under 15 years of age. In 2016, 1.8 (1.6–2.1) million people were newly infected with HIV and 1.0 (0.83–1.2) million people died from HIV/AIDS. Compared with the previous year, HIV incidence and HIV mortality were slightly lower.

Sub-Saharan Africa (divided now in UNAIDS reports into Eastern / Southern Africa and Western / Central Africa) bears the brunt of this epidemic, as it has done for the last two decades, with 25.5 million adults and children (69% of global total) living with HIV in 2016.[1,2] There were 1.16 million new HIV infections (64% of global total) and 730,000 deaths (73% of global total). Of the 160,000 new HIV infections globally in children, 137,000 (86%) occurred in sub-Saharan Africa. Southern Africa remains the worst affected region on the continent as it accounts for 76% (19.4 million) of the region's disease burden. Within this region, South Africa continues to have the largest HIV/AIDS epidemic in the world with an estimated 7.1 million people living with HIV.

By the end of 2016, there were 19.5 million people globally receiving ART, representing 53% of all people living with HIV.[1,2] In sub-Saharan Africa there has been excellent progress in terms of access to treatment, with over 13.8 million people on ART by 2016. In the world's most affected region, Eastern and Southern Africa, the number on treatment has more than doubled since 2010, reaching 11.7 million, representing 60% of people living with HIV. South Africa alone has almost 3.9 million people on treatment, more than any other country in the world. After South Africa, Kenya has the largest ART programme in sub-Saharan Africa with 1.0 million people on therapy by 2016, with Mozambique (990,000), Zimbabwe (980,000), Uganda (940,000), Tanzania (850,000) and Zambia (800,000) following closely behind.[1,2]

Since 2010, the annual number of new HIV infections (all ages) has declined by about 16%, but the pace of decline is far too slow to reach the Fast-Track Target agreed upon by the United Nations General Assembly in 2016.[1,2] However, sub-Saharan Africa is not doing badly: the steepest decline in new HIV infections between 2010 and 2016 was achieved in Eastern and Southern Africa (29% decline) with Western and Central Africa achieving a 9% decline. In contrast, in some regions of the world, the trend in new HIV infections is either stable (for example, Latin America) or increasing (for example, in Eastern Europe and Central Asia the annual number of new infections has increased by 60%).

This being said, there is no room for complacency in sub-Saharan Africa. Adolescent girls and young women in this region are still at particularly high risk of HIV infection due to poor access to education / sexual and reproductive health services, poverty, food insecurity and violence.

Advances in Antiretroviral Therapy Regimens

The consolidated WHO guidelines launched in July 2016 recommended that ART should be offered to any PLHIV regardless of WHO clinical stage or CD4 cell count and this includes adults, pregnant and breast feeding women, adolescents and children. Since 2016, WHO has been recommending new alternative ARV drug options: dolutegravir (DTG) and efavirenz 400 mg (EFV400) for first-line therapy, and darunavir / ritonavir (DRV/r) and raltegravir (RAL) for second- and third-line therapy.[3]

For first-line treatment, DTG is associated with higher antiretroviral efficacy, better tolerability, lower rates of treatment discontinuation, a higher genetic barrier to resistance and fewer drug interactions compared with other ARV drugs. EFV400 has comparable efficacy and improved safety compared with EFV at the standard dose of 600 mg daily. These two alternative first-line options are now becoming available in low- and middle-income countries (LMIC) as generic fixed-dose combinations at lower prices than the current preferred first-line regimens in use. Although the DTG- and EFV400-containing regimens have clinical and programmatic advantages compared with current standard first-line ART, there is little experience with their use in LMIC. More evidence is needed in these settings and for specific high risk-populations about efficacy and safety, especially during pregnancy.

