In Focus: Rheumatoid Arthritis - I

Global Summaries

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and more!
Coronary disease is associated with chronic inflammation, but whether the association is causal is not known. Genetic mutations associated with increased biomarkers of inflammation have not been associated with increased coronary risk, making a direct causal link less likely. Now, two meta-analyses of studies of a mutation (Asp358Ala) in the interleukin 6 (IL-6) receptor gene (IL6R) have suggested that there may be a causal relationship between coronary disease and IL6R-related pathways.

One meta-analysis included 82 studies of Asp358Ala, coronary risk factors, and inflammation biomarkers in 125,222 subjects. The frequency of the mutation was also studied in 51,441 patients with coronary disease and 136,226 controls. The minor allele frequency of Asp358Ala was 39% among people without coronary disease and 358Ala inherited.

These results suggest that 358Ala reduces the systemic inflammatory response and also reduces coronary risk, thus supporting the hypothesis that chronic inflammation promotes coronary disease. Modulation of IL6R pathways might prevent coronary disease, but the effects on conventional risk factors might be difficult to predict.


Brodalumab for psoriasis

T-cell production of interleukin 17 is important in the pathogenesis of psoriasis. Brodalumab is a human monoclonal antibody against interleukin 17RA, one of the six cytokines of the interleukin 17 cytokine family. A multicentre, international study has shown that brodalumab is effective treatment for chronic plaque psoriasis over a 12-week period.

The study included 198 patients with a score of at least 12 on the Psoriasis Area and Severity Index score (possible range, 0–72; higher scores indicating more severe disease) and at least 10% of body surface area affected. Randomization was to subcutaneous brodalumab or placebo. Brodalumab was given at doses of 70, 140, or 210 mg at day 1 and weeks 1, 2, 4, 6, 8, and 10 or 280 mg on day 1 and at weeks 4 and 8. At week 12, the improvement in PASI score was 45% with the 70-mg dose, 85.9% (140 mg), 86.3% (210 mg), 76.0% (280 mg), and 16% (placebo). An improvement of at least 75% was seen in 77% at the 140-mg dose and in 82% of the 210-mg group. An improvement of at least 90% was seen in 72% and 75% of these groups, respectively. No patient in the placebo group achieved these degrees of improvement. On the static physician’s global assessment at week 12, clear or minimal disease was recorded in 26%, 85%, 80%, and 69% of patients with increasing brodalumab doses and in 3% with placebo. Two patients, both in the 210-mg group, developed grade 3 neutropenia. The most common adverse events with brodalumab were nasopharyngitis (8%), upper respiratory tract infection (8%) and injection-site erythema (6%), all of which occurred at similar rates in the placebo group.

Brodalumab was effective treatment for psoriasis over a 12-week period.


Ixekizumab for psoriasis

IxEKizumab is a humanized monoclonal antibody against interleukin 17. A 16-week, multicentre trial has shown it to be effective against psoriasis.

A total of 142 patients with chronic, moderate-to-severe plaque psoriasis were randomized to subcutaneous ixekizumab or placebo at 0, 2, 4, 8, 12, and 16 weeks. Ixekizumab was given at doses of 10, 25, 75, or 150 mg. At 12 weeks, the proportions achieving a reduction in Psoriasis Area and Severity Index (PASI) score of at least 75% were 29% (10 mg dose), 77% (25 mg), 83% (75 mg), 82% (150 mg), and 8% (placebo); a significant improvement on placebo for all except the lowest dose of ixekizumab. For a reduction, in PASI score of at least 90%, the corresponding figures were 18%, 50%, 59%, and 71% with increasing doses of
ixekizumab and 0% with placebo; and for a 100% reduction, they were 0%, 17%, 38%, and 39% with ixekizumab and 0% with placebo. The proportions with clear or minimal disease on the static physician’s global assessment score were 25%, 70%, 72%, and 71% (ixekizumab), and 8% (placebo).

Ixekizumab was effective against psoriasis in a 16-week trial.


Topical ingenol mebutate for actinic keratosis

Actinic keratoses are common in light-skinned people and are premalignant. Treatment may be applied to lesions (cryosurgery) or to the whole area of affected skin (field therapy). Field therapy treatments include imiquimod, fluorouracil, diclofenac, and photodynamic therapy, and they often need to be applied for weeks or months. Ingenol mebutate is a pleiotropic effector that kills cells and promotes immune responses mediated through activation of protein kinase C delta, including neutrophil-mediated oxidative burst and clearance of tumours. Four multicentre US studies reported together have shown that 2 to 3 days of topical field therapy with ingenol mebutate gel is effective treatment for actinic keratoses.

In two trials, patients had lesions of the face or scalp, and in the other two the lesions were of the trunk or extremities. Patients were at least 18 years old and had four to eight typical lesions within a 25-cm² field of skin. They were randomized to apply either ingenol mebutate gel 0.015% or placebo (vehicle) gel to a 25-cm² contiguous field once daily for 3 days in the face or scalp lesions studies and in 2 days in the trunk and extremities lesions studies. Complete clearance at 57 days was achieved in 42.2% (ingenol mebutate) vs 3.7% (placebo) in the face and scalp trials and in 34.1% vs 4.7% in the trunk and extremities trials. Local skin reactions peaked at days 3 to 8 and returned to baseline levels by day 29. Adverse events were usually mild to moderate and resolved without sequelae.

Ingenol mebutate gel applied for 2 or 3 days as topical field therapy may be effective for actinic keratoses.


DPP-4 inhibitors for type 2 diabetes

Dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins) reduce the breakdown of incretin hormones, mainly glucagon-like peptide 1 (GLP-1), tending to correct glucose homeostasis without increasing body weight. Their role in the treatment of type 2 diabetes remains uncertain. The authors of a systematic review and meta-analysis have suggested that they may be used as second-line treatment after metformin.

The meta-analysis included 27 reports of 19 studies (13,881 patients) with randomization to a DPP-4 inhibitor or another antidiabetic drug. DPP-4 inhibitor monotherapy, compared with metformin monotherapy, was associated with a lesser decrease in glycated haemoglobin A1c levels. As a second-line treatment DPP-4, inhibitors were similarly effective to pioglitazone, slightly less effective than sulfonylureas, and inferior to GLP-1 agonists. Added to metformin, DPP-4 inhibitors were associated with less weight gain than were sulfonylureas or pioglitazone but not GLP-1 agonists. The risk of hypoglycaemia was less with DPP-4 inhibitors than with sulfonylureas when combined with metformin.

DPP-4 inhibitors could be used as added treatment when metformin is not completely successful. Guidelines all recommend starting treatment with metformin. When extra treatment is needed, US and European guidelines recommend adding insulin, a sulfonylurea, or a glitazone. UK (National Institute for Clinical Excellence) guidelines suggest a sulfonylurea, followed by insulin as a third-line option, with a DPP-4 inhibitor as a second-line option for patients at high risk of hypoglycaemia or intolerant of a sulfonylurea, or as third-line for patients who do not accept insulin. Studies of DPP-4 inhibitors with clinical end points are in progress.


White rice and diabetes

Many studies have examined the relationship between intake of white rice and risk of type 2 diabetes, but the findings have varied. Asian populations eat far more white rice than Western populations. A systematic review and meta-analysis has been reported.

The meta-analysis included data from seven cohorts: three Asian (Chinese and Japanese) and four Western (US and Australian). Baseline consumption of white rice averaged three to four servings a week in Asian populations and one to two servings a week in Western populations. In the Asian cohorts, those who ate the most white rice had a 55% increase in risk...
of type 2 diabetes compared with those who ate the least. In the Western cohorts, the corresponding increase in risk was 12%. Using pooled data from both populations, each increase in intake of one serving per day increased the relative risk of type 2 diabetes by 11%.

It is concluded that high intake of white rice is associated with increased risk of type 2 diabetes, and this increase is more marked in Asian populations.


**GENERAL MEDICINE**

**Inpatient harms in developing countries**

Harm to patients in hospital that results from misguided health care is well documented in developed countries. Now, a report from eight developing or transitional countries has shown a similar incidence of adverse events.

The study was based on a convenience sample of 28 hospitals in Egypt, Jordan, Kenya, Morocco, Tunisia, South Africa, Sudan, and Yemen. A total of 15,548 randomly selected patient records were reviewed, and 8.2% showed at least one adverse event (range, 2.5% to 18.4% in different countries). Mortality from these adverse events was 30%, and 83% of the adverse events were considered preventable. About one-third (34%) of the events were due to therapeutic errors in non-complex clinical situations. Inadequate staff training or supervision or non-adherence to policies or protocols accounted for most adverse events.

The rate of health-care-derived adverse events in these countries was similar to those reported from developed countries, but they were more often preventable and the consequences were more serious.


**NEUROLOGY**

**Tenecteplase versus alteplase for acute ischaemic stroke**

Alteplase, a recombinant tissue plasminogen activator, is effective thrombolytic treatment for acute ischaemic stroke, but reperfusion with this treatment is often incomplete and delayed. Tenecteplase is a genetically engineered mutant tissue plasminogen activator that may have advantages over alteplase and is apparently effective for stroke at lower doses than for myocardial infarction. Now, a study in Australia has shown better results with tenecteplase than with alteplase in highly selected patients.

