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Changes in the editorial staff of the Journal

At the beginning of this year, some changes in the editorial staff of the Journal came into effect. First of all, Professor Jos van der Meer has resigned as Editor in chief after serving the Journal for three years. He has been elected chairman of the board of the Internal Medicine Speciality Training Programme (Concilium Medicinae Internae), starting January 2005. In addition, he has been appointed chairman of the Department of Science of the Royal Netherlands Academy of Arts and Sciences (KNAW) as of May 2005. These responsibilities regrettably preclude the continuation of his work as Editor in chief of our Journal, which under his leadership underwent significant changes to make the Journal more attractive for our readers. However, Jos van der Meer will not disappear completely out of sight; he will become a member of our editorial board and continue to contribute his characteristic cartoons to the Journal. Nor will the Journal change the course that was taken three years ago.

The editors are pleased to announce the appointment of a new associate editor, Dr Joost Drenth (1963), as of 1 January 2005. Dr Drenth is an associate professor at the Department of Gastroenterology of the Radboud University Medical Centre, Nijmegen. He is a former recipient of a Fellowship of the KNAW (2001) and a VIDI laureate (2003). He has accepted this task with great enthusiasm.

Continuing effort is necessary to overcome the change in publisher three years ago, after which the Journal was not accessible on the internet for some time. This is probably the cause of the recent decline in impact factor. The increasing number of manuscripts we have received recently as well as the increase in quality assures us that this decline in impact factor will prove to be temporary!

Joost Drenth

We would also like to reiterate our remarks in our editorial of April 2003, where we pleaded to authors to consider the Journal as the scientific and clinical forum for internal medicine in the Netherlands and to publish their original articles in our Journal.[1]

On behalf of the editors Joost Drenth, Paul Smits and Theo Thien,

Anton F.H. Stalenhoef
Editor in chief

REFERENCE

1. Thien Th, van der Meer JWM, Stalenhoef AFH, Smits P. Why publish in the Netherlands Journal of Medicine? Neth J Med 2003;61:99.

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EDITORIAL

Gene therapy for genetic lipid disorders: lipoprotein lipase deficiency as a paradigm

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Severe, life-threatening genetic disorders of lipid and lipoprotein metabolism are attractive targets for the nascent field of gene therapy.[1] The pathophysiology of many of these disorders is well understood; the amount of transgene expression required to correct the defect is often modest; and measurement of plasma lipid levels provides a superb method for assessing the biological effects of effective transgene transfer and expression. Indeed, homozygous familial hypercholesterolaemia, due to genetic deficiency of the LDL receptor, was one of the first genetic disorders approached using gene therapy.[2]

In many ways, lipoprotein lipase (LPL) deficiency provides an outstanding paradigm for the development of *in vivo* gene replacement therapy for a genetic deficiency disease. In this issue of the *Netherlands Journal of Medicine*, the world's leaders in the development of gene therapy for LPL deficiency write of their early experience and plans for the future.[3] Several factors make LPL deficiency a particularly exciting target for the development of gene therapy and predict a high likelihood of clinical success. First, acute pancreatitis is a life-threatening clinical problem in LPL deficiency and is directly caused by the very high levels of serum triglycerides found in patients with this disorder; therefore, correction of the high triglycerides would be fully expected to prevent the most important clinical problem associated with this disease. Second, achieving even a low percent of the normal LPL activity levels should be adequate to markedly reduce triglyceride levels and prevent pancreatitis in these patients. Given that the ability to achieve high levels of transgene expression is one of the major barriers in the gene therapy field, this disorder provides an excellent opportunity to achieve physiological correction despite relatively low levels of transgene expression. This is also true for haemophilia, a major reason why that genetic disease is another that has been in the forefront of the development of new gene therapeutic approaches.[4] Third, LPL is normally expressed in skeletal muscle, making skeletal muscle a logical tissue for expression of the corrective LPL transgene. The ability to target skeletal muscle in the physiological correction of the disease avoids the need for systemic administration of gene transfer vectors and the potential risks associated with this approach. Finally, there is a naturally occurring large animal model of LPL deficiency, namely the LPL deficient cat. Large animal models are extremely useful in the gene therapy field as they permit better estimates with regard to scale up of vector and success in correcting the disease in large animal models is more highly predictive of the likelihood of success in humans. Indeed, the Dutch investigators report that they have been able to correct the severe hypertriglyceridaemia in LPL deficient cats through their intramuscular gene therapeutic approach of expressing LPL. This exciting result provides substantial hope that a similar approach in humans could be effective.

The vectors used in gene therapy are critical, as they are the vehicle for targeting the corrective transgene to the appropriate tissue and getting it to the nucleus where it can be effectively transcribed, optimally for a stable period of time. The vector being used by these investigators is known as adeno-associated virus serotype 1 (AAV_1). There is substantial interest within the gene therapy community in AAV-based vectors because they do not cause much local inflammation and they provide long-term stable transgene expression. Indeed, there has been some limited success using an AAV-based vector injected intramuscularly for the treatment of haemophilia.[5] Another interesting aspect

to their approach to LPL deficiency is the use not of the normal LPL gene, but rather a naturally occurring mutation in LPL, known as S447X, which actually has greater ability to hydrolyse lipoprotein triglycerides than does the normal LPL gene itself. The concept of using this 'super LPL' is rational, intriguing, and will establish a precedent within the gene therapy field. One can imagine that mutations in other genes that increase activity of the gene product may be attractive to consider using for gene therapy instead of the normal gene as a way of increasing clinical efficacy.

Given all of the encouraging data to date, it appears quite likely that AAV_1-LPL^{S447X} based intramuscular gene therapy will be effective in correcting the severe hypertriglyceridaemia in patients with LPL deficiency, thus protecting them from recurrent acute pancreatitis and permitting declaration of unqualified success. This will be an exciting result that will substantially advance the field of gene therapy. It will also raise questions about whether other patients with severe hypertriglyceridaemia and recurrent pancreatitis, many of whom have depressed levels of LPL activity even though they are not genetically deficient in LPL, could also benefit from AAV-LPL based gene therapy.

Indeed, after demonstrating effectiveness of this approach in LPL deficient patients, it will be exciting to contemplate the potential for this approach in other patients with severe hypertriglyceridaemia. It appears highly likely that successful gene therapy for LPL deficiency will be added to the list of major scientific contributions by Dutch biomedical investigators.

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Vasopressin: physiology and clinical use in patients with vasodilatory shock: a review

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ABSTRACT

Vasopressin is a nonapeptide synthesised in the hypothalamus and released upon stimulations such as hyperosmolality, hypotension and hypovolaemia. In acute shock states serum vasopressin levels increase rapidly and decrease in prolonged septic shock. The administration of vasopressin in healthy subjects has little effect, whereas in vasodilatory shock it increases the mean arterial pressure through V1 receptors and decreases the cardiac output. Vasopressin stimulates the V2 receptors in the kidney leading to reabsorption of water through aquaporin 2. However, in vasodilatory shock the antidiuretic effects are overcome by the effect vasopressin has on the kidneys: improvement of renal blood flow leading to water excretion. Twenty-four studies on the use of vasopressin in patients with vasodilatory shock are reviewed. They show that vasopressin potentiates norepinephrine effects, increases blood pressure significantly in patients with vasodilatory shock and may improve renal function. Side effects ranging from ischaemic skin lesions to possible intestinal ischaemia should not be underestimated. Above a dose of 0.04 U/min it may lead to cardiac arrest. Effects on mortality cannot be interpreted from these studies. Broad clinical use should await controlled trials to clarify its effects on clinical outcomes such as organ failure and mortality.

INTRODUCTION

In intensive care medicine vasopressin is reserved for patients with severe vasodilatory shock who are already receiving norepinephrine and still have hypotension, although it is used with the greatest caution because of the possible side effects.

In this review the physiology of vasopressin and its effects *in vitro* and in animal models are discussed. Thereafter a discussion is presented of the literature on studies with vasopressin treatment in patients with septic shock or vasodilatory shock of other origin. The goal of this review is to provide some insight into the current place of vasopressin in patients with vasodilatory shock.

PHYSIOLOGY AND EFFECTS OF VASOPRESSIN

Production and release of vasopressin

Vasopressin is a nonapeptide, which is synthesised in magnocellular neurons of the paraventricular and supraoptic nuclei in the hypothalamus.[1] Its production depends on vasopressin gene (chromosome 20p13) transcription, which increases on either hypertonic conditions, hypotension or hypovolaemia. From the magnocellular neurons the prohormone of vasopressin, consisting of vasopressin, vasopressin-associated neurophysin and a glycopeptide, is transported down long axons to the pars nervosa of the posterior pituitary where it is stored in granules. After stimulation, a generated action potential causes a calcium influx, followed by neurosecretory granule movement and release of vasopressin from the complex molecule with neurophysin and glycopeptide. The granules fuse with the cell membrane and extrude its contents into the perivascular space and the posterior pituitary capillary system.[2,3] The pituicytes surrounding axon terminals in the posterior

pituitary remove an immediate barrier between the axons and the perivascular space by retracting, thus facilitating diffusion of peptides into capillaries.[4,5] Control of hormone synthesis resides at the level of transcription; after transcription the mRNA is increased and vasopressin released.[6,7] The axonal transport is a regulated process linked to vasopressin synthesis, as shown in rat models.[8]

Vasopressin release is mainly stimulated by hyperosmolality and hypotension or hypovolaemia, as well as acidosis, pain, hypoxia, hypercapnia and vomiting.[9] Low central venous pressure alone in for instance slightly dehydrated people is not a trigger for releasing vasopressin; at least a 10% reduction in circulating volume is necessary to release vasopressin.[1]

The amount of vasopressin stored is enough for several days; however it appears that during prolonged shock states the amount stored does not meet the amount of vasopressin required. In both animals and humans in shock, the vasopressin levels first rise to supranormal levels and then decrease as the shock state persists. Three reasons can be found for this: firstly the depletion of neurohypophyseal stores of vasopressin, secondly autonomic insufficiency or high concentrations of norepinephrine which both have a central inhibitory effect on vasopressin release[10,11] and thirdly the nitric oxide inhibiting vasopressin production.[12]

MRI scans have shown, in both animals and humans, that a decreased vasopressin production accounts for at least some part of the vasopressin shortage. In patients with septic shock and inappropriately low vasopressin levels, brain MRIs performed to exclude brain damage for other reasons showed a depletion of vasopressin stores in the posterior pituitary.[10] Also, in animal studies prolonged and intense stimulation of vasopressin release by dehydration or salt loading produced a depletion of stored hormone in the posterior pituitary.[7,13-16]

Vasopressin is rapidly metabolised by liver and kidney vasopressinases and has a half-life of 10 to 35 minutes.[17] Normal vasopressin levels are 0.5 to 5 pg/ml in overnight fasted, hydrated humans.[18,19] Water deprivation increases plasma osmolality and raises vasopressin to 10 pg/ml,[20] whereas in acute shock states the level rises to 100 to 1000 pg/ml (dogs, monkeys)[21-23] and decreases in prolonged septic shock to ±3.1 pg/ml in humans.[24] Gradual recovery of the vasopressin stores in the pituitary occurs over several days.[25]

Vasopressin acts on the different vasopressin receptors: the V1 receptor, mainly causing vasoconstriction, the V2 receptor, regulating the water balance, and the V3 receptor, which stimulates corticotropin (ACTH). This subject will be discussed in more depth in following paragraphs.

Baroreflex and vasopressin

There has been much research about the exact trigger that releases the (high) amounts of vasopressin in response to circulatory failure. Plasma vasopressin does not increase in severe hypovolaemia until it causes a steep fall in the arterial pressure. The evidence suggests that it is the sudden unloading of arterial baroreceptors that triggers the surge in vasopressin secretion. These high pressure arterial baroreceptors are located in the carotid sinus and aortic arch. Low-pressure volume receptors are present in the atria and pulmonary venous system.[26,27] Afferent signals from these receptors are carried from the chest to the brain stem through cranial nerves IX and X to the hypothalamus. It has been established that vasopressin release is higher if the tonic inhibitory baroreceptor input is diminished or absent. This is the case in animal laboratory studies in which baroreflex denervation was performed and in septic shock, where the baroreflex system is diminished or even abolished.[28] The administration of vasopressin in healthy animals with intact baroreflex receptors produced stable mean arterial blood pressure (MAP), lower cardiac output (CO) and higher peripheral resistance, whereas baroreflex denervated animals showed a remarkable increase in MAP and stable CO at low vasopressin concentrations (0.017 μU/kg) and remained stable until much higher infusion rates of vasopressin. These experiments led to the theory that baroreceptors and volume receptors normally inhibit magnocellular neurons and that absence of this counter-regulation results in the release of vasopressin.

A rise in vasopressin levels does not disrupt osmoregulation because hypotension increases the plasma osmolality-vasopressin relationship so that higher plasma vasopressin levels are required to maintain normal osmolality.[19,29] There is, however, animal experimental research that says that baroreceptor denervation produces a state of heightened osmotic sensitivity for vasopressin neurons with evidence for increased central vasopressin release to both direct and peripheral hypertonic saline stimulation.[30]

Blood pressure and vasopressin

Vasopressin has a vasoconstricting effect by four known mechanisms:[31] activation of V1 vascular receptors, modulation of ATP-sensitive K^+-channels (K_{ATP}), modulation of nitric oxide and potentiation of adrenergic and other vasoconstrictor agents. The effect of vasopressin through V1 receptors is mediated by the phosphotidylinositol pathway. *In vitro*, the action of vasopressin on different types of vessels varies with the particular type or location of the vessel by heterogeneity of the V1 receptor.[32] Under normal circumstances, vasopressin generally induces an endothelium-independent contraction of the vessels by acting on the smooth muscle myocyctes and potentiates the norepinephrine effect. In intracerebral arterioles of rats, increasing concentrations of vasopressin appeared to induce a triphasic response of vasodilatation, vasoconstriction and vasodilatation.[33] The vasodilatation was endothelium dependent, whereas the constriction was not.

Vasodilatation as found in the intracerebral arterioles of rats also occurred in experiments with human forearms, in human pulmonary arteries and veins, and isolated basilar and left circumflex coronary arteries of dogs.[34-36] Experiments indicated that the vasodilatory effect is nitric oxide (NO) dependent.

Sepsis causes a downregulation of V1 receptors, an effect mediated through proinflammatory cytokines.[37] Endotoxins, through cytokines, initiate a vasodilatory effect on the vessels, which is nitric oxide mediated, for the NO synthase inhibitor NMA attenuates the effect. If animals or vessels alone are subjected to an endotoxin load, the norepinephrine effect of vasoconstriction is quickly attenuated. The vasopressin vasoconstricting effect lasts several hours longer than norepinephrine and has a positive effect on the contracting abilities of norepinephrine.[38,39] The next mechanism through which vasopressin restores blood pressure is inhibition of K_{ATP} channels in the smooth muscle cells of the blood vessels. These channels are important in the development of hypotension and vasodilatation in response to decreases in cellular ATP and increases in the cellular concentration of hydrogen ion and lactate.[31]

In vivo vasopressin has little effect on blood pressure under normal circumstances at physiological concentrations. However, during hypovolaemia with decreasing arterial blood pressure the vasopressin release is heavily stimulated and strongly contributes to maintaining normal blood pressure. This is shown in experiments with haemorrhaging animals that develop hypotension and in animals with acute endotoxin shock, in which V1 receptor antagonists caused more profound hypotension.[40,41] Secondly, in hypotensive subjects strongly elevated levels of vasopressin are measured.[22,24] The haemodynamic responses on administered vasopressin in patients with advanced vasodilatory shock, however, are independent of baseline vasopressin concentrations,[42] suggesting that the vasopressin has a direct pharmacological effect, rather than the effect of only the replacement of the vasopressin deficiency. Despite the downregulation of the V1 receptors the vasopressin has vasoconstricting effects in these cases, which may be explained by the other three mechanisms through which vasopressin acts, as described above.

