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REVIEW

Endovascular treatment of hepatic artery thrombosis following liver transplantation

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Summary

Hepatic artery thrombosis (HAT) is the most frequent vascular complication following orthotopic liver transplantation. Urgent retransplantation has been considered as the mainstay therapy. Surgical revascularization is an effective alternative in asymptomatic patients. Endovascular therapies including intra-arterial thrombolysis, percutaneous transluminal angioplasty (PTA), and stent placement have shown encouraging results in recent years; however, their use remains controversial because of potential risk of hemorrhage. Until June 2009, 69 cases were published in 16 reports describing therapeutic potential of endovascular modalities. Interventions were performed as early as within 4 h to as late as 120 days in patients ranging from 4 months to 64 years of age. Majority of published reports suggested the use of urokinase. Thrombolysis was successful in 47 out of 69 (68%) patients. Bleeding was the most common complication including fatal intra-abdominal hemorrhage in three patients. Twenty-nine out of 47 (62%) patients underwent further intervention in the form of PTA, stenting, or both. The follow-up patency ranged from 1 month to 26 months. In conclusion, whenever possible, efforts should be made to rescue the liver grafts through urgent revascularization (surgical and/or endovascular) depending on patient's condition and interventional expertise at the transplant center; reserving the option of retransplantation for failure, complications, and cases with severe clinical symptoms or allograft dysfunction.

Introduction

Hepatic artery thrombosis (HAT) is the most frequent and severe vascular complication following orthotopic liver transplantation (OLT) representing more than 50% of all arterial complications [1–7]. It is the foremost cause of graft failure necessitating retransplantation and carries a mortality of more than 50% [1–7]. Early surgical revascularization is a viable option for graft salvage, or may help as a bridging measure for a retransplantation in a less emergent setting [1,8,9]. This can be appreciated from the retransplantation rate of 25–83% in untreated HAT compared to 28–35% in HAT patients treated by graft revascularization [9–17]. Endovascular management including intra-arterial thrombolysis (IAT), percutaneous transluminal angioplasty (PTA), and stent placement has emerged as an attractive and less invasive alternative to surgical intervention in recent years [5,11,18–27]. Additionally, few cases of surgical revascularization in conjunction with IAT have been reported. However, use of IAT and PTA remain controversial in view of potential risks of hemorrhage in early postoperative period [1,2,19] and uncertain long-term patency. In view of poor outcomes of HAT despite retransplantation or surgical revascularization, and the debatable role of endovascular therapy, we reviewed the literature on endovascular management for HAT following LT.

Materials and methods

Hepatic artery thrombosis was defined as a thrombotic occlusion of the hepatic artery and has been classified

into two types depending on time of presentation following LT: Early HAT (within the first 30 days of LT) and Late HAT (after 30 days of LT) [11].

A systematic literature search of the PubMed database was conducted using the following key words in varied combinations: *HAT, Endovascular, Endoluminal, Interventional, Thrombolysis, Fibrinolysis, angioplasty, stenting, and LT*. Cited references in published articles were used to find further relevant publications. The search was restricted to English language publications up to June 2009. All articles mentioning endovascular treatment as the primary revascularization therapy with an aim to restore arterial blood flow of the occluded (thrombosed) hepatic artery were reviewed. Key variables included but were not limited to the following: definition of HAT; day of detection; age; number of recipients; type of LT (deceased donor or living donor); details of endovascular therapy. In order to analyse the impact of advancement in interventional radiology on outcomes of endovascular management for HAT over the years, we divided them into early period (1985–2000) and a late period (2000–2009). Published literature describing endovascular management for hepatic artery stenosis (HAS), kinks, and other forms of nonocclusive hepatic arterial complications were excluded from the study.

Thrombolysis was certainly required before instituting any other form of definitive endovascular management (PTA or stenting). Details of thrombolytic therapy include thrombolytic agent, dosage, methods of delivery, duration of therapy, adjunct use of heparin, monitoring, complications, and outcome. Definitive treatment was defined as a treatment modality required after a successful attempt of thrombolytic therapy in the form of endovascular (PTA and/or stenting), surgical revascularization, or retransplantation. A successful endovascular revascularization attempt was defined as a recipient who survived with the revascularized graft following total endovascular treatment. Failure of endovascular therapy, follow-up patency rates, graft loss rate, and mortality rates were noted. Failure was defined as the need of surgical intervention (retransplantation, thrombectomy, revision of the arterial anastomosis, or in combination) following endovascular therapy resulting from complications or technical difficulty.

Results

The data from published literature on endovascular therapy for HAT were extensively reviewed and shown in Table 1. Since the first reported use of IAT for HAT in 1985, there have been 69 published cases in 16 reports [5,6,19–24,26–33]. Sixty-four out of 69 (93%) cases have been reported after 2000. Thrombolysis was attempted in 44 patients (64%) with early HAT and 11 patients (16%) with late HAT. It was performed as early as within 4 h [22] to as late as 120 days [29] following LT. Type of HAT or day of presentation was not available in 14 cases [23,24,29,30]. Thrombolysis was attempted in patients ranging from 4 months [26] to 64 years of age. Sixty-three patients (91%) underwent thrombolysis following deceased donor LT and six patients have been reported following living donor LT (LDLT) [22,32].

The use of urokinase (UK) was reported in 12 studies [5,19–24,26–29,32]. Only two studies have reported the use of alteplase, a recombinant tissue plasminogen activator (t-PA) [5,27], and streptokinase [30,31]. Catheter-directed delivery of a thrombolytic agent has been used as continuous infusion, bolus or in combination. Clinical safety and efficacy have been demonstrated with different dosing regimens. Bovyat *et al.* have recommended a dose of 1–3 mg (t-PA) or 50 000–250 000 IU (UK) [18]. Zhou *et al.* have used upto 9 millions units of UK without any complication in one particular patient. The duration of thrombolytic therapy has been variably reported. Zhou *et al.* have recommended 2–4 days of therapy to complete the treatment successfully using different dosing regimens [21]. Others have suggested that IAT should be terminated, if there is residual thrombus or persistent HAT after 36–48 h of thrombolytic therapy [5]. Eleven studies have also recommended the adjunct use of heparin in 'conservative doses'. Conservative doses were defined as bolus of heparin followed by a continuous drip to maintain the partial thromboplastin time between 1.25 and 1.5 times the control value. Careful monitoring of coagulation profile and clinical symptoms are necessary during thrombolysis treatment. Fibrinogen levels have been used for monitoring in 10 out of the total number of reports. Several authors have also mentioned the use of prothrombin time (PT) and activated partial thromboplastin time (aPTT) for monitoring. Improvements in clinical symptoms and biochemical parameters, and delineation of re-establishment of hepatic arterial flow on check angiography have been used as the primary measure for success of thrombolytic treatment.

