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Nephrology

Management of Vascular Access: Asian Consensus Conference Recommendations on Dialysis Catheter Selection

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Coming in the September 2012 Issue of Medical Progress

• In Focus •

Diabetes
• Management of Type 1 Diabetes Mellitus
• Glycaemic Management of Type 2 Diabetes
• Reducing Cardiovascular Risk in Type 2 Diabetes Mellitus

and more!
A reduced ankle brachial pressure index is taken as evidence of peripheral vascular disease. Similarly, a difference in systolic blood pressure between the two arms of $>15$ mm Hg may be evidence of atherosclerosis. Guidelines recommend measuring the blood pressure in both arms in patients presenting with hypertension, but it is rarely done in UK general practice.

A systematic review and meta-analysis has included 20 studies. In five angiographic studies, subclavian stenosis of $>50\%$ was associated with a mean difference of 36.9 mm Hg in systolic pressure between the arms, and a difference of 10 mm Hg or greater was associated with a ninefold increase in likelihood of subclavian stenosis. Pooled data from non-invasive studies included 20 studies. In five angiographic studies, subclavian stenosis of $>50\%$ was associated with a mean difference of 36.9 mm Hg in systolic pressure between the arms, and a difference of 10 mm Hg or greater was associated with a ninefold increase in likelihood of subclavian stenosis. A genetic study has illustrated the connection between the Y chromosome and coronary disease in men.

Genotyping was performed on 11 markers of the MSY in 3,233 unrelated British men from three established cohorts. Each Y chromosome was tracked back to one of 13 ancient lineages (haplogroups), and the risk of coronary disease was related to haplogroup. Two haplogroups (R1b162 and I) accounted for 90% of Y chromosome variants. Carriers of haplogroup I had a 56% increase in risk of coronary disease compared with other haplogroups, independently of common cardiovascular and socioeconomic risk factors. Studies on macrophage transcriptome in men from one of the cohorts pointed to common genes related to inflammation and immunity.

The Y chromosome may play an important part in determining cardiovascular risk in men.


Closure of patent foramen ovale vs medical therapy after cryptogenic stroke

Up to 40% of acute ischaemic strokes are
New LDL cholesterol-lowering agent

The serine protease, proprotein convertase subtilisin/kexin type 9 (PCSK9) binds to LDL receptors and increases LDL cholesterol levels. REGN727 is a monoclonal antibody to PCSK9. Three phase I trials in the USA have shown that REGN727 is effective in lowering LDL cholesterol levels.

In a study on healthy volunteers, 40 subjects were given a single intravenous dose of REGN727 and 32 received a subcutaneous dose. The least squares mean decrease in LDL cholesterol level was up to 65% compared with placebo. The decrease was dose-dependent and lasted up to day 64. Two subsequent trials were randomized, placebo-controlled, multidose trials of REGN727 in 21 adults with heterozygous familial hypercholesterolemia on atorvastatin and 40 adults with non-familial hypercholesterolemia (30 on atorvastatin and 10 on a modified diet). REGN727 was given in doses of 50, 100, and 150 mg subcutaneously on days 1, 29, and 43. No subject on REGN727 had to discontinue because of adverse events. The successive doses lowered LDL cholesterol levels by 30.2%, 53.7%, and 61.0%, respectively, in atorvastatin-treated subjects.

REGN727 is effective in reducing LDL cholesterol levels. Further studies will assess the therapeutic potential of REGN727.


Computed tomographic angiography in possible acute coronary syndromes

Patients presenting to the emergency department with chest pain consistent with an acute coronary syndrome are often admitted to hospital, but most receive an alternative diagnosis. A US multicentre study has shown that coronary computed tomographic angiography (CCTA) might allow many of these patients to be sent home safely.


Rheumatoid arthritis, atrial fibrillation, and stroke

Rheumatoid arthritis is associated with increased risk of myocardial infarction and cardiovascular death. Now, a Danish national register study has shown that rheumatoid arthritis is also associated with increased risk of atrial fibrillation and stroke.

The study included all people in Denmark aged >15 years and without rheumatoid arthritis, atrial fibrillation, or stroke before 1997. Data were obtained from national inpatient and outpatient registers, and 18,247 people with rheumatoid arthritis were identified. The incidence of atrial fibrillation between 1997 and 2009 was 6.0 per 1,000 person-years in the general population and 8.2 per 1,000 person-years in people with rheumatoid arthritis. Rheumatoid arthritis increased the risk of atrial fibrillation significantly by 41%. The rate of stroke was 5.7 per 1,000 person-years in the general population and 7.6 per 1,000 person-years in people with rheumatoid arthritis, a significant 32% increase in risk.

Rheumatoid arthritis increases the risk of both atrial fibrillation and stroke. These risks should be borne in mind during the follow-up of people with rheumatoid arthritis.
A total of 1,370 patients with low-to-intermediate risk were randomized (2:1) to CCTA or standard care. The rate of discharge from the emergency department was 50% (CCTA) vs 23% (controls). In the CCTA group, 640 in 908 (70.5%) had a normal CCTA and none of these died or had a myocardial infarction within 30 days. The rate of detection of coronary disease was 9.0% (CCTA) vs 3.5% (controls).

The use of CCTA in the emergency department could allow more patients to be discharged safely.

Litt HJ et al. CT angiography for safe discharge of patients with possible acute coronary syndromes. NEJM 2012; 366: 1393–1403.

**GENERAL MEDICINE**

**Methotrexate refractory early rheumatoid arthritis: Sulfasalazine plus hydroxychloroquine vs infliximab as add-on therapy**

About 20–40% of patients with recent-onset rheumatoid arthritis respond well to treatment with methotrexate alone. For methotrexate refractory disease, there is uncertainty about the best add-on therapy. The Swedish Farmacotherapy (Swefot) trial, reported in 2009, showed better clinical outcomes at 1 year with added infliximab (an anti-tumor necrosis factor agent) compared with added sulfasalazine plus hydroxychloroquine (disease-modifying antirheumatic drugs [DMARDs]). Now, the 2-year results have been reported.

The study included 487 patients with rheumatoid arthritis for less than 1 year who received methotrexate for 3 months. A total of 258 non-responders were then randomized to added sulfasalazine and hydroxychloroquine (SSZ-HCQ) or added infliximab (INF). The proportion with a good European League Against Rheumatism response was 38% (INF) vs 29% (SSZ-HCQ) at 18 months and 38% vs 31% at 24 months, non-significant differences.

Radiological progression at 24 months was significantly greater with SSZ-HCQ than with INF. One patient in the SSZ-HCQ group and two in the INF group had serious adverse events.

These researchers conclude that, despite the better radiological appearances at 24 months in the INF group, the lack of significant clinical differences between the two groups at 24 months makes add-on DMARD treatment an appropriate option for patients who fail to respond satisfactorily to methotrexate. There is evidence, however, that adding a tumor necrosis factor inhibitor earlier might be beneficial.


**NEUROLOGY**

**Laquinimod for multiple sclerosis**

A total of 1,106 patients with relapsing–remitting multiple sclerosis were randomized at 139 sites in 24 countries to receive oral laquinimod 0.6 mg daily, or placebo, for 24 months. The mean annualized relapse rate was 0.30 (laquinimod) vs 0.39 (placebo), a significant difference. There was also a significant reduction in risk of confirmed disability progression (11.1% vs 15.7%). The cumulative number of gadolinium-enhancing lesions was also significantly reduced (1.33 vs 2.12), as was the number of new or enlarging lesions on T2-weighted images (5.03 vs 7.14). Transiently raised alanine aminotransferase levels were recorded in 24 patients (laquinimod) and eight (placebo).

Treatment with laquinimod reduced the rate of relapse and slowed disability progression.


**ONCOLOGY**

**PSA testing and prostate cancer mortality**

In 2008, a US task force recommended that prostate-specific antigen (PSA) screening for prostate cancer should not be offered to asymptomatic men. Now, follow-up in the European Randomized Study of Screening for Prostate Cancer has been extended to 11 years.

The study included 182,160 men aged 50–74 years (162,388 aged 55–69 years) in eight European countries. Randomization was to PSA screening or no PSA screening. After an average
Global Summaries

The trial, at 65 centres in the USA and Canada, included 289 men aged 48–82 with low-volume Gleason score 5–6 prostate cancer and at least one repeat biopsy during follow-up. They had all chosen active surveillance rather than more aggressive treatment. Randomization was to dutasteride 0.5 mg daily or placebo, and follow-up was for 3 years with repeat biopsies at 18 months and 3 years. At 3 years, the rate of prostate cancer progression was 38% (dutasteride) vs 48% (placebo), a significant difference. The rates of adverse events were similar in the two groups. Sexual adverse events or breast enlargement occurred in 24% vs 15%. There were no deaths from prostate cancer, and no subject developed metastatic disease. Cardiovascular adverse events occurred in 5% of each group.

Dutasteride might benefit men with low-risk prostate cancer who choose active surveillance. A Lancet commentator, however, points to previous evidence that dutasteride might have no effect on prostate cancer mortality (or might even increase the risk) and concludes that dutasteride, or any other treatment, cannot be recommended for these men. He believes that neither treatment nor diagnosis should be attempted for low-risk disease.


Aspirin and cancer prevention

Two successive papers in the Lancet have addressed the anticancer effects of aspirin. Data from all five large randomized trials in the UK of aspirin versus control for cardiovascular prophylaxis have been reanalysed from the point of view of an effect on cancer metastasis. A total of 17,285 subjects were followed up for an average of 6.5 years, and 987 developed a new solid cancer during follow-up.

Among subjects randomized to aspirin, the risk of cancer with distant metastases was reduced significantly by 36% overall. For adenocarcinoma, the reduction was 46%. For other solid tumours, there was a non-significant 18% reduction. There was a highly significant reduction of 48% in the proportion of adenocarcinomas with metastatic rather than local disease. Aspirin reduced both the risk of metastasis at diagnosis of adenocarcinoma and the risk of subsequent metastasis, especially in patients with colorectal cancer. Aspirin was associated with reduced cancer mortality among patients who developed adenocarcinoma and also reduced the overall risk of fatal adenocarcinoma in trial participants. The effect was greatest in smokers.

A search of the world literature has identified 51 trials of aspirin versus control (77,549 subjects) for cardiovascular prophylaxis. Aspirin reduced cancer deaths significantly by 15%, particularly after 5 years or longer. Non-vascular deaths were reduced significantly by 12%. In trials of primary prevention, 91% of deaths prevented would have been non-vascular deaths. In six trials of low-dose aspirin for primary prevention, aspirin reduced cancer incidence after 3 years, by 24% in women and 25% in men. The absolute reduction in cancer risk from 3 years onwards amounted to 3.13 per 1,000 patients per year.

Aspirin reduces the risk of metastasis from adenocarcinomas as well as the overall incidence of and mortality from cancer. Lancet commentators remain wary about recommending general use of aspirin for cancer prevention.

