NEWSPAPER POST

TheSynapse
The Medical Professionals' Network

MEDICAL IMAGING

Tuberculosis

by Pierre Vassallo
MD PhD FACA Artz für Radiologie
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Till the mid 1980s, there was a steady decline in the prevalence of tuberculosis. Since that time, however, there has been a resurgence of tuberculosis due to the acquired immunodeficiency syndrome (AIDS) epidemic and the increasing number of drug-resistant strains of *Mycobacterium tuberculosis.*

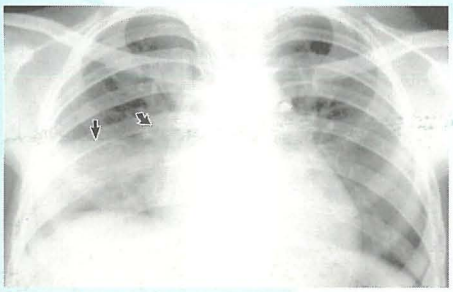


Figure 1. *Chest X-ray shows right middle lobe infiltrate (straight arrow) and right hilar lymphadenopathy (curved arrow).*

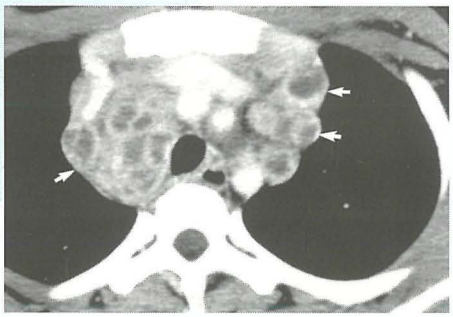


Figure 2. *CT scan shows bilateral hilar TB lymphadenopathy.*

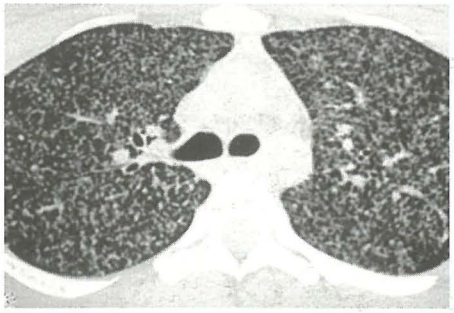


Figure 3. *CT scan showing military lung opacities.*

In addition to immuno-compromised individuals, other population groups who are at increased risk include minorities, the poor, alcoholics, immigrants from third world countries, prisoners, the aged, nursing home residents and the homeless.

Although manifestations of tuberculosis are usually limited to the chest, the disease can affect any organ system and in patients infected with human immunodeficiency virus usually involves multiple extrapulmonary sites including the skeleton, genitourinary tract and central nervous system.

Pulmonary tuberculosis is classically divided into *primary* and *postprimary* (reactivation) tuberculosis. There is considerable overlap in the radiologic manifestations of these two entities.

Although primary tuberculosis is the most common form of pulmonary tuberculosis in infants and children, it accounts for 23%–34% of all adult cases of tuberculosis.

Primary tuberculosis typically manifests radiologically as parenchymal disease (Figure 1), lymphadenopathy (Figure 2), pleural effusion, miliary disease (Figure 3), or atelectasis. Chest radiography may be normal in 15% of cases. Miliary opacities may also indicate varicella pneumonia, sarcoidosis, histoplasmosis, metastases, pneumoconiosis, or hemosiderosis.

Postprimary disease results from reactivation of a previously dormant primary infection in 90% of cases; in a minority of cases, it represents continuation of the primary disease. Postprimary tuberculosis is almost exclusively a disease of adolescence and adulthood.

Postprimary tuberculosis is almost exclusively a disease of adolescence and adulthood.

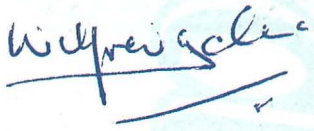
The radiologic features of postprimary tuberculosis can be broadly classified as parenchymal disease with cavitation (Figure 4), airway involvement (Figure 4), pleural extension, and other complications. Central airway involvement in tuberculosis can be the result of direct extension from tuberculous lymph nodes,

continues on page 2

Editor's Word

Hello and welcome to the second issue of TheSYNAPSE Magazine for this year. In this issue we have a number of articles focusing on **Infections**. The Medical Imaging Article deals with **Tuberculosis**, a condition that, up till the 80's was on the decline, but now is again re-emerging as an important, often forgotten illness we all have to be aware of especially because of atypical modes of presentation. Other articles dealing with infections include articles on **Community Acquired MRSA infections, Pharmacokinetics of Antiviral agents indicated in Influenza, Paediatric Urinary Tract Infections** as well as an **Update on the Current Status of the Avian Influenza**. We also bring you review articles on **Management of Depression** and **Migraine**. The **MoneyWise** article in this issue gives a useful insight on the performance of the Maltese Stock Market.

May I once again thank all members of staff and advertisers for making this issue yet another success.



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Tuberculosis

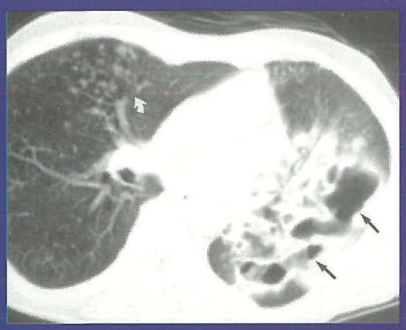

Figure 4. *CT scan showing cavitation (straight arrows) and tranbronchial spread of infection (curved arrow).*

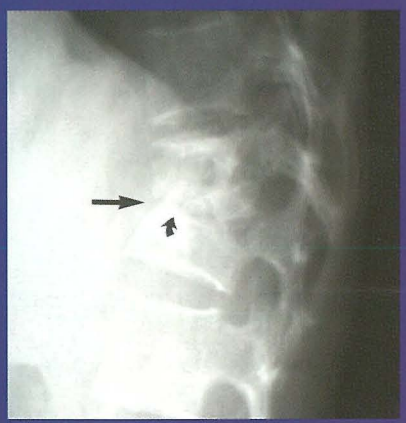

Figure 5. *X-ray showing tuberculous spondylodiscitis with lytic (straight arrow) and sclerotic (curved arrow) areas.*

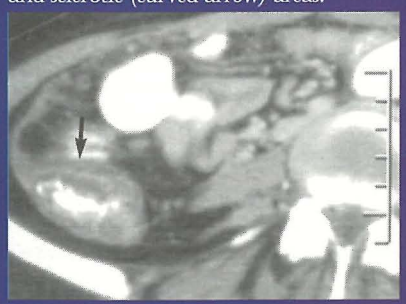

Figure 6. *CT scan showing thickening of the caecal wall due to tuberculosis.*

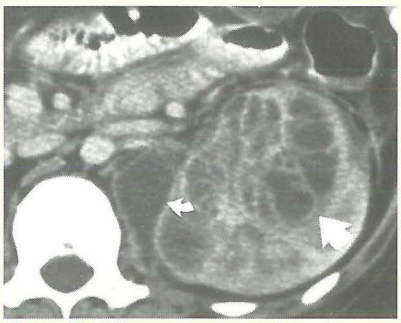

Figure 7. *CT scan showing tuberculous nephritis with gross parenchymal destruction and intra (straight arrow) and extra-parenchymal (curved arrow) abscesses.*

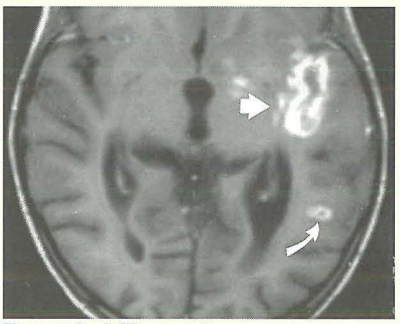

Figure 8. *MR scan showing contast enhancement in the left sylvian fissure (straight arrow) and in the sulci (curved arrow) due to tuberculous meningitis.*

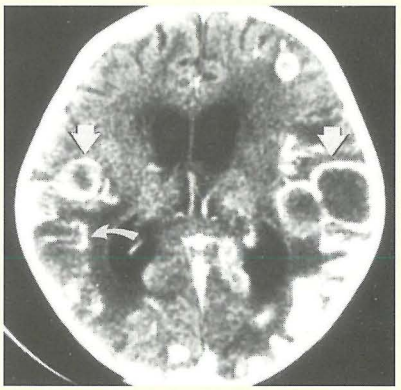

Figure 9. *CT scan showing cerebral solid (curved arrow) and cavitating (straight arrow) tuberculomas with calcification.*

endobronchial spread of infection, or lymphatic dissemination to the airway. Bronchial stenosis may result with persistent segmental or lobar collapse, lobar hyperinflation, obstructive pneumonia, or mucoid impaction.