Intra-arterial thrombolysis was successful in 47 out of 69 (68%) patients on whom the therapy was attempted. Hemorrhage was the most common complication. The severity of hemorrhage ranged from leakage of contrast or bloody abdominal fluid drainage in 15 patients (22%) to fatal intra-abdominal hemorrhage in three patients [5,24,30]. Eight patients did not undergo any further treatment and duration of their patency ranged from 3 months to 27 months. Follow-up patency details were not reported in 10 patients. Twenty-nine out of 47 (62%) patients underwent further intervention in the form of

Table 1. Published literature on thrombolysis in hepatic artery thrombosis (HAT) following liver transplantation.

			Thrombolytic therapy				
Author	*n*	Day of presentation	Drug	Dose and mode of delivery	Duration	Complication	Outcome
Zajko *et al.* (1985) [30]	1	NA	SK	NA	NA	Hemorrhage	D
Hidalgo *et al.* (1989) [19]	2	80, 94 days	UK	3000 IU/kg (B) 3000–4400 IU/kg/h (I)	3 h–24 h	None	S (2)
Figueras *et al.* (1995) [20]	1	3 days	UK	300 000 IU (B)	NA	None	S
Bjerkvik *et al.* (1995) [31]	1	21 days	SK	NA	72 h	None	S
Cotroneo *et al.* (2002) [29]	2	120 days, NA	UK	NA	48 h	NA	S (2)
Zhou *et al.* (2005) [21]	8	2–19 days	UK	100 000–250 000 IU (B) 50 000–100 000 IU/h (I)	12–24 h	Re-thrombosis (3), Hemorrhage (5)	S (8)
Wang *et al.* (2005) [28]	9	16 h–10 days	UK	NA	12 h–9 days	Hemorrhage (1)	S (7), F (2)
Kim *et al.* (2006) [22] LDLT	2	6 h, 4 h	UK	100 000 × 10 min 150 000 × 15 min (B)	NA	Hemorrhage (1)	S (2)
Li *et al.* (2007) [23]	9	NA	UK	250 000 IU (I)	3–6 days	Hemorrhage (2)	S (6), F (3)
Saad *et al.* (2007) [5]	5	7–71 days	UK/t-PA	120 000 IU/h (UK) or 0.5 mg/h (t-PA) (I)	16–24 h	Hemorrhage (1)	S (1), F (3), D (1)
Reyes *et al.* (2007) [33]	3	2–8 days	Abciximab infusion (1)	NA	NA	NA	NA
Bovyat *et al.* (2008) [27]	9	6 h–10 days	UK/t-PA	50 000–250 000 (UK) or 1–3 mg (t-PA)	NA	NA	S (9)
Yang *et al.* (2008) [24]	3	NA	UK	NA	NA	Hemorrhage (2)	S (1), D (1), F (1)
Lopez *et al.* (2008) [26]	1	3 days	UK	4400 U/Kg 6000 U/Kg (Boluses)	NA	None	S (1)
Jeon *et al.* (2008) [32] LDLT	4	1–13 days	UK	100 000–250 000 IU	NA	Hemorrhage (2)	S (2), F (2)
Duffy *et al.* (2009) [6]	9	3-Early HAT 6-Late HAT	NA	NA	NA	NA	S (1/3, 0/6)

n, number of patients; NA, not available; LDLT, living donor liver transplant; UK, urokinase; SK, streptokinase; t-PA, alteplase, B, bolus; I, infusion; D, died; S, successful; F, failure; HAT, hepatic artery thrombosis.

Table 2. Literature review on type of definitive treatment in patients who underwent thrombolysis for hepatic artery thrombosis (HAT) following liver transplantation.

Author	*n*	Outcome of thrombolysis	Definitive treatment		Follow-up
			Surgical/endovascular	Result	
Zajko *et al.* (1985) [30]	1	D	–	–	–
Hidalgo *et al.* (1989) [19]	2	S (2)	PTA (2)	Thrombosis (1)	P (1) at 1 month, No follow up (1)
Figueras *et al.* (1995) [20]	1	S	–	–	NA
Bjerkvik *et al.* (1995) [31]	1	S	PTA	S	Re-stenosis at 4 month
Cotroneo *et al.* (2002) [29]	2	S (2)	PTA + Stent (2)	NA	P (1) at 18 month, HAT at 4 month (1)
Zhou *et al.* (2005) [21]	8	S (8)	–	–	P (6) at 3–27 months, D (1), RT (1)
Wang *et al.* (2005) [28]	9	S (7), F (2)	Stenting (6)	S (6)	NA
Kim *et al.* (2006) [22] LDLT	2	S (2)	–	–	P (2) at 7 months
Li *et al.* (2007) [23]	9	S (6), F (3)	Stenting (5), RT (1)	D (1) despite of RT, D (2) because of hepatic failure and biliary complications	P (6) at 12–24 months
Saad *et al.* (2007) [5]	5	S (1), F (3), D (1)	PTA (3)	F (3)	SR (2), RT (1)
Reyes *et al.* (2007) [33]	3	S (3)	PTA + Stent (3)	S (3)	Re-thrombosis or re-stenosis in all patients between 4 months and 26 months
Bovyat *et al.* (2008) [27]	9	S (9)	Stenting (9)	S (9)	NA
Yang *et al.* (2008) [24]	3	S (1), D (1), F (1)	RT (1)	Died because of recurrent HAT	NA
Lopez *et al.* (2008) [26]	1	S (1)	PTA	S (1)	Patent at 8 months
Jeon *et al.* (2008) [32] LDLT	4	S (2), F (2)	SR (1), RT (1)	NA	NA
Duffy *et al.* (2009) [6]	9	S (1), F (8)	NA	NA	NA

n, number of patients; NA, not available; LDLT, living donor liver transplant; D, died; S, successful; F, failure; PTA, percutaneous transluminal angioplasty; SR, surgical revascularization; RT, retransplantation; HAT, hepatic artery thrombosis.

PTA in four [19,26,31], PTA with stenting in five [29,33], and stenting alone in 20 patients [23,27,28]. Among the PTA group, hepatic artery (HA) remained patent at 1 and 8 months in two patients; however, two developed re-thrombosis or restenosis within 4 months. Among the patients in PTA with stenting group, four of five (80%) patients developed re-thrombosis within 2 years [29,33]. In stenting group, five of 20 (25%) showed patency at 12–24 months and follow-up patency rates were not available for 15 patients. Among patients who had successful endovascular treatment (thrombolysis with or without PTA + stenting), either need of retransplantation or mortality was reported in only two patients. Failure of IAT was documented in 19 patients (27.5%) [5,6,23,24,27,32]. Among patients in the failed group, subsequent treatment was contemplated in the form of retransplantation and surgical revascularization in four and three patients respectively. Among them, two out of four (50%) patients died despite retransplantation (Table 2) and two patients died attributable to hepatic failure and biliary complications. Details of subsequent treatment or outcome were not available for 10 patients and none of the reports discussed the long-term results of endovascular therapy (Fig. 1).