Management of Vascular Access: Asian Consensus Conference Recommendations on Dialysis Catheter Selection

Tal MG, MD, MBA; Lai KN, MBBS, MD, DSc, FRCP (Lond), FRCP (Edin), Hon FRCP (Glas), FRCPath, FACP, FRACP, FAMS, FSCP, FHKCP, FHKAM; Lau T, MD, MRCP, FRCP; Yang WC, MD; Hsieh HC, MD; Ye CY, MD; Kim HC, MD; Choong HL, MBBS, M Med (Int Med), FAMS; Ungkitphaiboon W, MD; Wong HS, MD, M Med (Int Med), AM, FRCP (Edin); Ronsayro ARP, MD, FPCS, FPSTS, FPSVS, Diplomate, Philippine Board of Surgery; Bhalla A, MD, DM, MNAMS, FISM, MBBS

Placement and maintenance of effective haemodialysis vascular access is essential for safe and efficacious haemodialysis therapy. However, access-related complications remain one of the most important causes of morbidity amongst patients with end-stage renal disease. Optimizing vascular access is an ongoing clinical challenge, and a number of questions regarding access management remain to be answered.

Introduction

In Asia, end-stage renal disease (ESRD) is a significant public health issue. Recent evidence indicates that diabetic nephropathy is emerging as the most frequent cause of ESRD among newly diagnosed patients in many Asian countries. There also remains a significant proportion of patients with ESRD of undetermined aetiology. Many of these are classified as presumed chronic glomerulonephritis or chronic interstitial renal disease. Some may be related to hypertension, metabolic syndrome (without definite diabetes mellitus), and other cardiovascular risk factors (ischaemic nephropathy).

The acceptance and availability of dialysis
Nephrology

NEPHROLOGY

differ among countries in Asia and even between regions within a large country like India and China. Rural areas with low socioeconomic profile are particularly affected. Maintenance dialysis over the long term requires significant health-care cost that is beyond many individuals and their community in many parts of Asia.

While arteriovenous (AV) fistula is the best suited access for long-term haemodialysis, this option may not be possible in certain clinical settings. AV fistula requires preparation and lead time before use (time for maturation). Many ESRD patients in Asia are reluctant to prepare for dialysis access when they are still in the asymptomatic phase of the disease. Hence, unplanned urgent initiation of dialysis is common along with the use of central venous dialysis catheters. This is probably the greatest contributor to widespread use of catheters for haemodialysis.

US data indicate that 60–65% of patients initiate haemodialysis with a catheter, and 46% remain catheter-dependent even 2 months after initiation of dialysis.\(^1\) Data from various national registries from countries in Asia also share similar pattern with majority of newly diagnosed ESRD patients being treated by haemodialysis (Figure 1), and two-thirds of these patients (65%) required urgent haemodialysis via a dialysis catheter.\(^1\) Patients also find it difficult to accept a diagnosis of irreversible organ (kidney) failure, especially if they have remained relatively asymptomatic up to the point of diagnosis. Many will discount the need to prepare for ESRD options (eg, dialysis and preparation for dialysis access), preferring to try traditional remedies and alternative non-medical means to overcome the fear of being on long-term dialysis. Eventually, they present acutely with uraemic or volume overload symptoms requiring urgent life-saving dialysis intervention via catheter.

Accessibility to specialized nephrology care is limited in many Asian countries. This is expected to improve in the coming decade, given the rapid economic expansion in Asia and the opportunity for many young doctors from this region to receive nephrology training in established nephrology units worldwide. The International Society of Nephrology has a very successful twinning programme – partnering a less developed nephrology/medical unit (many in Asia) with a more mature and sophisticated nephrology unit for the purpose of bridging the skill and knowledge gap. Despite the ongoing effort to improve care, many with chronic kidney disease have no access to nephrology care until very late in the disease process. This again will contribute to unplanned urgent initiation of dialysis, and many will be initiated with dialysis catheter because this is the most appropriate choice of access in urgent situation.

Despite central venous catheters (CVCs) playing an important role in the management of patients requiring haemodialysis under different circumstances (as discussed in the next section), the use of dialysis catheters is associated with numerous complications. The main disadvantages are infection, catheter dysfunction/inadequate dialysis, and venous thrombosis or stenosis. However, complications such as infection are fewer with the use of tunnelled permanent catheters as compared with those of acute catheter use.\(^4\) Moreover, in the ESRD population, there is a greater risk of death associated with catheter use as compared with AV fistula (3.4 vs 1.4-fold).\(^5\) Part of the mortality risk may be related to known complications with its use, but patient factors are significant confounders as patients requiring dialysis catheters often have exhausted all other means of access.

Figure 1. Treatment modalities in newly diagnosed Asian patients with end-stage renal disease (n = 168).\(^1\)

<table>
<thead>
<tr>
<th>Conservative</th>
<th>Haemodialysis</th>
<th>Peritoneal dialysis</th>
<th>Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>20</td>
<td>60</td>
<td>20</td>
</tr>
<tr>
<td>Chinese</td>
<td>20</td>
<td>60</td>
<td>20</td>
</tr>
<tr>
<td>Malay</td>
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<td>Indian</td>
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<td>20</td>
</tr>
<tr>
<td>Other</td>
<td>20</td>
<td>60</td>
<td>20</td>
</tr>
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</table>
and tend to have pre-existing vascular disease and underlying immune dysfunction, and are more prone to infection.

As such, optimizing vascular access is an ongoing clinical challenge, and numerous questions regarding the preferred treatment of catheter thrombosis, the prevention and optimal clinical management of catheter-related bacteraemia (CRB), and which catheters with low dialysis blood flows require thrombolytic therapy remain to be answered.4

**Recommendations for Dialysis Catheter Selection Management**

To date, there are no formalized Asian guidelines for vascular access. The Asia Dialysis Clinical Advisory Board meeting was held in Shanghai to bring nephrologists, vascular and cardiothoracic surgeons, and radiologists from around the region together to share their country-specific experiences with dialysis and to gain a greater understanding of the challenge of managing Asian patients with ESRD. The meeting was organized under an unrestricted grant from Covidien Asia Pacific.

Based on the available evidence and clinical experience, the authors have formulated a number of consensus recommendations for the selection of dialysis catheters (Boxes 1–3). The panel noted that procedural complications associated with haemodialysis catheter placement are rare and have been reported to be less than 3–5%.9 However, the complication rate varies in accordance with the operator’s technical proficiency. Therefore, ultrasound or fluoroscopy is required for dialysis catheter insertion. The choice of catheter should reflect not only the clinical setting but also the design of the lumen, diameter, and length.

### Box 1. Consensus recommendations for acute versus chronic catheters

**Non-cuffed dialysis catheter**

In clinical practice, non-cuffed catheters are used for up to 3 weeks. A chest X-ray should be conducted to confirm tip placement. Catheter exchange can be done over the guidewire. For femoral catheter placement, the tip of the catheter should be in the inferior vena cava.

**Cuffed dialysis catheter**

The tunnelled cuffed dialysis catheter (TCC) can be used for months or years. It is recommended that TCC insertion is done under fluoroscopy. Recirculation on lumen reversal reduces treatment efficiency. For femoral cuffed catheter placement, the tip of the catheter should be in the lower right atrium.

### Box 2. Consensus recommendations for catheter placement

**Catheter tip placement**

The catheters placed through the internal jugular veins should reach the superior vena cava, and in case the femoral vein is the access site, the catheters should reach the inferior vena cava. The tunnelled cuffed dialysis catheter (TCC) tip should be placed in the mid to upper third of the right atrium.

**Preferred access site**

The right internal jugular vein placement is the preferred access site; femoral vein placement should be avoided. The panel’s recommended access sites in order of declining preference are

- Right internal jugular vein
- Right external jugular vein
- Left internal jugular vein
- Left external jugular vein
- Femoral vein/subclavian vein

The subclavian vein is preferred to the femoral vein for TCC in patients who have exhausted all possibilities to create an arteriovenous fistula. If the patient is considered for upper arm arteriovenous fistula creation, the subclavian vein is a last choice. Right-side jugular veins need to be exhausted before moving to left-side placement to prevent central vein stenosis. However, left-side cannulation can be used when right-side access is not possible.

**Non-traditional access site**

When peritoneal dialysis is not an option, non-traditional types of access should only be used if other upper extremities are not available. They include

- Translumbar TCC
- Transhepatic TCC (should only be done if translumbar is not possible)

### Clinical Indication for Dialysis Catheter

Although not the most ideal vascular access, CVCs are increasingly an inherent part of clinical practice. Catheters offer several distinct advantages including an assurance of high blood flow, immediate use following insertion, no requirement for an elaborate surgical suite, and adequate (usually) local anaesthesia. In addition, there are
no needling problems for nurses and hence no pain or soft tissue trauma to patients. Personnel training and accreditation are much easier to attain for CVC insertion.

In the acute setting, dialysis catheters may be indicated for an acute kidney injury requiring dialysis support or when there is acute, sudden, unexpected deterioration in a patient with pre-existing chronic kidney disease. Dialysis can also be initiated in patients with a late diagnosis of end-stage renal failure or those who decline AV access preparation when they require urgent dialysis. Asian patients with chronic kidney disease commonly present late with ESRD, and catheter access is often necessary in these patients as a temporary measure.

CVC may be required in ESRD patients with failed permanent access who require bridging access or those who have exhausted all sites for permanent access. It may also be considered as appropriate access in a selected ESRD population: patients with severe cardiac disease who require maintenance dialysis but may not tolerate an AV access; ESRD patients with limited life-expectancy (less than a year); patients with a needle phobia who are not suitable for peritoneal dialysis (PD); those with maturing PD access (ie, due to late insertion); those with temporary removal of PD access due to severe infection; and patients with anticipated kidney transplant soon after starting dialysis.

**Acute Versus Chronic Haemodialysis Dialysis Catheters**

The Kidney Disease Outcomes Quality Initiative’s clinical practice guidelines for vascular access recommend that non-cuffed, non-tunnelled (short-term) CVCs be used for a period of up to 1 week (usually in the acute setting). However, empirical antibiotics may be started when there is a high suspicion of clinical bacteremia. Antibiotic catheter lock solutions are effective as an adjunct to systemic antibiotics, with approximately 66% success rate. Early over-the-wire exchange is also recommended.

Chronic catheter removal should be avoided to prevent loss of the access site. The following steps are recommended for prevention of catheter-related infection:

- Proper aseptic technique should be strictly adhered to
- Elimination of *Staphylococcus aureus* nasal carriage
- Topical exit site application

**Tunnel infection management**

Preserve the vein insertion site and choose another exit site for the catheter. Using the same vein access point, it is possible to change the catheter to a temporary non-cuffed catheter, followed by creation of a new tunnel once the infection has cleared. Alternatively, changing to a new cuffed catheter with a new tunnel tract is possible.
NEPHROLOGY

“Infected complications are a major source of morbidity (and consequent risk of mortality) in patients undergoing haemodialysis with long-term TCCs”

Because the rigidity of the thermoplastic alters with temperature, it provides the needed stiffness (in room temperature) for ease of insertion but will ‘soften’ once it is in the vessel (body temperature). A softened or less rigid catheter will be less damaging to the vessel it occupies and has a lower risk of cardiac perforation as the tip of the TCC usually sits just past the entry into the right atrium.