The spine is the most frequent extrapulmonary site of osseous involvement in tuberculosis, with the upper lumbar and lower thoracic spine being involved most frequently (Figure 5). More than one vertebra is typically affected, and the vertebral body is more commonly involved than the posterior elements. Osteomyelitis and septic arthritis may occur anywhere in the skeleton.

Gastrointestinal TB is uncommon but most commonly affects the ileocecal region due to the abundance of lymphoid tissue (Figure 6). Urinary tract TB affects the kidneys, ureters and bladder with resulting scarring, deformity and calcification (Figure 7).

Most tuberculous infections of the central nervous system are a result of hematogenous spread. Intracranial tuberculosis results in two related pathologic processes: tuberculous meningitis (Figure 8) and intracranial tuberculomas (Figure 9).

Less common sites involved with tuberculosis include the middle ears structures, the eyes (retinitis) and the heart (pericarditis and rarely myocardial tuberculomas).

In conclusion, tuberculosis can affect virtually any organ system in the body and can be devastating if left untreated. The increasing prevalence of this disease in both immunocompetent and immunocompromised individuals makes tuberculosis a topic of universal concern.

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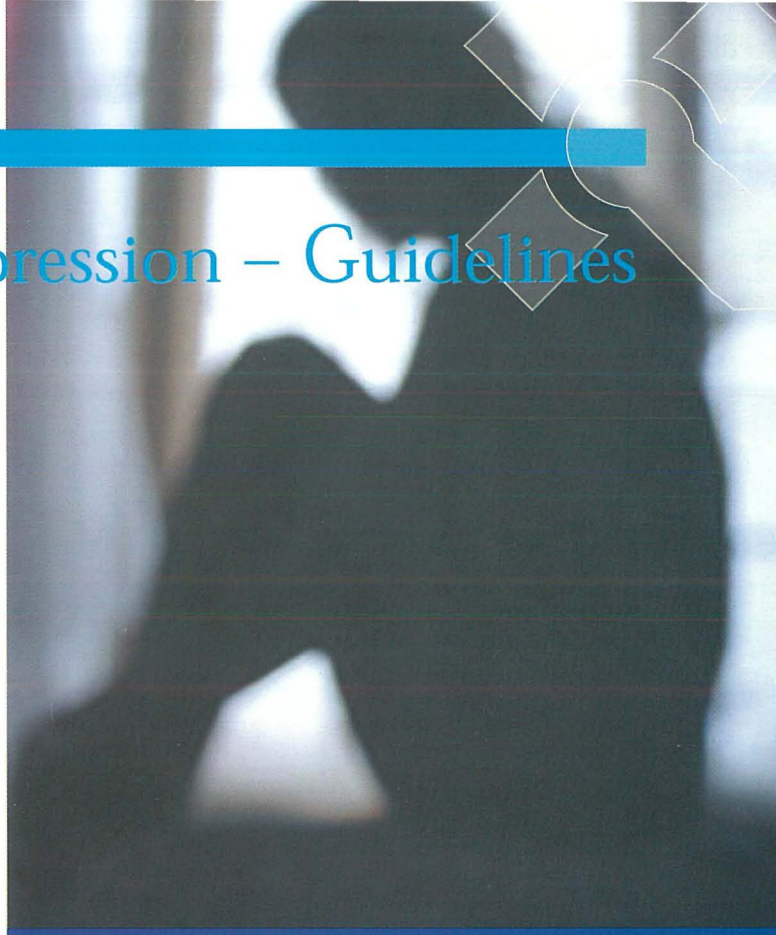
Management of Depression – Guidelines



by **Peter Muscat** *MD LRCP MRCS MRCPsych.*
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Senior Lecturer – University of Malta

1. Make an accurate diagnosis and elicit the signs and symptoms accompanying the depressive disorder

Is the depression basically endogenous or mainly reactive? Many also suffer from coexisting anxiety which may overshadow the depression. One should exclude other psychiatric conditions such as obsessive compulsive disorder, schizophrenia or personality disorder. Endocrine disturbances and occult carcinomas are notorious for initially presenting with depression. Patients with psychoactive substance abuse are often depressed. Although many patients complain of a miserable mood, others may only complain of apathy, loss of interest and enjoyment, reduced energy, which in turn causes tiredness, reduced activity and withdrawal. With some patients the main problems are reduced attention, concentration and consequent memory difficulties. Others have ideas of guilt, worthlessness and lowered self esteem. Several patients also complain of obsessive thoughts and behaviours.

Biological symptoms are usually more associated with endogenous depression and seasonal affective disorder. Previous severe mood swings and periods of elation are indicative of bipolar mood disorder. One should also assess for morbid ideation and suicide risk in a tactful way.

2. Adopt a biopsychosocial approach to management

It is better to hospitalise a suicidal patient on an emergency order rather than run the risk of a tragedy. Patients who are neglecting themselves, especially if they live alone, usually need admission.

Most patients with less severe depression can be treated by Family Doctors in the community. The support of other family members and or friends is invaluable and should always be sought.

The biological treatments of depression are essentially antidepressant medications.

Anxiolytic and antipsychotic medication may also be necessary in certain cases.

Although there are many antidepressant drugs available, I shall limit this presentation to drugs commonly available in Malta.

Since the 1950's the tricyclic antidepressants have been widely used with much success and are still useful nowadays. Amitriptyline and trimipramine can be used in patients who are agitated or who suffer from initial insomnia. Clomipramine is particularly useful when obsessive symptoms dominate the depressive picture. Patients who are very lethargic and apathetic do well with the less sedative tricyclics such as imipramine. The tricyclic antidepressants block the reuptake of the monoamines noradrenaline and 5-HT. They cause numerous side effects and are potentially fatal in overdose. The antimuscarinic action of these drugs, such as dry mouth, blurred vision, nausea, constipation, urinary retention and postural hypotension are the side effects which patients often do not tolerate and which lead to non compliance. Since they may impair alertness, patients should be warned not to drive, operate machinery or drink alcohol. Moreover they are toxic in overdose causing cardiac conduction defects, arrhythmias, convulsions, respiratory failure, coma and death.

To avoid side effects one should start at a low dose of about 25mg daily and gradually increase the dose to a more therapeutic dose of about 150mg daily over a 2-3 week period and according to the patient's symptoms and severity of depression. Besides, patients should be informed that the side effects may initially make them feel worse but that these will gradually improve over a few weeks, and that it may take about 2-3 weeks before a therapeutic response is felt.

The tetracyclic antidepressants mianserin and maprotiline are also rather sedating and useful in the elderly because of less cardiotoxic side effects. However mianserin can cause haematological and hepatic reactions.

Over the past fifteen years, the selective serotonin inhibitors (SSRIs) have become very popular and easy to use because of a lower side effect profile, quicker onset of action, and relative safety in overdose. When compared to tricyclics, a lower number of pills is usually necessary to achieve the same therapeutic effect. However they are more likely to cause some internal agitation, tremor, insomnia, nausea, vomiting and sometimes diarrhoea in the first two weeks of treatment. Sexual dysfunction, particularly delayed ejaculation and anorgasmia, are common complaints and often lead to a request for alternative medication.

The SSRIs are also successfully used in the treatment of obsessive compulsive disorder, bulimia nervosa, general anxiety disorders, panic and phobic disorders.

The commonest SSRIs used are citalopram, escitalopram (which is now replacing citalopram because of a lower side effect profile and quicker onset of action), fluoxetine, fluvoxamine, paroxetine and sertraline. Escitalopram is particularly useful in the elderly. Along with fluvoxamine it is reputed to cause less sexual side effects especially in the male. Fluoxetine is often used with much success especially where there is comfort eating accompanying the depression. Paroxetine is especially useful where obsessive symptoms accompany the depression. Sertraline seems to cause less agitation.

continues on page 6

Migraine

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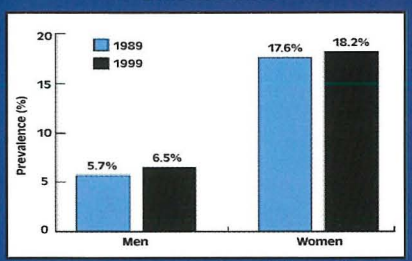
1. Epidemiology

Migraine is perhaps one of the commonest ailments afflicting mankind. Two of the most important studies about the prevalence of migraine are the American Migraine Studies 1 and 2. The first study was carried out in 1989 and the second was carried out in 1999. These studies showed that the prevalence of migraine remained the same overall. In 1989, 5.7% of the male population had migraine, while in 1999, the figure was 6.5%. The prevalence rates for women were 17.6% in 1989 and 18.2% in 1999.

