

Review Article

Role of antithrombin concentrate in treatment of hereditary antithrombin deficiency

An update

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Summary

Antithrombin (AT) functions as a potent natural anticoagulant and serine protease inhibitor that inactivates many enzymes in the coagulation cascade. Antithrombin also possesses anti-inflammatory properties, many of which are mediated by its actions as an anticoagulant. Hereditary AT deficiency is a rare, underrecognised medical condition that is associated with inadequate endogenous anticoagulation thought to result from impaired inhibition of serine protease coagulation factors. Inherited as an autosomal dominant trait, congenital AT deficiency typically reduces functional AT levels to 40–60% of normal. As a result, individuals with hereditary AT deficiency have a $\geq 50\%$ lifetime risk of venous thromboembolism (VTE). Specifically, AT deficiency is associated with a three- to seven-fold higher risk of VTE compared with other thrombophilias. Thus, maintaining adequate levels of AT during high-risk periods is an important

treatment goal. Long-term anticoagulant thromboprophylaxis is not recommended in asymptomatic patients with AT deficiency because of the increased risk of haemorrhage. However, treatment guidelines recommend short-term thromboprophylaxis in high-risk clinical settings, including surgery, trauma, and management of pregnancy, labour, and delivery. The goal of treatment for patients with hereditary AT deficiency is an initial increase in AT activity to $\geq 120\%$ of normal levels followed by maintenance of AT activity at $\geq 80\%$ of normal levels. Plasma-derived AT, heparin, fresh frozen plasma, and human recombinant AT are treatment options for individuals with hereditary AT deficiency. The objective of this review is to discuss hereditary AT deficiency and the role of AT replacement therapy in the treatment of patients with this congenital disorder.

Keywords

Hereditary antithrombin deficiency, venous thromboembolism, antithrombin, thromboprophylaxis

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Introduction

Antithrombin (AT, formerly AT-III) is a 58-kD glycoprotein that functions as a potent natural anticoagulant and is estimated to provide 80% of the inhibitory activity against thrombin (1). Synthesised in the liver and circulated in the plasma, AT is a serine protease inhibitor (serpin) that inactivates many enzymes in the coagulation cascade, though thrombin and factor Xa are its primary targets (2–4). In plasma, there are two isoforms of AT: alpha (90%–95%), a less potent inhibitor of coagulation, and beta (5%–10%), a potent inhibitor enriched in blood vessel walls (4, 5). In contrast to some direct thrombin inhibitors, which reversibly and transiently block thrombin activity, AT inhibition of thrombin is irreversible (6). AT inhibits coagulation enzymes in

a slow, progressive manner in the absence of heparin and heparin-like glycosaminoglycans (7). However, the presence of heparin induces conformational changes in AT that result in at least a 1,000-fold enhancement of AT activity (4, 6–8).

In addition to its potent anticoagulant activity, AT possesses anti-inflammatory properties, many of which are mediated by its actions in the coagulation cascade (Table 1) (4, 9). Most importantly, thrombin inhibition by AT blocks activation of many inflammatory mediators. Besides blocking thrombin-induced inflammatory pathways, AT also inhibits other coagulation enzymes that stimulate the production of several inflammatory mediators, including interleukin (IL)-6, IL-8, E-selectin, and other molecules involved in monocyte recruitment and adhesion to endothelial cells (4, 9, 10). Antithrombin may also interfere in

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Table 1: Antiinflammatory effects of AT (4, 9).

	Physiologic effects
Thrombin inhibition	<ul style="list-style-type: none"> ● Prevents activation of platelets and endothelial cells ● Suppresses factors that promote neutrophil-endothelial cell interactions (e.g. IL-1, IL-6, IL-8, MCP-1, P-selectin)
Factor Xa inhibition	<ul style="list-style-type: none"> ● Suppresses factors that promote neutrophil-endothelial cell interactions (e.g. IL-6, IL-8, E-selectin)
Factor VIIa inhibition	<ul style="list-style-type: none"> ● Prevents complex formation with tissue factor and subsequent upregulation of cytokines (e.g. IL-6, IL-8)
Prostacyclin synthesis/secretion	<ul style="list-style-type: none"> ● Suppresses platelet activity (aggregation and attachment) ● Inhibits attachment of neutrophils to endothelial cells ● Decreases release of IL-6, IL-8, and TNF by endothelial cells
Leukocyte inactivation	<ul style="list-style-type: none"> ● Prevents neutrophil rolling and adhesion and subsequent tissue damage

AT, antithrombin; IL, interleukin; MCP, monocyte chemotactic protein; TNF, tumor necrosis factor.

