• Medical Treatment of Ankylosing Spondylitis
  *Dr Chan Tak Hin (陳德顯醫生)*

• Novel Marker of Acute Kidney Injury – Neutrophil Gelatinase-associated Lipocalin (NGAL)
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• Dizziness – A New Geriatric Giant
  *Dr Shea Tat Ming, Paul (佘達明醫生)*
Comparison of the mean BASDAI scores for patients who originally received etanercept or placebo in the initial 24-week randomized controlled trial and who received etanercept in the open-label extension.

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Important Safety Information: Serious infections, including sepsis and tuberculosis, have been reported with the use of ENBREL. Some of these infections have been fatal. These infections were more common in patients with a history of a prior infection, had received prior TNF antagonist therapy, and were treated with concomitant medications. Treat patients with ENBREL and concomitant medications carefully. If a patient develops a serious infection, ENBREL should be discontinued. Consult the physician promptly. Antituberculosis therapy should be considered for any patient with a history of tuberculosis. See prescribing information for complete information.

**ABREVIATIONS AND INFORMATION**
- **Product Name:** Enbrel 25 mg powder and solvent for solution for injection. Enbrel 25 mg or Enbrel 50 mg solution for subcutaneous injection in prefilled syringes.
- **Composition:** Humanized anti-TNF-α monoclonal antibody directed against TNF-α.
- **Contraindications:** Hypersensitivity to any component of the product or anakinra, or anakinra-induced, anaphylaxis.
- **Warnings and Precautions:** Use with caution in patients with active infections or conditions that may exacerbate infections. Monitor patients for signs of infection, including tuberculosis. Discontinue if infection is severe or life-threatening. Consider anti-TNF therapy in patients with malignancy. Consider the benefits of ENBREL therapy against the potential risks of malignancy.
- **Interactions:** Consider using with caution in patients with active infections, including tuberculosis. Monitor for signs and symptoms of infection.
- **Pregnancy:** Category C. Use only if clearly needed.
- **Lactation:** Studies have not been performed in animals. Use only if clearly needed.
- **Pediatrics:** Safety and effectiveness in children have not been established.

**References:**
Editorial

Medical knowledge and technology have undergone explosive development in the last two decades. The body of information has grown tremendously so that it is not possible for any individual doctor to master all. Doctors have dealt with the change by going into specialties, subspecialties and super-specialties. While this is a necessity, it has also created problems. Sometimes we have the situations where a patient is attended to simultaneously by 10 teams of doctors of different specialties. Perhaps it is time to remind ourselves that a patient is not an organ or a system, and that he/she needs to be considered as a whole person. Apart from knowledge within their own subspecialties, doctors also need to have good understanding and awareness of other ailments in the same patient.

We hope the Journal will serve the purpose of reminding doctors of this need and updating them with general and all-rounded information in Internal Medicine.

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Introduction

Ankylosing spondylitis (AS) is a chronic, progressive, immune-mediated inflammatory disorder that characteristically affects young adults. Although the exact aetiology of AS is unknown, about 90% of AS patients have the HLA-B27 allele. Apart from the spine and peripheral joints, other organ systems, such as the lungs, eyes and heart, can also be affected. Inflammation around the enthesis (site of ligament insertion into bones) is characteristic of AS.

AS, the prototype of spondyloarthritis (SpA), is more common than previously estimated, with some studies suggesting a prevalence similar to that of rheumatoid arthritis (0.1%−1.1% of Caucasian population). Importantly, AS affects individuals at a time when they are economically active. The peak age of onset of AS is between 20 and 30 years. The disease has a major impact on the patient’s ability to work.

Currently, diagnosis of AS is made according to the modified New York criteria published in 1984, which relies on radiographically detectable damage. A definitive diagnosis of AS may be delayed for many years, because the time required for structural changes to develop may be up to 10 years. Modern imaging technique, such as magnetic resonance imaging (MRI), can detect sacroiliitis at an early stage.

Prognostic Indicators

Indicators of severe disease and possible poor outcome include:
- Hip arthritis;
- Dactylitis (sausage-like finger or toe);
- Poor response to non-steroidal anti-inflammatory drugs (NSAIDs);
- High erythrocyte sedimentation rate (ESR);
- Limitation of lumbar spine movement;
- Oligoarthritis; and
- Onset at less than 16 years of age.

A relatively better outcome may be expected if none of the above factors are present. Other factors that are associated with poor outcome are cigarette smoking, increasing severity of radiographic changes, high disease activity index, and functional impairment.

