ISSN 1391-0736

The Sri Lanka Prescriber

December 2024; Volume 32, No. 4

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The Sri Lanka Prescriber *is sponsored by the State Pharmaceuticals Corporation of Sri Lanka as a service to the medical profession*

The Sri Lanka Prescriber

Published by
Department of Pharmacology Faculty of Medicine
271, Kynsey Road, Colombo 8, Sri Lanka.
Telephone: + 94 11 2695300 Ext 315 and

State Pharmaceuticals Corporation
75, Sir Baron Jayathilake Mawatha, Colombo 1. Telephones + 94 11 2320356-9
Fax: + 94 11 447118
E-mail: prmanager@spc.lk Web site: www.spc.lk

Printed by
Colombo University Press
Stanley Wijesundera Mawatha, Colombo 07, Sri Lanka Telephone: + 94 114 596 686
E-mail: press@cmb.ac.lk

Cover Picture

The First Official Pharmacopoeia

The first governmentally sectioned Pharmacopoeia was published in Florence in 1498. Physicians and Pharmacists collaborated in preparing it; and the monk, Savonarola, current Florentine leader, served as political advisor.

The Sri Lanka Prescriber

Guidelines on rational use of human albumin

Background

Human albumin is costly. In Sri Lanka, the second highest consumption cost of the medicines budget in 2023 was spent on human albumin, with Rs 1.3 billion used for purchasing. It is however noted that sometimes human albumin is used without proper indications. Therefore, the guideline has been developed for rational use of human albumin in Sri Lanka. This guideline provides actionable recommendations for the most common indications for the use of albumin by any medical officer/prescriber but it does not apply to albumin use in peri-operative and surgical practice.

Box 1: Summary of indications for the use of human albumin

1. Large volume paracentesis (LVP) or "at risk" paracentesis in decompensated advanced chronic liver disease (dACLD) for the prevention of post-paracentesis circulatory dysfunction (PPCD)
2. Spontaneous bacterial peritonitis (SBP) in dACLD for the prevention of acute kidney injury (AKI)
3. For the diagnosis of suspected hepatorenal syndrome – acute kidney injury (HRS-AKI) or in confirmed HRS-AKI
4. Severe Nephrotic Syndrome*
5. Ascites with hypoalbuminemia in children
6. Septic shock*
7. As a replacement fluid in Plasma Exchange (PLEX)
8. Other special indications

*in specific situations

Indications for human albumin use

The following are the approved indications for human albumin and the dosing recommendation for each indication.

1. Large volume paracentesis or "at risk" paracentesis in decompensated advanced chronic liver disease (dACLD)

In decompensated advanced chronic liver disease (dACLD) when large volume paracentesis (LVP) is performed human albumin is used for the prevention of post-paracentesis circulatory dysfunction (PPCD) [1, 2]. LVP is defined as removal of more than five litres of ascitic fluid within 24 hours.

Dosing recommendation:

Intravenous (IV) 20% albumin, 8 g per each litre of ascitic fluid removed in excess of 5 litres is recommended.

Human albumin is also indicated in "at risk" paracentesis in dACLD for the prevention of PPCD. "At risk" paracentesis includes any amount of ascitic fluid removed in patients with

- Acute kidney injury (AKI)
- Circulatory dysfunction (SBP < 90 mmHg and/or MAP < 65 mmHg or on inopressors)
- Evidence of acute on chronic liver failure (as defined by high white cell count/ C reactive protein and more than one extrahepatic organ failure) in a patient with dACLD.

Dosing recommendation:

IV 20% albumin 8 g per litre for each litre of ascitic fluid removed

2. Spontaneous bacterial peritonitis in dACLD

Spontaneous bacterial peritonitis (SBP) is defined as patients with ascitic fluid white cell count >500/ mm^3 (with >50% polymorphonucleocytes) or polymorphonucleocytes ≥250 cells/mm^3 and/or positive ascitic fluid culture.

Dosing recommendation:

IV 20% albumin 1.5 g/kg within 6 hours of detection on day 1 and 1 g/kg on day 3

3. For the diagnosis of suspected hepatorenal syndrome – acute kidney injury (HRS-AKI) or in confirmed HRS-AKI

Suspected HRS-AKI [3] is defined as a rise of serum creatinine ≥0.3 mg/dL within 48 hours or an increase > 1.5 times (>50% increase) from baseline within the last 7 days or a drop of urine output to < 0.5 ml/kg/h for 6 hours, in the presence of dACLD, ascites and portal hypertension.