In situations where the baroreflex receptor system is impaired, for instance by cutting the nerve tracts or sepsis, the vasopressin effect is much more clear. The normally occurring leftward shift of the heart rate-arterial baroreflex curve through V1 receptors is absent and the vasopressin causes an increase in blood pressure, without increasing heart rate.[43,44]

In vivo in cases of septic shock, vasopressin is a powerful vasoconstrictor and potentiates the contracting abilities of epinephrine, which decrease in sepsis.[45] We will discuss the vasopressin effects in humans with vasodilatory shock in another paragraph.

The lungs and vasopressin

The lungs are organs on which vasopressin has a vasodilatory effect, in contrast to the rest of the body. Vasopressin significantly dilates arterial and venous lung segments in vasoconstricted rats through V1 receptors and NO.[46-48] Especially chronic hypoxic rats exhibited an augmented dilatory response to vasopressin compared with controls, which was due to enhanced dilation of precapillary segments.[49] Chronic hypoxia itself did not increase the NO synthase or vasodilatory effects. *In vitro* in canine pulmonary arteries and veins it was found that vasodilatation in veins is not only dependent on NO, but also prostaglandin I2.[50] A recent study by Leather in dogs, however, showed that vasopressin had a vasoconstricting effect in the lungs, leading to pulmonary hypertension.[51] So, although *in vitro* studies seem to show that vasopressin causes vasodilatation, this *in vivo* study shows possible pulmonary hypertension. Future long-term studies in humans will provide more insight into the reaction of the human pulmonary system to vasopressin.

The heart and vasopressin

As mentioned before, cardiac output decreases in the presence of vasopressin doses used in animals or humans with shock. Again, vasopressin acts through V1 receptors, which initiate coronary vasoconstriction and impaired cardiac relaxation, thus regulating cardiac function and myocardial perfusion.[52] V1 receptor activation probably has a positive inotropic effect due to an increase in calcium levels in the cardiac myocytes.[53] This seems contradictory to the fact that the CO decreases with vasopressin, but the positive inotropic effect might not be large enough to overcome the diminished coronary perfusion and impaired relaxation. If exposed to prolonged V1 receptor stimulation, the cardiomyocytes increase protein synthesis, leading to hypertrophy and cardiac remodelling.[54] Higher doses of vasopressin administered in vasodilatory shock in one study[55] led to cardiac arrest in six out of fifty patients. One case report mentions myocardial ischaemia intraoperatively in a hypotensive patient after administering 1 mg of terlipressin.[56]

The brain and vasopressin

Vasopressin has different effects on the several brain arteries. It is usually a powerful vasoconstrictor in larger cerebral arteries, acting through V1 receptors, as tested in isolated rings from medial cerebral arteries.[57] However, in experiments with dogs vasopressin and oxytocin dilated the basilar arteries through NO.[58] In experiments with rat intracerebral arterioles increasing concentrations of vasopressin induced the triphasic response of vasodilatation, vasoconstriction and vasodilatation, in which the vasodilatation was again endothelium and NO dependent.[33] It was hypothesised that vasopressin may constrict

smaller cerebral arterioles while dilating larger ones. Through the V3 receptor in the anterior pituitary gland vasopressin has a stimulatory effect on the release of corticotropin (ACTH), a process that also seems NO dependent. Corticotropin releasing factor (CRF), produced by the parvicellular division of the paraventricular nucleus, is necessary to maintain the ACTH secretion capacity.[59] Experiments in cattle showed that during induced sepsis, V3 and CRF1 receptor mRNAs are downregulated in the anterior pituitary, possibly resulting in a decreased ACTH secretion.[60] V3 receptors are also found in several peripheral tissues, such as kidney, adrenal medulla, pancreas, thymus, heart, lung, spleen, uterus and breast.[61] Its function there is not quite clear; it is however to be expected that there might be a local effect rather than a systemic one.

The kidneys, aquaporins and vasopressin

In the kidneys, water is mainly absorbed in the loop of Henle and the collecting duct, which is the more important site. In the collecting duct, vasopressin increases water permeability through V2 receptors, which are located on the principal cells of the collecting ducts. After stimulation of the V2 receptor, adenylate cyclase is generated, followed by an increase of intracellular c-AMP. c-AMP then causes fusion of aquaporin 2 (AQP-2) containing intracytoplasmic vesicles with the apical plasma membrane of the principal cell, thus reabsorbing water.[1,62,63] This system can be regulated quickly, depending on the amount of vasopressin secreted. If, however, the state of dehydration or shock with high levels of vasopressin persists, it will stimulate an increase in abundance of AQP-2 and AQP-3 water channels in the principal cells, allowing the ducts to achieve extremely high water permeability when necessary, and thus reabsorption of water.[64]

Throughout the literature, studies with vasopressin concerning renal blood flow seem to be inconsistent. These differences in outcome appear to be at least partly due to the wide range of doses used. Both afferent and efferent arterial diameters decrease significantly with vasopressin in low doses, which is a V1 receptor mediated effect.[65] Tamaki showed that vasopressin V1 stimulation led to a dose-dependent decreased lumen diameter of the afferent arterioles.[66] However, in the same article he mentions an increase in lumen diameter after adding vasopressin in norepinephrine constricted afferent arterioles through V2 receptors. Franchini showed in two studies a decrease in medullary flow of rat kidneys using a low vasopressin dose.[67,68] Another study[69] showed results of experiments on conscious rats in which kidney filtration decreased with low doses of vasopressin and increased with higher doses. Knowing these experimental results, one might be reluctant to use vasopressin in patients with already compromised kidney function, because it is not clear what the outcome will be. However, in patients with vasodilatory shock who received vasopressin, the urine production on average increased, counting for more than a vasoconstriction and water retention effect as described before. We will discuss this later.

VASODILATORY SHOCK AND VASOPRESSIN

Since 1997, several studies and case reports have been published about vasopressin effects in vasodilatory shock, either septic shock or vasodilatory shock after cardiopulmonary bypass (*table 1*). They were focused on short-term outcome such as haemodynamic effects and not designed to establish the effects on organ function or mortality.
A trial is now being conducted in Canada and the USA in patients with vasodilatory shock receiving vasopressin, aimed to evaluate organ function and mortality.
Studies already performed varied widely in the amount of vasopressin given, the duration of the vasopressin infusion and the measurements performed in the patient. It is therefore not simple to compare all these studies. Except for the randomised controlled trials, in most studies vasopressin was not given until norepinephrine dosages were very high or the patients' mean arterial pressure (MAP) decreased considerably. Vasopressin was therefore mostly used as 'last hope' medication. In the following section we will discuss the results of these studies.

Of the 24 studies, five were randomised controlled trials (*table 1*).[70-74] In these trials patients with vasodilatory shock were randomised to either the group receiving vasopressin added to norepinephrine (NE), or the group receiving increasing doses of norepinephrine only. Depending on the study protocol, the vasopressin improved the MAP and decreased the amount of NE necessary or it was possible to decrease the dose of NE while maintaining a stable MAP. Urine output and creatinine levels remained stable[71,72] or improved,[74] or were not mentioned.
In all studies, from single case reports to randomised controlled trials, the MAP increased significantly with a range of ΔMAP from 7 to 40 mmHg when vasopressin was added, without changing the administered dose and rate of catecholamines (*tables 1* and *2*). Some study protocols stated that the MAP should remain constant while adding vasopressin. Here the catecholamine administration could be decreased.
As mentioned before, vasopressin can exhibit a negative effect on the cardiac output, while increasing the MAP in vasodilatory shock. In the studies where the cardiac output or index was measured, vasopressin in general caused a decrease in cardiac output. This, however, did not seem to affect the rise in blood pressure.
Not all articles mention distinct features of organ perfusion,

Table 1

Overview of randomised controlled trials: vasopressin in vasodilatory shock

REFERENCE	STUDY	PATIENTS (TOTAL NO.; RANDOMISED TO AVP)	AVD DOSE (U/MIN)	DURATION AVP	ΔMAP MMHG	NE	ΔCI (*VS* NE)	SIDE EFFECTS MENTIONED (*VS* NE)	SURVIVAL (*VS* NE)	KIDNEY FUNCTION (*VS* NE)
70	RCT, crossover	Vasodilatory shock after LVAD implant (10/8)	0.1 0.1	1 h-7 d	↑ 27	↓ /stop	~	-	NR	NR
71	PRCT	Vasodilatory shock after CPB or in sepsis (48/24)	0.067	48 h	↑ 19 (0)	↓	↓ 10% (~)	New ischaemic lesions 7/24 (6/24); gastrointestinal perfusion better in AVP+NE than NE alone; bilirubin ↑	21/24 at 48 h	Creatinine stable
72	RCT	Septic shock (10/5)	0.04	>24 h	↑ 17	stop	↓ 7% (↓ 25%)	-	5/5 at 24 h (3/5)	Creatinine stable
74	DBRCT	Septic shock (24/13)	0.01-0.08	4 h	~	↓ ↓	↓ 8% (↓ 20%)	-	NR	UO doubled (~); creatinine clearance ↑ 75% (~)
73	DBRCT; prophylactic AVP	Vasodilatory shock after CPB (27/13)	0.03	6-72 h	-	AVP group 37% less NE	NR	Acute renal insufficiency 1/13 (1/14); right heart failure 1/13 (0); lethal haemorrhage 0 (1/14)	27/27 at 72 h	NR

AVP = vasopressin, MAP = mean arterial pressure, NE = norepinephrine, CI = cardiac index, RCT = randomised controlled trial, PRCT = prospective randomised controlled trial, DBRCT = double-blind randomised controlled trial, LVAD = left ventricular assist device, CPB = cardiopulmonary bypass, UO = urine output, NR = not reported. ↑ increase, ↓ decrease.

Table 2

Overview of other studies and cases: vasopressin in vasodilatory shock

REFERENCE	STUDY	PATIENTS	DOSE (U/MIN)	DURATION AVP	ΔMAP MMHG	NE	ΔCI	SIDE EFFECTS MENTIONED	SURVIVAL	KIDNEY FUNCTION
24	Matched cohort	Septic shock (19)	0.04	NR	↑ 27	↓	↓ 12%	-	NR	NR
55	Case series	Septic shock (50)	0.01-0.6	48 h	↑ ±10	↓33%	↓ 53%	6/50 cardiac arrest at AVP >0.05	8/50	UO ↑
75#	Case series	Vasodilatory shock after LVAD implant (50)	0.09±0.05	7±12 d	↑ 7	↓	ND	6% limb ischaemia in patient with CI <2 and AVP >10 U/h	50/50 (3d)	4/5 renal insuff. post-LVAD recovered
76	Case report	Septic shock (1); AVP 1st choice after dobutamine	0.04	23 h	↑ 23	No AVP	NR	Skin necrosis at peripheral infusion site	1/1	NR
78	Prospective clinical study	Septic shock (11)	0.04	4 h	↑ 7	~	~	↑ P(g-a)CO_2 gap	2/11	NR
79	Case series	Septic shock (12)	0.06-1.8	2-4 h	-	Stop	↓ 21%	↑ P(g-a)CO_2 gap	5/12	UO stable

AVP = vasopressin, MAP = mean arterial pressure, NE = norepinephrine, CI = cardiac index, LVAD = left ventricular assist device, CPB = cardiopulmonary bypass, dobu = dobutamine, milr = milrinone, SAP = systolic arterial pressure, UO = urine output, NR = not reported. ↑ increase, ↓ decrease, # includes 8 patients previously reported by Argenziano et al.[70]

Table 2 continued

REFERENCE	STUDY	PATIENTS	DOSE (U/MIN)	DURATION AVP	ΔMAP MMHG	NE	ΔCI	SIDE EFFECTS MENTIONED	SURVIVAL	KIDNEY FUNCTION
80	Case series	Septic shock (35), vasodilatory shock after cardiotomy (25)	0.067-0.1	0.5-384 h	↑ 22	↓	↓ 23%	↓platelets ↑liver enzymes ↑bilirubin	20/60	Creatinine stable
82	Case series	Septic shock (5)	0.04	1 h-21 d	↑ 25	↓/stop	↓ 11%	-	2/5	↑ /~
83	Case series	Vasodilatory shock after CPB (40)	0.1	1 h-6 d	↑ 24	↓	~	-	NR	NR
84	Case report	Vasodilatory shock after CPB (1)	Bolus 10 U; 0.23 U/min	2 d	↑ 40	↓	↓ 35%	-	1/1	UO ↑
85	Case series	Vasodilatory shock after cardiac transplant (20)	0.1	2 h-3 d	↑ 26	↓	↓ 17%	-	19/20	Creatinine stable
86	Case series, children	Vasodilatory shock after CPB (11)	0.0003-0.002 U/kg/min	6-144 h	↑ 15	↓	ND	-	9/11 at 2 wk	Creatinine stable
87	Case series	Vasodilatory shock in organ donors (10)	0.04-0.1	NR	↑ 18	↓/stop	ND	-	-	NR
88	Case series	Milrinone induced hypotension after CPB (3)	0.03-0.07	1-5 d	SAP ↑ 30-45	↓/stop	↓ 0-15%	-	2/3	UO ↑; Creatinine ↓
89	Case series	Milrinone induced hypotension in congestive heart failure (7)	0.03-0.07	>1 h	SAP ↑ 37	↓	~	-	NR	UO ↑
90	Case report	Septic shock, acute myocardial infarction (1)	0.02	5d	↑ 27	↓ ↓	↓ 24%	-	1/1	NR
91	Prospective case control	Septic shock (16)	0.04	16-284 h	↑ 4; 2/16 hypotension refractory	↑ (2/16 ↓)	~	-	9/16	UO ↑
92	Case series	Septic shock (7)	0.08±0.06	NR	NR	6/7 ↑ dobu/milr	↓ 31%	↓CI	NR	NR
93	Case series	Septic shock (8); terlipressin	1-2 mg	Bolus; effect ≥5 h	↑ 20	↓	↓ 21%	-	4/8	NR

AVP = vasopressin, MAP = mean arterial pressure, NE = norepinephrine, CI = cardiac index, LVAD = left ventricular assist device, CPB = cardiopulmonary bypass, dobu = dobutamine, milr = milrinone, SAP = systolic arterial pressure, UO = urine output, NR = not reported. ↑ increase, ↓ decrease, # includes 8 patients previously reported by Argenziano et al.[70]

such as kidney function. Some studies mentioned serum creatinine concentrations and/or urine output; in most cases, serum creatinine remained stable and the urine output increased. No patients are reported in whom kidney function deteriorated. Morales reported that in 18 out of 22 patients with renal insufficiency who received a left ventricular assist device (LVAD), the kidney function improved while administering vasopressin. It is not excluded that this effect resulted from the LVAD itself, but four out of five post-LVAD renal insufficiencies recovered with vasopressin, which makes a specific effect of vasopressin likely.[75] In Patel's double-blind randomised controlled trial (DBRCT), however, in patients with septic shock the urine output doubled and creatinine clearance improved by 75% compared with standard treatment.[74]

The reason for the stable or even improved kidney function in vasodilatory shock during vasopressin therapy is not apparent at first hand. Normally, one would expect that high doses of vasopressin stimulate the reabsorption of water through aquaporin-2, therefore creating lower diuresis. However, during hypotension or shock the kidneys are not well perfused, and are therefore not capable of building up the peritubular osmotic gradient through which urine can normally be concentrated. In the first period of vasopressin administration an improvement of renal blood flow is obtained with apparently increased glomerular filtration and thus an increase in water and electrolyte excretion. Secondly, due to better flow, the peritubular osmotic gradient will normalise, making it possible to reabsorb water and concentrate the urine.

