

## Vascular Access Thrombosis Prophylaxis

**Devasmita Choudhury**

Department of Medicine, University of Texas Southwestern Medical School, VA North Texas Health Care System, Dallas, Texas

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### ABSTRACT

Vascular access thrombosis in the hemodialysis patient leads to significant cost and morbidity. Fistula patency supersedes graft patency, therefore obtaining a mature functioning fistula in patients approaching end-stage renal disease (ESRD) by early patient education and referral needs to be practiced. Current methods to maintain vascular access patency rely on early

detection and radiologic or surgical prevention of thrombosis. Study of thrombosis biology has elucidated other potential targets for the prophylaxis of vascular access thrombosis. The goal of this review is to examine the current available methods for vascular access thrombosis prophylaxis.

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A patent vascular access is key for maintenance hemodialysis. Access thrombosis is a costly threat to patency in association with significant morbidity to the patient. Native fistula patency is significantly better than synthetic grafts and should be considered as the first method in maintaining long-term vascular access patency (1). However, with a growing elderly, diabetic, and female dialysis population, obtaining a mature and functioning native fistula can be challenging. Many have small-caliber vessels. In addition, arterial disease or repeated venipuncture injury to native vessels precludes appropriate fistula development. The mainstay of vascular access thrombosis prophylaxis currently relies on early detection of pending thrombosis. Monitoring venous pressures or access flow rates with techniques such as thermodilution and duplex Doppler ultrasound can be useful for screening early access failure (2–5).

Subsequent radiologic or surgical intervention with angioplasty, stenting, or revision can prevent an impending thrombosis (6,7). While surveillance and early intervention can prevent the immediate morbidity of urgent acute vascular access placement, hospitalization, or missed treatments associated with sudden access thrombosis, long-term access patency after interventional procedures, particularly for polytetrafluoroethylene (PTFE) grafts and basilic vein transposition fistulas, remains poor (8).

Vein outflow stenoses are the primary reason for vascular access thrombosis, with intimal hyperplasia of the draining vein identified as the most frequent culprit (9). Studies evaluating the pathobiology of access throm-

bosis suggest a procoagulant environment resulting from endothelial damage, inflammation, and intrinsic deficiency of antithrombotic factors adding to the mechanical obstruction associated with intimal hyperplasia. A better understanding of the various factors associated with access thromboses can open new doors for possible medical interventions in conjunction with current screening and interventional methods to prevent access thrombosis. This article summarizes current concepts and suggested prophylaxis underlying access thrombosis and its prevention.

### Native Fistula Placement: The First Prophylaxis Against Thrombosis

#### Why a Fistula?

While many factors, including appropriate arterial inflow, compatible venous outflow, and the skill of the surgeon creating the access, are important in the creation of arteriovenous fistulas (AVFs), it is clear that native fistulas have a longer patency life even after adjustment for age (10,11). In addition, infection, complication, and mortality rates are lower in AVFs in comparison to arteriovenous grafts (AVGs) (12). Unassisted fistula patency in 2 years is close to 73–75%, compared to 22–25% for AVGs (13). Cumulative patency for grafts can increase to 50% at 2 years, but requires three times as many interventions to keep the graft patent (13,14).

Fistula maturation failure may be problematic, particularly in elderly, female, or diabetic patients or in patients with underlying vascular disease. Therefore securing a patent fistula for dialysis should begin early and occur prior to dialysis initiation. Dual lumen tunneled catheters have the lowest unassisted patency rate of 9% per year. In addition, these catheters often provide inadequate dialysis and are associated with a high infection rate.

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*Address correspondence to:* Devasmita Choudhury, MD, Department of Medicine, University of Texas Southwestern Medical School, VA North Texas Health Care System, Dallas, TX 75216, or e-mail: Devasmita.Dev@med.va.gov.

*Seminars in Dialysis*—Vol 19, No 4 (July–August) 2006 pp. 335–342

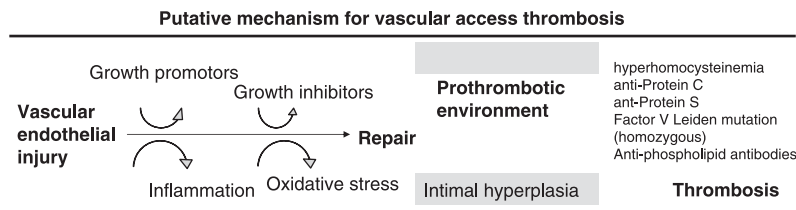


Fig. 1. Vascular endothelial injury incites growth promoters, growth inhibitors, inflammation, and oxidative stress during the process of repair and leads to vascular intimal hyperplasia. In the presence of thrombotic factors in patients with kidney failure, vascular access thrombosis can ensue.

Complications of vein stenosis, thrombosis, and limb edema can compromise fistula and graft placement. Maintenance long-term hemodialysis with these catheters should be avoided whenever possible (15).

### Optimizing Fistula Placement

A team approach, with the goal of securing a functioning AVF, between patient, nephrologist, interventionalist, surgeon, and dialysis staff may be the best approach in increasing fistula creation so that all involved understand the importance of timely and appropriate assessment and placement. Factors suggested to improve placement of a functioning mature fistula are early referral to a nephrologist, patient education, and protection of forearm and central vein vasculature from repeated cannulation injury, preoperative venous mapping to optimize the location and type of fistula placement and to rule out possible out-flow obstruction, aggressive salvaging of immature fistulas, adequate maturation time, and dialysis staff expertise with fistula cannulation (16,17). Experience in Europe, where the majority of dialysis accesses are fistulas, reinforces this belief (17).

Early referral of the chronic kidney disease (CKD) patient allows patient education to begin immediately regarding appropriate vascular care for fistula creation, in addition to long-term care of this important lifeline. Early referral also allows for adequate fistula maturation time and avoidance of temporary access placement. Avoidance of temporary central vein cannulation can prevent future central vein stenosis and vascular access compromise.

