

Renal allograft thrombosis

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Early graft thrombosis

Renal allograft thrombosis may be responsible for 2–7% of early allograft losses in adults [1] and up to 35% in children [2]. The North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) reported that graft thrombosis represented the main cause of graft failure in the first year. Most cases of renal allograft thrombosis occur early in the postoperative period with a peak incidence of 48 h. However, thrombus formation may be delayed until after the first week [3]. Thrombosis may initially involve the renal artery or more frequently the renal vein, but in some cases it is difficult to ascertain where the thrombosis originated.

Several factors may be involved in the pathogenesis of graft thrombosis. Thrombosis may be caused by technical errors, by vascular clamp injury or perfusion cannulation injury. Although vascular abnormalities in the donor kidney may be responsible for graft thrombosis [4] (thrombosis is reported in up to 36% of allografts with multiple renal arteries), however, in a multivariate analysis, the presence of atheroma was the only independent factor associated with the risk of arterial renal thrombosis [5]. Paediatric transplant recipients of kidneys from cadaver donors <5 years of age had a significantly higher thrombosis rate than did recipients from older donors [6]. This increased risk is attributable to the discrepancy in the size between the vessels of the donor and the recipient. In the past, cases of arterial thrombosis have been reported with cadaveric paediatric ‘en bloc’ transplantation. Recent results with this technique are excellent with no vascular thrombosis [7,8].

An increased risk of graft thrombosis was reported in kidney transplants from elderly donors [9,10]. This is probably because donor hypotension together with ischaemia-reperfusion injury may cause the activation of a proco-

agulant surface from cytokines and the recipient immune response in atherosclerotic vessels [1]. Renal artery graft thrombosis may be triggered by the administration of the monoclonal antibody OKT3 (Table 1) that can induce procoagulant activity [11,12]. The risk is increased in patients pretreated with high-dose intravenous methylprednisolone, which may activate the tissue factor/factor VII pathway [13]. Therefore, the dose of methylprednisolone for premedication should not exceed 8 mg/kg [14].

Renal vein thrombosis may be triggered by kinking of the renal vein or stenosis of the venous anastomosis. It also results from a hypercoagulable state [15]. Postoperative hypercoagulability is well documented after surgery and general anaesthesia. Moreover, some transplant recipients may have genetic coagulation abnormalities such as autosomal dominant inherited antithrombin deficiency [16] or mutations of factor V Leiden and of prothrombin gene G20210A [17,18]. Factor V is an important procoagulant factor. The factor V Leiden mutation is due to a single base-pair change (G1691A) that alters the initial cleavage site for activated protein C. Heterozygous carriers of this mutation have an impaired degradation of factor V by activated protein C; this yields a hypercoagulable state that predisposes to renal transplant vein thrombosis and early graft loss [19]. The presence of prothrombin gene G20210A polymorphisms that causes increased factor II levels may result in a severe course and graft loss [20]. In the immediate post-operative period, these abnormalities may interact with post-operative hypercoagulability, dehydration and hypovolaemia in favouring thrombosis. However, three recent studies, one on 772 consecutive cadaver kidney transplantations from a single centre [21], another on 676 first and 651 retransplant patients [22] and the third one on 562 renal transplant recipients and 457 kidney donors [23], in which various gene polymorphisms were investigated, failed to find statistically significant associations between any of the studied polymorphisms in donors and recipients and clinical outcomes (Table 2).

Carriers of antiphospholipid antibodies (APA) are at increased risk for allograft thrombosis. In a multicenter study, all four patients with APA who did not receive anticoagulation after transplantation lost their allograft within 1 week as a consequence of thrombosis, while only one of the seven patients given anticoagulants had a graft thrombosis [24].

Calcineurin inhibitors may cause hypofibrinolysis by enhancing the expression of plasminogen activator inhibitor

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Table 1. Predisposing factors for renal allograft thrombosis

Hypovolaemia
Atherosclerosis
Technique error
OKT3 (plus high-dose methylprednisolone)
Antiphospholipid antibodies
High dose steroids
Long cold ischaemia time
Delayed graft function recovery

[25], but there is no good evidence that they are responsible for an increased risk of graft thrombosis.