There was no alteration in the plasma concentration of sodium or other electrolytes in the patients with vasodilatory shock, when treated with vasopressin.

Survival cannot be interpreted in most studies as they often do not report how seriously ill the patients are. In the RCTs the results varied and were not always mentioned: vasopressin *vs* NE resulted in at least the same survival, with sometimes slightly better survival for vasopressin at short term (Malay *et al.* mention survival of 5/5 at 24 hours for vasopressin *vs* 3/5 for norepinephrine).[72] All RCTs that mention survival rates measured them at 24 to 72 hours after start of trial, so it would be difficult to draw conclusions for longer-term survival.

SIDE EFFECTS

Seven out of the 24 studies mention side effects besides decreased cardiac index, whereas the others mention none. Side effects include limb ischaemia in a patient with impaired cardiac output and a vasopressin dose >10 U/h which resolved after discontinuing the vasopressin.[75] Six out of 50 patients suffered from cardiac arrest at doses >0.05 U/min.[55] Skin necrosis developed at the peripheral infusion site of vasopressin in one case report.[76] In a study by Dunser[77] in retrospective analysis in 63 critically ill patients with vasodilatory shock, 30% developed ischaemic skin lesions. There was no relationship between the vasopressin dose or length of infusion and the development of these lesions. Increased gastric regional partial pressure of pCO_2, which could be indicative of intestinal ischaemia, was found in two recent studies with a total of 23 patients.[78,79] Only one study found that gastrointestinal perfusion seemed to be better in patients with vasodilatory shock with vasopressin and NE than NE alone.[71] There was no report of actual intestinal ischaemia.

Dunser found a remarkable increase of plasma bilirubin in two studies in patients with vasodilatory shock who received vasopressin.[71,80] There was no obvious explanation. Since there were no other reports mentioning this side effect, results should be carefully interpreted and more research needs to be done.

One study showed that patients with vasodilatory shock receiving only NE developed significantly more new-onset tachyarrhythmias than patients receiving NE and vasopressin.[71] This seemed to be associated with the fact that the last group received lower doses of NE, which is known to have cardiotoxic and proarrhythmic effects.[81]

DISCUSSION ON THERAPEUTIC USE OF VASOPRESSIN

In nonacute vasodilatory shock there is a shortage of serum vasopressin and patients are in need of catecholamines. The standard treatment of vasodilatory shock is, in general, norepinephrine if blood pressure decreases, after proper fluid replacement. Studies with vasopressin show that it potentiates norepinephrine effects and increases blood pressure significantly in patients with vasodilatory shock. It also seems to preserve or sometimes restore renal blood flow and urine output. Doses used in studies vary but there seems to be a critical upper dose – 0.04 U/min – above which side effects increase. Studies performed are, however, short-term studies, so side effects may increase with longer use of vasopressin. Side effects noticed are ischaemic skin lesions, bilirubin increase and possible intestinal ischaemia. Theoretically, vasopressin seems to be a promising drug in patients with vasodilatory shock, and in short-term studies it improves blood pressure and renal blood flow. As mentioned earlier, a study aimed at long-term effects of vasopressin is being carried out, so definite statements on the use of vasopressin in these patients should at least wait until these results are published. Until then, vasopressin should still be reserved for those patients with severe vasodilatory shock in whom other vasopressors fail; it should be used with the greatest caution, preferably in a trial setting, with doses between 0.01 and 0.04 U/min.

Terlipressin use is not advisable because it is a long-acting (2 to 8 hours) drug and possible serious side effects cannot be reversed. In the mean time, we await the long-term randomised controlled trials.

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REVIEW

Gene therapy for genetic lipoprotein lipase deficiency: from promise to practice

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ABSTRACT

Lipoprotein lipase (LPL) deficiency is a rare, hereditary disorder of lipoprotein metabolism characterised by severely increased triglyceride levels, and associated with an increased risk for pancreatitis. Since no adequate treatment modality is available for this disorder, we set out to develop an LPL gene therapy protocol. This paper focuses on the clinical presentation of LPL deficiency, summarises the preclinical investigations in animal models and describes the rationale to evaluate gene therapy for this monogenetic disorder of lipid metabolism in humans.

LIPOPROTEIN LIPASE

Lipoprotein lipase (LPL) is one of the key enzymes in the metabolism of triglyceride-rich lipoproteins (TRLs) and is produced in fat tissue, skeletal muscle and heart muscle. Activated by its cofactor apolipoprotein (apo) CII,[1] LPL mediates the hydrolysis of triglycerides (TG) in chylomicrons (CM) and very-low-density lipoproteins (VLDL) at the luminal side of the endothelium. The generated free fatty acids (FFA) are subsequently used for energy production in muscle tissue or stored as fat in adipose tissue. LPL also contributes to the high-density lipoprotein (HDL) pool by shedding of phospholipids and apolipoproteins during the hydrolysis of these lipoproteins.[2] Besides the *enzymatic* activity, LPL also enhances hepatic clearance of triglyceride-rich lipoproteins (TRL) by mediating receptor-mediated uptake of these atherogenic lipoprotein particles (‘*ligand*’ or ‘*bridging*’ function).[3,4] Through these actions LPL exerts antiatherogenic effects. Of note, subendothelially located LPL has been described to have proatherogenic effects by increasing oxidative susceptibility of LDL facilitating the uptake of TRLs by macrophages.[5] The latter promotes foam cell formation[6] i.e. the hallmark of atherogenesis.[7] In view of these heterogeneous effects, the exact role of LPL in atherogenesis is still a matter of debate.[8] The delicate balance between proatherogenic and antiatherogenic properties of LPL has been shown to depend in part on the exact location of this enzyme.[8]

LPL MUTATIONS

More than 100 mutations in the LPL gene have been described to date. While some mutations result in total loss of function, others only exert a moderate effect on LPL activity such as the D9N, N291S, and S447X mutations. The latter are frequently found in the general population and have provided valuable insight into the relationship between LPL and the progression of atherosclerosis. Carriers of LPL^{N291S} and LPL^{D9N} with a combined frequency of 5% in the general population are characterised by low HDL cholesterol and increased TG with a concomitant increased risk of cardiovascular disease.[9,10] Conversely, carriers of LPL^{S447X} with a frequency of 18 to 22% in the general population are characterised by increased levels of HDL cholesterol and lower TG levels. In line, this mutation has been reported to have a protective effect against cardiovascular disease (CVD).[9-15]

GENETIC LPL DEFICIENCY

Clinical presentation and diagnosis of genetic LPL deficiency

LPL deficiency is an autosomal recessive hereditary disease caused by mutations in the LPL gene. Homozygosity or compound heterozygosity for mutations in the LPL gene, resulting in loss of catalytically active LPL, is the basis of genetic LPL deficiency. The resulting clinical chylomicronaemia syndrome (see further in text) was first described by Bürger and Grütz in 1932 and 56 years later, in 1989, the first LPL mutation responsible for this phenotype was revealed.[16]

LPL deficiency typically manifests itself in early childhood with a variety of symptoms including severe abdominal pain, repetitive colicky pain, hepatosplenomegaly, failure-to-thrive and acute pancreatitis.[17,18] Increased irritability, diarrhoea and intestinal bleeding can occur even shortly after birth. Although the clinical presentation is non-specific, especially at a younger age,[19] the plasma of the patients is always milky white or lipaemic (*figure 1*), even under fasting conditions. On physical examination, eruptive xanthomas (*figure 2A* and *2B*) are frequently present. These xanthomas consist of small erythematous-based yellow papules ranging in size from one to several millimetres in diameter. Eruptive xanthomas frequently exhibit the Koebner phenomenon, also called the isomorphic response, which refers to the appearance of lesions at a site of injury or pressure. Therefore, eruptive xanthomas are usually formed on the buttocks, elbows, back, and knees, but they can also occur on any cutaneous surface including the oral mucosa. These lesions generally recede with reduction of the TG levels. In addition to these skin lesions, lipaemia retinalis and hepatosplenomegaly can be observed. In clinical practice, this combination of symptoms is often not recognised to be directly related to the hyperchylomicronaemia syndrome,[20] and the diagnosis often becomes clear only after the first occurrence of pancreatitis. Lipid analysis reveals 10 to 100 times increased plasma TG while HDL cholesterol levels are markedly decreased. In addition, LPL deficiency is characterised by reduced LDL cholesterol levels. In line, levels of apoB100, the main structural apolipoprotein of LDL and VLDL, are reduced. The increased TG concentration increases the risk of pancreatitis,[21] which can occur from TG concentrations of 10 mmol/l onwards.[22] This clinical complication, often recurrent in LPL-deficient patients, can be lethal. It is noteworthy that in these patients, pancreatitis cannot be excluded on the basis of normal plasma amylase concentrations, since high TG concentrations can interfere with the analytical method resulting in false-negative results.[23-25] Assessment of urine amylase excretion is more reliable as a diagnostic test for pancreatitis in a hypertriglyceridaemic patient.[26,27] Other laboratory investigations can also be disturbed as a result of increased TG levels, such as sodium

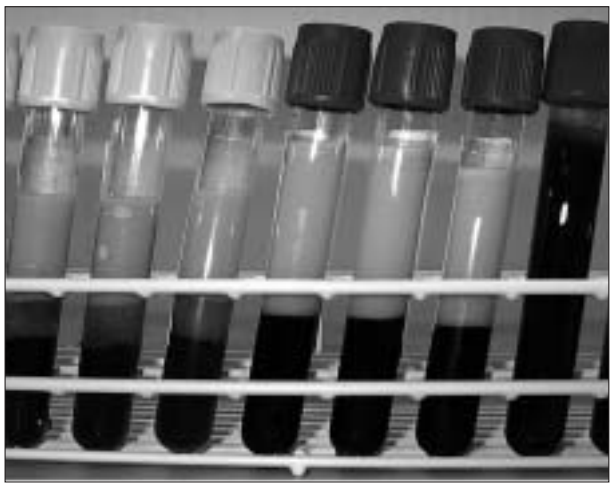

Figure 1
Lipaemic plasma from a patient with severe hypertriglyceridaemia (fasting TG = 46 mmol/l)

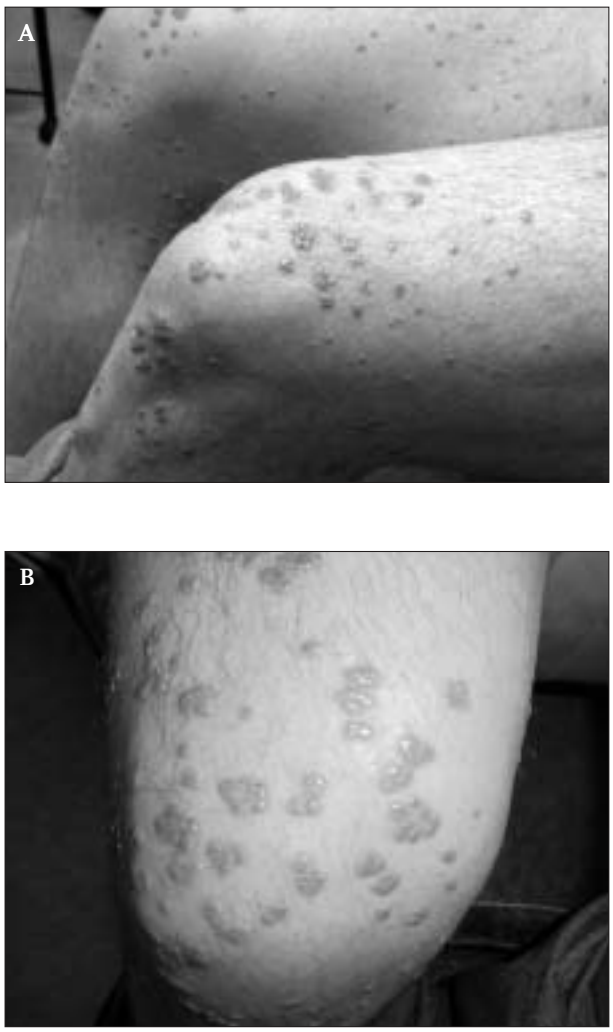

Figure 2
Eruptive xanthomas found on the upper legs (A) and knees (B) of a patient with severe hypertriglyceridaemia (fasting TG = 46 mmol/l)

(artificially low),[28] haemoglobin (artificially increased),[29] HbA_{1c} (artificially low)[30] and bilirubin (artificially increased).[31,32]

Prevalence of genetic LPL deficiency

Exact data on the prevalence of LPL deficiency are not available. The reported prevalences for genetic LPL deficiency vary between 1:1,000,000[33] and 1:5000 in French Quebec (caused by a so-called 'founder effect').[21,34] Based on extensive efforts to track down all LPL-deficient patients in the Netherlands, we estimate a prevalence of approximately 1:500,000.

LPL deficiency and clinical complications

The main clinical risk for LPL-deficient patients is the development of pancreatitis.[22] The exact aetiology of pancreatitis in hypertriglyceridaemia is unclear but it is believed that the high concentrations of CM in the pancreatic microcirculation result in increased 'free radical' activity, which in turn can result in episodes of pancreatic ischaemia. Inflammation of the pancreas is supposed to be the result of local fatty acid generation due to small amounts of free lipases in the microcirculation of the pancreas.
A disrupted microcirculation, caused by hyperchylomicronaemia, is suggested to damage pancreatic cells with ensuing increased release of lipolytic enzymes. The latter causes hydrolysis of abundantly present CM contributing to a strong increase in local FFA, followed by local pancreatic inflammation. This cascade of events is thought to eventually cause pancreatitis.[32]
Elevated TG levels are a strong independent risk factor for CVD.[35] It is unclear, however, whether LPL deficiency is associated with an increased CVD risk.[33] Whereas two publications have reported premature atherosclerosis in LPL-deficient patients,[36,37] LPL deficiency has also been described to be not associated with a dramatic increase in CVD.[33] The reported lack of atherosclerosis[38] has even been described to relate to the low concentrations of LDL cholesterol in these patients (a direct consequence of a disturbed catabolism of the precursor of LDL, i.e. VLDL). The latter phenomenon was nicely illustrated by a homozygous LPL-deficient patient suffering from familial hypercholesterolaemia (FH) with clearly lower LDL cholesterol levels compared with FH siblings and the absence of signs of CVD during follow-up.[39] Another potential mechanism antagonising atherogenesis is the inability of CM to penetrate in the vascular wall.[40] In line, the accumulation of TRLs in macrophages in the vascular wall has been shown to be reduced in patients with LPL deficiency.[41]

Therapeutic options in LPL deficiency

The primary objective of treating LPL-deficient patients is reducing the risk for pancreatitis. To reduce this risk, TG lowering below 10 mmol/l is desired.[42]

Diet

The intake of dietary fats has to be lowered to 20 to 25% of the total daily caloric intake, i.e. 40 to 50 grams dietary fat per day. If this has insufficient effect on TG, part of the fat can be replaced by medium-chain triglycerides. These TGs are transported to the organs for hydrolysis without the need for CM packaging, thus excluding the need for LPL. In our Western society, characterised by dietary fat intakes of approximately 120 grams per day, maintaining these strict dietary regimes has been proven to be most difficult, resulting in poor adherence. Consequently, the prevention of pancreatitis is often unsuccessful in LPL-deficient patients and additional therapeutic modalities are mandatory. Of note, it should be emphasised that consequent and strict adherence to a stringent low-fat diet is likely to be associated with effective lowering of the hypertriglyceridaemia with ensuing decrease in risk for pancreatitis.

