

## The digestive system involvement of antiphospholipid syndrome: pathophysiology, clinical characteristics, and treatment strategies

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### ABSTRACT

Antiphospholipid syndrome (APS) is an autoimmune disease mainly characterised by vascular thrombosis and pregnancy morbidity. APS has broad spectrum of clinical manifestations. The digestive system involvement of antiphospholipid syndrome is a critical but under-recognised condition. Digestive system involvement may be the result of direct (autoimmune-mediated) or indirect (thrombotic) mechanisms. Liver is the most commonly involved organ, followed by intestines, oesophagus, stomach, pancreas and spleen. This review describes possible digestive system manifestations in APS patients, and illustrates the epidemiology and possible pathophysiology of APS. The role of different treatment strategies in the management of digestive system manifestations of APS were also discussed.

### KEY MESSAGES

- Antiphospholipid syndrome is a multi-organ, multi-system disease and its clinical manifestation spectrum is gradually expanding. Since the first diagnosis of APS, the clinical manifestations of digestive system have been reported successively. This narrative review describes the major digestive system manifestations of APS and illustrates the epidemiology, pathophysiology and the role of therapeutic strategies of these patients.

### ARTICLE HISTORY

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### KEYWORDS

Antiphospholipid syndrome; antiphospholipid antibodies; autoimmune; thrombosis; digestive system

## 1. Introduction

Antiphospholipid syndrome (APS) is an autoimmune disease, characterised by presence of antiphospholipid antibodies (aPL) in the bloodstream that leave the patient in a potentially hypercoagulable state, leading to thrombosis at all segments of the vascular bed. It is also associated with pregnancy morbidity (miscarriages, late intrauterine fetal demise, and severe pre-eclampsia especially placental insufficiency) [1]. The clinically significant laboratory tests for aPL include lupus anticoagulants (LA), anti- $\beta$ 2-glycoprotein I antibodies (anti- $\beta$ 2GPI) and anticardiolipin antibodies (ACL) [2].

The diagnosis of APS utilizes the Sapporo criteria, including the presence of at least one clinical event and one durably positive laboratory criteria (over at least 12 weeks). Clinical criteria included [1]: vascular thrombosis events (venous and/or arterial) [2]; and/or pregnancy morbidity along with persistent presence of

aPL. While laboratory criteria included [1]: persistently medium/high titer anticardiolipin antibodies (including isotypes IgG and/or IgM) [2]; or medium/high titer anti- $\beta$ 2-glycoprotein I ( $\beta$ 2-GPI) antibodies (including isotypes IgG and/or IgM) [3]; or a positive lupus anticoagulant test) with two positive tests, spaced at least 12 weeks apart [3,4].

Based on etiology of other autoimmune diseases, APS is classified as primary and secondary APS. APS with no underlying cause identified is called primary APS (PAPS); while APS with an associated comorbidity, such as systemic autoimmune diseases, or malignancy, or secondary to certain medications, are called secondary APS (SAPS) [4].

APS can affect any organ or system with diverse clinical manifestations. Since the first diagnosis of APS, the clinical manifestations of digestive system have been reported successively [5,6]. The hepatic involvement is reported as the most common manifestation of the digestive system in APS, followed by

gastrointestinal tract [7]. Though these clinical features are associated with presence of aPL, they are not necessarily related to thrombosis. Several other mechanisms such as inflammation, complement pathway, and platelet activation have been postulated [4,8,9]. APS-related digestive symptoms are often overlooked by clinicians, and some doctors are even confused during the diagnosis and treatment. This narrative review describes the major digestive system manifestations of APS and illustrates the epidemiology, pathophysiology of these patients. The role of therapeutic strategies is also discussed.

We undertook a computer-assisted search of the literatures in MEDLINE, The National Library of Medicine until 2020, using the search items: antiphospholipid syndrome, anticardiolipin antibodies, lupus anticoagulant, antiphospholipid antibodies, catastrophic antiphospholipid syndrome, liver, hepato-biliary, pancreas, spleen, gastrointestinal, and abdomen. The relevant articles were grouped according to the involved organs and further classified by different disease entities in each group.