Discussion

Hepatic artery steno-occlusive disease is the most common arterial complication following LT. This includes HAT, hepatic artery stenosis, hepatic artery kinks (HAK), and aneurysms [15,34–36]. Although, HAS and HAK have been speculated as the initiating events [5], hypercoagulable states in perioperative period may also contribute without any underlying anatomical defect [1,6,7].

The time that divides early and late HAT has not been agreed on. However, as technical aspects and surgical complications are associated with HAT development in the first 30 days after OLT, it is a common practice to use 1 month from OLT to distinguish between early and late HAT. Hepatic artery thrombosis was reported to complicate 4–15% of OLTs [1,6] and was generally more frequent after pediatric LT (3–9% in adults vs. 11–26% in children) [16,17,37]. A recent single-center retrospective study reported an overall incidence rate of 5% [6]. Earlier published literature suggests that the incidence rates were higher for early HAT compared with late HAT. This was partly because of the limited detailed reports published for late HAT. Additionally, the natural history of late HAT usually remains clinically silent, and the published

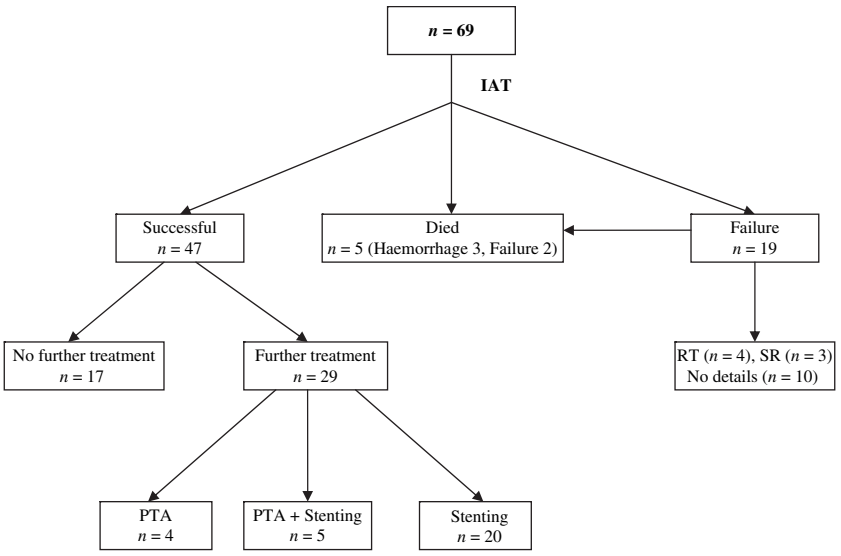

Figure 1 Outcome analysis of endovascular treatment for hepatic artery thrombosis (HAT) following liver transplantation. *n*, number of patients; IAT, intra-arterial thrombolysis; SR, surgical revascularization; RT, retransplantation; PTA, percutaneous transluminal angioplasty.

incidence may only reflect the symptomatic presentation. With improvements of perioperative care, the incidence rates have decreased for early HAT over last decade. A recent study reported the incidence rates of 2.9% in adults and 8.3% in children for early HAT [7].

Hepatic artery thrombosis carries a mortality rate of 27% to 58% [1–7]. Early HAT has been associated with higher mortality of 33.3% (range: 0–80%) [7]. This may be because of natural history of early HAT involving bile duct necrosis frequently followed by uncontrollable sepsis in the immunocompromised recipient resulting in death [38]. This is because of the fact that hepatic parenchyma and biliary tree rely mainly on the plexus of blood vessels derived from right and left hepatic arteries. Additionally, collateral supply to the liver is poor in the early post-OLT period. Arterial collaterals develop from the adhesions of the liver to the diaphragm, retroperitoneal tissue (mainly derived from the phrenic arteries), and omentum over a period of 2–4 months subsequent to OLT [11,39]. Angiographically, these collaterals have been demonstrated to develop as early as 2 weeks [40]. The development of these collaterals probably results in asymptomatic states of some patients and prevent a disastrous outcome in cases of late HAT [40–43].

Although the real cause for development of HAT remains unknown in most cases, few predisposing factors have been described. These include surgical (technical) causes (kinking, stenotic anastomosis), difficult anastomosis, small vessel size, presence of multiple arteries, complex anatomy, cytomegalovirus (CMV) recipient/donor mismatch, hypercoagulable state, rejection, prolonged ischemia, and transplant for primary sclerosing cholangitis [1,6,7]. Late HAT has been reported in association with some specific factors. These include female donor, the combination of female donor and male recipient, hepatitis C seropositive recipients, episode of severe acute rejection, tobacco use, and retransplantation for early HAT [44,45]. A higher incidence among pediatric OLTs is most likely explained by the small size of the vessels with associated technical difficulties [7]. A size mismatch between the donor- and recipient arteries may be an added factor, especially in pediatric recipients. It is a general belief that reduced size liver grafts are associated with a lower incidence of HAT than whole liver grafts [46,47]. The underlying thought is that reduced size liver grafts are often adult grafts [48], which have relatively larger vessel diameter and thus a technically less difficult anastomosis [49,50]. However, two publications dealing with this issue found conflicting results [51,52]. The incidence of HAT in LDLT has been reported to be significantly lower in comparison with incidence of HAT in the non-LDLT [53,54]. However, a recent study found no significant difference and reported an incidence of 3.1% and 4.6% in living donor LT and deceased donor LT respectively [7]. Furthermore, no difference was reported in incidence among centers using the operation microscope for the arterial anastomosis (3.1%) versus centers using loupe magnification (2.1%) [7].

Early diagnosis is mandatory to prevent graft loss. Early HAT always manifest clinically with fever, leukocytosis, severe elevation in liver enzyme levels, or septic shock [1,3]. Late HAT manifesting months or years after surgery may be asymptomatic or have an insidious course characterized by cholangitis, relapsing fever, and bacteremia [3,44,45]. Many patients may present with nonspecific symptoms like back pain, shoulder pain, fatigue, and can be diagnosed only on radiological investigations. Usually, initial nonfunction or severe allograft dysfunction

predominately occurs in patients with early HAT, whereas biliary tract complications are more frequent with late HAT. In late HAT, abnormal liver function test results are not a prominent feature and do not reflect the potential seriousness of the clinical problem. In symptomatic patients, clinical presentation may vary from an increase in serum transaminase levels with or without cholestasis, liver abscess, biliary complications including bile leak, cholangitis, bile duct stenosis or necrosis, to liver failure [11,21–24,44,45].