The diagnosis of migraine was based on the criteria established by the International Headache Society (IHS).

Figure 1
Prevalence of Migraine in the United States



Adapted with permission from Lipton RB. et al. Prevalence and burden of migraine in the United States: results from the American Migrain Study II. *Headache.* 2001; 41: 650.

Migraine is approximately three times more common in women than in men.

Approximately 1 household in every 4 includes an individual who suffers from migraine.

International Headache Society Migraine Classification

1. Migraine
   - 1.1 Migraine without aura
   - 1.2 Migraine with aura
     - 1.2.1 Migraine with typical aura
     - 1.2.2 Migraine with prolonged aura
     - 1.2.3 Familial hemiplegic migraine
     - 1.2.4 Basilar migraine
     - 1.2.5 Migraine aura without headache
     - 1.2.6 Migraine with acute-onset aura
   - 1.3 Ophthalmoplegic migraine
   - 1.4 Retinal migraine
   - 1.5 Childhood periodic syndromes that may be precursors to or associated with migraine
   - 1.6 Complications of migraine
     - 1.6.1 Status migrainosus
     - 1.6.2 Migrainous infarction
   - 1.7 Migrainous disorder not fulfilling above criteria

Reprinted with permission from Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. *Cephalalgia.* 1988; 8 (suppl 7): 13.

Figure 2

2. Diagnosis

Unfortunately, migraine is one of the more frequently misdiagnosed conditions and this leads to inappropriate treatment.

The criteria established by the International Headache Society should help clinicians make a more accurate diagnosis.

Examples of Reasons to Perform Neuroimaging Studies in Headache Sufferers

Neuroimaging may be imported for headache patients who have
- Abnormal unexplained neurological exam
- Rapidly increasing frequency and/or severity headaches
- Change in headache clinical features
- First or "worst headache ever experienced
- Headache with extremely abrupt onset
- New-onset headache after age 50
- Headache refractory to aggressive treatment
- Dizziness, numbness or tingling

Frishberg B, et al. Evidence-based guidlines in the primary care setting: neuroimaging in patients with acute headache. Available at: Http//:www.aan.com. 200: Accessed 11/14/01.
Evans RW, et al. Neuroimaging and other diagnostic testing in headache. In: Silberstein SD, Lipton RB, Dalessio DJ, editors. Wolfs Headache and other Pain. 7th ed. New York, NY: Oxford University Press; 2001. p. 27-49.

Figure 3

Essentially, the major forms of migraine are classified according to whether there is a preceding aura or not. The diagnosis of migraine is a clinical diagnosis, based on the history.

Tension Headache is often misdiagnosed as Migraine.

It is to be noted that Migraine and Tension Headache can co-exist in the same patient. Care should be taken to distinguish between the two.

Neuroradiological investigations are not normally necessary.

3. Genetic and Environmental Factors

Current evidence from family aggregation studies show that if patients suffer from migraine with aura, first degree relatives have a four-fold increase in risk.

If the patient has migraine without aura, the relative risk for first degree relatives is less. However the risk is still appreciably higher than that found in a normal population.

Current evidence would suggest that both genetic and environmental causes are important in the aetiology of migraine.

4. Acute treatment

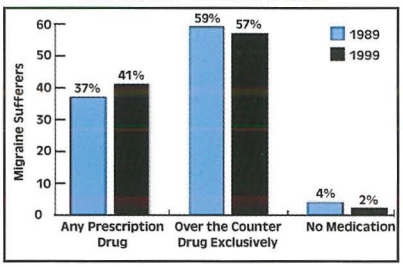
As both migraine with aura and migraine without aura are often self diagnosed, fewer patients tend to consult their Family Doctor or a Neurologist. Most patients self medicate with over the counter products. Around 60% of patients do well on such a regime (figure 4). Prescription medications are less often used.

The aims of Acute Treatment should include:

1. Restoration to normal function as soon as possible;
2. Optimization of self care;
3. Cost effectiveness;
4. Minimal or no adverse side effects.

Drugs which have been shown to be effective in well-designed, randomized clinical trials and which have yielded consistent satisfactory results include the following: Aspirin, Paracetamol, NSAIDS and the Triptans.

Figure 4
Patterns of Migraine Medication Use in the United States



Adapted with permission from Lipton RB. et al. Prevalence and burden of migraine in the United States: results from the American Migrain Study II. *Headache.* 2001; 41: 650.

Drugs which were shown to be effective in at least 1 double-blind controlled trial and where there is a clinical impression of benefit, include the anti-emetics Metoclopramide and Prochlorperazine.

The evidence for Ergotamine efficacy is conflicting. This drug should be avoided because of overuse and because of the risks of potential severe side effects.

5. Preventive Treatment

Individuals who experience frequent and disabling attacks may not be adequately managed by acute therapy alone. Drug prevention therapy will help to reduce the frequency, severity and duration of the migraine attacks in this group. It could help reduce the disability associated with attacks and reduce the risk of worsening the migraine condition by the overuse of acute medications.

Preventive treatment is to be considered in the following situations:

1. Migraine attacks which recur and interfere with daily functioning;
2. Frequent migraine attacks, occurring more than three times per month;
3. When acute medications are not well tolerated or ineffective;
4. When there are contraindications to acute medications.

A number of drugs are used as prophylaxis. These include Amitriptyline, Valproate and Methysergide. The efficacy of these drugs has been shown in multiple well-designed randomized clinical trials.

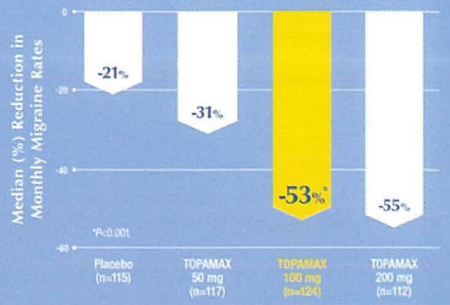
There is some evidence from clinical trials that Gabapentin, Atenolol and Verapramil are also effective.

Topiramate is a recent addition to the armamentarium.

NEW for migraine prevention

TOPAMAX effectively reduces the frequency of migraine attacks[1]

Significant Reduction in Migraine Frequency[2]



Results from a double-blind, 26-week, placebo-controlled trial of 469 patients.

Early onset of efficacy[3]

Initial reduction in migraines seen within the first month

Sustained migraine control[1]

Reduction in migraines maintained in long-term, 12-month trials[4]

[4]Based on 6-month, open-label extensions of double-blind, placebo-controlled trials.

References: 1. TOPAMAX prescribing information. Raritan, NJ: Ortho-McNeil Pharmaceutical, Inc; 2003. 2. Data on file: TOPAMAX Integrated Summary of Efficacy. Raritan, NJ: Ortho-McNeil Pharmaceutical, Inc; 2003. 3. Data on file: Raritan, NJ: Ortho-McNeil Pharmaceutical, Inc; 2003.

TOPAMAX® (topiramate)