### Fistula Site: Differences in Thrombosis Rates?

While the site of fistula creation is primarily a surgical decision, the forearm radiocephalic fistula is frequently the initial preferred site if appropriate vascular integrity is present. If maturation does not occur, then salvage of the fistula or fistula placement at another site needs to be considered (18). Brachiocephalic fistula placement may be preferred to transposed brachiocephalic fistulas as they are less likely to fail once matured. A 1 year thrombosis-free survival of 77–93% is noted with brachiocephalic fistulas when maturation failure is excluded (8). With maturation failure and thrombosis combined, there is little difference in fistula patency between brachiocephalic and transposed brachiocephalic vein fistulas (8), suggesting the possibility of earlier thrombosis with brachiocephalic fistulas. Radiobasilic fistulas also have similar

patency to brachiocephalic fistulas, although early thrombosis may also occur with slightly more frequency, but can be treated with secondary intervention (19). Assisted patency of transposed brachiocephalic vein fistulas is reported to be approximately 64–66% at 1 year, 53–58% at 2 years, and 43% at 3 years (20–22).

Increasing age (greater than 60 years), previous vascular access, and obesity are associated with greater risk of primary failure and need to be factored in when considering transposition fistula placement (20,23). Complication rates as high as 55–69% were noted, consisting of thrombosis, infection, stenosis, arm edema, bleeding, steal syndrome, and microaneurysms. Basilic vein transposition fistula placement may still be preferred, however, to synthetic upper arm graft placement, given the lesser likelihood of thrombosis and infection (8,21,22).

### Thrombosis Biology

Studies investigating the pathobiology of vascular access thrombosis suggest that the endothelial repair response to injury in the face of excess growth promoters, inflammation, and oxidative stress leads to luminal hyperplastic intimal growth. In the presence of a prothrombotic environment in the renal patient, vascular thrombosis can ensue (Fig. 1).

### Endothelial Response to Injury

The typical lesion of access thrombosis is neointimal vascular smooth muscle cell proliferation in the anastomotic draining vein. This can occur in response to endothelial injury (24) during graft or fistula placement secondary to foreign body reaction, pulsatile shear stress, excessive stretch from mismatch of elastic properties of the artery and vein, and repeated vein cannulation injury. Approximately 50–70% of lesions are within 3–5 cm of the vein anastomosis (13).

A haphazard hyperplastic smooth muscle response of the intima with angiogenesis occurring in both intima and adventitia is associated with the presence of macrophages and cytokines, including basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF) (25). Increased interleukin (IL)-1 $\beta$  and tumor necrosis factor (TNF)- $\alpha$  may act to increase endothelial prothrombotic production of IL-6 and plasminogen activator inhibitor (PAI)-1, intracellular adhesion molecule (ICAM)-1, and vascular endothelial cell adhesion molecule (VCAM)-1 (26,27). Transforming growth factor (TGF)- $\beta$  and PDGF

are both found at the venous anastomotic site (28). TGF- $\beta$  promotes fibronectin and collagen expansion. Higher TGF- $\beta$  excretion appears to be associated with lower primary access patency (29).

With endothelial injury, there is exposure of the endothelial basement membrane and extracellular matrix that activates platelets. As a result, smooth muscle cell proliferation promoters, including thromboxane A<sub>2</sub>, serotonin, and PDGF, are released (30). Shorter access survival was noted with elevated numbers of circulating activated platelets (31). Vascular injury initiates the extrinsic clotting cascade via release of von Willebrand factor and PAI-1 with an increase in thromboplastin tissue factor (32). Engraftment injury creates an environment in which growth promoters such as endothelin (33,34), PDGF, bFGF (35), and angiotensin (36) are increased over growth inhibitors such as heparan sulfate (37) and nitric oxide, as can be seen with saphenous vein grafts (24,38). Nitric oxide production also appears to decline with progression of renal failure (39).

### Inflammation

In addition to injury, a state of underlying chronic inflammation and oxidative stress may add to endothelial dysfunction and injury. The presence of renal failure is associated with a state of chronic inflammation (40). Increased levels of inflammation markers including C-reactive protein (CRP), IL-6, and soluble TNF are present in individuals with reduced renal function (41–45). Hypoalbuminemia in dialysis patients is likely the result of chronic inflammation and is associated with a greater risk for thrombosis (46,47). Inflammation can alter the expression of vascular and platelet adhesion molecules (48).

Evidence for oxidative stress, such as increased advanced glycation end-products (49) and decreased concentrations of endogenous antioxidants (50), are also noted in end-stage renal disease (ESRD) patients. Exposure to dialysis membranes was suggested as contributing to underlying oxidative stress and inflammation. Tissue inflammation and oxidative stress injury associated with uremia increase the expression of proteins (51) and growth factors associated with intimal hyperplasia such as endothelin-1 (34). A uremic milieu is also associated with hypofibrinolysis and elevated plasma inhibitors of tissue activator of plasminogen (PAI-1) (52), thereby contributing to a prothrombotic environment.

### Prothrombotic Factors

Recent studies also note a greater prevalence of anti-protein C and antiprotein S antibodies in dialysis patients with vascular access thrombosis, suggesting a role for hypercoagulability in addition to endothelial injury and inflammation (53). Elevated antiphospholipid antibodies were also found in patients on dialysis, however, a causative role for these antibodies in vascular access thrombosis still needs clarification (54–58). A homozygous mutation of factor V Leiden gene is associated with increased vascular access thrombosis, although this risk is not translated to heterozygous patients with this

mutation (59). In vitro studies demonstrate that hyperhomocysteinemia can induce vascular smooth muscle cell proliferation, while folate inhibits this proliferation. ESRD is associated with elevated serum homocysteine levels. Proportional hazards modeling revealed a 4% increase in the risk of access thrombosis for every 1  $\mu\text{mol/L}$  increase in predialysis plasma homocysteine levels in hemodialysis patients with a fistula or prosthetic graft followed for 18 months (60).

## Thrombosis Prophylaxis: What Can We Do?

### Screening for Access Flow Alterations

Flow abnormalities frequently occur when significant outflow (or less commonly, inflow) stenoses are present within the vascular access. Early detection of access stenoses may allow for early intervention to prevent access thrombosis (61). Findings of a high-pitched discontinuous harsh bruit over the access on physical examination or progressive edema of the access limb can be seen on occasion, but are not always evident or reliable. Similarly urea recirculation and unexplained decreases in delivered dialysis dose are also used to identify access dysfunction, though they are quite late manifestations of access dysfunction reflecting very low access blood flow.