Fibrates

Fibric acids normally affect TG metabolism by reducing the hepatic production of VLDL and enhancing VLDL clearance from the circulation.[43] Fibric acids are agonists of a family of transcription factors, i.e. peroxisome proliferators activated receptors (PPARs). These factors have been shown to reduce the production of hepatic apoCIII (an inhibitor of LPL activity) and thereby increase LPL-mediated lipolysis. Also, via direct stimulation of the LPL gene promoter LPL synthesis is upregulated. However, in LPL deficiency, upregulation of defective LPL will not render the desired effects. In addition, a decreased VLDL synthesis may help in managing TG levels; the primary problem of these patients is the lack of lipolytic activity. As a consequence, plasma TG levels in LPL-deficient patients are generally unaffected upon fibrate therapy.[33,44]

Statins

Statins inhibit HMG-CoA reductase, leading to a reduced hepatic cholesterol production and upregulation of LDL receptors. This results in enhanced hepatic uptake of LDL and TRL (VLDL and IDL),[45,46] reducing the concentrations of plasma LDL cholesterol and plasma TG. LPL-deficient patients, however, are characterised by reduced concentrations of LDL cholesterol through decreased turnover of VLDL to LDL[47] as well as increased LDL catabolism.[48] As a consequence, neither TG nor LDL levels are lowered by statin therapy.[33,44]

Nicotinic acid derivates

Nicotinic acid derivates (vitamin B3) normally inhibit the hepatic synthesis and esterification of FFA, resulting in a reduced hepatic VLDL production.[49,50] Nicotinic acid derivates also induce accelerated intracellular degradation of apoB[51] whereas a reduced hepatic clearance of apoAI

results in an increase in HDL cholesterol.[52] In LPL-deficient patients, the response to nicotinic acid derivates has been shown to be marginal.[33,44]

Omega-3 fatty acids

Daily use of a high dose of omega-3 fatty acids (4 grams/day) leads to enhanced clearance of plasma CM[53] in combination with a reduced production of hepatic VLDL[54] without affecting LPL activity.[55] In primary hypertriglyceridaemia by causes other than LPL deficiency, the effect of this treatment varies from a TG reduction of 29 to 50%.[56-60] Treatment with omega-3 fatty acids in genetic LPL-deficient patients has never been published and therefore may warrant further investigation.

Due to the lack of effective pharmacological interventions, modern treatment options are currently restricted to intensive dietary modifications. These strict dietary regimes have been proven to be most difficult, resulting in poor adherence. Consequently, the prevention of pancreatitis is unsuccessful in LPL-deficient patients and additional, effective therapeutic modalities are needed.

LPL GENE THERAPY

Rationale

Several facts have contributed to the development of gene therapy for LPL-deficient patients. First, as described above, LPL deficiency currently lacks an effective and successful therapy. Second, the diagnosis of genetic LPL deficiency can be accurately made. Third, the LPL gene is rather small, which allows the incorporation of the gene into a wide range of viral vectors. Fourth, appropriate animal models for the extensive testing of this gene therapy are available (LPL 'knock-out' mice and LPL-deficient kittens). Fifth, LPL is naturally produced in skeletal muscle. Not only can this tissue be easily reached via intramuscular injections, but it can also be targeted with vectors with a natural tropism for this tissue. Sixth, most patients present with detectable levels of inactive LPL protein in the circulation. This strongly diminishes the risk of a significant immune response against the transgenic LPL upon effective gene therapy. Finally, increases of LPL activity in the human circulation are only associated with beneficial effects. Not only does increased LPL activity result in significant lowering of both fasting and postprandial TG levels, it will likely increase antiatherogenic HDL cholesterol levels.

LPL gene therapy, choice of virus and preclinical experiments

Effectiveness of LPL gene therapy using adenovirus has long been established in animal models.[61] Since the duration of transgene expression upon adenoviral infection is limited, the nonpathological adeno-associated virus (AAV) has been put forward, a virus that has been used in several gene therapy studies in men.[62] As transgene, we have chosen a naturally occurring LPL variant (LPL^{S447X}) that has been shown to exhibit a beneficial effect on lipids profiles and a concomitant decreased CVD risk.[9-15]

In murine LPL-deficient models, a single intramuscular injection of AAV_1-LPL^{S447X} (dosage: 8×10^{12} AAV genome copies/kg body weight) resulted in a highly significant TG reduction of 97% for more than 12 months.[63] We have recently been able to confirm these promising results in LPL-deficient cats (dosage: 1×10^{11} AAV genome copies/kg body weight; unpublished). The result of biodistribution and toxicity studies with the recombinant virus are excellent and have paved the way for further development.

LPL-deficient patients

Awaiting the initiation of the AAV_1-LPL^{S447X} gene therapy trial, the first six LPL-deficient patients have been thoroughly investigated. All patients were characterised by TG levels >10 mmol/l, despite compliance to dietary restrictions. In addition, all patients had suffered from (recurrent) pancreatitis. The patients showed complete loss of enzymatic LPL activity, whereas circulating inactive LPL protein could be demonstrated in all (protein concentration 19 to 103% of normal). We furthermore cultured myoblasts from needle biopsies of the right upper leg of all six patients (Pro-mag 2.2 automatic biopsy system, N14GA/10 cm needle; MDTECH, USA). These myoblasts were infected with AAV_1-LPL^{S447X} after which all myocytes were shown to secrete catalytically active LPL (unpublished data).

CONCLUSION

LPL deficiency is a rare hereditary condition characterised by high TG levels that correlate with an increased risk for potentially lethal (recurrent) pancreatitis. In view of the lack of effective pharmacological agents, TG levels remain seriously elevated. We report here the successful implementation of an LPL gene therapy protocol using an AAV_1-LPL^{S447X} vector in both murine and feline models of LPL deficiency. In addition, we have demonstrated that the myocytes of our LPL-deficient patients are able to produce and secrete catalytically active LPL into culture media upon infection with AAV_1-LPL^{S447X}. Based on these promising results, the initiation of the first human LPL gene therapy trial in the Netherlands is expected soon. Other patient populations that may benefit from LPL gene therapy include heterozygote LPL-deficient patients with a clinical phenotype of the chylomicronaemia syndrome, patients with therapy-resistant hypertriglyceridaemia and maybe patients with hypertriglyceridaemia formerly characterised as (Fredrickson) type V hyperlipidaemia. For now, we will first evaluate the effectiveness in LPL-deficient patients.

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Endovascular stenting in neoplastic superior vena cava syndrome prior to chemotherapy or radiotherapy

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ABSTRACT

Background: The standard conventional palliative treatment of choice for patients with neoplastic superior vena cava syndrome (SVCS) is chemotherapy, radiotherapy or surgery. In our study, palliative stenting was used as a first-line therapeutic measure in all cases using self-expanding stents prior to any antitumour therapy.

Methods: 17 patients, 10 men and 7 women, all of whom presenting with the clinical diagnosis of SVCS confirmed by phlebography combined with CT, were referred for stenting of the superior caval vein. All procedures were performed after local anaesthesia without sedatives or general anaesthesia in the angiosuite at the radiology department. Symptom response was evaluated directly after the procedure at several intervals by clinical and nursing staff.

Results: 19 self-expanding Symphony® stents were successfully implanted in 15 of 17 cancer patients with SVCS in a period of five years. All 15 individuals remained free from SVCS after the successful stenting procedure. No stent-related complications occurred.

Conclusion: This study demonstrates that palliative SVC stenting prior to any antitumour therapy is feasible, easily performed without serious complications and provides a quicker symptom response than obtained with radiation therapy or chemotherapy alone. Primary stenting also provides the opportunity to establish a correct diagnosis before starting antitumour therapy.

INTRODUCTION

Obstruction of the superior caval vein may cause many symptoms such as cough, orthopnoea, dyspnoea, plethora, facial oedema and severe headache.[1] These symptoms are the result of venous hypertension in veins draining the upper extremities, thorax and head to the right atrium, due to significant narrowing or occlusion of the superior caval vein. The superior vena cava syndrome (SVCS) is caused predominately by malignancy (74 to 95%) and usually occurs at advanced stages of neoplastic disease.[2] Most common malignancies encountered are bronchogenic carcinoma and lymphoma.

Traditionally, the treatment of choice for patients with SVCS due to malignancy is radiotherapy, chemotherapy or surgery.[3] Initial success rates after radiotherapy and/or chemotherapy do not exceed 90%.[4,5] If standard conventional treatment reduces neither tumour volume nor caval compression, endoluminal stenting may be employed as an additional treatment to restore vessel lumen and prevent tumour or thrombotic occlusion.

In our study, palliative stenting was used as a first-line therapeutic measure in all cases using self-expanding stents prior to any radiotherapy and/or chemotherapy. We investigated feasibility, duration, complications and time to response of the therapy of stenting prior to radiation therapy or chemotherapy.

PATIENTS AND METHODS

Patients

During a period of five years, 17 patients (ten men) with SVCS of neoplastic origin were referred for stenting of the superior caval vein. All patients presented with the clinical

diagnosis of SVCS confirmed by phlebography combined with CT (*figures 1* and *2*). The mean age was 65 years (range 43 to 78).
Seventeen patients had superior caval vein obstruction of more then 90% according the Stanford classification (*table 1*).[6] They suffered from evident clinical venous obstruction symptoms and venous collateral pathways, proven by CT or phlebography, and were considered to be eligible to undergo the procedure. Informed consent was obtained.

Our patients had SVCS caused by various tumour types. None of the 17 individual patients had received chemotherapy or radiotherapy prior to the stenting procedure. The causes of caval obstruction were small cell lung carcinoma in six, non-small cell lung carcinoma in five patients, mediastinal adenopathy due to breast cancer in two, large B-cell non-Hodgkin lymphoma in one patient, leiomyosarcoma in one individual and of unknown origin in two patients. Exclusion criterion was the presence of a proven complete vessel occlusion.

Methods
All procedures were performed after local anaesthesia without sedatives or general anaesthesia in the angiosuite at the radiology department. Oxygen saturation, blood pressure, electrocardiograms, and pulse were continuously monitored. To ensure proper measurement and evaluation of the degree and extent of the VCS stenosis, we used digital subtraction equipment and spiral CT (Philips Medical Systems, Eindhoven, the Netherlands); CT parameters: 7 mm slices, 7 mm reconstruction, pitch 1.4, 100ml I/l Omnipaque® contrast medium.
The right femoral or brachial vein was used both for the phlebography as well as for stent insertion. We used a 7 French introduction system for the vein selected for stent insertion.

Symphony® (Boston Scientific, Natick, MA, USA) stents we employed in all patients. The self-expanded Symphony® stent diameter was 14 mm and in-stent length 4 or 6 cm. Further, we used a multipurpose catheter and a hydrophilic stiff Terumo guidewire (Terumo Europe N.V., Leuven, Belgium, Europe) to manage the stenotic caval vein. When necessary for better stent deployment (*figures 3* and *4*) we dilated using angioplasty balloons (Cordis Corporation, Miami, FL, USA) with a diameter range from 12 to 14 mm. No antibiotics were used. Heparin was not administered before or after the procedure.
Average contrast medium use was 150 ml 300 mg I/l Omnipaque. Postprocedural stent position, stent deployment and migration were evaluated by venography and chest radiographs and/or CT (*figure 5*).

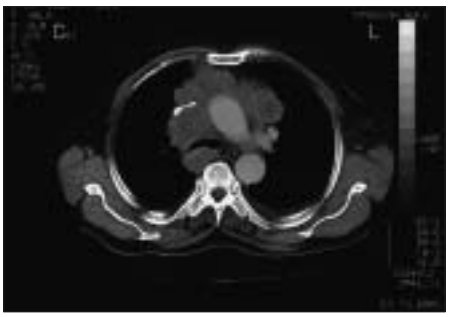

Figure 1
Spiral CT of patient presenting with symptoms of SVCS due to mediastinal adenopathy (breast cancer)

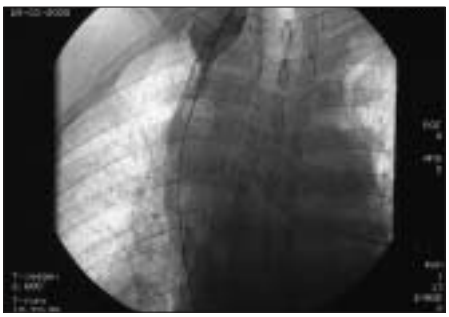

Figure 2
Phlebographic image of patient presenting with symptoms of SVCS due to mediastinal adenopathy (breast cancer)

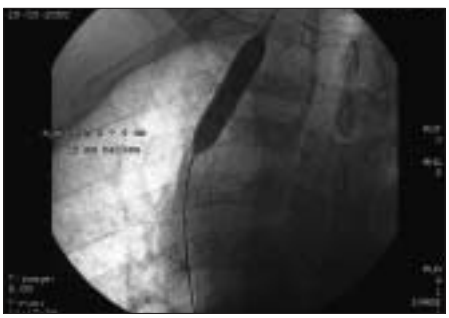

Figure 3
Plebographic image of deployment by angioplasty balloon of Symphony stent in superior vena cava

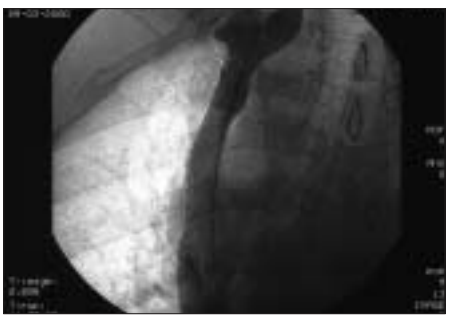

Figure 4
Postprocedural result of deployment by angioplasty balloon of Symphony stent in superior vena cava

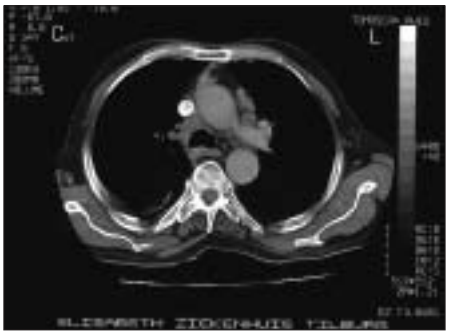

Figure 5
Follow-up spiral CT image of same patient after antitumour therapy

Clear regression of the mediastinal adenopathy and good sealing of the stent against the vessel wall without any migration is seen.

Postprocedural evaluation of symptom response before/after radiotherapy/chemotherapy

Vena cava repermeability was evaluated by monitoring symptom response. Symptom response was directly assessed after the procedure and further, at several intervals thereafter. The clinical and nursing staff of the radiology, internal medicine and pulmonary disease departments evaluated the symptom response.

RESULTS

Between August 1996 and July 2001, 19 self-expanding Symphony® stents were successfully implanted in 15 of 17 cancer patients with SVCS (*table 1*). In all 15 patients, correct positioning of the stents was achieved. No balloon angioplasty had been performed prior to stent placement.