Doppler ultrasonography (DUS) is a proven noninvasive investigation for assessment of hepatic artery patency [28,55,56]. In this study, all cases were initially detected by DUS. The most common findings on DUS are absence of arterial signals (sensitivity 92%) or increased resistive index (RI) of the hepatic artery. A gradual decrease in RI has been suggested as an indicator of expected HAT, having a sensitivity of 83% and specificity of 85% if RI < 0.6 [26]. Almost all centers do screening for HAT in the postoperative period; however, the screening protocols are highly variable with respect to frequency and interval of screening, and the time period after transplantation for which screening was performed [7]. Protocol surveillance ultrasound of the hepatic artery may disclose the reduced hepatic arterial flow and prompt intervention more timely, which may result in a higher success rate. The reported median time to detection of early HAT and late HAT were 6.9 days (range: 1–17.5 days postoperative) and 6 months (range: 1.8–79 months) respectively [7]. Once the patient is discharged from hospital, DUS examinations were usually performed based on clinical findings and/or in combination with laboratory findings. This may be an important reason for a highly variable median time for detection of late HAT. With elevations in liver enzymes in case of suspicious findings on DUS, an abdominal contrast-enhanced computed tomography or visceral angiography should be performed [17]. Although catheter angiography is the gold standard, multidetector computed tomographic angiography (MDCTA) has emerged as an accurate, fast, and noninvasive imaging modality for the diagnosis of vascular complications following LT [56–58]. It can precisely delineate the patency of the hepatic artery and anatomical defects such as stenosis or kinks. A sensitivity rate of 100% with a specificity rate of 89% and accuracy of 95% has been demonstrated [59]. Conventional catheter angiography can be used as a next step, possibly if any interventional treatment is contemplated (Fig. 2).

In general, there are three different treatment modalities for HAT: retransplantation, surgical revascularization, and endovascular revascularization. However, the most effective treatment approach remains controversial. Traditionally, retransplantation has been the first choice of therapy.

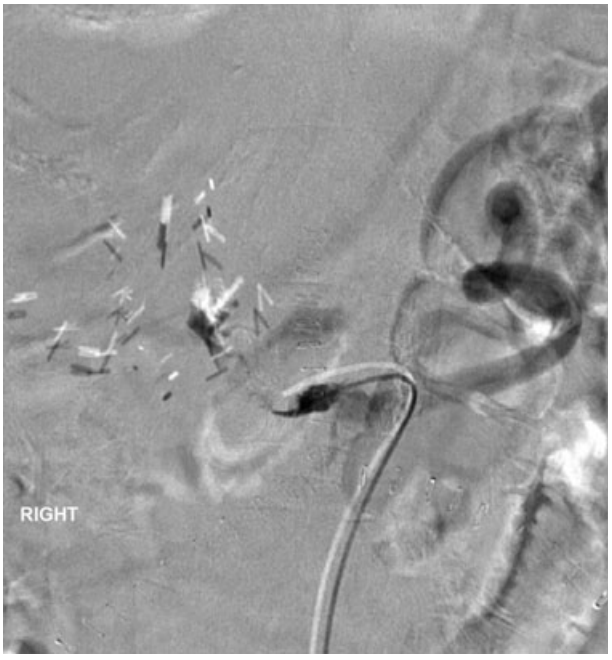

Figure 2 Visceral angiography showing no flow in hepatic artery suggestive of hepatic artery thrombosis.

In a systematic review by Bekker *et al.*, only 60% of the publications on HAT have mentioned the outcome after retransplantation [7]. They found that retransplantation was more frequently performed in children than in adults (61.9% vs. 50%) and was the treatment of choice in 53.1% of the cases of early HAT. In another study, retransplantation was required in 71% of patients with early- and 51% of patients with late HAT [6]. However, retransplantation is restricted by a limited donor pool as the disparity between the number of potential recipients and the available donors will continue to grow [7]. Further, some centers lack a back-up system for urgent retransplantation, making urgent revascularization of paramount importance [43,60]. Additionally, at transplant centers where LDLT is the most common type of LT, difficulties of finding a suitable donor in an emergent setting more often leads to mortality of the recipient with early HAT [61–63]. Urgent revascularization as a primary option offers the opportunity to prevent retransplantation, but probably only in asymptomatic patients or cases of very early detection [5–7]. The patient survival rates for symptomatic versus asymptomatic patients at the time of revascularization were 40% and 82% respectively [12]. Pinna *et al.* showed that 11 out of 17 patients who underwent urgent surgical revascularization combined with thrombectomy were alive without retransplantation, with a mean follow-up of 17 months [13]. They concluded that urgent revascularization combined with thrombectomy should be considered as the prime treatment option for patients with early HAT

and reserve the option of retransplantation for cases with severe clinical symptoms or failure of surgical revascularization. With revascularization, an overall success rate of about 50% was reported with similar rates among adults and children. The success rate was even higher (66.1%) with early HAT [7]. This is in contrast to success rate of 10.5% reported by another study [6]. Retransplantation was required in 30.3% [7] and 78% [6] of patients after an attempt of revascularization. The varying results of revascularization were mainly attributable to type of revascularization, varying threshold for retransplantation, and the degree of recipient well-being and graft function at the time of revascularization. This noteworthy difference may also be attributable to collective outcomes of surgical and endovascular revascularization (including thrombolysis) in one study [7] and individual outcome of surgical revascularization (thrombectomy and/or anastomotic revision) in another [6]. Nevertheless, it may direct us to consider that the use of endovascular therapy in combination may improve the success rates of surgical revascularization. Extended thrombosis involving entire intrahepatic arterial system cannot be relieved by surgical revascularization alone and thrombolysis is likely to help. Twelve cases of surgical revascularization in conjunction with IAT have been reported in six studies [9,13,14,63–66]. However, it was difficult to ascertain both clinical and angiographic details about an individual thrombolysis case and whether it was found to be advantageous to the transplant surgeon while performing the revascularization. After a successful revascularization, the 6- to18-month re-thrombosis and graft survival rates in these six studies were 22% (range: 0–50%) and 65% (range: 33–100%) respectively. Recently, HAT has been reported to be successfully managed with total endovascular management including transcatheter IAT, PTA, and stenting. Using them in combination, 69 cases have been reported in 16 studies as both rescue and definitive therapy with intention of reserving surgery for technical failures or complications.

Thrombolytic therapy

For the first time, Hidalgo *et al.* reported the successful use of IAT in two cases of late HAT [19]. Thrombolytic agents (plasminogen activators) convert plasminogen into plasmin, which further cleaves the fibrin strands within the thrombus, leading to clot dissolution. Thrombolysis was believed to be more effective in fresh clots because of high water content and relatively fibrin-poor matrix [20,36]. The present review showed that IAT have been attempted for both early and late HAT ranging from as early as 4 h [22] to as late as 120 days [29] after OLT. Although no specific guidelines exist for its application, Saad *et al.* have recommended a clinical therapeutic window of 1 week to 3 months considering risks and outcomes in their series [5].