Table 2: Genetic mutations associated with hereditary AT deficiency (21, 22).

Description	Number of mutations identified	Example
Type 1 deficiency		
Point mutations	80	Arg to stop in codon 129
Frameshift deletions/insertions	30	6-bp deletion in codons 106–108
Major gene deletions	12	2.8-kb deletion starting in intron 4
Type 2 deficiency		
Reactive-site mutation	12	Arg to Cys, His, or Pro at PI position 393
Heparin binding-site mutation	12	Ile to Asn at position 7
Pleiotropic effect mutation	11	Pro to Leu at position 407

AT, antithrombin; Arg, arginine; Asn, asparagine; bp, base pair; Cys, cysteine; His, histidine; Ile, isoleucine; kb, kilobase; Leu, leucine; Pro, proline.

the formation of complexes between tissue factor and factor VIIa, complexes that promote synthesis of inflammatory cytokines and chemokines (9).

Hereditary AT deficiency is associated with inadequate endogenous anticoagulation thought to result from the impaired inhibition of serine protease coagulation factors (1, 3, 11). Studies in patients with AT deficiency indicate persistent elevated plasma levels of the thrombin activation peptide, prothrombin fragments 1 and 2. This is evidence of continuous activation of coagulation in the absence of AT (12). Inherited as an autosomal dominant trait, congenital AT deficiency typically reduces functional AT levels to 40–60% of normal. As a result, individuals with hereditary AT deficiency have a ≥50% lifetime risk of venous thromboembolism (VTE) (1, 13). Although the true prevalence of congenital AT deficiency is unknown, estimates suggest that one in 500 to one in 20,000 individuals are affected (13, 15). Clinical studies suggest that low AT levels are associated with the potential for adverse events (AEs) and poor patient outcomes due to the increased risk of venous thrombosis associated with surgical procedures, pregnancy, and trauma (3, 16, 17). Thus, maintaining adequate levels of AT during high-risk states is an important treatment goal. The objective of this review is to discuss hereditary AT deficiency and the role of AT replacement therapy in the treatment of patients with this congenital disorder.

Overview of hereditary AT deficiency

The normal AT activity level in healthy adults is approximately 1 U/ml, with the specific range of 0.8 to 1.2 U/ml according to most assays (1). Thus, measurements of AT activity are often expressed as a percentage of normal (i.e. 80% to 120%). Antithrombin activity in healthy newborns is approximately 60% of the normal adult level. Antithrombin levels in children are slightly higher than adult levels (18, 19). Individuals with type 1 hereditary AT deficiency have low levels of circulating AT that are associated with an estimated 50% reduction in plasma AT antigen levels and activity. In contrast, type 2 hereditary AT deficiency is characterised by normal AT antigen levels, but dysfunctional protein, and is associated with a 50% reduction in plasma AT activity. Subtypes of type 2 AT deficiency are classified based on the site of genetic defect as type 2a (reactive-site defect), type 2b (heparin binding site), or type 2c (pleiotropic effect [i.e. reactive site and heparin binding site]) (20–22).

AT deficiency is inherited as an autosomal dominant trait, and in the majority of cases, hereditary AT deficiency is heterozygous (20–22). Homozygous deficiency is extremely rare and is associated with neonatal thrombosis, which is often fatal. The most common genetic mutations associated with type 1 hereditary AT deficiency are point mutations, followed by frameshift deletions/insertions and major gene deletions (Table 2) (21, 22). Type 2 hereditary AT deficiency is associated with

Table 3: Coinheritance of thrombophilic mutations increases the risk of VTE (27).