Possible predictors of good response to treatment, in particular to anti-tumour necrosis factor (TNF) agents, are:
- Younger age;
- Short disease duration;
- Good functional status;
- Presence of the HLA-B27 allele; and
- TNF antagonist-naïve.

Assessment

Treatment decision depends upon an accurate assessment of the degree of disease activity and the extent of damage. An international panel has proposed a core set of domains to aid in the assessment of disease activity, which include function, pain, spinal mobility, patient global assessment, stiffness, peripheral joints and enthuses, acute phase reactants, and fatigue.
Physical Therapy

Exercise and medications are the mainstay of treatment of AS. Physical therapy has been demonstrated to help maintain function and relieve symptom. A demonstration of exercise is available at the following website: http://www.nass.co.uk/public/exercises.htm.

Pharmacologic Therapy

Pharmacologic therapy for mild to moderate disease includes analgesics, NSAIDs, sulfasalazine, and methotrexate. Systemic corticosteroids have a limited role, but intra-articular steroid injection is useful for patients with inflamed peripheral joints.

NSAIDs

Issues relating to NSAID therapy in AS are the choice of NSAID, and continuous versus on-demand treatment. While there is anecdotal evidence suggesting that indomethacin is effective in some AS patients, many studies have demonstrated that other NSAIDs are equally effective. Regardless of the NSAID used, the maximum anti-inflammatory dose is usually required. Switching NSAIDs should only be done after a particular NSAID has been given at a sustained dose for at least 2 weeks.

One randomized trial suggests that continuous use of NSAIDs may suppress radiographic progression of AS.

NSAIDs have also been made with infliximab.

Sulfasalazine

Although sulfasalazine has documented efficacy in peripheral arthritis, its efficacy in axial spondylitis appears modest, if any.

A 2006 meta-analysis of 11 randomized trials concluded that sulfasalazine was more effective than placebo in reducing spinal stiffness and decreasing ESR. However, there was no significant difference between the actively treated group and the placebo group in terms of all other measures, such as pain, patient global assessment, spinal mobility, etc.

A typical dose of sulfasalazine for AS is 500 mg/day in the first week, which will be gradually increased in 4 to 6 weeks to 2–3 g/day in two divided doses. One may consider discontinuing the treatment if there is no significant improvement after 4 months.

Methotrexate

Some studies suggest that methotrexate may be effective in some AS patients. However, a 2006 meta-analysis of the efficacy of methotrexate in AS found no evidence of a beneficial effect. Additional studies are necessary to demonstrate a beneficial effect of methotrexate on AS.

Leflunomide

Limited data suggest that leflunomide has little or no beneficial effect on AS.

Glucocorticoids

The efficacy of systemic corticosteroids in AS has not been assessed in clinical trials. In view of its many side effects, long-term use of systemic corticosteroids in AS is not recommended. Intra-articular corticosteroid injections are generally considered safe and useful in patients with peripheral joint inflammation re-fractory to systemic treatment. Local injections into sites of enthesitis can also be considered. However, injection into the area of the Achilles tendon is not recommended because of the risk of tendon rupture.

Anti-TNF-alpha Treatment

TNF-alpha (TNF-α) is found at increased levels in the serum and synovium of AS patients, and has been shown to play an important role in the inflammatory response observed in AS. Anti-TNF-α agents have been demonstrated to improve the symptoms and signs of AS. The responses are typically rapid. A meta-analysis has shown that the three commercially available anti-TNF-α agents (adalimumab, etanercept, infliximab) have similar efficacy in AS patients. Approximately 80% of patients respond to treatment with one of these agents, and approximately half get at least 50% improvement in a composite index.

Anti-TNF therapy may also decrease the incidence of uveitis recurrence.

Adalimumab

Adalimumab is a humanized anti-TNF monoclonal antibody, which is given by subcutaneous injection every other week. A randomized control trial has demonstrated its efficacy through the 24-week double-blind period; the efficacy was subsequently maintained for up to 2 years in the open-label phase of the study.

A smaller, multicenter randomized study of 82 patients showed that adalimumab-treated patients had a 53 percent improvement in their scores of MRI spine and sacroiliac joints.

Non-response to adalimumab may be related to the development of anti-adalimumab antibodies and resulting low serum levels of drug. Similar observations have also been made with infliximab.

