

# 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

## Pharmacy Review

### Newly published books

#### 'Where they are No Pharmacists'

Most of us will be familiar with the book *Where There Is No Doctor*, published by Hesperian/MacMillan/TALC. This year saw the publication of *Where There Are No Pharmacists – A Guide To Managing Medicines For All Health Workers* by Sarah Andersson and Beverley Snell: ISBN 978-967-5412-17-2 published by TWN (Third World Network) and HAI (Health Action International) Asia Pacific.

*Where There Are No Pharmacists* is not a companion volume to *Where There Is No Doctor*, and it does not contain the same sort of information. The foreword explains that the book is about managing medicines; how to order them, store them, prepare them, dispense them, and use them safely and effectively.

The book has three main sections:

Section 1. This is about medicines and looks at national policies, selection of essential medicines, dosage forms (injections, tablets, etc.), rational use of medicines, the difference between brand names and generic names, and some of the legal classifications. Some of the information in this section may not apply in individual countries and is a bit muddled.

Section 2. The most useful section of the book is about stock control, ordering, storing, and managing medicines. There is great emphasis on stock control and record keeping – it explains very well how to record expired stock differently from stock issued, and how to record stock that has gone missing. It is only from accurately recording issues of medicines that the correct stock can be ordered in time. The concept of 'lead time' – the time between ordering and getting the delivery – is explained, and how this must be allowed for to hold enough buffer stock. There is a cartoon of a man surrounded by boxes of tablets to highlight the problems if you order the wrong quantity ('I meant 1000 tablets... not 1000 tins').

There is good advice on recognising counterfeit medicines, but more emphasis on substandard medicines, and how to recognise poor quality medicines from such things as crumbling tablets, missing information on labels, injections that aren't clear, and poor packaging.

Stock rotation is explained and the concept of FEFO (first expired, first out) is compared with FIFO (first in, first out) – FEFO is for medicines and other items with

expiry dates, FIFO is appropriate for other supplies, which don't have expiry dates.

Storage and security are mentioned, and there is a brief section on the construction of store rooms, and storage temperature. Good storage practice includes not storing anything directly on the floor, storing tablets above liquids to prevent them getting spoilt if the liquids leak. There is a useful tip to include bottles of water in refrigerators to help maintain the temperature if the power goes off for short periods.

Section 3. This looks at the dispensing of medicines and communicating with patients and communities. The different stages of dispensing are clearly laid out:

- receive the prescription, check the details with the patient;
- read and understand the prescription, check the dose is appropriate, check the medicine is appropriate (is the patient pregnant?);
- select the correct medicine – double-check;
- count or measure the quantity;
- pack and label, name of patient, name of medicine, strength, quantity, dose, date, other instructions;
- check;
- give the medicine to the patient, check you have the right person.

This section also includes information on pre-packing tablets into appropriate quantities.

There is information about educating communities on the correct use of medicines.

There is a list of resources – many of them from the World Health Organization (WHO), and a glossary of the words used.

The book is illustrated throughout with cartoons from a variety of sources, some better than others. The content of the book is good, but the presentation could be improved by leaving out some of the cartoons, and having better chapter titles. The book is good, and worth reading and it achieves what it says it is aiming for, but it would be improved by a more consistent style. There is a lot of useful information and a good index but don't let the appearance of the text put you off. A lot of the information in the book comes from different publications, these are all referenced.

#### 'British Medical Association New Guide to Medicines and Drugs'

There has just been a new edition (8<sup>th</sup>) of *British Medical Association New Guide to Medicines and Drugs*: ISBN 978-1-4053-6179-8 published by BMA/Darling Kindersley.

This book is probably about the best book available on how medicines work. There are three sections.

Part 1. Understanding and using drugs. This looks at the basic theory of drug action, drug interactions, different dose forms (tablets, injections, inhalers, etc.), drug tolerance (needing to give more to achieve the same effect), drug dependence (a compulsion to take more, causing physical or psychological harm), effects of overdose.