Thrombophilia	Patients, n	Patients with thrombosis	
		n (%)	Median age of first episode (range), years
AT deficiency	30	15 (50)	26 (20–49)
Factor V Leiden	5	1 (20)	40 (NA)
Both defects	12	11 (92)	16 (0–19)

AT, antithrombin; NA, not applicable; VTE, venous thromboembolism.

mutations that result in substitutions of specific amino acids and alter protein function (e.g. substitutions in the reactive site, heparin binding site, or both sites). More than 120 AT mutations have been described (23).

Hereditary AT deficiency is a rare and underrecognised medical condition (11, 15). In the general population, type 2 AT deficiency is more prevalent than type 1 deficiency. One clinical study identified 16 cases of hereditary AT deficiency among 9,669 healthy blood donors and reported that 14 patients (88%) were classified as having type 2 AT deficiency, whereas only two patients (13%) had type 1 AT deficiency (24). Alternatively, in symptomatic patients and their families, type 1 hereditary AT deficiency is more prevalent than type 2. A separate clinical study identified 25 AT-deficient patients who had experienced ≥ 1 thrombotic episode and an additional 85 first- and second-degree relatives with hereditary AT deficiency (25). Of these 110 individuals, 81 (74%) had type 1 AT deficiency and 28 (25%) had type 2 AT deficiency (data not reported for 1 patient). Overall, type 1 hereditary AT deficiency is associated with a greater risk of thrombosis than other thrombophilias (1, 25). Specifically, AT deficiency is associated with a three- to seven-fold higher risk of VTE compared with other thrombophilias (e.g. prothrombin gene mutation, factor V Leiden [heterozygous])

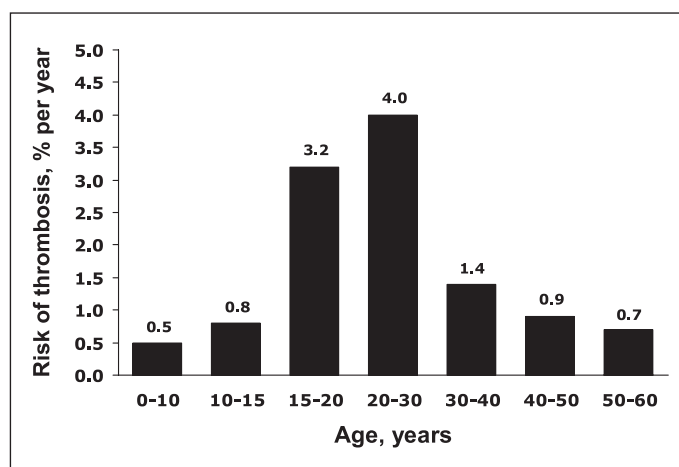


Figure 1: Risk of thrombosis (% per year, per age group) in individuals with hereditary antithrombin deficiency. Individuals with hereditary antithrombin deficiency aged 20 to 30 years are at greatest risk of thrombosis (4.0% per year) versus individuals < 10 years of age (0.5% per year) or individuals 50 to 60 years of age (0.7% per year) (13).

(26). Patients with VTE are 20 times more likely to have an AT deficiency versus the general population. Additionally, coinheritance of additional thrombophilic mutations substantially increases the risk of VTE at an earlier age (Table 3) (27).