## 2. Epidemiology

The prevalence of aPL in the general population ranges between 1% and 5% [2,10]. The positive antibodies may present in the following cases: (1) asymptomatic carriers, (2) patients with non-thrombotic conditions (such as thrombocytopenia, autoimmune hemolytic anemia, livedo reticularis, etc.), (3) patients with thrombosis and (4) health women during pregnancy. However, in general population, the epidemiology of APS is not well established. According to recent estimations, approximately 1–2 APS patients occurred per 100,000 persons per year, and APS may be more common than previously appreciated with a prevalence approximately ranges from 17 to 50 patients per 100,000 persons [11,12].

In the “Europhospholipid” cohort of the 1,000 APS patients, the incidence of gastrointestinal, splenic, pancreatic and hepatic manifestations were 1.5%, 1.1%, 0.5% and 0.7% respectively [6]. The APS associated gastrointestinal symptoms are rarely reported. The true incidence of APS-related digestive system manifestations might be largely underestimated. The main reason is that the APS related digestive system manifestations are diverse, complex, non-specific and often involves multiple organs, making the diagnosis difficult.

**Table 1.** Pathophysiological mechanisms mediated by aPL.

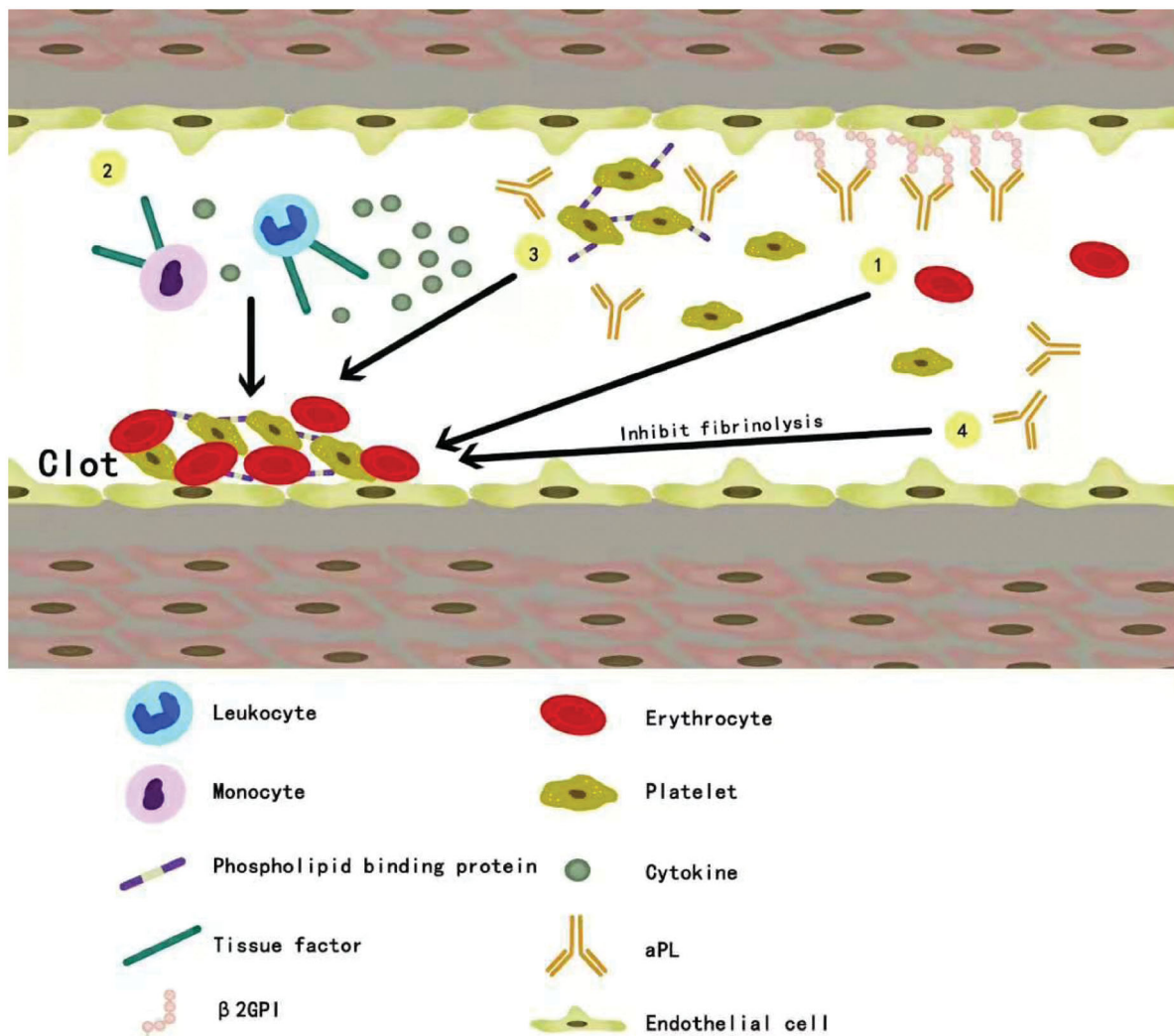
Thrombotic mechanisms:
Increased monocyte tissue factor expression [13]
Platelet activation [14,15]
Endothelial cell dysfunction [14,15]
aPL-mediated eNOS inhibition [14,15]
Increased production of endothelin-1 and tissue factor [14,15]
Release of neutrophil extracellular traps [16]
Complement system activation [17]
Increased thromboxane A2 production [18]
Disturbances of anticoagulant mechanisms [18]
Immune mechanisms:
Interference by lupus anticoagulants [9]
Immune complex deposition [19]
Immune cross-reactions [20]
The production of neoantigens in cell membrane rupture [20]
The direct action of antiphospholipid antibodies [22,23,25]

