

Recommendations for the use of antithrombin concentrates and prothrombin complex concentrates

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Antithrombin concentrates

Introduction

Antithrombin (AT) concentrates can be therapeutically useful in cases of primary and acquired AT deficiency; their use, to be reserved to clinical conditions in which low levels of functional AT are associated with a thrombotic imbalance in haemostasis, has yet to be supported by clear scientific evidence.

Notions of physiology

AT is a glycoprotein synthesised by the liver. Its molecular weight is 58,000 Da and it circulates in the plasma at a concentration of 150 mg/mL¹⁻³. Belonging to the family of serpins or inhibitors of serine proteases, it inhibits proteases. AT is the most potent naturally occurring inhibitor of coagulation and plays a fundamental role in maintaining haemostatic balance. Furthermore, it has anti-inflammatory and anti-aggregant properties mediated through the release of prostacyclins from endothelial cells³.

Normal values of AT activity in the plasma range from 80% to 120%. In normal conditions its biological half-life is 1.5-2.5 days; in conditions of acquired deficiency and in the presence of heparin, the half-life of AT can be notably shorter, being reduced to even a few hours.

Preparations of AT

AT concentrates, like all other plasma derivatives, are prepared from pools of human plasma, made from at least 1,000 different donors⁴.

Various companies have been licensed to manufacture this product for clinical use. AT preparations undergo microbial inactivation by

pasteurisation, sometimes followed by nanofiltration. Vials containing 500, 1,000, 1,500 and 2,000 UI are available.

Mechanism of action

AT is used as replacement therapy in conditions of acquired or inherited deficiency, in particular circumstances. Its anticoagulant activity is mainly due to the inhibition of thrombin, activated factor X (FXa) and, to a lesser degree, also other activated clotting factors (FIXa, FXIa, FXIIa)¹. The rate of formation of the thrombin-antithrombin complex is very greatly increased by heparan sulphate, present on the surface of endothelial cells. Subjects lacking AT have an increased risk of thrombosis, particularly in the presence of other thrombophilic conditions.

Congenital AT deficiency

The estimated prevalence is 1/2,000-5,000 in the general population and 2-3% in a selected population of patients with thrombotic events^{1,5}.

There are two different types of congenital deficiency of AT, which are inherited in an autosomal dominant manner:

- **TYPE I (quantitative defect)**, in which there are proportional decreases in the concentration and, therefore, functional activity of the AT.
- **TYPE II (qualitative defect)**, characterised by normal levels of protein, but a reduction in its functional activity.

Acquired AT deficiency

Various clinical conditions are associated with acquired AT deficiency^{5,6}:

- 1) Reduced production⁷⁻¹²:

- acute and chronic liver disorders;
 - premature neonates;
 - treatment with L-asparaginase.
- 2) Increased excretion/loss^{13,14}:
- protein-losing enteropathy;
 - nephrotic syndrome;
 - burns.
- 3) Dilution⁵:
- massive transfusion;
 - plasma exchange;
 - extracorporeal circulation.
- 4) Increased consumption^{3,15-23}:
- disseminated intravascular coagulation (DIC);
 - major surgery;
 - heparin infusion;
 - multiple trauma;
 - severe sepsis/septic shock;
 - severe thromboembolism;
 - haemolytic-uraemic syndrome;
 - pre-eclampsia.

Indications

The use of AT concentrates, to be reserved to clinical conditions in which low levels of functional

AT are associated with a thrombotic imbalance in haemostasis, has yet to be supported by clear scientific evidence.

1. Patients with congenital AT deficiency

In the absence of symptoms or risk factors, congenital AT deficiency is not an indication for replacement therapy with AT concentrates, which should be reserved, on a temporary basis and in association with heparin therapy, to the following circumstances (*Grade of Recommendation: 2C*)^{1,6}:

- **prophylaxis** of deep vein thrombosis and thromboembolism in high-risk conditions: major surgery, obstetric procedures (such as delivery or abortion), trauma, immobilisation;
- **treatment of ongoing thrombosis**, until the indicated level of oral anticoagulation is reached.