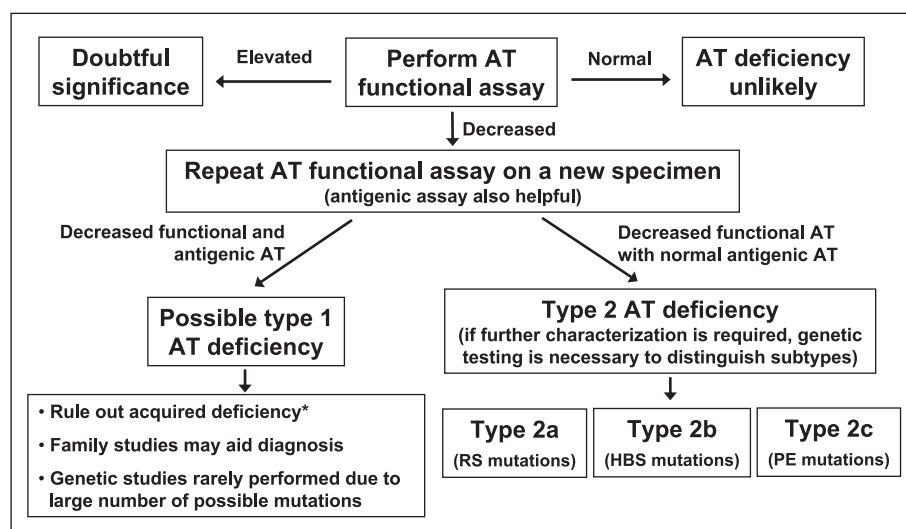
Hereditary AT deficiency often remains undiagnosed prior to the first thrombotic episode. The onset of thrombotic events occurs between the ages of 10 and 35 years (median age, 24 years) in 67% of patients with hereditary AT deficiency (28). The cumulative risk of thrombosis increases with age such that $\sim 10\%$ of patients 10 to 15 years of age will have experienced ≥ 1 thrombotic event, and 95% of individuals 50 to 60 years of age will have experienced ≥ 1 thrombotic event (13). However, individuals with hereditary AT deficiency aged 20 to 30 years are at greatest risk of thrombosis (4.0% per year) versus individuals < 10 years of age (0.5% per year) or individuals 50 to 60 years of age (0.7% per year; Fig. 1) (13). The incidence of thrombosis is often spontaneous (36%), but an increased risk for a thrombotic event is associated with pregnancy (13%), delivery (15%), surgery (13%), and trauma (3%) (28). Although lower-extremity thromboses are more common, VTE may develop in any location (e.g. iliac, mesenteric, or pulmonary veins). Lower extremity thromboses, in turn, exacerbate the risk of other complications such as pulmonary embolism (29). In patients with DVT, the risk of pulmonary embolism was 240% higher in patients with inherited AT deficiency.

Because diagnosis of hereditary AT deficiency is challenging, recognition of clinical features is crucial to achieving successful patient outcomes. Such clinical features include the occurrence of a thrombotic episode at an early age, a family history of VTE, recurrent VTE, or thrombosis at unusual sites (e.g. axillary vein or mesenteric vein) (13). Additional clinical signs include thrombosis during pregnancy and thrombosis resistant to heparin therapy. Laboratory screening assays have been implemented as diagnostic tools for hereditary AT deficiency (21). Functional AT assays employing amidolytic methods are often used as initial tests for AT deficiency. These functional tests are highly specific and sensitive and provide a positive predictive value of 96%. However, most cannot distinguish type 2b deficiency from other subtypes. Antigenic AT assays employing radial immunodiffusion methodology are highly specific and may be beneficial for distinguishing type 1 AT deficiency from type 2. However, radial immunodiffusion tests are characterised by low sensitivity. Radial immunodiffusion has largely been supplanted by ELISA, and more recently, the immunoturbidimetric test. Both assays have greater sensitivity and are easy to perform. Overall, the diagnosis and classification of hereditary AT deficiency is a complex, multifactorial process that involves the integration of clinical features, findings from laboratory screening assays, family history, and genetic testing (Fig. 2). Finally, although genetic tests may be of scientific interest to further define the mechanism of specific AT deficiency, these tests may not be necessary for the management of patients.

Management of hereditary AT deficiency

Long-term anticoagulant thromboprophylaxis is not recommended in asymptomatic patients with AT deficiency because of the increased risk of haemorrhage (1). However, treatment

Figure 2: The diagnosis of hereditary AT deficiency is a complex, multifactorial process that involves the integration of clinical features, findings from laboratory screening assays, family history, and genetic testing. *Due to heparin therapy, liver disease, disseminated intravascular coagulation, thrombosis, malignancy, L-asparaginase therapy, malnutrition, or nephrotic syndrome. The patient must not be on heparin when assaying AT levels. AT, antithrombin; HBS, heparin binding site; PE, pleiotropic effect; RS, reactive site. Adapted from Kottke-Marchant and Duncan (21). With permission from *Archives of Pathology & Laboratory Medicine*. Copyright 2002. College of American Pathologists.



guidelines recommend short-term thromboprophylaxis for individuals with hereditary AT deficiency in high-risk clinical settings, including surgery, trauma, management of pregnancy, labor, and delivery (21, 30). The goal of treatment for these patients is the initial increase in AT activity to $\geq 120\%$ of normal levels followed by maintenance of AT activity at $\geq 80\%$ of normal levels.