Majority of studies indicated the preferred use of urokinase (UK) as a thrombolytic agent. Although the biochemical actions of UK and alteplase are different; there is no documented advantage of one agent over the other [67]. Alteplase is a more potent activator of plasminogen and has higher affinity for fibrin within the clot, which can increase the activation of plasminogen by 400-fold to convert the entrapped plasminogen to plasmin. Thrombolytic agents that lack fibrin specificity are usually washed downstream from the clot site and induce lysis by promoting a systemic lytic state [67]. There is no consensus on the optimal technique for catheter-directed delivery of any thrombolytic agent as they have been successfully used as continuous infusion or bolus form [67]. Selective thrombolysis via hepatic artery has several advantages such as small thrombolytic dose, high localized concentration, and little influence on systemic coagulation [20–23]. Figueras *et al.* suggested that continuous thrombolytic therapy would be safer and more effective if the infusion catheter is placed inside the thrombus [20]. However, it is recommended that the physicians continue to use the catheter-based modality with which they are most comfortable.

Although the clinical safety and efficacy have been demonstrated with different dosing regimens; the lowest effective dosage and duration has not yet been determined. Bovyat *et al.* have recommended a dose of 1–3 mg (t-PA) or 50 000–250 000 IU (UK) [18]. Zhou *et al.* have reported revascularization in all of their patients with early HAT using continuous IAT and recommended 2–4 days of therapy to complete the treatment successfully using different dosing regimen. They have safely used upto 9 million units of UK [21]. The dosage and duration of treatment mainly depend on the radiological delineation of flow through vessel, improvement in laboratory and clinical parameters, or manifestation of any sign of complication (Fig. 3). Intra-arterial thrombolysis should be terminated, if there is residual thrombus or persistent HAT after 36–48 h of thrombolytic therapy [5]. Careful monitoring of coagulation profile and clinical symptoms are necessary during thrombolysis treatment. Monitoring of fibrinogen levels have been commonly used during prolonged lytic infusions, and it often needs titration (usually downward) to maintain the fibrinogen level above 100 mg/dl [67]. Notwithstanding this practice, there is no study to support that fibrinogen levels are predictive of adverse bleeding; as hemorrhagic complications can also occur with values above 100 mg/dl. PT and aPTT have also been used for monitoring adequate fibrinolysis. In the future, a more appropriate parameter may be the $[alpha]_2$-antiplasmin levels. This remains to be validated in clinical trials [67].

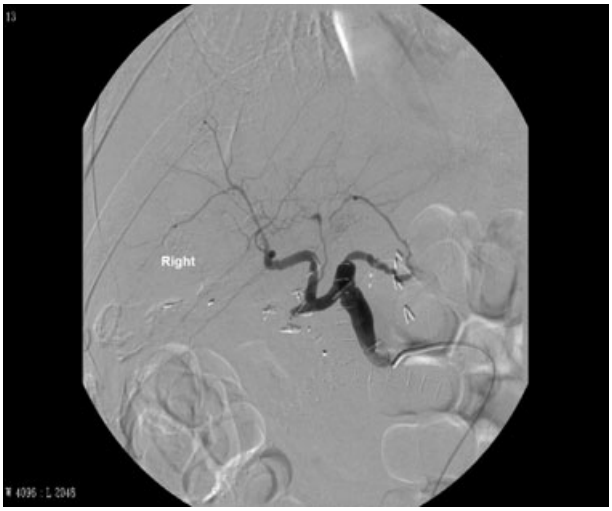

Figure 3 Check angiography-showing restoration of flow following 48 h of thrombolytic infusion.

Most of the studies recommended the use of heparin with thrombolytic therapy to maintain the partial thromboplastin time between 1.5 and 2.5 times the control value. Some authors have suggested addition of heparin if prothrombin time is <15 s [21]. However, propensity for adverse bleeding can increase when heparin was used as an adjunct and it may be higher with alteplase. Alteplase is incompatible with heparin and may precipitate when mixed directly with unfractionated heparin. Concomitant heparin therapy should be given through a separate intravenous line [67]. The role of adjunctive heparinization during alteplase infusion therapy is unknown and requires further investigation.

Hemorrhage was the most common complication seen in about 20% of the patients as bloody abdominal fluid drainage or leakage of contrast during the procedure. Fatal intra-abdominal hemorrhage was reported in three patients [5,24,30]. This was mainly surrogate to early postoperative period. However, other contributing risk factors include increased dose and duration of thrombolytic infusion, adjunctive antithrombotic therapy (heparin, aspirin, or any other antiplatelet agents), mechanical injury caused by catheter, and severity of ischemia. There was no relationship between the thrombolytic agent used, specific radiologic technique (continuous infusion or bolus), and complications. If adverse bleeding occurs during infusion therapy, thrombolytic agent should be immediately terminated, blood products (fresh frozen plasma or cryoprecipitate) should be administered to reverse coagulopathy, and immediate endovascular (balloon tamponade or stent) or surgical procedure must be contemplated. Intra-arterial thrombolysis failed in 19 patients [5,6,23,24,28,32], primarily because of technical reasons (inability to cross the lesion because of underlying anatomical defects such as stenoses or kinks) or abandonment of the procedure because of a complication. Among the failed group, survival and vessel patency rates were poor with mortality of up to 50% even with retransplantation. Novel approaches such as percutaneous thrombus aspiration may have a potential role as used in treating the patients with myocardial infarction [68]. However, their role in HAT remains undocumented.

Percutaneous transluminal angioplasty or stenting

Thrombolysis with restoration of flow without resolving underlying anatomic defects including kinking, anastomotic stenosis or stricture can lead to re-thrombosis, and often require percutaneous balloon angioplasty or stent placement [22–26]. Yang *et al.* have described endovascular management as the treatment of choice for hepatic arterial stenosis causing HAT following LT [24]. Among patients with successful IAT, 29 out of 47 (62%) patients underwent definitive endovascular treatment in the form of PTA with or without stenting. There is ongoing discussion regarding the best and safe time for definitive endovascular interventions after successful thrombolysis. Kodoma *et al.* suggested 7 days [69]; Ueno *et al.* suggested 3 weeks after LT [70]. Bovyat *et al.* have successfully performed stenting in patients presenting with early HAT, within 7 days following LT [18]. Multiple hepatic arterial stenoses and pediatric patients are also not a contraindication for interventional treatment in experienced hands. Recently, successful thrombolysis with PTA was performed in a 4-month-old infant following split LT [26]. Angioplasty may result in bleeding from hepatic artery in up to 5% cases [25]. This can be successfully treated by endovascular techniques using prolonged balloon inflation [69], or stent-graft [25], thus avoiding surgical intervention. Some recent studies have recommended the use of stents over balloon angioplasty to diminish the risk of anastomotic bleeding [32,70]. There seems to be a beneficial role of antiplatelet therapy following endovascular procedure for ischemic events [71]. Ueno *et al.* have recommended the use of acetylsalicylic acid or clopidogrel bisulfate for at least 3 months following endovascular stenting of hepatic artery. They have also suggested a follow-up DUS on day 1, at 1 month, 6 months, and 12 months following successful endovascular revascularization [70].