aPL:antiphospholipid antibodies; eNOS: endothelial nitric oxide synthase.

## 3. Pathophysiology

The pathophysiology of APS mainly includes two aspects: thrombotic mechanism and immune mechanism (Table 1).

Antiphospholipid antibodies plays an important role in thrombotic events in patients with APS. Studies have shown that aPL induces thrombosis mainly against  $\beta$ 2-glycoprotein I. The other targeted antigens include prothrombin, protein C, protein S, annexin A5, annexin A2, etc [13]. Anti- $\beta$ 2 GP I binds to the  $\beta$ 2 GP I receptor on endothelial cells to induce dimerization. The subsequent interaction between the dimerized  $\beta$ 2 GP I and apolipoprotein E receptor 2 mediated the APL induced endothelial nitric oxide synthase (eNOS) inhibition, increases expression of endothelial adhesion molecules, and increases production of endothelin-1 and tissue factors, leading to thrombosis [14,15]. The anti- $\beta$ 2 GP I also binds to the  $\beta$ 2 GP I receptor on platelets, leading to overexpression of thrombin, enhanced platelet adhesion to endothelial collagen, increased platelet aggregation, and induced thrombotic events [14,15]. Through the above target antigen, aPL can also activate mononuclear cells, inducing tissue factor, protease activated receptor and proinflammatory cytokines [13]. Neutrophil extracellular traps (NETs) is a key inducer in the process of blood coagulation and endovascular thrombosis. Studies have shown that aPL can further activate neutrophils to release NETs, leading to thrombosis [16]. In addition, the thrombogenic effects of aPL also involve activation of the classical pathway of the complement system [17]. In addition to accelerating the thrombosis, aPL can inhibit fibrinolysis through a variety of mechanisms. Studies have also shown that aPL can inhibit fibrinolysis by inhibiting the binding of plasminogen activators and plasminogen to annexin A2



**Figure 1.** Thrombotic mechanisms mediated by aPL. Thrombus formation can be promoted in the different ways [1]: aPL interacts with endothelial cells [2]; aPL activates mononuclear cells, induces expression of tissue factors, proteinase activated receptors and proinflammatory cytokines [3]; aPL interacts with platelets [4]; aPL inhibit fibrinolysis. aPL: antiphospholipid antibodies;  $\beta$ 2-GPI:  $\beta$ 2-glycoprotein I.

endothelial surface receptors and activating plasminogen activator inhibitor 1 overexpression [18]. A summary of pathophysiology has been demonstrated in Figure 1.