Patients who had a perfusion lesion of at least 20% greater than the infarct core on computed tomographic perfusion imaging at baseline and an associated vessel occlusion on computed tomographic angiography were selected. Using these criteria, 75 of 2,768 patients were enrolled within 6 hours of onset of stroke symptoms. They were randomized to intravenous alteplase 0.9 mg/kg, tenecteplase 0.1 mg/kg, or tenecteplase 0.25 mg/kg. Tenecteplase was given as a bolus, and alteplase as 10% of the dose by bolus, with the remaining 90% infused over the next hour. At 24 hours, the tenecteplase groups showed significantly greater reperfusion on perfusion-weighted magnetic resonance imaging and significantly greater clinical improvement on the National Institute of Health Stroke Scale. There were no significant differences between the groups in intracranial bleeding or other adverse effects. At 90 days, there was no serious disability in 72% (tenecteplase) vs 40% (alteplase). The 0.25 mg/kg dose of tenecteplase gave better results than the 0.1 mg/kg dose.

For these selected patients, tenecteplase was associated with better outcomes than alteplase.

Neck pain is a common problem. This article discusses the diagnosis and management of the musculoskeletal causes of neck pain, with emphasis on the neurological impairment and accompanying signs elicited by provocative manoeuvres during the evaluation of neck pain.

Most neck pain is caused by local mechanical problems.
Clinical Evaluation

The time frame for evaluation is important because acute neck pain most often is caused by trauma, whereas degenerative changes lead to chronic neck pain. Acute neck pain has a time frame of less than 3 weeks, and chronic neck pain is defined by a duration of 12 or more weeks; subacute neck pain falls in between. Degenerative changes are slow to develop, but injuries (eg, herniated disks) are likely to cause acute neck pain.

Physical Examination

The physical examination begins with careful inspection of the neck. The examiner should take note of any masses or asymmetries. Palpation, performed with the fingertips, includes evaluation of the thyroid gland, lymph nodes, muscles, and soft tissues.

Passive range of motion is assessed in three planes—flexion-extension; left-right rotation; and left-right flexion, or lateral bending. Most mechanical neck problems are asymmetrical, and passive range of motion may be limited asymmetrically by pain.

Provocative Testing

Along with testing of sensation, strength, and reflexes, several provocative manoeuvres are useful in evaluating cervical radiculopathy. Neck pain may radiate into the extremities, and it may be worsened by these various provocative manoeuvres. Provocative tests place the neck and arm in various positions to aggravate or relieve symptoms. Provocative manoeuvres and their resulting signs include the Spurling, Lhermitte, shoulder abduction, Adson, and Hoffmann signs.

Red Flag Symptoms

Noting the presence of red flag symptoms, such as intractable pain, fever, night sweats, unexpected weight loss, and gait disturbance, helps clinicians identify malignancy, infection, and other potentially serious diagnoses. Exquisite tenderness over a vertebral body is concerning for malignancy or compression fracture. When point tenderness occurs in the setting of fever, infection is a strong possibility.

Cervical osteomyelitis is a potential diagnosis in a patient who has fever and neck pain. Magnetic resonance imaging (MRI) evaluation along with blood cultures and an erythrocyte sedimentation rate help confirm this diagnosis.

Other Testing and Imaging

Electromyography and nerve conduction velocity studies are useful in determining which nerve is affected and
the location of the compression. These studies help differentiate a cervical radiculopathy from an entrapment neuropathy, such as ulnar or median neuropathy. An MRI scan of the spine is most useful in evaluating a patient with cervical radiculopathy to confirm the actual cause of the radicular pain. In addition, an MRI scan can be used to assess structural changes of the disk. Intra-articular anaesthetic injections with fluoroscopic guidance also may help confirm other causes of neck pain, such as facet joint arthropathy.6

Neck Pain Disorders

Cervical Spondylosis
This condition, the result of degenerative changes as a natural consequence of aging, may cause axial neck pain, radiculopathy, myelopathy, or a combination of these problems.7 Degenerative changes result in osteophyte formation, and osteophytes can impinge on adjacent structures.

The diagnosis of cervical spondylosis usually is made by clinical evaluation alone.1 Presenting features include neck pain aggravated by movement, poorly localized tenderness, limited range of movement, and vague paraesthesias of the upper extremity.1

Axial Neck Pain
This is the most common cause of neck pain. Lesions of the upper cervical nerve roots (C2-4) are uncommon and give rise to no motor deficits.1,8 Sensory involvement is as follows:

- C2—occipital area.
- C3—posterior aspect of neck.
- C4—trapezial area.

The C2-3 facet joints may be the source of occipital, or cervicogenic, headache.2,9 The C2-4 nerve roots are not associated with motor involvement.

Axial neck pain may radiate to the shoulders and head.7 In the absence of radicular symptoms, determining the source of the neck pain can present a diagnostic challenge.7

Cervical Radiculopathy
Eight pairs of cervical nerve roots originate from the spinal cord (Figure). Each cervical nerve root exits above the corresponding vertebra, except for the eighth nerve root, which exits above the first thoracic vertebra.

The brachial plexus is composed of nerve roots from the first thoracic and the lower four cervical levels (C5-T1). The nerve roots of C5 and C6 join to form the upper trunk; those of C8-T1 join to form the lower trunk. The nerve root of C7 alone makes up the middle
Several anatomical sources of chronic neck pain are shown in this transverse section. Compression at the nerve root level (eg, herniated disk) produces specific dermatomal symptoms (Table 1). Thoracic outlet syndrome (TOS), peripheral entrapment neuropathies, and other conditions have overlapping dermatomes.

Disk herniations may occur suddenly; nerve root compression related to spondylosis may develop slowly. Herniation of an intervertebral disk may be caused by degenerative processes or trauma. Disk herniations may occur centrally or laterally. Central disk herniations may compress the cervical cord directly; lateral disk herniations result in compression of a cervical nerve root.

Physical findings for cervical radiculopathy, a neurological condition characterized by pain in the neck and arm, include a combination of deficits in motor function, sensation, and reflexes. The disorder typically is caused by degenerative changes that result in foraminal encroachment. Radiculopathy resulting from nerve root compression usually occurs at the C5-7 level; the C7 nerve root is most frequently involved. Cervical radiculopathy typically manifests as pain radiating from the neck into the distribution of the affected nerve root. Sensory symptoms are more common than weakness.

The diagnosis of cervical radiculopathy most often can be made with the history and physical examination. There are no clear guidelines on when imaging is warranted. Red flag symptoms would justify imaging, as would neurological deficits. Nerve conduction studies could help differentiate cervical radiculopathy from a compressive peripheral entrapment neuropathy (eg, carpal tunnel syndrome [CTS]).

The Spurling test may be used to evaluate patients for cervical radiculopathy (Table 2). The sign is elicited by extending, rotating, and laterally flexing the patient's neck toward the symptomatic side. Then, the examiner applies axial pressure on the spine. Pressure applied on top of the head may intensify symptoms.

The Spurling test has a sensitivity of 30% to 60% and a specificity of 90% to 100%, quite similar to those of other provocative manoeuvres (low sensitivity but high specificity). Therefore, this test is not useful as a screening tool, but it does help confirm the diagnosis of cervical radiculopathy.

The Lhermitte sign is performed by having the patient flex his or her neck forward. An electric shock–like sensation radiating down the spine and into both arms is considered a positive test result. The sign also may provoke paraesthesias in the lower extremities.

Other signs and manoeuvres to consider in the evaluation of possible cervical radiculopathy include the arm abduction sign and manual traction. The shoulder abduction sign is performed by resting the patient's abducted arm on top of his forehead with the elbow flexed. Pain relief with the arm in this position is a positive finding.

Manual traction of the neck, or the neck distraction test, also may result in pain relief. To perform this manoeuvre, the examiner grasps the

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<th>Diagnosis</th>
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<td>Spurling</td>
<td>Elicited by extending and rotating the neck toward the symptomatic side; look for exacerbation of radicular pain</td>
<td>Cervical radiculopathy (eg, herniated disk)</td>
</tr>
<tr>
<td>Adson</td>
<td>Elicited by having the patient elevate the chin and rotate the head toward the affected side while inspiring deeply; look for obliteration of the radial pulse on the affected side</td>
<td>Thoracic outlet syndrome</td>
</tr>
<tr>
<td>Hoffmann</td>
<td>Elicited by firmly grasping the middle finger and quickly snapping or flipping the dorsal surface; look for a quick flexion of both the thumb and index finger</td>
<td>Cervical myelopathy (eg, cervical spinal stenosis)</td>
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"Cervical radiculopathy typically manifests as pain radiating from the neck into the distribution of the affected nerve root"
patient’s head under the chin and occiput and applies axial traction force.\textsuperscript{12}

\textbf{Mimics of cervical radiculopathy.} Conditions that may mimic cervical radiculopathy include Pancoast tumor, peripheral entrapment neuropathies, TOS, and herpes zoster. The peripheral entrapment neuropathies include CTS at the wrist (median nerve); cubital tunnel syndrome at the elbow (ulnar nerve); and ‘Saturday night palsy’, which involves compression of the radial nerve at the humeral spiral groove in patients with sustained compression (eg, an intoxicated person falls asleep with his arm over a chair).\textsuperscript{19}

The median nerve is derived from the C6-T1 nerve roots; the ulnar nerve is derived from the C8-T1 nerve roots, and the radial nerve is derived from the C5-T1 nerve roots. A detailed history and physical examination would help differentiate these causes of neck pain from cervical radiculopathy.