Static and dynamic venous pressure measurements are also used to screen for access stenosis. A static venous pressure measurement is the sum of the venous pressure (with the blood pump off) and the height difference between the venous drip chamber and access site. The static venous pressure normalized to the patient's systolic blood pressure yields a static venous pressure ratio (62,63). A ratio greater than 0.4 has been shown to predict access stenosis (62,63). Dynamic venous pressures are venous pressures recorded during the dialysis procedure. Recorded dynamic venous pressures greater than 150 mmHg taken during steady blood flow rates of 200–225 mmHg when the patient is cannulated with a 16-gauge needle suggest access outflow venous stenosis. Both prospective and retrospective studies using this criteria for noninvasive screening of stenosis were able to detect stenosis in approximately 85% of grafts (2,64). With the development of collateral venous circulation of some accesses, the presence of significant stenoses can frequently be missed by this method (64). Dynamic venous pressure measurement performed at higher blood flow rates (300 and 400 ml/min) increase line resistance and pressure and are not reliable for the detection of an underlying increase in access resistance that characterizes outflow stenosis (64).

Ultrasound and thermodilution flow measurements of access flow are utilized by many to screen for access stenosis (5,65–67). A low access blood flow rate or a decline from baseline flow measurements of 15% by the ultrasound dilution method should prompt a fistulogram to look for significant luminal narrowing (5). While access monitoring can prevent impending thrombosis, long-term access patency appears to be unaffected (68,69). Whether this is the result of repeated vascular injury from intervention salvage procedures still needs to be investigated.

## Intervention with Angioplasty, Stents, or Revision

Luminal narrowing of 50% or more, particularly in the presence of clinically low dialysis flow or clearance parameters, generally requires percutaneous transluminal angioplasty (PTA) of the stenoses. While access use is prolonged in the short term, restenosis frequently occurs, with 6 month patency as high as 60% (13,70). Repeat PTA intervention is often necessary. However, with each PTA intervention, interval patency diminishes (71). While stent placement to avoid elastic recoil after PTA seems logical, bare metal stent placement was not successful in increasing overall patency when compared to PTA alone (72). However, drug eluting stents may have potential in improving access patency. Sirolimus-coated stent use showed 77% improvement in intimal hyperplasia, with greater luminal diameter and improved graft flow compared to nonstented controls in porcine AVGs (37). Their potential benefit in hemodialysis patients needs to be tested. Recent animal studies using paclitaxel-coated stents (an antiplatelet inhibitor) also showed marked improvement in intimal hyperplasia of AVGs (73). Further studies may prove this to be an added tool in the prevention of access thrombosis.

Access salvage with revision may need to be considered in those accesses that have undergone multiple PTA procedures. While the use of tapered grafts to decrease flow turbulence and abnormal shear stress at the venous anastomosis seem to be promising, a recent trial did not suggest a benefit in long-term vascular access patency (74).

## Medical Intervention

With a greater understanding of the molecular aspects of endothelial injury and intimal hyperplasia, investigations with various pharmacologic agents in preventing access thrombosis have begun.

### Antiplatelet Agents

Platelet activation from endothelial injury may play an important role in stimulating platelet aggregators such as PDGF and thromboxane A<sub>2</sub>, in addition to directly stimulating vascular intimal proliferation. Therefore the therapeutic potential of antiplatelet agents including aspirin, sulfapyrazone, dipyridamole, and ticlopidine were tested. A double-blind randomized trial using the antiplatelet agents dipyridamole and aspirin evaluated the rate of thrombosis in both newly placed and previously placed PTFE grafts. This study suggested beneficial effects of using dipyridamole alone in newly placed AVGs, however, no benefit in graft thrombosis rates with the use of dipyridamole alone or in combination with aspirin were found in prevalent grafts (75).

Aspirin was found to improve secondary or assisted patency for AVGs on adjusted Cox regression analysis in the Dialysis Outcomes and Practice Patterns Study (DOPPS) database (76). Ticlopidine use in a randomized study of 107 patients with Scribner shunts and AVGs

suggested decreased clotting frequency (77). A small pilot study of 15 patients with recurrent vascular access thrombosis using low-dose aspirin (85 mg) and sulfapyrazone (200 mg) three times a day over 12 months showed a 65% decrease in thrombosis rate, but bleeding was noted to be a significant complication (78). Similarly a randomized double-blind placebo-controlled study to evaluate the effect of aspirin (325 mg) and the thienopyridine clopidogrel (75 mg) on the prevention of AVG thrombosis was terminated early by the study's safety monitoring board because of increased bleeding risk (79).

These data suggest that antiplatelet agents appear to have a role in the prevention of AVG thrombosis, with dipyridamole used for newly placed grafts and aspirin for secondary AVG patency. Currently the National Institutes of Health (NIH)-sponsored Dialysis Access Consortium is conducting an ongoing double-blind multicenter randomized evaluation of clopidogrel in AVF patency, and slow release dipyridamole (200 mg) and low-dose aspirin (25 mg) on primary unassisted AVG patency.

### Fish Oil

With increased oxidative stress and decreased concentrations of endogenous antioxidants in renal failure, the possible use of antioxidants may improve vascular access thrombosis. Since  $\omega$ -3 fatty acids decreased growth factor and cytokine release from platelets and inflammatory cells, and inhibited smooth muscle cell growth in addition to improving turbulence by modifying endothelial membrane fluidity, fish oil was evaluated in a randomized blinded prospective fashion in 24 patients with newly placed AVGs (80–82). This study revealed significant improvement in graft patency rate, with 75.6% in the treatment group compared to 14.9% in the control group at 1 year follow-up after enrollment closure (83). A larger multicenter trial using fish oil as prophylaxis for access patency is under way in Canada. This will further delineate the role of fish oil with maintenance of long-term vascular access patency.

### Angiotensin-Converting Enzyme Inhibitors

Intimal smooth muscle hyperplasia is induced by growth promoters such as angiotensin II. Angiotensin-converting enzyme (ACE) inhibitors blocked smooth muscle proliferation in animal studies of arterial injury after balloon angioplasty (24,36). The use of ACE inhibitors is common in renal patients with numerous cardiovascular comorbidities. Therefore the effect of this medication on AVGs was also evaluated. Single-center retrospective studies suggested improved AVG and AVF patency in patients using ACE inhibitors for other reasons (84–86). Patients with AVG on ACE inhibitors have a relative risk reduction of 53% compared to those not taking ACE inhibitors (84). Japanese investigators evaluating ACE inhibitor therapy on AVF patency noted an odds ratio of 1.79 for fistula occlusion in those not taking ACE inhibitors (86). The DOPPS database of patients on ACE inhibitor therapy with both AVG and AVF suggests

no benefit in either primary (unassisted) or secondary (assisted) AVG patency (76). However, there appeared to be a 44% risk reduction benefit for secondary AVF patency with ACE inhibitor use in the prevalent dialysis population. Recently we completed a randomized placebo-controlled trial evaluating the effect of ACE inhibitors in AV access patency that may be helpful in further determining whether this class of medication prolongs access patency.