Tunneled CVCs have a high success rate and can be inserted into multiple sites. Maturation time is not required; it negates the need for venipuncture and there are no haemodynamic consequences. These catheters are functional for months and are easily replaced. Thrombotic complications can be corrected with thrombolytic therapy. However, infectious complications are a major source of morbidity (and consequent risk of mortality) in patients undergoing haemodialysis with long-term TCCs. There may also be a risk of permanent central venous stenosis or occlusion in addition to patient inconvenience (of carrying an external catheter). However, TCCs are much better tolerated than non-tunneled CVCs as the point of catheter exit is downwards from the chest (unlike non-tunneled CVCs that is upwards in the neck). It is also difficult to be discreet when a patient is carrying a non-tunneled CVC because of the inherent nature of the position.

Catheter Selection

Ideally, double lumen catheters should be chosen because of their ease of use, fewer insertion complications, satisfactory flow rates, and lower infection rates. Tip geometry does not influence haemodynamic or catheter survival. The level of recirculation on lumen reversal reduces treatment efficiency.

Current evidence indicates that side holes may be detrimental to chronic catheter performance. A retrospective analysis comparing a cuffed, tunnelled, dual lumen catheter with side holes versus that without side holes reported similar mean blood flow rates and reduced infection rates per 1,000 catheter-days in catheters without side holes (2.545 vs 0.254; $P < 0.001$). Catheter infection

Arteriovenous fistula is the most ideal access for long-term haemodialysis.
necessitating removal occurred in 10 in 37 catheters with side holes and 1 in 17 without side holes.13 Furthermore, clots may be anchored to the walls around the different side holes. While in the short term, side hole catheters can decrease the overall resistance and provide a lower shear rate and therefore better flow, they also allow clots to adhere to the rough edges of the catheter. Therefore, in chronic catheters, side holes can increase the overall resistance. Side holes at the tip of chronic haemodialysis catheters are also thought to cause damage to the intima of the adjacent vessel.14 Intimal damage leads to thrombosis and vascular stenosis.

Challenges in Catheter Access

Catheter dysfunction may be caused by a malpositioned catheter tip, catheter kink (often caused by high access), development of a fibrin sheath, and/or thrombosis. Smooth muscle and endothelial cell deposition along the course of the catheter can cover and obstruct the end holes. The fibrin sheath propagates from a point of intimal injury or contact and extends up and down around the catheter. The fibrin sheath is the cause of not only catheter dysfunction but also central venous stenosis and it is closely associated with catheter-related infection. The development of thrombosis and subsequent development of a fibrin sheath are intimately linked. Therefore, thrombolytic therapy can be used for fibrin sheath management. One suggested protocol utilizes recombinant tissue plasminogen activator (r-TPA) infusion of 2.5 mg r-TPA in 50 mL normal saline at 17 mL/h for 3 hours per port. It has a patency rate of 67%, 61% and 51% at 30, 60 and 90 days, respectively. Urokinase can also be used in place of r-TPA. Similarly, infusion of urokinase is more effective than instillation/locking. Locking solution exerts its effect mostly for intraluminal clots and will be much less effective for externally enveloping fibrin sheath. Mechanical stripping is another intervention that is commonly employed. Should the decision be made to exchange the catheter, its fibrin sheath must be disrupted with the guidewire before placing the new catheter. Failure to do this will result in the new catheter being placed into the pre-existing sheath, leading to early catheter dysfunction.

Catheter thrombosis usually presents as flow problem encountered during haemodialysis treatment.2 It manifests as either suboptimal dialysis blood flow or in extreme cases by the inability to aspirate blood from the catheter port. The risk of developing catheter-related thrombosis may be reduced by

- using internal jugular vein access
- using small-diameter access catheters (devices should be chosen where the inner to outer diameter ratio is maximized to ensure good flow rates)
- good catheter tip positioning
- avoidance of left-sided catheter access
- the use of heparin-coated catheters
- the use of r-TPA as catheter lock

It is estimated that up to 50% of catheters either malfunction or need to be removed prematurely owing to infection.17 CRB is a serious complication and may be caused by the presence of bacteria on the biofilm coating the inside and/or outside of the catheter or bacteria migrating

Use of catheters is indicated for long-term vascular access when creation of an arteriovenous fistula or graft is not possible.
along the catheter from the exit site. Alternatively, CRB could potentially result from contamination during access manipulation (during use). Evidence indicates that non-side hole haemodialysis catheters are associated with a reduced catheter infection rate compared with catheters with side holes. Comparative data from 54 patients receiving a catheter demonstrated that catheter infection requiring catheter removal occurred in 10 in 37 catheters with side holes and 1 in 17 of those without. Infection rates per 1,000 catheter-days were 2.545 and 0.254, respectively ($P < 0.001$). One of the reasons for this observation may be that clot formed in the side holes served as a nidus for bacterial proliferation. However, it is worth noting that this reduction in infection rate associated with use of non-side holes catheter was at the expense of reliability in terms of flow rates.

While the optimal management of catheter-related infection is under debate, a catheter lock solution for prophylaxis against CRB has been shown to be effective. Gentamicin, minocycline, cefotaxime, taurolidine and 30% citrate lock solutions have all demonstrated efficacy. Retrospective data from haemodialysis patients admitted to a university teaching hospital in Hong Kong reported that the use of gentamicin lock solutions effectively reduced CRB (Figure 2), including patients with non-tunnelled catheters. Significant reductions in CRB episodes per 1,000 catheter-days were reported (Figure 1; $P = 0.002$). However, long-term use of antibiotic lock solution without antibiotic replacement is challenging, and attention is focused on the potential for evolution of resistant strains within the catheter. Meta-analytic data from five randomized controlled trials employing a follow-up period of approximately 12 months reported only one case of development of resistance, although no surveillance cultures were performed. It is important to note that these findings do not rule out the development of antibacterial resistance with longer, more extensive use of antibiotic lock solutions, and further studies are warranted.

Although catheter lock is intended as a ‘local treatment’, small amount of the lock solution will diffuse into the systemic circulation. High-concentration citrate has largely been discouraged because of this phenomenon for its association with complications related to citrate leak into the systemic circulation, especially with the 47% concentration. A lower-concentration 4% citrate (anticoagulant concentration) in combination with 30% ethanol has been shown in an in vitro study to be effective in CRB. A recent randomized controlled trial reported that once a week 1 mg r-TPA lock (in each lumen) is better than standard heparin lock in terms of catheter dysfunction and bacteremia rates (4.5% vs 13%). Other steps to minimize the risk of CRB include eradication of nasal carriage of *Staphylococcus*, exit site dressing with mupirocin, and chlorhexidine scrub before catheter insertion. It must be emphasized that the most effective measure of reducing risk of CRB is to reduce catheter-days (ie, restricting the use of catheters to the shortest period possible). Long-term permanent access planning and creation have to take place as soon as the catheter is in place.

In the acute setting, the reduction of thrombosis or microbial colonization may be successfully accomplished using catheters coated with antibiotics, silver, or heparin. The value of this approach in the chronic setting is less convincing and may be related to the disappearance of the bonded substance over time. It is hoped that heparin coating with antimicrobial, silver ion, and subcutaneous sleeve will reduce bacterial adhesion to the catheter. There are also ongoing efforts in bioengineering...
to develop a new synthetic material for the catheter that is inherently less thrombogenic and free from biofilm.

Summary

For ESRD patients to be successfully maintained on long-term haemodialysis, achieving effective vascular access is essential. Well-functioning vascular access for haemodialysis plays a key role in the quality of life and clinical outcome of maintenance haemodialysis patients. The use of CVCs has become more frequent in Asia (as it has worldwide) even though they are a temporary option, and the ideal solution is still a permanent access with the creation of AV fistulae. Access-related complications remain one of the most important causes of morbidity in this population. Proper implantation can avoid many of the complications associated with the placement of central venous access devices. When complications such as thrombosis or infections do occur, catheter-directed interventions are often the best management option. An integrated multidisciplinary approach to vascular access, involving nephrologists, vascular surgeons, interventional radiologists, and trained dialysis nurses, should be implemented in order to facilitate early detection of vascular access complications and failure. A successful multidisciplinary approach will reduce health-care costs and improve quality-adjusted life expectancy of the haemodialysis population in Asia.

Declaration of Interests

Michael Tal is a consultant for Covidien Inc.

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References

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.

How much do you know about rheumatoid arthritis?

1. The 2010 classification criteria for rheumatoid arthritis (RA) by the American College of Rheumatology and European League Against Rheumatism can be used as a diagnostic tool for RA.
2. The Multidimensional Health Assessment Questionnaire (MDHAQ) is a validated tool that measures the functional abilities of patients with RA.
3. The MDHAQ contains psychological items (ie, depression, anxiety, sleep disturbance, stress) which reflect organ system dysfunction.
4. Items on the MDHAQ can identify all activity limitations and always provide a complete picture of function.
5. Clinical observation of performance based on the MDHAQ may help identify patients with significant changes in function who can benefit from effective intervention.

See page 400 for answers
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.

Rheumatoid arthritis (RA) is a progressive immune-mediated disease involving the synovium that can culminate in joint destruction, significant functional impairment, and early mortality. An improved understanding of the pathogenesis over the past two decades has resulted in an explosion of effective therapeutic options. Consequently, there has been a paradigm shift in the approach to the treatment of patients who have RA—the emphasis now is on early initiation of effective disease-modifying antirheumatic drug (DMARD) therapy to prevent joint damage and achieve disease remission.

Years ago, it became apparent that the 1987 American College of Rheumatology (ACR)
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

Table. The ACR/EULAR 2010 classification criteria for RAa

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Joint involvement</td>
<td></td>
</tr>
<tr>
<td>1 large joint</td>
<td>0</td>
</tr>
<tr>
<td>2–10 large jointsb</td>
<td>1</td>
</tr>
<tr>
<td>1–3 small joints (with or without involvement of large joints)</td>
<td>2</td>
</tr>
<tr>
<td>4–10 small jointsc (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>B. Serology (at least one test result is needed for classification):</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 antibodiese</td>
<td>3</td>
</tr>
<tr>
<td>C. Acute phase reactants:</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>D. Duration of symptoms:</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; 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.

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 distal interphalangeal joints, first metatarsophalangeal joints, and first carpometacarpal joints because these joints typically are affected by osteoarthritis, and (2) the synovitis cannot be explained by another disease. Four criteria are then applied, resulting in a score of 0 to 10, with 6 or higher required for the classification of definite RA.
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.

Instead, significant weight is placed on serology, with the inclusion of anti–cyclic citrullinated protein antibodies, as well as 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, 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

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. 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, and it ranks among the common chronic illnesses with the worst quality of life. Within 10 years of diagnosis, 35% of patients with RA will be work-disabled. 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.
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.8–10 These recommendations are based on several studies that have shown improved outcomes for patients with RA based on quantitative measures of disease activity and treatment with intensive predetermined regimens of oral disease-modifying antirheumatic drugs (DMARDs) and biologic agents.11–16 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).17–22

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.23

“The MDHAQ is a validated tool that provides important information for assessing the functional abilities of patients with RA”

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

References
Understanding Function in RA: Importance and Measurement

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

The reasons why patients go to physicians to seek help for musculoskeletal problems, such as pain, difficulty in climbing stairs, and reduced work time, all are aspects of human function but refer to different aspects of function. In 2001, the World Health Organization published a classification to describe the health components of functioning and disability. Included is the entirety of a person’s health rather than just the consequences of his or her disease. Patient self-report measures, used in conjunction with routine office visits, provide a practical and feasible way of obtaining information about functional health. The Health Assessment Questionnaire, a frequently used tool, has played a major role in broadening the perspective of chronic disease management from biomedical measurements to include measurement of functional health.

