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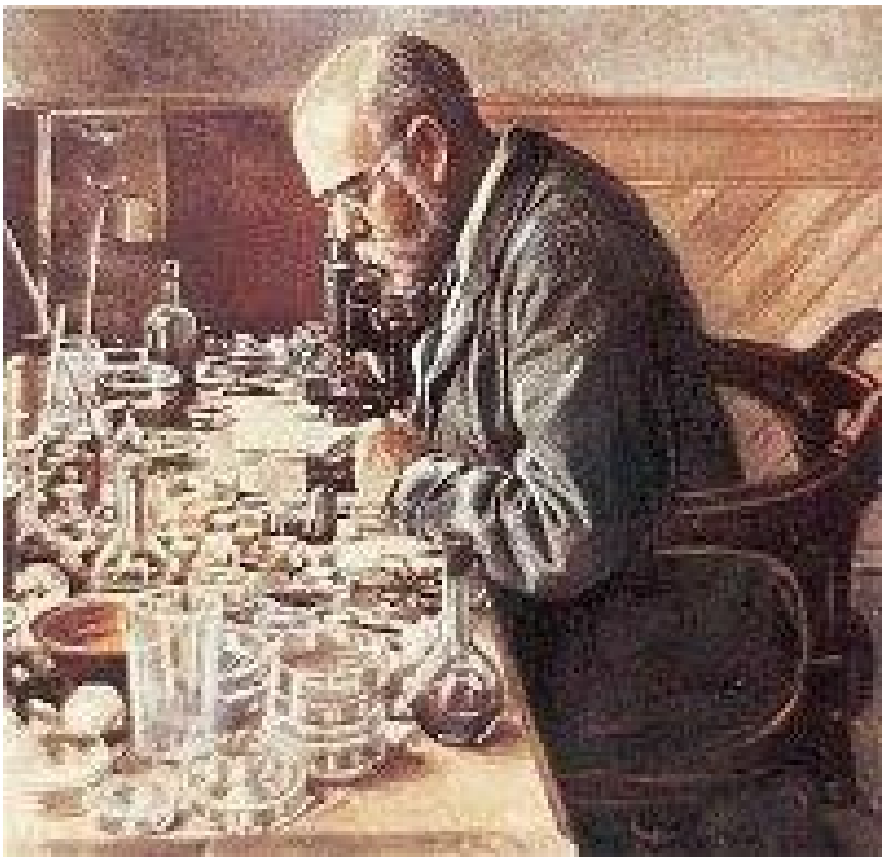

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# The Sri Lanka Prescriber

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Department of Pharmacology
Faculty of Medicine
271, Kynsey Road, Colombo 8, Sri Lanka.
Telephone: + 94 11 2695300 Ext 315
E-mail: phrm_cmb@hotmail.com

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State Pharmaceuticals Corporation
75, Sir Baron Jayathilake Mawatha, Colombo 1.
Telephones + 94 11 2320356-9
Fax: + 94 11 447118
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## Alert on thiazolidinediones (rosiglitazone and pioglitazone)

Rosiglitazone and pioglitazone are presently available in Sri Lanka for the treatment of type 2 diabetes, and the U.S. Food and Drug Administration (PDA) has reported an increase in the incidence of heart failure with the use of thiazolidinedione class of antidiabetic drugs. Continuation of therapy has been associated with poor outcomes, including death. Prescribers are advised to use alternative drugs for type 2 diabetes mellitus.

If a thiazolidinedione is used, all patients should be carefully monitored for symptoms and signs of heart failure such as shortness of breath, significant rapid weight gain and oedema after starting the drug therapy.

If patients develop features of heart failure they should be promptly treated and the use of the thiazolidinediones antidiabetic drug should be reconsidered. These drugs should not be prescribed for patients with heart failure.

**Drug Regulatory Authority of Sri Lanka**

**Reference**


WHO Pharmaceuticals Newsletter No 4, 2007


## The NICE guidelines on the use of glitazones for the treatment of type 2 diabetes

1. For people with type 2 diabetes, the use of a glitazone as second-line therapy added to either metformin or a sulphonylurea – as an alternative to treatment with a combination of metformin and a sulphonylurea – is not recommended except for those who are unable to take metformin and a sulphonylurea in combination because of intolerance or a contraindication to one of the drugs. In this instance, the glitazone should replace in the combination, the drug that is poorly tolerated or contraindicated.
2. The effectiveness of glitazone combination therapy should be monitored against treatment targets for glycaemic control (usually in terms of haemoglobin A1c [HbAlc] level) and for other cardiovascular risk factors, including lipid profile. The target HbA1c level should be set between 6.5% and 7.5%, depending on other risk factors.
3. The present UK licence does not allow the Institute to recommend the use of glitazones in triple combination therapy (with other oral antidiabetic agents), as monotherapy, or in combination with insulin. The use of a glitazone in triple combination (with other oral antidiabetic agents) is classified in the licence under 'special warnings and special precautions for use'. This precaution is based on the fact that at the time the licence was issued there was no clinical experience of triple combination therapy. When this guidance is reviewed the recommendations will take into account any extensions to the licence for the use of glitazones.