Table 1
Characteristics and results of stenting with regard to relief of symptoms and survival

PATIENT	SITE STENOSIS	STANFORD CLASSIFICATION	RELIEF OF SYMPTOMS (TIME AFTER STENTING)	TUMOUR THERAPY	CLINICAL COURSE AND SURVIVAL AFTER STENTING
1	Left anonyma, VCS	IV	Yes (3 hours)	Radiotherapy	†, 31/2 months, respiratory insufficiency
2	VCS	III	Yes (12-24 hours)	Chemotherapy	†, 14 months, progression of disease
3	Right anonyma, VCS	II	Yes (1 hour)	Chemotherapy	Alive, 48 months +, complete/ partial remission
4	VCS	II	Yes (12-24 hours)	None	†, 3 months
5	VCS	II	Yes (1 hour)	Not possible	†, 5 days, tumour progression dislocation of stent
6	Right anonyma, VCS	III	Yes (6-12 hours)	-	†, 4 days, respiratory insufficiency
7	Right and left anonyma, VCS	III	Yes (1 hour)	Chemotherapy	†, 10 days, progression of disease
8	Right and left anonyma, VCS	IV	Yes (6-12 hours)	Chemotherapy	†, 5 months, progression of disease
9	Right and left anonyma	IV	No, stenting not possible VCS completely occluded	Radiotherapy	†, progression superior VCS respiratory insufficiency
10	Right and left anonyma, VCS	-	No, stenting not possible thrombosis v. subclavia/ left v. anonyma	Radiotherapy	†, progression superior VCS and disease
11	Right and left anonyma, VCS	III	Partial (24-48 hours)	Chemotherapy	†, 3 months, sepsis after haemotherapy
12	Right and left anonyma, VCS	III	Yes (2 hours)	Chemotherapy	Alive, 39 months +, complete remission
13	VCS	II	Yes (4 hours)	Radiotherapy and chemotherapy	†, 8 months, progression of liver metastasis
14	Right and left anonyma, VCS	III	Yes (5 hours)	Chemotherapy	†, 16 months, progression of disease
15	VCS	III	Yes (1 hour)	Chemotherapy	†, 12 months, progression of disease
16	Right and left anonyma, VCS	III	Yes (2 hours)	Chemotherapy	†, 14 months, progression of disease
17	Right and left anonyma, VCS	III	Yes (12-24 hours)	-	†, 14 days, respiratory insufficiency

VCS = vena caval syndrome.

One patient with chronic SVCS had two unsuccessful recanalisation procedures (by femoral and brachial approach) due to complete obstruction. One patient achieved a successful repermeability by thrombolysis of extensive thrombosis in the superior caval and anonymamal vein. Endovascular follow-up treatment was no longer necessary. The longest distance stented in SVC was approximately 10 cm, requiring two self-expanding Symphony" stents, each with a length of 6 cm.
Six of the 17 patients presenting with SVCS were known to have a malignancy. Their malignancy had progressed before the SVCS developed.
In the remaining 11 patients, the cause of SVCS could only be established in three patients. In the other eight patients appropriate diagnostic procedures could not be performed before stenting SVCS. In seven of these eight patients, however, it was possible to perform diagnostic procedures within 24 hours after stenting to reveal the cause of SVCS.
In 14 of the 15 patients who underwent a successful stenting procedure total relief of symptoms was achieved within 24 hours after stenting (in most patients within six hours). One of the 15 individuals had partial relief of symptoms after 48 hours (*table 1*).

Complications
One patient showed partial migration of the stent without any consequences. This patient had a stent migration to the right atrium; the migration occurred before any additional antitumour therapy.
Cardiac arrhythmia (SVT) was seen in one patient during as well as after the procedure. This patient was treated temporarily with antiarrhythmic drugs in the intensive care unit. After the stenting procedure, three patients could not be treated with additional antitumour therapy as, despite stenting, their conditions did not allow the application of any available treatment.

Follow-up
The follow-up of these patients ranged from four days to four years. Of the 15 patients treated, two patients are still alive, 39 and 48 months, respectively, after stenting (*table 1*). All 15 individuals remained free from SVCS after the successful stenting procedure. Despite progression of disease in 13 of these 15 patients, no signs of SVCS were observed until death.

DISCUSSION

SVCS has long been, and sometimes still is, considered a potentially life-threatening medical emergency. The goals of treatment of SVCS are to relieve symptoms and to attempt to cure the primary malignant process.

As about 60% of patients develop SVCS before the primary diagnosis has been established several diagnostic procedures are considered in these patients. Although bronchoscopy, mediastinoscopy, thoracotomy, and percutanous transthoracic CT-scan guided fine-needle biopsy seem to be less hazardous than was thought in the past, it remains difficult to perform these diagnostic procedures in many patients because of the gravity of symptoms, as has been confirmed in our patients. For that reason radiotherapy/chemotherapy is often applied before histological diagnosis of the primary lesion has been established.
Although radiotherapy/chemotherapy is able to achieve a relief of symptoms, the onset of this relief is late and amelioration is often incomplete. Moreover, radiotherapy/chemotherapy may disturb the microscopic judgement of biopsies. Despite the limited numbers, our study clearly demonstrates that palliative SVC stenting prior to additional therapy is feasible, easily performed without complications and provides a quicker response (hours-days) than obtained with radiation therapy or chemotherapy alone (weeks) as mentioned in other studies.[7-10] Primary stenting also provides the opportunity to establish a correct diagnosis before starting antitumour therapy.
More research is needed to determine the long-term results of endovascular treatment and to find its role in benign and malignant disease.

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ORIGINAL ARTICLE

Antibiotic control measures in Dutch secondary care hospitals

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ABSTRACT

Control measures for the use of antibiotics are essential because of the potential harmful consequences of side effects. Various methods have been developed to help curb undesirable antibiotic prescription. We performed a survey in Dutch secondary care hospitals (response rate 73%) to make an inventory of these measures and elucidate possible shortcomings. Almost every hospital was using an antibiotic formulary (97%), sometimes supported by extra restrictions in antibiotic choice (55%). Local practice guidelines (95%) were commonly present, but effective implementation, for example using intranet applications, could be improved (21%). National guidelines had received little attention in the composition process of local guidelines (19%). Other measures such as educational programmes for specialists (11%) and feedback on antibiotic prescription (52%) remained largely underused, although their effective implementation may optimise antibiotic prescription in hospitals.

INTRODUCTION

Many studies have shown that the irrational prescription of antibiotics is an extensive problem world-wide.[1,2] Control measures for the use of antibiotics are essential for reasons including the potential harmful consequences of unnecessary exposure to toxic side effects[3,4] and the increase in healthcare costs. The cost of antibiotics consumes a significant part of hospital budgets all over the world.[5,6]

The use of antibiotics in Dutch hospitals, expressed as defined daily dose (DDD) per 100 bed-days, has gradually increased from 37.2 DDD per 100 bed-days in 1991 to 42.5 DDD per 100 bed-days in 1996.[7]

By far the most important danger of irrational antibiotic prescription is the increase in antimicrobial resistance. There is a considerable body of evidence that micro-organisms become resistant due to antibiotic (over)use.[8] In the Netherlands, antimicrobial resistance seems to be lower than that in most European countries,[9] and this has been related to the low use of antibiotics. Nevertheless the resistance of several indicator micro-organisms has shown a slow but steady increase.[10,11]

Clearly, a rational policy for the prescription of antibiotic therapy is warranted. Various methods have been developed to curb undesirable antibiotic prescription. Generally, these can be classified into educational strategies (e.g. dissemination of antibiotic guidelines, educational meetings, feedback and reminders), organisational measures (e.g. presence of an antibiotic committee, presence of an infectious disease physician at ward meetings) and restrictive strategies (e.g. publication of a formulary, restriction of antibiotic choice).[12] Research has been performed into the content of Dutch antibiotic formularies and guidelines.[13,14] The present study made an inventory of measures, including formularies and guidelines, which are used to improve antibiotic prescription in Dutch secondary care hospitals. The aim was to elucidate possible shortcomings in this field and promote successful strategies to improve the quality of antibiotic prescription behaviour.

[**]J.W.M. van der Meer was not involved in the handling and review process of this paper.

MATERIALS AND METHODS

Design and study population

All the secondary care hospitals in the Netherlands were invited to participate in a survey with questionnaires. Due to the large amount of merging and recent fusion between hospitals at the time of our survey, not all the hospitals within one group were using the same antibiotic policy. Hospitals that were still using their own policy were regarded as individual hospitals in the analyses.

Variables

A questionnaire was developed to gather information on hospital demographics (number of beds, teaching affiliation) and on specific strategies that are known to exist in hospitals to improve antibiotic prescription. An overview of the strategies is shown in *table 1*. The questionnaire contained 54 questions: yes/no questions, multiple-choice questions and open questions. Open questions were divided into meaningful categories after evaluation.

Data collection

In August 2002, all 92 Dutch secondary care hospitals were contacted through their infection prevention or antibiotic committees. A medical microbiologist or, if none was available, a hospital pharmacist, infectious disease physician or hospital infection control officer was asked to take part in the survey by filling in a questionnaire.
The questionnaire with a covering letter and a prepaid return envelope was sent to the hospitals that were willing to participate. Nonresponders were sent reminders three weeks and eight weeks later (with a copy of the same questionnaire enclosed). If the contact person was unable to answer particular questions him/herself, the covering letter suggested that these be passed on to other colleagues within the hospital, or be discussed accordingly. Participants could contact the study coordinator by e-mail or telephone.

Analysis

On receipt of the completed questionnaires, they were coded and the answers were entered into a computerised

Table 1
Overview of strategies and utilisation rates

	% (N/N TOTAL*)	TEACHING (%)	NONTEACHING (%)
Educational strategies			
Antibiotic guidelines present	95 (61/64)	97	94
Regular educational meetings on antibiotic prescription for residents	35 (22/63)	57	15**
Nonregular educational meetings on antibiotic prescription for residents	53 (30/57)	67	37**
Education (regular and nonregular) on antibiotic prescription for specialists	11 (7/61)	17	6
Audit and feedback			
Feedback on antibiotic therapy as soon as cultures become available	52 (33/64)	50	53
Organisational strategies			
Presence of medical microbiologist at ward meetings	79 (49/62)	97	65**
Presence of clinical pharmacist at ward meetings	39 (23/59)	56	27**
Presence of antibiotic committee	69 (44/64)	83	56**
Presence of infection prevention committee	95 (60/63)	90	100
Restrictive strategies			
Antibiotic formulary	97 (62/64)	100	94
Extra restriction in antibiotic choice	55 (35/64)	63	47
Automatic stop order	10 (6/63)	7	12
Antibiotic order form	3 (2/64)	7	0
Quality of care policies			
Quality improvement projects on antibiotic use performed in past 5 years	52 (30/58)	54	50

**Number of questionnaires, excluding missing values, **significant difference: p<0.05 (Chi-square test).*

data programme (Microsoft Access). Descriptive analyses were performed: frequencies, percentages and averages were calculated with SPSS 11.0 software. The influences of teaching status and hospital size were studied using the Chi-square test.

RESULTS

Response

A total of 92 hospitals were contacted by telephone; 88 out of the 92 hospitals agreed to receive a written questionnaire. Completed questionnaires were returned by 64 hospitals (73%) within 12 weeks.

Hospital demographics

The median number of beds in the participating hospitals was 434 (range 138 to 1350), with 58 beds in the internal medicine department (range 21 to 170) and 23 in the respiratory care department (range 0 to 61). Thirty hospitals had a teaching affiliation with a University Medical Centre and employed residents in speciality training programmes for internal and/or respiratory medicine and/or medical microbiology. The remaining 34 nonteaching hospitals employed junior medical staff, either as locum senior house officers or GP registrars. Here, all the undergraduate medical staff are referred to as residents. Senior staff are referred to as specialists.

EDUCATIONAL MEASURES

Antibiotic guidelines

The vast majority of respondents (95%) reported that a written policy was available for antibiotic therapy in their hospital. These guidelines were geared more towards assisting the clinician to choose an appropriate antibiotic therapy for a clinical (infectious) condition (100%) than towards commenting on the use of a specific (class of) antibiotic(s) (26%).

Local antibiotic policies had generally been formulated by consensus procedure (80%) by a group that contained a medical microbiologist, a hospital pharmacist and other clinical specialists, depending on the speciality for which the guideline was intended. For the composition of local practice guidelines, respondents reported that they had used several sources, mainly local practice guidelines from other hospitals and international guidelines (*table 2*).

Updating local guidelines

Local practice guidelines were revised an average of once every 2.6 (CI 2.2 to 3.0) years by 80% of the hospitals. In 66%, current local antimicrobial resistance surveillance data were taken into account when updating the practice guideline.

Table 2
Sources of local guidelines

	% (N/N=61*)
Local practice guidelines from other Dutch hospitals	**44 (27)**
University medical centres	16 (10)
Secondary care hospitals	13 (8)
Regional (transmural) antibiotic policies	16 (10)
International guidelines	**36 (22)**
National guidelines	**19 (12)**
SWAB guidelines (National antibiotic policies)	15 (9)
CBO guidelines (National multidisciplinary guidelines)	8 (5)
NHG standards (Guidelines for general practice)	7 (4)
SOA bulletin (STD guidelines)	7 (4)
National guidelines for paediatricians	2 (1)
Literature	**15 (9)**
Recent literature review	12 (7)
Mandell's Infectious Diseases handbook	3 (2)
Compendium Infectieziekten (Infectious Diseases handbook)	3 (2)
Hartstichting (National Heart Foundation)	2 (1)

**Total number of questionnaires, excluding missing values.*

Dissemination of guidelines

In 95% of the participating hospitals, local practice guidelines had been converted into a printed 'antibiotic booklet'. Other methods of guideline dissemination were reported less frequently, such as placing guidelines on the intranet or using mailings (*table 3*).

Table 3
Dissemination of guidelines

	% (N/N=61*)
Dissemination of an antibiotic booklet	95 (58)
Presentations	16 (10)
Introduction on intranet	21 (13)
Mailings	10 (6)
Other	10 (6)

**Total number of questionnaires, excluding missing values.*

Location of guidelines

According to our respondents, a printed version of the local practice guidelines was readily available at many locations within the hospitals: doctor's offices, departments of microbiology and clinical wards were mentioned most often. Only one fifth of the hospitals had installed a desktop application of the guidelines on hospital computers (*table 4*).

Table 4
Where can guidelines be found?

	% (N/N=61*)
Doctor's office	83 (52)
Department of medical microbiology	75 (45)
Clinical wards	61 (37)
Casualty department	49 (30)
Hospital pharmacy	28 (17)
Intranet (desktop application)	21 (13)
Operating theatre	2 (1)

**Total number of questionnaires, excluding missing values.*

Educational activities

Educational activities for specialists

There was very little educational input for internal medicine or respiratory medicine specialists in the hospitals (11%).

Regular education for residents

In this survey, educational strategies to improve antibiotic use were only assessed in departments of internal medicine and respiratory medicine. Approximately one third of the hospitals organised regular educational activities to improve residents' knowledge of antibiotic policies (n = 22/63). Half of these initiatives comprised small (interactive) educational meetings which were generally organised seven times a year (CI 1.5-12.4). It was obligatory for residents to attend these educational meetings in 50% of the hospitals that organised such programmes.

