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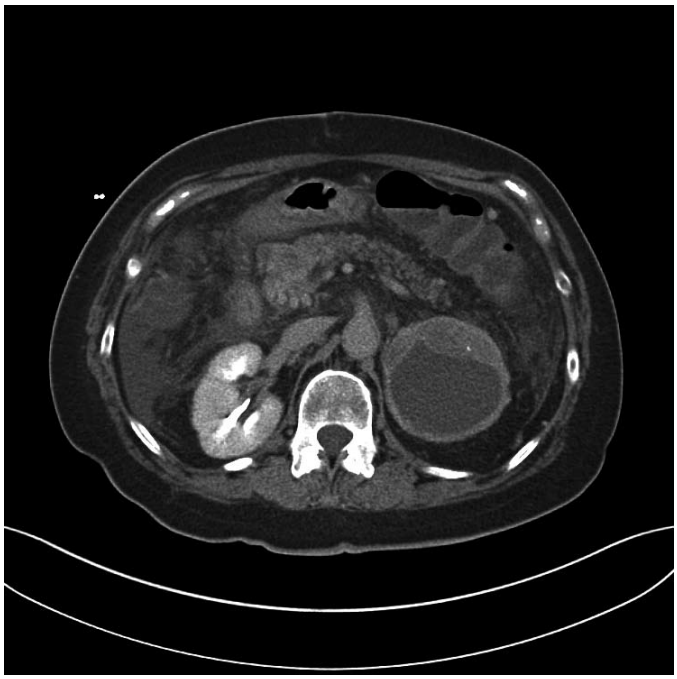

PHOTO QUIZ: Undulating blood pressure, see page 212

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Geeralien Derksen-Willemsen
Radboud University Nijmegen Medical Centre
Department of General Internal Medicine 463
PO Box 9101
6500 HB Nijmegen
The Netherlands
Tel.: +31 (0)24-361 04 59
Fax: +31 (0)24-354 17 34
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EDITORIAL

Pyogenic liver abscess – predicting failure to improve outcome

Y.F.A. Chung

Department of General Surgery, Singapore General Hospital, Outram Road, Singapore 169608,
e-mail: alexander.chung.y.f@sgh.com.sg

Pyogenic liver abscess (PLA) has been and still is a life-threatening medical emergency. Newer potent antibiotics, improved critical care and advances in imaging have lowered mortality in patients with PLA. The shift from surgery to percutaneous decompression as the first-line treatment is also perceived to lower mortality, albeit the lack of robust comparative data.[1] This underlies Chen *et al.*'s effort in defining poor prognostic factors in patients with PLA in the hope of advocating more aggressive treatment to further improve outcome.[2]

Chen *et al.* classified the poor prognostic factors to patient's severity of health, assessed by the Acute Physiology And Chronic Health Evaluation (APACHE) II score, and characteristics of the offending pathology. The systemic effects of sepsis with multi-organ failure as poor prognostic factors are well borne out in many large retrospective studies, while malignancy especially associated with the hepatopancreaticobiliary type carries a grave prognosis (*table 1*).[3-10] However, these easily recognisable features need not be scored with the tedious APACHE score by busy clinicians to warrant aggressive intensive critical care.

Of particular interest in this recent work is the finding of multi-drug resistant (MDR) isolates and anaerobes to be poor prognostic factors. Clinicians should be aware of the potential need for more potent drugs according to isolate sensitivity and the continual inclusion of metronidazole in systemic antibiotics for PLA. Other local factors previously described include rupture, multiple abscesses, gas-forming, large size and multi-loculation.[3,5-7,9] Multivariate analysis has not shown them to be independent risk factors in most studies. While the reasons are not fully apparent in these retrospective series, local factors may be the all important elements in deciding aggressive treatment.

What is aggressive treatment? Other than aggressive intensive critical care, the authors' suggestion that open surgical drainage is the more aggressive treatment is contentious. It is, however, the surgical dictum

Table 1. *Large retrospective studies with poor prognostic factors in patients with pyogenic liver abscess*

		Independent risk factors*		
Study, reference	**No.**	**Systemic**	**Local**	**Mortality (%)**
Chen *et al.*[2] (Taiwan)	253	APACHE II ≥15 Urea↑	Gas-forming, MDR, anaerobe	9.1
Chou *et al.*[3] (Taiwan)	352	Sepsis Age↑, bilirubin↑, urea↑, creatinine↑, albumin↓	-	19.6
Chu *et al.*[4] (Hong Kong)	83	Concomitant malignancy, bilirubin↑, prothrombin time↑	-	18
Barakate *et al.*[5] (Australia)	89	Concomitant malignancy	-	8
Alvarez *et al.*[6] (Spain)	133	Sepsis, shock Urea↑, haemoglobin↓	Biliary origin, multiple abscess	14
Lee *et al.*[7] (Taiwan)	135	Sepsis	-	6
Ruiz *et al.*[8] (Spain)	84	Sepsis, shock	-	19
Ng *et al.*[9] (Hong Kong)	143	Urea↑, prothrombin time↑	Size (mean diameter 6.5 cm)	13

APACHE = Acute Physiology And Chronic Health Evaluation score; MDR = multi-drug resistant. *Multivariate analysis.

to operate on patients with peritonitis from abscess rupture, concomitant ruptured viscus or other causes of concomitant surgical abdomen. Otherwise, percutaneous drainage is the appropriate first-line intervention to reduce the septic load without additional stress to the patient's decompensated health.[1] While this procedure may be complementary in certain situations, the guidelines and monitoring of endpoints of failure are not well defined. Its failure can lead to the continual sepsis and superinfection with MDR alluded to earlier with grave consequences. Logically, the two local factors that may hamper effective decompression to aid resolution of sepsis are large size and multi-loculation, hence the proposal by some investigators for open surgery in these abscesses.[11,12]

It borders on a thin ethical line to propose randomised comparative studies between surgery and percutaneous drainage. Informed consent from patients will be difficult to obtain, on top of potential legal implications of subjecting them to a more invasive and risky alternative. Thus, there is a need for prospective protocols with standardised parameters and well-defined endpoints of therapy to elucidate these potential local risk factors in large, multicentred trials. Currently, the appropriate aggressive management of patients with PLA benefits from local experiences which individualise therapy according to the patient's clinical status and local factors.

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REVIEW

Reality of severe metformin-induced lactic acidosis in the absence of chronic renal impairment

L.A. Bruijstens[1], M. van Luin[2], P.M.M. Buscher-Jungerhans[3], F.H. Bosch[1*]

Departments of [1]Internal Medicine, [2]Clinical Pharmacy and [3]Anaesthesiology, Rijnstate Hospital, PO Box 6500, 6800 TA Arnhem, the Netherlands, [*]corresponding author: tel.: +31 (0)26-378 74 46, e-mail: FH.Bosch@alysis.nl

ABSTRACT

Background: Lactic acidosis in metformin use is a widely recognised but rare side effect. Case reports usually describe elderly patients with conditions which in themselves can cause lactic acidosis or with known contraindications to metformin. We present cases of an elderly woman, a younger woman and a man who developed serious metformin-induced lactic acidosis in the absence of chronic renal impairment.

Results: Laboratory results showed acute renal failure in all patients. The pH was 6.77, 6.98 and 6.7, respectively, and lactate levels were 18.2, 18.4 and 11.7 mmol/l, respectively. Metformin plasma levels were 58, 57 and 39 mg/l. All patients received continuous veno-venous haemofiltration (CVVH), using bicarbonate as a buffer solution shortly after arrival on our ICU. In the subsequent hours, a steep decline in the plasma levels was observed, with a concomitant increase in pH. No other diagnoses were made, so we concluded that all patients were suffering from metformin-induced lactic acidosis. Despite the severity of the metabolic acidosis, both female patients survived. Our male patient died after a prolonged stay in the ICU, but this was not related to metformin.

Conclusion: Metformin-induced lactic acidosis does exist. Metformin-induced lactic acidosis may occur in patients with previously normal renal function, even in young patients. Patients with extreme (lactic) metabolic acidosis caused by metformin can survive when CVVH treatment is initiated rapidly. Intercurrent symptoms or diseases that affect renal perfusion can precipitate lactic acidosis.

KEYWORDS

Continuous veno-venous haemofiltration, lactic acidosis, metformin

INTRODUCTION

Metformin is a biguanide that is widely used in the treatment of type II diabetes mellitus. Its association with lactic acidosis is rare with an estimated incidence of 6.3 per 100,000 patient years.[1] Mortality is described as being about 50%.

Most reports describe cases of patients with concurrent conditions, such as advanced age, liver disease, alcoholism, cardiopulmonary disease or renal failure, which in themselves can cause lactic acidosis or metformin accumulation. Other reports describe self-inflicted or accidental overdose. We present three patients who all used metformin and developed serious lactic acidosis in the absence of chronic renal impairment.

CASE REPORTS

Patient A, a 45-year-old woman with a history of diabetes mellitus type II, mental retardation and bipolar disorder presented to the accident and emergency department (A&E) after she had collapsed at home and had not regained consciousness. She had been nauseous, with vomiting and experiencing diarrhoea for about a week. She was on metformin 500 mg three times daily and flupentixol 40 mg once every two weeks. At presentation, she was first suspected of having a neurological disorder. After computed tomography imaging of the brain showed no signs of brainstem infarction or basilaris thrombosis, lumbar puncture was performed and revealed no abnormalities. She became haemodynamically unstable, was intubated and transferred to our ICU where she was ventilated. Laboratory results showed renal failure and lactic acidosis (serum urea 30.8 mmol/l, serum creatinine 1177 µmol /l, pH 6.77, bicarbonate 5 mmol/l, and lactate

18.2 mmol/l). CVVH with a bicarbonate buffer solution was started three hours after hospitalisation. Dopamine and noradrenaline were continued for three days. Nine days after admission the CVVH was stopped, and she was extubated. Five days later she was transferred to a general medical ward where she needed no further renal replacement therapy. After six days on the ward she was discharged with normal renal function. Her creatinine was 77 µmol/l. On specific questioning, she reported taking all her medications as prescribed and denied an intentional overdose. This was confirmed by her parents.