Etanercept

Etanercept is a soluble p75 TNF-α receptor fusion protein. Multiple placebo-controlled studies have shown that it is effective in relieving the symptoms and signs of AS. Weekly dosing of 50 mg/week appears to be effective. However, 2 years of treatment with etanercept does not appear to inhibit radiographic progression. One hypothesis is that inflammation and bone remodelling are two independent processes, and only inflammation is controlled by etanercept.

Golimumab

Golimumab is a human anti-TNF-α monoclonal antibody administered once monthly by subcutaneous injection. Its efficacy in AS appears similar to that of other anti-TNF agents. A randomized trial of 356 patients demonstrated that improvement as measured by the Assessment in Ankylosing Spondylitis (ASAS) response criteria (ASAS 20) occurred in 59%, 60%, and 22% of patients in three groups (golimumab 50 mg, 100 mg, placebo), respectively. The recommended dose is 50 mg subcutaneously every 4 weeks.

Infliximab

Infliximab is a chimeric (human/mouse) monoclonal anti-TNF-α antibody. In randomized placebo-controlled studies of patients with a definitive diagnosis of AS (modified New York criteria) and early spondyloarthropathy, significantly more
patients in the active treatment group achieved improvement in AS symptoms and signs, and MRI activity score. This indicates that anti-TNF agents may not be able to inhibit radiographic progression.

The recommended dose of infliximab for treatment of AS is 5 mg/kg, which is higher than the usual starting dose of 3 mg/kg for rheumatoid arthritis. Routine use of methotrexate in AS patients receiving infliximab is not necessary.

### International Consensus

The ASAS, an international society of AS experts, proposes that for initiation of anti-TNF treatment, there should be a definitive diagnosis of AS, which is active and refractory to treatment with NSAIDs, sulfasalazine, and intra-articular steroids (if indicated). Treatment efficacy should be monitored using a set of domains, such as the ASAS core set for clinical practice and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Discontinuation of anti-TNF treatment in non-responders should be considered after 6 to 12 weeks. Response is defined by improvement of at least 50% or 2 units (on a 0–10 scale) of the BASDAI.

### Conclusion

Treatment of patients with AS must be individualized. NSAIDs and exercise programme are the initial therapy for almost all patients. Sulfasalazine can be added to the drug regimen for patients with peripheral arthritis not responding well to NSAID treatment. Systemic glucocorticoids are generally not recommended, but intra-articular steroids are safe and effective in some patients with persistent peripheral joint inflammation, enthesitis at sites other than the Achilles tendon, and for sacroiliitis.

Treatment with TNF-α-blocking agents (eg, adalimumab, etanercept, golimumab, infliximab) has been demonstrated to safely and effectively reduce the symptoms and signs of AS, and significantly improve health-related quality of life. In addition, these agents have been shown to suppress bone inflammation as detected on MRI. Unanswered questions regarding anti-TNF treatment include why some patients do not respond to these interventions, and whether these drugs can really halt radiographic progression.

Physicians should monitor patients’ response to treatment using measurable clinical indices, such as the ASAS core set for daily practice and the BASDAI. The treatment plan should be adjusted according to the patient’s response to the therapy.

### References:

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Novel Marker of Acute Kidney Injury – Neutrophil Gelatinase-associated Lipocalin (NGAL)

For a long period of time, creatinine has been at the centre stage of kidney function testing. Creatinine is produced by muscles and excreted through the kidneys. When kidney function is impaired, creatinine is excreted less efficiently and serum creatinine level rises. This principle has been well tested both in laboratory and in various clinical scenarios. Although creatinine is not a perfect marker of kidney disease, and its measurement and interpretation is frequently plagued by minor problems, we still use it as the marker of kidney function. With the recent Modification of Diet in Renal Disease (MDRD) formula, serum creatinine is used as an indicator of glomerular filtration rate (GFR) in chronic stable patients.

Cystatin C has also been advocated as an indicator of kidney function. It is a protein synthesized by all nucleated cells at a constant rate, which is then released into the blood and excreted by the kidneys. It is a sensitive marker of GFR and usually rises before serum creatinine is elevated. However, the basic principle behind both serum creatinine and cystatin C is the same. When kidney function is impaired, GFR falls, and serum cystatin C rises.

Both creatinine and cystatin C reflect kidney function. They only rise when GFR falls. In other words, when GFR does not fall, creatinine and cystatin C will remain unchanged.