### Calcium Channel Blockers

Retrospective medication analysis of large datasets revealed that calcium channel blockers may exert a significant positive effect on new graft survival, particularly in diabetic patients (87). This was also seen in the DOPPS study evaluating various drugs used in relation to vascular access thrombosis, where a significantly lower risk of 14% was noted for primary unassisted AVG patency (76). Randomized prospective studies need to be done to better delineate the use of calcium blockers in dialysis access thrombosis prevention.

### Anticoagulants

Thrombosis prophylaxis using anticoagulants becomes important in the face of underlying thrombophilia. Dialysis patients with a propensity for thrombotic events, including deep vein thrombosis, pulmonary embolus, and repeated vascular and vascular access thrombosis, should be evaluated for hypercoagulability. A case-control study evaluating the association of a thrombophilic disorder in dialysis patients noted that 55% of patients with access thrombosis had evidence of at least one of the disorders tested, including factor V Leiden, prothrombin gene mutation, factor XIII genotype, methylenetetrahydrofolate reductase genotype, lupus anticoagulant, elevated concentrations of anticardiolipin antibody, factor VIII, homocysteine, and lipoprotein (a). Approximately 39% of those without access thrombosis also had thrombophilia (88). A study evaluating the use of warfarin, unfractionated heparin, and low molecular weight heparin in dialysis patients with recurrent vascular thrombosis noted that 19 of 29 patients did not have thrombosis recurrence over a 7 month median follow-up period, however, bleeding risk was significant (89).

These studies, while not randomized trials, suggest that recurrent access thrombosis should prompt evaluation for possible underlying thrombophilia. Furthermore, treatment for thrombophilia in the dialysis patient using anticoagulants must be carefully individualized and monitored given the high bleeding risk in dialysis patients.

### Other Medical Therapies Under Investigation

While several cross-sectional, cohort, and retrospective studies did not show an association of vascular thrombosis and elevated serum homocysteine levels (90–92), other prospective studies noted an increase in both AVG and fistula thrombosis with elevated homocysteine levels (60,93). A multicenter randomized placebo-controlled

Veterans Affairs cooperative trial evaluating the effect of high-dose folate (40 mg) and vitamin B supplementation in the treatment of hyperhomocysteinemia on cardiovascular outcomes and thrombosis in chronic renal failure and dialysis patients (HOST trial) is currently under way (94). This trial may provide further information regarding thrombophilia and prophylaxis for vascular thrombosis associated with elevated homocysteine levels.

Matrix metalloproteinase inhibitors (MMPi) decrease vascular smooth muscle migration and arterial and venous neointimal hyperplasia. Porcine models with AVG intimal hyperplasia receiving MMPi had a 52% decrease in intimal hyperplastic growth (95). Further evaluation of this treatment may add to current pharmacologic strategies to improve access patency.

### Newer Endovascular Strategies to Prevent Vascular Thrombosis

Inhibiting intimal hyperplastic growth after endothelial injury after angioplasty or stent placement was achieved with endovascular radiation in animal studies (96). AVG intimal hyperplasia was minimized in animal models (97). Local ionizing radiation causes single- and double-stranded breaks in the purine and pyrimidine bases, thereby preventing vascular smooth muscle cell proliferation (37). This prompted a multicenter randomized trial of brachytherapy on access patency that is in progress (98).

Local photodynamic therapy uses the concept of accumulating a photosensitizer at the target vascular smooth muscle cells of the affected vasculature. Monochromatic light then activates this light-sensitive compound to produce free radicals that inhibit intimal hyperplasia (37,99). This concept is still being tested in animal models (99).

With developing technologies in gene therapy, the potential to manipulate local cytokine and growth factors by overexpressing inhibitors of intimal hyperplasia are being investigated. Adenoviral vector delivery of C-type natriuretic peptide in the periadventitial area of porcine AVGs to decrease adventitial fibroblasts reduced venous medial thickening and luminal diameter (100). This prompted a randomized clinical trial of periadventitial adenoviral VEGF delivery in AVGs using a sialastic collar (101). Gene transfer and overexpression of MMPi of injured arteries and vein grafts also decreased intimal hyperplasia (102,103). In addition, other studies of gene transfer of inducible nitric oxide synthase to porcine vein grafts inhibited intimal hyperplasia (104). These studies indicate that future local therapies to prevent vascular access thrombosis will be forthcoming.

### Conclusion

Vascular access thrombosis prophylaxis needs to start early in the ESRD patient. A team approach with nephrologists, surgeons, interventionalists, the patient, and the nursing staff, as well as the primary care staff is needed to preserve the vasculature for eventual fistula placement

and ensure appropriate maturation. Screening for vascular access stenosis and surgical or radiologic intervention may prevent the emergent morbidity of thrombosis, however, long-term patency remains unaffected. Emerging medical therapies to prolong access patency are being actively investigated. Furthermore, developing technologies of brachytherapy, photodynamic therapy, and gene therapy may be important future therapies for vascular access thrombosis prophylaxis.