Patient B, a 69-year-old woman, presented to the A&E complaining of drowsiness and hypoglycaemia. Her medical history included diabetes mellitus type II, multiple cerebral infarctions and cardiovascular disease. On admission she was on acetylsalicylic acid, carvedilol, furosemide, gliclazide, telmisartan, atorvastatin, insulin and metformin one gram three times daily. She had been experiencing nausea, vomiting and diarrhoea for a couple of days. On examination her airway was clear and secured, saturation was 99%, but ventilation was manually assisted, blood pressure could not be measured and her pulse was weak. She was given a total of 1.5 mg atropine, fluids and glucose intravenously. She remained comatose and bradycardic, and dopamine and isoprenaline were started. A cardiac arrest was treated with 1 mg of adrenaline and a short episode of cardiac massage. Laboratory results then revealed renal failure (potassium level of 9 mmol/l, serum urea 29.9 mmol/l, and serum creatinine 458 µmol/l). Blood gas analysis showed pH 6.98, bicarbonate 5.3 mmol/l, pO_2 7.7 kPa, pCO_2 3.08 kPa, and lactate 14.8 mmol/l. Still in a coma, she was taken to the ICU where she was intubated and ventilated. By then she had become anuric and CVVH with a bicarbonate buffer solution was started five hours after admission. Blood glucose levels had normalised. Further physical examination revealed only subtle pre-existing oedema on the lower legs. After CVVH was commenced her condition started to improve. Blood gas analysis was normal within 20 hours and one day later she regained consciousness. Three days after admission the CVVH was stopped and she could be extubated. After five days on our intensive care she was transferred to a general medical ward. She was discharged after another 14 days. Her haemodynamic and ventilatory status remained stable and she needed no further renal replacement therapy. Her creatinine concentration was 165 µmol/l.

Patient C, a 72-year-old man, with a history of type II diabetes mellitus, mild valvular heart and peripheral vascular disease and *Staphylococcus aureus* bacteriaemia presented to our A&E comatose and in respiratory distress. He had been experiencing gastrointestinal discomfort for days. Laboratory results showed renal failure and lactic acidosis (serum urea 50 mmol/l, serum creatinine 811 µmol /l, pH 6.70 and lactate 11.7 mmol/l). He was on metformin 1000 mg three times daily, tolbutamide, simvastatin, hydrochlorothiazide and enalapril. He was immediately intubated and transferred to the ICU where he was put on a noradrenaline infusion. Cultures remained negative and the cardiologist excluded the possibility of endocarditis. Six hours after hospitalisation, CVVH with bicarbonate buffer solution was started. After 30 days his intensive care stay had been complicated by catheter sepsis and ventilator-acquired pneumonia. He could not be extubated within 30 days of ICU stay. Eventually a tracheotomy was performed. Fifty days after admission he became haemodynamically unstable, developed an ileus and had progressive necrosis of his lower extremities. It was decided that further medical treatment would not be beneficial and he died after all therapies had been discontinued.

Regarding our patients' medication regimes it has to be noted that patients B and C were both on drugs that inhibit the renin-angiotensin-aldosterone system. These drugs are known to possibly cause renal function disorders. Both patients had been using these drugs for a longer period of time in which renal function had always been normal. Unfortunately, the exact duration of treatment with metformin in our patients prior to presentation at the emergency room was unknown.

DISCUSSION

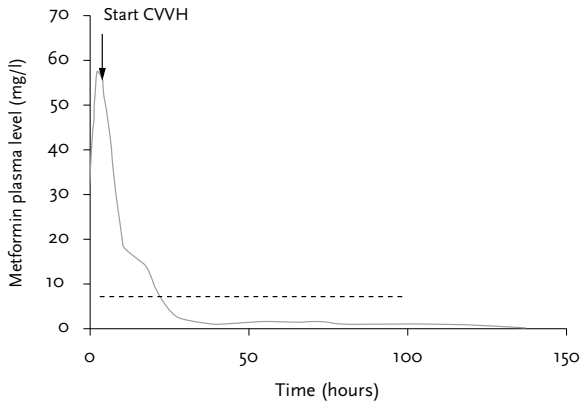
Pharmacokinetics of metformin

After oral intake, metformin has a maximum plasma level at 2.5 hours. When large amounts of metformin are swallowed, maximum plasma levels may appear later.[2] Protein binding of metformin is negligible. The mean volume of distribution is 63 to 276 litres. These two properties of metformin mean that haemodialysis or haemofiltration can effectively remove metformin from serum. Even low blood flow has appeared to be effective in removing metformin.[3] Metformin is not metabolised and mainly (90%) excreted by kidneys. Tubular secretion and glomerular filtration are considered the major routes of metformin elimination.[2] The blood elimination half-life is around 6.5 hours in patients with a normal renal function.[3] It is prolonged in patients with renal impairment. Reduction in creatinine clearance is proportional to reduction in metformin clearance.

In all patients plasma was taken to determine metformin levels; metformin was measured in plasma using liquid chromatographic-tandem mass spectrometry (LC-MS-MS), at the laboratory of the Department of Clinical Pharmacy

of the University Medical Centre Groningen. In the first hours after hospitalisation, the metformin plasma level increased twofold in patient A. An autointoxication was considered. Approximately three hours after the patient was hospitalised, CVVH was initiated. In the first eight hours of haemofiltration, around two-thirds of the metformin was eliminated and the pH improved from 6.77 to 7.25. Patient B presented with pH 6.98 and a metformin level of 57 mg/l. Approximately five hours after patient B was hospitalised, CVVH was instituted. In this case, metformin appeared to be cleared with a half-life of approximately 12.5 hours. During the first 20 hours of treatment, the pH improved from 6.98 to 7.41. Patient C presented with a pH 6.70 and a metformin level of 39 mg/l, which increased to 45 mg/l within the next four hours. CVVH was initiated three hours after admission to our ICU (two hours after the moment of first metformin measurement). Unfortunately no other measurements of metformin levels were done. His pH improved to normal within 31 hours. *Table 1* shows clinical parameters of all patients, *figures 1* and *2* show metformin levels. In all cases the metformin plasma levels appeared to be extremely high. In controlled clinical trials, maximum metformin plasma concentrations did not exceed 4 mg/l.[2] In our three patients CVVH succeeded in treating the extreme acidosis and stabilising the patients.

Figure 1. *Metformin plasma levels in patient A*



Therapeutic levels generally do not exceed 4 mg/l (dotted line). CVVH = continuous veno-venous haemo-filtration.

Pathophysiology of lactic acidosis

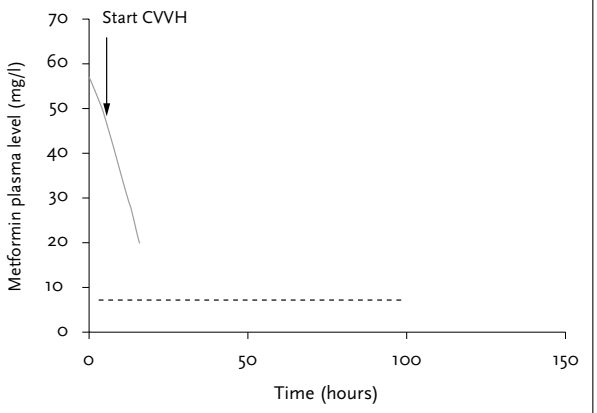
Lactic acidosis is a broad anion gap metabolic acidosis: pH <7.35 and lactate > 5 mmol/l.[4] Cohen and Woods[5] classified lactic acidosis into type A and type B. In general, type A lactic acidosis represents lactate overproduction: situations in which the body has to regenerate ATP in the absence of oxygen. Recently, both experimental and human studies have demonstrated that in situations comparable with hyperkinetic septic shock, skeletal muscle is a

Table 1. *Metformin plasma level, serum lactate and creatinine and pH following severe lactate acidosis*

Date	Time	Metformin plasma level (mg/l)	Creatinine (µmol/l)	Lactate (mmol/l)	pH
Patient A					
1-8-2006	13:59	32.6	1177		ND
	16:42	58.5	1098	18.2	6.77
	23:59	18.7	587	13.1	7.25
2-8-2006	08:00	14.3	356	3.9	7.30
3-8-2006	18:38	2.3	130	1.4	7.33
4-8-2006	08:34	1.4	136	ND	ND
5-8-2006	08:44	1	127	ND	ND
6-8-2006	08:56	1	146	ND	ND
7-8-2006	08:33	0	150	0.8	7.35
Patient B					
27-10-2006	12:48	ND	440	18.4	6.98
	16:00	57	358	12.3	7.20
	20:00	50	314	7.7	7.29
28-10-2006	08:00	20	161	2.7	7.41
29-10-2006	08:00	ND	142	ND	ND
Patient C					
22-2-2007	13:15	ND	811	11.6	6.70
22-2-2007	16:00	39	ND	13.7	7.00
22-2-2007	20:00	45	ND	10.6	6.96
23-2-2007	02:00	ND	ND	15.4	7.27
23-2-2007	08:00	ND	423	8.9	7.28
23-2-2007	20:30	ND	345	3.4	7.38

ND = not done.

Figure 2. *Metformin plasma levels in patient B*



Therapeutic levels generally do not exceed 4 mg/l (dotted line). CVVH = continuous veno-venous haemo-filtration.

leading source of lactate production by exaggerated aerobic glycolysis through Na^+/K^+ /ATP-ase stimulation.[6] This creates a hyperlactataemia that is not mainly caused by hypoxia. Type B lactic acidosis represents underutilisation of lactate and involves impaired removal of lactic acid by oxidation or gluconeogenesis. So, high lactate production can be caused by aerobic or anaerobic causes. Furthermore, a decrease in lactate clearance may contribute to high lactate levels.

Lactic acidosis and metformin

For about 40 years, metformin has been used in the treatment of diabetes mellitus type II. The UK Prospective Diabetes Study Group provided evidence that metformin reduced the risk of morbidity and death in treatment of diabetes mellitus type II.[7] Known side effects are nausea, anorexia, and diarrhoea and lactic acidosis. In order to record the incidence of fatal and nonfatal lactic acidosis per patient-year, Salpeter *et al.*[1] reviewed all studies of metformin treatment from 1966 up to August 2005. Their data revealed no cases of fatal or nonfatal lactic acidosis. Also, there was no difference in lactate levels between metformin and placebo or other treatment groups. They concluded that there is no evidence that metformin is associated with an increased risk of increased lactate levels or lactic acidosis. Nevertheless, over the last years, several case reports have been published on the association between metformin and lactic acidosis. Lalau and Race[8] suggested the link between metformin and lactic acidosis should be carefully referred to as metformin-unrelated, metformin-associated (metformin and concurrent pathologies as co-precipitating factors of lactic acidosis) or metformin-induced (metformin as the only precipitating factor). To be able to distinguish between the terms suggested by Lalau and Race and to make data more comparable, at the very least reports should publish metformin levels, serum creatinine levels, arterial lactate levels, history of concurrent pathologies and a clear context of the case.