Dosing recommendation:

IV 20% albumin 1 g/kg/day for 2 days (dose up to a maximum of 100 g per day)

Confirmed HRS-AKI [3] is defined as AKI in the presence of dACLD, ascites and portal hypertension in the absence of the following:

- Dehydration/shock
- Ongoing use of nephrotoxic drugs
- Proteinuria >500 mg/day
- Haematuria >50 red cells per high-power field
- Structurally abnormal kidneys/urinary tract

AKI is defined as a rise of serum creatinine ≥0.3 mg/dL within 48 hours or an increase > 1.5 times (>50% increase) from baseline within the last 7 days or urine output to < 0.5 ml/kg/h for 6 hours

Dosing recommendation:

IV 20% albumin 1g/kg on D1 followed by 20-40g daily thereafter with a vasoconstrictor (IV terlipressin or noradrenaline) for up to 14 days

4. Severe Nephrotic Syndrome [4, 5]

In severe nephrotic syndrome human albumin is indicated for

- Diuretic-resistant oedema, defined as an inadequate response to a maximum dosage of a combination of loop diuretic, mineralocorticoid receptor antagonists, and thiazide-like diuretics (sequential nephron blockade) manifested as refractory oedema and reduced urine output
- Hypovolemia with pre renal AKI

Dosing recommendation:

Adults - IV 20% albumin 20 - 30 g followed by IV Loop diuretics to facilitate the action of diuresis. Additional dosing must be approved by the nephrology team attending.

Children

- Hypovolaemia with shock - resuscitate with 5% albumin, 10 mL/kg body weight as a bolus
- Hypovolaemia without shock - resuscitate with
  - 20% albumin - 0.5-1 g/kg body weight infusion over 4 hours with mid-transfusion furosemide 1mg/kg body weight or
  - 5% albumin - 10 mL/kg body weight over 1 hour

5. Ascites with hypoalbuminemia in children [5, 6]

Dosing recommendation:

20% Albumin 0.5-1 g/kg, depending on the cause of hypoalbuminaemia and clinical judgement with midway loop diuretics.

6. Septic shock [7]

Albumin is considered in sepsis or septic shock in those who received large (>50ml/kg) volumes of crystalloids and are still fluid responsive.

Dosing recommendation:

- Adults: 5% albumin 12.5 g bolus, repeated as needed
- Children: 5% albumin 5-10 ml/kg, repeated as needed

7. As a replacement fluid in Plasma Exchange (PLEX) [8]

Dosing recommendation:

For one volume of PLEX- two-thirds will be replaced by 5% albumin and the rest by 0.9% saline

The choice of replacement fluid depends on the clinical diagnosis and the risk of bleeding while the percentage of albumin used depends on clinical status.

8. Special situations

Albumin will be indicated in special situations like Single-pass albumin dialysis (SPAD) in children with liver failure [9]

Box 2: Situations where human albumin is not indicated due to lack of evidence

1. To correct plasma albumin in patients with hypoalbuminemia not described above.
2. To treat malnutrition, protein-losing enteropathies, or malabsorption
3. As fluid resuscitation in patients with acute trauma
4. Treatment of hepatic encephalopathy in patients with cirrhosis
5. Acute Respiratory Distress Syndrome [10]
6. In dACLD with portal hypertension for the sole purpose of reducing portal pressure
7. Repeated infusions in hospitalized patients with dACLD to prevent AKI, infection or death
8. Low serum albumin alone in nephrotic syndrome

Box 3: Useful practical information

- Albumin is contraindicated in fluid resuscitation of patients with traumatic brain injury [11]
- 20% human albumin
  - is used in fluid/sodium intake restricted patients or to mobilize fluid.
  - is hyper-oncotic. A 100 ml of 20% albumin will expand to approximately 400 ml within 25 minutes of transfusion. Rapid administration can lead to rapid volume expansion and cardiac failure. Therefore, 100ml of 20% albumin is usually infused over 30 minutes.
  - should be used with extreme caution in neonates, due to the risk of intraventricular haemorrhage from rapid expansion of the intravascular volume. Therefore, slow infusion is recommended
- 5% human albumin is used in hypovolemic patients or intravascularly depleted patients.
  - to make 5% albumin, 20% albumin will need to be reconstituted as 5% albumin is non-formulary as well as costly.
- Albumin doses should be rounded to the nearest vial size where possible.
- Considering the availability and cost of albumin, alternative therapies like cryo-supernatant plasma may be considered for use

Monitoring the use of human albumin according to these guidelines is recommended. A request form provided by the pharmacy needs to be filled by the doctor prescribing human albumin to any patient. The pharmacists are accountable for the human albumin issued to units and to collect the form. Plans are to audit the usage of human albumin by analysis of data on the information provided in the forms. In case where the request for albumin is not in accordance with these guidelines, the request must come through a consultant-grade clinician only. Adherence to these guidelines and monitoring the usage is expected to improve rational and cost-effective usage of human albumin.

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Diabetic Retinopathy

The latest International Diabetes Federation (IDF) Diabetes Atlas reports that 11.1% or 1 in 9 of the adult population (20-79 years) is living with diabetes, with over 4 in 10 unaware that they have the condition [1].

By 2050, IDF projections show that 1 in 8 adults, approximately 853 million, will be living with diabetes, an increase of 46%. Furthermore, it is projected that the number of people with diabetes in the southeast Asian Region will increase 68%, reaching 152 million by 2045.