That is why nephrologists have been looking for a different type of marker, an indicator of acute kidney injury. The new marker should be able to tell us something different from what serum creatinine or cystatin C have already done. As we have learnt from both experiments and clinical situations, when the kidneys suffer from an acute insult, be it ischaemic or nephrotoxic in origin, GFR does not change until much later.

In animal experiments, when oxygen supply to the kidneys is stopped completely, there will be no consequences on kidney function if the hypoxia is reversed soon enough. When tubular cells are normal, kidney function as measured by GFR does not change. It is only when hypoxia continues that there is patchy and focal loss of cell(s) from the tubular epithelium, with resultant areas of denuded basement membrane. This is known as acute tubular necrosis. GFR will then be affected and creatinine will rise later. That is why when the kidney suffers from a severe acute hypoxic insult, creatinine rises only 24 to 48 hours later.

NGAL as a New Marker

Neutrophil gelatinase-associated lipocalin (NGAL) may play an interesting role for doctors to diagnose acute kidney injury during hypoxia. NGAL is one among many proposed markers of kidney problem. Others include interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), liver-type fatty acid-binding protein (L-FABP), etc.

NGAL, with a molecular weight of 25 kDa, is a single disulfide-bridged polypeptide chain of 178 amino acid protein. It is a member of the lipocalin family, usually expressed by neutrophils and different tissues. Under normal condition, it is present only in a small amount in renal tubules. It was initially proposed as a marker for infections and certain adenocarcinomas. It was then found that after ischaemic or nephrotoxic kidney

Key words: Urine NGAL (尿中中性粒細胞明膠酶相關戴脂蛋白), NGAL (中性粒細胞明膠酶相關戴脂蛋白), marker (標記), acute kidney injury (急性腎臟損傷), diagnosis (診斷)
injury, NGAL in the injured kidney tissue increases by many folds. NGAL is then excreted in urine. This early and dramatic rise in urine NGAL makes NGAL an ideal marker of acute kidney injury, be it ischaemic or nephrotoxic in origin.

Studies showed that urine NGAL is a good way to measure NGAL level because after injury, elevated NGAL passes out with urine. It has also been suggested that urine NGAL may be superior to serum NGAL level in diagnosing kidney problem. As blood NGAL level may be elevated in medical conditions other than acute kidney injury, this may complicate the interpretation of serum NGAL.

**Urine NGAL Rises Early After Kidney Injury**

Urine NGAL has been shown to increase as early as 2 hours after kidney injury. (Table) Early rise of urine NGAL in the course of kidney injury gives doctors a much earlier signal of hypoxic kidney injury. This will allow doctors much more time to intervene and protect the kidneys from getting into more serious damage. In contrast, serum creatinine will remain normal for quite a while following acute kidney injury, until GFR decreases.1 (Figure) There is a time lag between the rise in serum creatinine and the time of kidney injury. When a rise in serum creatinine is seen, damage to the kidney has already been done, and all remedial actions to save and protect the kidney may be too late.

### Table. Proposed urine NGAL level

<table>
<thead>
<tr>
<th>NGAL level</th>
<th>Diagnosis</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100 ng/mL</td>
<td>Low risk of acute kidney injury</td>
<td>Conventional medical care</td>
</tr>
<tr>
<td>&gt;150 ng/mL</td>
<td>High risk of acute kidney injury</td>
<td>• More intensive medical care?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. Treat remediable medical problem; aggressive fluid replacement in dehydrated patient</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Avoid nephrotoxic agents such as aminoglycosides and non-steroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Renal dose dopamine?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Atrial natriuretic peptide?</td>
</tr>
</tbody>
</table>

NGAL = neutrophil gelatinase-associated lipocalin

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**Distinguishing Urine NGAL From Creatinine**

Conceptually, urine NGAL is completely different from serum creatinine and cystatin C. Urine NGAL indicates acute renal injury while creatinine and cystatin C reflect kidney function (i.e., GFR).2 To draw an analogy, it is like troponin-I and B-type natriuretic peptide (BNP) to the heart. BNP is an indicator of heart failure and fluid overload in the body, and it is more related to heart function. Troponin-I is an indicator of myocardial injury, usually ischaemic in origin, such as in coronary artery disease. It does not reflect heart function, but is a marker of acute insult to the heart muscle. Nowadays, when patients are hospitalized for chest pain, troponin-I is commonly used to assess whether there is ischaemic heart disease or not. BNP may not be very helpful in the clinical situation of chest pain, as it does not tell us whether the patient suffers from acute ischaemic attack or not. However, BNP is very useful in diagnosing congestive heart failure.