Since APS is an autoimmune disease, autoimmune responses through inflammatory mechanisms may also play a role in its pathogenesis. Pathology confirmed evidence of sub endocardial immunoglobulin deposition in the heart valves in APS patients with valvular heart diseases, suggesting that aPL may be involved in the sub endocardial inflammatory process through interaction with valve surface antigens [19]. Similar immune mechanism mediated by aPL occurs in digestive system. LA, as a member of aPL, causes autoimmune esophagitis, resulting in reduced intestinal wall strength and an increased risk of spontaneous esophageal rupture [9]. aPL is also involved in cross-

immune responses. There are a large number of mitochondria in the liver, which contain cardiolipin. ACL may cross-react with mitochondria present in the liver [20]. In addition, in some patients with primary sclerosing cholangitis, *S. Cerevisiae*, as an environmental factor, may cross-react with aPL [21]. The significantly increased rate of positive aPL occur in inflammatory bowel disease, nodular regenerative hyperplasia, pancreatitis and other diseases. It is speculated that the direct effect of aPL may influence the occurrence and development of diseases [22–24].

#### 4. Clinical presentations

Digestive system involvement in APS comprises a wide spectrum of clinical manifestations that include esophageal disease (esophageal necrosis and rupture),

**Table 2.** Summary of digestive system manifestations associated with APS.

Gastrointestinal Organ	Manifestations
Esophagus	Oesophageal necrosis [25,27] Oesophageal rupture [26]
Stomach	Gastric ulcer [28] Gastric gangrene [29]
Intestine	Intestinal infarction [32–35] Inflammatory bowel disease [38,40]
Liver	Budd-Chiari syndrome [44–54] Hepatic infarction [57–61,63–65] Hepatic venous-occlusive disease [68–74] Nodular regenerative hyperplasia [22,77–81] Portal hypertension [82–87] Autoimmune liver disease(Autoimmune hepatitis [92,93] Primary biliary cirrhosis [89,90] Primary sclerosing cholangitis [91,94]
Spleen	Splenic infarction [95–98] Autosplenectomy or functional asplenia [100–102]
Pancreas	Pancreatitis [24,103–106,108–110] Pancreatic duct injury [107,111]

gastric disease(gastric ulcer and gangrene), intestinal disease(intestinal infarction and Inflammatory bowel disease), liver disease(thrombotic liver diseases, obstruction of small hepatic veins, hepatic infarction, non-thrombotic liver diseases), splenic disease(splenic infarction, auto splenectomy or functional asplenia) and pancreatic disease(pancreatitis, pancreatic duct injury) [5,7,10]. Table 2 summarizes the major digestive system manifestations associated with APS.

#### 4.1. Esophageal manifestations

The esophageal diseases associated with APS are esophageal necrosis and rupture. The earliest case, reported by Cappell MS, can date back to 1994 [25], later, related cases of esophageal involvement were also reported by Naitoh H [26] and Padma A [27].

#### 4.2. Gastric manifestations

Two case reports have mentioned APS related gastric lesions, clinical manifestations were giant gastric ulcer [28] and massive gastric gangrene [29]. The main reason for gastric ischemic necrosis as rare manifestation is that the vessel diameter that supply stomach is relatively large and has well collateral circulations [30]. Therefore, extensive occlusion of all major vessels or the coeliac trunk is required to cause gastric ischemia. It is important to note that APS thrombosis tends not to be limited to the large vessels, but also to any small blood vessels (arterioles/venules) supplying the organs [31].

#### 4.3. Intestinal manifestations

A number of APS patients have been reported with intestinal infarction from mesenteric thrombosis [32–35]. Intestinal venous or arterial thrombosis and infarction appear to be prominent features of APS associated small intestinal involvement. However, it should be noted that mesenteric venous thrombosis is the least common cause of mesenteric ischemia [36]. Mesenteric artery thrombosis accounts for 25% to 30% of all ischemic events. Almost all cases of mesenteric ischemia due to arterial thrombosis occur in the context of severe atherosclerotic disease [37].

Inflammatory bowel disease (IBD) includes ulcerative colitis (UC) and Crohn's disease (CD). Since the first reported association between IBD and APS in 1992 [38], few related cases have also been reported [39–42].

#### 4.4. Hepatic manifestations

Hepatic involvement is the most common digestive system manifestation of APS. A wide range of hepatic diseases have been reported in association with APS, that vary from thrombotic diseases (Budd-Chiari syndrome) to non-thrombotic diseases [7]. It has been reported that APS may also cause hepatic artery thrombosis after liver transplantation [43]. This article mainly reviews APS-related digestive system manifestations in clinical background, so we will not summarize the relevant situation here.