Diabetes mellitus (DM), a disease with microvascular complications has its effects on many organs of the body including the kidney, heart and brain. However, the eye is the target organ in many of the patients leading to significant reduction in quality of life.

Diabetes affects the eye in many ways. Increased incidence of infections ranging from increased incidence of corneal ulcers to endophthalmitis and diplopia due to involvement of vasa nervorum of cranial nerves supplying extra ocular muscles, unstable refractive errors due to poor glycaemic control, recurrent corneal erosions and retinal vein occlusions and increased incidence of glaucoma and cataract. Out of all, the most common and the most significant complication of diabetes in the eye leading to vision loss is diabetic retinopathy (DR).

In 2010, of an estimated 285 million people worldwide with diabetes, over one-third have signs of DR, and a third of these are afflicted with vision-threatening diabetic retinopathy (VTDR), defined as severe non-proliferative Diabetic Retinopathy (NPDR) or proliferative DR (PDR) or the presence of diabetic macular edema (DME) [2]. DR remains a leading cause of preventable blindness among working-age adults globally and represents a significant burden on public health systems.

Prevalence of diabetic retinopathy is estimated to be around 34.6% globally with 10.2% causing vision threatening diabetic retinopathy. In South Asia, the prevalence of DR ranges from 10% to 26%, and this number is expected to increase with the growing incidence of type-2 diabetes mellitus (T2DM) in low- and middle-income countries. Patients with type-1 diabetes mellitus (T1DM) are at greater long-term risk, particularly if glycaemic control is suboptimal.

Chronic hyperglycaemia leads to:

- Pericyte loss and endothelial dysfunction
- Increased retinal capillary permeability
- Capillary non-perfusion
- Retinal ischemia and neovascularization in advanced stages.

Diabetic retinopathy is a progressive, vision-threatening microvascular complication of diabetes mellitus caused primarily by chronic hyperglycaemia.

Pathophysiology reveals damage to the retinal vasculature including loss of pericytes, leading to increased vascular permeability of red cells and plasma. Basement membrane thickening and increased cellular adhesions leading to capillary occlusion, and pathologic neovascularization due to capillary non perfusion and upregulation of vascular endothelial growth factor (VEGF).

As DR develops, the activation of Müller cells and microglia promotes the production of multiple inflammatory mediators and various vascular growth factors (e.g. VEGF), as well as advanced-glycation end products (AGEs), thus exacerbating the pathogenicity of the disease and potentially affecting other retinal cell types such as retinal ganglion cells and retinal pigment epithelium [3].

In advanced disease rupture of the friable new blood vessels result in vitreous haemorrhage and tractional retinal detachment. These vascular changes progress silently and may remain asymptomatic until vision is severely affected highlighting the importance of regular screening.

Neovascular glaucoma is a result of new vessel formation in the irido-corneal angle, causing impedance to aqueous drainage. The resulting high intraocular pressure will lead to severe pain and vision loss due to optic nerve damage.

Classification of Diabetic Retinopathy [4]

The International Clinical Diabetic Retinopathy Disease Severity Scale provides a standardized classification based on the severity of retinal lesions. DR is broadly categorized as Non-Proliferative Diabetic Retinopathy and Proliferative Diabetic Retinopathy with Diabetic Macular Oedema as a

sight-threatening complication that can occur with any stage.

A. Non-Proliferative Diabetic Retinopathy (NPDR)

NPDR is characterized by microaneurysms, intraretinal haemorrhages, venous beading, and intraretinal microvascular abnormalities (IRMA). It is further graded as:

- Mild NPDR - Presence of at least one microaneurysm. Usually asymptomatic and reversible with glycaemic control
- Moderate NPDR - More extensive microaneurysms and haemorrhages. Cotton wool spots, hard exudates. Increased risk of progression
- Severe NPDR - Based on the 4-2-1 rule:
  - 4 quadrants with haemorrhages/microaneurysms
  - 2 quadrants with venous beading
  - 1 quadrant with IRMA (Intra retinal microvascular abnormalities)

High risk of progression to PDR within one year

B. Proliferative Diabetic Retinopathy (PDR)

It represents the advanced stage of DR. Neovascularization of the disc (NVD) or elsewhere (NVE). This may increase the risk of vitreous haemorrhage, tractional retinal detachment.

Vision loss can be sudden and severe in this situation and requires urgent ophthalmologic referral.

C. Diabetic Macular Edema (DME)

Defined as retinal thickening or hard exudates involving the macula it is detected by clinical examination or macular optical coherent tomography (OCT).

DME can be associated with any stage of DR and is known to be the leading cause of central vision loss due to Diabetes.

Classification of DR (per International Clinical Diabetic Retinopathy Disease Severity Scale):

- Mild Non-Proliferative Diabetic Retinopathy (NPDR)
- Moderate NPDR
- Severe NPDR
- Proliferative Diabetic Retinopathy (PDR)
- Diabetic Macular Edema (DME) – can occur at any stage

Box 1: Factors aggravating DR

Several modifiable risk factors [5] are known to aggravate DR

- Chronic hyperglycaemia
- Hypertension
- Dyslipidaemia
- Duration of diabetes
- Nephropathy
- Pregnancy
- Smoking
- Anaemia

Management of Diabetic Retinopathy

Systemic control of Diabetes and other risk factors

Systemic control of Diabetes mellitus is of prime importance to management of DR. Control of modifiable risk factors is the next important step [6].