Part 2. Major drug groups. This looks at different parts of the body, and the drugs used to treat conditions. For example, the section 'Brain and Nervous System'

includes analgesics, antidepressants, anticonvulsants, anti-emetics (anti-sickness medicines), and how they work.

Part 3. A–Z of drugs. This includes a page on each of the main medicines in use in the UK, but most international medicines are included. The information on each medicine includes doses, how quickly the medicines start to work, what to do if a dose is missed, adverse effects, and problems in pregnancy or breast feeding.

This edition leaves out a section from previous editions of photograph of commonly used branded medicines. The omission of this section improves the book as it could never include everything and was never particularly useful in identifying tablets. The space taken up by the photographs has been replaced by expanding the information in the other sections.

I recommend this book for all students and teachers. It could form the basis of a syllabus for nurses, pharmacists, or doctors or any other medical professional wishing to learn about how medicines work, and how to use them.

#### 'WHO Model Formulary for Children 2010'

At the end of last year WHO published *WHO model formulary for children 2010*: ISBN 9789241599320. 528 pages. This book is published only on-line at [http://whqlibdoc.who.int/publications/2010/9789241599320\\_eng.pdf](http://whqlibdoc.who.int/publications/2010/9789241599320_eng.pdf). I have not been able to find out if there will be a paper edition published. The book is essential for all treatment centres and gives doses for neonates (0–28 days), infants (1–12 months), and children (1–12 years) for virtually all medicines. The book can be downloaded as a pdf file and printed out, but I would prefer a paper edition. The file size is 2.8 Mb, too big for a floppy disc, but well within the capacity of a USB memory stick.

#### 'Essential Drugs – Practical Guidelines'

Médecins sans Frontières (MSF, Doctors Without Borders) has published an excellent book *Essential Drugs – Practical Guidelines*: ISBN 2-906498-78-5. 362 pages. Available only online at [http://www.refbooks.msf.org/msf\\_docs/en/Essential\\_drugs/ED\\_en.pdf](http://www.refbooks.msf.org/msf_docs/en/Essential_drugs/ED_en.pdf).

Part 1 of the book is based on the WHO Model formulary, but the monographs are simplified with one drug per page so that individual monographs can be printed and kept with the drugs. The monographs include doses for infants, children, and adults. The book is not arranged in therapeutic classes, but alphabetically with separate sections for oral drugs, injectable drugs, infusion fluids, vaccines, and antiseptics. Some of the drugs are not in the WHO Essential Drugs list, but these are clearly marked.

Part 2 includes assorted information such as; use of antibacterials, how to handle disinfectants, drug storage. There is even a section on the layout of a pharmacy.

The pdf file is 2.44 Mb, again too big for a floppy disc. The book includes the WHO Essential Drugs list.

#### Medicines news

##### Oral contraceptives interactions

The Faculty of Sexual and Reproductive Health has

revised its guidance on drug interactions with oral contraceptives (see <http://www.ffprhc.org.uk/pdfs/CEUGuidanceDrugInteractionsHormonal.pdf>).

The main difference is that unless the antibiotics induce liver enzymes 'Additional contraceptive precautions are not required during or after courses of antibiotics'. The only antibiotics listed as enzyme inducers are rifampicin and rifabutin. However, antiretrovirals are still included as enzyme-inducing drugs, and additional contraceptive measures must still be taken.

#### Paracetamol (acetaminophen) dosing in children

The MHRA (the UK body responsible for licensing medicines and healthcare products) has changed the age-related dose bands for paracetamol to achieve more accurate dosing. The new dosage bands are:

- three to six months of age: 2.5 ml of 120 mg/5 ml solution (60 mg);
- six months to two years: 5 ml of 120 mg/5 ml solution (120 mg);
- two to four years: 7.5 ml of 120 mg/5 ml solution (180 mg);
- four to six years: 10 ml of 120 mg/5 ml solution (240 mg);
- six to eight years: 5 ml of 240/250 mg/5 ml solution (240 mg);
- eight to 10 years: 7.5 ml of 240/250 mg/5 ml solution (360 mg);
- 10 to 12 years: 10 ml of 240/250 mg/5 ml solution (480 mg).