##### 4.4.1. Thrombotic liver diseases

Budd-Chiari syndrome (BCS) may be the first clinical manifestation of APS [7]. After Pomeroy C et al [44] published the first case report describing the correlation between BCS and APL, several cases were reported afterwards [45–54]. BCS is a major vascular disorder of the liver, characterised by structural and functional abnormalities of the liver resulting from the obstruction of the hepatic venous outflow from hepatic veins(the small hepatic veins, main hepatic veins and suprahepatic inferior vena cava) [55,56]. Some myeloproliferative diseases (MPDs) and predisposition to thrombotic conditions are considered as possible causes of BCS. In contrast, primary BCS is usually associated with risk factors for thrombosis (e.g. protein C and protein S deficiency, primary thrombocytopenia, etc.) [55,56]. APS may be the second most common cause of non-neoplastic BCS after primary MPDs [49].

Hepatic infarction is a rare disease because of its dual blood supply system (portal vein and hepatic artery) that protects the liver from ischemia. However,



in the APS context, cases of hepatic infarction were occasionally reported [57–61], and most of the reported cases were pregnant women, that may be related to physiological characteristics such as venous stasis, coagulation tendency and changes in fibrinolytic system during pregnancy [60,62]. Moreover, most of the reported cases of hepatic infarction in pregnant women with APS were related to HELLP syndrome [63,64]. HELLP syndrome may appear as an initial characteristic of APS and highly suggest the further development of catastrophic antiphospholipid syndrome (CAPS) [65].

#### **4.4.2. Hepatic veno-occlusive disease (obstruction of small hepatic veins)**

Hepatic veno-occlusive disease (HVOD) is a rare liver disease and a common life-threatening complication of bone marrow transplantation [66]. It is thought to be caused by direct damage to the sinusoidal endothelium which can lead to non-thrombotic concentric narrowing of the central lobular vena cava, obstructing liver circulation and leading to stem cell necrosis [67]. The association between HVOD and APS was first suggested by Pappas *et al* [68]. Since then, several cases with HVOD and APL have been reported [69–74].

#### **4.4.3. Non-thrombotic liver diseases**

Nodular regenerative hyperplasia (NRH) is often associated with a variety of systemic diseases [75], characterised by diffuse transformation of liver parenchyma into small regenerative nodules in the absence of significant fibrosis [76]. A total of 6 cases about the relationship between NRH and APS have been published [22,77–81].

APS related idiopathic non-cirrhotic portal hypertension (INCPH) cases have been reported [82–87]. Currently, the etiology of INCPH can be divided into five categories, and APS plays an important role in the pathogenesis of autoimmune disease and pre-thrombotic state [88].

Autoimmune liver disease (ALD) includes autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), and overlap syndrome. Few APS-related cases of autoimmune liver disease have been reported recently [89–94].

#### **4.5. Splenic manifestations**

The splenic manifestations associated with APS are primarily splenic infarcts which are often associated with vascular damage to other abdominal organs [95–98].

In a study of 89 patients with splenic infarction found that 39% of the patients had APS, especially in young patients under 50 years of age, and APS is the leading cause of splenic infarction [99]. Auto splenectomy or functional asplenia, is a rare complication occurring in APS. Auto splenectomy or functional asplenia usually occurs in patients with SAPS, especially those secondary to systemic lupus erythematosus. Only three cases of APS has been reported with this complication so far [100–102].

#### **4.6. Pancreatic manifestations**

A total of 10 APS related pancreatic lesions have been reported to date [24,103–111]. Pancreatitis was the main manifestation in 8 cases and pancreatic duct injury in the other 2 cases. One of these cases was characterised by recurrent acute pancreatitis, therefore special attention should be paid to APL in patients with idiopathic pancreatitis [108].

#### **4.7. The catastrophic antiphospholipid syndrome (CAPS)**

Catastrophic antiphospholipid syndrome (CAPS) refers to the widespread thrombosis of small or large and small blood vessels in the body within a short period of time (usually within a few days to a few weeks), resulting in ischemia and necrosis of multiple organs [1]. About 1% of patients with APS will develop CAPS [1]. The main difference between APS and CAPS is the higher incidence of microthrombosis in CAPS patients, meanwhile, the mortality rate of CAPS patients was significantly higher than that of APS patients [112]. Intestinal tract is the most common abdominal organ involved in CAPS patients, mainly presenting with abdominal pain, abdominal distension, nausea, vomiting and other symptoms of intestinal ischemia and necrosis, and in severe cases, diffuse necrosis of large and small intestine may occur. Autopsy of CAPS patients showed intestinal involvement in 30.5%, spleen involvement in 28.8%, liver involvement in 20.3%, pancreas and gallbladder involvement was relatively small [113].