## References

- National Kidney Foundation: NKF-K/DOQI clinical practice guidelines for vascular access. *Am J Kidney Dis* 37:S169, 2001
- Schwab SJ, Raymond JR, Saeed M, Newman GE, Dennis PA, Bollinger RR: Prevention of hemodialysis fistula thrombosis. Early detection of venous stenoses. *Kidney Int* 36:707–711, 1989
- Sands J, Young S, Miranda C: The effect of Doppler flow screening studies and elective revisions on dialysis access failure. *ASAIO J* 38:M524–M527, 1992
- Tessitore N, Bedogna V, Gammara L, Lipari G, Poli A, Baggio E, Firpo M, Morana G, Mansueto G, Maschio G: Diagnostic accuracy of ultrasound dilution access blood flow measurement in detecting stenosis and predicting thrombosis in native forearm arteriovenous fistulae for hemodialysis. *Am J Kidney Dis* 42:331–341, 2003
- Neyra NR, Ikizler TA, May RE, Himmelfarb J, Schulman G, Shyr Y, Hakim RM: Change in access blood flow over time predicts vascular access thrombosis. *Kidney Int* 54:1714–1719, 1998
- Tynan-Cuisiner G, Berman SS: Advances in endovascular techniques to treat failing and failed hemodialysis access. *J Endovasc Ther* 11(suppl 2):II134–II139, 2004
- Sands JJ, Miranda CL: Prolongation of hemodialysis access survival with elective revision. *Clin Nephrol* 44:329–333, 1995
- Oliver MJ, McCann RL, Indridason OS, Butterly DW, Schwab SJ: Comparison of transposed brachio-basilic fistulas to upper arm grafts and brachiocephalic fistulas. *Kidney Int* 60:1532–1539, 2001
- Swedberg SH, Brown BG, Sigley R, Wight TN, Gordon D, Nicholls SC: Intimal fibromuscular hyperplasia at the venous anastomosis of PTFE grafts in hemodialysis patients. Clinical, immunocytochemical, light and electron microscopic assessment. *Circulation* 80:1726–1736, 1989
- Woods JD, Turenne MN, Strawderman RL, Young EW, Hirth RA, Port FK, Held PJ: Vascular access survival among incident hemodialysis patients in the United States. *Am J Kidney Dis* 30:50–57, 1997
- Ascher E, Gade P, Hingorani A, Mazzarioli F, Gunduz Y, Fodera M, Yorkovich W: Changes in the practice of angioaccess surgery: impact of dialysis outcome and quality initiative recommendations. *J Vasc Surg* 31:84–92, 2000
- Feldman HI, Kobrin S, Wasserstein A: Hemodialysis vascular access morbidity. *J Am Soc Nephrol* 7:523–535, 1996
- Schwab SJ, Harrington JT, Singh A, Roher R, Shohaib SA, Perrone RD, Meyer K, Beasley D: Vascular access for hemodialysis. *Kidney Int* 55:2078–2090, 1999
- Miller PE, Carlton D, Deierhoi MH, Redden DT, Allon M: Natural history of arteriovenous grafts in hemodialysis patients. *Am J Kidney Dis* 36:68–74, 2000
- Hodges TC, Fillinger MF, Zwolak RM, Walsh DB, Bech F, Cronenwett JL: Longitudinal comparison of dialysis access methods: risk factors for failure. *J Vasc Surg* 26:1009–1019, 1997
- Allon M, Bailey R, Ballard R, Deierhoi MH, Hamrick K, Oser R, Rhynes VK, Robbin ML, Saddekni S, Zeigler ST: A multidisciplinary approach to hemodialysis access: prospective evaluation. *Kidney Int* 53:473–479, 1998
- Hemphill H, Allon M, Konner K, Work J, Vassalotti JA: How can the use of arteriovenous fistulas be increased? *Semin Dial* 16:214–223, 2003
- Berman SS, Gentile AT: Impact of secondary procedures in autogenous arteriovenous fistula maturation and maintenance. *J Vasc Surg* 34:866–871, 2001
- Gormus N, Ozergin U, Durgut K, Yuksek T, Solak H: Comparison of autologous basilic vein transpositions between forearm and upper arm regions. *Ann Vasc Surg* 17:522–525, 2003
- Segal JH, Kayler LK, Henke P, Merion RM, Leavey S, Campbell DA Jr: Vascular access outcomes using the transposed basilic vein arteriovenous fistula. *Am J Kidney Dis* 42:151–157, 2003
- Murphy GJ, White SA, Knight AJ, Doughman T, Nicholson ML: Long-term results of arteriovenous fistulas using transposed autologous basilic vein. *Br J Surg* 87:819–823, 2000
- Taghizadeh A, Dasgupta P, Khan MS, Taylor J, Koffman G: Long-term outcomes of brachio-basilic transposition fistula for haemodialysis. *Eur J Vasc Endovasc Surg* 26:670–672, 2003
- Rao RK, Azin GD, Hood DB, Rowe VL, Kohl RD, Katz SG, Weaver FA: Basilic vein transposition fistula: a good option for maintaining hemodialysis access site options? *J Vasc Surg* 39:1043–1047, 2004
- Gibbons GH, Dzau VJ: The emerging concept of vascular remodeling. *N Engl J Med* 330:1431–1438, 1994
- Roy-Chaudhury P, Kelly BS, Miller MA, Reaves A, Armstrong J, Nanayakkara N, Heffelfinger SC: Venous neointimal hyperplasia in polytetrafluoroethylene dialysis grafts. *Kidney Int* 59:2325–2334, 2001
- Vaziri ND, Gonzales EC, Wang J, Said S: Blood coagulation, fibrinolytic, and inhibitory proteins in end-stage renal disease: effect of hemodialysis. *Am J Kidney Dis* 23:828–835, 1994