\textbf{Thoracic Outlet Syndrome}

There is no objective confirmatory test for this syndrome. Arm claudication, exercise-induced paraesthesia, and hand cyanosis and pallor after exercise are strong clues to the diagnosis.\textsuperscript{20,21} TOS also may mimic Raynaud phenomenon. The paraesthesias most often are distributed in the ulnar aspect of the hand and forearm (C8-T1 distribution).\textsuperscript{10,20}

TOS occurs when there is compression of the brachial plexus, subclavian vein, and subclavian artery. This neurovascular bundle passes through the interscalene triangle, which is bordered anteriorly by the anterior scalene muscles, posteriorly by the middle scalene muscles, and inferiorly by the first rib.\textsuperscript{20} Neurogenic TOS, with involvement of the brachial plexus, is more common than vascular TOS, with involvement of the subclavian vein or artery.\textsuperscript{21}

A cervical rib, an anomalous enlargement of the transverse process of the seventh cervical vertebra,\textsuperscript{22} is a predisposing factor for the development of TOS. Symptomatic cervical ribs usually produce symptoms of neurogenic TOS.

\textbf{Cervical Myelopathy}

The onset of myelopathy, a potential complication of cervical spondylosis that results from spinal cord compression, is gradual; patients with myelopathy often have a history of chronic neck, shoulder, and arm pain.\textsuperscript{2} Red flags for cervical myelopathy include gait disturbance, hand clumsiness, and combined neurological deficits (eg, upper motor neuron signs in the legs with lower motor neuron signs in the arms).

Cervical radiculopathy typically manifests as pain radiating from the neck into the distribution of the affected nerve root; patients with cervical spondylotic myelopathy typically present with hand clumsiness, difficulty with grasping and holding objects, and gait disturbance. Patients may have a spastic paraparesis of the lower limbs; cervical spondylotic myelopathy is the most common cause of acquired spastic paraparesis in adults.\textsuperscript{7} Bladder dysfunction is a late symptom.\textsuperscript{1} MRI, the study of choice for evaluation of cervical myelopathy, provides critical information about the extent of cord compression.

Physical findings associated with myelopathy include hyperreflexia; clonus; and the Babinski, Hoffmann,
and Lhermitte signs. A positive Hoffmann sign reflects the presence of an upper motor neuron lesion resulting from spinal cord compression; the test is performed by firmly grasping the middle finger and quickly snapping or flipping the dorsal surface. The sign is positive if quick flexion of both the thumb and index finger results.2 The Babinski sign is an upturning reflex as evidenced by dorsiflexion of the big toe on stimulation of the sole of the foot with a blunt instrument.

Treatment
Non-steroidal anti-inflammatory drugs (NSAIDs) have combined analgesic and anti-inflammatory properties. However, prolonged NSAID use is limited by gastrointestinal, renal, and cardiovascular toxicity.25 Acetaminophen is the preferred agent for mild to moderate pain.25 Opioid analgesics should be used, with caution, for moderate to severe pain.25 Muscle relaxants are helpful in the presence of associated muscle spasms. Anticonvulsants, such as gabapentin and pregabalin, are useful adjunctive medications in the management of radiculopathy. Pregabalin has been shown to be effective in the management of cervical radiculopathy.26 Gabapentin has been used to manage chronic neuropathic pain syndromes. To my knowledge, however, there have been no studies of gabapentin for the treatment of patients who have cervical radiculopathy. Non-operative, non-pharmacological interventions include physical therapy, cervical traction, use of soft collars, manual therapy, thermal therapy, and acupuncture.25 A multimodal approach using physical therapy, medication, and injection therapy is best. Surgery may be considered for patients who have medically refractory pain or signs of myelopathy.

Conservative treatment is acceptable in the absence of red flag symptoms or myelopathy.

Conclusion
The reasons for neck pain can be complex, although most neck pain is caused by local mechanical problems. The diagnosis most often can be made with the history and physical examination. Serious diagnoses, including malignancy and infection, should not be overlooked. Red flag symptoms should be noted and followed up with further imaging of the neck structures.

Declarations of Interest
None.

References

About the Author
Dr Karnath is associate professor of medicine at the University of Texas Medical Branch at Galveston.
The revised classification criteria for rheumatoid arthritis (RA) have enabled the identification of patients at high or low risk for RA. Using treat to target strategies, health-care professionals can help maximize the functional activities and quality of life of these patients.
New Classification Criteria for RA

Jaya Philipose, MD; Atul Deodhar, MD

An improved understanding of the pathogenesis of rheumatoid arthritis (RA) has resulted in effective new therapeutic options and a paradigm shift in the approach to treatment. The emphasis now is on early initiation of effective disease-modifying therapy to prevent joint damage and achieve disease remission. Because the 1987 American College of Rheumatology (ACR) classification criteria for RA lacked sensitivity for recognizing the earlier stages of disease, the ACR and the European League Against Rheumatism recently collaborated in an initiative to revise them. The new criteria are not a diagnostic tool but instead are intended to differentiate among patients who are at high or low risk for persistent or erosive disease or both.
classification criteria for RA lacked sensitivity for recognizing the earlier stages of disease. With this in mind, the ACR and the European League Against Rheumatism (EULAR) recently collaborated in an initiative to revise the 1987 classification criteria (Table). The 2010 revision focuses on features found at the earlier stages of disease before the late features identified by the previous criteria develop. Note that the new criteria are not a diagnostic tool but instead are intended to differentiate among patients who are at high or low risk for persistent or erosive disease or both.3

In this article, we discuss the need for and advantages of the recently revised classification criteria for RA.

The Process of Developing New Criteria

The ACR/EULAR joint committee included more than 35 contributors. Their aim was to develop a set of rules to be applied to newly presenting patients with undifferentiated synovitis that would (1) identify the subset at high risk of chronicity and erosive damage; (2) be used as a basis for initiating disease-modifying therapy; and (3) not exclude the capture of patients later in the disease course.3

The new criteria were developed in three phases. The first phase was a data-driven approach to identify factors and their relative weights of importance that were most predictive of the decision to start methotrexate therapy in more than 3,000 patients from nine early arthritis patient cohorts. The initiation of DMARD therapy was considered to be an indication that the patient would be at risk for persistent or erosive disease or both.

The second phase consisted of assembling an expert panel of 24 rheumatologists who refined these factors and their weights by using real-life case scenarios. They employed a consensus-based, decision science-informed approach to calculate the likelihood score of RA developing in a person; a higher score indicated a greater likelihood.

The final phase combined the findings from the first two phases, further refining the scoring system and determining the ideal cut point to define ‘definite RA’. That cut point was verified by applying the new scoring system to three cohorts that had been included in phase 1 and to three cohorts that were not.3

Before the new classification criteria are applied to patients presenting with inflammatory arthritis, two requirements must be met: (1) there must be at least one joint with definite synovitis, excluding the DIP joints, first MTP joints, and first CMC joints, and (2) in whom the synovitis cannot be explained by another disease.

Table. The ACR/EULAR 2010 classification criteria for RA

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Joint involvement</strong></td>
<td></td>
</tr>
<tr>
<td>1 large joint</td>
<td>0</td>
</tr>
<tr>
<td>2–10 large jointsa</td>
<td>1</td>
</tr>
<tr>
<td>1–3 small jointsa (with or without involvement of large joints)</td>
<td>2</td>
</tr>
<tr>
<td>4–10 small joints (with or without involvement of large joints)</td>
<td>3</td>
</tr>
<tr>
<td>&gt; 10 joints (at least 1 small joint)</td>
<td>5</td>
</tr>
<tr>
<td><strong>B. Serology (at least one test result is needed for classification):</strong></td>
<td></td>
</tr>
<tr>
<td>Negative RF and negative anti-CCP antibodies</td>
<td>0</td>
</tr>
<tr>
<td>Low-positive RF or low-positive anti-CCP antibodiesd</td>
<td>2</td>
</tr>
<tr>
<td>High-positive RF or high-positive anti-CCP antibodiesd</td>
<td>3</td>
</tr>
<tr>
<td><strong>C. Acute phase reactants:</strong></td>
<td></td>
</tr>
<tr>
<td>Normal CRP level and normal ESR</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal CRP level or abnormal ESR</td>
<td>1</td>
</tr>
<tr>
<td><strong>D. Duration of symptoms:</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 6 weeks</td>
<td>0</td>
</tr>
<tr>
<td>≥ 6 weeks</td>
<td>1</td>
</tr>
</tbody>
</table>

ACR = American College of Rheumatology; EULAR = European League Against Rheumatism; RA = rheumatoid arthritis; DIP = distal interphalangeal; MTP = metatarsophalangeal; CMC = carpometacarpal; MCP = metacarpophalangeal; PIP = proximal interphalangeal; IP = interphalangeal; RF = rheumatoid factor; anti-CCP = anti–cyclic citrullinated protein; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

aTo be applied to patients: (1) who have ≥ 1 joint with definite synovitis, excluding the DIP joints, first MTP joints, and first CMC joints, and (2) in whom the synovitis cannot be explained by another disease.
bLarge joints = shoulders, elbows, hips, knees, ankles.
cSmall joints = MCPs, PIPs, second to fifth MTPs, thumb IPs, wrists.
dLow-positive is < 3 times the upper limit of normal.
eHigh-positive is > 3 times the upper limit of normal.
A score lower than 6 does not classify a patient as having definite RA, but patients may meet criteria as their disease evolves over time; subsequently, they may be classified as having definite RA. In addition, patients may present at a later stage of the disease with typical RA erosions. As a result, those with long-standing disease that retrospectively would have fulfilled the 2010 criteria also should be classified as having definite RA.