Glycaemic control: Intensive glycaemic control reduces the incidence and progression of DR. Target HbA1c: <7.0%,

Hypertension management: Lowering blood pressure will slow down DR progression. Target BP: <140/90 mmHg

Lipid control: Statins and fenofibrate have shown benefit in reducing DR progression.

Renal function optimization: Diabetic nephropathy is a predictor of DR progression.

Ophthalmic Interventions

Referral to an ophthalmologist is warranted when DR is present or if visual symptoms arise.

The modality of treatment will defer based on severity and other patient factors.

A. Laser Photocoagulation

- Focal or grid laser: Used for localized DME.
- Pan-retinal photocoagulation (PRP): Indicated in PDR to reduce neovascularization and prevent complications such as vitreous haemorrhage.

B. Intravitreal Pharmacotherapy

Pharmacological treatment delivered via intravitreal injection is now the mainstay in managing DME and PDR:

- Anti-VEGF agents [7]: Ranibizumab, Aflibercept, and Bevacizumab

  They are humanized recombinant monoclonal antibody fragments which bind to the receptor binding site of Anti VEGF and prevent endothelial proliferation, vascular permeability and neovascularization.

- Intravitreal corticosteroids: Dexamethasone implant

  Used in steroid-responsive patients or those unresponsive to anti-VEGF therapy. Act by reducing inflammation and reducing oedema. Known side effects include elevated intraocular pressure and cataract

C. Combination therapies

Intravitreal anti-VEGF + laser photocoagulation

Surgical Management

Pars plana vitrectomy (intra ocular surgery) is indicated in advanced cases with non-clearing vitreous haemorrhage or tractional retinal detachment.

Medications That May Aggravate Diabetic Retinopathy

1. Insulin therapy: Rapid improvement in glycaemic control can transiently worsen DR. It is important to educate the patient about the transient refractive errors due to changes in the focusing power of the lens during this transitory period.
2. Glucocorticoids: Induce hyperglycaemia, exacerbate retinal vascular dysfunction. (Additionally, it may cause progression of cataract and glaucoma).
3. Thiazolidinediones [7] (e.g., pioglitazone, rosiglitazone): Associated with fluid retention and macular oedema causing deterioration of central vision.
4. SGLT2 inhibitors: Current evidence inconclusive, but important to monitor
5. Anabolic steroids and testosterone therapy: Can influence vascular permeability

It is important to liaise with the ophthalmologist when initiating or adjusting these agents.

Screening for DR

Patients with T1DM should have initial dilated and comprehensive eye examination within five years of onset; patients with T2DM should be referred to at the time of diagnosis. If any level of diabetic retinopathy is present on eye examination, the patient should receive dilated retinal examinations at least annually8. If symptoms of progress or sight is threatened, more frequent examinations are required.

Role of the Physician in managing DR

Early-stage DR is often asymptomatic, screening and timely detection are vital. Primary care doctors as well as specialists treating patients with DM play a key role in the optimum management of patients with DR.

Risk factor management [9] (glycaemic, lipid, and blood pressure control), identifying high-risk medications aggravating DR, as well as advocating regular screening and prompt referral of patients with any visual symptoms or signs suggestive of DR is of prime importance. Patient education and follow-up is the key to success. Multidisciplinary approach with good teamwork among Primary care doctors, Physicians, Endocrinologists and Ophthalmologists will ensure optimum care to the patients.

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Diagnosis and management of antiphospholipid syndrome

SUMMARY

Antiphospholipid syndrome is an autoimmune disease characterised by thrombotic and/or obstetric manifestations with persistent antiphospholipid antibodies. Diagnosis involves confirming the persistence of antiphospholipid antibodies in symptomatic patients, using validated classification criteria as a guide. The likelihood of obtaining false positive or false-negative test results in certain settings, and the lack of standardisation between laboratory methods, are important considerations. Patients who have had thrombotic manifestations require lifelong anticoagulation from the first thrombotic event, typically with warfarin. Patients with a history of thrombotic and/or obstetric manifestations who become pregnant should receive low-molecular-weight heparin and low-dose aspirin during pregnancy and postpartum. Testing asymptomatic people is not recommended, except in the context of systemic lupus erythematosus. Management of asymptomatic people with persistent antiphospholipid antibodies depends on their individual antibody profile and risk factors.

Keywords

anticoagulants, antiphospholipid antibodies, antiphospholipid syndrome, fetal death, thrombosis

(Aust Prescr 2024;47:179–85)

Introduction

Antiphospholipid syndrome (APS) is a rare, multisystem autoimmune disorder that is characterised by thrombotic and/or obstetric manifestations with persistent antiphospholipid antibodies. It has an estimated prevalence of 17 to 50 per 100,000 population [1,2].