#### Medication errors

A study published in *The International Journal of Clinical Practice* 2011; 65 (7): 733–40 looked at causes and frequency of medication errors in seven countries (five in Europe + Canada and USA). The common causes of errors were: lack of communication between different healthcare providers; more complex health needs (multiple chronic conditions, multiple specialists/consultants). The number of different medications and the number of doctor visits did not make medication errors more likely. The study advocates better communication between different healthcare providers.

This is something that the NHS in the UK has been struggling with for years, a major computerised system of patient health records is years behind its schedule and millions of pounds overspent, and it still looks as if it is going nowhere. Life would be so much easier if everybody carried their own health records, as they do with maternity records in the UK.

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## Paediatrics Review

### New guidelines for treatment of tuberculosis (TB) in children

There is no consensus on the regimens for the treatment of TB in children, in particular, tuberculous meningitis (TBM). Major differences are in drug dosages,

especially isoniazid (INH), and duration of therapy for extra-pulmonary TB. For example, recommended INH dosage (mg/kg) is 10–15 mg according to the American Academy of Pediatrics,<sup>1</sup> 5–10 mg according to the British Thoracic Society,<sup>2</sup> and 5 mg according to the International Union against Tuberculosis and Lung disease and the World Health Organization (WHO).<sup>3</sup> However, dosage in children might be better calculated on body surface area than body weight.<sup>4</sup>

In young children, development of pathways which may increase drug metabolism occurs.<sup>5</sup> In a study of 56 children hospitalised for treatment of TB, median peak concentrations of INH in patients prescribed 4–6 mg/kg were 58% lower than those prescribed 8–12 mg/kg.<sup>6</sup> The latter dose achieved peak concentrations approximating to adults treated with 300 mg daily. Intermediate or fast acetylator genotype predicted a 38% (95% CI 21–51%) reduction in peak concentrations compared with the slow acetylator genotype. The younger the child the lower the peak concentration.

Information on the pharmacokinetics of rifampicin (RMP) is sparse. A study of 54 children – 21 HIV-infected and 33 HIV-uninfected – admitted for treatment of severe forms of TB was undertaken.<sup>7</sup> The patients were on a fixed-dose formulation, mean dosage was 9.6 mg/kg and RMP levels were estimated at 1 month and 4 months of treatment. The mean calculated 2-hour concentrations of RMP were 3.9 and 4.8 µg/ml in the HIV-infected and non-infected patients, respectively, at 1 month ( $p=0.2$ ) and 4.0 and 4.6 µg/ml after 4 months treatment. The lower limit for RMP concentration in adults is 8.0 µg/ml. A recent review estimated that children require twice the mg/kg body weight dose of RMP to reach serum concentrations equivalent to adults.<sup>8</sup> Clearly both the dose of INH 5 mg (4–6)/kg and RMP 10 mg (8–12)/kg are inadequate for young children.

### Tuberculous meningitis

A systematic review of anti-microbial treatment for tuberculous meningitis (TBM) found a lack of good-quality evidence regarding appropriate therapy.<sup>9</sup> INH, pyrazinamide (PZA) and ethionamide (ETH) are the only drugs for TBM known to reach adequate concentrations in the cerebrospinal fluid (CSF). RMP penetrates the CSF less well (maximum concentration 30% of plasma) but is a mandatory drug for treatment of TB.<sup>10</sup> Neither of the fourth drugs, ethambutol (EMB) or streptomycin (SM), penetrate the CSF well in the absence of inflammation. Theoretically, ETH is a better alternative.