Musculoskeletal problems are some of the main reasons why patients go to physicians or other healthcare professionals. The reasons for seeking help are quite variable. For example, a person may be experiencing persistent knee pain after a fall or noticing increased difficulty in walking up stairs or feeling that he or she is no longer able to work full-time because of joint symptomatology.

Although pain, difficulty in climbing stairs, and reduced work time all are aspects of human function, they refer to very different aspects of function—pain focuses on a part of the body, climbing stairs emphasizes a specific activity, and work time highlights a social role. In turn, these distinctions can have significant implications for the patient’s assessment and treatment.
Variations in application of the term ‘function’ also can prevent clear communication about functional problems among physicians and between physicians and their patients. The rheumatologist typically uses function in relation to a joint, the nurse in relation to a specific activity, and the occupational therapist in regard to a social role.

In this article, we first present a standardized vocabulary for describing function, based on the World Health Organization’s (WHO’s) International Classification of Functioning, Disability and Health (ICF) and then apply it to an assessment tool frequently used in rheumatology, the Health Assessment Questionnaire (HAQ).

**International Classification**

In 2001, the WHO published a classification—to be used in conjunction with the International Statistical Classification of Diseases and Related Health Problems (ICD-10)—to describe the health components of functioning and disability, namely, the ICF. Included in the ICF is the entirety of a person’s health rather than just the consequences of the disease.

**Classification Parts and Components**

The ICF classification has two major parts. The first part, labelled *Functioning and Disability*, identifies and defines various types of human function. It has two components, *Body Functions and Structures*, and *Activities and Participation*.

*Body Functions and Structures* refers to issues related to body systems, such as the joints, bones, and structures of the upper extremity. Dysfunctions in these body systems and functions, called impairments, include pain, joint contractures, and muscle weakness. In the ICD-10, impairments are the signs or symptoms of disease.

In *Activities and Participation*, the second component of *Functioning and Disability*, ‘activity’ refers to function at the level of the person rather than a body system and relates to the performance of tasks or actions. Stair climbing, bathing, dressing (Figure), cooking, and vacuuming are examples that illustrate the wide spectrum of activities.
Dysfunctions in activities are called activity limitations. Participation relates to a person’s involvement in a life situation, such as being a caregiver, student, secretary, or plumber. Dysfunctions in participation are called participation restrictions. Although there is no clear distinction between activities and participation, the latter typically involves a sequence of tasks and has a social aspect; activities may not have these features.

The second part of the ICF classification, labelled Contextual Factors, is composed of Environmental Factors and Personal Factors. These are factors that can significantly modify functional health, which encompasses the unique characteristics of a person that are considered in management interventions.

Environmental Factors include the various physical, social, and attitudinal environments in which patients live, work, and play. Stairs, lack of handicapped parking, and colleagues who do not understand fluctuations in functional health associated with arthritis are examples of negative environmental factors; low-rise ramps, adequate handicapped parking spaces, and hiring policies that implement reasonable accommodations (as defined by the Americans with Disabilities Act) are positive environmental factors. The Environmental Factors component of the ICF directs attention to these determinants of function.

Note that Personal Factors encompass individual characteristics that are not a part of the health condition per se but may have a significant influence on it. Examples are the person’s sex, age, race, and education level.

A Standardized Vocabulary
Thus, the Functioning and Disability part of the ICF provides a standardized vocabulary for designating dysfunction at the organ or organ system level (impairment), personal level (activity limitations), and societal level (participation restrictions). The Contextual Factors part includes the multitude of factors that can modify a person’s health and functional ability.

“The HAQ has played a major role in broadening the perspective of chronic disease management from biomedical measurements to include measurement of functional health”

Although management of patients’ impairments (abnormalities of body functions and structures) is a key to improving health, it does not necessarily reduce activity limitations or participation restrictions. Assessing manifestations of function as described by the ICF, and then providing interventions specific for them, helps health-care providers improve patients’ functional health, which, in turn, can affect biological health. Patient self-report measures, used in conjunction with routine office visits, provide a practical and feasible way of obtaining information about functional health.

Health Assessment Questionnaire

Many valid, reliable, and responsive self-report measures are available. The HAQ, a frequently used tool, was developed by Dr James Fries at the Stanford Arthritis Center in 1980. It was among the first ‘patient reported outcome’ measures.

The HAQ has played a major role in broadening the perspective of
chronic disease management from biomedical measurements to include measurement of functional health. Routine measurement of activities, and to some extent participation on the HAQ, helps define the consequences of the health condition (arthritis) and medical management on daily functions.

**Twenty Questions in Eight Categories**

The HAQ Disability Index (HAQ-DI) has 20 questions in eight categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities. Each category has two or three questions. Patients rate questions on a 0 to 3 scale: 0 means without difficulty; 1, with some difficulty; 2, with much difficulty; and 3, unable to do. The most limited activity in a category determines the category score. Use of assistive devices (eg, button hook) to perform an activity is taken into consideration in the scoring.

The HAQ-DI is the average score of the eight categories; it ranges from 0 to 3. Three additional items in the HAQ-DI query general physical ability, pain, and general health.

In 1999, Pincus and associates modified the HAQ-DI to simplify it and to incorporate evaluation of more strenuous activities. This modification, known as the Multidimensional Health Assessment Questionnaire (MDHAQ), retained eight items from the original HAQ—dress yourself, including tying shoelaces and doing buttons; get in and out of bed; lift a full cup or glass to mouth; walk outdoors on flat ground; wash and dry entire body; bend down to pick up clothing from the floor; turn regular faucets on and off; and get in and out of car, bus, train, or airplane. The six more advanced activity/participation items that were added are run errands and shop, climb up a flight of stairs, walk 2 miles, run or jog 2 miles, drive a car 5 miles from your home, and participate in sports as you would like.

The MDHAQ also includes four psychological items: depression, anxiety, sleep disturbance, and stress. The ICF would classify these items as impairments because they reflect organ system dysfunction. Separate average scores are calculated for the original HAQ activities, the advanced activities, and the psychological items; patients rate all items using the 4-point ordinal scale.

**Ideal Instrument for Developing an Assessment**

The emphasis on self-care activities and the inclusion of impairment items make the MDHAQ an ideal instrument for developing an assessment for the physician’s office. Because participation involves activities that are community-based, such as shopping, observing these activities in the office is very difficult.

As a self-report measure, the MDHAQ has the same limitations as other self-report measures of function. First, patients are not always able to identify the presence and extent of activity limitations accurately, especially if they have not done an activity recently. Overestimating or underestimating activity limitations is common. Research suggests that the degree of agreement between self-report and actual performance varies with the type of activity; the range is from 30% to 50%.5

Second, self-report instruments indicate that an activity is difficult for the patient but not what about it causes difficulty. Patients may recognize that they have a problem but not specifically what is causing it or what could be done.

These two limitations suggest that assessment of activity should include observation of patients performing activities to identify what is causing the difficulty. The MDHAQ questions provide an ideal anchor for individual patient assessment in the physician’s office.

**Declaration of Interests**

None.

**References**


**About the Author**

Dr Rogers is in the department of occupational therapy at the University of Pittsburgh School of Health and Rehabilitation Sciences and in the School of Nursing at the University of Pittsburgh. Dr Baker is in the department of occupational therapy at the University of Pittsburgh School of Health and Rehabilitation Sciences. Dr Shlenk is in the School of Nursing at the University of Pittsburgh. Drs Levesque and Starz are in the department of medicine, division of rheumatology and clinical immunology, at the University of Pittsburgh School of Medicine, PA, USA.
Understanding Function in RA:
The Role of Impairments

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

Knowing how rheumatoid arthritis (RA) symptoms are affecting patients’ everyday activities enhances your ability to provide best ‘treat to target’ practice interventions. Impairments can result in activity limitations and participation restrictions. An important impairment in RA is structural joint deformities; others are pain, fatigue, and adverse emotional reactions. Persons with RA often make some type of adaptation to their activities. Activity performance may be assessed by patient self-report with directed questions and by direct observation. Knowledge about RA and perspectives on what constitutes a particular activity differ greatly among patients. A challenge during an office visit is to make an accurate assessment of patients’ functional activities. Identifying problems is easier if attention is focused on specific body areas that are likely to be problematic.

Assessing function in patients with rheumatoid arthritis (RA) is a challenging but important part of the rheumatology office visit. Knowing how the symptoms of RA are affecting patients’ everyday activities enhances your ability to provide best ‘treat to target’ practice interventions for improved patient outcomes and quality of life.

This article describes how impairments in body systems caused by RA can affect function, and how patients can adapt their activities to cope with these impairments. We review methods to obtain information about patient function, including observations of activity performance during an office visit.
Impairments Can Affect Function

The International Classification of Functioning, Disability and Health (ICF) model developed by the World Health Organization provides a framework for classifying the health components of functioning and disability. The model suggests that impairments can result in activity limitations and restrictions in participation in a variety of life situations. An important impairment caused by rheumatoid synovial inflammation is structural joint deformities. They may cause restrictions in joint range of motion and decreased muscle strength, both of which contribute to reduced function.

Additional impairments seen frequently in RA are pain, fatigue, and adverse emotional reactions. Pain, which has been associated with decreased function, may have a cascading effect, ranging from interference with the performance of even simple tasks to major participation restrictions. For example, finger pain may affect patients’ ability to use electronic devices and manipulate small objects, such as coins. As a result, they may experience difficulties with computer or cell phone use and avoid shopping so they do not need to make change.

Fatigue, defined by the ICF as the subjective experience of extreme and persistent mental or physical tiredness that is not relieved by rest, is experienced by up to 90% of patients with RA. Fatigue may profoundly affect activity performance, such as house-cleaning or working an 8-hour day, as well as participation in social events, hobbies, and parenting. As a result, patients may need to reduce their number of tasks, take rest breaks, or eliminate activities.

“Pain, which has been associated with decreased function, may have a cascading effect”

In addition to physical challenges, patients with RA may experience emotional reactions, including depression and anxiety. The prevalence of depression in RA is 20% to 40%, and anxiety occurs in 13% to 20% of patients. Depression has been linked to decreased function, although the causal direction of the association is not clear. Decreased function may increase depression, and having depression may reduce function. A similar relationship between anxiety and function has been suggested.

Adapting Activities to Promote Function

Persons who have RA often are remarkably resourceful. One study
reported that 96% of 464 patients with RA made some type of adaptation to their activities. A variety of methods may be used. One is modifying the activity’s performance elements, or mechanics. Components may be simplified, such as cooking with prechopped vegetables or wearing clothing that does not have buttons or zippers. Patients also may alter an activity by using one extremity to help another, such as lifting a cup or other object with two hands. Tasks that typically are performed when standing, including dressing and bathing, may instead be done sitting. More time may be taken for activity completion, such as cleaning a room in 30 minutes instead of 10.

Another type of adaptation involves assistive devices. In one study, 89% of patients with RA used a variety of devices. For lower extremity problems, canes and walkers can maintain patients’ mobility and provide stability. For personal care, function restrictions resulting from joint involvement may be helped with long-handled shoehorns, reachers, bottle openers, hook and loop fasteners, thicker handles, and touch-free dispensers. Environmental issues may be addressed with stair glides, grab bars, and shower chairs.