The pathogenesis of metformin-associated lactic acidosis is not completely understood. Metformin has affinity for the mitochondrion membrane.[9,10] Due to this affinity, metformin affects the electron transport (NADH concentration increases) and thereby inhibits oxidative metabolism. Especially when metformin levels are high, oxidative phosphorylation is reduced and aerobic metabolism switches to anaerobic metabolism. Metformin can also delay or decrease gastrointestinal glucose absorption, hepatic gluconeogenesis, and increase intestinal lactate production and peripheral insulin-related glucose reuptake.

Metformin accumulation

Since metformin clearance is mainly renal, it seems logical to expect metformin accumulation in high serum creatinine levels in oliguric or anuric patients. However, in Stades' case series,[11] the severity of renal failure expressed as serum creatinine levels neither correlated with lactate levels nor with metformin levels. Other mechanisms of metformin accumulation have been suggested. One case report describes metformin accumulation in a patient with intestinal obstruction due to volvulus in the absence of renal failure.[12] An animal experiment used to examine the relationship between metformin levels and intestinal obstruction indeed showed metformin retention but no accumulation or lactic acidosis.[12] In cases where lactic acidosis is accompanied with high serum creatinine levels, the plasma concentration of metformin is not necessarily abnormally high. On the other hand patients with previously normal renal function and acute renal failure in the A&E can have high metformin levels. The latter situation could suggest that renal failure had a gradual onset. Metformin levels do not have to be extremely high to cause lactic acidosis. But once lactic acidosis has commenced, it can cause or aggravate any organ failure. Onset of renal failure and last intake of metformin seem essential in determining whether renal failure is primary or secondary to concurrent conditions precipitating lactic acidosis. Metformin levels are important in the context, but do not predict outcome.

Treatment of lactic acidosis in metformin use

The mainstay of treatment involves repairing acid-base balance, removing causes of lactic acidosis and supportive therapy. Haemodialysis with bicarbonate replacement fluid has been used successfully in the treatment of lactic acidosis in metformin use. Haemodialysis not only corrects the acidosis but also efficiently removes metformin from plasma,[13] preventing further lactate overproduction and

removes lactate. Although haemofiltration is thought to treat lactic acidosis (regardless of metformin use), kinetic studies of lactate removal, however, suggest that removal can not significantly counteract lactate production.[14] In haemodynamically unstable patients, continuous renal replacement therapy (CRRT) does the same things more gradually than conventional haemodialysis and could therefore be considered preferable. A disadvantage compared with conventional haemodialysis could be the relatively slower clearance rate.[15] Activated charcoal can absorb metformin and prevent absorption by the intestines so it is recommended in treating metformin overdose. Sodium bicarbonate or dichloroacetate are controversial treatments.

We have presented three patients who developed lactic acidosis in the absence of other causes of lactic acidosis. We have emphasised their previously normal renal function. Several reports have also described patients with previously normal renal function and a pH less than 7.00. Stades *et al.*[11] published data of 47 cases of metformin use and lactic acidosis. Of those 47 patients, eight had no history of chronic renal failure, had a pH less than 7.00 and survived. Of these eight, all had acute renal failure, two had a history of cardiovascular disease, two had been given contrast fluid intravenously, four were in shock, one had a history of alcoholism, one had a history of COPD and two had sepsis on admission.

In our series, all patients had been suffering from gastrointestinal symptoms prior to admission. These symptoms could have been side effects of metformin or first signs of a developing lactic acidosis. Moreover, these symptoms could have deteriorated their previously normal renal function by dehydration. They all had acute renal failure, were haemodynamically unstable and in respiratory distress. Since there were no other reasonable explanations for lactic acidosis, in all patients a diagnosis of metformin-induced lactic acidosis was made.

In all three cases it is likely that due to pH alterations caused by elevated lactate, metabolism changed and negative effects of metformin accumulated. Changes in acid-base balance probably caused the deterioration. They all had high metformin levels, which could have been a sign of gradual onset of lactic acidosis and relatively acute renal failure.

Even though our patients did not experience chronic renal failure, their acute reversible prerenal failure prior to hospital admission, combined with ongoing use of metformin, could have caused a series of events eventually leading to metformin accumulation and lactic acidosis.

Our series is in accordance with the hypothesis that neither the level of lactate nor the level of plasma metformin predicts outcome.[11,16] Serum creatinine does not necessarily appear to be associated with metformin levels or outcome either. Our two female patients had normal renal function before admission, acute renal failure on presentation and improved renal function after discharge.

As mentioned, our patients all experienced gastrointestinal discomfort prior to their deterioration. We would like to emphasise the importance of giving patients full information about this side effect. Gastrointestinal symptoms could be the very first sign of developing lactic acidosis and should therefore be closely monitored. Physicians who prescribe metformin should instruct their patients to immediately report the onset of gastrointestinal discomfort. Patients who have been using metformin without side effects and start to develop gastrointestinal discomfort should stop taking metformin until the symptoms have disappeared. Moreover, the presence of any intercurrent disease that may affect renal perfusion should alarm doctors to temporarily stop metformin and/or any drug that influences renal function.

CONCLUSION

Lactic acidosis in metformin use is not only a problem in patients with pre-existing risk factors. In fact, by definition, metformin-induced lactic acidosis is diagnosed in the absence of other causes of lactic acidosis. Neither metformin levels, nor lactate levels, nor creatinine levels seem to predict outcome in lactic acidosis in metformin use. Patients with previously normal renal function and younger patients with no other comorbid conditions at all can develop metformin-induced lactic acidosis. Gastrointestinal discomfort or any intercurrent disease that affects renal perfusion in patients using metformin could precipitate lactic acidosis. CVVH can be a very successful treatment when started aggressively and rapidly, even in patients who have pH levels far below 7.0 and are unstable.

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ORIGINAL ARTICLE

Chronic hepatitis C responds poorly to combination therapy in chronic hepatitis B carriers

H. Senturk[1], V. Tahan[2*], B. Canbakan[1], S. Uraz[3], Y. Ulger[1], R. Ozaras[4], F. Tabak[4], A. Mert[4], G. Ozbay[5]

Departments of [1]Gastroenterology, [4]Infectious Diseases and [5]Pathology, Cerrahpasa Medical Faculty, Istanbul University, Istanbul, Turkey, [2]Department of Gastroenterology, Marmara University School of Medicine, Altunizade, Uskudar, 34662 Istanbul, Turkey, [3]Department of Gastroenterology, Florence Nightingale Hospital, Istanbul, Turkey, [*]corresponding author: tel.: +90 216-326 70 73, e-mail: veytahan@yahoo.com

ABSTRACT

Background: The effect of conventional interferon-based therapy of hepatitis B virus (HBV) and hepatitis C virus (HCV) dual infection is controversial. Yet, no studies have been carried out into pegylated interferon treatment for chronic HBV/HCV coinfection. We aimed to evaluate the response rate and side effects of conventional or pegylated interferon combined with ribavirin on chronic HBV/HCV coinfection therapy.

Methods: The study included 36 chronic hepatitis patients (M/F: 28/8, mean age 47±12 years) who were positive for HBsAg and anti-HCV. They were tested for the presence of HBV-DNA by hybridisation assay, and the samples giving negative results were retested by polymerase chain reaction (PCR). All patients were tested for HCV-RNA using PCR, and the HCV genotype was determined.

Results: Nineteen patients were given standard interferon either alone or in combination with ribavirin, whereas 17 were given pegylated interferon and ribavirin combination therapy. None of the patients had HBV-DNA positivity; however, all had HCV-RNA detectable by PCR. All the patients had HCV genotype 1b. The mean alanine aminotransferase and aspartate aminotransferase levels were 118±65 U/l and 90±95 U/l respectively. Five patients in each group discontinued the treatment due to side effects. Only two patients (one from each group) reached sustained virological response.

Conclusion: Neither pegylated nor conventional interferon based regimes were effective for HBV/HCV coinfection, in which the dominant virus was HCV. Pegylated interferon and ribavirin therapy was not superior to conventional interferon based regimes in the treatment of HBV/HCV coinfection.

KEYWORDS

Chronic hepatitis B, chronic hepatitis C, co-infection, dual infection, pegylated interferon

INTRODUCTION

It is estimated that throughout the world 400 million people are chronically infected with hepatitis B virus (HBV), and 170 million people with hepatitis C virus (HCV).[1,2] Dual infection with HBV and HCV in the same host ranges from 1 to 15%.[3-9] It has been suggested that the actual prevalence of dual infection is much higher in regions where HBV is moderately to highly endemic. There, HBV-DNA can be detected in serum and/or liver tissue in a large proportion of patients with chronic HCV, even in those who are HBsAg negative.[10-12] The literature contains conflicting data on the prognosis of HBV/HCV dual infection. Whereas several studies report that dual infection leads to a more severe histological picture and more rapid progression to cirrhosis,[4-6,13] other studies do not support these findings.[14,15] There are also limited data regarding treatment, since dual infection is an exclusion criterion in all HBV or HCV treatment studies. A few trials indicate that the success rate of interferon monotherapy is very low.[9,16,17] On the other hand, another study in HBV-HCV dual-infected patients reported promising results with interferon-ribavirin combination therapy.[18]

Peginterferon plus ribavirin has yielded higher sustained virological response (SVR) rates compared with conventional interferon plus ribavirin for all genotypes

of chronic HCV monoinfection[19] and is now considered the gold standard of care.[20] However, a study of pegylated interferon treatment for chronic HBV/HCV dual infection is lacking. So far, there has been only one reported case in which a successful therapy response was achieved for both HBV and HCV in dual-infection chronic hepatitis.[21] To the best of our knowledge, our study is the first comprehensive study to evaluate the response rate and side effects of pegylated interferon treatment of chronic HBV/HCV dual infection.

PATIENTS AND METHODS

Patients with chronic HBV/HCV dual infection seen between January 1991 and February 2006 at the Department of Gastroenterology, Cerrahpasa Medical Faculty, University of Istanbul were considered for inclusion. Patients who had acute hepatitis, decompensated cirrhosis or hepatocellular carcinoma were excluded from the study. A total of 1950 chronic HBV or HCV patients were tested for HBsAg, HBeAg, anti-HBe, anti-HBc and anti-HCV positivity by third-generation ELISA. HBV-DNA was tested by the hybridisation technique without amplification, and the samples with negative results were retested by polymerase chain reaction (PCR) (Digene Hybrid-capture; Murex Diagnostics, Dartford, UK). All patients were also tested for HCV-RNA by RT-PCR (Roche, Amplicor, Basel, Switzerland), and the genotype was determined by the acid-guanidium-phenol-chloroform method in the patients who were HCV-RNA positive.[22] We selected 36 treatment-naive, dual-infected patients. Patients were treated according to the regimen that represented standard care at that time. The primary endpoint of the study was HCV SVR. Statistical evaluation was performed using the χ^2 test. A $p<0.05$ value was considered statistically significant.