Hypofibrinolysis is present in patients treated by long-term haemodialysis or peritoneal dialysis [26]. Some investigators found that arterial allograft thrombosis was more frequent in peritoneal dialysis than in haemodialysis patients [27,28]. In a large paediatric series [29], vascular thrombosis accounted for 11.6% of graft losses and was the major single cause of graft failure in peritoneal dialysis versus haemodialysis-treated patients. However, others reported no difference in the incidence of renal graft thrombosis between peritoneal dialysis and haemodialysis patients [30–32].

Also, hypovolaemia, either induced by haemodialysis or by posttransplant polyuria, may be a contributing factor for graft thrombosis.

The characteristics of the recipient are also important. A past history of renal or extrarenal venous thrombosis, diabetic nephropathy, peri- and early post-operative poor haemodynamic status is significantly associated with an increased risk of graft thrombosis [32].

Early events after transplantation may also favour the development of vascular thrombosis. Allograft thrombosis is more frequent in patients with delayed graft function [32], or acute rejection [28]. In a retrospective study, the length of cold ischaemia time was significantly longer in children with graft thrombosis [6], but in adults, the association of graft thrombosis with cold ischaemia time is controversial [27,31]. Also, the role of erythropoietin treatment is doubtful [32–34]. CMV positive and seroconverted renal transplant recipients tend to have an increased risk of venous thrombosis compared to CMV negative recipients [35]. A study in children reported that patients receiving rabbit antithymocyte globulins (ATG) showed a significant decrease in the platelet count and incidence of graft thrombosis, suggesting a role for ATG-related effect on platelet count [36]. A paediatric survey report found that IL-2

Table 2. Synopsis of thrombophilia studies

Author	Type of study	Type of thrombophilia	Results
Irish <i>et al.</i> 1997 [71] (32 pts.) ^(a)	Retrospective	FVL ^b	Significant association with worse graft outcome (OR 4)
Heidenreich <i>et al.</i> 1998 [17] (97 pts.)	Retrospective	FVL ^b	Significantly higher incidence of acute rejection ($P = 0.017$)
Fischereder <i>et al.</i> 1998 [72] (132 pts.)	Retrospective	FVL ^b	Higher graft loss at 1 year (RR 3.5)
Ekberg <i>et al.</i> 2000 [73] (109 pts.)	Retrospective	FVL ^b	Significantly worse 1-year graft survival ($P = 0.02$)
Fischereder <i>et al.</i> 2001 [74] (270 pts.)	Retrospective	G20210A ^c	Significantly worse graft survival (RR 2.95)
Wuthrich <i>et al.</i> 2001 [19] (202 pts.)	Retrospective	FVL ^b	Significantly higher graft loss ($P = 0.004$)
Pherwani <i>et al.</i> 2003 [23] (562 Tx pts., 457 Tx donors)	Retrospective	FVL ^b , G20210A	No significant association with graft outcome
Heidenreich <i>et al.</i> 2003 [18] (165 pts.)	Prospective	Protein C, S ^d , G20210A, MTHFR ^e -T677T ^f FVL ^b Antithrombin.	Significant association with a rejection at 3 months. Transplant loss at 1-year higher in pts. with G20210A mutation (OR 10)
Kranz <i>et al.</i> 2006 [48] (66 paediatric pts.)	Prospective (prophylactic treatment)	Protein C, S, Antithrombin ^d , FVL ^b , G20210A and MTFHR	No significant difference in 1 and 3-year incidence of acute rejection and 3-year graft survival
Meyer <i>et al.</i> 2007 [22] (1327 pts.)	Retrospective	FVL ^b , G20210A, MTHFR-T677T	No significant association with graft outcome
Alakulppi <i>et al.</i> 2007 [74] (764 pts.)	Retrospective	FVL ^b , G20210A, MTHFR-C677T ^g , F13A1-V34L ^h , TFPI-P151L ⁱ , PROC-W380G ^j	No significant association with graft outcome

Adapted from Pherwani *et al.* [23].

^aCitation no. 71.