A third type of adaptation is obtaining assistance from another person, such as a family member, friend, or professional caregiver. Assistance may be as simple as asking family members to help tie shoes or as complex as asking them to do all shopping and household tasks. Still another method is reducing the frequency of an activity or eliminating it. Patients may eliminate activities because they become too difficult or because they do not have enough time or energy to perform them.

An important consideration about a patient’s specific adaptation is the potential risk of injury. For example, using a shower curtain or soap dish to maintain balance when entering or exiting the shower increases the chances of falling.

Activity performance may be assessed by patient self-report with directed questions and by direct observation of the patient. Each method provides important information about functional status, but each also has limitations.

Patient self-report about specific activities may be obtained verbally in an interview or by a written questionnaire. Both approaches provide information about patients’ perception of their abilities and are particularly useful for tasks that cannot be observed. However, many complex factors determine how patients and health-care professionals interpret and respond to self-report questions. Knowledge about RA and perspectives on what constitutes a particular activity differ greatly among patients. For example, a patient may overestimate his or her abilities and answer ‘no difficulty’ in dressing without accounting for the spouse laying out clothing. Or, a patient may be embarrassed to admit that completing an activity, such as cooking a meal or cutting the grass, now takes much longer than it used to.

On the other end of the scale, patients may underestimate their abilities and report ‘much difficulty’ because their performance does not match their personal expectations. Observation involves watching patients perform activities and assessing their abilities. This method may provide direct insight into patients’ actual capabilities. However, because the environment can influence performance, patients may not be able to perform an activity in the physician’s office that they could.
Patients may adapt by reducing the frequency of or eliminating an activity.

accurately assess the functionality of patients with RA, including who will benefit from interventions. Patients often report having no function difficulties when they actually have difficulties. Or, they may express no perceived problems because they made adaptations but may not recognize or understand how their activities of daily living may be affecting their arthritis adversely.

Accurate Assessment a Challenge

A challenge during an office visit is to make an accurate assessment of the functional activities of patients with RA, including who will benefit from interventions. Patients often report having no function difficulties when they actually have difficulties. Or, they may express no perceived problems because they made adaptations but may not recognize or understand how their activities of daily living may be affecting their arthritis adversely.

One self-report questionnaire, the Multidimensional Health Assessment Questionnaire (MDHAQ)—a modification of the Health Assessment Questionnaire16—allows health-care professionals to evaluate the patient’s perception of the difficulty of a variety of activities. The MDHAQ queries eight domains of function—dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

Although items on the MDHAQ can identify certain activity limitations, they do not always provide a complete picture of function. Actual observation of patients performing functional tasks in the office can help health-care professionals assess whether patients are underestimating or overestimating their function and adaptations. The MDHAQ may serve as an anchor for the combination of self-report and observation during an office visit.

Focus on Specific Body Areas

When activities are observed during an office visit, identifying problems is easier if attention is focused on specific body areas that are likely to be problematic during a particular activity. Three general body areas to observe are the upper body, including the head, shoulders, arms, and hands; the trunk, including the back and hips; and the lower body, including the legs and feet.

Some items on the MDHAQ generally emphasize one body area. For example, the task of ‘lifting a full cup or glass to the mouth’ focuses on the upper body.

Other examination items combine several body areas. A challenge during an office visit is to make an accurate assessment of the functional activities of patients with RA, including who will benefit from interventions. Patients often report having no function difficulties when they actually have difficulties. Or, they may express no perceived problems because they made adaptations but may not recognize or understand how their activities of daily living may be affecting their arthritis adversely.

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Some items on the MDHAQ generally emphasize one body area. For example, the task of ‘lifting a full cup or glass to the mouth’ focuses on the upper body.

Other examination items combine several body areas. Arising from a chair involves a two-step sequence—the patient first uses his lower body to position his feet and then his trunk to move to the edge of the chair, and he then shifts his weight and centre of gravity forward. Also, observing a patient getting on and off the examination table can provide clues about his upper and lower body coordination. The movements are similar, in part, to those involved in transferring to and from a car or bed and in walking stairs.

Visual Cues to Task Difficulty

Certain visual cues—speed and smoothness of movement, the number of attempts needed for completion, substitution of movement, and the presence of pain behaviours—may help determine whether a patient is having difficulty with a task. Those who are experiencing task difficulty typically...
“Research suggests that some patients with high levels of pain may exhibit few pain behaviours”

move slowly. Their movements may be jerky and appear constrained. When writing, patients may move their hand slowly and hesitate between strokes of the pen (Figure). The finished writing may be uneven, less legible, and unsatisfactory to them.

For a well-learned activity, such as the ones on the MDHAQ, most patients complete the task without difficulty on the first attempt. Those who are experiencing difficulty may require repeated attempts. They may fumble or backtrack to obtain the desired outcome.

Patients who have limitations in strength and range of motion or who are experiencing pain often compensate by substituting movements by less impaired body parts for those by more impaired body parts. When reaching for the faucet, for example, patients may use trunk flexion at the waist for shoulder flexion.

Patients who are experiencing pain may exhibit pain behaviours, such as grimacing, sighing, guarding, assuming
“The MDHAQ . . . is limited in that it does not assess a patient’s community participation”

protective postures, and rubbing the affected area. These signs are variable; research suggests that some patients with high levels of pain may exhibit few pain behaviours.18

Raising a Red Flag

Any of these cues may raise a red flag indicating possible difficulty with an activity. A limitation of observing activities in the office lies in the ability of patients with RA to adapt an activity in their own home. Although in your office they may struggle with unfamiliar objects in an unfamiliar environment, they may have modified their own home to facilitate and support their function.15

Asking patients directed questions when an activity appears difficult is important. The question, ‘Is this typical of the way you do this at home? If not, can you tell me what’s different here in the office?’ can elicit useful information about home adaptations.

Using the MDHAQ as an anchor for an observational assessment of RA function is limited in that it does not assess a patient’s community participation, such as work or travel. Additional directed questions may help provide details about participation. For example, a physician can ask, ‘Since your last doctor’s visit, have you changed activities that you perform outside of the house, such as visiting, hobbies, work, or shopping?’

Declaration of Interests

None.

References


About the Authors

Dr Baker is in the department of occupational therapy at the University of Pittsburgh School of Health and Rehabilitation Sciences. Dr Schlenk is in the department of medicine, division of rheumatology and clinical immunology, at the University of Pittsburgh School of Medicine. Dr Rogers is in the department of occupational therapy at the University of Pittsburgh School of Health and Rehabilitation Sciences and in the School of Nursing at the University of Pittsburgh. Dr Starz is in the department of medicine, division of rheumatology and clinical immunology, at the University of Pittsburgh School of Medicine, PA, USA.
Understanding Function in RA: Practical Evaluation in the Outpatient Setting

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

A challenge with the aggressive new care model for patients with rheumatoid arthritis has been determining which measures to use to assess disease activity and response to therapy. With an observed functional assessment based on the Multidimensional Health Assessment Questionnaire domains, both the physician and the patient can gain important insights into function during a standard office visit. The presence of impairments in strength, joint range of motion, pain, and coordination—including balance and dexterity—can affect patients’ ability to perform functional activities. This assessment allows a physician to observe the impact of these impairments on function. It may help identify patients with significant changes in function who can benefit from effective intervention.

Treatment of patients with rheumatoid arthritis (RA) has undergone tremendous advances related to greater understanding of its pathophysiology and the introduction of effective disease-modifying medications. New management strategies for RA use ‘treat to target’ objectives with an intensive individualized approach and evidence-based outcomes.1,2

One challenge with this aggressive new care model has been determining which measures to use to assess disease activity and response to therapy. In the past, clinical assessment of joint swelling and tenderness, along with X-ray films and laboratory studies of acute phase reactants, formed the basis of the rheumatologist’s decision making. These tools provided
perspectives about RA but offered limited information about the impact of synovitis on an individual patient’s function.

This article discusses how functional assessment may be incorporated into clinical practice.

**Assessment of Function**

Information about function may be obtained in the following three ways: (1) asking the patient to self-report, using a questionnaire; (2) asking the patient directed questions; and (3) observing the patient perform activities. In 1980, Dr James Fries and the Stanford group introduced the Health Assessment Questionnaire (HAQ), which provides a patient-centred self-report outcome tool that includes functional measures. The Multidimensional Health Assessment Questionnaire (MDHAQ), developed by Dr Theodore Pincus, is a modification of the HAQ; this tool includes the eight function domains in the HAQ—dressing and grooming, arising (Figure), walking, eating, hygiene, reach, grip, and activities. This widely used self-report tool assesses standardized parameters of function. There is one question for each domain in the MDHAQ.

Research indicates that patient self-reports about function may have limitations. In addition, the clinician’s preconceived perspective of how a patient performs a particular task may be quite different from the actual performance.

With an observed functional assessment based on the MDHAQ domains, both the physician and the patient can gain important insights into function during a standard office visit. For the purpose of this assessment, the body is divided into three areas: upper body, trunk, and
lower body. In some activities, such as turning on a faucet, the primary emphasis will be on one body area; other activities, such as picking up a shirt from the floor, require a combination of areas.

The presence of impairments in strength, joint range of motion, pain, and coordination—including balance and dexterity—can affect patients’ ability to perform functional activities. This assessment allows a physician to observe the impact of these impairments on function.

Before the evaluation, patients should complete the MDHAQ, which provides information about self-perceived performance of specific tasks. A physician, nurse, or other health-care professional can perform the functional assessment in several minutes as part of the usual visit using items in a standard examination room plus a disposable cup.

To begin the assessment, the evaluator should ask the patient to sit in a straight-backed chair in an examination gown with shoes on. The examiner explains that as part of the visit, a brief functional assessment will be conducted to gain better understanding of how RA is affecting the patient’s day-to-day activities. As part of your visit today, I want to evaluate how you perform certain basic activities. Let’s review your answers on the self-assessment form, and then you can show me how you do certain activities. If any are too difficult, or if you feel unsafe, let me know, and we can skip them.’

Patients generally become more engaged in the process when they specifically understand its purpose. Note that patients may answer ‘without any difficulty’ to a question about an activity but actually may have a problem with it. During the examination, if patients are unable to perform an activity, ask, ‘What makes it difficult for you to do this?’

**Dressing and Grooming**
The first two activities address the domain of dressing and grooming. Begin by confirming that patients dress themselves at home and asking whether they have difficulty. You also may inquire whether they have made adaptations that make getting dressed easier, such as using a button hook tool, hook and loop fasteners, and a long-handled shoehorn.

Ask each patient to fasten one or two buttons on an article of clothing. If he or she is wearing a shirt, coat, or pants that have a button, use one of those buttons. If not, an extra laboratory jacket is an alternative.

Because buttoning is an in-hand manipulation activity that requires finger joint range of motion and dexterity to shift objects about, watch the patient’s hands carefully. Note that the buttons on women’s shirts are on the left and they use their left fingers to hold the button and their right fingers to open the buttonhole; men’s buttons are on the right side, and they are buttoned left over right. Either way, the patient should be able to place the button inside the hole smoothly and without repeated movements.