**Cover picture**

A famous photograph of a famous microbiologist, who along with Louis Pasteurchanged the entire course of medical thinking and of human history: Robert Koch, discovere of the organisms causing tuberculosis, cholera, gonorrhoea, diphtheria, typhoid and many other diseases.

# Management of oral ulcers

Ulcers are one of the most common complaints of the mouth. Oral ulcers can be the manifestation of a variety of disease processes ranging from the simple traumatic breach of the epithelium to epithelial damage caused by an immunological response as in pemphigus, or damage caused by an immune defect as in HIV infections such as herpes, or nutritional defects such as vitamin deficiencies, or neoplasia. The diagnosis of the condition is usually simple. However, the clinician may have to ask for a number of investigations ranging from simple blood tests to sophisticated immunoflorescence examinations to unravel the underlying aetiology.

This article outlines the management of oral ulcers considered under several headings based on their aetiology.

**Ulcers due to local causes**

Trauma from sharp dental appliances and jagged teeth are the common local causes. Occasionally self-inflicted ulcers are seen. Burns from heat eg. hot food consumed following dental procedures under local analgesia, and chemical burns of oral mucosa eg. following local application of aspirin on decayed teeth are not uncommon.

Management includes identification and removal of the cause and use of an antiseptic mouth wash eg. 0.2% chlorhexidine. These ulcers heal spontaneously. Any traumatic ulcer that does not heal in 3 weeks after removal of the aetiological factor should be biopsied to exclude malignancy.

**Drug induced ulcers**

Drugs can cause mouth ulcers by various mechanisms. The following are common examples.

1. Cytotoxic drugs (eg. methotrexate) produce non-specific ulcers.
2. Some antihypertensive, antidiabetic, non-steroidal anti-inflammatory agents can produce lichen planus-like reactions with ulceration.
3. Agents causing local chemical burns (eg. aspirin) is already explained.
4. Sulphonamides, barbiturates, etc, can cause erythema multiforme with ulceration of oral mucosa.

Modify the treatment and use topical benzydamine and 0.2% chlorhexidine as a mouthwash.

**Ulcers of unknown aetiology**

***Recurrent aphthous ulceration***

Aphthous ulcers are persistently recurring painful oral ulcers of unknown aetiology. A genetically determined autoimmune factor is being investigated. There are three types of aphthous ulcers viz. minor, major and herpetiform.

Although its aetiology is unknown, a few patients have ulcer in association with deficiency of iron, vitamin B12 or folic acid, coeliac disease, menstruation, stress, cyclic neuropenia, Behcet syndrome and Reiter disease. These should be identified and managed accordingly.

Aphthous ulcers are rarely cured, but can often be controlled by the following drugs

1. Antiseptic mouthwashes

(i) 0.2% chlorhexidine digluconate ("corsodyl", "oralon" )

(ii) Povidone iodine (betadine, vocadine)

2. Antibiotic mouthwash. eg. 2.5% tetracycline
3. Topical steroids in orabase. 0.1% triconsinolone acetamide, betamethasone. eg. Kenalog, Oral - T, Orrepaste

Necrotising sialometaplasia produces crater-like ulcers that mimic malignant ulcers. Confirmation is by biopsy. No active treatment is necessary and the ulcers heal within 8 weeks.

**Malignant ulcers**

Malignant ulcers such as squamous cell carcinoma, melanoma, antral carcinoma, salivary neoplasm (adenocarcinoma) and secondaries from other parts of body may be seen in the mouth. Of these, more than 90% are squamous cell carcinoma, which is discussed below.

*Squamous cell carcinoma*

Aetiological factors acting on a genetically susceptible host include sepsis, smoking, spices, spirits, sunlight and syphilis. Betel chewing is the most important factor in Sri Lanka. There are some premalignant or potentially malignant states recognised. Oral submucous fibrosis, dysplastic leukoplakia, erythroplasias, erosive lichen planus, chronic immuno-suppression, discoid lupus erythematosis, tertially syphilis and Plumer Vinson syndrome fall into this group.

Management includes habit intervention, identifying and observing premalignant or potentially malignant condition,

early diagnosis and definitive treatment. Surgical removal, radiotherapy and chemotherapy form the modes of treatment.

### Systemic causes

They include blood disorders, gastrointestinal disorders, dermatological disorders and infections.

### Blood disorders

1. Leukopenia due to various causes predisposes to persistent mouth ulcers without an inflammatory halo.
2. Leukaemia manifests as oral ulcers with bleeding and swollen gums, and superadded infection with herpes and candida.
3. Cyclic neutropenia is already mentioned under aphthous ulcers.

Treatment of ulcers due to these blood disorders should be directed to treatment of the cause, along with supportive care with topical 0.2% chlorhexidine, oral antimicrobials and improvement of oral hygiene.