RESULTS

We recruited 36 chronic HBV/HCV dual-infected patients (mean age 47±12 years) for the purpose of this study (*table 1*). The proportion of male patients was higher (78%; M/F: 28/8).

Five patients had compensated cirrhosis. All patients were HBsAg, anti-HBe and anti-HCV positive. PCR analyses confirmed absence of HBV-DNA, but all 36 patients carried HCV-RNA. The exclusive HCV genotype was 1b. All patients were subjected to a liver biopsy, which showed minimal hepatitis in nine patients, mild disease in 14 patients, moderate disease in eight patients and cirrhosis in five patients. Of the 36 patients, 32 had elevated serum transaminases. Mean alanine aminotransferase (ALAT) levels (118±65 U/l) and aspartate aminotransferase levels (90±95 U/l) were elevated (N: 5-37 U/l).

A total of 17 patients (M/F: 13/4, age: 46±11 year), received the combination therapy of pegylated interferon (16: pegylated interferon α2a 180 µg/week and 1: pegylated interferon α2b 120 µg/week) and ribavirin (1000 or 1200 mg/day); there were four patients with fibrosis stage 3 and two patients with fibrosis stage 4 by Knodell. Nineteen patients (M/F: 15/4, 48±12 years) received conventional interferon combination therapy; six patients had fibrosis stage 3 and three patients fibrosis stage 4 by Knodell. In 5/19 patients (26.3 %), treatment had to be stopped due to the side effects (*table 2*). Fourteen patients completed the therapy. There was no viral response by week 12, and only one patient responded in weeks 24 and 48 and finally reached SVR (*table 3*).

A total of 19 patients were given standard interferon and ribavirin combination therapy for 48 weeks. We discontinued therapy in five patients because of side effects (*table 2*). None of the patients showed an early virological response at week 12. However, we decided to continue the therapy in this special patient group and five patients (29%) were HCV negative at weeks 24 and 48, and

Table 1. *Features of the therapy groups of the chronic hepatitis B and C dual hepatitis, in which the active infection was hepatitis C*

Chronic hepatitis B and C dual hepatitis patients (n=36) (mean ± SD)	Peginterferon and ribavirin combination therapy group (n=17)	Conventional interferon and ribavirin combination therapy group (n=19)	P
Age	46±11	48±12	NS
Sex (male/female)	13/4	15/4	NS
ALAT (N:5-37) U/l	122±64	114±67	NS
ASAT (N:5-37) U/l	92±94	88±96	NS
HCV RNA IU/ml	1996,660±1871,628	2094,420 ± 1764,532	NS
HAI	10.1±3.1	12.1±4.2	NS
Fibrosis	1.8±1.4	2.0±1.6	NS

ALAT = alanine aminotransferase; ASAT = aspartate aminotransferase; NS = not significant; HAI = hepatitis activity index.

Table 2. *Side effects related with the discontinuation of the therapy in chronic hepatitis B and C dual hepatitis patients, in whom the active infection was hepatitis C virus*

Patients	Combination therapy group	Side effect related with the discontinuation of the therapy
Case 1	Pegylated interferon and ribavirin	Nausea, alanine aminotransferase flare
Case 2	Pegylated interferon and ribavirin	Pruritus, severe flare up
Case 3	Pegylated interferon and ribavirin	Pneumonia
Case 4	Pegylated interferon and ribavirin	Severe weakness, low compliance
Case 5	Pegylated interferon and ribavirin	Severe weakness
Case 6	Conventional interferon and ribavirin	Severe weakness, low compliance
Case 7	Conventional interferon and ribavirin	Severe weakness
Case 8	Conventional interferon and ribavirin	Leucopenia
Case 9	Conventional interferon and ribavirin	Leucopenia
Case 10	Conventional interferon and ribavirin	Thrombocytopenia

Table 3. *The therapy responses of the chronic hepatitis B and C dual hepatitis, in which the active infection was hepatitis C*

n (male/female)	Treatment combination	Discontinuation of the therapy for side effect (n) (%)	End of therapy response (n) (%)	Sustained response (n) (%)
17 (13/4)	Peginterferon and ribavirin	5 (29%)	5 (29%)	1 (6%)
19 (15/4)	Conventional interferon and ribavirin	5 (26%)	1 (5%)	1 (5%)

one patient reached SVR (*table 3*). There was no difference between ALAT, viral load or histological severity between those who did reach SVR and those who did not.

DISCUSSION

This study presents the results of retrospective analysis of an HBV/HCV dual-infected cohort. HBV and HCV can coexist and suppress each other's replication,[5,6] indicating a mutual interference.[5,23] In general, HBV replication is most affected, suggesting that HCV plays a dominant role.[5] HCV was the dominant feature in our dual-infected patients.

Few data exist on treatment of dual infection (*table 4*). Response rates with conventional interferon monotherapy have been low. Zignego *et al.* detected HBV-DNA with PCR in the serum of 11/125 successive hepatitis C patients; no SVR was reached with interferon monotherapy.[16] This in comparison with a recent study[18] in 21 chronic HBV/HCV dual-infected patients treated with conventional interferon plus ribavirin. The dominant infection was HCV: 57% were HCV genotype 1 and 43% HCV genotype 2. HCV-RNA was undetectable at 24 weeks, at the end of the treatment, in 9/21 (43%) dual-infected patients, which was similar to the data from 30 HCV monoinfected controls (60%, p=0.63). They concluded that the treatment was as effective as in monoinfection. Hung *et al.* evaluated 36 chronic HBV/HCV dual-hepatitis patients. Adverse events led to withdrawal in three patients receiving conventional interferon. HCV clearance rate was seen in 69% at 48 weeks. Two (11%) of 18 pretreatment viraemic patients had negative serum HBV-DNA (<200 copies/ml). They concluded that conventional interferon and ribavirin combination therapy was effective in achieving sustained HCV clearance in patients with HBV/HCV dual infection[24] and that this combination was more efficient and better tolerated in patients with dual infection compared with HCV infection alone. However, in our patient group with chronic HCV, conventional interferon and ribavirin led to SVR in only 1/19 patients. Indeed, pegylation of interferon increases the half-life and improves the pharmacokinetics of the protein.[25] Although pegylated interferon has not been used in any clinical trials for dual-infected patients (*table 4*),[20] it will replace standard interferon in the treatment protocol of HBV/HCV dual infection. Rautou *et al.* report the only case, a 32-year-old man of Kampuchean origin, with genotype 1. On therapy with pegylated interferon 2a-b plus ribavirin, HCV-RNA became undetectable at weeks 17 and 48 of treatment. Two years after the end of the treatment, HCV-RNA and HBV-DNA were still undetectable. It was concluded that pegylated interferon based combination therapy is effective for both viral infections in dual infection.[21] However, in our group treated with pegylated interferon and ribavirin, only 5/17 patients showed the end of therapy response, and a mere 1/17 patients achieved SVR. In the conventional interferon and ribavirin based therapy, only 1/19 patients reached SVR. In the present study, SVR was achieved only in 2/36 patients. However, the majority of patients were male and were infected with HCV genotype 1. These factors may have an impact on the poor response

Table 4. *Summary of the therapies for chronic hepatitis B and C dual hepatitis patients*

Reference, year	HBV-DNA/ HCV-RNA	n	Treatment x duration	HBV-DNA negative	HCV-SVR
Weltman *et al.*, 1995[17]	-/+	8	IFNα 3 MU tiw x 6 months	NA	NA
Liaw *et al.*, 1997[27]	+/+	15	IFNα 9 MU tiw x 14 weeks or IFNα 4-6 MU tiw x 12 weeks	7%	0% 0%
Zignego *et al.*, 1997[16]	+/+	14	IFNα 3 MU tiw x 12 months	0%	0%
Utili *et al.*, 1999[28]	±/±	16	IFNα 5 MU tiw x 12 months	NA	44%
Guptan *et al.*, 1999[29]	+/+	7	IFNα 6 MU tiw x 6 months	86%	29%
Villa *et al.*, 2001[9]	+/+	30	IFNα 9 MU tiw x 6 months or IFN 6 MU tiw x 6 months	67%	31% 17%
Liu *et al.*, 2003[18]	+/+	21	IFNα 6 MU tiw x 3 months + 3 MU tiw x 3 months + ribavirin x 6 months	35%	43%
Marrone *et al.*, 2004[30]	+/+	8	IFNα 5 MU tiw x 12 months + lamivudine x 18 months	37.5%	50%
Chuang *et al.*, 2005[31]	+/+	42	IFNα 6 MU tiw + ribavirin x 6 months	31%	69%
Hung *et al.*, 2005[23]	+/+	36	IFNα 3-5 MU tiw +ribavirin x 6 months	11%	69%
Present study	-/+	17 19	Pegylated IFN* + ribavirin x 12 months and IFNα 3-4.5 MU tiw + ribavirin x 12 months	NA	6% 5%

HBV = hepatitis B virus; HCV = hepatitis C virus; SVR = sustained viral response; tiw = thrice weekly; IFN = interferon; thrice weekly; NA = not available; *16: peginterferon α2a 180 μg/week and 1: peginterferon α2b 120 μg/week.

rate. Successful treatment of HCV infection may induce HBV reactivation and flaring.[26] We did not observe this, probably due to the poor response rate.

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ORIGINAL ARTICLE

Predictors of mortality in patients with pyogenic liver abscess

S.C. Chen[1,2], S.J. Tsai[2,3], Y.T. Lee[2,4], C.H. Yen[1,2], C.C. Huang[2,5], D.B. Lin[6], P.H. Wang[2,3*], C.C. Chen[1,2*], M.C. Lee[1,3]

Departments of [1]Family Medicine, [4]Internal Medicine and [5]Surgery, [3]Institute of Medicine, and Schools of [2]Medicine and [6]Medical Laboratory and Biotechnology, Chung Shan Medical University, No.110, Sec.1, Jianguo N. Rd., South District, Taichung City 40201, Taiwan, *corresponding authors: tel.: +886-4-2473 95 95 ext. 34955, fax: +886-4-2324 81 37, e-mail: (Dr. C.C. Chen) cccy218@yahoo.com.tw, (Dr. P.H. Wang) phwy222@yahoo.com.tw

ABSTRACT

Background: Pyogenic liver abscess (PLA) is uncommon but potentially life-threatening. The objective of this study was to identify the prognostic factors for PLA.