Also, note whether the patient shows signs of discomfort or pain. Avoid offering assistance in dressing or buttoning and other tasks so that you can make an accurate assessment of the patient’s abilities. If the patient struggles with the activity, ask how he manages at home, including whether he uses assistive devices.

Next, ask the patient to take off his shoes and put them back on. If the patient is wearing shoes that have laces, this activity should include tying them. If the shoes do not have laces, ask the patient whether he has difficulty in tying shoes.

The knees, hips, and ankles also are involved with shoe tasks. Patients who have knee or hip swelling or range of
motion abnormalities may slide their feet into shoes with or without laces rather than lift them. Observe whether the patient bends over to tie his shoes on the floor or crosses his legs and ties at waist level. Also, foot deformities may affect shoe activities and influence the patient’s preferred style of shoes.

Observing shoe activities can provide clues to patients’ difficulties with other dressing tasks that involve the lower body, such as putting on trousers and socks. Many patients with RA have developed safe, acceptable workaround strategies for dressing. If they are satisfied with their alternative and it poses no safety issues, no intervention is needed.

Arising
As part of assessment of the arising and activities domains, ask the patient to stand up from the chair. The patient should be wearing shoes, which is important for preventing slips and falls. Arising has the following three components: placing the feet in position, centring the body for balance, and lifting the body up. Each body area—upper, trunk, and lower—and the elements of strength, joint range of motion, pain, and coordination are part of this activity.

Watch carefully as the patient stands. Does he prepare to stand by inching toward the edge of the seat? Are his feet placed behind the edge of the chair before he moves forward and up? The knees must flex beyond 90° to facilitate moving the centre of gravity of the upper body over the feet. The hip and knee extensor muscles then lift the body up. Arising often is assisted by the upper body muscles and joints, especially the shoulders, elbows, and wrists, to push the body to standing.

Other things to look for include the following: Does it take the patient more than one try to arise? Is the patient slow or deliberate in the process? Does he have expressions of pain or grimaces? Also, does he appear to be stable when he reaches the standing position?

Arising from a straight-back chair has components that simulate other arising activities, such as getting out of a car or a bed. Ask patients about these other activities. For example, when the patient arises from these other locations, are there issues with lower or upper extremity strength and range of motion? Can the patient twist his trunk and swing his legs to the side? How much does he use his upper extremities to pull himself up? The height of the car or bed and the depth of the car seat can affect performance—arising from higher surfaces is easier.

Walking
The next domain to be assessed is walking. Once the patient is standing, ask him to walk five steps and turn around and walk back. If the patient typically uses a cane or walker, ask him to use it to perform this task. Focus your attention on the patient's lower extremities, and consider the smoothness, stability, and speed of his gait. Does he limp or favour one leg? Does he hold onto furniture and put a

“Observing shoe activities can provide clues to patients’ difficulties with other dressing tasks that involve the lower body”
hand to the wall for balance? Does he exhibit signs of pain?

Now ask the patient to sit back down in the chair. Like standing, this task provides an excellent opportunity to observe the effect on functional activities of impairments in strength, joint range of motion, pain, and balance. Does the patient ease into the chair using his arms to steady himself? Does he have difficulty in bending his hips or knees? Does he fall into the seat? The components involved with sitting also have similarities with getting into a car and bed. You can take this opportunity to review these activities with the patient and note your observations.

**More Dressing**
The next activity helps you further assess dressing. Ask the patient to stand and take several steps forward. Then ask him to put on his shirt or coat. If he does not have one with him, simulate the activity. Observe the shoulders— they have the greatest range of motion of any joint and are actively engaged in positioning the arms and hands when a shirt is donned, as are the elbow and wrist joints.

**Grip**
While the patient is standing, ask him to go to the sink and turn the faucet on and off. This task helps in assessing grip. Focus attention on the distal upper body along with the shoulders, elbows, and forearms. The positioning of the fingers is particularly important in this task. Although patients with RA have joint impairments, many have developed effective adaptations to perform these kinds of daily activities.

When the patient is bent down, ask him to pretend to pick up a piece of clothing from the floor, which demonstrates reach and hand dexterity. Consider the speed and smoothness of the performance.

If the patient has limitations in bathing or reaching, ask whether he uses an adaptive device at home. If a patient can reach below his knees, to his lower back, and to his head, he probably can bathe himself and pick up clothing from the floor. You can take this opportunity to inquire about whether the patient has any issues with other personal hygiene activities.

**Hygiene and Reach**
The next domains to be tested are hygiene and reach. Explain to the patient that you would like him to simulate washing and drying himself. Ask whether he bathes in a shower or tub and whether he stands or sits to wash and dry. Inquire how he bathes his back and front and upper and lower extremities.

Begin by asking the patient to place his hands on top of and then behind his head and simulate washing his hair. Ask him to put his hands to his shoulders, then behind his back, and then to the front.

Next, ask whether the patient can bend down to reach his knees or below. If yes, instruct him to pretend that he has a cloth and to slowly wash and dry his legs. Stand beside him and carefully watch for balance and stability, and immediately stop him if you sense that he is having difficulty.

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Patients with advanced RA may clamp the cup between their hands. Consider the speed and smoothness of the task when judging the efficiency of the performance. Does liquid spill from the cup? If the task seems manageable but awkward, ask how the patient feels about his performance. Is he satisfied? Is he embarrassed?

The disposable cup is different from other containers; the patient may report that he typically uses cups with handles. Difficulties with the faucet or cup activities may indicate other functional challenges with hand movements, such as picking up coins, opening car doors or jars, using a computer or cell phone, and writing.

Arising and Activities
The next activity includes some components of the arising and activities domains involving getting in and out of a car or bed. Begin by pulling out the step on the examination table. Ask the patient to stand facing the table and step up using the side of the table cushion or wall beside it as a simulated banister. This activity may be challenging. Immediately stop the patient if safety is an issue.

As the patient steps up, first focus your attention on movement in the lower extremities, including hip and knee flexion. Which foot does the patient first place on the step? Then note whether the patient uses his arms to pull the body forward. Upper and lower extremity strength, joint range of motion, and balance are integral to stepping up and onto the examination table. Assessment of this activity also may provide perspective on how well the patient can climb stairs.

Next, have the patient turn around on the step and sit at the end of the table for the final activity, which addresses bed mobility. Direct the patient to lie down and roll onto his side. Focus your attention initially on the upper body and trunk as the patient turns. Then, as he lies down, watch for smoothness, speed, and control of motion. Does it take more than one attempt? Are the patient’s arms and legs used to provide the strength to push the body over? Is the effort painful? Because this activity is performed on the examination table, it may serve as a natural segue into the physical examination.

Summary
Clinical observation of patients’ performance with the use of this procedure provides the physician, other healthcare professionals, and patients with clues to their functional abilities, with an emphasis on personal care tasks and mobility issues. The assessment may help identify patients with significant changes in function who can benefit from effective intervention. This may mean altering medication prescriptions to better manage pain, stiffness, and inflammation, or it may mean referring the patient to an occupational therapist, the member of the health-care team who specializes in the evaluation and management of function.

Declarations of Interests
None.

References


About the Authors
Drs Starz and Levesque are in the department of medicine, division of rheumatology and clinical immunology, at the University of Pittsburgh School of Medicine. Dr Schlenk is in the School of Nursing at the University of Pittsburgh. Drs Baker and Rogers are in the department of occupational therapy at the University of Pittsburgh School of Health and Rehabilitation Sciences. Dr Rogers also is in the School of Nursing at the University of Pittsburgh, PA, USA.

Psoriatic Arthritis: Expanding Therapeutic Options

Andreea Coca, MD; Christopher T Ritchlin, MD, MPH

The therapeutic options for psoriatic arthritis (PsA) have expanded rapidly and improved patients’ pain, function, and quality of life. However, many patients do not respond to the current disease-modifying medications or cannot take them. Oral methotrexate is the leading disease-modifying anti-rheumatic drug used in PsA. Anti–tumor necrosis factor α (anti–TNF-α) agents have been successful, but many patients do not achieve the American College of Rheumatology 20 end point. Abatacept and rituximab have proved effective for patients with rheumatoid arthritis who have had an inadequate response to anti–TNF-α agents, but data from pilot studies for PsA highlight the different pathophysiological mechanisms underlying the diseases. Few options are available for patients with PsA whose treatment with TNF-α inhibitors is not successful, but the pipeline looks promising.

For patients with psoriatic arthritis (PsA), the rapid expansion of therapeutic options, particularly the anti–tumor necrosis factor α (anti–TNF-α) agents, has contributed to great improvement in pain, function, and quality of life. However, many patients do not respond to the current disease-modifying medications or cannot take these agents because of their cost or adverse effects. In addition, consideration of important metabolic, vascular, and extra-articular co-morbidities is essential if physicians are to provide patients with high-quality comprehensive care. Fortunately, the pipeline of potential agents against novel targets for patients with psoriatic disease holds great promise for continued advances in the near future.

This article reviews the latest studies that address the effectiveness of methotrexate (MTX) and biologic agents for patients with psoriatic disease and provides a brief overview of new agents in the pipeline.
Although MTX currently is used in clinical practice, placebo-controlled double-blind trials are urgently needed to examine the efficacy of this agent in MTX-naive populations.
in design to the Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes study that was performed in RA. The time has come to establish the position of MTX in PsA therapy definitively with a well-designed clinical trial that includes the multiple relevant domains so that clinicians can base treatment decisions on high-level evidence and not on data abstracted from RA and psoriasis studies.

**Anti–TNF–α Agents**

In 2009, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) published evidence-based treatment recommendations for PsA. The group analysed the effectiveness and safety of therapies in the five key domains of PsA: peripheral arthritis, psoriasis, axial disease, dactylitis, and enthesitis. The anti–TNF–α agents showed the highest effect sizes for management of the various components of PsA, although most trials with DMARDs did not include these key domains as end points.

In the NOR-DMARD registry, patients with PsA who were receiving MTX were compared with patients receiving a TNF–α inhibitor; at 6 months, the latter had a significantly greater reduction in ESR and in DAS28, 36-Item Short Form Health Survey, Modified Health Assessment Questionnaire (HAQ), and patient global assessment scores in spite of having greater baseline disease activity. In a subsequent comparison of 1-year retention rates from the same Norwegian registry, survival with TNF–α inhibitor treatment was significantly higher in patients who had PsA or ankylosing spondylitis than in those who had RA.

Golimumab, a new TNF–α inhibitor, was approved in 2009 for the treatment of patients with PsA. In the pivotal phase III trial, this fully human monoclonal antibody against TNF–α was analysed for efficacy and safety in 405 patients with active moderate to severe PsA. Patients were randomized to receive the active drug (50 or 100 mg) or placebo every 4 weeks.

At week 14, 48% of patients who were receiving golimumab achieved an ACR 20 response, compared with 9% of placebo patients. Of patients who entered the trial with 3% or more body surface area, 40% in the 50-mg group and 58% in the 100-mg group achieved the PASI 75 end point. The enthesitis and dactylitis scores at week 24 also were significantly improved. Radiographic progression, measured by the modified van der Heijde-Sharp score, decreased in the group treated with the active drug, a result similar to that seen with other anti–TNF–α medications. The adverse-effect profile was quite good—8.6% of the patients treated with golimumab (34 of 394) experienced serious adverse events through week 104, eight cases of malignancy (three were basal cell carcinomas and one was fatal lung cancer) were noticed, and one case of histoplasmosis was managed successfully.