Thrombolysis with PTA and/or stenting had better patency and survival rates compared with thrombolysis alone. Among the patients who had successful endovascular treatment, the present review showed a variable

follow-up patency of 1 month to 26 months. Bovyat *et al.* used interventional treatment in 20 patients for hepatic arterial complications following OLT. Stent occlusion was documented in three patients without any apparent clinical symptoms at 3–9 months and minimal intimal hyperplasia in three patients on follow-up angiography at 1-year [27]. Cotroneo *et al.* reported patency in all of their four patients who underwent stent placement for hepatic arterial stenosis or thrombosis during a follow-up of 18–25 months [29]. In contrast, Reyes *et al.* reported that long-term patency is unlikely even with the use of Paclitaxel-coated stents as all patients in their study develop re-thrombosis or re-stenosis within a follow-up of 4 to 26 months [33]. None of the series reported the long-term results of endovascular treatment.

The association of biliary complications with hepatic artery occlusion is well established. None of the studies reviewed have described their associations and outcomes following therapeutic intervention for HAT. Biliary complications can vary in severity and type depending on type of HAT. They may present as biliary leak, ischemic strictures (extrahepatic and/or intrahepatic), intrahepatic biloma, abscess, or diffuse biliary tree necrosis [44]. Early treatment of HAT may minimize the biliary complications. Eventually, biliary complications may require percutaneous, endoscopic, or surgical correction [44,45,72–75]. Aggressive repeated interventions may be required and may necessitate retransplantation [72–75]. The individual details of the management of biliary complications following HAT were beyond the scope of this paper.

Being retrospective in nature, this study has limitations. Publication bias for successful case series is an issue for all systematic reviews. Considering the number of liver transplants and incidence of HAT, endovascular management is likely to be reported only in the form of case reports or small case series. However, there appears to be a growing interest in this modality as initial reluctance may be attributable to lack of defined guidelines, risk of bleeding, and eventual long-term outcome. Protocol surveillance DUS may help in early detection of the reduced hepatic arterial flow and prompt intervention more timely, and could contribute to improved outcomes. In view of effects of HAT on outcomes of LT, ongoing shortage of donor organs, and prospective advantages of endovascular therapy, prospective studies need to be performed. Recommendations based on this review are summarized in Table 3.

Table 3. Recommendations for endovascular therapy in hepatic artery thrombosis (HAT).

Protocol surveillance DUS facilitate the early detection of HAT
Better outcomes in asymptomatic patients
Avoid in patients with severe allograft dysfunction or sepsis
Cautious use within first week following OLT, increase risk of hemorrhagic complications
May use Urokinase or Alteplase
Infusion therapy, bolus therapy, or combination give equivalent results
Urokinase-50 000–250 000 IU, Alteplase 1–3 mg
Adjunct use of heparin in conservative doses; watchful use with alteplase
Clinical and biochemical monitoring (LFT, Fibrinogen, PT, aPTT) 8-hourly
Check angiogram twice in every 24 h
Continue thrombolysis for 48–72 h in responders
Stop thrombolysis if no significant difference for 12 h or signs of complications
Correction of detected anatomical defect: Endovascular (PTA or stenting) or Surgical
If stented, clopidogrel in prophylactic doses
Following successful revascularization, follow-up DUS on day 1, at 1 month, 6 months and 12 months

DUS, Doppler ultrasonography; HAT, hepatic artery thrombosis; OLT, orthotopic liver transplantation; PTA, percutaneous transluminal angioplasty; PT, prothrombin time; aPTT, activated partial thromboplastin time; LFT, liver function tests.

Conclusion

Hepatic artery thrombosis remains a major complication following LT. Conclusive diagnosis is best obtained with angiography where therapeutic options may be explored at the same time. Thrombolysis may be effective by itself or may reveal underlying predisposing cause such as anatomical anomalies, which may then be corrected by interventional procedures such as stent placement, balloon angioplasty or a surgical intervention. The endovascular treatment is highly individualized and dependent on expertise available at the transplant center. Patients with severe allograft dysfunction and symptoms related to arterial thrombosis in early post-transplant period need retransplantation. However, in view of current organ shortage and high mortality related to retransplantation, thrombolysis and other interventional procedures may salvage the liver allografts in selected patients thereby preventing retransplantation or facilitate the transplantation in more elective setting.

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References

1. Tzakis AG, Gordon RD, Shaw BN, *et al.* Clinical presentation of hepatic artery thrombosis after liver transplantation in the cyclosporine era. *Transplantation* 1985; **40**: 667.