Methods: The medical records of 253 patients, 148 men and 105 women with a mean age of 56.4 years (SD: 15.0 years), who were hospitalised due to a PLA between January 1995 and June 2007 were reviewed. The underlying medical disorders, clinical signs and symptoms, laboratory values, imaging studies, microbiological features, treatments, morbidity and mortality were recorded. Factors related to in-hospital case fatality were analysed.

Results: The mean Acute Physiology And Chronic Health Evaluation (APACHE) II score at admission in patients with PLA was 8.7 points (SD 5.4 points). The most common co-existing disease was diabetes mellitus (41.9%), followed by biliary stone disorders (32.0%). *Klebsiella pneumoniae* was the most frequent pathogen, followed by *Escherichia coli*. The in-hospital case-fatality rate was 9.1%. Multivariate analysis revealed that gas-forming abscess (p=0.019), multi-drug resistant isolates (p=0.026), anaerobic infection (p=0.045), blood urea nitrogen level >7.86 mmol/l (p=0.004), and APACHE II score ≥15 (p= 0.004) were associated with mortality.

Conclusions: The prognosis of PLA may depend chiefly on the severity of the basic physical condition and underlying pathology. As the primary treatment for PLA is not completely effective, a more aggressive approach should be considered, especially for patients with poor prognosis.

KEYWORDS

Fatal outcome, prognosis, pyogenic liver abscess, retrospective study, risk factors

INTRODUCTION

Pyogenic liver abscess (PLA) is an uncommon but potentially life-threatening disorder with a crude annual incidence rate worldwide ranging from 2 to 45 cases per 100,000 hospital admissions.[1-4] In 1938, Ochsner *et al.* reported the first comprehensive case series of PLA, in which the case-fatality rate was 77%.[5] In the last two decades, the case-fatality rate has decreased to 6 to 26%.[2,3,6-15] Although several attempts to identify predictors of mortality in PLA patients have been made, there is no consensus regarding which factors are proven. Reported prognostic factors for PLA include older age, high Acute Physiology And Chronic Health Evaluation (APACHE) II score, elevated counts of white blood cells, blood urea nitrogen (BUN), serum creatinine, total bilirubin, low levels of serum albumin and haemoglobulin, septic shock, liver abscess of biliary origin, multiple abscesses, concomitant malignancy, and pleural effusion.[1,3,4,6-9,12-15] In some series, liver abscess is less likely to be fatal when caused by *Klebsiella pneumoniae* and is more likely to have a torpid clinical course when caused by *Escherichia coli*.[16,17] Because previous reports of patients with PLA have seldom included bacterial characteristics in the analysis of mortality, we collected microbiological data and other clinical information from PLA patients to identify the prognostic factors for this condition. We also investigated the clinical features, abscess characteristics, causative pathogens, treatments, and outcomes in these patients over a 12-year period.

PATIENTS AND METHODS

Study patients

Medical records of consecutive patients aged 18 years or older who were admitted with a first-time diagnosis of PLA to the Chung Shan Medical University Hospital, a 1250-bed medical centre in Taichung City, Taiwan, between 1 January 1995 and 30 June 2007 were reviewed by a physician. We defined a case-patient as a patient with (a) recovery of bacterial pathogens from blood or liver abscess cultures and (b) identification of one or more discrete abscess cavities in the liver by imaging studies (endoscopic retrograde cholangiopancreatography (ERCP), abdominal ultrasonography (US) and/or computerised axial tomography (CT) scans with contrast enhancement). For each case-patient identified, we reviewed records and abstracted demographic data, underlying medical conditions, clinical features, laboratory data, imaging and microbial findings, and treatment. Altogether, 262 patients were enrolled by an electronic systematic search of the patients' records for diagnostic codes. After review of these patients' records, nine patients were excluded for the following conditions: amoebic liver abscess (n=4), fungal liver abscess (n=2), tuberculous liver abscess (n=1), parasitic liver abscess (n=1), and infected biloma (n=1). The remaining 253 patients with PLA were included in this study.

Parameter definition and collection

The clinical parameters comprised demographic data, underlying medical conditions, the severity of illness at admission (the first 24-hour APACHE II score[18] after admission), the origin of liver abscess, and treatment. The origin of the abscess was based upon the available imaging studies (ERCP, abdominal US and/or CT scans with contrast enhancement) as well as clinical, pathological and/or surgical findings. Abscesses were considered cryptogenic in origin when no causative lesions could be demonstrated. Imaging parameters included location, number, and size of abscesses and the presence of gas-forming abscess, abscess rupture, and pleural effusion. Microbiological parameters included multi-drug resistant (MDR) isolates, bacteraemia, polymicrobial infection, *K. pneumoniae* infection, *E. coli* infection, and anaerobic infection. Multi-drug resistance was defined as resistance to three or more of the antimicrobial classes. Polymicrobial infection was defined as mixed bacterial recovery of blood or abscess cultures. Anaerobic infection was defined as anaerobic isolates yielded from blood or abscess cultures. The abscess specimen obtained from an invasive procedure, including image-guided (US or CT) percutaneous needle aspiration (PNA), image-guided percutaneous catheter drainage (PCD), or a direct surgical approach, had been processed for Gram stain, bacterial cultures (standard aerobic and anaerobic diagnostic methods), and tests for antimicrobial susceptibility. Antimicrobial susceptibility had been determined by the disk diffusion method (BD BBL, Sensi-Disc Antimicrobial Susceptibility Test Discs, Sparks, MD), based upon the pathogen isolated. The results were evaluated according to the recommendations of the National Committee for Clinical Laboratory Standards[19] (now known as the Clinical and Laboratory Standards Institute). Laboratory parameters included white blood cell count, prothrombin time, blood haemoglobin, serum total bilirubin, serum albumin, aspartate aminotransferase, BUN, and serum creatinine.

The initial empirical broad-spectrum antibiotics were given intravenously after the blood and/or liver abscess specimens had been drawn, and the antimicrobial agents were tailored, if necessary, based on the results of the cultures and susceptibility tests. Response to treatment was evaluated in each patient by a series of follow-up US or CT scans of the liver in the hospital and/or subsequent office visits after discharge. Case fatality was defined as death during hospitalisation.

Statistical analysis

Descriptive data were summarised as means with standard deviations (SDs) for continuous data and as percentages for categorical data. Comparisons between groups for continuous variables were made using the Student's t test. Categorical variables were compared between groups using either the χ^2 test or Fisher's exact test (if the expected value of at least one cell was <5), as appropriate. The relation between (a) demographic, clinical, imaging, microbiological, and laboratory factors and (b) mortality were analysed. The statistically significant independent factors obtained by univariate analyses were entered into a multiple stepwise logistic regression model. The prognostic factors independently related to mortality were then identified. Odds ratios (ORs) and their 95% confidence intervals (CIs) were also calculated. Statistical significance was considered to have been achieved when $p<0.05$. All p values were two-tailed.

RESULTS

Demographic data, underlying diseases, and symptoms/signs

The 253 patients with PLA, 148 men and 105 women, were a mean age of 56.4 years (SD 15.0 years) (*table 1*). Prior to admission, these patients were symptomatic for a mean of 5.5 days (SD 4.8 days). The mean APACHE II score at 24 hours after admission was 8.7 points (SD 5.4 points). The mean duration of definite diagnosis made after admission was 2.7 days (SD 6.5 days). The most common co-existing disease was diabetes mellitus, followed by biliary stone

disorders. Twenty patients had concomitant malignancies, which included hepatocellular carcinoma (n=8), colonic carcinoma (n=5), gastric cancer (n=2), cholangiocarcinoma (n=2), brain cancer (n=2), and cervical cancer with colonic metastasis (n=1). The most common symptom/sign was fever/chills (91.3%), followed by right upper quadrant tenderness (49.0%) and abdominal pain (48.6%).

Imaging, laboratory and microbiological findings

Every patient had a chest and plain abdominal x-ray on admission. All patients underwent abdominal US examination, and 88% of patients had an abdominal CT scan with contrast enhancement. The most common origin of liver abscess was biliary tract disorders (29.6%) (*table 2*). No source could be determined in 170 patients, despite thorough investigation. Twenty-four patients (9.5%) had a gas-forming abscess of the liver, and 162 patients (64.0%) had pleural effusion on admission. Among the 24 patients with gas-forming liver abscesses, 23 (95.8%) had diabetes mellitus and 22 (91.7%) had *K. pneumonia* infection. Patients with gas-forming liver abscesses had a higher frequency of diabetes mellitus (p<0.0001) and *K. pneumonia* infection (p<0.05) than those with a non-gas-forming liver abscess. Most abscesses

Table 1. *Demographic data, underlying diseases, and presenting symptoms/signs in 253 patients hospitalised with pyogenic liver abscess, 1995-2007*

Variable	No. (%) of patients
Gender, male/female	148 (58.5)/105 (41.5)
Age, mean ± SD (years)	56.4 ± 15.0
Duration of symptoms before admission, mean ± SD (days)	5.5 ± 4.8
Duration of diagnosis made after admission, mean ± SD (days)	2.7 ± 6.5
APACHE II score at admission, mean ± SD (points)	8.7 ± 5.4
Underlying diseases:[1]	
• Diabetes mellitus	106 (41.9)
• Biliary stone disorders[2]	81 (32.0)
• Alcoholism	29 (11.5)
• Liver cirrhosis	28 (11.1)
• Uraemia	24 (9.5)
• Malignancy	20 (7.9)
Symptoms:[1]	
• Fever/chills	231 (91.3)
• Abdominal pain	123 (48.6)
• Malaise	99 (39.1)
• Respiratory symptoms[3]	90 (35.6)
• Anorexia	72 (28.5)
• Nausea/emesis	68 (26.9)
• Weight loss	19 (7.5)
• Diarrhoea	18 (7.1)
Signs:[1]	
• Body temperature >38.3°C	219 (86.6)
• RUQ tenderness	124 (49.0)
• Jaundice	69 (27.3)
• Shock	40 (15.8)
• Murphy's sign[4]	39 (15.4)
• Hepatomegaly	23 (9.1)
• Disturbance of consciousness	14 (5.5)
• Ascites	10 (4.0)

APACHE = Acute Physiology and Chronic Health Evaluation; RUQ = right upper quadrant; SD = standard deviation. [1] When patients fit into more than one category, they were counted in each category. [2] Biliary stone disorders: cholelithiasis, choledocholithiasis, or hepatolithiasis. [3] Respiratory symptoms: cough, short of breath, and/or chest pain. [4] Murphy's sign: deep inspiration or cough during subcostal palpitation of the RUQ producing increased tenderness and inspiratory arrest.