**Abatacept and Rituximab in PsA**

Although the use of TNF–α inhibitors has been successful in managing PsA, more than one-third of patients do not achieve the ACR 20 end point in clinical trials and many patients cannot take these medications because of adverse effects or cost constraints. Because abatacept and rituximab have proved effective for patients with RA who have had an inadequate response to anti–TNF–α agents, pilot studies were designed to test their effectiveness in PsA.

Patients with moderate to severe PsA were enrolled in a phase II, double-blind, randomized, placebo-controlled clinical trial to assess the efficacy of abatacept, a fusion molecule that inhibits T-cell co-stimulation.

Potential new agents in the pipeline for psoriatic arthritis look promising.
These data . . . present a challenge to examine alternative immune and inflammatory pathways for therapeutic targets in psoriasis and PsA

Therapeutic Pipeline
Few options are currently available for patients with PsA who experience an inadequate response or cannot tolerate TNF-α inhibitors, but the pipeline looks very promising (Table). Ustekinumab, an antibody that binds to the p40 subunit of interleukin (IL)-12/23, has been approved for psoriasis and was effective for PsA in a phase IIB trial. Tocilizumab, the IL-6R inhibitor, has been approved for RA and is anticipated to be effective for PsA as well. Apremilast, a phosphodiesterase-4 inhibitor, is in trials in psoriasis and PsA. Tofacitinib, a drug that inhibits Janus kinase, is in phase II trials in psoriasis; it is expected to be tested in PsA. Both agents are oral medications. IL-17 and IL-22 are key cytokines in psoriasis; because recent data indicate that helper T 17 cells produce increased amounts of IL-17 in the blood and joints of patients with PsA, agents against these targets hold great promise in psoriatic disease. In addition, denosumab, an antibody against receptor activator of nuclear factor-κB ligand recently approved...
for osteoporosis, has the potential to inhibit aggressive bone loss observed in some forms of PsA.

**Summary**

The number of safe and effective therapeutic options for patients with PsA has increased significantly. In addition, potential new agents hold great promise for the years ahead.

**References**


**About the Authors**

Dr Coca is assistant professor of medicine and Dr Ritchlin is professor of medicine at the University of Rochester Medical Center, Rochester, New York, USA.

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MANUSCRIPT PREPARATION

Title Page

A title page should contain the following information:

• Title of the paper
• Full names of all authors
• Academic qualifications of all authors
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Abstract/Introduction

(Clinical Reviews only) The abstract should be a concise outline of the main purpose of the paper containing approximately 50 words.

Illustrations/Figures

Illustrations include photographs, photomicrographs, charts and diagrams; they must be of professional quality and of a size permitting some reduction in the final copy. Patient identification should be obscured, and transfer arrows should be used to indicate subtle but salient points.

Tables

Each column should have a short or abbreviated heading. Place explanatory matter in footnotes, not in the heading. Non-standard abbreviations used in each table should be defined in the footnotes.

Language and Style

British spelling is used. Système International (SI) units are used except for blood pressure values which are to be reported in mm Hg. For the expression of length, area, mass and volume, metric system is used. Temperatures are to be given in degree Celsius. Non-proprietary names should be used for the mentioning of medical substances unless the specific trade name of a drug is directly relevant to the discussion.

References

References must be numbered consecutively in order of appearance in the text. When listing references, follow the Vancouver style. Journal names should be abbreviated according to Index Medicus. List all authors and/or editors up to six; if more than six, list the first three and et al. Examples for referencing style:

Journal article:

Book:

Website:

Thesis:
This continuing medical education service is brought to you by the Medical Progress Institute, an institute dedicated to CME learning. Read the article 'Psoriatic Arthritis: Expanding Therapeutic Options' and answer the following questions. Answers are shown at the bottom of this page.

CME Article:  
Psoriatic Arthritis: Expanding Therapeutic Options

Please answer True or False to the questions below.

1. Anti–tumor necrosis factor α (anti–TNF-α) agents have not been of much therapeutic value for patients with psoriatic arthritis (PsA).

2. Oral methotrexate is the leading disease-modifying anti-rheumatic drug used to treat patients with PsA.

3. A combination of methotrexate and infliximab resulted in an excellent ACR 20 response of 86.3% in the RESPOND trial.

4. Over one-third of patients with PsA do not achieve the ACR 20 end point in clinical trials of anti–TNF-α inhibitors.

5. Studies have shown that abatacept was just as effective for patients with PsA who had inadequate responses to TNF-α inhibitors as it was for patients with rheumatoid arthritis.

6. Tocilizumab targets IL-6 receptors.

7. Ustekinumab targets IL-17A.

8. Apremilast targets phosphodiesterase 4 and blocks cytokines and immune response.


10. Denosumab promotes bone resorption.

Answers:
Anaemia is a common reason for referral to any gastrointestinal service. The type of anaemia and any clinical symptoms often delineate the most appropriate investigations. However, iron-deficiency anaemia can be the sole reason for referral and, depending upon patient’s age, necessitates endoscopic investigation of the gastrointestinal tract. This article gives a brief overview of the most common presentations of anaemia relevant to the gastrointestinal system.

Anaemia is a common reason for referral to any gastroenterological service. Iron-deficiency anaemia (IDA) is the most frequent, making up to 13% of referrals. The type of anaemia and any clinical symptoms often delineate the most appropriate investigations. However, IDA can be the sole reason for referral and, depending upon patient’s age, necessitates endoscopic investigation of the gastrointestinal (GI) tract.

The functional definition of anaemia is a circulating red cell mass insufficient to meet tissue oxygen requirements. However, arbitrary criteria are often used to define anaemia, the most frequently used being the World Health Organization criteria of 13 g/dL for males, 12 g/dL for non-pregnant females, and 11 g/dL for pregnant women.

Anaemia results from either defective production, or an increased destruction or loss of cells, and can be classified by red cell indices, particularly the mean cell volume (MCV).

It can be divided into three main categories. The classification of anaemia in association with gastroenterology includes:
- microcytic (Table 1)
- normocytic
- macrocytic.

### Microcytic Anaemia

**Iron-deficiency Anaemia – Definition**

Iron-deficiency anaemia characteristically results in reduced MCV, mean cell haemoglobin, and hypochromia.

The blood film shows poikilocytes (variation in shape), anisocytes (variation in size), and target cells (Table 2).

A microcytosis is characteristic of IDA but can be present in thalassaemia when the low MCV is out of proportion to the anaemia, and the diagnosis can be confirmed by a haemoglobinopathy screen.

An increased red cell distribution width will often indicate coexistent vitamin B12 or folate deficiency.

Serum markers of iron deficiency are low serum ferritin, low serum iron, and increased total iron-binding capacity (TIBC) and transferrin-binding receptors.

Ferritin reflects the quantity of stored iron. However, serum ferritin is also an acute phase reactant and is elevated in infective, inflammatory or malignant disease and in chronic renal failure. Ferritin remains the most powerful test for IDA. A serum ferritin <12 µmol/L is diagnostic of IDA. A serum ferritin >100 µmol/L has...
a 96.1% specificity for anaemia not being caused by IDA. A low serum iron and TIBC suggest chronic disease rather than iron deficiency. It is only occasionally necessary to assess iron stores in bone marrow.

Response of haemoglobin concentration to a course of oral iron can sometimes clarify whether iron deficiency has caused a microcytic anaemia.

Causes of Iron-deficiency Anaemia (Table 3)
Iron-deficiency anaemia affects 30% of the world’s population. It has a prevalence of 2–5% in adult men and postmenopausal women in the developed world. Overt and occult bleeding from the GI tract is the most frequent cause for IDA in such patients. Bleeding points are identified in 50% of people with IDA. In premenopausal women, menstrual blood loss and pregnancy-related iron loss explain most IDA. Hookworm infestation is the most prevalent cause worldwide. Dietary insufficiency contributes to the high prevalence of IDA in developing
countries.

Iron is abundantly present in the ferric (Fe³⁺) form, which has poor bioavailability. Ferrous (Fe²⁺) iron is more readily absorbed. Non-haem iron is reduced in the stomach to the more readily absorbed ferrous ion. It is then transported across the duodenal mucosa. Factors affecting this process, such as coeliac disease, achlorhydria or *Helicobacter pylori* infection, will cause IDA. *H pylori* decreases the intestinal absorption of iron and increases blood loss from gastritis. Eradication can lead to correction of IDA in those infected patients with gastritis.

Sources of small intestinal bleeding are dependent on the age of the patient. Younger patients are likely to have small intestinal tumours, Meckel's diverticulum, Dieulafoy's lesion, or Crohn's disease, whereas vascular lesions and non-steroidal anti-inflammatory drug-induced small bowel disease are more common causes of small bowel bleeding in older patients. Overt blood loss from the GI tract can be associated with IDA from either per rectal loss or haematemesis. Targeted investigations are easier to choose in this setting.

**Investigations**

Upper and lower GI investigations should be considered in all male and postmenopausal female patients with confirmed iron deficiency.

Iron deficiency without anaemia is three times as common as iron deficiency alone. Large studies have shown that the prevalence of serious GI pathology in premenopausal women with iron deficiency alone is 0%, and 0.9% in postmenopausal women and adult males.

The method of investigation depends on local protocols but should involve the upper and lower GI tract. The appropriateness of investigation in those with significant co-morbidities should be explored with these patients particularly if results of investigations would not alter management.

Although the British Society of Gastroenterology suggests both upper and lower GI investigations, there is no consensus as to which investigation to perform first. Recent data have suggested that the diagnostic rate from performing lower GI investigations by means of a barium enema or colonoscopy is 14 times greater than performing upper GI investigations first. They recommend bidirectional investigation or lower GI investigation as the primary examination. In some centres, colonoscopy has been reserved for younger patients, where bowel preparation is more successful. However, a recent study looked at elderly patients (>75 years) referred with high-risk symptoms (haematochezia, anaemia, positive faecal occult blood test, weight loss, or a personal or family history of colorectal polyps or cancer) and low-risk symptoms (abdominal pain, constipation, diarrhoea, and a change in bowel habit). It found that colonoscopy has a higher diagnostic yield in the elderly high-risk group (44% vs 20%).

Urine testing for blood is recommended in all patients with IDA because approximately 1% of patients with IDA have renal tract malignancy. All patients, including premenopausal women, should be screened serologically for coeliac disease, followed by an upper GI endoscopy and distal duodenal biopsies for confirmation. Recent studies have shown the prevalence of coeliac disease in European populations to be 1 in 100, most being undiagnosed.

The only upper gastrointestinal pathology apart from coeliac disease that should be accepted as a cause of IDA is the presence of oesophageal or gastric carcinoma. In the absence
of these pathologies, colonic investigation should be performed. Current guidelines also suggest that if a patient has a normal gastroscopy, antral biopsies should be taken to look for the presence of *H. pylori* followed by eradication therapy if it is found.

Lower GI investigation should be by means of a colonoscopy, double-contrast barium enema with sigmoidoscopy (flexible or rigid) or computed tomographic colonography. Colonoscopy is the preferred method because of its greater sensitivity for cancer, which can be missed in around 10% of barium enemas, and because it can directly visualize mucosa and detect lesions such as angiodysplasia.