How the New Criteria Differ From the Old

The new criteria notably do not take into account such features as morning stiffness and symmetry of joint involvement as the previous criteria did. These factors were determined to be not significant. In addition, radiographic changes were excluded because they are considered late features and are not expected to be found in patients with early inflammatory arthritis.1–5

Instead, significant weight is placed on serology, with the inclusion of anti–cyclic citrullinated protein antibodies and rheumatoid factor, which could account for three of the six points needed for definite RA. Ultimately, however, the diagnosis of RA remains a clinician-based decision and the new criteria are not expected to be used as a diagnostic tool.

Advantages and Potential Uses of the New Criteria

Until now, the lack of validated and uniformly accepted criteria to classify early disease has prevented investigation of the effectiveness of earlier treatment for patients with RA. In a study conducted by van der Linden and associates,6 the 2010 criteria were found to have a sensitivity of 0.84 compared with 0.61 for the 1987 criteria when the start of methotrexate therapy was the outcome. The specificity was lower in the 2010 criteria but, at 0.60, was still considered acceptable.

This increased sensitivity of the new criteria for early disease associated with a poor prognosis allows for identification of patients who may benefit from early therapeutic intervention or entry into clinical trials. Consequently, the new criteria will increase the diversity of a typical RA study population, and patients at an earlier stage of the disease could be compared with those who have long-term disease. In the future, the discovery of new biomarkers is expected to lead to further revisions of the classification criteria as well as to identify additional subsets of patients to enhance personalized medicine.

Declaration of Interests

None.

References


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Understanding Function in RA: An Update on ‘Treat to Target’

Marc C Levesque, MD, PhD; Joan C Rogers, PhD, OTR; Nancy A Baker, ScD; Elizabeth A Schlenk, PhD, RN; Terence Starz, MD

Joint pain and joint damage resulting from rheumatoid arthritis (RA) lead to functional limitations that reduce patients’ quality of life and make activities of daily living difficult. Recent guidelines have emphasized treat to target strategies for minimizing joint destruction in patients with RA and maximizing their functional well-being, but these strategies have not been tested in usual-care settings and have not focused on the functional improvements that occur when disease activity is reduced by medication. The Routine Assessment of Patient Index Data 3, a composite of patient self-reported measures, includes a Multidimensional Health Assessment Questionnaire (MDHAQ). The MDHAQ provides questions to determine patients’ ability to perform activities related to function. Additional treatment strategies that focus on directly addressing functional disabilities may be needed.

Rheumatoid arthritis (RA), which affects an estimated 1.3 million Americans, is a complex inflammatory disorder associated with synovitis and joint destruction. \(^1\)\(^-\)\(^3\) Both joint pain and joint damage resulting from RA lead to functional limitations that reduce patients’ quality of life and make activities of daily living difficult.

For example, RA is associated with significant morbidity, a reduced life span, and lost work productivity\(^4\)\(^,\)\(^5\) and it ranks among the common chronic illnesses with the worst quality of life.\(^6\) Within 10 years of diagnosis, 35% of patients with RA will be work-disabled.\(^7\) In addition to its toll on patients’ physical and emotional health, RA is associated with losses to the US economy that were estimated at $58 billion in 2008.\(^5\)
New RA management strategies have ‘treat to target’ objectives, but determining which measure to use to assess disease activity and response to therapy has been a challenge. In the past, clinical assessment of joint swelling and tenderness, along with imaging and laboratory studies, formed the basis of decision making. However, these tools offered limited information about the impact of synovitis on a patient’s function.

Treat to Target Strategies in Patients With RA

The importance of treat to target strategies for minimizing joint destruction in patients with RA and maximizing their functional well-being has been emphasized in recent guidelines from the American College of Rheumatology (ACR), the European League Against Rheumatism (EULAR), and an international task force. An incentive to perform quantitative clinical disease activity measures in the routine care of patients with RA also is driven by quality of care initiatives that require quantitative measures of disease activity.

RA Disease Activity and Functional Assessments

Treat to target studies have shown that patients with RA achieve lower levels of disease activity and a better quality of life with intensive therapy and quantitative monitoring of disease activity. However, treat to target strategies have not been tested in usual-care settings and have not focused on the functional improvements that occur when disease activity is reduced by medication.

This highlights important differences between RA disease activity as measured by instruments such as the 28-joint Disease Activity Score (DAS 28) and the Clinical Disease Activity Index (CDAI) and the functional ability of patients with RA as measured by instruments such as a Health Assessment Questionnaire (HAQ) and the Routine Assessment of Patient Index Data 3 (RAPID3). The RAPID3 is a composite of patient self-reported measures that includes a Multidimensional HAQ (MDHAQ), and the DAS 28 and CDAI are primarily physician-reported measures that rely on physician assessments of tender and swollen joints. Techniques for assessing tender and swollen joints are demonstrated in an article.

The 2010 criteria for the diagnosis of RA established by the ACR and the EULAR were developed to promote the diagnosis of early disease. The original 1987 ACR criteria for a diagnosis of RA included radiographic signs that typically occur with chronic disease. The differences between the old and new criteria for a diagnosis of RA highlight an important distinction.

Occupational therapy is probably the best way to improve function when irreversible structural joint changes have occurred.

“The MDHAQ is a validated tool that provides important information for assessing the functional abilities of patients with RA”
between reversible synovial inflammation as emphasized by the new ACR/EULAR criteria and irreversible structural joint changes that are part of the 1987 ACR criteria. With reversible inflammation of the joint, there is a greater probability that medications will lead to functional improvements. In contrast, when irreversible structural changes have occurred, occupational therapy probably is the best way to improve function for these patients with RA.

Some authors have proposed that the RAPID3 may be used as a measure of RA disease activity for targeted treatment decisions. In addition to the patient-reported MDHAQ functional questions, the RAPID3 is a composite score that also includes visual analog scales (VAS) of patient pain and patient global arthritis disease.

The MDHAQ consists of a set of questions that patients answer to determine their ability to perform activities related to function. Several functional domains are assessed by the MDHAQ: questions for each domain include dressing and grooming, arising, eating, walking, hygiene, grip, and reach (Figure). For example, the MDHAQ asks patients whether they have no, some, or much difficulty in getting in and out of bed.

The VAS that are part of the RAPID3 ask patients to rate their pain and arthritis disease on a scale of 0 to 10 (10 being the worst). There is a moderately good correlation between the RAPID3 and DAS 28 measures, although they have important differences. While there may be a good correlation between joint pain and swelling and a patient’s functional ability as measured by tools such as the MDHAQ, some patients with good DAS 28 scores clearly have poor scores on the RAPID3. Our own research findings suggest that among patients with RA in DAS 28 remission, as many as 40% report moderate or severe functional disabilities as assessed by the RAPID3.

The Tight Control for Rheumatoid Arthritis study, which used a treat to target strategy, and other studies have demonstrated that adjusting DMARD therapy to improve disease activity using the DAS 28 improves patient disease activity and quality of life. However, oral DMARDs and biologic agents probably will not improve the functional abilities of patients with RA in DAS 28 remission who also have high RAPID3 scores and chronic damage resulting from RA and other diseases. Therefore, additional treatment strategies that focus on directly addressing functional disabilities, such as evaluation...
and treatment by an occupational therapist, may be needed to treat patients with RA who have good DAS 28 scores but poor scores on assessments such as the RAPID3, which emphasize functional abilities.

Summary

The MDHAQ is a validated tool that provides important information for assessing the functional abilities of patients with RA. This tool can be incorporated into routine clinical practice easily and provides information that differs from that provided by quantitative disease activity measurements such as the DAS 28 and CDAI.

Declaration of Interests

None.

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Answers to questions on page 308: 1. F, 2. T, 3. T.
Decadurabolin in Postmenopausal Osteoporosis

Bhavuk Garg

Osteoporosis is a major public health issue. It is typically a disease of the elderly and with population aging it has become one of the most frequent and relevant health problems, especially among women. Postmenopausal osteoporosis is associated with significant morbidity, mortality, reduction in quality-of-life and increasing health care costs. Since, low bone mass is the major risk factor for fractures, the treatment of osteoporosis should focus on agents that prevent bone loss or even increase bone mass. The management of osteoporosis today incorporates multiple modalities of therapy. The therapeutic profile of nandrolone decanoate is that of inhibitor of bone resorption with temporary increase in bone formation. Clinical study results reveal that nandrolone decanoate significantly increases bone mineral density and is effective in the treatment of postmenopausal osteoporosis.