### Gastrointestinal disorders

1. **Coeliac disease** produces aphthous type ulcers, angular stomatitis and glossitis. Confirmation is by small bowel biopsy. Gluten-free diet, and dietary supplement of iron, vitamin B12 or folic acid will generally resolve the oral ulcers. Local treatment is similar to that of aphthous ulcers.
2. **Crohn disease** may present as oral ulcers, cobblestone appearance of oral mucosa, and facial and labial swelling. Treatment includes topical or intralesional injection of steroids and systemic and topical sulphasalazine.
3. **Ulcerative colitis** produces irregular chronic ulcers and mucosal pustules in the mouth. Topical steroids and occasionally systemic sulphasalazine or corticosteroids are required.

### Dermatological disorders

The following dermatological disorders produce oral ulcerations.

1. **Epidermolysis bullosa** causes bullae in the mouth which break down to form ulcers. Potent corticosteroids may be required.
2. **Lichen planus** is a whitish lesion and appears as lines, striae, papules or plaques. Erosions appear in some cases, and need to be observed carefully as a small percentage may become malignant. Topical steroids, sometimes intralesional steroids for intractable cases, are necessary for management.
3. **Pemphigus** bullae appear and rapidly break down to form irregular ragged ulcers. Biopsy with imunoflorescence is required for confirmation. High doses of steroids with steroid sparing agents such as levamisole are indicated.
4. **Pemphigoid** is more common than pemphigus. Bullae lasts for a longer time before breaking down to ulcers. Immunoflorescence may be required for diagnosis. Topical steroids are effective.
5. **Erythema multiforme** is characterised by typical target or bulls' eye lesions on the skin and ulceration with crusting of blood on the lips, tongue etc. The major form, Steven-Johnson syndrome, with widespread lesions affects the mouth, eyes, skin and genitals, with fever and toxicity. Systemic steroids and 0.2% chlorhexidine are effective.

### Infections

#### 1. Herpes simplex

Both primary and secondary (recurrent) infections produce ulcers.

***Primary***

There is a single episode of widespread oral vesicles that break down to leave ulcers which are pin-point at first, and later coalese to produce irregular painful ulcers. Gingival oedema and erythema along with cervical lymphadenopathy are common.

***Recurrent***

Macular, papular, vesicular and pustular lesions appear and break down to form ulcers which heal without scarring. They are seen at the mucocutaneous junctions of the lip and nose. Soft diet, adequate fluids, analgesics and antiseptic mouthwashes are effective. Systemic acyclovir or other anti-viral drugs may be required in immunocompromised patients.

#### 2. Herpes zoster

Herpes zoster usually affects the thoracic region but in 30% of cases it affects trigeminal region. Mouth ulcers occur if the maxillary or mandibular divisions are involved. If the maxillary division is involved ulcers are seen in the ipsilateral palate and vestibule. If the mandibular division is involved ulcers appear on the ipsilateral buccal and lingual muscosa.

Management includes analgesics, high dose acyclovir orally or parenterally.

**3. HIV**

Different types of ulcers may manifest in HIV infected individuals, including,

(i) non-specific aphthous, especially major aphthous ulcers

(ii) herpes simplex and zoster type ulcers

(iii) ulcers caused by bacteria or fungi

(iv) ulcers due to malignant neoplasms such as Kaposi sarcoma or lymphoma

Anti-retroviral agents such as nucleosides (zidovudine, AZT), protease inhibitors (such as saquinavir) are effective. Infections and tumours should be dealt with appropriately.

**Syphilis.** Syphilitic ulcers are seen in all three stages. Primary chancres, secondary mucus patches and snail-track ulcers, and tertiary gumma are the oral lesions. Penicillin is effective.

**Tuberculosis** produces undermined ulcers, particularly on the dorsum of the tongue and the palate. Combination chemotherapy is required.

**Deep mycoses** can cause persistent ulcers and are treated with antifungal drugs such as ketaconazole or fluconazole.

**Further reading**


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**S Yogendranathan,** BDS (Cey), FDSRCS (Eng), FDSRCPS (Glasg), FFDRCS (Irel), *Dental and maxillofacial surgeon.*


# Antibiotic resistance and prescribing

Since their discovery, antimicrobial drugs have proved effective for the control of bacterial infections. Up to now a vast array of antimicrobials have been developed that have altered the course of medical history. However, it was soon evident that bacterial pathogens were unlikely to surrender lamely, as they started developing resistance to antimicrobials.

**Mechanism of bacterial antibiotic resistance**

Antimicrobial agents exert strong selective pressure on the bacterial population that enables survival of organisms resistant to them. Resistance to antimicrobials occurs as a result of genetic variability, by a variety of mechanisms. Point mutations called micro-evolutionary changes occur in chromosomes. These may alter the target site of an antimicrobial agent, interfering with its activity.

A second level of genomic variability referred to as macro-evolutionary change results when rearrangements of large segments of DNA occur as a single event. These are frequently created by specialised genetic elements known as transposons or insertion sequences, which move independently as a unit from the rest of the bacterial genome.

A third level of genetic variability in bacteria is created by acquisition of foreign DNA carried by plasmids, bacteriophages etc. Once an antibiotic resistant gene evolves, the resistance determinant can spread to other bacteria and there are several distinctive mechanisms by which antibiotic resistance is expressed by bacteria (1).