**Further Investigation**

Up to 50% of patients with IDA have no identifiable cause for their anaemia after upper and lower GI investigations. Further investigation is currently recommended only if patients are transfusion-dependent. Follow-up studies of this group have shown that IDA frequently resolves without recurrence with iron supplementation alone. Long-term follow-up studies have shown that a small proportion of patients (6%) may have GI pathology when followed up for nearly 6 years, the main pathology being colorectal carcinoma.10

Further small bowel investigation can be with push enteroscopy, wireless capsule endoscopy, barium follow-through, or Meckel’s isotope scan.

Capsule endoscopy allows visualization of the entire small bowel and has the highest diagnostic yield, detecting 31–76% of cases of obscure GI bleeding. This number has recently been shown to be higher in the older population, the diagnostic yield increasing from 50% in those under age 50 to 73% in the over-85 population.11

**Treatment of IDA**

Treatment of iron deficiency should involve treatment of the underlying disorder. Oral iron supplementation is given to correct the anaemia. Iron is best absorbed in the ferrous form in the duodenum and jejunum. Ferrous sulphate 200 mg tablets (= 60 mg ferrous iron) three times daily is best taken when the patient is fasting. Common adverse effects are constipation, nausea and occasionally diarrhoea. If adverse effects are problematic, the dose may be reduced and taken for a longer period, or a different preparation can be used (ferrous gluconate 300 mg = 35 mg ferrous iron).

Repletion of iron stores can take up to 6 months. Failure to correct this

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**Table 4. Macrocytic anaemia**

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anaemia or restore iron stores may be the result of non-compliance with medication, ongoing bleeding/malabsorption or an incorrect diagnosis (eg, thalassaemia).

Parenteral iron replaces iron stores faster than its oral equivalent, but the haematological response is similar. Iron infusions are composed of iron surrounded by a carbohydrate shell of dextrans, sucrose, dextrin, or gluconate. There is a small risk of anaphylaxis, but newer preparations such as ferric carboxymaltose have a significantly lower rate of anaphylaxis and obviate the need for a test dose.12

**Anaemia of Chronic Disease**

This is one of the most common forms of anaemia and can be normocytic or microcytic. It occurs with chronic infections (tuberculosis, osteomyelitis), inflammatory diseases (rheumatoid arthritis, systemic lupus erythematosus, Crohn’s disease), or malignancy. There is a decrease in release of iron from bone marrow to erythroblasts, an insufficient erythropoietin response to anaemia, and diminished red cell survival. The specific mechanisms behind this are unclear but are thought to be mediated by inflammatory cytokines such as tumor necrosis factor α, interleukin 1, and interferons.

Serum iron concentration and TIBC are reduced. Serum ferritin can be normal or raised. The serum transferrin receptor is normal. Iron is seen in the bone marrow but not in the developing erythroblasts. This anaemia does not respond to iron therapy. Treatment is of the underlying disorder.

**Macrocytic Anaemia (Table 4)**

These can be divided into megaloblastic and non-megaloblastic types, depending on the reticulocyte count and bone marrow findings.

Megaloblastic anaemia is characterized by the presence of erythroblasts with delayed nuclear maturation, secondary to defective DNA synthesis in the bone marrow. The peripheral blood film shows not only macrocytes but also hypersegmented polymorphs, and if severe there can also be leukopenia and thrombocytopenia.

Causes of megaloblastic anaemia include deficiency or abnormal metabolism of vitamin B₁₂ and folic acid, other defects of DNA production such as congenital enzyme deficiencies (eg, hereditary orotic aciduria) or drug therapy (azathioprine, 6-mercaptopurine, methotrexate, zidovudine, hydroxyurea, and trimethoprim), and myelodysplasia.

**Vitamin B₁₂ Deficiency**

Vitamin B₁₂ is synthesized by microorganisms, and humans are entirely reliant upon dietary sources such as meat, fish and eggs. The average adult stores of vitamin B₁₂ can take up to 2–3 years to be depleted.

Vitamin B₁₂ (cobalamin) is released from protein complexes in the stomach by gastric acid and then pepsin. It then binds to a vitamin B₁₂-binding protein (‘R’ binder) present in saliva and gastric juice. Cobalamin bound to ‘R’ binders is not absorbed, but in the alkaline environment of the duodenum, pancreatic proteases degrade ‘R’ binders, leaving cobalamin available to bind to gastric-derived intrinsic factor (IF). The IF/cobalamin complex binds to a specific ileal receptor, cubilin, and is absorbed in an energy-dependent process. Vitamin B₁₂ deficiency or utilization has several causes (Table 5).

**Investigation of low vitamin B₁₂ deficiency. It is important to take a thorough history, including diet, when investigating cobalamin deficiency.**

Malabsorption because of pancreatitis, coeliac disease, or treatment with metformin or proton pump inhibitors tends not to cause significant vitamin B₁₂ deficiency.

Serological testing should include anti-tissue transglutaminase antibodies, IF, and parietal cell autoantibodies.
Continuing Medical Education

Pernicious anaemia is an autoimmune disease causing atrophic autoimmune gastritis, achlorhydria and loss of gastric parietal cells, resulting in loss of IF production and impaired vitamin B₁₂ absorption. It is the most common cause of vitamin B₁₂ deficiency in the elderly, with a prevalence of 1/8,000 (or 2–4%) in those over the age of 60, mainly in women. It is associated with other autoimmune conditions, such as thyroid disease, adrenal Addison’s disease and vitiligo. Parietal cell antibodies are found in 90% but are also found in patients with gastric atrophy and are not specific for the diagnosis. However, IF antibodies, which are found in only 50% of those with pernicious anaemia, are specific for the diagnosis.

Treatment of B₁₂ deficiency: hydroxocobalamin is given intramuscularly at the dose of 1 mg three times a week for 2 weeks then 1 mg every 3 months. However, if there is neurological involvement (progressive peripheral polyneuropathy involving the posterior and lateral columns of the spinal cord or subacute combined degeneration of the cord), the dosing is initially 1 mg on alternate days until no further improvement and then 1 mg every 2 months.¹³

Oral vitamin B₁₂ is poorly absorbed from the GI tract, on average 10% of intake being absorbed. However, it is now also recommended that patients with pernicious anaemia can have high-dose oral supplementation because 1–2% of an oral dose is absorbed by diffusion, without the action of IF.

Hypokalaemia, iron deficiency and hyperuricaemia can occur when replacing vitamin B₁₂.

Folate Deficiency

Folate occurs in leafy vegetables such as spinach, and offal such as liver and kidney. However, cooking obliterates up to 90% of dietary folate.¹⁴ The main reason for folate deficiency is poor dietary intake, but malabsorption and excess utilization also account for folate deficiency. Common causes of folate deficiency are listed in Table 6.

Diagnosis and treatment of folate deficiency: red cell folate (as opposed to serum folate) is the most frequently used method of folate assay because it is more indicative of tissue folate concentration. Treatment is with folic acid 5 mg daily for 4 months and correction of any underlying disorders (eg, coeliac disease). Prophylactic folate is given during pregnancy to prevent neural tube disorders, and in those with chronic haematological disease with high cell turnover and those taking methotrexate.

“Pernicious anaemia should be distinguished from other forms of vitamin B₁₂ deficiency”
postulated that lysolecithin acts only on the action of lysolecithin, and it is been shown to have an inhibitory effect by a rapid fall in lipids. Cholesterol has molysis is thought to be precipitated by a circulating haemolysin, such as lysolecithin. Haemolysis, possibly through a circulating to be abnormal, predisposing to hepatic dysfunction, hyperlipidaemia, and transient haemolytic anaemia associated with alcohol excess. Red blood cell production (eg, haemolysis) is decreased, possibly through a circulating haemolysin, such as lysolecithin. Haemolysis is thought to be precipitated by a rapid fall in lipids. Cholesterol has been shown to have an inhibitory effect on the action of lysolecithin, and it is postulated that lysolecithin acts only when lipid concentrations fall.15

### Table 6. Causes of folate deficiency

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<th>Nutritional</th>
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<td>Old age</td>
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<td>Starvation</td>
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<td>Alcoholism</td>
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<td>Anorexia</td>
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<th>Antifolate drugs</th>
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<td>Anticonvulsants (eg, phenytoin, primidone)</td>
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<td>Methotrexate</td>
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<th>Excess utilization – physiological</th>
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<th>Excess utilization – pathological</th>
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<td>Haematological disease with excess red cell production (eg, haemolysis)</td>
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<td>Malignant disease with increased cell turnover</td>
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<td>Metabolic disease (eg, homocystinuria)</td>
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<td>Haemodialysis</td>
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### Anaemia Following Bariatric Surgery

Bariatric surgery is becoming more prevalent. It was estimated that in 2008, over 220,000 people underwent some form of weight reduction surgery.16 Gastroenterologists need to be aware of these procedures and the potential consequence of the malabsorptive state induced.

There are three main forms of bariatric surgery:

- Restrictive procedures (vertical-banded gastroplasty and laparoscopic adjustable gastric band)
- Restrictive malabsorptive procedures (Roux-en-Y gastric bypass)
- Malabsorptive procedures (bilio-pancreatic diversion and bilio-pancreatic diversion with duodenal switch).

Restrictive procedures restrict the capacity of the stomach but do not produce a malabsorptive state. However, anaemia can still develop because the intake of food is dramatically reduced and dietary deficiency is common.

The literature suggests that bariatric surgery patients undergoing malabsorptive procedures are at risk of post-operative deficiency of vitamins B12, B1, C, folate, A, D, and K, along with the trace minerals iron, selenium, zinc, and copper. Over-the-counter preparations are inadequate sources of micronutrients. It is recommended that post-bariatric surgery patients receive prophylactic lifelong supplementation.

### Declaration of Interest

None.

### References


### About the Authors

Helen Fellows is a gastroenterology specialist registrar at the Norfolk and Norwich University Hospital, UK. Ian Fellows is a Consultant Gastroenterologist at the Norfolk and Norwich University Hospital, and Honorary Senior Lecturer at the University of East Anglia, Norwich, UK.
CME Article:
Anaemia and the Gastrointestinal Tract

Please answer True or False to the questions below.

1. Anaemia is defined as a circulating red cell mass insufficient to meet tissue oxygen requirements.  
   True  False

2. Anaemia can be divided into two main categories: microcytic and macrocytic anaemia.  
   True  False

3. One characteristic of iron-deficiency anaemia (IDA) is microcytosis which can also be present in thalassaemia.  
   True  False

4. An increased red cell distribution width is often indicative of coexistent vitamin B6 or folate deficiency.  
   True  False

5. Reticulocyte count is the most powerful test for IDA.  
   True  False

6. Overt and occult bleeding from the gastrointestinal tract is the most frequent cause of IDA in adult men and postmenopausal women.  
   True  False

7. Urine testing for blood is recommended for all patients with IDA, as 1% of patients have renal tract malignancy.  
   True  False

8. Ferrous sulphate is best taken on a full stomach.  
   True  False

9. In normocytic anaemia, there is presence of erythroblasts with delayed nuclear maturation.  
   True  False

10. Prophylactic folate is given during pregnancy to prevent gestational diabetes.  
    True  False