Table 2. *Abscess, imaging, laboratory and microbiological characteristics in 253 patients hospitalised with pyogenic liver abscess, 1995-2007*

Variable	No. (%) of patients
Origin of abscess:	
• Biliary origin[1]	75/253 (29.6)
• Cryptogenic origin	170/253 (67.2)
• Others[2]	8/253 (3.2)
Location of abscess:	
• Right lobe	181/253 (71.5)
• Left lobe	38/253 (15.0)
• Caudate lobe	2/253 (0.8)
• Bilobar involvement	32/253 (12.6)
Abscess size, diameter:	
• <5 cm	102/253 (40.3)
• 5-10 cm	128/253 (50.6)
• >10 cm	22/253 (9.1)
Number of abscess:	
• Solitary	171/253 (67.6)
• Multiple	82/253 (32.4)
Gas-forming abscess	24/253 (9.5)
Rupture of liver abscess	3/253 (1.2)
Pleural effusion	162/253 (64.0)
Laboratory studies:	
• White blood cell count >10 x 10^9/l	191/253 (75.5)
• Haemoglobin <8.68 mmol/l in male, <7.44 mmol/l in female	196/253 (77.5)
• Aspartate aminotransferase >0.67 µkat/l	173/253 (68.9)
• Serum total bilirubin >20.52 µmol/l	88/253 (34.8)
• Blood urea nitrogen >7.86 mmol/l	58/253 (22.9)
• Serum creatinine >115 µmol/l	64/253 (25.3)
• Serum albumin <35 g/l	130/211 (61.6)
• Prothrombin time >13.1 seconds	38/141 (27.0)
Microbiological studies:	
• Bacteraemia	171/249 (68.7)
• Polymicrobial infection[3]	28/253 (11.1)
• Anaerobic infection[4]	19/253 (7.5)
• MDR isolates	22/253 (8.7)

MDR = multi-drug resistant. [1] Biliary origin of liver abscess including suppurative cholangitis and acute cholecystitis. [2] Other origin of liver abscess including subphrenic abscess (n=4), recent surgery (n=2), and receiving transcatheter arterial embolisation for hepatocellular carcinoma (n=2). [3] Polymicrobial infection: a mixture of different bacteria growing in blood or abscess cultures. [4] Anaerobic infection: anaerobic isolates growing in blood or abscess cultures.

(71.5%) were located in the right lobe of the liver. Multiple abscesses were present in 82 patients (32.4%). The liver abscess ruptured in three patients during hospitalisation. The most common laboratory abnormality was low serum haemoglobin level, which was seen in 77.5%.

The recovery frequency of blood culture was 68.7% (171/249 patients) with 184 isolates obtained in patients who had blood cultures. The recovery percentage of abscess cultures was 94.6% (227/240 patients) with 276 isolates in patients in whom abscess cultures were obtained. *K. pneumoniae* was the most commonly isolated aerobe in both blood and abscess cultures, followed by *E. coli* (*table 3*). Twenty-eight (11.1%) of the infections were polymicrobial. *Bacteroides fragilis* was the most frequently isolated anaerobic organism. Nine out of the 11 streptococci isolates obtained from abscess cultures were *Streptococcus constellatus* while the remaining two belonged to α-haemolytic viridans streptococci. Anaerobic isolates from blood and/or abscess cultures were found in 19 patients (7.5%). Among the 19 patients with anaerobic infection, 15 were infected with polymicrobial pathogens. MDR isolates were cultured in 22 patients (8.7%).

Table 3. *Microbiological spectra in patients with pyogenic liver abscess in 253 patients hospitalised with pyogenic liver abscesses, 1995-2007*

Micro-organism	Blood (249 patients)	Abscess (240 patients)
Gram-negative aerobes:		
• *Klebsiella pneumoniae*	136	175
• *Escherichia coli*	21	37
• Other *Klebsiella* spp.	2	2
• *Pseudomonas* spp.	2	6
• *Morganella* spp.		4
• *Proteus* spp.		8
• *Aeromonas* spp.		2
• *Pantoea* spp.	2	3
• *Edwardsiella* spp.		3
• *Enterobacter* spp.		2
• Unidentified Gram(–) bacilli	2	4
Gram-positive aerobes:		
• *Enterococci* spp.	5	2
• *Staphylococci* spp.	8	2
• *Streptococci* spp.		11
Anaerobes :		
• *Bacteroides fragilis*	6	6
• *Prevotella* spp.	2	2
• *Fusobacterium* spp.		3
• *Peptostreptococcus* spp.		4
• Anaerobic Gram(+) non-spore foaming bacilli	2	
Total isolates	*184*	*276*

Treatment, morbidity, and outcome

Initial empirical antibiotics included the cephalosporin group, penicillin group, aminoglycosides, and metronidazole. Most (77.1%) of the agents consisted of a first/second-generation cephalosporin and a gentamicin. All patients received appropriate antibiotic treatment on the basis of the results of the antibiotic susceptibility profiles. The use of initial treatment for PLA was based on the preference of the physician in charge or the condition of the patient. The four initial treatments were: antibiotics alone (n=21), antibiotics plus image-guided PNA (n=36), antibiotics plus image-guided PCD (n=194), and antibiotics plus surgical intervention (n=2) (*table 4*).

Patients who received only antibiotics had the following conditions: end-stage malignancies with a frail status, decision not to use any invasive treatment, or abscess location/size which was difficult to drain. Two patients, including one with concomitant peritonitis and empyema of the gallbladder and one with co-existing peritonitis and multiple abscesses with multiloculation, initially had surgery and then survived. Fourteen patients needed subsequent treatment. Two patients treated with antibiotics alone subsequently required surgery and eventually survived. Five patients who initially had image-guided PNA subsequently required PCD and recovered completely. Seven patients who received image-guided PCD as primary treatment needed a subsequent surgical intervention. Of these seven patients, four had drainage failure, and in three the abscess ruptured during hospitalisation. The four patients in whom the initial PCD was not successful, including two in whom it was decided not to perform surgery and two with co-existing hepatic cell carcinoma, died of overwhelming

Table 4. *Morbidity, treatment, and outcome in 253 patients with pyogenic liver abscess, 1995-2007*

Variable	Initial treatment				
	Antibiotics alone	PNA plus antibiotics	PCD plus antibiotics	Surgery plus antibiotics	Total
	n=21	n=36	n=194	n=2	n=253
Requirement of a subsequent treatment	2 (9.5)	5 (13.9)	7 (3.6)	0	14 (5.5)
Metastatic infection	2 (9.5)	2 (5.6)	11 (5.7)	0	15 (5.9)
Relapse	2 (9.5)	0	8 (4.1)	0	10 (4.0)
Rupture of abscess	0	0	3 (1.5)	0	3 (1.2)
Death	6 (28.6)	0	17 (8.8)	0	23 (9.1)

PCD = percutaneous catheter drainage; PNA = percutaneous needle aspiration. Values represent N (%).

sepsis. Of the three patients with a ruptured abscess, two had a good clinical response to subsequent operation, and one died of peritonitis and concomitant uncontrolled sepsis. Two patients with image-guided PCD died among these patients with relapse. Fifteen patients had metastatic infection: splenic abscess (7), subcutaneous abscess (5), endophthalmitis (2), and splenic abscess with concomitant infectious endocarditis (1). All 15 patients were infected with *K. pneumoniae*. None of these 15 patients died. Mean hospital stay in all 253 patients was 21.4 days (SD 20.3 days). The mean follow-up of patients after discharge was 5.5 months (SD 3.3 months). Mean duration of antibiotics taken was 35.4 days (SD 22.5 days). Twenty-three patients in this case series died, yielding an overall case-fatality rate of 9.1%.

Analysis of prognostic factors related to mortality

Factors associated with death on univariate analysis were diabetes mellitus, malignancy, uraemia, gas-forming abscess, multiple abscesses, MDR isolates, bacteraemia, non-*K. pneumoniae* infection, anaerobic infection, polymicrobial infection, initial antibiotics alone, serum total bilirubin level >20.52 µmol/l, BUN level >7.86 mmol/l, serum creatinine level >115 µmol/l, and APACHE II score ≥15 (*table 5*). When these 15 statistically significant variables were subjected to multivariate analysis, only five variables – gas-forming abscess, MDR isolates, anaerobic infection, BUN level >7.86 mmol/l, and APACHE II score ≥15 – fitted the stepwise logistic regression model (*table 6*).

DISCUSSION

Our findings were similar to those of previous reports in that gas-forming liver abscess, BUN, and APACHE II score are prognostic factors in predicting mortality of PLA.[7,15,20,21] In addition, our data revealed that some

Table 5. *Significant factors in relation to mortality by univariate analysis in 253 patients hospitalised with pyogenic liver abscess, 1995-2007*

Variables	Category	Mortality (%)	Odds ratio (95% CI)	P value
Diabetes mellitus	Yes	15/106 (14.2)	2.9 (1.2-7.0)	0.017
	No	8/147 (5.4)	1.0	
Uraemia	Yes	8/24 (33.3)	7.1 (2.6-19.3)	<0.0001
	No	15/229 (6.6)	1.0	
Malignancy	Yes	5/20 (25.0)	4.0 (1.3-12.2)	0.024
	No	18/233 (7.7)	1.0	
MDR isolates	Yes	10/22 (45.5)	14.0 (5.1-38.3)	<0.0001
	No	13/231 (5.6)	1.0	
Bacteraemia	Yes	19/171 (11.1)	4.8 (1.1-20.9)	0.024
	No	2/78 (2.6)	1.0	
Anaerobic infection[1]	Yes	7/19 (42.9)	7.9 (2.8-23.0)	<0.0001
	No	16/234 (6.8)	1.0	
Polymicrobial infection[2]	Yes	7/28 (25.0)	4.4 (1.6-11.8)	0.007
	No	16/225 (7.1)	1.0	
Non-*K. pneumoniae* infection[3]	Yes	11/63 (17.5)	3.1 (1.3-7.5)	0.008
	No	12/190 (6.3)	1.0	
Multiple abscesses	Yes	12/82 (14.6)	2.5 (1.1-5.9)	0.034
	No	11/171 (6.4)	1.0	
Gas-forming liver abscess	Yes	6/24 (25.0)	4.2 (1.5-11.9)	0.013
	No	17/229 (7.4)	1.0	
APACHE II score at admission	≥15	17/37 (45.9)	29.8 (10.5-84.0)	<0.0001
	<15	6/216 (2.8)	1.0	
Serum total bilirubin, µmol/l	>20.52	18/88 (20.5)	8.2 (2.9-23.0)	<0.0001
	≤20.52	5/165 (3.0)	1.0	
Blood urea nitrogen, mmol/l	>7.86	16/58 (27.6)	10.2 (4.0-26.4)	<0.0001
	≤7.86	7/195 (3.6)	1.0	
Serum creatinine, µmol/l	>115	16/64 (25.0)	8.7 (3.4-22.2)	<0.0001
	≤115	7/189 (3.7)	1.0	
Antibiotics alone	Yes	6/21 (28.6)	5.1 (1.7-14.7)	0.002
	No	17/232 (7.3)	1.0	