APS may occur as a primary autoimmune disorder (53 to 59% of people with APS) [3,4], or as a secondary condition in association with an autoimmune connective tissue disease, most commonly systemic lupus erythematosus (SLE), but also systemic sclerosis, primary Sjögren syndrome and rheumatoid arthritis [3]. Patients with APS usually require tertiary care as part of a multidisciplinary team to optimise patient management.

Diagnosis

Patients are usually investigated for APS following the occurrence of a suggestive clinical manifestation. Confirming the diagnosis involves testing for the persistence of antiphospholipid antibodies and interpreting these results in the context of the patient's clinical presentation, using validated classification criteria as a guide.

Clinical manifestations

Thrombotic manifestations

Venous thromboembolism resulting in deep vein thrombosis is the most common presenting manifestation of APS, affecting approximately 32% of people with APS. Pulmonary embolism occurs in approximately 9% of people with APS [5].

Arterial thromboembolism secondary to APS most commonly presents as stroke, representing around 13% of first presentations of APS. Transient ischaemic attack is also a common first presentation (approximately 7%) [5]. APS may also be associated with rare stroke syndromes, such as cerebral venous sinus thrombosis. Other possible arterial thromboembolic manifestations are acute myocardial infarction, acute lower limb ischaemia, avascular necrosis of bone, mesenteric infarction and renal vessel occlusion [6].

Microvascular thrombosis secondary to APS can result in acute and chronic antiphospholipid antibody nephropathy, adrenal and pulmonary haemorrhage, and myocardial disease. Cutaneous manifestations including lower limb ulceration, subungual splinter haemorrhages and livedo racemosa (a violaceous

branching and non-continuous discolouration of the skin) can also occur [7,8].

Catastrophic APS is a rare, life-threatening presentation in people with thrombotic manifestations of APS, whereby microvascular or small-vessel thrombosis leads to concurrent multiorgan dysfunction (e.g. acute kidney injury, mesenteric ischaemia, myocardial infarction). It should be suspected in patients with thrombosis with 2 or more organs concurrently involved; involvement of 3 organs concurrently is diagnostic. Catastrophic APS most commonly occurs when there has been an interruption to or a change in long-term anticoagulation in patients with known APS (e.g. in the perioperative period; in concomitant inflammatory states such as infection, surgery or malignancy) [4].

Obstetric manifestations

Early and late obstetric manifestations, such as fetal loss, pre-eclampsia or placental insufficiency, are possible sequelae of APS. In a study among pregnant women with APS-related complications, the most common complication in the mother was pre-eclampsia (9.5%). Early fetal loss occurred in approximately 35% of pregnancies and late fetal loss in 17% of pregnancies. Approximately 11% of live births were premature [5]. There is also an increased risk of maternal venous thromboembolism in APS.

Other clinical manifestations

Valvular heart disease with cardiac valve thickening (with occasional significant valve masses) resulting in regurgitation (Libman–Sacks endocarditis) is the most common cardiac manifestation [9]. Mild to moderately severe thrombocytopenia is the most common haematological manifestation of APS. An uncommon manifestation is haemolytic anaemia, which can occur either secondary to thrombotic microangiopathy or with an autoimmune association [5].

Antiphospholipid antibodies

As thrombotic and obstetric manifestations are not unique to APS, reliable confirmation of persistent antiphospholipid antibodies is crucial for accurate diagnosis. Antiphospholipid antibodies encompass a heterogeneous group of immunoglobulins that bind phospholipids, phospholipid-binding plasma proteins and phospholipid–protein complexes at cell surfaces. They activate the endothelium, platelets and leucocytes, which promotes thrombotic and inflammatory complications [10-12].

The 3 commonly tested antiphospholipid antibodies are anticardiolipin, anti-beta2-glycoprotein I and lupus anticoagulant (Table 1). Of all 3 antibodies, a persistently positive lupus anticoagulant carries the highest risk for developing future clinical manifestations [19,20]. With regard to anticardiolipin and anti-beta2-glycoprotein I, the immunoglobulin G (IgG) isotype confers a higher risk than the immunoglobulin M (IgM) isotype [14].

Some people may test positive for more than one antibody. Individuals with double antibody positivity are considered to have a high-risk antibody profile. Triple-positive APS, defined as the persistence of all 3 antibodies, confers the highest risk for development of thrombotic and obstetric manifestations [21,22].

Indications for testing

Testing for antiphospholipid antibodies should be limited to patients in whom there is a high clinical suspicion of APS. Testing may be warranted in younger individuals (especially those under 50 years) who present with unexplained venous thromboembolism or arterial thrombosis (e.g. ischaemic stroke, transient ischaemic attack, acute myocardial infarction). Testing may also be indicated in those with adverse pregnancy outcomes such as recurrent early fetal losses, or one or more fetal deaths later in pregnancy [23].