Duration of therapy is arbitrary and presently varies from 6 months to 12 months. However, there are few reports of relapse on standard regimens.<sup>9</sup> The main prediction for outcome is the stage of disease at presentation. Some 80–100% of children with TBM have abnormal brain imaging on admission, e.g. hydrocephalus. A small proportion of patients have a slow response to treatment but this does not necessarily mean inadequate drug therapy. WHO, until recently (see below), has recommended a 6 month duration of therapy with standard drug doses with the fourth drug as SM.<sup>3</sup> The American Academy of Pediatrics advises a 9–12 month course of treatment and the fourth drug

either SM or ETH<sup>1</sup> and a South African regimen has 6 m duration with ETH as the fourth drug.<sup>11</sup> For the latter, all four drugs (including PZA) are given for 6 m and doses of INH and RMP are 20 mg/kg.

Although there is no evidence one way or the other, for HIV-infected children with TBM, in view of the often slow response to treatment, a 9-month course of treatment could be justified. Other problems to be considered in HIV-infected patients are poor absorption of drugs and tolerance to drugs and reactions to antiretroviral agents.<sup>12</sup>

### Rapid advice for treatment of tuberculosis in children

At a meeting in March 2010 in Geneva the following changes to the WHO recommendations for treatment of TB in children were made.<sup>5</sup> As evidence is low-grade, decisions were based on study by study rather than systematic reviews.

Doses of standard drugs are now (mg/kg):

INH: 10 mg (10–15), maximum 300 mg/day

RMP: 15 mg (10–20), maximum 600 mg/day

PZA: 35 mg (30–40)

EMB: 20 mg (15–25)

SM should not be used as part of first-line regimens for pulmonary TB or peripheral lymphadenitis. It should be reserved for treatment of multi-drug resistant TB with known drug susceptibility to SM.

Duration of treatment for TBM should be 12 months. The upper end of the dosage range should be considered. However, there was no mention of ETH for treatment of TBM. As 30% of the children with miliary TB have central nervous system involvement the advice is to treat with a 12-month regimen. However, there was no consideration regarding whether this takes into account a normal or abnormal CSF. In osteoarticular TB, as there is difficulty in determining cure, a four-drug regimen is advised and the duration of therapy should be 12 months. Infants (0–3 months) with TB should receive standard regimens as outlined above taking care to monitor closely those on high doses. For children requiring INH prophylaxis the dose should be 10–15 mg/kg.

Children living in settings where the prevalence of HIV is high or where resistance to INH is high or where there is extensive pulmonary disease, should be treated with a four-drug regimen.

For HIV-uninfected children living in settings with well-established DOT the continuation phase can comprise thrice-weekly regimens (not twice-weekly).

Some of the research needs for childhood TB that were identified included duration of treatment for TBM, pharmacokinetic studies of all four first-line drugs at recommended dosage in both HIV-uninfected and -infected children.

A second edition of the recommendations comprising the full guidance should be available in 2011.

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## Surgery Review

### Compartment syndrome of the leg in children

All of us who have dealt with much trauma will realise the frequency and importance of compartment syndrome.

I always used to emphasise to my staff that as soon as the diagnosis is suspected, that is the time to be wheeling the patient to theatre for fasciotomy (cutting of the fascia to relieve tension or pressure). We also all know that timing is of the essence in these cases. There are many medical epithets in this regard: 'if you think you need to do a fasciotomy, you need to do it.'

Perhaps children are different in that their tissues are more giving, therefore their muscles might survive compression more than adults. However, I would not rely on that.

The first paper I wish to review<sup>1</sup> is from the heart of America where you would imagine everything is done correctly first time. The authors have reviewed a series of 43 cases in 17 years.

As we all know the time to fasciotomy is the crucial matter in this condition, making the difference between a normal leg and partial disability. This matter has been the subject of much debate over the years. However certain time scales are accepted. After 6 hours of ischaemia muscle starts to die. The optimum time for the muscles to be decompressed is up to 8 hours. How can doctors stay within these limits? Other papers have explained their time delay in getting patients to theatre. One major centre of great repute had an average of 16 hours in getting patients to theatre for fasciotomy.