*Enzymatic inhibition*

Resistance to beta-lactam antibiotics is mainly due to the production of the enzyme beta lactamase by bacteria that split the beta-lactam ring. Staphylococci are the major pathogens that produce beta-lactamases. Enterococci and gram-negative bacteria also produce beta -lactamases. These are encoded by plasmids and are a special concern because of the possibility of spread among different bacterial strains and species.

Aminoglycoside modifying enzymes are coded by the genome on plasmids or chromosomes. Several of these enzymes are capable of acetylation, nucleoitidylation and phosphorylation of the antimicrobial. Resistance to chloramphenicol in gram-positive and negative organisms is primarily mediated by chloramphenicol acetytransferase.

*Alteration of bacterial membranes*

The lipid bilayer of bacterial cell wall impedes the entry of hydrophobic antibiotics such as erythromycin, so the passage of antibiotics occur through the pore proteins in the lipid bilayer. Mutations in the pore proteins can cause resistance to antimicrobials.

*Promotion of antimicrobial efflux*

A major mechanism of resistance to tetracyclines in enteric bacteria is decreased accumulation of the drug. This is mainly due to active efflux of the antibiotic across the cell membrane. These determinants are found in chromosomes or plasmids.

*Alteration of the target sites*

Resistance to a wide variety of antimicrobial agents,

including tetracyclines, macrolides, and aminoglycosides may result in alteration of ribosomal binding sites. Failure to bind will disrupt its ability to inhibit protein synthesis and cell growth.

*Bypass antibiotic inhibition*

Some organisms develop the ability to use an altered metabolic pathway, that bypasses the reaction inhibited by the drugs.

**Current issues in antimicrobial resistance**

*Staphylococcus aureus* was highly sensitive to penicillins in the 1930s and 1940s until penicillinase producing staphylococci were recognised in late 1940 (2). The resistance was found to be plasmid mediated and most probably transferred among bacteria by means of bacteriophages. This type of resistance spread quickly in hospitals and communities around the world, and at present penicillin susceptible *S. aureus* are scarce. Hence, penicillin should be avoided to treat infections suspected of being due to *S. aureus* unless laboratory confirmation is available regarding its sensitivity.

Development of penicillinase resistant penicillins methicillin, cloxacillin and flucloxacillin were developed to treat penicillinase producing *S. aureus* infection. However, in 1960 *S. aureus* resistance to these penicillins surfaced. Such strains were identified because of their resistance to methicillin, hence known as methicillin resistant *S. aureus* (MRSA). Standard therapy for MRSA infection (not colonisation) is vancomycin or teicoplanin. MRSA colonisation does not require systemic antibiotics.

Many strains of *Streptococcus pneumoniae*, causing invasive disease such as community acquired pneumonia and meningitis are usually sensitive to penicillin. Low-level penicillin resistant strains were reported in Papua New Guinea in 1967 (3). These strains can still be treated **effectively** with penicillin, except in cases of meningitis. Strains that exhibit high level resistance to penicillin can be treated with a third generation cephalosporin such as cefotaxime or vancomycin. Although no reported data is available, prevalence of low level resistant strains is thought to be low in Sri Lanka.

Enterococci are ubiquitous organisms frequently identified as normal commensals in a variety of body sites. Enterococci cause infection in debilitated people and in individuals with underlying structural abnormalities. They are becoming increasingly important as a cause of nosocomial infection because of intense use of antimicrobials in health care institutions. Enterococci are intrinsically resistant to many antimicrobials. Hence infections caused by enterococci are usually treated by combination therapy, such as a cell wall active agent (penicillin or vancomycin) with an aminoglycoside. Cephalosporins, clindamycin and trimethoprim/sulfamethoxazole are not recommended. Intrinsic resistance has led to an increase in prevalence of enterococcal infection, but acquired resistance has led to emergence of infections which are more difficult to treat. Acquired resistance to aminoglycosides will abolish synergistic activity. Strains with penicillin resistance can usually be treated with vancomycin, but emergence of vancomycin resistant enterococci (VRE) has further limited therapeutic options.

*Neisseria gonorrhoeae* causes purulent urethritis, pelvic inflammatory disease and sometimes disseminated disease. Initially penicillin was the mainstay of therapy but in 1975 penicillinase producing *N. gonorrhoeae* (PPNG) was identified (2). Third generation cephalosporins such as ceftriaxone as well as spectinomycin and ciprofloxacin are alternative antibiotics.

*Pseudomonas aeruginosa* is intrinsically resistant to early generation penicillins and cephalosporins, co-trimoxazole, tetracycline, chloramphenicol and erythromycin. Effective agents include anti-pseudomonal penicillins (ticarcillin, piperacillin, mezlocillin), aminoglycosides (gentamicin, amikacin) carbapenams (imipenam, meropenam) and fluoroquinolones (ciprofloxacin). But acquired resistance to most agents is common.

Resistance among members of *Enterobactericeae* is increasing, especially in organisms known to harbour extended spectrum beta-lactamases (ESBL), cephalosporinases and carbapenemases. Other types of resistance noted world-wide among the *Enterobacteriaceae* include imipenam resistance. This typically emerges during treatment of ceftazidime and aminoglycoside resistant strains, and is reversible with cessation of therapy (4). Ciprofloxacin resistance, influenced by extensive use as well as clonal spread of strains containing ESBL has been found in *Klebsiella* species.