^bFVL: Factor V Leiden heterozygosity.

^cG20210A: Prothrombin mutation.

^dProtein C, S, Antithrombin: defect of protein C, or preprotein S or antithrombin III.

^eMTFHR: methylentetrahydrofolate reductase.

^fMTFHR-T677T: T677T polymorphism (homozygous variant).

^gMTFHR-C677T: C677T polymorphism (heterozygous variant).

^hF13A1: coagulation factor XIII A1 polypeptide.

ⁱTFPI: tissue factor pathway inhibitor.

^jPROC: protein C polymorphism.

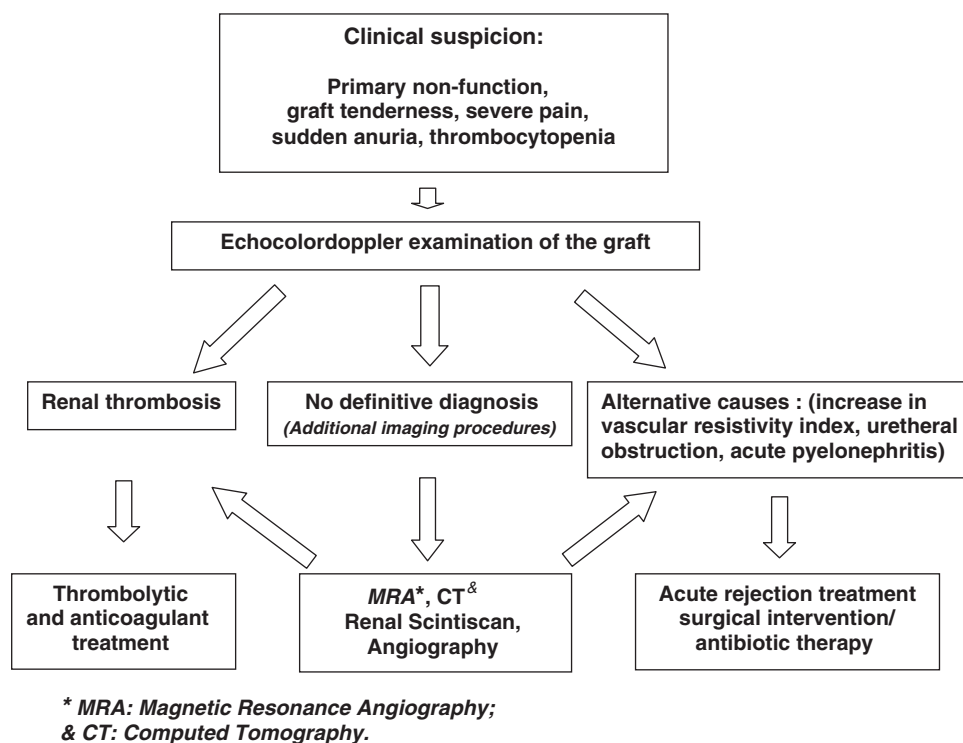


Fig. 1. Algorithm for the diagnosis of allograft thrombosis. *MRA: magnetic resonance angiography; &CT: computed tomography.

receptor antibodies as induction therapy were associated with a significantly decreased risk of graft failure due to thrombosis [2].

Diagnosis

Post-transplant graft thrombosis is usually heralded by sudden anuria and by tenderness and severe pain over the graft region. Thrombocytopenia may occur after a few hours because of platelet accumulation in the thrombus. A suspicion of graft thrombosis merits urgent investigation because it may be potentially correctable, while a delay in the diagnosis or management results in graft loss [37] (Figure 1). Echocolor Doppler is a simple and reliable technique and is generally used to detect renal artery or vein thrombosis [38,39]. The typical findings of graft thrombosis are represented by a rapid drop of systolic frequency shifts and retrograde plateau during diastole at the level of the main renal artery and its proximal branches, with the absence of venous Doppler signal. Additional imaging modalities have also been used to detect or confirm renal vascular thrombosis, including angiography, scintigraphy, computed tomography and magnetic resonance.