### **5. Treatment strategies**

#### **5.1. Drug treatment**

Anticoagulation is the basis of treatment for patients with thrombotic APS. Long-term anticoagulation therapy is recommended for patients with digestive system involvement by thrombotic APS. The target

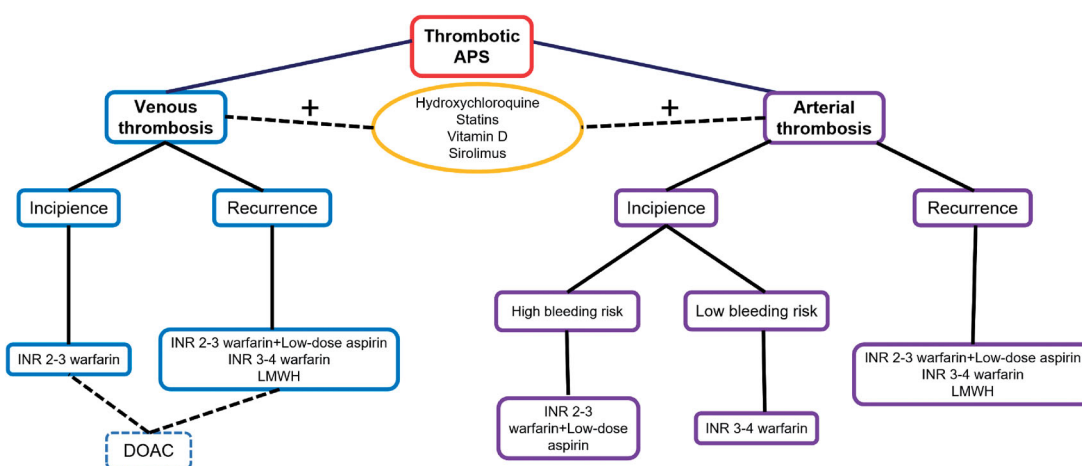
International Normalized Ratio (INR) 2-3 or 3-4 is recommended depending on clinical scenario [114]. Warfarin therapy with target INR of 2-3 is recommended for patients with incipient venous thrombosis. While, for patients with recurrent venous thrombosis, addition of low-dose aspirin (LDA,75-100mg) or up-regulated target INR of 3-4 with warfarin therapy or low molecular weight heparin (LMWH) may be considered [114]. With warfarin therapy, target INR is recommended to be 3-4 in patients with low bleeding risk for arterial thrombosis. For patients at high bleeding risk, the target INR can be controlled at 2-3 with a co-administration of LDA (114). It should be noted that APS patients with target INR of 2-3 are more likely to have recurrent thrombosis events than APS patients with target INR of 3-4. And, the mortality of APS patients is higher due to thrombosis compared with bleeding [115]. In patients with recurrent arterial thrombosis despite adequate treatment with warfarin, after evaluating potential causes, an increase of target INR to 3-4 or addition of LDA or switch to LMWH can be considered [114].

There are drawbacks of treatment with warfarin, including frequent laboratory monitoring, increased risk of bleeding and many interactions with diet and other medications. The direct oral anticoagulants (DOAC) become more attractive due to lack of dietary restrictions and regular laboratory monitoring, and relative ease of administration. DOAC is a single-enzyme anticoagulant that outperforms warfarin in many ways. It has less interactions with other medications and foods, and it doesn't necessitate INR testing on a regular basis [116]. There is insufficient evidence to endorse or condemn the use of DOAC in

thrombotic APS, according to Cochrane systematic review [117]. However, according to recent randomised clinical trials and meta-analyses, in patients with triple positive aPL, there was a higher risk of thromboembolism recurrence and a higher incidence of major bleeding events in APS patients taking DOAC than those taking warfarin [118–120]. The EULAR recommends DOAC as a possible treatment for patients with either absolute contraindication to warfarin or difficulty reaching the goal INR range [114].