- Mysliwiec M: Vascular access thrombosis—what are the possibilities of intervention? *Nephrol Dial Transplant* 12:876–878, 1997
- Weiss MF, Scivittaro V, Anderson JM: Oxidative stress and increased expression of growth factors in lesions of failed hemodialysis access. *Am J Kidney Dis* 37:970–980, 2001
- Heine GH, Ulrich C, Sester U, Kohler H, Girmdt M: Transforming growth factor beta1 genotype polymorphisms determine AV fistula patency in hemodialysis patients. *Kidney Int* 64:1101–1107, 2003
- Ross R, Glomset J, Kariya B, Harker L: A platelet-dependent serum factor that stimulates the proliferation of arterial smooth muscle cells in vitro. *Proc Natl Acad Sci USA* 71:1207–1210, 1974
- Chuang YC, Chen JB, Yang LC, Kuo CY: Significance of platelet activation in vascular access survival of haemodialysis patients. *Nephrol Dial Transplant* 18:947–954, 2003
- Cassery LF, Dember LM: Thrombosis in end-stage renal disease. *Semin Dial* 16:245–256, 2003
- Masood I, Porter KE, London NJ: Endothelin-1 is a mediator of intimal hyperplasia in organ culture of human saphenous vein. *Br J Surg* 84:499–503, 1997
- Wilkie ME, Khandan-Nia N, Ghatei MA, Bloom SR, Raftery MJ, Cunningham J: Does the arteriovenous fistula in chronic haemodialysis patients stimulate endothelin-1 release? *Nephrol Dial Transplant* 7:1019–1021, 1992
- Sapienza P, di Marzo L, Cucina A, Corvino V, Mingoli A, Giustiniani Q, Ziparo E, Cavallaro A: Release of PDGF-BB and bFGF by human endothelial cells seeded on expanded polytetrafluoroethylene vascular grafts. *J Surg Res* 75:24–29, 1998
- Daemen MJ, Lombardi DM, Bosman FT, Schwartz SM: Angiotensin II induces smooth muscle cell proliferation in the normal and injured rat arterial wall. *Circ Res* 68:450–456, 1991
- Rotmans JI, Pasterkamp G, Verhagen HJ, Pattynama PM, Blankestijn PJ, Stroes ES: Hemodialysis access graft failure: time to revisit an unmet clinical need? *J Nephrol* 18:9–20, 2005
- Angelini GD, Christie MI, Bryan AJ, Lewis MJ: Surgical preparation impairs release of endothelium-derived relaxing factor from human saphenous vein. *Ann Thorac Surg* 48:417–420, 1989
- Vaziri ND: Effect of chronic renal failure on nitric oxide metabolism. *Am J Kidney Dis* 38:S74–S79, 2001
- Verma S, Li SH, Badiwala MV, Weisel RD, Fedak PW, Li RK, Dhillon B, Mickle DA: Endothelin antagonism and interleukin-6 inhibition attenuate the proatherogenic effects of C-reactive protein. *Circulation* 105:1890–1896, 2002
- Shlipak MG, Fried LF, Crump C, Bleyer AJ, Manolio TA, Tracy RP, Furberg CD, Psaty BM: Elevations of inflammatory and procoagulant biomarkers in elderly persons with renal insufficiency. *Circulation* 107:87–92, 2003
- Panichi V, Migliori M, De Pietro S, Taccola D, Bianchi AM, Giovannini L, Norpoth M, Metelli MR, Cristofani R, Bertelli AA, Sbragia G, Tetta C, Palla R, Colombo R: C-reactive protein and interleukin-6 levels are related to renal function in predialytic chronic renal failure. *Nephron* 91:594–600, 2002
- Mezzano D, Pais EO, Aranda E, Panes O, Downey P, Ortiz M, Tagle R, Gonzalez F, Quiroga T, Caceres MS, Leighton F, Pereira J: Inflammation, not hyperhomocysteinemia, is related to oxidative stress and hemostatic and endothelial dysfunction in uremia. *Kidney Int* 60:1844–1850, 2001
- Halwachs G, Tiran A, Reisinger EC, Zach R, Sabin K, Folsch B, Lanzer H, Holzer H, Wilders-Truschig M: Serum levels of the soluble receptor for tumor necrosis factor in patients with renal disease. *Clin Invest* 72:473–476, 1994
- Bolton CH, Downs LG, Victory JG, Dwight JF, Tomson CR, Mackness MI, Pinkney JH: Endothelial dysfunction in chronic renal failure: roles of lipoprotein oxidation and pro-inflammatory cytokines. *Nephrol Dial Transplant* 16:1189–1197, 2001
- Churchill DN, Taylor DW, Cook RJ, LaPlante P, Barre P, Cartier P, Fay WP, Goldstein MB, Jindal K, Mandin H, et al.: Canadian hemodialysis morbidity study. *Am J Kidney Dis* 19:214–234, 1992
- Kalman PG, Pope M, Bhola C, Richardson R, Sniderman KW: A practical approach to vascular access for hemodialysis and predictors of success. *J Vasc Surg* 30:727–733, 1999
- Kaysen GA: The microinflammatory state in uremia. causes and potential consequences. *J Am Soc Nephrol* 12:1549–1557, 2001
- Kaysen GA, Stevenson FT, Depner TA: Determinants of albumin concentration in hemodialysis patients. *Am J Kidney Dis* 29:658–668, 1997
- Becker BN, Himmelfarb J, Henrich WL, Hakim RM: Reassessing the cardiac risk profile in chronic hemodialysis patients: a hypothesis on the role