Prevention

A thrombophilic evaluation is suggested in transplant candidates to identify those at an increased risk of thrombosis, although the evidence of this recommendation still needs prospective studies [21]. Particular attention is recommended in children, in patients with a previous history of vascular thrombosis and in those who lost a first kidney

transplant because of graft thrombosis not related to technical errors [40]. In patients with APA or congenital coagulation abnormalities, graft thrombosis can be prevented by intravenous heparin treatment [41,42]. To reduce the risk of haemorrhage while preventing thrombosis, the partial thromboplastin time ratio should be kept between 1.5 and 2 [15]. Long-term maintenance with warfarin or low doses of heparin should be taken into consideration, targeting INR values at 2.5 [15].

Whether it is worthwhile giving full [43], low [44] or no anticoagulation [45] or antiaggregation to transplant recipients at a low risk of thrombosis is still debatable: some authors [15] reported that after the implementation of screening for hypercoagulability and use of anticoagulation therapy after transplantation, the thrombosis incidence declined by 2.6-fold. The same authors moreover suggest that a previous allograft loss due to thrombosis is an indication to anticoagulation after retransplantation; this procedure has obtained 100% allograft function at 2 ± 1.8 years in some series.

In unselected patients at low clinical risk, aspirin (75–150 mg/day) with or without a short period of unfractionated heparin (5000 U twice a day for 5 days) appeared to significantly reduce the risk of renal allograft thrombosis with a low risk of bleeding, especially when compared with low-molecular-weight heparins that may accumulate in renal failure [46,47].

Some authors [48] were unable to show any beneficial effect of i.v. heparin, switching to low-molecular-weight heparin and then shifting to aspirin for 1 year in paediatric patients screened for various gene mutations (Table 2). On the other hand, a retrospective analysis on 830 adult