In addition, new treatment strategies are proposed recently for thrombotic APS. The anticoagulants are co-administered with hydroxychloroquine, statins, vitamin D and sirolimus. However, further studies are required to know the efficacy of these drugs in thrombotic APS treatment [121]. A flow chart of the drug treatment strategies for thrombotic APS is illustrated in Figure 2.

For non-thrombotic APS patients, active intervention should still be carried out to prevent thrombotic events and accelerated atherosclerosis. Prophylaxis with low-dose aspirin is recommended for asymptomatic aPL patients to reduce the risk of adverse events such as antibody titres and thrombosis [114]. The prophylactic treatment regimen for high-risk asymptomatic aPL patients remains low-dose aspirin. Studies have shown that traditional cardiovascular risk factors (such as hyperlipidemia, hypertension, smoking, obesity, diabetes, etc.) have additional effects on thrombosis and accelerated atherosclerosis in APS patients, therefore, non-thrombotic APS patients should actively control the traditional cardiovascular risk factors by changing their lifestyle and corresponding pharmacological management (such as



**Figure 2.** Drug treatment strategies for thrombotic APS. APS: antiphospholipid syndrome; LMWH: low molecular weight heparin; DOAC: direct oral anticoagulants.

lipid-lowering drugs, hypoglycemic drugs, antihypertensive drugs, etc.) to prevent accelerated atherosclerosis and arterial thrombosis [114,115].

APS patients generally do not need hormone or immunosuppressive therapy, but for SAPS, the use of hormones or immunosuppressive agents should be considered according to the actual situation [114]. As for the APS-related non-thrombotic digestive system manifestations mentioned above, due to the lack of reported cases and the lack of corresponding randomised clinical trials and systematic reviews, it is not clear whether hormones or immunosuppressants are beneficial to the disease progression and prognosis. However, the EULAR recommends the combination of glucocorticoids, heparin, and plasma exchange or intravenous immunoglobulin as the first-line treatment for CAPS patients [114].

### 5.2. Interventional treatment

In terms of interventional therapy, there are currently no clinical trials to guide clinical decision-making. Only a few active cases of arterial thrombectomy have been documented [122–124]. There are no reported cases of venous thrombectomy. Intravascular interventions such as balloon angioplasty and/or stenting are still controversial because of the hypercoagulability of APS patients and the risk of exacerbating thrombosis with interventional therapy. In addition, intravenous or arterial thrombolytic therapy were reported successfully dissolving venous thrombosis [125] and effectively reducing acute macrovascular thrombosis [126].

### 5.3. Surgical treatment

Surgical treatment of APS patients should be considered in patients with clinical symptoms, imaging and laboratory findings suggestive of necrosis or perforation of digestive tract [127]. For these patients, open abdominal laparotomy is recommended to determine the viability of the bowel and the necessity of resection [128]. It appears to be feasible to reconstruct arteries, but how to establish optimal anticoagulation regimes and long-term management after surgery is another challenge [129]. There is inadequate large-scale clinical data and retrospective analysis to assess the long-term clinical efficacy and prognosis of surgical intervention in patients with acute thrombosis induced by APS.

## 6. Conclusion

Antiphospholipid syndrome includes a wide spectrum of thrombotic and non-thrombotic manifestations of the digestive system. The manifestations are diverse, complex and non-specific, easily confused with other abdominal diseases, making diagnosis difficult and leading to misdiagnosis. Attention should also be paid to the digestive system of APS patients, and the possibility of APS should be considered for recurrent multiple digestive organ lesions or multiple organ injuries. Anticoagulant therapy and prophylaxis are the basis of APS treatment. The proper treatment strategy should be considered according to the actual situation of patients to reduce the burden of thrombosis and bleeding. Interventional therapy and surgical treatment may increase the risk of thrombosis in APS patients. The advantages and disadvantages should be recognised and weighed on the basis of adequate anticoagulation.

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## Data availability statement

The data that support the findings of this study are available in [Pubmed] at [DOI:10.1016/s0163-7827(02)00048-6, DOI:10.1002/art.10187, DOI:10.1038/nrrheum.2017.124, DOI:10.1002/art.40901], reference number [2,6,10,11].

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