Heparin and low-molecular-weight heparin

Heparin and low-molecular-weight heparin (LMWH) are the most commonly administered anticoagulants in high-risk clinical settings (20, 30). Heparin alone has no direct anticoagulant effect but potentiates the activity of AT by enhancing AT-mediated inhibition of coagulant enzymes more than 1,000-fold as the result of a conformational change in AT (31). Administration of heparin is limited in some instances. For example, an inadequate response to heparin, known as heparin resistance, has been reported in up to 22% of patients undergoing major surgery (32–37). Including AT deficiency, several other mechanisms for heparin resistance have been identified such as increased heparin clearance, elevations in various heparin-binding proteins, and elevations in factor VIII and fibrinogen levels (38). Medications such as aprotinin and nitroglycerin can cause drug-induced heparin resistance. In practical experience, heparin resistance is more commonly observed among patients receiving unfractionated heparin as opposed to LMWH, which may be explained by absorption of unfractionated heparin to various plasma proteins, macrophages, and endothelial cells. Additionally, heparin administration has been increasingly discontinued during labor and delivery in patients with hereditary AT deficiency because of the risk of bleeding following delivery or in relation to epidural anesthesia (1). Patients with AT deficiency would be expected to exhibit heparin resistance in the absence of AT replacement.

Fresh frozen plasma

Fresh frozen plasma (FFP) is an additional treatment option for individuals with hereditary AT deficiency; however, clinical evidence demonstrating its efficacy is lacking. In addition, safety

issues are associated with the administration of human blood products (39, 40). Transmission of viral infections, such as human immunodeficiency virus (HIV), hepatitis B, and hepatitis C is a small but not insignificant risk associated with transfusion of homologous blood products such as FFP (39). Other viral risks, including emerging viruses, may be related to transfusion of blood products. The recent epidemic of West Nile virus (WNV) is notable, as the prevalence of WNV among blood donors in the United States was reported to range from approximately 1 in 1,000 to 1 in 23,000 between 2002 and 2004 (40). In addition to risks associated with viral transmission, there remains a risk of clerical errors associated with collection, storage, and administration of blood products. Furthermore, prions that cause variant Creutzfeldt-Jacob disease are carried in plasma, but the risk of transfusion-related transmission is uncertain.

AT concentrate

Plasma-derived AT concentrate (Thrombate®; Talecris Biotherapeutics, Inc, Research Triangle Park, North Carolina, USA) is the only product approved by the United States Food and Drug Administration (FDA) for the treatment of hereditary AT deficiency and is indicated for the treatment of patients with hereditary AT deficiency in connection with surgical or obstetrical procedures or when these patients suffer from thromboembolism (41). Antithrombin concentrate is derived from the pooled human plasma of healthy donors. The rigorous heat treatment and purification process implemented in manufacturing AT has been shown to effectively achieve viral inactivation (42, 43). No cases of viral transmission have been reported in patients who have received AT and were not transfused with other blood products (11, 31, 44, 45). Two cases of hepatitis B seroconversion in patients who received AT were considered to be related to multiple transfusions with other blood products (44). Similarly, no case of viral transmission related to AT administration has been reported in patients who underwent cardiac surgery (45). Thus, AT is potentially safe with respect to infectious disease transmission.

Table 4: Antithrombin concentrates that are available worldwide.

Product	Company	Indications
Atenativ®	Octapharma (Lachen, Switzerland)	Congenital deficiency Acquired AT deficiency
Atryn®	GTC Biotherapeutics (Framingham, MA, USA)	Hereditary AT deficiency
Kybernin®	CSL Behring (King of Prussia, PA, USA)	Acquired AT deficiency
Anthrobin PI500	CSL Behring (King of Prussia, PA, USA)	Congenital AT deficiency Disseminated intravas- cular coagulation

AT, antithrombin.