Nonregular education for residents

Nonregular educational activities on antibiotics or management of infectious diseases were organised in a wide variety of forms in 30 of the hospitals (*table 5*). As expected, educational efforts were more common in teaching hospitals than nonteaching hospitals (*table 1*), but no education at all on antibiotic management was organised for residents in six out of the 30 teaching hospitals (20%)

Table 5
Education for residents on antibiotic policies

	% (N/N=61*)
Regular education	**36 (22/61)**
Provision of educational material	32 (7/22)
Large-scale educational meetings	50 (11/22)
Small-scale (interactive) educational meetings	50 (11/22)
Nonregular education	**49 (30/61)**
General educational meeting with variable programme: continuous medical education, symposia and clinical conferences	50 (15/30)
Morning reports, evening reports, ward rounds in which clinical patients are discussed	43 (13/30)
Personal education by receiving feedback from a medical microbiologist on individual patient management	23 (7/30)

**Total number of questionnaires, excluding missing responses.*

AUDIT AND FEEDBACK

Feedback on antibiotic prescription behaviour was a common control measure in the participating hospitals. It was generally provided by a medical microbiologist or an infectious disease physician (if present) and less frequently by a pharmacist.

At 33 out of the 64 (52%) hospitals, clinicians were contacted routinely as soon as relevant culture results became available and they advised about antibiotic choices. This was done by medical microbiologists in 44% and by hospital pharmacists in 22%. In the majority of cases, only positive cultures from sterile compartments (blood, CSF, etc.) were brought to the attention of the clinician. In 12 hospitals, clinicians were contacted and advised about positive culture results from all possible compartments (including sputum and urine cultures).

ORGANISATIONAL MEASURES

Local committees

An infection prevention committee was present at all but three of the hospitals (95%) and contained a medical microbiologist, a hospital infection control officer, a senior hospital pharmacist and other staff from clinical departments (*table 6*).

In 69% of the hospitals, an antibiotic committee was present, often in the form of a subgroup of the hospital formulary committee. A member of the undergraduate staff was invited to join the committee in only two hospitals, while a quality improvement officer was invited in one hospital. Meetings took place on average six times a year.

Presence of a medical microbiologist or pharmacist at ward meetings

A common measure to influence decision-making on the prescription of antibiotics in Dutch hospitals is the presence of a medical microbiologist at clinical ward meetings. Medical microbiologists attended ward meetings regularly to discuss clinical patients in 79% of the participating hospitals.

A microbiologist was always present on ICU rounds (5 or more times a week) in 67% of the hospitals. In 51%, a microbiologist attended general internal medicine rounds, usually once a week, whereas ward rounds on the respiratory medicine ward were attended far less frequently (8%). The haematology department, where complicated

Table 6
Composition of local committees

	INFECTION PREVENTION COMMITTEE % (N/N=60)	ANTIBIOTIC COMMITTEE % (N/N=44)
Medical microbiologist	98 (59)	98 (43)
Hospital infection control officer	98 (59)	7 (3)
Senior clinical pharmacist	88 (53)	98 (43)
Internist	72 (43)	73 (32)
Surgeon	78 (47)	48 (21)
Paediatrician	33 (20)	36 (16)
Nurse	30 (18)	2 (1)
Manager	42 (25)	5 (2)
Infectious disease physician	10 (6)	21 (9)
Resident	0 (0)	5 (2)
Quality improvement officer	0 (0)	2 (1)

infectious disease issues are prominent, was visited regularly by microbiologists in 31% of the participating hospitals.
Pharmacists also attended ward rounds, although not as commonly as medical microbiologists (39%). A member of staff from these hospital pharmacy departments was almost always present at ICU meetings, a minimum of five times a week. However, they seldom attended or were invited to meetings on general internal medicine wards. An infectious disease specialist was present in 12 of the hospitals. Ward meetings were attended routinely in seven hospitals; ICU meetings were attended every day in three hospitals and general internal medicine department meetings were attended in six hospitals.

RESTRICTIVE STRATEGIES

Antibiotic formulary

The most common control measure for antibiotic use was the publication and dissemination of an antibiotic formulary; 62 of the hospitals (97%) were using a formulary in daily practice.

Other restrictive strategies

In 55% of the hospitals, the use of certain antibiotics – while appearing in the formulary – was further restricted: these antibiotics could generally only be prescribed when authorised by a medical microbiologist or a pharmacist. Carbapenems (74%), vancomycin (35%) and third-generation cefalosporins (36%) were included in most of the restriction lists. An automatic stop order was used in only six hospitals: in five of these hospitals, this measure concerned all antibiotic prescriptions, while in one hospital it only applied to a list of approximately 20 broad-spectrum antibiotics.
An antibiotic order form was used in two (3%) of the hospitals. In one case, a written indication for antibiotic use was requested on the order form. In the other case the exact content of the order form (although requested) was not clarified.

PROJECTS TO IMPROVE ANTIBIOTIC USE

Of the hospitals, 52% had participated in some kind of project to improve the prescription of antibiotics in the five years prior to completing our questionnaire. Projects that encouraged a timely switch from intravenous antibiotics to oral therapy were most common (*table 7*).

INFLUENCES OF TEACHING STATUS AND HOSPITAL SIZE

There were no differences in the presence of local antibiotic guidelines, formularies, infection prevention committees and feedback measures for antibiotic prescriptions between teaching and nonteaching hospitals, or between large hospitals (>450 beds) and small hospitals (<450 beds) (*tabel 1*). As expected, regular (57 *vs* 15%, p=0.01) and nonregular educational efforts (67 *vs* 37%, p=0.025) and the presence of medical microbiologists (97 *vs* 65%, p=0.002) or clinical pharmacists (56 *vs* 27%, p=0.026) at ward meetings were more common in teaching hospitals than in nonteaching hospitals. More of the teaching hospitals had antibiotic committees than the nonteaching hospitals (83 *vs* 56%, p=0.018).

DISCUSSION

In this survey, we made an inventory of measures used to improve the prescription of antibiotics in Dutch hospitals.

Table 7
Projects to improve antibiotic use (over the past 5 years)

	N=58*
Switch project	13
Implementing a new antibiotic formulary, new practice guidelines or protocol	10
Implementing restrictive measures: automatic stop order or restrictive list	7
Implementing surveillance of postoperative wound infections, improving perioperative antibiotic prophylaxis	3
Audit and monitoring the use of aminoglycosides	3
Implementing feedback programmes to clinicians on expensive or broad spectrum antibiotics	2
Implementing direct feedback by medical microbiologist or pharmacist to the clinician on indication, antibiotic choice, dose, dose interval and length of therapy	2
Implementing a new organisational structure of antibiotic committees or forming an antibiotic committee	1
Audit of complications of intravenous of antibiotic use (phlebitis)	1
Others	15

**Total number of questionnaires excluding missing responses.*

The most common antibiotic control measure reported in our survey was the use of an antibiotic formulary or restricted drug list. This measure was being applied in 97% of the hospitals. In a study conducted in 1991 on Dutch hospitals with >500 beds and <500 beds, this percentage was 53 and 32%, respectively.[14,15] A similar survey performed in the United Kingdom by the British Society of Antimicrobial Chemotherapy[16] in 1990 reported a utility rate of 79%. Thus, there has been a substantial increase in the use of antibiotic formularies in the Netherlands over the past decade. An antibiotic formulary is a straightforward method to restrict the use of antibiotics in hospitals. In half of the hospitals, an even more powerful restriction measure was put in place: a list of a small number of antibiotics could only be prescribed with the specific approval of a medical microbiologist or a pharmacist.
Automatic stop orders and antibiotic order forms are often applied in the United States,[17] but these measures are not popular in the Netherlands, although efforts to implement the antibiotic order form have been made in a Dutch University Hospital setting.[18]
Infection prevention committees and antibiotic committees are known to be essential to achieve successful local antibiotic policies.[15] Such committees were present and regular meetings were held in most of the participating hospitals. In 1976, the Dutch Health Council advised hospitals to formulate guidelines for the rational use of antibiotics.[19] Accordingly, the presence of written antibiotic policies (local practice guidelines) appeared to be very common in our respondents' hospitals (95%). In a survey in United States hospitals in 1998, 70% reported that they were using antibiotic guidelines.[20]
A wide variety of sources were used to compose local practice guidelines, mostly in consensus. National guidelines for infectious diseases seemed to have been underused in this process, even less than international guidelines. This is surprising, as reports in the past have suggested that medical specialists tend to prefer consulting guidelines from their own national scientific society.[21]
SWAB guidelines were only used sporadically (15%), although a recent survey suggested a somewhat higher utilisation percentage.[22] In our questionnaire we did not ask specifically whether the SWAB guidelines had been used, but we asked participants to give the name of the national guidelines that they had referred to. This may have underestimated the true figures for SWAB guideline use. Nevertheless we believe there is reason to improve the implementation of national guidelines in secondary care hospitals. National guidelines can be expected to provide more accurate and tailored information than international guidelines on aspects such as local resistance patterns, which are regarded as forming an essential part of guidelines on the prudent use of antibiotics.
To achieve prolonged effect, policies need continuous updating, feedback and monitoring.[23] About 80% of the hospitals renewed their guidelines at least once every three years. From an international perspective, this seems to be a reasonable rate.[15]
Dissemination and implementation strategies for guidelines on a hospital level have mainly concentrated on producing an 'antibiotic booklet' for professionals. Very few supportive tools were being applied in hospitals to help implement the guidelines. Thus, the digital revolution era has apparently not yet fully entered Dutch hospitals: only 13 hospitals were using desk top applications to implement their guidelines in daily practice. There are some excellent examples in the literature on how computer applications can be used to improve the prescription of antibiotics.[24]

Education for physicians who prescribe antibiotics may improve their usage, but the effects of most educational programmes are modest.[25] However, education is seen as

an important prerequisite for the successful implementation of guidelines. This method seems to be underused in Dutch hospitals, as only 11% of the specialists reported receiving any form of education on antibiotic use. On the other hand, specialists may have been actively providing clinical lectures for nurses and undergraduate staff, which would obviously require considerable self-study.
The responders to our questionnaire (70% of the hospitals) were more likely to have a keen interest in control measures for antibiotic use than the nonresponders. Thus, they were more likely to be running control systems than nonparticipants, which might have over-represented the proportion of hospitals that were using control methods for antibiotic prescription.

At most of the Dutch secondary care hospitals, antibiotic formularies and guidelines were present and were being combined with at least one other control measure. However, some control measures remained largely unused. We therefore recommend that hospitals take a closer look at all the possible control measures and implement existing measures in daily practice to achieve further improvements in antibiotic prescription behaviour.

NOTE

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CASE REPORT

Stridor and Horner's syndrome, weeks after attempted right subclavian vein cannulation

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ABSTRACT

A 23-year-old woman presented with renal failure resulting from polycystic kidney disease (PKD) aggravated by tubulo-interstitial nephritis. Emergency haemodialysis was planned, and cannulation of the right subclavian vein was attempted, but failed. During this procedure, inadvertent arterial puncture occurred. Transient mild ischaemia of the right arm, and a transient Horner's syndrome were noted. Seven weeks later she presented with severe stridor with impending respiratory failure necessitating emergency intubation; the right-sided Horner's syndrome had recurred. CT imaging showed a large pseudo-aneurysm of the brachiocephalic artery resulting in severe compression of the trachea. Using a prosthetic graft, the operation for the pseudo-aneurysm was successful; there were mild neurological sequelae. Although her family history was negative, autosomal dominant PKD should be considered, and we discuss the possible role of a pre-existing PKD-associated aneurysm.

INTRODUCTION

Mechanical complications may occur during attempted cannulation of central veins.[1,2] One of these adverse events is inadvertent arterial puncture with subsequent potentially fatal injury to the subclavian artery.[3,4] Bleeding may result in acute-onset airway obstruction,[5] but also late onset sequelae, such as complications from false aneurysms of the vertebral artery and thyrocervical trunk have been reported.[6,7] Horner's syndrome has been reported after internal jugular vein puncture.[8,9] We report both sequelae (i.e. Horner's syndrome and airways obstruction) resulting from pseudo-aneurysm formation of the brachiocephalic artery after attempted cannulation of the right subclavian vein.

CASE REPORT

A 23-year-old woman presented to the nephrology division of our hospital with malaise and a skin rash. Her previous medical history was remarkable for recurrent pyelonephritis and polycystic kidneys. She had been treated by her family physician for a urinary tract infection with amoxicillin-clavulanic acid; a urinary specimen grew *E. coli* >10^6 colony-forming units per ml. Dysuria had subsided and her urinary output was unchanged. Apart from the skin rash, and the palpable kidneys, and slight overweight, physical examination was unremarkable. Her blood chemistry showed mild anaemia (Hb after rehydration, 5.7 mmol/l) and renal failure (urea 115 mmol/l, serum creatinine 1810 μmol/l). Arterial blood gas analysis showed pH 7.33, paO_2 16.3 kPa, $paCO_2$ 2.5 kPa, HCO_3- 10 mmol/l. She was admitted to hospital and haemodialysis was planned. During attempted insertion of a haemodialysis catheter into the right subclavian vein, inadvertent arterial puncture occurred. This was followed by transient ischaemia of the right arm, and an incomplete right-sided Horner's syndrome was observed, with ptosis and miosis of the right eye; she also had a hoarse voice. The procedure was converted to cannulation of the femoral vein, followed by haemodialysis. A renal biopsy showed tubulo-interstitial nephritis, presumably resulting from an adverse effect of the antimicrobial therapy that was given for her urinary tract infection. The Horner's syndrome

subsided gradually but incompletely, and the hoarseness of her voice was no longer noticeable. Her renal failure subsided gradually after corticosteroid treatment was started (60 mg of prednisolone for four weeks, then gradually tapered) and she was discharged home after three weeks of admission.

One month after discharge – seven weeks after attempted cannulation of the right subclavian vein – she presented to the emergency department of our hospital with severe dyspnoea. She had noticed gradual swelling of her face, and gradually increasing dyspnoea over the last three days. On examination her face was cushingoid, and her neck was swollen; there was an audible stridor. Her right arm was oedematous with no arterial pulsations. She was admitted to the intensive care unit, and developed respiratory failure during the first night of observation, and had to be intubated and mechanically ventilated.

A portable chest radiograph showed a right paratracheal mass, with deviation of the trachea to the left, and compression of the tracheal lumen (*figure 1*). Contrast-enhanced computed tomography showed gross aneurysmatic dilatation of the brachiocephalic artery starting just above the artery's origin at the aortic arch, and extending beyond the right subclavian artery. The lumen of the subclavian artery could not be visualised (*figure 2*).