APACHE = Acute Physiology And Chronic Health Evaluation, CI = confidence interval, *K. pneumoniae* = *Klebsiella pneumoniae*, MDR = multi-drug resistant. [1]Anaerobic infection: anaerobic isolates growing in blood or abscess cultures. [2]Polymicrobial infection: a mixture of different bacteria growing in blood or abscess cultures. [3]Non-*K. pneumoniae* infection: other isolates rather than *K. pneumoniae* growing in blood or abscess cultures.

Table 6. *Prognostic factors in relation to mortality by multivariate analysis in 253 patients hospitalised with pyogenic liver abscess, 1995-2007*

Variable	Odds ratio (95% CI)	P value
Gas-forming liver abscess	8.3 (1.4-48.8)	0.019
MDR isolates	16.6 (1.4-197.0)	0.026
Anaerobic infection[1]	10.4 (1.1-103.3)	0.045
Blood urea nitrogen >7.86 mmol/l	30.2 (3.0-305.6)	0.004
APACHE score ≥15	8.5 (2.0-35.9)	0.004

APACHE = Acute Physiology And Chronic Health Evaluation, CI = confidence interval; MDR = multi-drug resistant. [1]Anaerobic infection: anaerobic isolates growing in blood or abscess cultures.

bacterial characteristics – anaerobic infection and MDR isolates – may play an important role in the prognosis of PLA. As far as we are aware, this finding has not been reported before. We acknowledge that our study results are limited by their retrospective nature. Our data were limited to what had been recorded in the medical records. However, there was no significant difference in missing measurements at admission between the case-fatality and the non-case-fatality groups. The possible influence of this non-random effect of missing data on the study results was minimised. On the other hand, the majority of the previous reports of prognostic factors for PLA were based upon either small sample sizes or univariate analysis.[1,3,4,6-9,12-15] We applied multivariate analysis in the present study which is one of the largest published case series on PLA.

The case-fatality rate of PLA was 9.1% in our study, which is in accordance with the level reported in the past two decades.[2,3,6-15] The predominance of *K. pneumonae* and cryptogenic causes in our study is consistent with previous Asian reports;[6,7,9,13-17] in contrast, reports from Western countries do not all reach the same conclusion.[1-3,8,11,12] PLA with *K. pneumonae* may lead to septic extrahepatic metastases, especially in diabetic patients.[16,17,22-24] Several investigators have reported that capsular serotype K1 or K2, and *magA* gene may be associated with virulence and phagocytosis resistance in *K. pneumoniae* liver abscess and these virulent factors, capsular serotype K1 especially, may play a potential determinant role in developing metastatic complications and causing PLA.[25-27] The serotype K1 isolate was uncommon among *K. pneumoniae* isolated from Western countries,[27-31] which may account for aetiological differences among regions. Some recent reports from the United States have noted an increase in the proportion of PLA patients with *K. pneumoniae*.[32,33] This phenomenon seems to indicate that *K. pneumoniae* liver abscess is an emerging infectious disease and may become a potential global concern.

The recovery frequency of anaerobic isolates in PLA patients varies in published reports, ranging from 7 to 46%.[1-3,6-9,12-14,34] The anaerobic recovery in our study, 7.5%, is located at the lower end of the range. This may be influenced by inadequate methods for transportation and cultivation of specimens. The effect of anaerobes on infection has been gradually recognised in the past 30 years. Patients experience shock, injury, or surgery, and those with blood vessel disease or malignancy are at high risk of anaerobic bacterial infection. The virulence of anaerobes – toxin production, capsule formation, and superoxide dismutase activity – may contribute to tissue damage, protect the pathogen from host defences, or induce abscesses.[35-37] Furthermore, anaerobes may not only protect facultative pathogens by suppressing phagocytic activity and/or blocking opsonic pathways but also create an environment where control and eradication of co-infecting pathogens are particularly difficult, thereby enhancing the virulence of mixed infections.[37,38] The findings of the above studies may explain why polymicrobial infection is associated with mortality in some reports and in our univariate analysis and why anaerobic, but not polymicrobial infection, is a prognostic factor for PLA mortality in multivariate analysis.

MDR isolates are known to contribute to high morbidity and mortality in several infectious diseases, such as tuberculosis, malaria, acute respiratory diseases and gastroenteritis, because they may cause infections that are more difficult to treat.[39-41] However, the influence of MDR isolates on PLA is less well understood. The emergence of MDR is a complicated problem and may be driven by numerous interconnected factors, including the use of antimicrobials in animals, plants and human beings.[42,43] Previous studies show that inappropriate antibiotic use is the most important factor responsible for increased antimicrobial resistance, especially in developing countries.[30,31] The majority of PLA patients in our study reported an average of >5 days' prodrome of fever, chills, or respiratory/gastrointestinal symptoms, and they may have received antibiotics to treat their illnesses prior to hospital admission. However, information regarding antibiotic use before admission had not been recorded in the medical records in this series, so a definite conclusion cannot be made.

Few reports have studied BUN as an indicator of mortality in PLA patients.[7] In our work, a raised BUN level was a significant prognostic factor for PLA, a finding that is consistent with previous reports.[7] Designed to measure the severity of disease for patients admitted to intensive care units, the APACHE II score system has also been used extensively to predict treatment outcome in a variety of ill patients.[18] Mischinger *et al.*[8] found a high APACHE II score to be an independently significant risk factor of mortality in PLA patients; in contrast, Alvarez Perez *et al.*[12] found a high APACHE II score (≥10) to be statistically associated with mortality in univariate analysis but not

in multivariate analysis. Recently, Hsieh *et al*. identified an APACHE II cut-off score of ≥15 as a good positive predictive indicator of mortality from PLA.[15] Similarly, we found the APACHE II score of ≥15 to be a significant predictor of adverse outcome in PLA patients, with an 8.5-fold increased risk of death compared with the risk of death in patients with a score of <15. Some parameters of the APACHE II score system that have been identified as predicting mortality in PLA patients include age, blood pressure, white blood cell count, haematocrit and serum creatinine levels, and underlying medical conditions (malignancy, liver cirrhosis, and uraemia).[1,3,4,6-9,12-15] The APACHE II score seems to be more representative and convenient than the above parameters for predicting mortality of patients with PLA. Additionally, this finding indicates that a poor underlying physical condition may be related to mortality of PLA.

Since it was first described by Smith in 1944,[46] gas-forming liver abscess has been increasingly found with the evolution of diagnostic imaging techniques. The proportion of gas-forming liver abscesses in PLA patients ranges from 11 to 29%,[20,47] and the case-fatality rate is as high as 37%.[48] In accord with previous reports,[33,36] we found gas-forming liver abscess to be an independent predictor of mortality in PLA patients. As described in previous studies, gas-forming liver abscess is associated with *K. pneumoniae* infection and diabetes mellitus.[20,21,47,48] However, this finding is less often seen in Western reports.[4] This may be attributed to variant study populations and geographical differences. A possible pathophysiological mechanism includes gas-forming pathogens that may damage local tissue through rapid catabolism and impaired transport of the end products at inflammatory sites. Diabetic microangiopathy would compound this infection by slowing the transport of catabolic end products away from these foci, resulting in gas accumulation.[21,47,49] Considering our study results and these biological mechanisms, we hypothesise that gas-forming liver abscess is associated with more severe tissue destruction and a poorer outcome than other liver abscess.

With the advances in image techniques (US or CT scans), PCD under image guidance has now become the treatment of choice for PLA in most institutions due to its less invasive approach and greater feasibility,[1-3,6-15,21] although some clinicians still prefer surgical intervention.[50] Several groups have documented that image-guided PCD is appropriate as primary treatment for PLA: it has good results with a low case-fatality rate ranging from 0 to 15%.[2,3,10,12,14,51] Evidence from our case-patient series – a success rate of 87.2% and a case-fatality rate of 8.7% in patients who had image-guided PCD – supports this recommendation.

Recently, some studies have shown that image-guided PNA produces satisfactory results, with case-fatality rates of 0 to 6%.[2,51] Similarly, in our patients with PNA no deaths and no recurrences were seen. Image-guided PNA has advantages over image-guided PCD: less invasive, less expensive, less nursing care required, more patient acceptability, and less procedure-related complications. We did not deduce which therapeutic modality is better because the patients who had different treatments were not exactly comparable, but the results seem to suggest that PNA could be an effective, and perhaps superior, alternative for treating PLA. The effectiveness of antibiotics alone for treating PLA is still disputed.[2,3,52] Patients treated with only antibiotics in our study had a high case-fatality rate – 28.6 *vs* 7.3% in all other patients – although the rate ratio did not reach statistical significance in multivariate analysis.

Several authors today believe that antibiotics alone and surgical approach are not a routine primary treatment modality for PLA; antibiotics alone may be an alternative in patients too ill to undergo invasive approaches and in patients with small multiple abscesses not amenable to drainage intervention; and surgical approach may be reserved only for patients unsuitable for further percutaneous drainage and patients with primary intra-abdominal pathology.[1-3,10,34] However, some PLA patients had a severe infection at arrival and may rapidly progress to an adverse outcome. In this situation, the patients would probably die before clinicians could change treatment strategy from percutaneous drainage to surgery. Our results suggest that physicians should use an aggressive approach as soon as possible for PLA patients with initial high fatality risk and poor response to primary treatment, especially for those patients with APACHE II score ≥15 at admission. There is still a lack of useful and definite criteria to follow when determining whether to use a surgical procedure in PLA patients; further prospective experimental studies should be conducted.