Patients with congenital AT deficiency and repeated episodes of thromboembolism must receive life-long oral anticoagulant therapy (*Grade of Recommendation: 2C+*)^{1,6} (Table I).

2. Patients with acquired AT deficiency

There is little evidence concerning treatment with

Table I – Indications for the use of antithrombin

Clinical conditions	Notes	GoR
Congenital antithrombin deficiency		
Prophylaxis of deep vein thrombosis and thrombo-embolism in high-risk situations	For the entire time that the high-risk state is present	2C
Treatment of ongoing thrombosis	Until the indicated level of oral anticoagulation is reached This latter must be maintained life-long in cases of repeated thromboembolism	2C 2C+
Acquired antithrombin deficiency		
Increased consumption (in DIC associated with severe sepsis)	Administration of high doses, not associated with heparin, may improve survival	2C+
- DIC associated with trauma, burns, pregnancy - neonates of mothers with AT deficiency or a family history of venous thromboembolism - ongoing thrombosis with low levels of AT and resistance to heparin - acute thromboembolism during treatment with L-asparaginase - extracorporeal circulation - thrombosis of the hepatic artery following orthotopic liver transplantation - veno-occlusive disease following bone marrow transplantation - chronic, not decompensated conditions of deficiency: acute or chronic liver disease, nephrotic syndrome, protein-losing enteropathy, pre-eclampsia, neonatal respiratory distress syndrome, multiple trauma and post-operatively in the absence of DIC.	There is little evidence of the efficacy of treatment with AT in these clinical circumstances	

GoR: Grade of Recommendation

AT in conditions of acquired deficiency; replacement therapy with AT may be useful, although the levels of evidence are not high, in DIC associated with severe sepsis, in which the use of high doses, not associated with heparin, could improve the survival of patients (*Grade of Recommendation: 2C+*)^{3,5,15-18,20-36}.

Further studies are needed on the use of AT concentrates in the case of^{1,6}:

- DIC associated with trauma, burns, pregnancy;
- neonates of mothers with AT deficiency or a family history of severe venous thromboembolism;
- ongoing thrombosis with low levels of AT and resistance to heparin;
- acute thromboembolism during treatment with L-asparaginase⁹⁻¹²;
- extracorporeal circulation;
- thrombosis of the hepatic artery following orthotopic liver transplantation;
- veno-occlusive disease following bone marrow transplantation^{37,38};

Furthermore, the use of AT is not generally indicated (given the lack of proof of clinical efficacy), even when AT levels are considerably below normal, in the following conditions of chronic, not decompensated deficiency: acute or chronic liver disease, nephrotic syndrome, protein-losing enteropathy, pre-eclampsia, neonatal respiratory distress syndrome, multiple trauma and post-operatively in the absence of DIC (Table I).

Calculation of the dose of AT to administer

There is no evidence that higher than normal levels of AT provide greater protection than physiological levels, just as an overdose does not imply an increased risk of bleeding. Before starting replacement therapy with a specific concentrate, it is advisable to assay AT functional activity. Given that the administration of 1 UI/kg of body weight increases plasma AT activity by 1.5%, the dose to administered is calculated as follows:

$$\text{units of AT} = \text{body weight (kg)} \times [\text{desired level} - \text{assayed activity}(\%)]/1.5.$$

For example:

$$60 \text{ kg} \times (100 - 38\%)/1.5 = 2,480 \text{ UI.}$$

The dose and timing of subsequent administrations are based on the results of monitoring plasma AT activity every 12-48 h.

Monitoring indices for clinical auditing

Use of AT treatment in the following conditions:

- congenital AT deficiency in the absence of symptoms or risk factors and/or with AT values > 70%.

Side effects and adverse reactions

AT infusions are generally well tolerated; allergic-type reactions are, however, possible.

The use of AT concentrates contemporaneously with heparin increases the risk of bleeding and careful clinical and laboratory monitoring is, therefore, necessary, particularly in patients at high haemorrhagic risk.