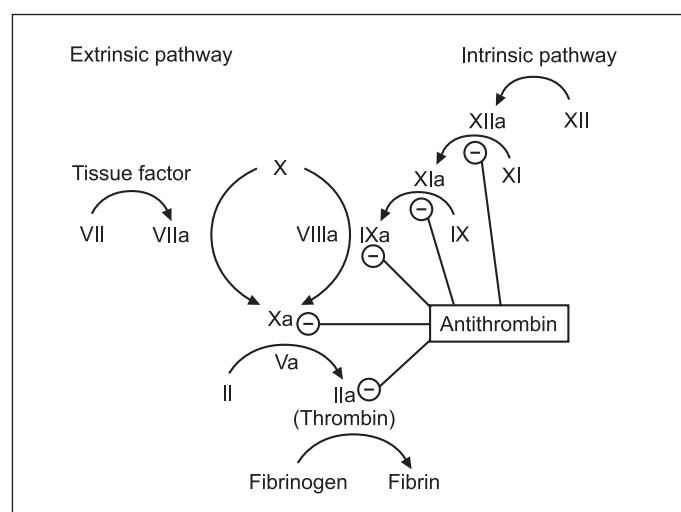


Figure 3: Antithrombin functions as a potent natural anticoagulant and serine protease inhibitor (serpin) that inactivates many enzymes in the coagulation cascade. Thrombin and factor Xa are the primary targets. From Maclean and Tait (1). With permission.

Although Thrombate is the only marketed plasma-derived AT concentrate in the United States, there are several concentrates available worldwide (Table 4), and others are in development. These agents are either derived from large plasma pools or are developed using recombinant methods, and in some cases they have been used successfully for many years. A recombinant human AT (rhAT; Atryn® was approved by the US FDA on February 6, 2009), produced in the milk of transgenic goats, is available that is distinguished from plasma-derived AT by a different glycosylation pattern that results in greater affinity for heparin (46). The clinical efficacy of rhAT is being evaluated; however, administration of rhAT replacement has been described in a small case series including six procedures in five patients (47, 48). All individuals who received rhAT had a significant history of thrombosis and underwent major surgical procedures without experiencing VTE or a major bleeding episode.

Use of AT replacement therapy in patients with hereditary AT deficiency

Recommendations for the use of AT replacement therapy are based on several critical sources including evidence-based guidelines (20, 30), drug labelling, and clinical experience. Although practice guidelines are important to clinical decision making, they often differ between each other and experts often disagree. Indeed, clinical experience with AT concentrates in inherited AT deficiency is quite limited. In this context, there is significant need for expert interpretation. In the present review, the majority of the data presented are consistent with the FDA-approved congenital AT deficiency indication for AT and are consistent with how the agent is used in the author's practice.

Hereditary AT deficiency is associated with inadequate endogenous anticoagulation thought to result from the impaired inhibition of serine protease coagulation factors (1, 3, 11, 12). Antithrombin possesses potent natural anticoagulant properties that promote neutralisation of coagulation enzymes (Fig. 3) (1). In addition to inhibiting thrombin, AT inhibits factors IXa, Xa, XIa, and XIIa. Plasma-derived AT is currently indicated for thromboprophylaxis for patients with hereditary AT deficiency with a medical history of thromboembolism or in high-risk clinical settings including surgical or obstetrical procedures (1, 41).

Inherited AT deficiency and other thrombophilic disorders are linked to maternal thromboembolism and adverse pregnancy outcomes (49–51). In the general population, the incidence of pregnancy-associated VTE is approximately 1 in 1,000 deliveries, with a greater risk postpartum versus antepartum (20). In contrast, the incidence of thrombotic complications during pregnancy may be as high as 70% in women with hereditary AT deficiency (52). Thromboprophylaxis with heparin or vitamin K antagonist during pregnancy and for six weeks after delivery was associated with a 15-fold reduction in fetal loss rate in a study of women with hereditary thrombophilia, including women with AT deficiency (53). Yamada et al. (54) reviewed 12 reports of 25 women with hereditary AT deficiency who received AT treatment for managing pregnancy. Seven women (28%) who received thromboprophylaxis that included AT experienced antepartum thrombosis and one woman (4%) experienced postpartum thrombosis. However, most pregnancies ended in a favorable outcome, with 15 vaginal deliveries (60%), four cesarean sections (16%), and six cases of unknown mode of delivery (24%). Antithrombin treatment was not associated with reported fetal AEs.