**Introduction**

**Postmenopausal osteoporosis: A major public health issue**

Osteoporosis, the most common bone disorder, is an important public health problem in older adults. Osteoporosis results in skeletal weakening, which is recognized by reduction in bone mass and bone quality, thereby increasing the bone brittleness and fracture risk.

The consequences of these fractures which include chronic pain, disability, deformity and sometimes death, are well recognized clinical sequelae of osteoporosis. Osteoporosis defined by low bone mineral density (BMD) (i.e., 2.5 standard deviations below the average value in young women), is a progressive disease with high prevalence affecting 1 in 3 women and 1 in 8 men by the time they reach 90 years of age.

High risk of fractures due to low BMD is mainly observed in non-vertebral bones (wrist or the hip). A hip fracture might require prolonged hospital stay, surgical repair or replacement and rehabilitation therapy. Reports have also shown higher risk of mortality after hip fracture. Osteoporosis may also lead to vertebral fractures. The clinical symptoms include height loss (stooped posture) or compressed spinal vertebra. Figure 1 represents the common sites for fractures due to osteoporosis. The main mechanisms through which osteoporosis develop include an inadequate bone loss, increase in bone resorption and an inadequate formation of new bone. These factors result in the development of fragile bone tissue ultimately increasing the risk of fracture.

**Prevalence and incidence of postmenopausal osteoporosis**

Osteoporosis is most common in postmenopausal women. Approximately, 80% of the women are affected with osteoporosis. With the increase in age, the prevalence of osteoporosis and the associated risk of fracture...
also increases. With respect to the incidence of fractures it is found that, osteoporosis is responsible for more than 1.5 million fractures annually, including more than 3,000,000 hip fractures, 7,000,000 vertebral fractures, 2,500,000 wrist fractures and 3,000,000 fractures at other sites.

In Indian population, it was found that, particularly in the Western population, osteoporotic fractures were a major cause of morbidity and mortality, particularly in the elderly. The census report of 2001 showed that, approximately 163 million Indians are above the age of 50; and the number is expected to rise to 230 million by 2015. The investigators also suggested that, approximately 20% of women and about 10–15% of men would be osteoporotic. It is estimated that, approximately 25 million people may be affected with osteoporosis. Another study result showed that women in western countries suffered more from osteoporosis when compared to men and the effects were largely due to menopause.

Postmenopausal osteoporosis and risk of fractures

The clinical risk factors associated with fracture or low BMD in postmenopausal women include the following (Figure 2): Osteoporosis has no clinical manifestations until there is a fracture. This is an important fact, since many patients with achy hips or feet assume that their complaints are due to osteoporosis.

Treatment of postmenopausal osteoporosis

Since, low bone mass is the major risk factor for fractures, the treatment of osteoporosis should focus on agents that prevent bone loss or even increase bone mass. Osteoporosis, however, is a multifactorial disease and skeletal fragility results from various factors.

The treatment of patients with postmenopausal osteoporosis incorporates multiple modes of both pharmacologic and non-pharmacologic therapy. Non-pharmacologic approach mainly includes comprehensive patient education. With respect to pharmacological intervention, its initiation should begin with a long-term management strategy. Selection of a particular therapeutic agent for the management of osteoporosis should be based on an evidence-based approach.

Role of nandrolone decanoate

Nandrolone decanoate (ND) also plays a major role in increasing BMD. ND inhibits bone resorption with temporary increase in bone formation, followed by an absence of suppression of bone formation, indicating uncoupling of bone resorption and formation. This increases the bone mineral content (BMC) at the proximal and distal radius and also in few patients at the lumbar spine. ND also helps in increasing calcium balance and muscle mass. It also diminishes vertebral pain and increases the mobility of the spine.

Clinical evidences for nandrolone decanoate

Increased BMD with nandrolone decanoate in elderly women with osteoporosis

Frisoli et al. conducted a randomized, double-blind, placebo-controlled clinical trial to evaluate the effect of a 2-year treatment with ND on BMD of lumbar spine, femoral neck and trochanter and on vertebral fracture rate, muscle mass and hemoglobin levels. A total of 65 osteoporotic women ≥70 years were randomized to receive:

- **Injections** All patients of 50 mg received 500 mg ND (n=32) calcium tablets
- **Placebo daily** (n=33)

The investigators reported the following results:

![Figure 2. Risk factors associated with fracture in postmenopausal women](image-url)

- **Excessive alcohol intake**
- **White or Asian race**
- **Family history**
- **Excessive alcohol intake**
- **History of falls**
- **Lack of exercise**
- **Low body weight**
- **Increasing age**
- **Low calcium or vitamin D intake**

**Clinical risk factors**

- **Personal history of fracture**
- **Lack of exercise**
- **Excessive alcohol intake**
- **History of falls**
- **Low body weight**
- **Low calcium or vitamin D intake**
- **Increasing age**

- **All patients received 500 mg calcium tablets daily**

The investigators reported the following results:
When compared to baseline, treatment with ND increased the BMD of the lumbar spine (3.4%±6.0 and 3.7%±7.4; p<0.05) and femoral neck (4.1%±7.3 and 4.7%±8.0; p<0.05) after 1 and 2 years, respectively (Figure 3).

Significant increase in BMD level of trochanter was observed after the first year (4.8%±9.3, p<0.05).

When compared with placebo, ND significantly increased the BMD levels of trochanter and neck.

Significant reduction in incidence of new vertebral fractures was observed in ND group when compared with placebo (21% vs. 43%) (Figure 4).

In terms of lean body mass, ND showed statistically significant increase after the first (6.2%±5.8; p<0.01) and second years (11.9%±29.2; p<0.01).

A 2-year treatment with ND significantly increased hemoglobin levels compared to baseline (14.3%; p<0.01) and placebo (p<0.01).

From the study results, the investigators concluded that, ND when compared with placebo in elderly osteoporotic women:
- Increased BMD, hemoglobin levels and muscle mass.
- Reduced the vertebral fracture rate.

**Nandrolone decanoate significantly increased BMD levels and reduced the incidence of new vertebral fractures**

Flicker et al. conducted a randomized study design to evaluate over 2 years the effect of intranasal salmon calcitonin and IM ND on bone mass in elderly women with established osteoporosis. A total of 123 women aged 60–88 years who had sustained a previous osteoporotic fracture or had osteopenia were included in the study. The patients were randomized to four different groups:

- **Group 1**: Daily placebo nasal spray.
- **Group 2**: 400 IU intranasal calcitonin daily.
- **Group 3**: 20 IM injections of 50 mg ND (given as two courses of 10 injections) plus placebo nasal spray.
- **Group 4**: 20 injections of 50 mg ND plus 400 IU intranasal calcitonin daily.

All patients received 1000 mg calcium supplementation on daily basis. The outcomes measured included changes in BMD at the lumbar spine, as measured by dual-energy quantitative computed tomography (DEQCT), changes in BMD of the proximal femur, BMD and BMC of the lumbar spine and forearm, as measured by dual-energy X-ray absorptiometry (DXA).

The following results were observed:
- ND group was associated with a 3.8±1.8% (p<0.05) gain in DXA BMD at the proximal femur.
- Significant positive changes from baseline in DXA BMC at the lumbar spine were observed over 2 years in the calcitonin group (5.0±1.9%, mean±SE) and in the ND group (4.7±1.9%) but not in the placebo group (1.1±2.2%).
or the combined therapy group (0.7±1.8%).

- Intranasal calcitonin was associated with harmful effects on trabecular BMD at the lumbar spine and total BMD at the proximal femur.

The investigators concluded that ND was associated with significant improvement in BMD at the proximal femur of elderly women with post-menopausal osteoporosis.

Nandrolone decanoate exerts positive effect on vertebral BMD in established postmenopausal osteoporosis

Passeri et al. conducted a double-blind, randomized, placebo-controlled study in 46 postmenopausal women with established osteoporosis to determine the long-term effects of ND on the BMD of the lumbar vertebrae and of the distal third of the radius and on the biochemical markers of bone turnover. The patients were treated with IM injections of placebo or 50 mg ND every three weeks for 18 months. Thirty-two of the initial 46 patients completed 1 year of study and 25 completed the whole study period of 18 months.

The investigators reported the following results:

- An increase by 2.9% in vertebral BMD was observed in ND group and the values fell by 2.3% in the placebo group.
- Radial BMD showed a slight but transient improvement, with a subsequent return to basal levels in the ND group, whereas there was a progressive decrease in the placebo group.
- ND group patients complained less of bone pain after the treatment.
- Patients treated with ND also complained less of bone pain.
- Slight decrease in HDL cholesterol concentrations were observed in ND group.
- ND was associated with significantly increased hemoglobin levels. Overall, from the results, the investigators concluded that ND exerts positive effects on vertebral BMD and on bone pain in patients with established postmenopausal osteoporosis.