**Advantages of Urine NGAL**

Theoretically, when the kidney is at risk (e.g., hypoxic injury), urine NGAL should be helpful in informing us that the kidney is injured. When the injury is mild and the kidney recovers itself, kidney function...
as measured by GFR may not change at all. Therefore, creatinine will remain the same. However, this does not change the fact that the kidney is at risk or suffers from an acute injury. The kidney just recovers itself enough so that its function has not changed. When the kidney is injured to such a degree that its function decreases, GFR will decrease, and serum creatinine will rise only much later.

**Unsettled Issues on Urine NGAL**

Urine NGAL may be very useful in various clinical settings. However, how to best utilize urine NGAL is far from being a settled issue. Aminoglycoside and amphotericin B are known to cause renal tubular damage, while cyclosporine overdose is known to affect tubular cells. When patients suffer from cyclosporine nephrotoxicity, renal biopsy would show isometric vacuoles in tubular cells. The question is whether urine NGAL is able to indicate if the patient suffers from aminoglycoside and amphotericin B nephrotoxicity well before deterioration of kidney function. Another question is whether cyclosporine toxicity can be diagnosed with urine NGAL without a kidney biopsy. Only prospective, randomized, double-blind controlled trials will be able to give us more scientific data to address these questions.

The author believes that urine NGAL is a powerful diagnostic tool, although there are still many issues about its use. All the studies were done abroad. Further data is needed on the cut-off level for Chinese patients, the effect of other medical conditions (eg, acute pyelonephritis) on urine NGAL level, the possibility of false negative or false positive value, and the effect of medicines on urine NGAL level (as in cimetidine on creatinine excretion). Only time and experience will shed more light on different aspects of this novel marker. In the meantime, we look forward to having more new biomarkers, such as urine NGAL, to assist us in diagnosing and differentiating acute kidney problems early in the course of the event. Only when we can diagnose kidney injury early enough that we may be able to initiate preventive measures or treatment to save and protect the kidney, and preserve as much kidney function as possible.

**Summary**

Because of the difference in physiology of NGAL, creatinine and cystatin C, NGAL rises much earlier than the other two following acute kidney injury. Creatinine and cystatin C usually remain steady until kidney function or GFR decreases.

**References**

Traditionally, immobility, instability, incontinence and mental insane were named “Geriatric Giants” by a British Geriatrician, Bernard Issac. Dizziness is the most common presenting complaint in clinics for patients aged >75 years. It is often an untreated symptom, and is associated with extensive disability and psychological morbidity. Dizziness is a common and often vague symptom, and thus poses a diagnostic challenge to clinicians in the management of elderly patients. Dizziness is thus labelled as a new Geriatric Giant.1

Dizziness is a vague term describing a variety of sensations, including light-headedness, fainting, giddiness, unsteadiness, vertigo, collapse, syncope, imbalance, and dysequilibrium. Different presentations may mean different pathology of the dizziness.2,3 (Table 1)

Differential Diagnosis

Several studies have reported the common diagnosis of chronic dizziness. In a study of patients presenting to emergency room with dizziness as the major complaint, the final diagnosis can be attributed to medical causes (33%), otological causes (24%) and unknown causes (41%). Seven percent of patients had suffered major morbidity or had died as a result of the causes of the index episode of dizziness. Hypotension, cardiac arrhythmias and coronary artery diseases attributed to one third of medical causes of dizziness. The remaining two third were due to infection, adverse effect of drug and hypoglycaemia.4

Underdiagnosed Causes of Dizziness

Common diagnoses of dizziness such as otological causes are not discussed here. Primary care physicians and otologists are the first-line medical professionals to manage all these causes of dizziness. However, in many clinical settings, dizziness becomes resistant to treatment,

<table>
<thead>
<tr>
<th>Table 1. Clinical classification of dizziness symptoms</th>
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<tbody>
<tr>
<td><strong>Category</strong></td>
</tr>
<tr>
<td>Vertigo</td>
</tr>
<tr>
<td>Presyncope</td>
</tr>
<tr>
<td>Dysequilibrium / imbalance</td>
</tr>
<tr>
<td>Others or light-headedness</td>
</tr>
</tbody>
</table>

Adapted from reference 3.
Orthostatic Hypotension

Orthostatic or postural hypotension is a commonly underdiagnosed cause of dizziness in older patients. It is defined as reduction of systolic blood pressure of ≥20 mm Hg or diastolic blood pressure of ≥10 mm Hg within 3 minutes of standing. In the elderly, it is associated with a variety of problems, including weakness, light-headedness on standing, falls and their consequences, syncope, cerebrovascular accidents, and myocardial infarction. Orthostatic hypotension is a side effect of many common medications used by older persons, including antihypertensives, antianginal medications, and antidepressants.