Treatment guidelines recommend prophylactic therapy during pregnancy and the postpartum period for women with AT deficiency, regardless of VTE history (55). Oral anticoagulants cross the placenta and carry the risk of fetal haemorrhage and teratogenic effects (11). Heparin does not cross the placenta and is a common treatment choice; however, heparin may have a reduced efficacy in AT deficiency due to heparin resistance and must be discontinued at the time of delivery (11, 20). Thus, treatment with AT replacement therapy is recommended during delivery (55). Numerous case studies have reported safe and effective thromboprophylaxis with AT monotherapy or in combination with heparin during pregnancy (11, 54, 56–60), labor

and delivery (11, 48, 54, 56–63), and postpartum (11, 44, 48, 54, 57, 59, 60, 63).

Surgery and trauma activate the coagulation cascade, resulting in consumption of AT (17). Clinical studies have demonstrated the association of low AT levels and adverse patient outcomes, including development of sepsis, thromboembolic events, need for infusion of blood products, organ failure, prolonged hospital stay, and mortality (1). Successful thromboprophylaxis with AT or rhAT as monotherapy or in combination with other anticoagulants has been demonstrated in a variety of clinical settings including cardiac or vascular surgeries, hysterectomy, gastrointestinal or urinary tract surgeries, and orthopaedic surgery (11, 44, 47, 64–67). Treatment with AT in these studies was associated with a favorable safety profile with no reported thrombotic complications in >20 case reports. For example, in a clinical study of 452 evaluable AT infusions administered to patients with hereditary or acquired AT deficiency, 13 (3%) mild-to-moderate AEs were reported (e.g. chest tightness, abdominal cramps, dizziness, fever), no serious AEs were observed, and treatment with AT was associated with favorable viral safety (e.g. no evidence of hepatitis or HIV seroconversion) (11).

Regarding dosing of plasma-derived AT, the goal of the initial loading dose is to elevate the plasma AT level to 120%, based on an expected 1.4% increase above baseline activity level per IU/kg of AT administered (11). Because 1 IU of AT corresponds to the activity of AT in 1 ml of normal human plasma, and 1 vial of AT containing approximately 500 IU AT is reconstituted with water to 10 ml of solution, administration of a minimal volume of drug achieves a dramatic increase in AT concentration (3, 41). Alternatively, the larger volume load associated with other therapies (e.g. FFP) is a safety concern for at-risk patient populations due to the risk for volume overload and haemodilution (67).

The expense associated with AT administration is an important practical consideration. Though the 2006 Red Book price for AT is \$2.07 per IU (68), most institutions acquire plasma-derived AT for approximately \$1.68 per IU. Thus, a standard 500-ml dose of AT is associated with a cost of approximately \$840. Antithrombin is a more expensive treatment to use compared with the

other therapies (FFP costs approximately \$70 to \$110 for 500 ml), but this does not include the additional costs of thawing and transporting units to the operating room. Antithrombin can be reconstituted and available for administration in a matter of minutes (69), increasing the speed with which patients may be treated. The elimination of waiting time may decrease hospital costs and improve patient outcomes.

Conclusions

AT is the predominant naturally occurring inhibitor of coagulation and plays a central role in maintaining haemostasis during hypercoagulable states. Additionally, AT is well positioned to provide protection against inflammation because of its central inhibitory role in many coagulation processes. Inherited AT deficiency is associated with a 50% reduction in plasma AT activity, which increases the risk of thromboembolic events and poor patient outcomes (21). Indeed, patients with hereditary AT deficiency are at greater risk of thrombotic complications compared with individuals with other hereditary thrombophilias (e.g. defects in protein C or protein S) (26). Thus, treatment of patients with hereditary AT deficiency is indicated in clinical settings of high thrombotic risk. Antithrombin concentrate is an approved treatment for hereditary AT deficiency and has been proven to be a safe and effective agent for thromboprophylaxis when used appropriately in approved patient populations since 1992 (11, 44, 47, 48, 52, 55–63, 65, 66). Additionally, administration of AT is associated with a favorable safety profile with no reports of thrombotic complications or serious AEs. In conclusion, AT replacement in patients with hereditary AT deficiency is associated with a favorable benefit-to-risk ratio and may provide substantially improved patient outcomes for individuals with this congenital disorder.

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