- of oxidant stress and other non-traditional cardiac risk factors. *J Am Soc Nephrol* 8:475–486, 1997
51. Roselaar SE, Nazhat NB, Winyard PG, Jones P, Cunningham J, Blake DR: Detection of oxidants in uremic plasma by electron spin resonance spectroscopy. *Kidney Int* 48:199–206, 1995
  52. Segarra A, Chacon P, Martinez-Eyarre C, Argelaguer X, Vila J, Ruiz P, Fort J, Bartolome J, Camps J, Moliner E, Pelegri A, Marco F, Olmos A, Piera L: Circulating levels of plasminogen activator inhibitor type-1, tissue plasminogen activator, and thrombomodulin in hemodialysis patients: biochemical correlations and role as independent predictors of coronary artery stenosis. *J Am Soc Nephrol* 12:1255–1263, 2001
  53. Molino D, Lucia D, Marotta R, Perna A, Lombardi C, Cirillo M, De Santo NG: In uremia, plasma levels of anti-protein C and anti-protein S antibodies are associated with thrombosis. *Kidney Int* 68:1223–1229, 2005
  54. Garcia-Martin F, De Arriba G, Carrascosa T, Moldenhauer F, Martin-Escobar E, Val J, Saiz F: Anticardiolipin antibodies and lupus anticoagulant in end-stage renal disease. *Nephrol Dial Transplant* 6:543–547, 1991
  55. Gronhagen-Riska C, Teppo AM, Helanterä A, Honkanen E, Julkunen H: Raised concentrations of antibodies to cardiolipin in patients receiving dialysis. *Br Med J* 300:1696–1697, 1990
  56. Haviv YS: Association of anticardiolipin antibodies with vascular access occlusion in hemodialysis patients: cause or effect? *Nephron* 86:447–454, 2000
  57. Brunet P, Aillaud MF, San Marco M, Philip-Joet C, Dussol B, Bernard D, Juhan-Vague I, Berland Y: Antiphospholipids in hemodialysis patients. relationship between lupus anticoagulant and thrombosis. *Kidney Int* 48:794–800, 1995
  58. Prakash R, Miller CC 3rd, Suki WN: Anticardiolipin antibody in patients on maintenance hemodialysis and its association with recurrent arteriovenous graft thrombosis. *Am J Kidney Dis* 26:347–352, 1995
  59. Fodinger M, Mannhalter C, Pabinger I, Koizar D, Rintelen C, Horl WH, Sunder-Plassmann G: Resistance to activated protein C (APC) mutation at Arg506 of coagulation factor V and vascular access thrombosis in haemodialysis patients. *Nephrol Dial Transplant* 11:668–672, 1996
  60. Shemin D, Lapane KL, Bausserman L, Kanaan E, Kahn S, Dworin L, Bostom AG: Plasma total homocysteine and hemodialysis access thrombosis: a prospective study. *J Am Soc Nephrol* 10:1095–1099, 1999
  61. McCarley P, Wingard RL, Shyr Y, Pettus W, Hakim RM, Ikizler TA: Vascular access blood flow monitoring reduces access morbidity and costs. *Kidney Int* 60:1164–1172, 2001
  62. Besarab A, Frinak S, Sherman RA, Goldman J, Dumler F, Devita MV, Kapoian T, Al-Saghir F, Lubkowsky T: Simplified measurement of intra-access pressure. *J Am Soc Nephrol* 9:284–289, 1998
  63. Besarab A, Sullivan KL, Ross RP, Moritz MJ: Utility of intra-access pressure monitoring in detecting and correcting venous outlet stenoses prior to thrombosis. *Kidney Int* 47:1364–1373, 1995
  64. Choudhury D, Lee J, Elivera HS, Ball D, Roberts AB, Ahmed Z: Correlation of venography, venous pressure, and hemoaccess function. *Am J Kidney Dis* 25:269–275, 1995
  65. Paun M, Beach K, Ahmad S, Hickman R, Meissner M, Plett C, Strandness DE Jr: New ultrasound approaches to dialysis access monitoring. *Am J Kidney Dis* 35:477–481, 2000
  66. Dousset V, Grenier N, Douws C, Senuita P, Sassouste G, Ada L, Potaux L: Hemodialysis grafts: color Doppler flow imaging correlated with digital subtraction angiography and functional status. *Radiology* 181:89–94, 1991
  67. Robbin ML, Oser RF, Allon M, Clements MW, Dockery J, Weber TM, Hamrick-Waller KM, Smith JK, Jones BC, Morgan DE, Saddekni S: Hemodialysis access graft stenosis: US detection. *Radiology* 208:655–661, 1998
  68. Dember LM, Holmberg EF, Kaufman JS: Randomized controlled trial of prophylactic repair of hemodialysis arteriovenous graft stenosis. *Kidney Int* 66:390–398, 2004
  69. Shahin H, Reddy G, Sharafuddin M, Katz D, Franzwa BS, Dixon BS: Monthly access flow monitoring with increased prophylactic angioplasty did not improve fistula patency. *Kidney Int* 68:2352–2361, 2005
  70. Beathard GA: Percutaneous transvenous angioplasty in the treatment of vascular access stenosis. *Kidney Int* 42:1390–1397, 1992
  71. Kanterman RY, Vesely TM, Pilgram TK, Guy BW, Windus DW, Picus D: Dialysis access grafts: anatomic location of venous stenosis and results of angioplasty. *Radiology* 195:135–139, 1995
  72. Gallego Beuter JJ, Hernandez Lezana A, Herrero Calvo J, Moreno Carriles R: Early detection and treatment of hemodialysis access dysfunction. *Cardiovasc Intervent Radiol* 23:40–46, 2000
  73. Masaki T, Rathi R, Zentner G, Leyboldt JK, Mohammad SF, Burns GL, Li L, Zhuplatov S, Chirananthavat T, Kim SJ, Kern S, Holman J, Kim SW, Cheung AK: Inhibition of neointimal hyperplasia in vascular grafts by sustained perivascular delivery of paclitaxel. *Kidney Int* 66:2061–2069, 2004
  74. Dammers R, Planken RN, Pouls KP, Van Det RJ, Burger H, Van Der Sande FM, Tordoir JH: Evaluation of 4-mm to 7-mm versus 6-mm prosthetic brachial-antecubital forearm loop access for hemodialysis: results of a randomized multicenter clinical trial. *J Vasc Surg* 37:143–148, 2003
  75. Sreedhara R, Himmelfarb J, Lazarus JM, Hakim RM: Anti-platelet therapy in graft thrombosis: results of a prospective, randomized, double-blind study. *Kidney Int* 45:1477–1483, 1994
  76. Saran R, Dykstra DM, Wolfe RA, Gillespie B, Held PJ, Young EW: Association between vascular access failure and the use of specific drugs: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis* 40:1255–1263, 2002
  77. Kobayashi K, Maeda K, Koshikawa S, Kawaguchi Y, Shimizu N, Naito C: Antithrombotic therapy with ticlopidine in chronic renal failure patients on maintenance hemodialysis—a multicenter collaborative double blind study. *Thromb Res* 20:255–261, 1980
  78. Domoto DT, Bauman JE, Joist JH: Combined aspirin and sulfapyrazone in the prevention of recurrent hemodialysis vascular access thrombosis. *Thromb Res* 62:737–743, 1991