Screening for antiphospholipid antibodies in asymptomatic individuals is not recommended, including in those with a family history of APS, or who are pregnant or planning pregnancy. This is to avoid incidental findings which can lead to patient anxiety and unnecessary treatment [23]. The exception to this is people with SLE. Antiphospholipid antibodies are present in 20 to 30% of patients with SLE and may lead to increased risk of thrombotic or obstetric manifestations. Antibody testing in patients with SLE can be considered, especially in those who are pregnant or planning pregnancy, and in the context of other factors that increase the risk of thrombosis such as commencing estrogen-containing contraception [3,24]

Potential pitfalls of testing

When ordering antiphospholipid antibody tests or interpreting test results, there are potential pitfalls that should be considered (Table 2).

Classification criteria

Classification criteria for APS were developed to identify homogeneous patient cohorts for clinical studies; however, they can be helpful in practice to guide diagnosis. Classification criteria outlining clinical manifestations and laboratory criteria were initially proposed in 1998, then updated in 2006[30]. The American College of Rheumatology and European Alliance of Associations for Rheumatology published a further update in 2023 to capture advancements in the understanding of APS and address limitations of the 2006 criteria, such as the lack of evidence-based definitions for individual manifestations [7].

The 2023 classification criteria apply weighting to individual criteria and have a higher specificity (99%) but lower sensitivity (86%) compared with the 2006 criteria. According to the 2023 criteria, patients can be classified as having APS if they score at least 3 points from the clinical criteria and 3 points from the laboratory criteria, with at least one clinical criterion and one laboratory criterion present within 3 years of each other (Table 3) [7].

The 2023 classification criteria specify anticardiolipin and anti-beta2-glycoprotein I antibody titres as measured by enzyme-linked immunosorbent assay; however, in practice, many laboratories in Australia employ other analytical methods with differing cut-off values. Given this, there are challenges in directly applying the laboratory classification criteria to all test results and results may be incomparable between laboratories.

Table 1: Description of commonly tested antiphospholipid antibodies

Antiphospholipid antibody	Description
Anticardiolipin antibodies (IgG or IgM)	These antibodies target cardiolipin, an anionic phospholipid component of the inner mitochondrial membrane. Nonpathological anticardiolipin antibodies (associated with a lower risk of thrombosis) can be transiently produced at low titres in response to infection, some autoimmune diseases and malignancy [13]. IgG antibodies are more strongly correlated with thrombosis than IgM antibodies [14].
Anti-beta2-glycoprotein I antibodies (IgG or IgM)	These antibodies target beta2-glycoprotein 1. A phospholipid binding protein that acts as a naturally occurring inhibitor of platelet aggregation in plasma and inhibits contact activation of the coagulation cascade [15]. IgG antibodies have been strongly associated with thrombotic events: IgM antibodies have less clinical relevance [14, 16, 17].
Lupus anticoagulant	Lupus anticoagulant is not a single antibody itself, but refers to a collection of antibodies that interfere with phospholipid-dependent coagulation [18].

A persistently positive lupus anticoagulant carries the highest risk for developing future clinical manifestations compared with anticardiolipin and anti-beta2-glycoprotein I antibodies [19,20].

IgG= immunoglobulin G; IgM = immunoglobulin M

Table 2: Potential pitfalls of antiphospholipid antibody testing and practical considerations

Potential pitfall of testing	Practical considerations
Non-persistence of antiphospholipid antibodies	Antiphospholipid antibodies may be transiently present in individuals without APS [25]. To reduce the likelihood of a false-positive result, a follow-up test should be performed at least 12 weeks after the initial test to confirm persistence of antibody positivity.
False-negative and false positive results	False-positive results can occur because of transient anticardiolipin antibodies during infection, some autoimmune diseases and malignancy [26]. Immunoglobulin infusions, plasmapheresis or antibody-depleting therapy can interfere with antibody titres [23]. Vitamin K antagonists (e.g. warfarin) have been associated with both false-positive and false-negative results for lupus anticoagulant [23]. Direct-acting oral anticoagulants can interfere with lupus anticoagulant testing and produce false-positive results, even at low doses [23].
Lack of standardisation of antibody tests	Methods for detection of antiphospholipid antibodies (in particular anticardiolipin and anti-beta2 glycoprotein I antibodies), diagnostic cut-offs and normal reference ranges differ between laboratories. Therefore, it can be difficult to apply titre cut-offs specified in classification criteria and inaccurate to compare results from different laboratories [27-29].