Summary

- Osteoporosis is the most common bone disorder in postmenopausal women.
- The prevalence of osteoporosis and the associated risk of fracture rise with increase in age.
- The underlying mechanism of osteoporosis is an imbalance between bone resorption and bone formation.
- Fractures are caused due to osteoporosis in postmenopausal women which can hinder the QoL.
- Low bone mass is the major risk factor for fractures in postmenopausal women with osteoporosis.
- The treatment strategies should mainly focus on the prevention of bone loss or on measures that might help in increasing BMD.
- ND plays a major role in increasing BMD.
- ND inhibits bone resorption with temporary increase in bone formation, followed by an absence of suppression of bone formation, indicating uncoupling of bone resorption and formation.

References


About the Authors

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An Adult Male with Progressive Paraplegia with Sudden Deterioration

Introduction

The differential diagnosis of progressive paraplegia with sudden deterioration in an adult include tumour with bleeding spinal bone tumour with pathological fracture, arteriovenous malformations (AVM) with bleeding, spontaneous haematoma (subdural vs extradural).1-3 In this case study authors discusses the clinical and imaging findings in a 55 year old male, known hypertensive, non-compliant to treatment and was on oral anti-platelet agents presented with progressive paraplegia with sudden deterioration.

Case details

A 55 year old male patient presented with progressive weakness of both lower limbs of 1 month duration. He developed sudden complete paralysis 2 days prior to the presentation to the emergency department and had urinary retention for which he was catheterised. There was no history of fever or trauma. He was a known hypertensive for 5 years (was on tab amlodipine 10 mg OD) and was non-compliant to treatment. He had an episode of chest pain 3 years back and was diagnosed to have unstable angina. He has no history of diabetes or tuberculosis. The patient was on low dose of acetylsalicylic acid. There was local tenderness at D6 level but no gibbus. On initial neurological exami-
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In the patient’s nation, there was flaccid paralysis of lower limbs with grade 0/5 power, with absent superficial and deep tendon reflexes. There was sensory loss below D6 level to all modalities. An emergency magnetic resonance imaging (MRI) of the dorsal spine revealed heterogeneously hypointense lesion on T1W images, becoming heterogeneously hyperintense on T2W images with hypointense area seen in the inferior part of the mass lesion at D6 level (Figure 1, 2 and 3). On Fast Imaging Employing Steady State Acquisition (FIESTA) images the lesion was heterogeneously hyperintense with hypointense inferior part of the mass (Figure 4). Based on clinical presentation and imaging findings a diagnosis of tumour with bleed was suspected. In view of acute onset of bowel and bladder disturbances the patient underwent D5-7 laminectomy in emergency. The dura was tense and non-pulsatile. Over the dura there was abnormal dilated vein. After opening the dura dark altered blood came out. There was bunch of abnormally dilated, tortuous vessel over the spinal cord. After the decompression the dura was closed. As the details of AVM were not evident pre-operatively the further procedure was deferred. The patient was discharged to an inpatient rehabilitation hospital. Although the patient was able to feel pain but there was no motor recovery at six month follow up.

Discussion

Patients with spinal tumours commonly present with gradually progressive symptoms of radicular pain, paresthesia, or paraparesis, as these lesions are generally slow growing with gradual mass effects on the normal neural tissue. However these patients can deteriorate suddenly after intratumoural haemorrhage manifesting as acute paraparesis and urinary incontinence. Similarly spinal vascular malformations have the potential to cause progressive symptoms and sudden serious neurological deterioration. Although MRI is recognised as a crucial pre-operative modality the evaluation of such spinal cord lesions and treatment planning, the present case illustrates the unexpected presentation of spinal lesions and difficulty in diagnosis even after imaging. MRI is the primary method for noninvasive examination of patients with clinical evidence of a spinal cord lesion; however, MRI findings are often nonspecific and may be due to spinal cord tumour, inflammation, or vascular disease. Because vascular malformations are a treatable cause of myelopathy, noninvasive techniques for depicting abnormal spinal vessels are desirable.
Schwannomas are common intradural extramedullary spinal tumours, typically hypointense relative to the cord on T1-weighted MRI and mild to marked hyperintensity on T2-weighted images as compared to the spinal cord.\textsuperscript{8,9,12-14} That variable homogeneous or heterogeneous enhancement on Gd-DTPA images.\textsuperscript{7,8} Also in homogeneous T2-weighted images with focal areas of hyperintensity and hypointensity corresponds to cyst formation, haemorrhage, dense cellularity, or collagen deposition in schwannomas.\textsuperscript{8,15} To complicate the issue further haemorrhagic change associated with spinal cord tumours can affect the signal intensity within the tumour on T1- and T2-weighted images (depending on the duration after onset and the type of haemorrhage) resulting in signal intensity changes to hyperintense on T1-weighted images, and hypointense center changing to hyperintense with hypointense rim on T2-weighted images.\textsuperscript{9} In present case, both conventional and T2-weighted gradient-echo MRI that showed mixed hypointensity within the lesion, highly suggestive of the presence of blood degradation products.\textsuperscript{4}

Spinal AVMs have been classified as intramedullary and extra medullary (retromedullary,\textsuperscript{6} intramedullary AVMs are usually seen in young patients and are characterised by acute haemorrhagic stroke and an anterior blood supply while extra medullary retro-medullary as in present case) are often seen in elderly men and are characterised by progressive neurological deficits and a posterior blood supply.\textsuperscript{16} Enlarged and abnormally tortuous intradural vessels in the subarachnoid space are often seen as serpentine areas of low signal intensity (flow voids) on T2-weighted images, guiding the diagnosis toward a vascular malformation or a vascular tumour.\textsuperscript{16,17} In these reports AVMs showed high-velocity signal loss,\textsuperscript{5} and MRI proved especially useful in describing intramedullary components of AVMs.\textsuperscript{18} Although, MR angiography has been suggested as a promising complementary tool to MRI for detection and characterisation of spinal vascular malformations.\textsuperscript{19}
References


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The role of ascorbic acid as anti-\textit{H. Pylori} agent in peptic ulcer diseases is most likely to be preventive rather than curative. It is preferable to complete the standard course of anti-pylori regimen, which might then be followed by vitamin C supplementation therapy for extended period which would prevent from reinfection in susceptible subject.

\section*{Introduction}

In spite of initial success of eradication treatment for \textit{Helicobacter pylori} in peptic ulcer diseases using combination of a proton pump inhibitor and antibiotics, emergence of antibiotics resistance in recent years, leads to frequent treatment failure in at least 10-20\% of the patients. \cite{1} Non antibiotic therapies, including phyto-medicines, probiotics and antioxidants have been increasingly investigated as potential adjuvants for the treatment of \textit{H. pylori}. \cite{2} Several clinical studies have been shown that high \textit{H. pylori} infection rate is related to low ascorbic acid level in serum as well as in gastric juice. \cite{3}

\section*{Mechanism of \textit{H. pylori} Survival at low gastric pH}

\textit{H. pylori} synthesises large amount of urease, which is found in its cytosol. The urease catalyses the hydrolysis of urea present in the gastric juice, to yield carbonic acid and ammonia. Thus \textit{H. pylori} makes a cloud of ammonia on its surface to neutralize the gastric acid which enables it to colonise the gastric epithelium. \cite{4} Once successfully colonised, \textit{H. pylori} resides below the gastric mucus layer which has a higher pH than gastric lumen. So in chronic infection, the role played by urease, in survival of the bacteria seems less important. However, besides protecting from acid, urease also aids in colonisation by providing ammonia for bacterial protein in synthesis.

\section*{Different Roles of Vitamin C in therapeutics}

- Vitamin C as biological antioxidant: Vitamin C is an acidic molecule with strong reducing activity and is an essential component of most living tissues. It has two major redox forms: Ascorbic acid and dehydro-ascorbic acid (DHA), the reduced and oxidised form, respectively, and they are all inter convertible. Within the cell DHA is rapidly converted to ascorbic acid by the specific enzyme systems like DHA reductase, glutaredoxins and protein disulfide isomerase in presence of glutathione or other thiols as electron donors. Unlike ascorbic acid, DHA is relatively unstable and undergo rapid spontaneous irreversible hydrolysis particularly at a pH>4. \cite{5}
- Vitamin C as a reducing agent for transition metals: Few transition metals like Fe(III), Cu(II), Hg(II), Cr(VI) are able to accept electron from ascorbic acid, resulting in their reducing and simultaneous oxidation of ascorbic acid to DHA. In presence of strong biological oxidants like oxygen, hydrogen peroxide the oxidation of ascorbic acid is accelerated, where the metal ions act predominantly as catalyst.
- Vitamin C as an anti-\textit{H. pylori} agent: Normally ascorbic acid is actively secreted from plasma to the gastric juice. High concentration of ascorbic acid in
gastric juice favour reduction of Ni^{2+} centres, coordinated to the histidine residues of the urease, secreted from H. pylori, leading to inactivation of the enzyme followed by acid denaturation (Figure 1). This reduction of the transition metal ion by ascorbic acid, also accelerated at low pH of gastric juice as in case of reduction of ferric iron by Ascorbic acid.