Recommendations

It is recommended that all the details of the product infused, including its batch number, are recorded in the clinical records.

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Prothrombin complex concentrates

Introduction

Prothrombin complex concentrate (PCC) may be therapeutically useful for the acute and temporary correction of deficiencies of factors in the prothrombin complex. There are no randomised, controlled clinical trials providing clear evidence on the use of PCC, but only observational or retrospective studies, on the basis of which the following recommendations were formulated. Reference is also made to the guidelines from the Italian Association of Haemophilia Centres (AICE) and the Italian Federation of Anticoagulation Clinics (FCSA)¹⁻³.

Preparations of PCC

PCC contain factor II (FII), factor IX (FIX) and factor X (FX), with procoagulant effects, as well as naturally occurring and physiological inhibitors of coagulation such as protein C, protein S and traces of antithrombin, heparin and vitronectin⁴. PCC containing unactivated clotting factors and one concentrate of activated factors are available. PCC, like all other plasma derivatives, are prepared from pools of human plasma, made from at least 1,000 different donors⁵.

Various companies have been licensed to manufacture PCC for clinical use. These products are subjected to viral inactivation, both by physical methods (heating or vapour) and chemical methods (use of solvent-detergent). Vials containing 200, 500 and 1,000 UI are available.

Indications

Congenital deficiencies

Unactivated PCC is used only in the case of documented isolated deficiencies of FII and FX, for the prophylaxis or treatment of bleeding (table II); if it is not available, fresh-frozen plasma (FFP) can be used as an alternative. Similarly, in cases of congenital deficiencies of FVII and FIX, PCC should only be used when the specific clotting factor is not available (*Grade of Recommendation: 2C*)^{1,6-8}.

Activated PCC is a therapeutic option, together with recombinant activated factor VII (rFVIIa), for the treatment of bleeding episodes in patients with haemophilia A with inhibitors (*Grade of Recommendation: 2C*)^{1,6,9}.

The dose indicated for congenital deficiency of FII or FX is 20-30 UI/kg, depending on the severity, site and extension of the bleeding. Once the first dose has been administered, the level of the individual deficient factor must be monitored in order to be able to decide the subsequent maintenance dose, taking into consideration that the minimum level required for haemostasis is 20-30 UI/dL for FII and 10-15 UI/dL for FX.

Greater detail can be gained from the AICE guidelines or by referring to Centres with expertise in the management of disorders of haemostasis¹ (Table II).

Acquired deficiencies

In patients with acquired deficiencies of factors in the prothrombin complex (due to severe liver disease,

Table II – Indications for the use of PCC

Congenital deficiencies of clotting factors in the prothrombin complex	GoR
Deficiencies of factors II and X: for prophylaxis or treatment of bleeding. If PCC are not available, FFP can be used as an alternative.	2C
Haemophilia B and inherited factor VII deficiency: when the specific factor IX and VII concentrates are not available.	
Haemophilia A with inhibitors, during bleeding episodes (activated PCC).	
Acquired deficiencies of clotting factors in the prothrombin complex (Factors II, IX, X)	GoR
Bleeding episodes in the presence of deficiencies of one or more factors of the prothrombin complex.	2C
Limitations to the use of FFP because of the risk of circulatory overload or the need for immediate haemostasis, in the following circumstances:	
-severe liver disease with serious bleeding or in preparation for elective surgery carrying the risk of bleeding (liver transplantation);	
-vitamin K deficiency in the presence of life-threatening bleeding;	
-acquired haemophilia (activated PCC).	2C
-Excessive doses of dicoumarols or the need to suspend them in emergency conditions (acute haemorrhage, urgent surgery).	2C+

GoR: Grade of Recommendation

reduction due to loss or dilution) PCC can be administered, as a second choice alternative to FFP, taking into account that the risk of thrombosis is higher with PCC than with plasma¹⁰⁻¹².