Table 3: Summary of 2023 classification criteria for antiphospholipid syndrome [7] [NB1]

Clinical criteria	Points
Macrovascular manifestations [NB2]	
Venous thromboembolism:	
• with high risk venous thromboembolism profile	1
• without high risk venous thromboembolism profile	3
Arterial thrombosis:	
• with high-risk cardiovascular disease profile	2
• without high risk cardiovascular disease profile	4
Micro vascular manifestations	
One or more of the following suspected: • livedo racemosa (examination) • livedoid vasculopathy lesions (examination) • acute or chronic antiphospholipid antibody nephropathy (examination or laboratory results) • pulmonary haemorrhage (symptoms or imaging)	2
One or more of the following established: • livedoid vasculopathy (pathology)	5

• acute or chronic antiphospholipid antibody nephropathy (pathology)	
• pulmonary haemorrhage (bronchoalveolar lavage or pathology)	
• myocardial disease (imaging or pathology)	
• adrenal haemorrhage (imaging or pathology)	
Obstetric manifestations	
• 3 or more consecutive prefetal (less than 10 weeks) and/or early (from 10 weeks to 15 weeks and 6 days) fetal deaths	1
• fetal death (from 16 weeks to 33 weeks and 6 days) without pre-eclampsia or placental insufficiency with severe features	1
• pre-eclampsia or placental insufficiency with severe features (less than 34 weeks) with or without fetal death	3
• pre-eclampsia and placental insufficiency with severe features (less than 34 weeks), with or without fatal death	4
Other clinical manifestations	
• cardiac valve thickening	2
• cardiac valve vegetation	4
• thrombocytopenia	2
Laboratory criteria [NB3][NB4]	
• positive lupus anticoagulant (single, one time)	1
• positive lupus anticoagulant (persistent)	5
• moderate or high positive IgM antibodies to anticardiolipin and/or anti-beta2-glycoprotein I (persistent)	1
• moderate positive IgG antibodies to anticardiolipin and/or anti-beta2-glycoprotein I (persistent)	4
• high positive IgG antibodies to anticardiolipin or anti-beta2-glycoprotein I (persistent)	5
• high positive IgG antibodies to anticardiolipin and anti-beta2-glycoprotein I (persistent)	7

IgG = immunoglobulin G; IgM = immunoglobulin M

NB1: A person is classified as having antiphospholipid syndrome if they score at least 3 points from the clinical criteria and at least 3 points from the laboratory criteria, with at least one clinical criterion and one laboratory criterion present within 3 years of each other.

NB2: Determination of the risk of venous thromboembolism and cardiovascular disease is based on general population guidelines – refer to full classification criteria.[7]

NB3: Persistence of antiphospholipid antibodies is defined as positive laboratory results on 2 occasions, at least 12 weeks apart.

NB4: The classification criteria specify antibody titres as measured by coagulation-based functional assay (for lupus anticoagulant) and enzyme-linked immunosorbent assay (for anticardiolipin and anti-beta2-glycoprotein I antibodies).

Adapted from Barbhaiya M, Zuily S, Naden R, Hendry A, Manneville F, Amigo MC, et al. The 2023 ACR/EULAR Antiphospholipid Syndrome Classification Criteria. Arthritis Rheumatol 2023;75:1687-702. https://doi.org/10.1002/art.42624

Management

Patients with thrombotic manifestations

In patients with persistent antiphospholipid antibodies, the first thrombotic episode would confirm the diagnosis of APS. These patients should be initially treated with standard therapeutic anticoagulation (i.e. subcutaneous low-molecular-weight heparin or intravenous unfractionated heparin) [31].

Secondary prophylaxis with warfarin is required lifelong from the first thrombotic episode, with a target INR of 2 to 3. Some patients may require a higher target INR (e.g. recurrent venous thromboembolism despite an INR of 2 to 3) [31].

Direct-acting oral anticoagulants (DOACs) (e.g. rivaroxaban, apixaban) are not appropriate for secondary prophylaxis as the rate of recurrent thromboembolism with DOACs is significantly higher than with warfarin in patients with APS [32,33]. However, DOACs may be considered in patients who are unable to achieve target INR, unable to adhere to regular INR monitoring, or who have contraindications to warfarin [31]. In patients with a low risk of APS (e.g. low titre antibody positivity with single thrombotic event in the context of provoking factors), it is unclear if warfarin remains superior to DOACs.

If subsequent thrombotic episodes occur despite therapeutic anticoagulation with warfarin, the addition of an antiplatelet drug such as low-dose aspirin or dipyridamole should be considered [34].

For management of a patient with thrombotic manifestations who becomes pregnant, see below.

Patients with obstetric manifestations

People with APS who plan to conceive are recommended to receive preconception assessment, including counselling on the increased risk of adverse maternal and fetal outcomes and how these risks may impact the perceived benefits of having a child. After pregnancy is confirmed, these patients should be referred to an obstetrician or obstetric medicine physician as their situation would be considered a high-risk pregnancy. All patients with SLE, especially those with persistent antiphospholipid antibodies, should also be encouraged to discuss plans for conception with their treating specialist.

If a patient with a history of obstetric manifestations (but no history of thrombotic manifestations) becomes pregnant, both prophylactic-dose low-molecular weight heparin and low-dose aspirin are recommended for the duration of the pregnancy and postpartum for 6 to 12 weeks [31,35]. As low-molecular-weight heparin is associated with an increased risk of osteoporosis, it is important to limit the treatment duration of this drug to a maximum of 12 weeks postpartum (in addition to the duration of pregnancy). Patients should be checked for, and advised on, appropriate dietary intake of calcium and vitamin D. If there are recurrent obstetric complications despite treatment, increasing the heparin dose to a therapeutic dose or adding hydroxychloroquine may be considered [31].