QUALITATIVE AND QUANTITATIVE COMPOSITION: Each tablet contains 25, 50, 100 and 200 mg of topiramate. Inactive Ingredients: Lactose monohydrate, Pregelatinized starch, Carnauba wax, Microcrystalline cellulose, Sodium starch glycolate, Magnesium stearate, OPADRY White, Yellow, Pink, Red (depending on the tablet color and concentration) **Therapeutic indications:** Migraine: prophylaxis of migraine headache in adults. Initiation of treatment with topiramate should be restricted to specialist care and treatment should be managed under specialist supervision or shared care arrangements. **Dosage and administration:** General: For optimal seizure control in both adults and children, it is recommended that therapy be initiated at a low dose followed by titration to an effective dose. Migraine: Adults and children over 16 years: Titration should begin at 25 mg nightly for 1 week. The dosage should then be increased in increments of 25 mg/day administered at 1-week intervals. If the patient is unable to tolerate the titration regimen, longer intervals between dose adjustments can be used. The recommended total daily dose of topiramate as treatment for the prophylaxis of migraine headache is 100 mg/day administered in two divided doses. Some patients may experience a benefit at a total daily dose of 50 mg/day. No extra benefit has been demonstrated from the administration of doses higher than 100 mg/day. Dose and titration rate should be guided by clinical outcome. Children: Topamax in migraine prophylaxis has not been studied in children under 16 years. **Contraindications:** Hypersensitivity to any component of this product. **Special warnings and special:** General: Antiepileptic drugs, including Topamax, should be withdrawn gradually to minimise the potential of increased seizure frequency. In clinical trials, dosages were decreased by 100 mg/day at weekly intervals. In some patients, withdrawal was accelerated without complications. Metabolic Acidosis: Hyperchloraemic, decreased serum bicarbonate below the normal reference range in the absence of respiratory alkalosis, is associated with topiramate treatment. Chronic metabolic acidosis in paediatric patients can reduce growth rates. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing topiramate (using dose tapering). Migraine Prophylaxis: Before discontinuation of treatment, dosage should be gradually reduced over at least 2 weeks to minimise the possibility of rebound migraine headaches. Weight loss: Significant weight loss may occur during long-term topiramate treatment for migraine prophylaxis. In clinical studies of topiramate 100 mg in migraine prophylaxis, a continuing weight decrease was observed with a mean weight decrease of 5.5 kg over 20 months. Twenty-five per cent of patients treated with topiramate for migraine prophylaxis had a weight loss of ³ 10% of their body weight. **Interaction:** Effects on Other Antiepileptic Drugs: The addition of Topamax to other antiepileptic drugs (phenytoin ,carbamazepine, valproic acid, phenobarbital, primidone) has no clinically significant effect on their steady-state plasma concentrations, except in some patients where the addition of Topamax to phenytoin may result in an increase of plasma concentrations of phenytoin. Consequently, it is advised that any patient on phenytoin should have phenytoin levels monitored. A pharmacokinetic interaction study of patients with epilepsy indicated the addition of topiramate to lamotrigine had no effect on steady state plasma concentration of lamotrigine at topiramate doses of 100 to 400 mg/day. In addition, there was no change in steady state plasma concentration of topiramate during or after removal of lamotrigine treatment (mean dose of 327 mg/day). Effects of Other Antiepileptic Drugs on Topamax: Phenytoin and carbamazepine decrease the plasma concentration of topiramate. The addition or withdrawal of phenytoin or carbamazepine to Topamax therapy may require an adjustment in dosage of the latter. This should be done by titrating to clinical effect. The addition or withdrawal of valproic acid does not produce clinically significant changes in plasma concentrations of topiramate and, therefore, does not warrant dosage adjustment of Topamax. Other Drug Interactions: Digoxin: When Topamax is added or withdrawn in patients on digoxin therapy, careful attention should be given to the routine monitoring of serum digoxin. CNS Depressants: Because of the potential of topiramate to cause CNS depression, as well as other cognitive and/or neuropsychiatric adverse events, topiramate should be used with caution if used in combination with alcohol and other CNS depressants. Oral Contraceptives: In an interaction study with a combined oral contraceptive, Topamax increased plasma clearance of the oestrogenic component significantly. Consequently, and bearing in mind the potential risk of teratogenicity, patients should receive a preparation containing not less than 50 µg of oestrogen or use some alternative non-hormonal method of contraception. Patients taking oral contraceptives should be asked to report any change in their bleeding patterns. Hydrochlorothiazide (HCTZ): The steady-state pharmacokinetics of HCTZ were not significantly influenced by the concomitant administration of topiramate. Clinical laboratory results indicated decreases in serum potassium after topiramate or HCTZ administration, which were greater when HCTZ and topiramate were administered in combination. Metformin: When Topamax is added or withdrawn in patients on metformin therapy, careful attention should be given to the routine monitoring for adequate control of their diabetic disease state. Pioglitazone: When Topamax is added to pioglitazone therapy or pioglitazone is added to Topamax therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state. Others: Topamax, when used concomitantly with other agents predisposing to nephrolithiasis, may increase the risk of nephrolithiasis. While using Topamax, agents like these should be avoided since they may create a physiological environment that increases the risk of renal stone formation. The interaction with benzodiazepines has not been studied. **Additional Pharmacokinetic Drug Interaction Studies:** Interaction studies showed that Topamax did not significantly alter the serum levels of amitriptyline, propranolol or dihydroergotamine mesylate. The combination of Topamax with each of these drugs was well tolerated and no dose adjustments were necessary. **Pregnancy and lactation:** Topiramate was teratogenic in mice, rats and rabbits. In rats, topiramate crosses the placental barrier. There are no studies using Topamax in pregnant women. However, Topamax should not be used during pregnancy unless, in the opinion of the physician, the potential benefit outweighs the potential risk to the foetus. Before starting Topamax, women of childbearing potential should be fully informed of the possible effects of Topamax on the unborn foetus and the risks should be discussed with the patient in relation to the benefits of Topamax treatment in migraine prophylaxis. In post-marketing experience, hypospadias has been reported in male infants exposed in-utero to topiramate, with or without other anticonvulsants; however, a causal relationship with topiramate has not been established. It is recommended that women of child bearing potential use adequate contraception. Topamax should not be used during breast-feeding. **Effects on ability to drive and use machines:** As with all antiepileptic drugs, Topamax may produce CNS related adverse events. These adverse events could potentially be dangerous in patients driving a vehicle or operating machinery, particularly until such time as the individual patient's experience with the drug is established. **Undesirable effects** Migraine prophylaxis: fatigue, paraesthesia, dizziness, hypoaesthesia, language problems, nausea, diarrhoea, dyspepsia, dry mouth, weight decrease, anorexia, somnolence, difficulty with memory, difficulty with concentration/attention, insomnia, anxiety, mood problems, depression, taste perversion, abnormal vision. Fifty per cent of patients in these trials experienced paraesthesia. Weight decrease was reported as an adverse event in 1% of all placebo-treated patients and in 9% of all patients receiving topiramate 100 mg/day. In clinical trials weight loss continued with long-term topiramate treatment. Children: The effect of Topamax in children less than 16 years old with migraine has not been studied. General: Nephrolithiasis, reduced sweating has been rarely reported mainly in children, Acute myopia associated with secondary acute angle closure glaucoma has been reported rarely, Metabolic acidosis has been reported. **Incompatibilities:** None known. **MARKETING AUTHORISATION HOLDER:** A.M.Mangion Ltd., Mangion Buildings, New Street in Valetta Road, Luqa- Malta. **LEGAL CATEGORY:** POM **For complete information, please refer always to updated Summary of product characteristics and pack insert leaflet.**

JANSSEN-CILAG

Management of Depression – Guidelines

continued from page 3

A more recent introduction are the selective noradrenaline and serotonin reuptake inhibitors (SNRIs), such as venlafaxine. This seems to have a quicker onset of action than the SSRIs. The side effect profile is similar but may cause more problems in overdose due to sinus tachycardia, ventricular tachycardia, bradycardia and seizures.

The patient should be treated for at least six months with antidepressants following the end of the depressive episode and followed up regularly.

The use of benzodiazepines as anxiolytics and hypnotics has been steadily declining since the 1980s, due to dependence and tolerance. However they can be prescribed for a short period of time as an adjunct to the antidepressant when agitation, anxiety and insomnia are very troublesome.

The antipsychotic drugs, such as trifluperazine, chlorpromazine, haloperidol and the newer generation ones such as risperidone, olanzepine and quianeptine are used when the patient is deluded, hallucinated, aggressive or suicidal. When the depression is of such a severity, the involvement of a psychiatrist is often needed.

In bipolar disorder and chronic relapsing depression, lithium carbonate and the anticonvulsant drugs, carbemezapine, sodium valproate and lamotrigine are usually prescribed by psychiatrists to control these disorders. It is important for Family Doctors to know when this is done so as to be careful when prescribing other medications for other physical disorders so as not to cause inadvertent drug interactions.

Electroconvulsive therapy is often carried out on an out patient basis and therefore the involvement of the patient's Family Doctor is required to deal with any other difficulties that the patient or relatives present.

The psychological treatments include a number of different types of psychotherapies, useful for mildly or moderately depressed patients. Most Family Doctors can and should offer supportive psychotherapy. The basic requirements are time and a good deal of empathy. Other more specialised therapies such as cognitive behaviour therapy, marital and family therapy are offered by psychiatrists, clinical psychologists and psychotherapists. In cognitive behaviour therapy the patient is taught to deal with personal depressive cognitions and behaviour. Group therapy is only starting to be practised in Malta and mostly by support groups. Alcoholic anonymous and Gamblers anonymous are invaluable groups for patients who either become depressed by their addiction or who actually resort to such behaviours because of their depression.

The social treatment of depression has been recognised for a long time. The patient should be encouraged to meet other people and develop confiding relationships, as this has a protective function in preventing relapse. Returning to work boosts one's self confidence and esteem. One should be encouraged to adopt a healthier lifestyle that includes healthy eating, exercise and enough rest, hobbies and recreational activities.