Multidrug resistant tuberculosis (MDR-TB) is a form of tuberculosis that is resistant to two or more drugs (isoniazid and rifampicin). Since early 1990 several outbreaks of MDR -TB have been reported in different regions of the world. Usually MDR-TB occurs in chronic infection. It is not common in those who have not taken anti-tuberculous drugs.

The WHO estimates that up to 50 million persons world-wide may be infected with drug resistant tuberculosis. Also 300 000 new cases of MDR-TB are diagnosed around the world each year and 791 MDR-TB cases now show resistance to three or more drugs (5). MDR-TB has been a particular concern among HIV infected persons. Some of the factors that have contributed to MDR-TB include, a delay in diagnosis and determination of drug susceptibility, imuunocompromised individuals, inadequate isolation, non- and intermittent compliance.

To improve compliance innovative treatment options such as directly observed therapy (DOT) have been developed. The regimens for MDR-TB are based on in vitro drug susceptibility tests. Effective agents include the newer fluoroquinolones (ciprofloxacin), macrolids (azithromicin), and aminoglycosides (amikacin).

**Panel**

Strategies for the management of antimicrobial resistance

1. Reduce the need for antimicrobial agents

- Prevent infection by increasing levels of immunity
  - Improve health and nutritional status
  - Specific immunisation programmes for pathogens (*Haemophilus influenzae* type b, *Streptococcus pneumoniae*)
- Prevent spread of infection
  - Safe food and water supply
  - Reliable sewage and waste disposal
  - Good hygiene and infection control practices

2. Better use of existing antibiotics

- Correct selection and administration of antibiotics in consultation with a microbiologist where possible
- Use only in infections where antimicrobials are indicated
  - Educate health care workers/patients
  - Use laboratory diagnostic facilities for identification and susceptibility testing
- Ministry of Health to
  - Disseminate information on local/regional prevalence of resistance
  - Have guidelines on local purchase of antibiotics
  - Establish antimicrobial policies ad treatment guidelines
- Antimicrobial formulary restriction

3. Develop new antibiotics and therapeutic strategies

- Modify existing drugs
- Develop new drug classes with novel target sites

The emergence and dissemination of resistant bacteria is a natural, unpredictable and unpreventable adaptation of bacterial population to a hostile environment with anti-bacterial agents. This is evident by tremendous variation in the prevalence of resistance in health care facilities and in the community throughout the world. Conclusion: more intense the use of antibiotics, greater the chance of development of resistance. The panel shows strategies for minimising the development of microbial resistance to antibiotics.

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**Dr Neluka Fernando** MBBS, Dip Micro (Col), PhD ( Lond), *Senior Lecturer,* **Dr Ruvanika Rajapakse-Mallikahewa** MBBS, Dip Micro (Col), MD-Micro (Col), *Lecturer, Department of Microbiology, Faculty of Medical Sciences, University of Sri Jayewardenepura, Nugegoda.*

Correspondence: NF <neluka@eureka.lk>

# Treatment of multidrug resistant tuberculosis

This article describes the current approach to treatment of multidrug resistant tuberculosis in countries where resources for drug sensitivity testing for first and second line drugs are available. In countries such as Sri Lanka a modified approach of management may have to be used based on first line drug testing only, until such time as laboratory resources are available. Recent trends in extension of drug resistance world-wide have been taken very seriously by the WHO which now considers that drug sensitivity testing is a priority in all countries

The standard 6-month treatment regimen for tuberculosis (TB), which is the basis for TB control in most parts of the world, uses the key bactericidal agents isoniazid (H) and rifampicin (R) throughout, with supplementation by ethambutol (E) and pyrazinamide (Z) in the first 2 months. This regimen as well as the 9-month treatment course without pyrazinamide, are based on evidence from randomised controlled trials (RCTs) and have good outcomes with less than 5% relapse or failure (1). Cure rates however are poor, about 50% or less, in multidrug resistant TB (MDR-TB), a term that refers to disease which is resistant to both isoniazid and rifampicin, with or without additional resistance. The regimen uses 2 powerful bactericidal drugs together with the effect of rifampicin against dormant persistent organisms (1, 2). TB programmes in resource poor countries use empiric treatment with good effect in mostly drug susceptible disease, but there is a danger of extension of resistance if MDR-TB is treated with the 6-month Directly Observed Therapy, short course (DOTS) regimen of the WHO, or the streptomycin containing retreatment regimen. DOTS programmes can lead to increased prevalence of resistance in populations with high rates of existing drug resistance although they are effective in preventing new resistance. The WHO now recommends the more sophisticated DOTS plus programmes for these settings (3).

Countries with adequate resources usually adjust regimens using individual drug sensitivity tests (DSTs). Current treatment of MDR-TB relies on the use of fluoroquinolones, injectable aminoglycosides or polypeptide agents and other drugs from a bygone era. Such treatment is complex, prolonged, expensive and needs expert management.