In second-line therapy, the DRV/r co-formulation is comparable with other boosted protease inhibitors with no significant differences in terms of adverse reactions or treatment discontinuation, hence supporting its use as an alternative medication in second-line regimens. RAL has been approved for children, adults and pregnant women and is effective and well tolerated for second- and third-line regimens after failure of protease-inhibitor-based regimens. Currently, the prices of formulations for these second-line drugs from the pharmaceutical companies, the pill burden and the lack of affordable generic fixed-dose combinations limit their large scale use in LMIC, but this is likely to change in the near future.

The development of new and better ARV drugs is a fast moving field. Two new drugs (cabotegravir and rilpivirine) are in development as long-acting injectable formulations, with a recently published 96-week duration, non-inferiority trial in North America and Europe demonstrating similar efficacy, acceptability and tolerance compared with the current three-drug oral therapy.[4] While it will be challenging for ART programmes in LMIC to keep pace with these new advances and especially to translate them to implementation in the field, it will be important for them to do so, given the increasing prevalence of HIV drug resistance. This has increased from 11% to 29% since the global rollout of ART in 2001, with some countries (for example,

Uganda, Zimbabwe and Namibia) seeing pre-treatment drug resistance rates (primary resistance) surpassing 10%.[5]

Preventing, diagnosing and managing co-morbidities, including tuberculosis and hypertension

Although it is recommended that PLHIV can start ART as soon as they are diagnosed, more than a third of persons present late with advanced HIV-related disease and up to 10% may die soon after starting therapy.[6] The REALITY trial in Uganda, Zimbabwe, Malawi and Kenya showed that a package of trimethoprim-sulfamethoxazole, isoniazid-pyridoxine, fluconazole, azithromycin and albendazole given to PLHIV starting ART with CD4 cell counts < 100/mm3 was associated with a 27% lower rate of death at 24-weeks compared with standard prophylaxis of just trimethoprim-sulfamethoxazole.[7] The lower death rate was accompanied by reduced risks of tuberculosis, cryptococcal infection and oral / oesophageal candidiasis.

However, there are two caveats with regards to the implications of these findings from the REALITY trial. First, widespread use of fluconazole and azithromycin may potentially increase the risk of antimicrobial resistance to the two drugs. Second, the WHO's recommended "HIV Test and Treat" approach in general obviates the need for baseline CD4 cell counts, as everyone who is HIV-positive is eligible for ART. Nevertheless, CD4 cells counts are crucial for assessing the risk of severe disease and in the context of this trial they were necessary for deciding who would benefit from blanket antimicrobial prophylaxis. HIV/AIDS programmes will need to weight up the advantages and disadvantages of implementing such an approach.

A follow-up of the TEMPRANO ANRS 12136 trial in Cote d'Ivoire assessed the benefits of early ART and 6-months isoniazid preventive therapy (IPT) among PLHIV for a median time of 5 years. 6-months IPT was associated with 37% reduction in mortality regardless of when ART was started and regardless of baseline CD4 cell count or baseline interferon gamma-release assay.[8] The study has important implications. The findings strongly suggest that IPT should be added to ART in any PLHIV provided there is no evidence of active tuberculosis, but whether isoniazid should be for six-months or longer is contextual and relates to the amount of tuberculosis in the community. An editorial accompanying this paper strongly supports the findings, arguing that large numbers of deaths could be avoided if the strategy was accepted and implemented.[9]

Finally, PLHIV have higher frequencies of risk factors for cardiovascular disease that include cigarette smoking, unfavourable lipid profiles and endothelial dysfunction compared with HIV-negative persons. Hypertension is one of the modifiable biological risk factors. In one cross-sectional study amongst PLHIV attending a large University teaching Hospital in Nigeria, 19% had hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or self-reported pharmacological treatment for hypertension) at registration and a further 31% developed hypertension twelve months after starting ART, with increasing age and body mass index being important independent risk factors.[10] While more needs to be done in sub-Saharan Africa to understand the association between ART and hypertension, it makes sense for ART programmes to start thinking now about integrating services for non-communicable diseases. Measurement of blood pressure is a relatively easy activity to start with, and ART programmes need to work out how to do this and also how to manage hypertension once it is diagnosed.

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