If a patient with a history of thrombotic manifestations (but no history of obstetric manifestations) becomes pregnant, therapeutic-dose low-molecular-weight heparin and low-dose aspirin are recommended for the duration of the pregnancy and for 6 to 12 weeks postpartum [35]. Patients previously on warfarin should be switched to low-molecular-weight heparin because of the risk of birth defects with warfarin [31].

Long-term thromboprophylaxis for patients with a history of obstetric manifestations who are not pregnant or hoping to conceive is not recommended; however, low-dose aspirin may be considered short

term in high-risk situations (e.g. long-haul flights, surgery).

People with a history of obstetric manifestations who develop a thrombotic episode should be managed as per patients with APS-associated thrombosis (i.e. lifelong secondary prophylaxis with warfarin) [31].

Catastrophic antiphospholipid syndrome

If catastrophic APS is suspected, the patient should be immediately referred to a hospital for assessment and management. Initial treatment involves anticoagulation and high-dose corticosteroids, and is often followed by plasma exchange and/or rituximab or cyclophosphamide [4].

Asymptomatic people with persistent antiphospholipid antibodies

Investigating for antiphospholipid antibodies is not recommended in asymptomatic individuals, except in patients with SLE. If an asymptomatic person is ARTICLE antibody positive on the initial test, a follow-up test is recommended to confirm antibody persistence.

Asymptomatic people with persistent antiphospholipid antibodies do not have a diagnosis of APS; however, management may be required based on an assessment of the individual's risk of developing future clinical manifestations. Their risk is informed by their individual antibody profile, coexistence of other systemic autoimmune diseases such as SLE, and the presence of thromboembolic and cardiovascular risk factors [31]. All people with persistent antiphospholipid antibodies should be educated on the relevance of antiphospholipid antibodies and supported to address their modifiable thromboembolic and cardiovascular risk factors, such as smoking and obesity [31].

There is uncertainty surrounding the role of primary prophylaxis with aspirin for asymptomatic people with persistent antiphospholipid antibodies [36,37]. The benefits and harms of using low-dose aspirin should be considered on an individual basis. Thromboprophylaxis with low-dose aspirin may be considered in asymptomatic people with a high-risk antibody profile (e.g. persistent lupus anticoagulant, triple antibody positivity) who are trying to conceive and have strong unmodifiable risk factors for thrombosis [31,33]. Short-term thromboprophylaxis (e.g. with low-molecular-weight heparin) may also be considered in situations with a high risk of developing venous thromboembolism (e.g. peripartum period, surgery, flights).

In patients with SLE and a high-risk antibody profile, prophylactic low-dose aspirin is recommended[31]. Hydroxychloroquine is the mainstay treatment for people with SLE and may have additional benefits for people with SLE who have persistent antiphospholipid antibodies [3].

All patients with SLE who are hoping to conceive should receive preconception counselling. In asymptomatic pregnant women with persistent antibodies (with or without SLE), prophylactic low dose aspirin before 16 weeks gestation has been recommended with careful monitoring of the fetus and the mother [31,35].

Conclusion

Testing for antiphospholipid antibodies should only be initiated in patients in whom there is a high clinical suspicion of APS or with SLE. The detection of persistent antiphospholipid antibodies is key to the diagnosis and risk stratification of patients with APS. However, there are challenges with the interpretation of test results.

Patients with thrombotic manifestations of APS should be initially treated with therapeutic heparin, followed by warfarin for long-term secondary prophylaxis.

Pregnant patients with APS require low-dose aspirin and low-molecular-weight heparin at either a

therapeutic or prophylactic dose, depending on prior manifestations, during pregnancy and postpartum.

Asymptomatic people with persistent antiphospholipid antibodies do not have a clinical diagnosis of APS. The decision to initiate thromboprophylaxis in this group is based on their individual antiphospholipid antibody profile and other risk factors.

Conflicts of interest: Paul Kubler has received funding from AbbVie for trials of upadacitinib for systemic lupus erythematosus.

Paul was a member of the expert group for Therapeutic Guidelines: Rheumatology Version 4 (under review).

Yeri Ahn, Carolyn Hawkins and Eliza Pearson have no conflicts of interest to declare

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Current information about drug registration

New chemical entities registered

Generic name	Brand name	Dosage form	Manufacturer	Importer	Therapeutic class / use(s)
Emicizumab	Hemlibra	Injection, 30 mg/1 mL & 60 mg/0.4 mL	Chugai Pharma, Japan/ Hoffmann La Roche	Slim Pharmaceuticals	Postoperative inflammation following cataract surgery
Eflornithine	Epila	Cream, 13.9%	Valor, Pakistan, India	Slim Pharmaceuticals	Antiprotozoal
Melatonin	Melo 3	Tablet, 3mg	Newgen, Sri Lanka	--------	Insomnia

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