Community acquired MRSA infections – a new challenge

by **Michael A. Borg** *MD MSc DLSHTM FMCPath DipHIC*
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Resistance to methicillin (the first beta-lactamase stable penicillin and precursor to flu/cloxacillin) was first seen amongst hospital isolates of *Staphylococcus aureus* (*S. aureus*) in the early sixties. Since then methicillin-resistant *S. aureus* (MRSA) has become widespread in hospitals and particularly intensive care units around the world. In addition, resistance to methicillin has extended to other antimicrobial groups including macrolides, quinolones and aminoglycosides such that the term MRSA is also often used as an abbreviation for multiply-resistant *S. aureus*. MRSA is now one of the most common causes of bacterial hospital infections, accounting for 40 - 70% of the *S. aureus* infections in intensive care units. This is particularly the case in the local setting where prevalence of MRSA is amongst the highest in Europe (Figure 1).

Until some years ago, acquisition of MRSA colonisation or infection was generally considered to be restricted to the nosocomial setting and isolates of MRSA from individuals in ambulatory care would invariably be traced to a previous hospitalisation or close contact with a recently hospitalised individual. However, in the past decade new strains of MRSA have emerged in the community, causing aggressive infections in young, otherwise healthy people. Suppurative skin infections and less frequently severe necrotising pneumonias are the most well-known clinical syndromes caused by these new strains.

The ability of new community-acquired MRSA (CA-MRSA) strains to colonise hosts in the community and cause clinical syndromes is mediated by unique combinations of traditional and newly described virulence factors. The most well-known community-acquired MRSA virulence factor is Panton Valentine Leucocidin (PVL), which elicits tissue necrosis and may contribute substantially to the clinical findings in young otherwise healthy individuals. CA-MRSA isolates have been associated with many of the clinical presentations known to occur with traditional *S. aureus* infection.

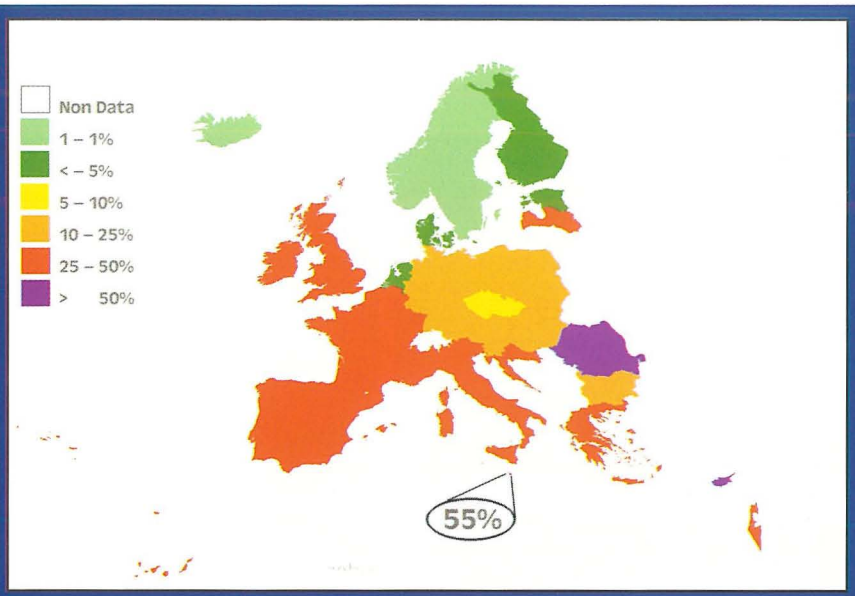

Figure 1: *Prevalence of methicillin resistance in S. aureus isolates from blood cultures in hospitals participating in the European Antimicrobial Resistance surveillance System (EARSS) [www.earss.rivm.nl]*

However, outbreaks of epidemic furunculosis and severe invasive paediatric infections caused by community acquired MRSA have been particularly noteworthy.

The main mode of transmission of CA-MRSA is, like its hospital equivalent, via hands which may become contaminated by contact with colonized or infected body sites of other individuals or devices, items or environmental surfaces contaminated with body fluids containing MRSA. Other factors contributing to transmission include skin-to-skin contact, crowded conditions and poor hygiene.

The criteria for distinguishing (CA-MRSA) from healthcare/hospital-associated MRSA (HA-MRSA) includes:

- Diagnosis of MRSA made in the outpatient setting or by a culture positive for MRSA not later than 48 hours after admission to the hospital;
- No medical history of MRSA infection or colonization;
- No medical history in the past year of:
  - Hospitalization,
  - Admission to a nursing home, skilled nursing facility or hospice,
  - Dialysis,
  - Surgery;
- No permanent indwelling catheters or medical devices that pass through the skin into the body.

Because of different definitions of community acquired infections used in the literature and the limited number of population-based studies that include molecular typing techniques, the reported prevalence of MRSA in the community varies widely. However, regardless of the definition, prevalence of CA-MRSA seems to be increasing. In a meta-analysis, Salgado and colleagues summarised many studies reporting the prevalence of community onset MRSA both with and without health-care associated risk factors in the community. When *S. aureus* strains isolated from routine clinical specimens were used as the baseline and cases were defined based on the timing of isolation of MRSA in relation to the time of admission, the pooled data from 27 retrospective studies (5932 patients) and from five prospective studies (636 patients) showed prevalence of community-onset infection among hospitalised patients with MRSA isolates of 30·2% and 37·3%, respectively. Around 85% of community-onset MRSA patients in both the retrospective and prospective groups reported at least one healthcare/hospital associated risk factor.

continues on page 12

The Pharmacokinetics of the Anti
What Are The Cli

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Several of the recent advances in antiviral drug development indicated in drugs now available. There are four licensed influenza antiviral agents v administered orally, while zanamir is given as a dry powder that is self-ad drugs differ in terms of their pharmacokinetics, and how this knowledge adjustments in varying age groups and in pa

Introduction

Advances in antiviral drug development and in rapid diagnostic methods have resulted in more efficient management strategies in the treatment of influenza.[1] Several of these advances have been particularly due to the improved pharmacokinetic properties of the drugs now available.[2]

Four licensed antiviral agents indicated in influenza are now available: the adamantanes (amantadine and rimantadine) with activity against influenza A viruses but not influenza B viruses; and the newer class of neuraminidase inhibitors (zanamivir [Relenza®] and oseltamivir [Tamiflu®]), which have activity against both influenza A and B viruses.[3]

The Adamantanes: Amantadine and Rimantadine

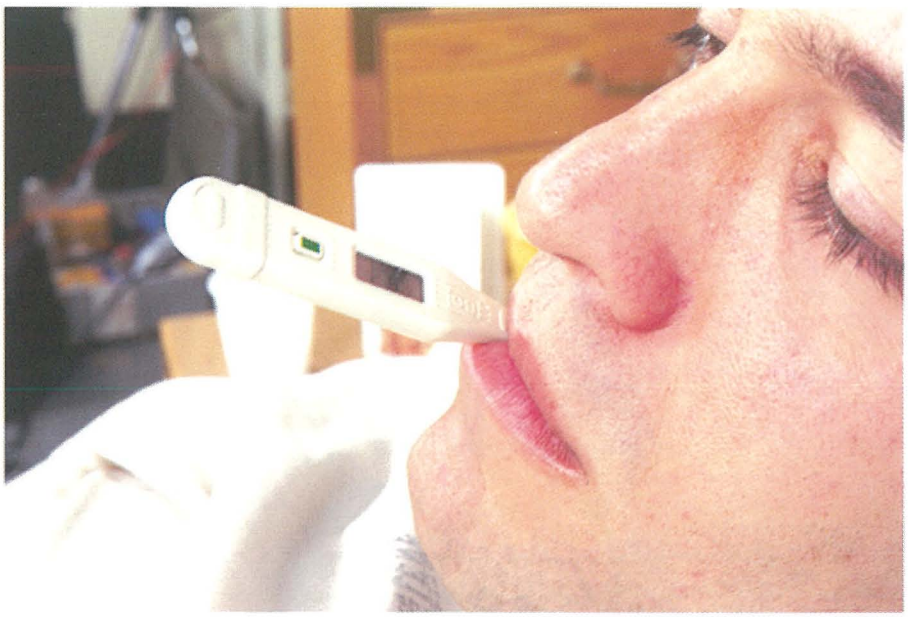
Amantidine is the oldest drug in this group having being marketed since 1966. Approximately 90% of amantadine is excreted unchanged in the urine by glomerular filtration and tubular secretion.[4] On the other hand, approximately 75% of rimantadine is metabolized by the liver and the apparent clearance of rimantadine has been found to be 50% lower for persons with severe liver dysfunction.[5] Rimantadine and its metabolites are then excreted by the kidneys.