Postural Orthostatic Tachycardia Syndrome (POTS): Postural Dizziness Without Postural Hypotension

Older persons commonly complain of dizziness when they stand up, and postural hypotension is a well-known cause. However, persons with this kind of dizziness rarely meet the criteria for orthostatic hypotension. In POTS, the light-headedness or fainting is also accompanied by a rapid increase in heartbeat of >30 beats per minute, or a heart rate of >120 beats per minute, within 10 minutes of rising. The sensations of fainting or light-headedness of POTS are relieved by lying down. Therapeutic options for this type of postural dizziness without orthostatic hypotension are similar to those with orthostatic hypotension.

Benign Paroxysmal Positional Vertigo

Benign paroxysmal positional vertigo (BPPV) is a very common mechanical disorder of the inner ear in which, vertigo, with concomitant nystagmus and autonomic symptoms, is precipitated by certain head movements. BPPV is generally thought to be due to debris which has collected within a part of the inner ear. This debris can be thought of as “ear rocks”, although the formal name is otoconia. Ear rocks are small crystals of calcium carbonate derived from a structure in the ear called the utricle. Often, the diagnosis can be made with history and physical examination alone. The Dix-Hallpike test is the classic test to elicit BPPV. For treatment, medication should be avoided. The Epley manoeuvre is the standard physical management for BPPV.

Neurocardiogenic Syncope

Neurocardiogenic syncope is caused by an abnormal or exaggerated autonomic response to various stimuli, the most common of which are standing and emotion. The vasodilatation and bradycardia of neurocardiogenic syncope are
a type of Bezold-Jarisch reflex resulting from stimulation of cardiac ventricular mechanoreceptors, the cardiac C fibres. Loss of consciousness or near syncope in patients with neurocardiogenic syncope may be preceded by prodromata such as nausea, diaphoresis, light-headedness, blurred vision, headaches, palpitations, paraesthesia and pallor, which usually occur in the upright position (with downward displacement of 300–800 mL of blood), resolve almost immediately when the patient assumes the supine position.

**Cervical Dizziness**

Neck problems frequently cause dizziness. Cervical dizziness is of two distinct types: vascular and proprioceptive. Vascular cervical dizziness involves temporary disruption of blood flow through one of the vertebral arteries. Typically, this happens when turning the head or looking up causes an osteoarthritis spur to pinch the nearby vertebra. In clinical setting, this kind of dizziness is rarely seen.

Proprioceptive cervical dizziness arises because the facet joints of the neck contain proprioceptive receptors that, when overstimulated, cause light-headedness or vertiginous sensations. Acute muscle spasm in the neck, commonly seen in young persons, is often associated with dizziness because the muscle tension (which is often asymmetric) disturbs the normal configuration of the facets joints. In older persons, a flare-up of facet joint osteoarthritis is the most common cause of proprioceptive cervical dizziness.

**Stroke**

Vertigo is a prominent feature of several well-known vertebrobasilar syndromes. Occlusion of the vertebral artery (or its posterior inferior cerebellar branch) causes infarction of brainstem at the dorsolateral medulla. Occlusion of the anterior inferior cerebellar artery results in infarction of the labyrinths, portions of the pontomedullary region and the inferolateral cerebellum. Cerebellar infarction causes severe vertigo, vomiting and ataxia. Because brainstem signs are often absent, it can be mistaken for labyrinthisis.

Lacunar strokes are less well documented but probably a more common cause of dizziness than the classical stroke syndrome. Lacunar infarction of the cerebellum may be a particularly common cause of unexplained dysequilibrium. The typical clinical scenario is a person who feels “under the weather” for a few days, during which he notices imbalance when standing, which persists after functional status has returned to normal. The diagnosis is mainly clinical, based on history and subtle neurological findings such as asymmetry in cerebellar testing. Computerized tomography is unable to provide adequate imaging to the infratentorial area. Magnetic resonance imaging can identify diffuse lacunar disease, but is rarely helpful in identifying a specific causal lesion.