In low gastric pH, once urease is inactive it becomes difficult for H. pylori to survive and colonise in stomach. But once it successfully colonises into stomach wall, H. pylori stays within the gastric mucosa, where the pH is suitable for the survival of the bacteria, due to the bicarbonate buffer from gastric epithelium secreted into the luminal surface. Patients with already low serum ascorbic acid likely to be more prone to get infection by H. pylori, because low ascorbic acid in gastric juice might favour colonization by the bacteria. Moreover low antioxidant level in chronically infected gastric mucosa, causes elevation of reactive oxygen species (ROS) contributing perpetuation of inflammation and infection cycle.6

**When to supplement Vitamin C?**

Vitamin C supplementation at a dose of 500mg b.d. following triple therapy seems to be quite effective as shown from a preliminary study by Sezikli et al.7 More clinical trials are required in this direction to determine the optimum dosage and regimen keeping in mind the increasing pro-oxidative role of vitamin C at higher dose (500mg/day) as observed by Podmore et al.8 However, a few recent studies report an increased eradication of H. pylori when triple therapy was supplemented with vitamin C.9

**Structural features of H. pylori Urease**

In the active site of urease these are two Ni^{2+} centres held by co-ordination bonding. Ni(I) is coordinated by two imidazole ligands from two histidine residues and a water molecule Ni(II) is coordinated by two histidine residues as well as with an aspartate and a water molecule. Supramolecular assembly of urease create a pore within the complex which serves as a pathway for diffusion of urea toward the 12 clutered active sites which protect each other from acid inactivation by producing localised cloud of ammonia from breakdown of urea.10

**Conclusions**

The role of ascorbic acid as anti H. pylori agent in peptic ulcer diseases is most likely to be preventive rather than curative. Rather than supplementing high doses of ascorbic acid along with conventional anti-pylori regimen it is preferable to complete the standard course of anti-pylori regimen which might then be followed by vitamin C supplementation therapy for extended period which would prevent from reinfection in susceptible subjects. Considering the short biological half life of this water soluble vitamin and the chances of toxicity from single daily bolus dose, split multiple doses/sustained release formulations would be more effective to maintain constant protective level of vitamin C in plasma and gastric juice.

**References**


**About the Authors**

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Chronic fatigue syndrome (CFS) has no clear cause.
common in persons in their 40s and 50s. In children, the typical age of onset is 13 to 15, but cases can occur in those as young as 5 years (see the box on this page). The condition affects persons of all ages, social classes, and ethnic groups. Overall, the evidence suggests a population prevalence of at least 0.2% to 0.4%. In a primary care setting, it is possible that 40 of every 10,000 patients have CFS.

CFS is two to four times more common in women than in men and is more frequently reported in the United States and Canada than in the rest of the world. However, sex has not been confirmed as a risk factor for CFS because women may be more likely than men to report their symptoms.

At least 25% of persons who have CFS are unemployed or are receiving disability payments. The CDC has estimated that the average family affected by CFS forges almost US$20,000 annually in lost earnings and that CFS costs the United States US$9.1 billion per year in lost productivity.

### Etiology

#### Possible Causes

CFS has no clear cause. The following conditions have been proposed as possible causes:

- **Hypoglycaemia**
- **Viral infection, such as Epstein-Barr virus or human herpesvirus 6 (HHV6) infection**
- **Imune system dysfunction**
- **Hypothalamus, pituitary, or adrenal gland dysfunction**
- **Mild chronic hypotension**
- **Peripheral neuropathy**

Although some reports mention that depression, iron deficiency, allergies, thyroid dysfunction, and neuritis are possible causes of CFS, they rather can cause fatigue or may be co-occurring conditions. In most patients with CFS, no serious underlying infection or disease has been found.

### A Three-stage Illness

A consensus has emerged in considering CFS as a three-stage illness that involves predisposing, precipitating, and perpetuating factors.

#### Predisposing Factors

Studies of twins suggest that genetic predisposition plays a role in CFS,
which may help explain the slightly higher than expected familial incidence.13 Profiles in the peripheral blood of patients with CFS and that of age- and sex-matched healthy subjects were conducted using a custom microarray carrying complementary DNA probes for 1,467 stress-responsive genes. The genetic profiles identified 12 genes whose messenger RNA levels were changed significantly in CFS patients. Quantitative real-time analysis validated the changes in nine genes encoding in activated T or natural killer cells, energy regulators, proteasome subunits, putative protein kinase inhibitors, and signal transducers and activators of transcription. The results of these genetic studies suggest that the defined gene cluster (nine genes) may be useful for detecting pathological responses in CFS patients.

Precipitating Factors
Many patients with CFS report that their illness followed an infection.12–16 A wide variety of viral infections—including glandular fever, hepatitis, meningitis, and parvovirus and entrovirus infections—are known to trigger CFS. Non-viral infections such as Q fever (Coxiella burnetii infection) are occasionally implicated as well. Although infections are a common trigger, most current evidence suggests that persistent viral infection is not part of the ongoing pathology. Immunizations, organophosphate pesticides, toxins, and physical trauma have been reported as the principal trigger in a small minority of cases. About 25% of patients with CFS describe a gradual onset of their illness with no obvious precipitating factor.

Perpetuating Factors
There is evidence, some of it replicated, to indicate that abnormalities in the central and autonomic nervous systems, possibly linked to a viral trigger and ongoing immune system dysregulation, play a key role in the pathophysiology of CFS.14 Recently, scientists identified a virus in 68 of 101 patients who had received a diagnosis of CFS. Whether the virus known as xenotropic murine leukemia virus causes the syndrome is still unclear.17

"Thyroid function tests are useful in ruling out other disorders that may be associated with fatigue"

Diagnostic Criteria

CDC Criteria
The diagnostic criteria for CFS were defined by the CDC in 198813, these criteria were revised in 2001. They are summarized in Table 1.

The major inclusion criterion is clinically evaluated, unexplained, persistent, or relapsing fatigue that is of new or definite onset, not a result of ongoing exertion, and not alleviated by rest and that results in a substantial reduction in previous levels of occupational, social, or personal activity.

The minor inclusion criterion is the presence of four or more of the following symptoms that persist or recur during 6 or more consecutive months of illness and that do not predate the fatigue:
- Self-reported impairment of short-term memory or concentration
- Sore throat
- Tender lymph nodes
- Muscle pain
- Multi-joint pain without swelling or redness
- Headaches of a new type, pattern, or severity
- Unrefreshing and/or interrupted sleep
- Post-exertion malaise lasting more than 24 hours.

Exclusion criteria include the following:
- Active, unresolved, or suspected disease that is likely to cause fatigue
- Depression with psychotic or melancholic features, bipolar depression (but not uncomplicated major depression)
- Psychotic disorders
- Dementia
- Anorexia or bulimia nervosa
- Alcohol or other substance abuse
- Severe obesity

Oxford Criteria
The Oxford criteria differ slightly from the CDC criteria in that they emphasize the presence of mental fatigue.15,16,18,19 The major inclusion criterion is severe disabling fatigue of at least 6 months’ duration that affects both physical and mental functioning and is present more than 50% of the time. Other symptoms, particularly myalgia and sleep and mood disturbances, may be present.

The exclusion criteria are similar to those of the CDC; however, the Oxford criteria do not list substance abuse or severe obesity.
Additional Symptoms
Although the symptoms described here are the official diagnostic criteria, many patients with CFS also have a variety of other symptoms, which are listed in Table 2.15,16,18-20

Evaluation

History and Physical Examination
Obtain a detailed history that includes an assessment of predisposing, precipitating, and perpetuating factors; sleep disturbances; and psychosocial stressors.2-4,10,14 In addition, perform a complete physical examination. The initial examination may reveal the following signs:
- Low blood pressure, particularly orthostatic hypotension
- Low oral temperatures (less than 36.1°C [97°F])
- Slightly elevated oral temperatures (but less than 37.7°C [100°F]), which are part of a constellation of persistent flu-like symptoms
- Tachycardia
- A positive Romberg sign

Laboratory Studies
These tests can be used to exclude other diseases associated with fatigue.12-16 The most consistent laboratory abnormality in patients with CFS is an extremely low erythrocyte sedimentation rate (ESR), which approaches zero. Typically, patients with CFS have an ESR of 0 to 3 mm/h. A normal ESR or one that is in the upper reference range suggests another diagnosis.

Thyroid function tests—chiefly, measurement of thyroid-stimulating hormone—are useful in ruling out other disorders that may be associated with fatigue. In addition, consider ordering adrenal tests (with measurement of morning and evening cortisol levels), Lyme titres, and HIV serology.

Results of liver function tests are typically normal in patients with CFS. Increased levels of serum transaminases, alkaline phosphatase, or lactic dehydrogenase should prompt a search for another disorder. Urinalysis findings are usually unremarkable.

The white blood cell count in patients with CFS is also typically normal. Leukopenia, leukocytosis, or an abnormal cell differential count indicates a diagnosis other than CFS.

Results of serum protein electrophoresis are normal in patients with CFS, but this test may be used to rule out other diseases that cause fatigue, including lymphoma and myeloma.