Reduction in doses with amantadine and rimantadine are thus recommended in patients with any degree of renal insufficiency, but no reduction in dosage is recommended on the basis of age alone.[6]

The Neuraminidase Inhibitors: Zanamivir And Oseltamivir

Although related in terms of their mode of pharmacological activity, these two drugs have very varying pharmacokinetic parameters.

Zanamivir shows poor oral bioavailability in human volunteers, and in fact is administered as a dry powder using an oral inhaler. Zanamivir thus becomes highly



concentrated in the respiratory tract: 10 to 20 % reaches the lungs, and the rest is deposited in the oropharynx.[7] Five to 15 % of the total dose is then absorbed and excreted in the urine, resulting in a relative bioavailability of about 2%, with a half-life of 2.5 to 5.1 hours,[8] a feature that is potentially advantageous in situations in which a systemic drug is undesirable.[3]

This poor bioavailability, however, may be a problem in patients for whom inhalation may be difficult or when it is necessary to deliver the drug to sites of viral replication, as in cases of pneumonic disease.[8]

Population parameters for zanamivir have been estimated by a nonlinear mixed-effect modeling software program (NONMEM), using a one-compartment model with first-order absorption[9] Formulation and route of administration were found to be the most significant factors affecting the pharmacokinetics of zanamivir. No significant differences in pharmacokinetic parameters were observed when demographic variables, indices of infection, or concurrent medication use were considered in either phase I or phase II population analyses. Limited data is available regarding the safety and efficacy of zanamivir for patients with impaired renal function.[9]

Oseltamivir is really the ethyl ester prodrug of the active metabolite, oseltamivir carboxylate (GS4071 or Ro 64-0802).[10, 11, 12] Oseltamivir is efficiently converted to GS4071 after high and consistent site-specific absorption (around 80%) of both capsule and suspension formulations, from the gastrointestinal tract.[11, 12] This is an advantage of oseltamivir over zanamivir since the former achieves high plasma levels and thus can act outside the respiratory tract.

These studies also indicate that absorption is similar in the proximal and distal small bowel, but reduced from the ascending colon and they support the usefulness of a modified-release product.[12] Snell et al., found that the co-administration of various antacids with oseltamivir has no effect on the bioavailability or pharmacokinetics of either oseltamivir or the active metabolite.[13]

After conversion by hepatic carboxylesterases in the liver to the active metabolite, oseltamivir carboxylate, the latter distributes throughout the body, including the upper and lower respiratory tract.[10] Neither compound interacts with

viral Agents indicated in Influenza: nical Implications?

influenza have been due to the improved pharmacokinetic properties of the which are now available. Amantadine, rimantadine, and oseltamivir are ministered via oral inhalation. This brief review summarises how the four nay help to predict drug interactions and side effects, and estimate dosage tients with underlying pathological conditions.

cytochrome P450 mixed-function oxidases or glucuronosyltransferases.[14]

The active metabolite is detectable in plasma within 30 minutes and reaches maximal concentrations after 3 to 4 hours.[11] The pharmacokinetic profile of the active metabolite is linear and dose-proportional and it is 3% bound to human plasma proteins. After peak plasma concentrations are attained, its concentration declines with an apparent half-life of 6 to 10 hours. Steady-state plasma concentrations are achieved within 3 days of twice daily administration, and at a dosage of 75mg twice daily, the steady-state plasma trough concentrations of the active metabolite remain above the minimum inhibitory concentration for all influenza strains tested.[11] Exposure to the active metabolite at steady-state is approximately 25% higher in elderly compared with young individuals; however, no dosage adjustment is necessary. The pharmacokinetics in patients with influenza are qualitatively similar to those in healthy young adults

The active metabolite is eliminated through the kidneys by a first-order process as the unchanged drug by glomerular filtration and tubular secretion by an anionic transporter system.[10, 15] Given these characteristics, its potential for adverse interactions with other drugs appears limited to those arising from competitive inhibition of excretion by the renal tubular epithelial cell anionic transporter. In patients with renal impairment, metabolite clearance decreases linearly with creatinine clearance.[10]

Oo et al., assessed the metabolic and excretory capacity of oseltamivir and its active carboxylate metabolite in young children and the results demonstrated that infants as young as one year old can metabolize and excrete oseltamivir efficiently.[16]

Conclusion

This brief review has shown the importance of pharmacokinetics parameters when considering the choice, dosage, duration of therapy and use of influenza antiviral medications. During the decision making process, clinicians should also take into account the patient's age, weight, renal function, presence of other medical conditions and the potential for interaction with other medications.

No published data is as yet available concerning the safety or efficacy of using combinations of any of these four influenza antiviral drugs. Future investigations may also help to clarify the therapeutic role and pharmacokinetic advantages of novel antiviral drugs and formulations still in the development phase.

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Paediatric Urinary

by **Paul Caruana** *MD MSc FMCPath*
Consultant Microbiologist
St Luke's Hospital

Epidemiology and pathophysiology

The incidence of urinary tract infections (UTIs) is highest during the first year of life, with the majority of infections occurring in males. These rates then fall off in boys, with the risk being 4 to 10 times greater in uncircumcised males, while they remain relatively high in females. A study by Hellstorm et al. (1991) reported a cumulative incidence rate of 7.8% in girls by the age of seven.[1]

The importance of this condition is highlighted by various published papers, including Hoberman et al. (1993), in which it was reported that up to 5% of young children (<2 yrs) presenting with fever at pediatric casualty would have a UTI.[2]

Viruses, fungi and even parasites can all infect the urinary tract. However, most cases of infective pathology of the urinary system, at least in our part of the world, are caused by bacteria.

Common urinary isolates principally from hospitalized patients of all ages in St Luke's hospital include:

- *Escherichia coli* (which is by far the most commonly encountered organism)
- *Proteus mirabilis*
- *Enterococcus faecalis*
- *Pseudomonas aeruginosa*

These last three are isolated as above at more or less equal frequencies, but much less than *E. coli*.

In addition, various other gram positive and negative bacteria are isolated from time to time as being potential infective candidates from a patient's urine, but at a much reduced incidence when compared to the above four agents.

Laboratory Diagnosis

There are obvious difficulties in taking a history and examining the very young patient. In this case, laboratory diagnosis has an especially important role.

The gold standard for confirming a UTI is still by growing bacteria from a patient's urine. What may appear as a relatively easy procedure is fraught with difficulties, with the taking of a proper specimen especially problematic in a child.

In the very young, the "mid-stream urine" (MSU) technique is not feasible to perform, while the urine bag is considered to give a high rate of false positive cultures. Suprapubic aspiration is very specific but is a somewhat invasive procedure and is said to have a low success rate unless done under ultrasound guidance.

During specimen collection, bacterial contamination is inevitable, even when a proper MSU is obtained. For this reason, a cut off point was established early on in this branch of clinical bacteriology, such that 100 000 colony forming units per ml (cfu/ml) of urine is the established infection

Tract Infections

Test done on a urine specimen	% Sensitivity	% Specificity
Gram stain	93 (80 – 98)	95 (87 – 100)
Dipstick – Nitrite	50 (16 – 72)	98 (95 – 100)
Dipstick – L. Esterase	83 (64 – 89)	84 (71 – 95)
Either Nitrite or Esterase positive	88 (71 – 100)	93 (76 – 98)

Table 1: *A comparison of sensitivity and specificity values for different tests carried out on urine samples*

threshold for adults. Urinary bacterial counts which are lower than this are normally considered to signify the presence of bacterial contaminants, and typically ignored.

It has been suggested that this cutoff point may be too high for young children, with a 10 000 cfu/ml of urine a better cutoff point in these case. In fact, a study by Hoberman *et al.* (1994) showed that 65% of urine specimens taken from febrile children with a bacterial count of 10 000 – 49 000 cfu/ml showed evidence of contamination. If, in the attempt to increase sensitivity, a lower threshold is chosen (i.e. 10 rather than 10 cfu/ml), then one must accept a higher incidence of false positive results.

Another significant drawback of relying on a urine culture for diagnosis is the time delay, with the result not being available for at least 24 hours. Such delays in starting treatment may not be acceptable. In this case, rapid testing, preferably by the patientís bedside, may be useful in helping to confirm a clinical impression. But which tests, and how useful are they in practice?

A meta analysis by Gorelick *et al.* (1999) compared the predictive value of a number of rapid laboratory tests. The results are summarized in Table 1.