**Drug-induced Dizziness**

Medications are common causes of dizziness in medical patients. Drugs for the treatment of hypertension or other cardiovascular diseases are commonly seen to cause dizziness. Diuretics and peripheral vasodilators (peripheral alpha blockers) are the commonest drugs that may induce dizziness due to orthostatic hypotension.

Drugs with anticholinergic side effects, such as antihistamines and tricyclic antidepressants, may cause dizziness. Commonly prescribed vestibular sedatives such as meclizine, cinnarzine and prochlorperazine can worsen dizziness caused by nonlabyrinthine disease. Most ototoxic agents such as aspirin, cisplatin and the aminoglycosides cause vertigo and even permanent bilateral labyrinthine damage with consequent dysequilibrium. It is commonly seen in patients with impaired renal function. All psychotropic medications such as antianxiety agents, antipsychotics, sedatives/hypnotics, antidepressants, muscle relaxants and anticonvulsants commonly cause dizziness.

**Diagnostic Approach to Dizzy Patients**

There are probably at least a hundred potential causes of dizziness. Because the diagnostic possibilities are so vast, each patient must be approached individually. A diagnostic algorithm may be helpful in managing the dizzy patients more effectively and efficiently.

**History**

Because dizziness is a symptom that cannot be measured objectively, the history is essential. After the patient’s initial description, the following question should be asked:

1. How many kinds of dizziness does the patient have? It is not uncommon to hear a very contradictory history only to find that the patient has more than one kind of symptom.
2. What does the patient mean when he says he is dizzy? Dizziness is usually categorized into one of the four characteristic groups:
   - Vertigo
   - Presyncope or impending faint/light-headedness
   - Imbalance / dysequilibrium
   - Others (floating, light-headedness)
3. What is the symptom pattern (acute, recurrent, positional or continuous)? Are all the episodes the same?
4. Are there any associated symptoms (eg, hearing loss, tinnitus, nausea, dysarthria, sweating, palpitation, syncope, neck pain)?
5. Are there any precipitating or aggravating factors?
6. What medications (including alcohol) does the patient take or has he taken recently (eg, aspirin, anticonvulsants, antidepressants, aminoglycoside, vasodilators, antihypertensives)?
7. What diseases does the patient have? Has he or she been sick recently?
8. What is the general level of activity, and how has this been affected?

**Physical Examination**

The physical examination should focus on the systems that are involved in postural control and dizziness, namely vision, cranial nerves (including eye movement and nystagmus), cerebellar function, the neck, leg neuromuscular status, and cardiovascular status.

The history and physical examinations usually enable clinicians to identify serious underlying pathology such as cerebellar or brainstem ischaemia, haemorrhage, arrhythmias, or other central...
nervous system lesions. If no definite diagnosis can be made, further investigations are required to identify the underlying disorders. According to the characteristics of the symptoms, the following test can be done:

1. Halipike manoeuvre: Refer to the section of benign paroxysmal positional vertigo.

2. Vigorous head and neck movement test: It may precipitate the attack of vertigo, nystagmus, gait disorders or drop attacks. Loss of balance or “suddenly lurching to one side” may be seen. It is common in patients with cervical spondylosis.

3. Two minutes of voluntary overbreathing (hyperventilation test): The consequences of forced hyperventilation are hypopcapnia and alkalosis, which produce a reduction in cerebral blood flow, dilated peripheral vessels and nonspecific electrocardiography (ECG) changes. Symptoms of dizziness and muscular incoordination can readily be demonstrated in fit young volunteers by hyperventilation. Hyperventilation-induced dizziness is regarded as part of an anxiety state or major depression, and is more commonly seen in younger patients.

4. Heel-to-toe walking: The presence of abnormal gait (marche a petis pas) with abnormal reflex, tone, plantar reflex and coordination of lower limbs is suggestive of cerebrovascular disease or “pseudo-Parkinsonism”. Its association with postural instability and falls is well recognized.

5. Ambulatory cardiac monitoring: Ambulatory ECG (Holter) is usually performed for 24 hours or for multiples of a day, and the diagnostic yield increases with the duration of monitoring. According to a study of 95 patients presenting with syncope with any obvious aetiological clue by history and physical examination, 28% of patients benefited diagnostically by 1 day of Holter monitoring, an additional 12% by 2 days, and an additional 7% by 3 days.10

6. Carotid sinus massage: Carotid sinus reflex sensitivity is assessed by measuring the heart rate and blood pressure in response to carotid sinus massage. It is a longitudinal massage performed over the point of maximum carotid impulse (usually located at the level of the upper border of the thyroid cartilage) on the right and then left sides, allowing a 30 second interval between stimuli. Five seconds for each stimulus is optimal. The maximal fall in heart rate or blood pressure usually occurs within 5 seconds of the onset of massage.