2. Langnas AN, Marujo W, Stratta RJ, Wood RP, Shaw BW. Vascular complications after orthotopic liver transplantation. *Am J Surg* 1991; **161**: 76.
3. Drazan K, Shaked A, Olthoff KM, *et al.* Etiology and management of symptomatic adult hepatic artery thrombosis after orthotopic liver transplantation (OLT). *Am Surg* 1996; **62**: 237.
4. Margarit C, Hidalgo E, Lazaro JL, Murio E, Charco R, Balsells J Biliary complications secondary to late hepatic artery thrombosis in adult liver transplant patients. *Transplant Int* 1998; **11** (Suppl.): S251.
5. Saad WEA, Davies MG, Saad NEA, *et al.* Transcatheter thrombolysis of thrombosed hepatic arteries in liver transplant recipients: predictors of definitive endoluminal success and the role of pre-operative thrombolysis. *Vasc Endovasc Surg* 2007; **41**: 19.
6. Duffy JP, Hong JC, Farmer GE, *et al.* Vascular complications of orthotopic liver transplantation: experience in more than 4,200 patients. *J Am Coll Surg* 2009; **208**: 896.
7. Bekker JS, Ploem S, de Jong KP. Early hepatic artery thrombosis after liver transplantation: a systematic review of the incidence, outcome, and risk factors. *Am J Transpl* 2009; **9**: 746.
8. Marujo WC, Langnas AN, Wood RP, Stratta RJ, Shaw BW. Vascular complications following orthotopic liver transplantation: outcome and the role of urgent revascularization. *Transplant Proc* 1991; **23**: 1484.
9. Langnas AN, Marujo WC, Wood RP, Stratta RJ, Shaw BW. Hepatic allograft rescue following arterial thrombosis: role of urgent revascularization. *Transplantation* 1991; **51**: 86.
10. Lerut J, Gordon RD, Iwatsuki S, Starzl TE. Surgical complications in human orthotopic liver transplantation. *Acta Chir Belg* 1987; **87**: 193.
11. Stange BJ, Glanemann M, Nuessler NC, Settmacher U, Steinmüller T, Neuhaus P. Hepatic artery thrombosis after adult liver transplantation. *Liver Transpl* 2003; **9**: 6l2.
12. Sheiner PA, Varma CV, Guerrera JV, *et al.* Selective revascularization of hepatic artery thrombosis after liver transplantation improves patient and graft survival. *Transplantation* 1997; **64**: 1295.
13. Pinna AD, Smith CV, Furukawa H, Starzl TE, Fung JJ. Urgent revascularization of liver allografts after early hepatic artery thrombosis. *Transplantation* 1996; **62**: 1584.
14. Bhattacharjya S, Gunson BK, Mirza DF, *et al.* Delayed hepatic artery thrombosis in adult liver transplantation- a 12-year experience. *Transplantation* 2001; **71**: 1592.
15. Cavallari A, Vivarelli M, Bellusci R, Jovine E, Mazziotti A, Rossi C. Treatment of vascular complications following liver transplantation: multidisciplinary approach. *Hepatogastroenterology* 2001; **48**: 179.
16. Karatzas T, Lykaki-Karatzas E, Webb M, *et al.* Vascular complications, treatment, and outcome following orthotopic liver transplantation. *Transplant Proc* 1997; **29**: 2853.
17. Pawlak J, Wroblewski T, Malkowski P, *et al.* Vascular complications related to liver transplantation. *Transplant Proc* 2000; **32**: 1426.
18. Boyvat F, Aytekin C, Firat A, *et al.* Diagnostic and therapeutic management of hepatic artery thrombosis and stenosis after orthotopic and heterotopic liver transplantation. *Transplant Proc* 2003; **35**: 2791.
19. Hidalgo EG, Abad J, Cantarero JM, *et al.* High-dose articleintra-arterial urokinase for the treatment of hepatic artery thrombosis in liver transplantation. *Hepatogastroenterology* 1989; **36**: 529.
20. Figueras J, Busquets J, Diminguez J, *et al.* Intraarterial thrombosis in the treatment of acute hepatic artery thrombosis after liver transplantation. *Transplantation* 1995; **59**: 1356.
21. Zhou J, Fan J, Wang JH, *et al.* Continuous transcatheter arterial thrombolysis for early hepatic artery thrombosis after liver transplantation. *Transplant Proc* 2005; **37**: 4426.
22. Kim BW, Won JH, Lee BM, *et al.* Intraarterial thrombolytic treatment for hepatic artery thrombosis immediately after living donor liver transplantation. *Transplant Proc* 2006; **38**: 3128.
23. Li ZW, Wang MQ, Zhou NX, *et al.* Interventional treatment of acute hepatic artery occlusion after liver transplantation. *Hepatobiliary Pancreat Dis Int* 2007; **6**: 474.
24. Yang Y, Hua LI, Sheng FU, *et al.* Hepatic artery complication after orthotopic liver transplantation: interventional treatment or retransplantation? *Chin Med J* 2008; **12**: 1997.
25. Yamakado K, Nakatsuka A, Takaki H, *et al.* Stent graft for the management of hepatic artery rupture subsequent to transcatheter thrombolysis and angioplasty in a liver transplant recipient. *Cardiovasc Intervent Radiol* 2008; **31**: S104.
26. Lopez BR, Schlieter M, Hallscheidt PJ, *et al.* Successful arterial thrombolysis and percutaneous transluminal angioplasty for early hepatic artery thrombosis after split transplantation in a 4-month-old baby. *Pediatr Transpl* 2008; **12**: 606.
27. Boyvat F, Aytekin C, Harman S, *et al.* Endovascular stent placements in patients with hepatic artery stenosis or thrombosis after liver transplantation. *Transplant Proc* 2008; **40**: 22.
28. Wang XH, Yan LN, Zhang F, *et al.* Early experiences on living donor liver transplantation in China: multicenter report. *Chin Med J* 2006; **119**: 1003.
29. Cotroneo AR, DiStasi C, Cina A, *et al.* Stent placement in four patients with hepatic artery stenosis or thrombosis after liver transplantation. *J Vasc Interv Radiol* 2002; **12**: 508.
30. Zajko AB, Brom KM, Starzl TE, *et al.* Angiography of liver transplantation patients. *Radiology* 1985; **157**: 305.
31. Bjerkvik PS, Vatne K, Mathisen O, Soriede O. Percutaneous revascularization of postoperative hepatic artery thrombosis in a liver transplant. *Transplantation* 1995; **59**: 1746.