Random mutations causing isoniazid and rifampicin resistance develop at rates of 1/106, and 1/108 respectively, but occurrence of resistance to both drugs is very rare (1x 1014 ) and extremely unlikely to occur in previously untreated patients who are receiving at least two front line drugs. Polydrug therapy ensures elimination of randomly developing drug resistant mutants. MDR-TB, has occurred due to erratic drug therapy, loss to follow up, poor regimen selection, mismanagement of side effects or discontinuation of drug supplies (4, 5). MDR-TB should be considered in previously treated cases, contacts of drug resistant index cases, failures on treatment, HIV infected persons and those from regions with high MDR prevalence such as countries of the former Soviet Union and former parts of Asia (6).

Current treatment regimens for MDR-TB are designed using evidence from small and medium sized retrospective case series, mostly from high resource countries (7), rather than RCTs. In the last few years community based MDR-TB treatment with affordable therapy was reported from low income countries (9). Resources for such treatment can be accessed through WHO agencies such as the Green Light Committee (GLC). A recent review of the treatment of MDR-TB (7), provide some guidelines for regimen selection. A fluoroquinolone, especially one of the newer agents is the mainstay of treatment and other older TB drugs are now being recalled for use. Surgery in selected cases has been found to be effective in specialised centres and reports cite the cure rate of MDRTB using fluoroquinolones and selected surgery to be 87% when compared to rates of 48% in the pre-quinolone era (8).

**Case series of multidrug resistant tuberculosis**

The reader is referred to the excellent review by Mukherjee, et al (7) for a more detailed description of the studies that inform current practice.

The best outcomes are obtained by using fluoroquinolone containing regimens guided by first and second line drug sensitivity testing, and judicious use of surgery for those which cannot be cured by chemotherapy. However surgery has only been performed in a few specialized centres, dealing with cases resistant to a wide range of drugs and where advanced infection control practices need to be followed. When second line testing is not available, the regimen should be individually designed based on the patients region of origin, contact history and history of past treatment.

**Classes of drugs used to treat MDR-TB**

The current consensus is to use drug combinations from the five following groups as appropriate.

*Group 1: Available oral first line drugs:* Ethambutol (E), pyrazinamide (Z). Drugs should be given in maximal dosage for duration of course

*Group 2: Fluoroquinolones (FQ):* ciprofloxacin (CPX), ofloxacin (oflx), levofloxacin, moxifloxacin. Moxifloxacin is as effective as ethambutol in drug susceptible disease in the initial phase and has bactericidal effects between that of isoniazid and rifampicin, but is expensive for. The FQ should be used by the individual programme for duration of course (18-24 months after culture conversion).

*Group 3: Injectables:* Streptomycin (S) , kanamycin (KM) amikacin ( AMK), capreomycin (CM). Streptomycin has disadvantages such as toxicity and wide prevalence of resistance. Sensitivity may be retained to other aminoglycosides such as kanamycin, amikacin or capreomycin.

*Group 4: Oral drugs:* Ethionamide (Etd) or prothionamide (Ptd), cycloserine (CS), para-amino salycilic acid (PAS) , thiacetazone (Tct). These bacteriostatic drugs are added as required until there are at least 5 drugs to which the organism is susceptible. Thiacetazone is not recommended.

*Group 5: Other oral drugs:* Amoxicillin-clavulanic acid, clarithromycin, clofazimine. These drugs, which have shown some efficacy against *Mycobacterium tuberculosis* in laboratory and animal studies, have not been tested in clinical trials and are used when others are not available. Isoniazid in high doses may be given, since some organisms may retain susceptibility at high doses.

Current recommendations for best practice advise an individually designed regimen of 5 drugs or more based on DSTs to first and second line agents. This includes any first line drugs, one each from group 2 and 3, as many as needed from group 4, with agents from group 5 making up the shortfall. Supervised therapy is recommended for at least 18-24 months after culture conversion, but the injections, can be stopped 6 months after culture conversion.

**Treatment in countries with no facilities for second line drug testing: standard/individualised treatment**

When second line DSTs are not available, the drug combination is based on predicted susceptibility, avoiding previously used drugs and reference to prevailing patterns of drug resistance. Individually designed regimens have better outcomes than standard "one size fits all' regimens (7). An axiom of TB treatment is never to add a single drug to a failing regimen and to ensure adherence both in and out of hospital. In Sri Lanka this would be the approach to be followed, and current WHO regimens would suit if second line agents have not been previously used.

The WHO recommendations are based on DSTs to the first line drugs. The recommended treatment is as follows:

| Resistance pattern | Intensive phase | Continuation phase |
|---|---|---|
| H R S | 3-6 m : E Z Amk Ptd FQ | 18m E Z FQ Ptd |
| H R S E | 3-6 M : Z Amk Ptd FQ CS | 18m Z Ptd FQ CS |
| S H R Z E | 3-6 m : Amk Ptd FQ CS PAS | 18m Ptd FQ CS |

**Management of side effects**

Patients should be given adequate information on minor side effects and symptomatic treatment. Minor alteration in dosage or schedules may help in some. Antihistamines, analgesics and other medications are effective in non-life-threatening symptoms. Cessation of optimal therapy is occasionally necessary for severe intolerance or threat to life.