Patients with CFS may have two or three of the following abnormalities:
- Elevated IgM/IgG coxsackievirus B titre
- Elevated IgM/IgG HHV6 titre
- Elevated IgM/IgG Chlamydia pneumoniae titre
- Decreased natural killer cells, either the percentage or their activity

Although no laboratory abnormality is specific for CFS, the pattern of findings can support the

<table>
<thead>
<tr>
<th>Table 2. Non-diagnostic symptoms associated with chronic fatigue syndrome</th>
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<tbody>
<tr>
<td>- Allergies</td>
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<td>- Chemical sensitivities</td>
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<td>- Cognitive impairment, including short-term memory loss and difficulty in concentrating and in doing word searches and math problems</td>
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<td>- Cystitis, particularly interstitial cystitis in a patient whose urine cultures are negative</td>
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<td>- Digestive disturbances, such as chronic constipation or diarrhoea</td>
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<td>- Headaches, migraines</td>
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<tr>
<td>- Night sweats or spontaneous daytime sweats, unaccompanied by fever</td>
</tr>
<tr>
<td>- Pain (almost universal in patients with CFS)</td>
</tr>
<tr>
<td>- Premenstrual syndrome</td>
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<tr>
<td>- Secondary infections, including Candida and viral infections</td>
</tr>
<tr>
<td>- Sleep disorders, including excessive sleep (hypersomnia), light sleep, or an inability to sleep for more than an hour (hyposomnia), which at times is a result of recurrent nightmares. Fatigue associated with sleep disturbance may persist from 1 to 3 hours after awakening; during this period, patients are too exhausted to get out of bed (dysania)</td>
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<tr>
<td>- Vision and eye problems, including sensitivity to light (photophobia), dry eyes, tunnel vision, night blindness, and difficulty in focusing</td>
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<tr>
<td>- Weakness, muscle fatigue, and myalgia</td>
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CFS = chronic fatigue syndrome.
### Table 3. Differential diagnosis of chronic fatigue syndrome

<table>
<thead>
<tr>
<th>Category</th>
<th>Diagnoses</th>
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<tbody>
<tr>
<td>Endocrine and metabolic disorders</td>
<td>Addison disease, hypothyroidism, hyperthyroidism, adrenal insufficiency, Cushing disease, diabetes mellitus, haemochromatosis, hypercalcaemia, hypocalcaemia, fluid retention syndrome</td>
</tr>
<tr>
<td>GI disorders</td>
<td>Celiac disease, Crohn disease, irritable bowel syndrome</td>
</tr>
<tr>
<td>Infections</td>
<td>Infectious mononucleosis (chronic Epstein-Barr virus infection), influenza, tuberculosis, brucellosis, giardiasis, hepatitis B and C, HIV infection, AIDS, Lyme disease, other viral infections (HHV6, retroviruses, enteroviruses, parvovirus), post-polio syndrome, Q fever toxoplasmosis</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Hodgkin lymphoma, pituitary tumour, occult malignancy</td>
</tr>
<tr>
<td>Respiratory disorders</td>
<td>Sarcoïdosis, obstructive sleep syndromes (sleep apnoea, narcolepsy)</td>
</tr>
<tr>
<td>Rheumatologic disorders</td>
<td>Fibromyalgia, Sjögren syndrome, systemic lupus erythematosus, rheumatoid arthritis, polymyalgia rheumatica, giant cell arteritis, polymyositis</td>
</tr>
<tr>
<td>Neuromuscular disorders</td>
<td>Chiari 1 malformation, Parkinson disease, multiple sclerosis, myasthenia gravis, myopathies and neuropathies</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Mood disorders (depression, bipolar disorder), anxiety disorders (generalized anxiety disorder, panic disorders, post-traumatic stress disorder), psychotic disorders (schizophrenia, schizoaffective disorder, delusional disorders), somatiform disorder, sleep disorders, dementia, eating disorders (anorexia, bulimia), alcohol or other substance abuse</td>
</tr>
<tr>
<td>Medication effects</td>
<td>Adverse effects secondary to medications used to treat medical and psychiatric conditions</td>
</tr>
<tr>
<td>Other causes</td>
<td>Gulf War syndrome, nasal obstruction (allergies, sinusitis, anatomic abnormalities), chronic illness (congestive heart failure; renal, hepatic, and pulmonary diseases; autoimmune conditions), heavy metal exposure and toxicity (eg, lead), body weight fluctuation (severe obesity or marked weight loss)</td>
</tr>
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GI = gastrointestinal; HHV6 = human herpesvirus 6.

diagnosis in patients with cognitive dysfunction in whom other diseases have been excluded as a cause of fatigue. Controversial laboratory tests that are not indicated in the workup of CFS are listed in the box on page 102.

### Imaging Studies

CT or MRI scanning of the brain is useful for ruling out CNS disorders in patients with otherwise unexplained CNS symptoms. Results of CT and MRI scans may be normal in patients with CFS. Positron emission tomography scans may show hypoperfusion in the frontoparietal/temporal region. The results of CNS imaging studies are not specific for CFS and are thus used to rule out other conditions rather than to diagnose CFS.

### Differential Diagnosis

Other disorders that are associated with fatigue must be distinguished from CFS. The differential diagnosis is listed in Table 3. Conditions that are characterized by chronic fatigue should initially be ruled out; these include fibromyalgia, hypothyroidism, and Lyme disease. In veterans who served in Operation Desert Shield/Desert Storm, Gulf War syndrome should be excluded.

### Fibromyalgia

The American College of Rheumatology guidelines recommend testing 18 points of body tenderness; the presence of at least 11 of the points may indicate fibromyalgia. Although many clinicians find these guidelines controversial, trigger points are characteristic of fibromyalgia; they are not present in patients with CFS.

Most patients with fibromyalgia are female and have a chief complaint of ‘hurting all over, all the time’. The constant pain in those with fibromyalgia is usually described as burning, aching, and associated with soreness. The location of the pain migrates, and its intensity varies. Many patients report only a single painful area, such as the low back or neck. Most patients also
have morning stiffness of variable duration. In addition, concurrent restless legs syndrome is common.

Hypothyroidism
This condition typically manifests as a general slowing in physical and mental activity, but in some patients it may be asymptomatic. Classic manifestations include cold intolerance, puffiness, decreased sweating, and coarse skin; however, symptoms and signs are often subtle and are neither sensitive nor specific. Hypothyroidism can be differentiated from CFS on the basis of clinical suspicion, and the diagnosis can be confirmed by laboratory testing.

“Conditions that are characterized by chronic fatigue should initially be ruled out”

Lyme Disease
This disease can be differentiated from CFS in various ways. Patients who live in areas with endemic Lyme disease may have elevated IgG Lyme titres. Some patients have neuroborreliosis; this diagnosis is made on the basis of simultaneous measurement of cerebrospinal fluid (CSF) and serum IgM and IgG Lyme titres. CSF titres that are higher than serum titres indicate neuroborreliosis. Acute Lyme disease usually has a neurological component, but chronic neuroborreliosis is distinctly uncommon. Patients with chronic neuroborreliosis do not have the same cognitive defects as patients with CFS and usually do not present with fatigue as their chief complaint.

Gulf War Syndrome
Gulf War syndrome, or Gulf War illness, has been used to describe a constellation of chronic signs and symptoms reported by US, British, Canadian, Czech, Danish, Saudi, Egyptian, Australian, and other Coalition Armed Forces who were deployed in 1990 to 1991 during Operation Desert Shield/Desert Storm. It is estimated that 1 in 4 of the 697,000 US Gulf War veterans has this condition.

The syndrome is characterized by disabling fatigue, intermittent fever, night sweats, arthralgia, myalgia, headache, rashes, intermittent diarrhoea, abdominal bloating, chronic bronchitis, photophobia, transient visual scotomata, short-term memory impairment, confusion, irritability, and depression. The symptoms are not localized, and the signs and routine laboratory test results are not consistent with a single, specific disease. The incidence of amyotrophic lateral sclerosis may also be higher in Gulf War veterans. In addition, an increase in birth defects and stillbirths, as well as in cases of motor neuron disease and leukaemia, has been reported among children of these soldiers.

Controversial laboratory tests
The following tests, which are often promoted as diagnostic of chronic fatigue syndrome, are generally not indicated; they add only an unnecessary burden for patients and primary care clinicians:
- Extensive immunological testing, which may show low natural killer cell counts; elevated levels of interferon alpha, tumor necrosis factor α, and interleukin-1 and -2; T-cell activation; altered T4:T8 cell ratios; low T-cell suppressor cell (T8) count; fluctuating B- and T-cell counts; antinuclear antibodies; immunoglobulin deficiency; and antithyroid antibodies
- Tests for viral infections, such as those caused by cytomegalovirus, Epstein-Barr virus, human herpesvirus 6, and coxsackievirus
- Assessments of oxidative stress
- Measurement of homocysteine levels
- Measurement of C-reactive protein levels
- Toxin analysis, including heavy metals, pesticides, and organic chemicals
- Measurement of red blood cell magnesium levels
- Allergy testing, particularly serological tests for Candida

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