32. Jeon GS, Won JH, Wang HJ, *et al.* Endovascular treatment of acute arterial complications after living donor liver transplantation. *Clin Radiol* 2008; **63**: 1099.
33. Reyes-Corona J, Gonzalez-Huezo MS, Zea-Medina MV, *et al.* Paclitaxel coated-stent for early onset thrombosis after liver transplantation. *Ann Hepatol* 2007; **6**: 272.
34. Sanchez-Bueno F, Robles R, Ramirez P, *et al.* Hepatic artery complications after liver transplantation. *Clin Transplant* 1994; **8**: 399.
35. Stange B, Settmacher U, Glanemann M, Nuessler NC, Bechstein WO, Neuhaus P. Aneurysms of the hepatic artery after liver transplantation. *Transplant Proc* 2000; **32**: 533.
36. Nüssler N, Settmacher U, Haase R, Stange B, Heise M, Neuhaus P. Diagnosis and treatment of arterial steal syndromes in liver transplant recipients. *Liver Transpl* 2003; **9**: 596.
37. Oh CK, Pelletier SJ, Sawyer RG, *et al.* Uni- and multivariate analysis of risk factors for early and late hepatic artery thrombosis after liver transplantation. *Transplantation* 2001; **71**: 767.
38. Crossin JD, Muradali D, Wilson SR. US of liver transplants: normal and abnormal. *Radiographics* 2003; **23**: 1093.
39. Heffron TG, Pillen T, Welch D, *et al.* Hepatic artery thrombosis in pediatric liver transplantation. *Transplant Proc* 2003; **35**: 1447.
40. Wozney P, Zajko AB, Bron KM, Point S, Starzl TE. Vascular complications after liver transplantation: a 5-year experience. *Am J Roentgenol* 1986; **147**: 657.
41. Raby N, Karani J, Thomas S, O'Grady J, Williams R. Stenoses of vascular anastomoses after hepatic transplantation: treatment with balloon angioplasty. *Am J Roentgenol* 1991; **157**: 167.
42. Segel MC, Zajko AB, Bowen A, *et al.* Hepatic artery thrombosis after liver transplantation: radiologic evaluation. *Am J Roentgenol* 1986; **146**: 137.
43. Matsuda H, Yagi T, Sadamori H, *et al.* Complications of arterial reconstruction in living donor liver transplantation: a single-center experience. *Surg Today* 2006; **36**: 245.
44. Gunsar F, Rolando N, Pastacaldi S, *et al.* Late hepatic artery thrombosis after orthotopic liver transplantation. *Liver Transpl* 2003; **9**: 605.
45. Leonardi MI, Boin I, Leonardi LS. Late hepatic artery thrombosis after liver transplantation: clinical setting and risk factors. *Transplant Proc* 2004; **36**: 967.
46. Nakazato PZ, Cox KL, Concepcion W, Berquist WE, Esquivel CO. Revascularization technique for reduced-size liver transplantation for infants weighing less than 10 kg. *J Pediatr Surg* 1993; **28**: 923.
47. D'Alessandro AM, Ploeg RJ, Knechtle SJ, *et al.* Retransplantation of the liver—a seven-year experience. *Transplantation* 1993; **55**: 1083.
48. Atkison PR, Ross BC, Williams S, *et al.* Long-term results of pediatric liver transplantation in a combined pediatric and adult transplant program. *Can Med Assoc J* 2002; **166**: 1663.
49. Tan KC, Yandza T, de Hemptinne B, Clapuyt P, Claus D, Otte JB. Hepatic artery thrombosis in pediatric liver transplantation. *J Pediatr Surg* 1988; **23**: 927.
50. Mazzaferro V, Esquivel CO, Makowka L, *et al.* Hepatic artery thrombosis after pediatric liver transplantation—amedical or surgical event? *Transplantation* 1989; **47**: 971.
51. Heffron TG, Welch D, Pillen T, *et al.* Low incidence of hepatic artery thrombosis after pediatric liver transplantation without the use of intraoperative microscope or parenteral anticoagulation. *Pediatr Transplant* 2005; **9**: 486.
52. Rela M, Muiesan P, Bhatnagar V, *et al.* Hepatic artery thrombosis after liver transplantation in children under 5 years of age. *Transplantation* 1996; **61**: 1355.
53. Reding R, Goyet Jde V, Delbeke I, *et al.* Pediatric liver transplantation with cadaveric or living related donors: comparative results in 90 elective recipients of primary grafts. *J Pediatr* 1999; **134**: 280.
54. Goss JA, Shackleton CR, McDiarmid SV, *et al.* Long-term results of pediatric liver transplantation: an analysis of 569 transplants. *Ann Surg* 1998; **228**: 411.
55. Garcia-Criado A, Gilabert R, Nicolau C, *et al.* Early detection of hepatic artery thrombosis after liver transplantation by Doppler ultrasonography. *J Ultrasound Med* 2001; **20**: 51.
56. Vignali C, Bargellini I, Cioni R, *et al.* Diagnosis and treatment of hepatic artery stenosis after orthotopic liver transplantation. *Transplant Proc* 2004; **36**: 2771.
57. Kayahan EM, Coskun M, Ozbek O, *et al.* Accuracy of multidetector computed tomographic angiography for detecting hepatic artery complications after liver transplantation. *Transplant Proc* 2007; **39**: 3239.
58. Saba L, Mallarini G. Multidetector row CT angiography in the evaluation of the hepatic artery and its anatomical variants. *Clin Radiol* 2008; **63**: 312.
59. Brancatelli G, Katyal S, Federle MP, Fontes P. Three dimensional multislice helical computed tomography with the volume rendering technique in the detection of vascular complications after liver transplantation. *Transplantation* 2002; **73**: 237.
60. Eid A, Lyass S, Venturero M, *et al.* Vascular complications post orthotopic liver transplantation. *Transplant Proc* 1999; **31**: 1903.
61. Okazaki M, Asato H, Takushima A, *et al.* Hepatic artery reconstruction with double-needle microsuture in living-donor liver transplantation. *Liver Transpl* 2006; **12**: 46.
62. Uchiyama H, Hashimoto K, Hiroshige S, *et al.* Hepatic artery reconstruction in living-donor liver transplantation: a review of its techniques and complications. *Surgery* 2002; **131**(Suppl. 1): S200.
63. Inomoto T, Nishizawa F, Sasaki H, *et al.* Experiences of 120 microsurgical reconstructions of hepatic artery in living related liver transplantation. *Surgery* 1996; **119**: 20.

64. Sarfati PO, Boillot O, Bauddin F, *et al.* Acute hepatic artery thrombosis in pediatric liver transplantation: surgical thrombectomy and *in-situ* fibrinolysis. *Ann Chir* 1992; **46**: 605.
65. Zheng SS, Yu ZY, Liang TB, *et al.* Prevention and treatment of hepatic artery thrombosis after liver transplantation. *Hepatobiliary Pancreat Dis Int* 2004; **3**: 21.
66. Garcia-Gallont R, Bar-Nathan N, Shaharabani E, *et al.* Hepatic artery thrombosis in pediatric liver transplantation: graft salvage after thrombectomy. *Pediatr Transplant* 1999; **3**: 74.
67. Semba CP, Bakal CW, Calis KA, *et al.* Alteplase as an alternative to urokinase. *J Vasc Interv Radiol* 2000; **11**: 279.
68. Svilaas T, Vlaar PJ, van der Horst IC, *et al.* Thrombus aspiration during primary percutaneous coronary intervention. *N Engl J Med* 2008; **358**: 557.
69. Kodoma Y, Sakuhara Y, Abo D, *et al.* Percutaneous transluminal angioplasty for hepatic artery stenosis after living donor liver transplantation. *Liver Transpl* 2006; **12**: 465.
70. Ueno T, Jones G, Martin A, *et al.* Clinical outcomes from hepatic artery stenting in liver transplantation. *Liver Transpl* 2006; **12**: 422.
71. CAPRIE Steering Committee. A randomised, blinded trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE). *Lancet* 1996; **348**: 1329
72. Amesur NB, Zajko AB. Interventional radiology in liver transplantation. *Liver Transpl* 2006; **12**: 330.
73. Buis CI, Hoekstra H, Verdonk RC, Porte RJ. Causes and consequences of ischemic-type biliary lesions after liver transplantation. *J Hepatobiliary Pancreat Surg* 2006; **13**: 517.
74. Lee HW, Suh KS, Shin WY, *et al.* Classification and prognosis of intrahepatic biliary stricture after liver transplantation. *Liver Transpl* 2007; **13**: 1736.
75. Nishida S, Nakamura N, Kudano J, *et al.* Intrahepatic biliary stricture after liver transplantation. *J Hepatobiliary Pancreat Surg* 2006; **13**: 511.