## Table 1. Management of side-effects

**Minor side-effects (continue drugs )**

| Side-effect | Drugs likely to be responsible | Management |
|---|---|---|
| Minor GI side-effects | All | Timing changes, antiemetics, antidiarrhoeals<br>Avoid antacids if using FQ |
| Minor skin rash or itching | Most drugs | Topical creams and antihistamines |
| Joint pains | Z | Aspirin |
| Burning feet | Ptd , aminoglycosides, CS E high dose H | Pyridoxine |
| Asymptomatic rise of liver transaminases (<5x normal) | Z FQ Ptd High dose H | Monitor carefully |
| Hypothyroidism | Ptd and PAS | Replace thyroxine |
| Minor mood disturbances | Ptd FQ (CS usually causes severe disturbance) | Antidepressants or counselling |

**Major side-effects which need cessation of drug**

| Side-effect | Drugs likely to be responsible | Management |
|---|---|---|
| Clinical hepatitis, jaundice<br>Disturbance of transaminases over 5X normal | Z FQ Ptd High dose H | Stop and monitor<br>Use aminoglycoside and E and /or FQ as holding regimen<br>While reintroducing drugs gradually |
| Severe skin rash<br>Hypersensitivity and Stephen Johnson reaction | Stop offending drug | Antihistamine, sometimes steroids and supportive treatment |
| Cardiotoxicity, | FQ | Stop drug |
| Visual impairment | E | Stop drug |
| Deafness or vestibular dysfunction | Aminoglycosides capreomycin more rarely | Stop drug |
| Severe electrolyte disturbance usually hypokalaemia | CM | Replace IV fluids - if severe stop drug |
| Severe psychosis depression | CS FQ Ptd H | Stop if not responsive to anti-depressants or antipsychotic |
| Seizures | | Anticonvulsants for seizures |
| Blood dyscrasias | Any drug but more commonly rifamycins aminoglycosides | Stop offending agent |
| Nephrotoxicity | Aminoglycosides less with CM | Stop drug |

## Table 2. Drugs used in the treatment of multidrug resistant tuberculosis (9)

(For conciseness, isoniazid and rifampicin have not been included in this list, although isoniazid may sometimes be added to the regimen since there may be some effect at high doses in some cases)
This information is not comprehensive and is meant for general guidance only (9).

| Name of drug and dose | Side effects | Comments |
|---|---|---|
| Ethambutol<br>15-25mg /kg body wt<br>Use at higher doses<br>if not contraindicated | Rare; usually well tolerated<br>optic neuritis (0.8% ) dose related, more in renal failure<br>arthralgia, GI upset, headache, dizziness, neuropathy, blood dyscrasias, fever, rash (0.5%) | Pregnancy : yes<br>Children : in older children only if vision can be monitored<br>Adjust dose in renal failure (complex see reference)<br>Renally excreted<br>Poor CNS penetration through uninflamed meninges<br>No interactions reported |
| Pyrazinamide<br>30-40 mg/kg upto 2 G for >50<br>1.5G for <50 kg | Arthropathy, hepatitis, hyper uricemia,<br>GI upset, rash, impaired diabetes control<br>rarely dysuria, fever, hypersensitivity | No interactions reported<br>Monitor liver function<br>Pregnancy: benefits outweigh risks in MDRTB, but will need to monitor LFT carefully<br>Dosage adjustment in renal failure<br>Children: use at lower dose range |
| Fluoroquinolones<br>Ciprofloxacin 750 mg oral bd<br>Levofloxacin 500 mg oral /dy<br>Moxifloxacin 400 mg /dy<br>Ofloxacin 400mg oral bd | Well tolerated well absorbed side effects uncommon<br>GI upset, headache, dizziness, insomnia, seizures (seen more in elderly)<br>skin : photosensitivity, rash,<br>More rarely arthralgia, intersititial nephritis, palpitations (QT interval prolongation with moxifloxacin) rarely liver disturbances | Adjust for renal failure<br>When creatinine clearance < 50ml/mt<br>not FDA approved for use in pregnancy (teratogenic for joints in immature animals) excretion renal |