This particular paper breaks down the groups of patients into five starting from 0–8 hours (time from

injury to fasciotomy) followed by 8–16 hours. These two groups would be classed as 'acceptable' and the 'just acceptable', respectively, but of their 43 legs reviewed only 25 fell into these categories. The last three groups had progressively longer delays before fasciotomy, i.e. 16–24 hours, 24–48 and (even) longer than 48 hours in three patients.

Two major factors strike one here. After 16 hours is there any point in carrying out fasciotomy? Is the process of muscle death reversible? Do patients in the later groups have good residual function? I frankly do not believe that fasciotomy after 24 hours will do any good – but let me hasten to add that if in doubt I would always do it.

The authors state that even those patients who had fasciotomy after 24 hours had no permanent loss of function. I find this difficult to believe. Only those patients decompressed after 48 hours had some loss of function and were classed as 'fair'; there were no poor results. Unfortunately this is a retrospective study – which is a major flaw.

The incidence of compartment syndrome in Africa is high and the causes very variable – not just trauma. But this would be a field worthy of study, with the specific intent of focusing on the time between diagnosis and fasciotomy.

### Non-operative treatment of abdominal gunshot wounds

Some years ago papers appeared from Baragwanath Hospital in Johannesburg showing that it was quite safe in certain circumstances not to explore stab wounds of the abdomen. This selective non-operative policy saved much time and some later morbidity (since negative laparotomies are not harmless).

There is now gathering evidence that gunshot wounds of the abdomen can similarly be subjected to a selective non-operative approach. It would obviously be of great advantage for hospitals to avoid laparotomy – particularly if their resources are scarce. So this technique, Selected Non-Operative Management (SNOM), would be of value.

Until recently there have been no papers exploring the details of this approach. However, an article has recently been published in the *Archives of Surgery*; the results presented in the paper are discussed below. The authors have reviewed their experience of abdominal gunshot wounds over 11 years, involving involving 125 patients. They implemented SNOM and studied the results.

First it is clear that some patients require laparotomy because of the nature of their injury. Thus patients who are bleeding or who have signs of peritonitis, have signs of injury to a major organ, or who have a tangential wound need immediate operation.

The abdominal computed tomography (CT) scan – becoming universal in many situations – has complicated the situation because even some injuries to solid organs do not necessarily need operation.

Of the total patients with abdominal gunshot wounds, inevitably some died on admission due to other injuries (head/neck). After exclusion there were

125 patients of whom 87 required laparotomy leaving 38 for non-operative management. The problem arises when some patients in this group need to be readmitted. There were few in this group and none waited a long time before delayed operations.

The authors then made a comparison of the immediate laparotomy group with the SNOM. This showed that the SNOM had fewer complications and a shorter hospital stay.

There are many other aspects of this paper which are worth studying, but the main message is clear. If you can avoid operation on a gunshot wound of the abdomen you have done the patient a favour. The skill to make this decision needs to be acquired and practised but will greatly assist in your management of these cases in the future.

*Prof Ken Rankin, OBE, FRCSEd (Ortho), FCS (Orth) SA, Orthopaedic Surgeon, Dundee, Scotland*

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**Ken Rankin (1939 – 2011)**

It is with great sadness that we must record the passing of our redoubtable friend and surgical reviewer, Professor Ken Rankin who suffered a haemorrhagic stroke on 3rd July. Only 2 days earlier he had emailed his words above with a comment that one more commentary would be sent after the weekend. Ken was a great champion of Africa and a strident anti-apartheid activist. He was married for almost 40 years to Joyce Sikakane, the South African journalist and political activist. As an orthopaedic surgeon, Ken was a practitioner, teacher, and innovator, spending time working in South Africa, Mozambique, Zimbabwe, Zambia... and also his native Scotland. He participated with us at several Medic Africa meetings, and has written this column in *Africa Health* for 15 years. He will be sadly missed and our heartfelt commiserations go out to his wife and family.



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