7. Head-up tilt able test: Based on physiological studies, the tilt angle employed should be between 60 to 90 degrees. The test is usually performed in the morning following overnight fasting. Any cardioactive medications that could interfere with the test are discontinued for 5 half-lives prior to the study. A secure intravenous line is placed, and the patient is connected to a standard ECG monitor. A cardiac resuscitation cart is present during the procedure. A standard sphygmomanometer or a similar device is used to measure blood pressure. The patient is placed on a standard tilt table with a foot board made for weight bearing. After a supine period of 15–10 minutes, the patient is positioned at an angle of 80 degrees for up to 45 minutes. ECG monitoring is done continuously, and blood pressure is measured every 3 minutes. If hypotension and bradycardia occur during the upright period, reproducing the patient’s symptom, the test is considered positive. The patient is then lowered from the supine position, and the study ends.

8. Active standing with blood pressure monitoring (for orthostatic hypotension): Refer to the section on postural hypotension.


Issues in the Management of Dizziness

Some causes of dizziness are curable. Most of these are acute or subacute problems, such as anaemia, cardiac arrhythmias, adverse effects of drugs, systemic infections (including neurosyphilis), cerumen against the tympanic membrane, acoustic neuroma, and otitis media. Many other causes of dizziness are not curable but can be improved with therapy. These include migraine, neck osteoarthritis, physical deconditioning, and psychological diagnoses such as hyperventilation in anxiety, and depression. Still others such as viral illnesses, labyrinthitis and BPPV, are self-limiting and will resolve over time. Thus, many causes of dizziness are eminently treatable, provided that a correct diagnosis is made.

Older patients may have multiple medical illnesses requiring multiple medications, with impaired daily activities. Impairment of vision and proprioception – the two most important strategies the body uses to compensate for dizziness and imbalance – is usually present in older patients. The dizziness in these patients is generally multifactorial and not easily curable. Thus, these patients are challenging to manage. Inappropriate prescription of vestibular sedatives, such as cinnarizine, betahistine (antihistamine) and prochlorperazine (phenothiazine), may suppress normal vestibular function and worsen dizziness of central (central nervous system) origin, frequently leading to falls and even fractures.

Prescription for the treatment of dizziness is very easy. However, successful treatment of dizziness is sometimes challenging. Usually, physicians may not be able to recognize treatment failure because symptomatic patients may have already been sent to neurosurgical or orthopaedic departments due to dizziness-related fall injury.

References

Coming Soon...

“Go! Go! Go!" The First Once-Monthly Subcutaneous Anti-TNF α Agent is ready for a shot
# Monotherapy or Combination therapy?

## Consensus Guideline on Management of Onychomycosis

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Topical</th>
<th>Oral</th>
<th>Combination</th>
<th>Nail removal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Involvement &lt; 50% nail plate</td>
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<tr>
<td>2. Minimum number (3 or 4) of nails involved</td>
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<tr>
<td>3. Unable to swallow pills</td>
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<td>4. No melanonychia</td>
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<td>5. Known drug interaction/allergy</td>
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<tr>
<td>6. Mycological exam – causative fungi known drug interaction/allergy</td>
<td>✔️</td>
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<tr>
<td>7. &gt;50% nail involvement</td>
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<tr>
<td>8. Matrix area involvement (25.84% of cases in the recent EUROO study)</td>
<td>✔️</td>
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<td>9. Topical drug penetration suboptimal</td>
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*After nail removal

**Drug of Choice for Treating Onychomycosis**

- Highly efficacious in treating onychomycosis
- Excellent safety profile
- Require no baseline liver function test
- Simple, once-weekly usage

**Loceryl Nail Lacquer**

- Onychomycosis < 50% area of nail plate and without matrix involvement

**Loceryl Nail Lacquer + oral antifungal Combination therapy**

- Onychomycosis > 50% area of nail plate or with matrix involvement

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**References:**

Prescribing information available on request.
Galderma Hong Kong Ltd. Tel: 2824 0333 Fax: 2827 7760
Unit 1401, 14/F, Ming An Plaza, Phase 1, 8 Sunning Road, Causeway Bay, Hong Kong.