  79. Kaufman JS, O'Connor TZ, Zhang JH, Cronin RE, Fiore LD, Ganz MB, Goldfarb DS, Peduzzi PN: Randomized controlled trial of clopidogrel plus aspirin to prevent hemodialysis access graft thrombosis. *J Am Soc Nephrol* 14:2313–2321, 2003
  80. Cartwright IJ, Pockley AG, Galloway JH, Greaves M, Preston FE: The effects of dietary omega-3 polyunsaturated fatty acids on erythrocyte membrane phospholipids, erythrocyte deformability and blood viscosity in healthy volunteers. *Atherosclerosis* 55:267–281, 1985
  81. Fox PL, DiCorleto PE: Fish oils inhibit endothelial cell production of platelet-derived growth factor-like protein. *Science* 241:453–456, 1988
  82. Shiina T, Terano T, Saito J, Tamura Y, Yoshida S: Eicosapentaenoic acid and docosahexaenoic acid suppress the proliferation of vascular smooth muscle cells. *Atherosclerosis* 104:95–103, 1993
  83. Schmitz PG, McCloud LK, Reikes ST, Leonard CL, Gellens ME: Prophylaxis of hemodialysis graft thrombosis with fish oil: double-blind, randomized, prospective trial. *J Am Soc Nephrol* 13:184–190, 2002
  84. Gradzki R, Dhingra RK, Port FK, Roys E, Weitzel WF, Messana JM: Use of ACE inhibitors is associated with prolonged survival of arteriovenous grafts. *Am J Kidney Dis* 38:1240–1244, 2001
  85. Choudhury D: ACE-inhibitors prolong PTFE graft survival in hemodialysis patients. *J Am Soc Nephrol* 11:182A, 2000
  86. Sone M: Angiotensin II inhibition prevents the occlusion of arterio-venous fistula in hemodialysis patients: a prospective case-control study. *J Am Soc Nephrol* 11:197A, 2000
  87. Diskin CJ, Stokes TJ, Thomas SG, Ravis W, Lock S, Thomas J, Panus LW, Dansby L, Carter T: An analysis of the effect of routine medications on hemodialysis vascular access survival. *Nephron* 78:365–368, 1998
  88. Knoll GA, Wells PS, Young D, Perkins SL, Pilkey RM, Clinch JJ, Rodger MA: Thrombophilia and the risk for hemodialysis vascular access thrombosis. *J Am Soc Nephrol* 16:1108–1114, 2005
  89. O'Shea SI, Lawson JH, Reddan D, Murphy M, Ortel TL: Hypercoagulable states and antithrombotic strategies in recurrent vascular access site thrombosis. *J Vasc Surg* 38:541–548, 2003
  90. Manns BJ, Burgess ED, Parsons HG, Schaefer JP, Hyndman ME, Scott-Douglas NW: Hyperhomocysteinemia, anticardiolipin antibody status, and risk for vascular access thrombosis in hemodialysis patients. *Kidney Int* 55:315–320, 1999
  91. Sirrs S, Duncan L, Djurdjev O, Nussbaumer G, Ganz G, Frohlich J, Levin A: Homocyst(e)ine and vascular access complications in hemodialysis patients: insights into a complex metabolic relationship. *Nephrol Dial Transplant* 14:738–743, 1999
  92. Hojs R, Gorenjak M, Ekart R, Dvorsak B, Pecovnik-Balon B: Homocysteine and vascular access thrombosis in hemodialysis patients. *Ren Fail* 24:215–222, 2002
  93. Mallamaci F, Bonanno G, Seminara G, Rapisarda F, Fatuzzo P, Candela V, Scudo P, Spoto B, Testa A, Tripepi G, Tech S, Zoccali C: Hyperhomocysteinemia and arteriovenous fistula thrombosis in hemodialysis patients. *Am J Kidney Dis* 45:702–707, 2005
  94. Jamison RL, Hartigan P, Gaziano JM, Fortmann SP, Goldfarb DS, Haroldson JA, Kaufman J, Lavori P, McCully KS, Robinson K: Design and statistical issues in the homocysteinemia in kidney and end stage renal disease (HOST) study. *Clin Trials* 1:451–460, 2004
  95. Rotmans JI, Velema E, Verhagen HJ, Blankensteijn JD, de Kleijn DP, Stroes ES, Pasterkamp G: Matrix metalloproteinase inhibition reduces intimal hyperplasia in a porcine arteriovenous-graft model. *J Vasc Surg* 39:432–439, 2004
  96. Schopohl B, Leirmann D, Pohl LJ, Heyd R, Strassmann G, Bauersachs R, Schulte-Huermann D, Rahl CG, Manegold KH, Kollath J, Bottcher HD: 192Ir endovascular brachytherapy for avoidance of intimal hyperplasia after percutaneous transluminal angioplasty and stent implantation in peripheral vessels: 6 years of experience. *Int J Radiat Oncol Biol Phys* 36:835–840, 1996
  97. Trerotola SO, Carmody TJ, Timmerman RD, Bergan KA, Dreesen RG, Forney M: Brachytherapy for the prevention of stenosis in a canine hemodialysis graft model: preliminary observations. *Radiology* 212:748–754, 1999
  98. Roy-Chaudhury P, Duncan H, Barrett W, Elson H, Narayana A, Foley J, Misra S, Lynch PM, Zuckerman D: Vascular brachytherapy for hemodialysis vascular access dysfunction: exploring an unmet clinical need. *J Invasive Cardiol* 15(suppl A):25A–30A, 2003
  99. Barton J, Nielsen H, Rychnovsky S, Farooq M, Freischlag J, Grove R: PhotoPoint photodynamic therapy inhibits intimal hyperplasia in arteriovenous access grafts. *Cardiovasc Radiat Med* 3:147–151, 2002
  100. Rotmans JI, Verhagen HJ, Velema E, de Kleijn DP, van den Heuvel M, Kastelein JJ, Pasterkamp G, Stroes ES: Local overexpression of C-type natriuretic peptide ameliorates vascular adaptation of porcine hemodialysis grafts. *Kidney Int* 65:1897–1905, 2004
  101. Fuster V, Charlton P, Boyd A: Clinical protocol: a phase IIb, randomized, multicenter, double-blind study of the efficacy and safety of Trinam

- (EG004) in stenosis prevention at the graft-vein anastomosis site in dialysis patients. *Hum Gene Ther* 12:2025–2027, 2001
102. Cheng L, Mantile G, Pauly R, Nater C, Felici A, Monticone R, Bilato C, Gluzband YA, Crow MT, Stetler-Stevenson W, Capogrossi MC: Adenovirus-mediated gene transfer of the human tissue inhibitor of metalloproteinase-2 blocks vascular smooth muscle cell invasiveness in vitro and modulates neointimal development in vivo. *Circulation* 98:2195–2201, 1998
103. George SJ, Lloyd CT, Angelini GD, Newby AC, Baker AH: Inhibition of late vein graft neointima formation in human and porcine models by adenovirus-mediated overexpression of tissue inhibitor of metalloproteinase-3. *Circulation* 101:296–304, 2000
104. Kibbe MR, Tzeng E, Gleixner SL, Watkins SC, Kovesdi I, Lizonova A, Makaroun MS, Billiar TR, Rhee RY: Adenovirus-mediated gene transfer of human inducible nitric oxide synthase in porcine vein grafts inhibits intimal hyperplasia. *J Vasc Surg* 34:156–165, 2001