If we are to take the gram stain as our 'gold standard' for rapid urine testing, then it is comforting to know that by using a good urine dipstick, we can get excellent sensitivity and specificity, comparable to the gram.

Treatment of UTI

Below are listed some treatment options:

- Amoxicillin – is a good first line agent, however, a significant proportion of hospital acquired *E. coli* infections are ampicillin resistant. The extent to which this occurs in the community is unclear.
- Co-amoxiclav – some hospital acquired *E. coli* infections will also show intermediate or full resistance to this. Once again, we have no data on resistance rates outside hospital.
- Third generation cephalosporins, such as cefpodixime – are usually active against most strains of *E. coli* and *Proteus mirabilis*, but not *Enterococcus faecalis*.
- Trimethoprim – sulfamethoxazole – mostly effective against *E. coli* and *Proteus mirabilis*.
- Nitrofurantoin – will usually work against *E. coli* and *Enterococcus faecalis*, but not *Proteus mirabilis*.

In practice, all listed antibiotics have strengths and weaknesses. A *Pseudomonas* UTI, especially if confirmed by repeated isolations from the same patient, would require specialized treatment.

While there has been the tendency to try and shorten the duration of antibiotic therapy in adults, in children various studies such as Keren *et al* (2002) have suggested an optimal antibiotic treatment duration of between 7 to 14 days.[6] This is also the recommendation by the American Academy of Pediatrics (1999) for all children between the ages of 2 months to two years with urinary tract infections.[3]

Epilogue

Repeated infections in childhood require careful investigation to rule out abnormalities of the urinary tract. Sometimes no obvious abnormality will be detected. In this case, one would do well to check on the child's bowel habits. One paper by Newmann (1973) reported a decrease in recurrent UTI by correcting constipation.[7]

A more controversial topic is the existence of a condition sometimes referred to as dysfunctional elimination ñ which is sometimes suggested to be a cause of repeated UTIs in children with an apparently normal urinary tract. It has been described as a disorder of the normal voiding or emptying reflexes, leading to a chronic abnormal pattern of elimination which does not allow the bladder or bowel to empty completely.

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Winning with TheSYNAPSE

TheSYNAPSE Internet Portal has, for the past few months, been publishing a number of eQUIZes for Maltese Medical Doctors. We are pleased to publish the winners of the eQUIZes for the first Quarter of 2006.

Company	Product	Winner
Sanofi Aventis	**Telfast**	Dr Michael A. Borg
Sanofi Aventis	**Ketek**	Dr Tania Van Avendonk
Sanofi Aventis	**Tavanic**	Dr Mary Rose Cassar
Bayer	**Avalox**	Dr Alex Magri
Actavis	**Tirabicin**	Dr Doreen Cassar
Lundbeck	**Cipralex**	Dr Tonio Bugeja
Sanofi Aventis	**Rhinatiol**	Dr Julian Mamo

There are lots of other planned eQUIZes and other opportunities planned for the coming months and you could be one of the winners. Be sure you are eligible to participate by making sure you are a member of TheSYNAPSE internet community and receive your weekly eNEWS. If you have any queries please contact our helpdesk by email on helpdesk@thesynapse.net .

Note

Part II of the series Cardiology Today by Prof. Albert Fenech will be featured in the next issue of TheSYNAPSE magazine and not in this issue as previously announced.

Errata...

A number of articles in the November 2005 Issue were published without the list of references. All references will now appear in the on line version of the magazine which is being published. We apologise to the authors and audience for the inconvenience.

Community acquired MRSA infections – a new challenge

continued from page 7

In the second group, ten studies reporting the prevalence of MRSA in the community using surveillance cultures were analysed. The pooled data (8350 patients) showed a prevalence of 1·3% for MRSA colonisation. Again, most people colonised with MRSA had associated risk factors. After excluding those patients, the prevalence of MRSA colonisation was only 0·2%.

There is no local data at this time that would shed light on the prevalence of CA-MRSA in Malta. Microbiological investigations sent to St Luke's Hospital are few and far between and even when available, it is impossible to know whether the patient in question had previous hospital exposure.

Nevertheless equivocal circumstances would indicate that CA-MRSA is present in the local ambulatory care environment. We have seen a number of cases of children admitted to hospital with pyrexia of unknown origin in which blood culture has yielded isolates of CA-MRSA. In addition it is not uncommon for (usually young) adults suffering from recurrent boils and/or skin infections which appear refractory to treatment to be referred to the SLH microbiologists for advice and who after bacteriological tests of the lesions and/or screening swabs from nose, axilla and/or groin yield isolates of CA-MRSA. In general the resistance profile of these strains tends to be less extensive than that found in hospital strains and would be amenable to treatment with alternative oral antibiotics and or topical antiseptics.

It is therefore vital for clinicians to be aware of the possibility of CA-MRSA in circumstances where infective skin lesions such as boils and furuncles do not respond to conventional therapy. In general, if initial antibiotic therapy is not effective, a culture should be obtained from the infection site and sent to a microbiology laboratory. This is best done by obtaining either a small biopsy of skin or drainage from the infected site. A culture of a skin lesion is especially useful in recurrent or persistent cases of skin infection, in cases of antibiotic failure and in cases that present with advanced or aggressive infections. Where a swab for culture is taken from pus after excision of a skin boil, it is important that the skin is prior disinfected with 70% alcohol which is left to dry before incision and swabbing. In this way the possibility of contamination of the swab with skin commensals is eliminated. Expert advice on the antibiotic management of patient with CA-MRSA from a microbiologist or infectious disease physician is always recommended.

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Aspirin Induced Asthma

(AIA) is more common than previously suggested

Aspirin Induced Asthma (AIA), also known as aspirin sensitive asthma, is a distinct clinical syndrome characterised by the onset of asthma 30 minutes to three hours after taking aspirin.[1] Asthma attacks triggered by aspirin and NSAIDs are often accompanied by symptoms of rhinitis and facial flushing and can be very severe, even life threatening.[2]

21% of adult asthmatics may suffer from AIA

Although AIA is well researched, until recently its prevalence was not well defined. A clearer picture emerged in 2004 when the British Medical Journal published a landmark systematic review on AIA.[1]

This systematic review published in the British Medical Journal has found that the prevalence of AIA in the general asthmatic population is higher than previously suggested, at:

- 21% for adults and
- 5 % for children.

It is widely recognised that asthmatics who are sensitive to aspirin are also highly cross-sensitive to other non-steroidal anti-inflammatory drug (NSAIDs) including ibuprofen, naproxen sodium and diclofenc.[1] For example 98% of adult aspirin induced asthmatics are also sensitive to OTC doses of ibuprofen.

In contrast, the incidence of cross-sensitivity to paracetamol is low at approximately 7% of aspirin induced asthmatics (figure 1), which is less than 2% of the general asthma population.

Reactions to paracetamol are significantly milder and easier to reverse than reactions to aspirin.[3]

Patient characteristics	Recommendation
Anyone positively identified with Aspirin Induced Asthma	Avoid all products that contain aspirin or NSAIDs indefinitely
Anyone who has ever experienced an asthmatic reaction to aspirin or NSAIDs (such as ibuprofen, diclofenac, naproxen sodium)	Paracetamol should be recommended, unless contraindicated
Anyone with severe asthma symptoms, nasal polyps, urticaria or chronic rhinitis (ie high risk features of AIA)	
Younger than 40 years of age or	AIA may develop late in life, so patients should be informed of the risks of aspirin and NSAIDs
Have not used aspirin or NSAID recently without incident	Paracetamol should be recommended, unless contraindicated
	If NSAIDs are necessary, the first dose should be taken under medical supervision
All other asthmatic patients	Any analgesic may be considered
	If patients experience any respiratory symptoms they should stop treatment and see their doctor

Table 1: *Recommendation for the use of analgesics in asthmatic patients.*[1]

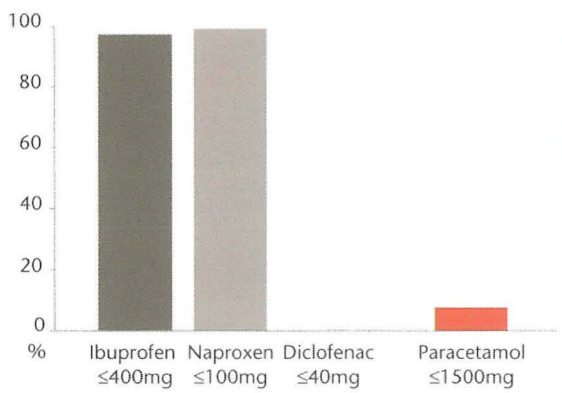

Figure 1: *Inidence of aspirin cross-sensitivity to common analgesics.*[1]

KEY PRACTICE POINT:

Many asthmatics are unaware of AIA,[4] GPs should take appropriate opportunities to counsel their asthmatic patients about the risks and provide appropriate advice about the use of analgesics.