| Name of drug and dose | Side effects | Comments |
|---|---|---|
| Aminoglycosides<br>Streptomycin, Amikacin, Kanamycin<br>15mg /kg im /day<br>KM and AMK can be given IV | Adverse effects common 8.2%<br>Pain at injection site, hypersensitivity<br>Ototoxicity (cochlear ) dose related hearing loss, facial paraesthesia, renal toxicity (may be irreversible) | Adjust dose for renal insufficiency<br>Contraindicated in pregnancy |
| | Peripheral neuropathy, rash, vestibular toxicity (vertigo, nausea, vomiting)<br>Anaphylaxis, hemolysis, neuromuscular blockade, | Drug interactions<br>Diuretics increase risk of ototoxicity<br>Pancytopenia |
| Capreomycin<br>1 G im /day | Similar to aminoglycosides but less nephrotoxic and ototoxic<br>More electrolyte disturbances mainly hypokalaemia | Adjust for renal failure<br>Contraindicated in pregnancy (teratogenic)<br>Neuromuscular blockade with ether anaesthesia |
| Ethionamide 500-1000 mg/day<br>Prothionamide 500-1000mg/day<br>Increase gradually | GI upset is common nausea vomiting abdominal pain, loss of appetite, metallic taste,<br>hypothyroidism, arthralgia rash neuropathy photosensitivity optic neuritis seizures psychosis | Contraindicated in pregnancy (teratogenic)<br>Administer with pyridoxine |
| Cycloserine<br>500-1000 mg /day<br>Give with pyridoxine<br>Increase to maximum dose | Neuropsychiatric effects common (around 20%) and could be serious including severe depression, psychosis with risk of suicide, seizures, headaches tremors | Renal excretion readily penetrates CNS<br>Interaction with alcohol phenytoin |
| Para aminosalycilic acid<br>4 g oral /day<br>Delayed release granules (PASER) with acidic food or drink | Adverse effects common 10% usually severe GIT disturbances nausea vomiting diarrhea, hypersensitivy rashes<br>Occasionally liver disturbances electrolyte abnormalities | Renally excreted<br>Reduces isoniazid acetylation<br>Decreased rifampicin absorption and<br>Decreased vitamin B12 uptake |
| Clofazimine<br>200-300 mg per day<br>Start at 300mg and Decrease when skin bronzes | Discoloration of skin and eyes GI upset photosensitivity and rashes<br>Malabsorption abdominal distress | Efficacy not proven against M TB |
| Thiacetazone<br>150 mg per day oral | GI upset severe skin rashes hypersensitivity<br>reactions including Steven Johnson reactions more in HIV infected patients<br>Bone marrow suppression | Not recommended |

Outcomes of treatment of MDR-TB have improved (9), but increase of resistance to second line agents called XDR-TB was reported in 2006. The term denotes virtually untreatable disease with a pattern of resistance which includes isoniazid, rifampicin, fluoroquinolones and aminoglycosides/ polypeptides. XDR-TB is likely to occur when second line agents have been frequently used without supervision.

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**Dr Hiranthi Walpola,** MD, MRCP, MPH, *Senior Medical Officer, Queensland Tuberculosis Control Centre, Brisbane, Australia.*

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# Self-assessment questions

*(And clinical physiology in small doses)*

(Select the **best** response in each question)

1. The human diploid cell derived and purified chick embryo cell derived vaccines for rabies post-exposure therapy
   a. are contraindicated in pregnancy.
   b. are contraindicated in children under 3 years of age.
   c. can be stored up to 24 hours at 2-8°C after opening the vial without loss of potency.
   d. may be given safely without a prior sensitivity test.
   e. need not be given if the biting animal is alive and healthy 7 days after the bite.
2. Which statement is true regarding rabies immunoglobulin?
   a. A sensitivity test is essential before administering Human Rabies Immunoglobulin.
   b. The adult doses of the Equine Rabies Immunoglobulin and Human Rabies Immunoglobulin are identical.
   c. The selected rabies immunoglobulin dose should be injected in and around all washed wounds, and the balance intramuscularly.
   d. Rabies immunoglobulin may be mixed in the syringe with the first dose of cell derived vaccine.
   e. Rabies immunoglobulin administration is essential after major exposure even in individuals who have previously had a full course of post-exposure therapy with a cell derived vaccine.
3. Which statement regarding rabies is true?
   a. The virus belongs to the family Bunyavirus and genus Hantavirus.
   b. The annual incidence in Australia and New Zealand is 5 - 10 cases.
   c. The virus replicates in muscle tissue near the wound and reaches the central nervous system via the bloodstream.
   d. Hydrophobia (fear of water) is present in over 90% of patients.
   e. Negri bodies are found at post-mortem in 30 - 50 % of patients.
   f. Aerophobia (fear of air and wind, the fanning test) is pathognomonic.

**Answers to self-assessment questions**

Question 1. The correct response is (d). The vero cell and chick embryo cell derived vaccines are not contraindicated in pregnancy or young children, do not require prior sensitivity testing, and must be used within 8 hours when the opened vial is stored at 2-8°C. If the biting animal is observable, alive and healthy at 15 days no post-exposure therapy is required.

Question 2. The correct response is (c). The human rabies immunoglobulin needs no prior sensitivity testing (but testing is **mandatory** for the equine variety); its dose of 20 units/kg is half that of the equine immunoglobulin; it must not be mixed in the same syringe as the rabies vaccine (indeed, the two should be given at widely separate sites); and it's not essential in previously properly immunised bite victims (but vaccine may be necessary).

Question 3. The correct answer is (f). The family is *Rhabdovirus* and genus *lyssavirus*; it travels to the central nervous system via nerve axoplasm; and Negri bodies and hydrophobia (fear of water) are present respectively in about 90% and 50% of patients. Aerophobia is considered pathognomonic. Rabies has been reported from all continents, but **never** from New Zealand, Australia and the Antarctic.

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**Professor Colvin Goonaratna,** FCCP, FRCP, PhD, Hon DSc. E-mail <si7np5e@gmail.com>.



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