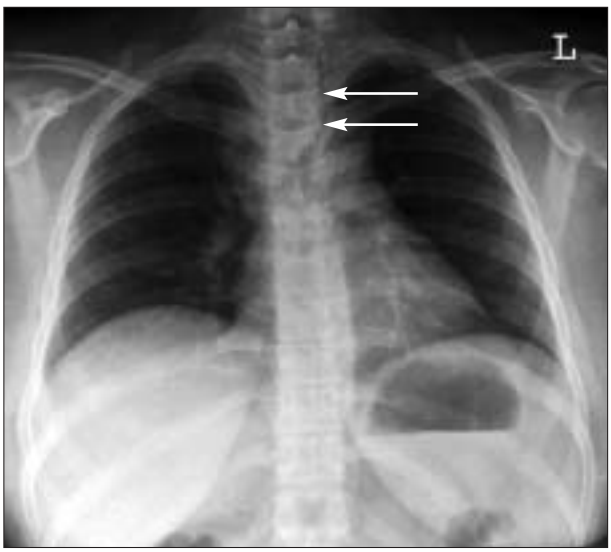

Figure 1
Posteroanterior chest radiograph taken in upright position, showing severe deviation of the trachea to the left (arrows), and severe narrowing of the tracheal lumen, extending from the thoracic inlet to the main carina

During the operation, through a mid-sternal approach with upward extension of the incision to the right, the brachiocephalic vein and artery and the right carotic artery were identified and mobilised; the brachiocephalic artery showed

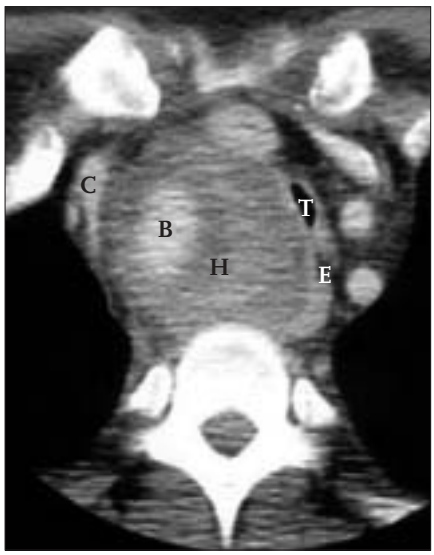

Figure 2
Contrast-enhanced computed tomography showing a large haematoma (H) around a small contrast-enhanced lumen of the brachiocephalic artery (B); deviation and compression of the trachea (T); deviation of the superior caval vein (C), and of the oesophagus (E)

gross aneurysmatic dilatation. In order to explore the right carotic artery, the anterior scalenic muscle had to be sacrificed. After clipping the aneurysm was opened, and intimal dehiscence was noticed; there was no communication with the haematoma surrounding the lumen. Blood clots were evacuated, and fresh bleeding appeared to come from the apparently damaged right subclavian artery. A vascular prosthetic graft was used to bypass the brachiocephalic artery; the graft connected the aortic arch and the right carotid artery. A second prosthetic graft was used to connect the right subclavian artery to the first graft end-to-side. After surgery, pulsation of arteries was satisfactory, and the postoperative course was uneventful. Post-extubation, the right hemidiaphragm was partly elevated, probably due to pressure to the right phrenic nerve during surgery; and there was hoarseness of her voice that appeared to be due to right vocal cord paresis. A mild transient paresis of her left arm was believed to result from clamping of the right carotid artery during surgery.

DISCUSSION

Our patient sustained late-onset airways obstruction, and Horner's syndrome, resulting from pseudo-aneurysm formation, seven weeks after inadvertent puncture of the brachiocephalic artery. She also had an injury to the right subclavian artery that caused flow limitation to the right arm, but apparently, collateral circulation prevented her from developing ischaemic symptoms. Although she

complained of a swollen face, no clear superior caval vein compression resulted from the aneurysm. The right vocal cord dysfunction was diagnosed as a recurrent laryngeal nerve injury, and although this was believed to result from compression during surgery, compression resulting from the aneurysms cannot be ruled out.

We only found one case report in the non-English literature on false aneurysm formation of the brachiocephalic artery after attempted cannulation of the right subclavian vein,[10] but a combination of this uncommon but life-threatening complication with Horner's syndrome has not been reported. False aneurysm of the subclavian artery with stridor and dysphagia resulting from tracheal and oesophageal obstruction has, however, been reported.[11,12]

Could she have developed these problems because of a pre-existing aneurysm, associated with an inherited syndrome that caused autosomal dominant polycystic kidney disease (ADPKD) and aneurysm formation? Although she did not admit to having family members with ADPKD, most of these patients have mutations in one of the two genes – PKD 1 and 2[13] – which code for the protein polycystin that is also expressed in the vascular wall,[14] and some 10% of these individuals may develop arterial aneurysms.[13] Aneurysms usually occur intracranially,[15] but occasionally other vascular structures including carotid and vertebral arteries may be affected.[16]

In most cases of inadvertent arterial puncture during attempts to cannulate the internal jugular and subclavian veins, no adverse events are noted.[2] Our patient had severe azotaemia with subsequent thrombocytopathia, and impaired platelet function may have aggravated the arterial bleeding.[1,3] Other identifiable risk factors were also present – obesity being one and, possibly, multiple attempts and failure to cannulate the subclavian vein.[17,1,2] Experience is important[1,2] but the attending physician's great experience did not prevent this complication from occurring. In our opinion, however, experience comes from learning, and the learning process is unavoidable; indeed, training and learning are paramount for any teaching hospital.

Some authors advocate ultrasound guidance, but in one large prospective randomised controlled trial with a very experienced team who inserted central venous catheters, no benefit could be demonstrated regarding prevention of failures and complications.[1] Ultrasound guidance has been advocated for selected, high-risk cases.[2,18] A recent meta-analysis of randomised studies including predominantly medical personnel with limited experience in inserting catheters showed, however, significant reduction in the complication rate when ultrasound guidance was used for cannulation of the subclavian and internal jugular veins.[19]

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Severe hypocalcaemia associated with extensive osteoblastic metastases in a patient with prostate cancer

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ABSTRACT

A patient with an untreated carcinoma of the prostate was admitted with dehydration, stupor and a surprisingly deep hypocalcaemia. The severe hypocalcaemia was largely attributed to extensive osteoblastic activity due to widespread skeletal metastases although contributing factors to the severity of the hypocalcaemia were a relative vitamin D deficiency, hypomagnesaemia and renal impairment, preventing the mounting of an adequate homeostatic response. There was significant clinical and biochemical improvement after antitumour treatment using androgen deprivation, and supplementation with calcium and vitamin D.

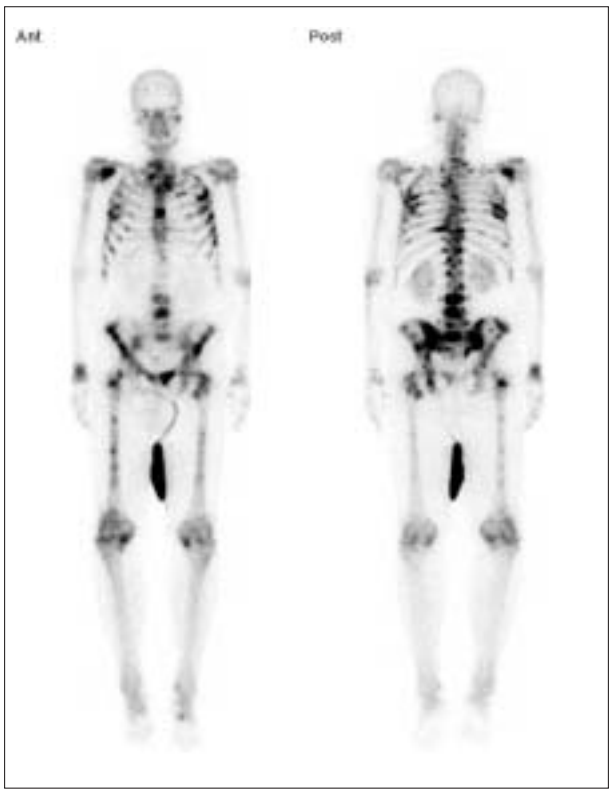
INTRODUCTION

Hypercalcaemia is a relatively common complication of malignancy, particularly in its terminal stages. Clinically significant hypocalcaemia is much less common. Reported causes of malignancy-associated hypocalcaemia are hypoalbuminaemia, vitamin D deficiency, tumour lysis syndrome usually following chemotherapy, and increased calcium utilisation by extensive osteoblastic skeletal metastases. This last cause of hypocalcaemia has mostly been reported in the advanced stages of prostate cancer. However, even in the terminal stages of this malignancy, hypocalcaemia is usually an asymptomatic, incidental finding. In this case report we present a patient with an untreated carcinoma of the prostate who presented with unusually severe, life-threatening hypocalcaemia. A combination of androgen deprivation, high doses of calcium and an active metabolite of vitamin D led to a significant clinical and biochemical improvement.

CASE REPORT

A 67-year-old patient was referred for admission because of progressive lethargy, anorexia and dehydration. An adenocarcinoma of the prostate had been diagnosed by transrectal biopsy three months previously, with Gleason score (4 + 4). ^{99m}Tc-hydroxymethylene-diphosphonate bone scintigraphy performed at the time of diagnosis showed evidence of limited metastatic involvement of the skeleton (*figure 1*). Besides a chest X-ray, no standard X-rays were taken.

The patient was then largely asymptomatic and it was decided not to start hormonal treatment as yet.
On admission, the patient was disorientated in time and place and in a semi-stupor state. He was apyrexial and showed signs of dehydration. Chvostek and Trousseau's signs could be clearly elicited. Results of initial laboratory investigations are shown in the *table 1* (first column). Renal function was significantly impaired. There was a severe hypocalcaemia associated with mild hyperphosphataemia, but an only moderately (fourfold) increased PTH concentration despite the severe hypocalcaemia, probably because of the prevailing significantly decreased serum magnesium concentration. Serum alkaline phosphatase activity was increased more than 20-fold and serum PSA concentration was markedly elevated suggesting significant tumour load. This was also suggested by bone marrow suppression as evidenced by the low haemoglobin concentration and the low white blood cells and platelets counts. 25-hydroxy vitamin D concentration was low and 1,25-dihydroxy-vitamin D concentration inappropriately normal for the degree of hypocalcaemia. No abnormalities were detected on plain radiographs of the chest.



Figuur 1
^{99m}Tc-HDP bone scintigraphy at time of the diagnosis of prostate carcinoma

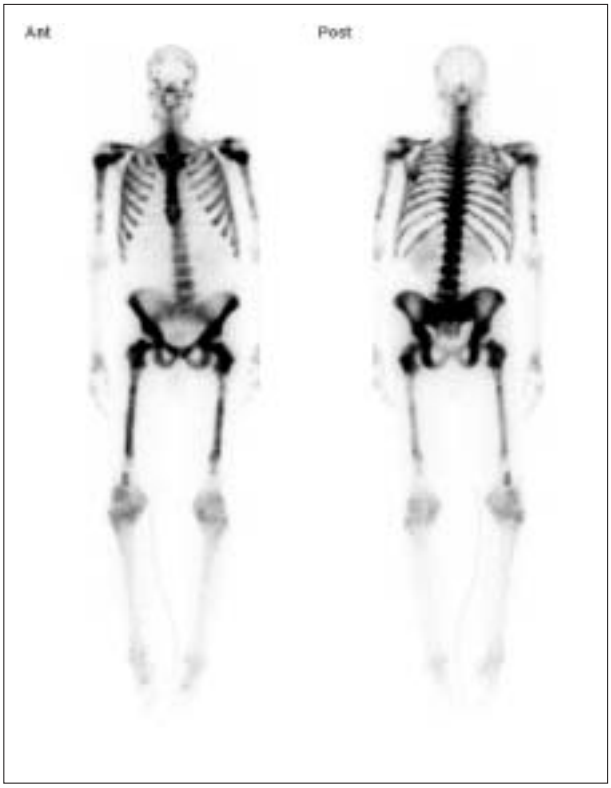


Figure 2
^{99m}Tc-HDP bone scintigraphy at time of the admission with hypocalcaemia

Table 1
Biochemical data on admission and 10 and 20 days after institution of therapy in a patient with prostate cancer and widespread skeletal metastases

	ON ADMISSION	10 DAYS LATER	20 DAYS LATER	NORMAL VALUES
Haemoglobin	4.5	6.6	6.3	7.2-9.8 mmol/l
White blood cell count	7.4	9.4	7.6	4.0-11.0 x 10^9/l
Platelets	75	113	179	150-400 x 10^9/l
Sodium	141	134	139	136-146 mmol/l
Potassium	5.7	4.7	4.8	3.5-4.5 mmol/l
Creatinine	306	92	105	62-106 µmol/l
$Calcium_{(total)}$	<1.0	1.56	1.95	2.10-2.60 mmol/l
Albumin	30	26	30	36-47 g/l
$Calcium_{(ionised)}$	0.46		0.99	1.10-1.35 mmol/l
Magnesium	0.56	0.80	0.83	0.70-1.0 mmol/l
Phosphate	1.65	1.69		0.70-1.40 mmol/l
Alkaline phosphatase	2430	1880	2090	<90 U/l
Lactate dehydrogenase	2110	940	760	<300 U/l
Prostatic specific antigen	946	156		<4 µg/l
25-hydroxy-vitamin D_3	21			30-100 nmol/l
1,25-dihydroxy-vitamin D_3	62			40-160 pmol/l
Parathyroid hormone	35.9	26.1	27.1	1.5-9.0 pmol/l
Testosterone	13.0		0.3	10-40 nmol/l

After exclusion of a post-renal cause for the renal impairment, the patient was intensively rehydrated together with intravenous supplementation with calcium gluconate and administration of calcitriol. Primary treatment of the prostate cancer by androgen deprivation was concurrently instituted using leuprolin, an LHRH analogue, and bicalutamide, an androgen-receptor blocker. Repeated ^{99m}Tc-HDP bone scintigraphy now showed the pattern of a 'superscan', indicating extensive skeletal metastases. Clear progression could be demonstrated compared with the bone scintigraphy performed at the time of diagnosis (*figure 2*).

Within a few days of starting treatment, a marked improvement was noted in the patient's general condition including his mental status. This clinical improvement was paralleled by a significant improvement in all biochemical parameters measured including PSA concentrations (*table 1*). After ten days of intravenous substitution, calcium was given orally at a daily dose of 1000 mg and calcitriol was continued at the same dose of 1 μg a day. The patient could be discharged home in a relatively good condition with significantly improved renal function although still demonstrating mild hypocalcaemia (ionised serum calcium 0.99 mmol/l). Serum magnesium had normalised but secondary hyperparathyroidism persisted probably due to the combination of persistent hypocalcaemia and still impaired renal function.

Within the following three months, the patient's clinical condition deteriorated significantly with the development of extensive liver metastases. The patient developed a clear Cushing's syndrome in this phase (24 hour cortisol >5000 nmol/l), suggesting a neuro-endocrine component. A biopsy of one of the liver metastases showed a small cell anaplastic carcinoma. Since there were no signs of tumour on the chest X-ray, the liver metatases had originated in the prostate.

NSE and chromogranin A levels were not determined. Although there was no recurrence of hypocalcaemia, there was a rapidly downhill clinical course and the patient died a few weeks later. An autopsy examination was not undertaken.

DISCUSSION

An unusual feature of the case we report here is the severe symptomatic hypocalcaemia at presentation in a patient with prostate cancer metastatic to the skeleton. In a survey of more than 7000 patients with cancer, hypocalcaemia was indeed found to be present in only 1.6% of cases.[1] In malignant diseases, the most common cause of hypocalcaemia is vitamin D deficiency associated with the malignant state. Rare reported causes of hypocalcaemia in cancer are hypoparathyroidism due to destruction of parathyroid glands by metastases from a breast carcinoma,[2,3] severe hypomagnesaemia due to paraneoplastic renal loss of magnesium described in ovarian carcinoma,[4] renal impairment, or a tumour lysis syndrome following the use of various chemotherapeutic agents.[5] The presence of bone metastases increases the prevalence of true hypocalcaemia to 5 to 13%, depending on the formula used to correct for serum albumin concentrations.[6] Osteoblastic metastases have been reported to be associated with hypocalcaemia in patients with breast carcinoma,[2,7] but the most frequently encountered tumour causing hypocalcaemia is prostate cancer metastatic to the skeleton.[8] In the study by Riancho *et al.*, 75% of cases of hypocalcaemia were due to prostate cancer.[6] In prostate cancer metastatic to the skeleton, hypocalcaemia is more likely because of the predominantly osteoblastic nature of the metastatic process leading to an increased influx of calcium into bone due to increased bone formation. Hypocalcaemia is usually mild and clinical signs are rare. In a study of 112 patients with metastatic prostate cancer only 0.9% of the patients were actually found to have symptomatic hypocalcaemia[8] although cases of severe hypocalcaemia have also occasionally been reported.[9-12]

In our patient, the marked tumour load and the subsequent rapid disease progression despite adequate androgen deprivation point to increased utilisation of calcium by avid osteoblastic metastases as playing a central role in the pathophysiology of the hypocalcaemia observed. It is of note, however, that our patient was also vitamin D deficient, with inappropriately normal 1,25-hydroxyvitamin D concentrations, probably due to impairment of the synthetic capacity of the kidney for 1,25-hydroxyvitamin D production and to the inappropriate increase in PTH concentrations because of the prevailing hypomagnesaemia.