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This information service is provided by Glaxo Smithkline Consumer Healthcare.

Current Status of Avian/Pandemic Influenza

by Tanya Melillo Fenech *MD MSc*
Chairperson of the National Influenza Pandemic Standing Committee

The situation regarding avian H5N1 virus is only getting worse. Since the beginning of February 2006 affected wild birds – mainly swans – have been recorded, since the beginning of February 2006, in 14 European countries, without involvement of domestic poultry (Austria, Bosnia, Bulgaria, Croatia, Germany, Greece, Hungary, Italy, Poland, Slovakia, Slovenia, Sweden & Switzerland). In France, a commercial turkey farm, adjacent to a site where infected swans were located, has also been found infected. Other countries like Albania, Azerbaijan, China, Egypt, India, Indonesia, Malaysia, Niger, Russia and Romania have poultry affected with the virus.

The situation in Africa is of particular concern. It is now obvious that H5N1 has become significantly endemic and widespread in poultry populations outside South East Asia. The discovery in Germany and Austria of H5N1 virus affecting also domestic cats has only complicated the picture. Other animals that have been infected with H5N1 include tigers, pigs, civets and ferrets.

In Germany, on the 10th of March it was also discovered in a stone marten (a member of the weasel family). To date only domestic poultry have been shown to play a role in the transmission cycle of the virus from animals to humans.

Further investigation is needed to determine whether evidence of H5N1 infection in new mammalian species has any significance for the risk of human infection or the potential of this virus to adapt to mammals, including humans.

Studies done this year on H5N1 viruses show that multiple lineages of the virus are now established in poultry in parts of Asia. Poultry to poultry transmission is thought to sustain endemicity of the virus in this region. H5N1 virus has been isolated from apparently healthy migratory birds in southern China suggesting that migratory birds can carry the virus for long distances.

According to the WHO, the cumulative number of confirmed cases of human avian virus a up to 10th March by WHO is 176 cases and 97 deaths (case fatality rate of 55%).

Seasonal Influenza Surveillance

From October 2005 to date there has been low reporting of influenza cases in Europe compared to previous years. Virological studies have shown that 68% of cases where found to be Influenza B while 32% were found to be influenza A (H3N2 and H1N1).

Infact, it has been recommended that the 2006-07 influenza vaccine will consist of "Wisconsin" strain for Influenza A (H3N2) replacing "California" strain, and "Malaysia" strain for Influenza B replacing "Shanghai" strain. The "New Caledonia" strain of H1N1 used for this year's vaccine will be used again as the third component of the trivalent vaccine.

The information is correct as on 13/3/06.

For further information check the Disease Surveillance Unit Web Portal website on http://www.health.gov.mt/dsu/

What price advice?

by **J. G. P. Bonello**, *F.I.I.A., Managing Director*
Financial Planning Services Limited
Financial Adviser since 1967

"Every time you brush your teeth; every time you fill your petrol tank; every time you shop at the supermarket – virtually every time that you *spend* money – somebody is *making* money. Why not share in the profits they make off you?" That sentence was the injection of my passion for equities 40 years ago.

During a TV interview on the 17th February, I highlighted the long-term value of solid equities. Anyone who invested Lm1,500 to buy 1,000 shares in the then Mid-Med Bank Ltd. in July 1991, today – after 2 shares splits – holds 4,000 shares of HSBC (which will become 16,000 shares on 19th April) with a current market value of Lm44,200. And this does not include dividends received over this 15-year period, which alone would have repaid the initial investment. See why I believe in the long-term value of well-chosen equities?

Relate this to the Pensions saga: Assume that this investor was a 45-year old in 1991. Today he is a 61-year old pensioner. Is he as reliant on his "first pillar" guaranteed national minimum pension, as his contemporary who put his Lm1,500 in a fixed deposit at the bank? The question is as rhetorical as "Who has best inflation-proofed his capital?"

Risk and Reward – the "comeback-and-go-beyond" theory

With equities it is not always days of wine and roses. HSBC shares – and others which are major MSE Index components – burned many speculators' fingers in Malta's first bull market which peaked 6 years ago. From an 18th January 2000 closing price of Lm3.80, and an intra-day high of Lm3.81, HSBC shares more than halved by 1st November 2002 to Lm1.73. These prices are adjusted to reflect the 1 for 1 split on 1st April 2005. Thousands swore that they would never touch shares again – especially those who cashed in their chips at the bottom of market.

Nobody had told them about what I call the stockmarket "comeback-and-go-beyond" theory. Let's look at the weather-vane of world markets, the Dow Jones Industrial Average. In the infamous Wall Street crash of October 1929, the Dow peaked at 381.17 on 3rd September 1929. For the only time in its history which goes back to 1896, the Dow Jones Index fell, *for four consecutive years*, to bottom at 41.22 on 8th July 1932. The comeback to the pre-crash peak did take till 1954 – but by 1964, the Dow had more than doubled to 900. On 28th February 2006 it stood at a sliver under 11,000. According to Professor Roger Ibbotson of Chicago, quoted in the late 1990's, by 2015 the Dow will clear 34,000.

What about Japan? Any streetwise Samurai will tell you that Japan's Nikkei index hit its all-time closing high on the 29th December 1989 at an astronomical 38,915.90. To get back to this level, from its 28th February 2006 close, requires an increase of 140%. Even if this takes another 10 years, it would equate to 14% simple interest per annum. I believe that the Japanese stockmarket has started a long recovery and, though I expect a lot of volatility, the Mount Fujiyama peak of 40,000 on the Nikkei will again be climbed.

Even Malta's barely into-its-teens stockmarket proves the "comeback-and-go-beyond" theory. In its first bull run, the MSE Index hit 4,013.371 on 24th January 2000. It then slipped, stumbled and fell to 1,747.522 on 30th October 2002. At that stage, those who had piled into the market at the peak, two years and nine months earlier, were contemplating the Maltese equivalent of Harakiri. Our advice was not only to hold on, but to buy more at the then lower prices – thereby bringing down one's average cost. But most were then as keen to invest more, as they would today be to take a holiday break in Bagdad. Those who did take our advice are now smiling into their sushi.

"Ethics – a verb of conviction, not a noun of convenience"

Because not only did the MSE index recover its previous peak (of 24th January 2000) on the 4th October 2005 at 4,031.46, but it has since charged ahead, breaking new barriers on the 21st February 2006 at an all-time peak of 6,314.069. That is an increase of 261%. On 28th February, exactly three years and four months from the October 2002 low, the index stood at 6,087.65 for a gain of just under 250% – see graph overleaf.

By comparison, the Nasdaq, the tech-laden US index, has only gained 72% in the same period. Yet, it is still 54.8% below its all-time closing high of 5,048.62 on 10th March 2000. This means it has to climb a further 121%, just for the comeback part.

In October 2002, when MSE officials were asked about the Maltese market drop, they were quoted by the media as having said that the Maltese market had followed all other stock-markets down.

So should the corollary to such an argument be that the potential of the Nikkei is not only to climb to 38,915, but then to actually exceed this by 51.7%? Or for the Nasdaq to climb 121% to 5,048.62 – and then a further 51.7% to 7,657.82? Is it a case of *Malta fior del mondo* or *Malta fuor del mondo*?

The graph overleaf clearly highlights the attractiveness of the world's major markets when compared to the Maltese Index. The readings of the seven foreign market indices have been taken as at 30th October 2002, so as to rebase all calculations in comparison to the MSE index's post-boom low point. The visual impact is stunning in the sense that none of the foreign major indices have yet achieved the comeback stage – let alone the go-beyond one. By comparison the MSE index is up 51.7% – and that is from the previous high, *not* from the post-boom low point. The conclusion *vis-à-vis* which markets have the better potential is obvious.

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What price advice?

But how do you distinguish between market *highs* and market *hype*?

It is not about "tricks", or about guessing – or second-guessing – market tops and bottoms. Neither does it lie in seeking refuge under the blanket bromide "past performance is not a guide to future returns". ***It is*** about knowledge, about experience and about preparation. ***It is*** about applying one's intelligence, combined with the decades-long acquisition of that sixth sense called intuition.

Finally, and fundamentally, ***it is*** about ethics – that branch of knowledge concerned with moral principles. At Financial Planning Services Ltd., we have, since inception, practised ethics as a verb of conviction – not as a noun of convenience.