The administration of PCC is indicated (Table II):

1. in patients with deficiency of one or more of the factors of the prothrombin complex, in the presence of bleeding (*Grade of Recommendation: 2C*)^{7,8,13,14}.
2. when there are limitations to the use of FFP because of the risk of circulatory overload or the need for immediate haemostasis, in the following circumstances:
 - severe liver disease with serious bleeding or in preparation for elective surgery carrying the risk of bleeding (liver transplantation) (*Grade of Recommendation: 2C*)^{13,14};
 - vitamin K deficiency (due to antibiotic treatment, persistent diarrhoea, malabsorption, malnutrition), in the presence of life-threatening bleeding (*Grade of Recommendation: 2C*)^{13,14}.
3. to correct excessive use of dicoumarols or when suspending oral anticoagulant therapy in emergency circumstances (acute major haemorrhage, urgent surgery) (*Grade of Recommendation: 2C+*)^{2,3,15-28}.
In the case of oral anticoagulant therapy, PCC may be the treatment of first choice, although depending on the cause, site and extent of the potential or actual bleeding, the use of other therapeutic strategies, such as vitamin K and/or FFP, should be considered.
Although results from adequate clinical trials are not yet available, in life-threatening, extremely urgent situations, an infusion of rFVIIa can be considered as a replacement for PCC, when this latter is not available (as stated by the FCSA) (*Grade of Recommendation: 2C*)^{2,3}.
4. in acquired haemophilia, in which PCC containing activated clotting factors can be used (*Grade of Recommendation: 2C*)^{9,29-33}.

Posology and method of administration

The doses and duration of replacement therapy must be decided on the basis of the haemostatic imbalance, the site and extent of the bleeding, and the clinical situation^{10,22,28}.

Before PCC is administered –compatibly with the urgency of the clinical situation –tests of haemostasis should be performed (PT/INR, aPTT and, if possible,

assays of the factors in the prothrombin complex), in order to decide the dose and duration of the treatment.

In the case of severe bleeding or major surgery, the average first dose to administer, as a bolus, is 20-25 UI/kg. The PT and INR must be evaluated 30-60' after the administration of the PCC, in order to determine whether to continue with this treatment and, if so, at what dose.

Correction of excessive anticoagulation from oral anticoagulant therapy

In the case of major bleeding or surgery that cannot be postponed^{2,3}:

- a) suspend the ongoing oral anticoagulant therapy;
- b) measure the INR.
- c) administer vitamin K intravenously at a dose of 10 mg/100 mL of physiological saline, slowly over about 30'.
- d) infuse the following doses of PCC slowly, over about 10-15':
 - for INR < 2 administer 20 UI/kg;
 - for INR between 2 - 4 administer 30 UI/kg;
 - for INR > 4 administer 50 UI/kg.
- e) measure the INR again at the end of the infusion and ensure that is < 1.5; if this is not the case, repeat the administration of PCC, according to the above scheme.

Alternatively, and particularly if PCC is not available, administer FFP at a starting dose of 15-20 mL/kg.

Monitoring indices for clinical auditing

Use of PCC treatment in the following conditions:

- in the absence of major bleeding;
- in patients on oral anticoagulation undergoing elective surgery with an INR < 1.5.

Contraindications, side effects and adverse reactions

DIC is a contraindication to the use of PCC¹⁰.

Possible side effects and adverse reactions are¹⁰⁻¹²:

- thromboembolic complications;
- allergic and anaphylactic reactions;
- fever;
- development of inhibitors of the clotting factors present in the PCC.

As other blood derivatives, PCC can be considered safe from an infectious point of view, although with some query concerning the potential transmission of prions.

Recommendations

It is recommended that all the details of the product infused, including its batch number, are recorded in the clinical records.

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Appendix A

Working methods of the study group and grades of recommendation

The process of developing these Recommendations, in compliance with the indications contained in the methodological manual of National Programme for Guidelines¹, was based on a systematic review of the literature and updating of existing recommendations on the subject: the recommendations will be discussed in a multidisciplinary context in a subsequent stage and in the relevant institutions. Furthermore, an explicit evaluation of the quality of the proof and the strength with which the single recommendations are adopted and implemented is provided¹.