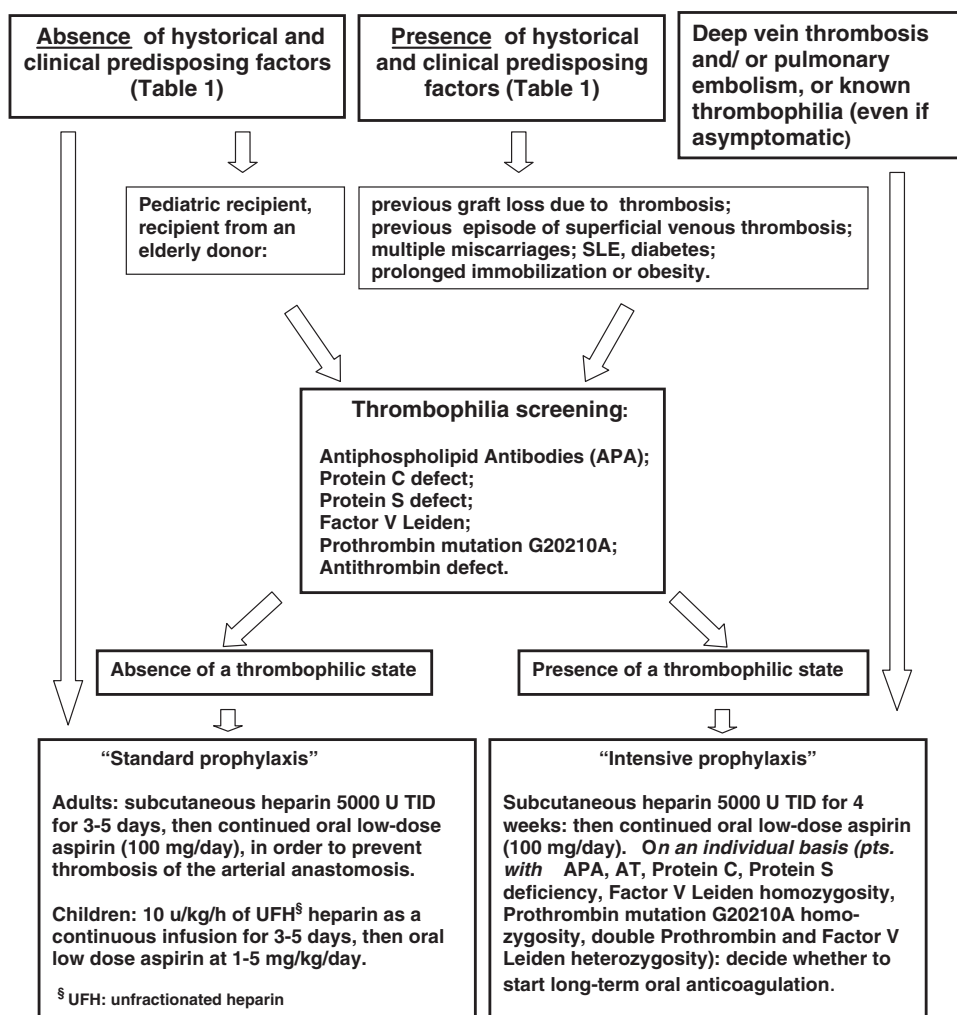


Fig. 2. Algorithm proposed by the authors for antithrombotic prophylaxis.

patients and another one on 105 renal transplant recipients receiving aspirin at 100 mg/day showed substantial improvement in renal allograft function and survival [47] and in the rate of primary allograft thrombosis [49,50]. The proposed mechanism of action of aspirin is through platelet inhibition and subsequent deceleration of transplant vasculopathy, but others also suggested an inhibition of CD40, CD80, CD86 and MHC class II expression on dendritic cells [51].

In Figure 2 we propose an algorithm for anticoagulant treatment, which reflects our actual clinical practice.

Prognosis and treatment

Allograft thrombosis generally causes irreversible loss of function. Treatment of graft thrombosis is generally disappointing. However, a few cases of renal graft vein thrombosis were successfully rescued by intra-arterial injections of anti-fibrinolytic agents, such as recombinant tissue plasminogen activator or urokinase [52] or by percutaneous endoluminal thromboaspiration carried out with full heparinization [53] or by surgical thrombectomy [54,55].

Late allograft thrombosis

Renal artery thrombosis

Late allograft thrombosis has been defined as occurring later than 14 days postoperatively [15], but rarely renal artery thrombosis may develop a few months post-transplantation. Traumatic thrombosis is the most common aetiology. Thrombosis may arise as a complication of angiography, angioplasty or stent placement. It may also occur during intraoperative abdomino-pelvic compression [56]. Renal artery thrombosis may slowly develop in kidneys with vascular abnormalities or as a consequence of a late haemolytic uraemic syndrome [57] or in carriers of antiphospholipid antibodies [58].

The presentation of acute late thrombosis is similar to that of an early acute thrombosis. However, segmental renal arterial thrombosis may cause asymptomatic infarcts and focal scarring of difficult diagnosis [59]. The prognosis depends on the extent of thrombosis and infarction. The longer the warm ischaemia time the poorer the prognosis. Surgical revascularization or intra-arterial thrombolytic therapy is the most frequent treatment.

Renal vein thrombosis

Renal allograft vein thrombosis may be induced by renal vein kinking or by renal vein compression caused by lymphocele or other fluid collection, and often results from extension of deep vein thrombosis to the renal allograft vein [60]. In this regard, a review of the USRDS data [61] found that in renal transplant recipients deep vein thrombosis had an incidence of 2.9 episodes/1000 persons-year; the risk was greater for patients with renal insufficiency and with nephrotic syndrome [62], increased haematocrit, rejection [63], infection [64] or factor V Leiden mutation [65].

The clinical diagnosis (easy in cases of acute renal vein thrombosis) can be difficult in cases of chronic vein thrombosis that is usually asymptomatic. The prognosis is poor because many patients lose their graft function [66], but some may be rescued depending on the timelines of the diagnosis. Pulmonary embolism is a complication of renal vein thrombosis especially with deep vein thrombosis.

Treatment with streptokinase [67] or urokinase [63,68] may be useful particularly in case of acute or partial vein thrombosis [69]. Percutaneous mechanical thrombectomy and localized catheter-directed thrombolysis may also allow the return of kidney function in some patients [70].

Conflict of interest statement. Claudio Ponticelli is a Consultant of Novartis Pharma, Italy.

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