The cause of the significantly decreased magnesium concentration, particularly in the presence of renal impairment, is not clear although probably paraneoplastic as the disturbance spontaneously reverted following institution of hormonal therapy. Reversal of renal impairment by successful rehydration and supplementation with calcium and an active metabolite of vitamin D resulted in a significant and rapid clinical and biochemical improvement with near normalisation of serum calcium concentrations. These, however, remained below the normal laboratory reference range and were associated with persistently elevated serum PTH concentrations suggesting that, in retrospect, higher doses of calcitriol may have achieved a more complete correction of calcium homeostasis than the dose used in our patient. The significant decrease in PSA concentration following androgen deprivation points to a decrease in tumour load with the decreased skeletal utilisation of calcium also contributing to correction of the hypocalcaemia.

This case underlines the fact that in malignant diseases, a probably otherwise common vitamin D deficiency may hold significant clinical consequences, particularly when calcium homeostasis is already jeopardised by the presence of skeletal metastases.

In summary, we present a patient with prostate cancer and severe symptomatic hypocalcaemia, predominantly due to extensive osteoblastic metastases, in whom primary treatment of the tumour and supplementation with calcium and vitamin D resulted in a significant clinical and biochemical response.

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The Journal of Medicine

Malaise, anorexia, progressive limb paresis and multiple defects in the kidneys

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CASE REPORT

A 32-year-old bisexual man presented with malaise, anorexia, periods of fever, and a progressive paresis of the left foot. At presentation, he had a temperature of 36.5°C and a blood pressure of 190/120 mmHg. He had an elevated ESR; serum creatinine, liver enzymes and urine analysis were normal. The initial chest X-ray showed no abnormalities. Because of the rapidly progressive paresis, initially a CT scan of the pelvis was carried out, which showed no abnormalities of the bony structures. However (unexpected) multiple defects in both kidneys were seen (*figure 1*).

Within a couple of days he was transferred to the intensive care unit for mechanical ventilation because of respiratory insufficiency. At that moment bilateral opacities were seen on the chest X-ray (*figure 2*).

From neurological studies it was concluded that he was suffering from a mononeuritis.

WHAT IS YOUR DIAGNOSIS?

See page 40 for the answer to this photo quiz.

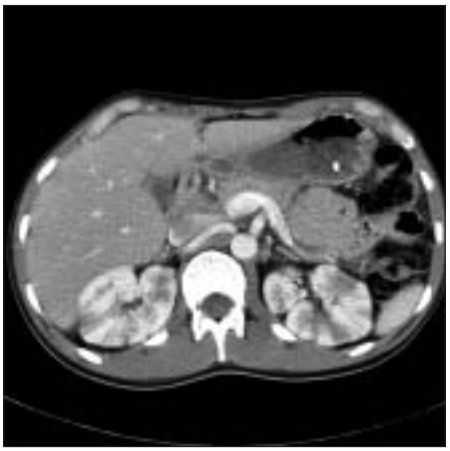

Figure 1

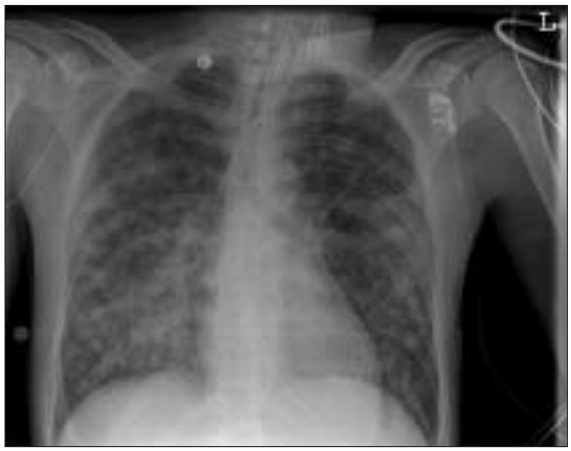

Figure 2

LETTER TO THE EDITOR

Approach to the patient with gastrointestinal bleeding and anticoagulation

In the year 2003 the Netherlands Association for Internal Medicine (NIV) published guidelines regarding upper and lower gastrointestinal bleeding. The result is a compact but complete summary concerning frequently seen problems in the practice of internal medicine. However, we have noticed a practical problem. In the case of first treatment to stabilise the patient when using the oral anticoagulant coumarin, the guidelines state that this should be corrected by either prothrombin complex (cofact) or fresh frozen plasma whenever it is indicated. Indications are haemodynamic instability or an international normalised ratio (INR) above 1.5. Our problem is the word 'or'. In daily practice it regularly occurs that a patient with upper or lower gastrointestinal bleeding is haemodynamically stable with an INR in the therapeutic range (between 2.5 and 4.5). In our opinion treatment with vitamin K is sufficient and safe, but the guidelines advise the expensive and potentially risky prothrombin complex or fresh frozen plasma. In the literature there is no evidence for the use of vitamin K, prothrombin complex or fresh frozen plasma in gastrointestinal bleeding and the guidelines are, at this point, based on expert opinions. In one report, successful haemostasis was achieved with endoscopic therapy in 91% of 52 patients with acute upper gastrointestinal bleeding after correcting the INR to 1.5 to 2.5, a success rate comparable with a control population of patients who were not anticoagulated.[1]
To that point we would advise formulating the text more carefully in order to prevent superfluous treatment. Our suggestion is to use prothrombin complex or fresh frozen plasma in case of haemodynamical instability. When the INR is above 1.5 this should be corrected in case of active bleeding and/or haemodynamical instability. If not, the use of vitamin K will be sufficient.

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1. Choudari CP, Rajgopal C, Palmer KR. Acute gastrointestinal haemorrhage in anticoagulated patients: diagnoses and response to endoscopic treatment. Gut 1994;35:464-6.

REACTION FROM AUTHOR

Gaytant *et al.* have a semantic problem with the word 'or' in the paragraph on use of oral anticoagulant therapy in the guideline on bleeding in the gastrointestinal tract. First of all, it is regrettable that they did not use the opportunity to discuss specific comments through the website of the NIV prior to acceptance and publication of this guideline.
Gaytant *et al.* state that if the patient with bleeding and on coumarin therapy is haemodynamically stable with an INR within the therapeutic range, treatment with vitamin K is sufficient. They state that treatment with prothrombin complex is expensive and potentially risky. They are correct in stating that the advice to use prothrombin complex or fresh frozen plasma in these cases is based on expert opinion and not on evidence-based data. However, sound data are not available in the literature, so an expert-based opinion is all the committee had. If a patient presents with upper gastrointestinal bleeding the clinician can never predict for certain whether the patient will stay haemodynamically stable or whether the patient will go into hypovolaemic shock due to massive ongoing or recurrent bleeding. Use of coumarins is a definite risk factor. Haemodynamic stability in these patients can change dramatically in a matter of seconds. Endoscopy is necessary to determine the cause of bleeding and make an estimation on the risk of recurrent bleeding. If one bears in mind that mortality rates of upper gastrointestinal ulcer bleeding are still around 10%, regardless of all endoscopic therapy, it is advisable and safe to counteract the effects of coumarin use with the 'expensive' and 'risky' prothrombin complex or fresh frozen plasma. This is even more important since in normal daily practice it is often not possible to do immediate endoscopy and, hence, establish the cause of bleeding. Of course not every 'bleed' is a bleed, and not every bleed is clinically significant. Every clinician, in the daily emergency practice usually a resident, should take a careful medical history and make a clinical estimation of risk factors before asking for endoscopy or before starting treatment with prothrombin complex. If the patient appears to have significant bleeding or has many risk factors than it is certainly advisable to counteract the effects of coumarin derivates in the only proper way. The text of the guideline was very carefully formulated. It is a guideline and not a protocol. It is up to the judgement of every individual clinician whether he or she will take the risk of ongoing or recurrent bleeding when deciding to use oral anticoagulant therapy.

R.J.L.F. Loffeld
Chairman of the steering committee on the 'Guideline bleeding in the digestive tract', Zaans Medical Centre, Zaandam

ANSWER TO PHOTO QUIZ (ON PAGE 38)

MALAISE, ANOREXIA, PROGRESSIVE LIMB PARESIS AND MULTIPLE DEFECTS IN THE KIDNEYS

An arteriogram of the left kidney confirmed the diagnosis of polyarteritis nodosa, demonstrating multiple microaneurysms (*figure 3*). Serology revealed an active hepatitis B infection. He was treated with pulse cyclophosphamide, prednisolone and lamivudine.
In classic polyarteritis nodosa, in which medium-sized or small arteries are involved, pulmonary capillaritis is unusual. However, involvement of arterioles, venules and capillaries (the last being responsible for pulmonary damage) are described. Cardiac involvement of polyarteritis nodosa may form another explanation for the abnormalities found on the chest X-ray in this patient. Indeed, cardiomyopathy was found by echocardiography, which might have been responsible for cardiac pulmonary oedema.

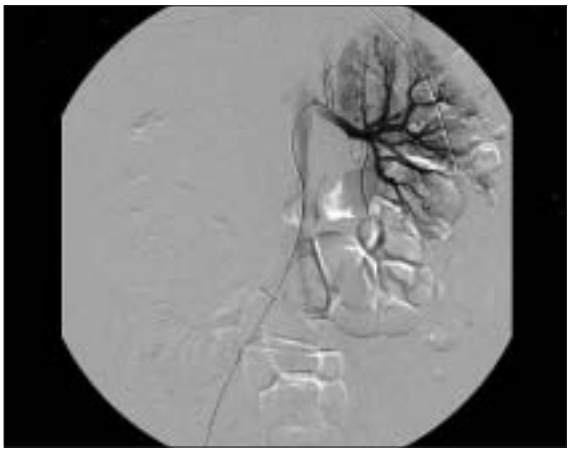

Figure 3

DIAGNOSIS

Hepatitis B associated polyarteritis nodosa.

ABOUT THE COVER

'Sporen van Leven?'

Paula van den Elshout

Paula van den Elshout, a graphic artist from Rotterdam, attended the Free Academy of Art there. To a great extent, her work expresses her own experiences and emotions; reflections of these emotions can be recognised in the characters in her work and in the titles her work has been given. Most of them are metaphorical. Van den Elshout experiences her work as an archaeological excavation: digging for pieces from long ago, sometimes of humanity, sometimes of her personal past.

Since 2000 she has been exposing her work in several group exhibitions, including Kunst Ahoy Rotterdam, Open Monumentendag and SFGalerie Rotterdam.

This print, entitled 'Sporen van Leven?',is a polymer etching on Arches etching paper. An original print is available at a price of € 80 from Galerie Unita, Rijksstraatweg 109, 6573 CK Beek-Ubbergen, the Netherlands or by e-mail: galerie-unita@planet.nl.

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Language
The language of the Journal is English. English idiom and spelling is used in accordance with the Oxford dictionary. Thus: Centre and not Center, Tumour and not Tumor, Haematology and not Hematology.

Preparation of manuscripts
Type all pages with double spacing and wide margins on one side of the paper. To facilitate the reviewing process number the pages; also we would appreciate seeing the line numbers in the margin (Word: page set-up – margins – layout – line numbers). Divide the manuscript into the following sections: Title page, Abstract, Introduction, Materials and methods, Results, Discussion, Acknowledgements, References, Tables and Figures with Legends.

A *Covering letter* should accompany the manuscript, identifying the person (with the address, telephone and telex numbers, and e-mail address) responsible for negotiations concerning the manuscript: the letter should make it clear that the final manuscript has been seen and approved by all authors. Conflicts of interest, any commercial affiliations, consultations, stock or equity interests should be specified. In the letter 1-3 sentences should be dedicated to what this study adds. All authors should sign the letter.

The *Title page* should include authors' names, degrees, academic addresses, address for correspondence including telephone, fax and e-mail, and grant support. Also the contribution of each author should be specified.
The title should be informative and not exceed 90 characters, including spaces. Avoid use of extraneous words such as 'study', 'investigation' as well as priority claims (new, novel, first). Give a running title of less than 50 characters. If data from the manuscript have been presented at a meeting, list the name, date and location of the meeting and reference and previously published abstracts in the bibliography. Give a word count (including references, excluding tables and legends) at the bottom of this page.

Subheadings should not exceed 55 characters, including spaces.

Abbreviations: Measurements should be abbreviated according to SI units. All other abbreviations or acronyms should be defined on the first appearance in the text. Use a capital letter for proprietary names of substances and materials. At first mention of a chemical substance, use the correct chemical designation as well as the generic name.

The *Abstract*, not exceeding 200 words, should be written in a structured manner and with particular care, since this will be the only part of the article studied by some readers. In original articles, the abstract should consist of four paragraphs, labelled Background, Methods, Results, and Conclusion. They should briefly describe the problem being addressed in the study, how the study was performed and which measurements were carried out, the most relevant results, and what the authors conclude from the results.

The *Introduction* should be brief and set out the purposes for which the study has been performed.

The *Materials and methods* should be sufficiently detailed so that readers and reviewers can understand precisely what has been done without studying the references directly. The description may be abbreviated when well-accepted techniques are used.

The *Results* should be presented precisely without discussion.

The *Discussion* should directly relate to the study being reported. Do not include a general review of the topic, but discuss the pertinent literature.

Acknowledgement: All finding sources should be credited here. Also a statement of conflicts of interest should be put here.

References should be numbered consecutively (in square brackets) as they appear in the text. Type the reference list with double spacing on a separate sheet. References should be conform the 'Vancouver' style for biomedical journals (N Engl J Med 1991;324:424-8). Journal abbreviations should conform to the style used in the Cumulated Index Medicus. Examples:

1. Smilde TJ, van Wissen S, Wollersheim H, Kastelein JJP, Stalenhoef AFH. Genetic and metabolic factors predicting risk of cardiovascular disease in familial hypercholesterolemia. Neth J Med 2001;59:184-95.
2. Kaplan NM. Clinical Hypertension. 7th ed. Baltimore: Williams & Wilkins; 1998.
3. Powell LW, Isselbacher KJ. Hemochromatosis. In: Braunwald E, Fauci AS, Kasper DL, et al., editors. Harrison's Principles of Internal Medicine. 15th edition. New York: McGraw-Hill; 2001. p. 2257-61.

Please note that the first six authors should be listed; when seven or more, list only the first three and add *et al*. Do not include references to personal communications, unpublished data or manuscripts either 'in preparation' or 'submitted for publication'. If essential, such material may be incorporated into the appropriate place in the text. Recheck references in the text against reference list after your manuscript has been revised.

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Figures must be suitable for high-quality reproduction. Submit line drawings made in Word or other computer programmes but not in a PowerPoint file. India ink drawings or sharp, strongly contrasting photographic prints on glossy paper are also acceptable. Lettering should be complete, of professional quality, and of a size appropriate to that of the illustration of drawing, with the necessary reduction in size taken into account. Figures should be no larger than 12.5 x 18 cm. Submit half-tone illustrations as black-and-white prints on glossy paper, with as much contrast as possible. Identify each figure on the back with a typed label, which shows the number of the figure, the name of the leading author, the title of the manuscript and the topside of the figure. Colour figures are occasionally possible and will be charged to the authors.
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