The methodology used to prepare the grades of recommendations was drawn from that used by the Consensus Conference of the American College of Chest Physicians in 2004².

The recommendations are classified by **grade**, expressed in Arabic numbers (1,2), according to their strength, and in **letters** (A, B, C), according to the evidence and type of study.

In detail (Table I):

- **Grade 1:** the authors are certain that the benefits are greater (or less) than the costs in terms of risk and financial expenditure. This is, therefore, a strong **recommendation**.
 - **Grade 2:** the authors are less certain concerning the above points and, therefore, make a weaker recommendation.
- As far as regards the classification by letters:
- **Grade A:** a recommendation derived from the evidence of numerous, consistent randomised studies.
 - **Grade C+:** a recommendation derived from the analysis of observational clinical studies, but with very consistent results, or from results unequivocally extrapolated from randomised studies.
 - **Grade B:** the clinical studies providing the evidence were randomised, but had important limitations (discordant results, methodological flaws).

- **Grade C:** the recommendation derives from an analysis of observational studies, with less consistent results, or from results extrapolated with a lower degree of certainty from randomised studies; recommendations based on the clinical experience/opinion of experts are also classified as grade C.

The verb "*recommend*" is used for the higher grades (1A, 1C+, 1B, 1C), while the verb "*suggest*" is used for the lower grades (2A, 2C+, 2B and 2C).

In general, any recommendation other than Grade 1A implies that the authors recognise that there are alternative interpretations of the available evidence and that there are other clinical policies that can reasonably be considered appropriate. Furthermore, even the Grade 1A recommendations cannot be applied indiscriminately in every circumstance and in every patient.

The conventional classification of evidence is based on mathematical and statistical criteria, assigning the "strength" of evidence, in order, to: meta-analysis, randomised, controlled, experimental studies, retrospective analyses, prospective follow-ups, transverse population studies, reviews, anecdotal evidence. This is correct as far as concerns the purely clinical studies, particularly therapeutic studies focused on objective outcome evaluations.

In some fields the recommendations remain weak; in others, however, data from clinical studies that have been carried out with methodological rigour in a sufficiently large population have enabled the formulation of specific and more certain recommendations.

Furthermore, it is not always possible to use the aggregated data from meta-analyses: these variables increase the margins of individual decision for each doctor and for each patient.

The recommendations are accompanied by indicators intended to enable clinical auditing¹.

The present document will be revised annually, to include new information that has

become available in the meantime.

Each member making up the study group has signed a statement declaring a lack of conflict of interests, conforming with that adopted by the National Programme for Guidelines¹.

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Table I - Grades of Recommendations

Grade of Recommendation	Clarity of Risk /Benefit	Methodological strength of supporting evidence	Implications
1A	Clear	Randomised controlled trials without important limitations	Strong recommendation; can apply to most patients in most circumstances without reservation
1C+	Clear	No randomised controlled trials but strong results from randomised controlled trials can be unequivocally extrapolated, or overwhelming evidence from observational studies	Strong recommendation; can apply to most patients in most circumstances
1B	Clear	Randomised controlled trials with important limitations (inconsistent results, methodological flaws)	Strong recommendations; likely to apply to most patients
1C	Clear	Observational studies	Intermediate-strength recommendation; may change when stronger evidence is available
2A	Unclear	Randomised controlled trials without important limitations	Intermediate-strength recommendation; best action may differ depending on circumstances or patients' or societal values
2C+	Unclear	No randomised controlled trials but strong results from randomised controlled trials can be unequivocally extrapolated, or overwhelming evidence from observational studies	Weak recommendation; best action may differ depending on circumstances or patients' or societal values
2B	Unclear	Randomised controlled trials with important limitations (inconsistent results, methodological flaws)	Weak recommendation; alternative approaches likely to be better for some patients under some circumstances
2C	Unclear	Evidence obtained from respected authorities or from expert committee reports or opinion of the group of experts responsible for these recommendations	Very weak recommendations; other alternatives may be equally reasonable