In conclusion, five main prognostic factors are related to mortality of PLA: presence of gas-forming abscesses, MDR isolates, anaerobic infection, high level of BUN, and high APACHE II score at admission. The severity of the patient's basic physical condition and underlying pathology may play an important role in the prognosis of PLA. As the primary treatment for PLA is not fully effective, a more aggressive therapeutic approach should be considered, especially for those patients with poor prognostic factors.

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CASE REPORT

Colchicine-induced neuromyopathy in a patient with chronic renal failure: the role of clarithromycin

W. van der Velden[1], J. Huussen[2,4], H. ter Laak[3], R. de Sévaux[2*]

Departments of [1]Haematology, [2]Nephrology and [3]Pathology, Radboud University Nijmegen Medical Centre, PO Box 9101, 6500 HB Nijmegen, the Netherlands, [4]current address: department of Internal Medicine, Slingeland Hospital, Doetinchem, the Netherlands, [*]corresponding author: tel.: +31 (0)24-361 47 61, fax: +31 (0)24-354 00 22

ABSTRACT

Neuromyopathy is a rare side effect of chronic colchicine therapy, most often occurring in patients with chronic renal failure. Drugs interacting with colchicine metabolism through CYP3A4 and P-glycoprotein can accelerate accumulation and toxicity. We describe a case of an interaction between clarithromycin and colchicine resulting in acute neuromyopathy, and we conclude that combined use of macrolides and colchicine should be avoided.

KEYWORDS

Clarithromycin, colchicine, CYP3A4, neuromyopathy, P-glycoprotein, simvastatin

INTRODUCTION

Neuromyopathy is a rare side effect of chronic colchicine therapy.[1,2] We present a case of acute neuromyopathy in a patient with chronic renal failure who was taking colchicine for gouty arthritis. The side effect was probably induced by a drug interaction with clarithromycin prescribed for a pulmonary infection. The present case illustrates that use of colchicine for maintenance therapy, especially in patients with chronic renal failure, can lead to severe side effects. A temporary increase of the colchicine dose or the use of drugs that interfere with colchicine metabolism might turn out to be hazardous.

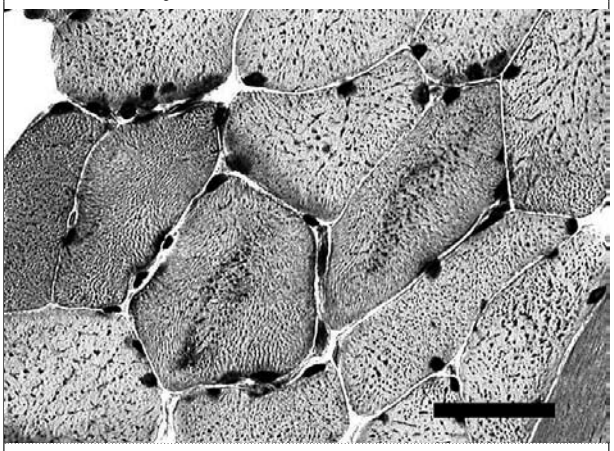
CASE REPORT

A 73-year-old man with chronic renal failure due to atherosclerosis and hypertension was admitted because of fatigue and myalgia in the upper and lower extremities.
His medical history included severe cardiovascular disease (ischaemic heart disease with heart failure, and occlusion of the abdominal aorta), chronic obstructive airway disease, and gout. Because of an allopurinol-induced dermal vasculitis, he was switched to maintenance therapy with colchicine (0.5 mg once daily) one year before. Simvastatin therapy was instituted three months before admission (20 mg once daily).
Two weeks before admission he was treated with clarithromycin for ten days because of pneumonia. One week later he developed fatigue, muscle weakness and muscle tenderness. Because of progression of these symptoms he was admitted to the hospital. He had neither fever nor any cardiac or respiratory symptoms. Cardiovascular, pulmonary and abdominal examination was unremarkable except for a pre-existent cardiac murmur. Neurological examination revealed general muscle weakness (Medical Research Council grade 4)3 and slightly decreased sensation of the lower extremities, with mainly his left foot affected. Minor symmetric hyporeflexia, but no myotonia was present.
On admission, laboratory examination revealed: haemoglobin 8.9 mmol/l, leucocyte count 3.2 x 10^9/l, thrombocyte count 78 x 10^9/l, creatinine 369 µmol/l, aspartate aminotransferase 219 U/l, alanine aminotransferase 345 U/l, creatine kinase (CK) 1396 U/l, lactate dehydrogenase 649 U/l, C-reactive protein <5 mg/l and erythrocyte sedimentation rate of 24 mm/hour. There were no signs of liver insufficiency. Serum electrolytes and thyroid-stimulating hormone were normal. Antinuclear antibodies and extractable

nuclear antigens were negative. Microbiological investigations showed no signs of viral infections or *Mycoplasma pneumoniae*. Radiological examinations were unremarkable.

It was suspected that the patient was suffering from a drug-induced neuromyopathy, and colchicine and simvastatin were discontinued. Electromyography (EMG) revealed polyphasic motor unit potentials with low amplitude and short duration, indicative of myopathy. No signs of myotonia or fibrillations were noticed. Furthermore, a sensory motor axonal polyneuropathy, mainly of the distal lower extremities, was seen. A muscle biopsy showed a vacuolar myopathy with multiple small vacuoles in the centre of the muscle fibre (*figure 1*). The lysosymal nature of these vacuoles was confirmed by a strong acid phosphatase positivity. In electron microscopy these lysosomes were filled with autophagic material. These observations were consistent with previously reported pathological features of colchicine toxicity. No signs of statin-induced myopathy, such as myonecrosis, were seen. After the discontinuation of colchicine a rapid decrease of the CK level and a rapid recovery of the pancytopenia occurred. The muscle weakness disappeared gradually in two weeks.

Figure 1. *Muscle biopsy: characteristic multiple small basophilic vacuoles accumulated in the central part of several muscle fibers*



The black bar represents 50 μm. (Hematoxylin-Phloxine stained frozen section).

DISCUSSION

Our patient developed colchicine-induced neuromyopathy after low-dose colchicine therapy for more than one year. Since he had no liver failure, this probably resulted from chronic colchicine accumulation in the presence of his renal failure. However, the recent use of clarithromycin and initiation of lipid-lowering therapy with simvastatin raise the possibility of a drug interaction, especially because both drugs share metabolic pathways with colchicine, namely via the CYP3A4 and the P-glycoprotein. Inhibition of these proteins increases serum colchicine levels, with accelerated accumulation and possible toxicity.

An interaction between simvastatin and colchicine appears less likely, because although both drugs are substrates of CYP3A4 and the P-glycoprotein, they have no relevant inhibitory effect on these metabolic pathways themselves.[4] However, macrolides, including clarithromycin, are known inhibitors of the CYP3A4 and P-glycoprotein systems[5] and have been shown to increase the colchicine serum level.[6] Therefore, it is very likely that this inhibition by clarithromycin was responsible for the occurrence of colchicine-induced neuromyopathy in our patient. In support of this possibility are several recent reports on an interaction between clarithromycin and colchicine.[7,8] In addition, in one retrospective study an incidence of severe toxicity in as much as 10% of patients receiving concomitant therapy with colchicine and clarithromycin is mentioned.[9] However, these studies did not specifically regard the occurrence of neuromyopathy.[7-9]

Colchicine-induced neuromyopathy

Neuromyopathy due to colchicine therapy is infrequently encountered, and most often seen after chronic use in patients with renal or liver failure.[10,11] Patients present with proximal muscle weakness and sometimes muscle tenderness. On neurological examination minor distal sensory loss and hyporeflexia can be found. Various degrees of serum level elevations of CK have been described, usually up to 10 times the upper limit of normal, but severe rhabdomyolysis can occur. Additional investigations are necessary to exclude myopathy caused by thyroid disease, viral infections and other drugs. EMG shows aspecific changes indicative for myopathy, with polyphasic motor unit potentials with low amplitude and short duration, and often a mild sensory motor polyneuropathy of the axonal type. On the contrary, muscle biopsy yields highly specific and pathognomic abnormalities, revealing a vacuolar myopathy with accumulation of autophagic vacuoles (*figure 1*).[12] Although muscle biopsy is not always necessary, in case of rapid recovery after cessation of colchicine, it may be necessary in cases where several drugs are the possible cause of myopathy and stopping either drug is not desirable.

The pathophysiological mechanism of colchicine-induced neuromyopathy has been studied in animal models.[12] Disruption of intracellular microtubule formation due to the toxic effects on tubulin results in disrupted exocytosis of autolysosomes with subsequent accumulation and formation of autophagic vacuoles, the last causing the typical image seen on muscle biopsy.

Colchicine toxicity results from elevated plasma levels due to altered pharmacokinetics. In otherwise healthy patients the elimination half time of colchicine is approximately 3 to 10 hours. The drug is partially demethylated in the liver by the cytochrome P450 system, mainly by the isoenzyme CYP3A4, and excreted as a metabolite or unchanged in the bile and urine by the P-glycoprotein.[13] Colchicine undergoes enterohepatic recirculation.

In the presence of hepatic or renal failure accumulation occurs and toxicity is promoted at normal therapeutic doses. This can result in diarrhoea, neuromyopathy, elevated liver enzymes and pancytopenia often occurring simultaneously. Toxicity can be induced or accelerated by drugs interacting with colchicine metabolism such as macrolides, cyclosporin A, azoles and protease inhibitors.[2,9] Cessation of colchicine and possible interacting drugs often results in quick recovery, although fatalities are not uncommon in case of severe pancytopenia.[9] Therapy is supportive as there are no specific antidotes or methods to decrease toxic plasma levels.

CONCLUSION

We describe a case of acute colchicine-induced neuromyopathy in a patient with chronic renal failure who was on colchicine maintenance therapy. The toxicity was most probably accelerated by the addition of the CYP3A4 and P-glycoprotein inhibitor clarithromycin increasing colchicine serum levels. Although this interaction is increasingly recognised, our case was the first one reported to the Netherlands Pharmacoviligance Centre Lareb (safety report 45076). Care should be taken when prescribing colchicine as maintenance therapy, especially in patients with chronic renal failure who are taking many different drugs. Awareness of the pharmacokinetic properties of these drugs and their possible interactions remains crucial if toxicity is to be prevented. The combined prescription of clarithromycin or other CYP3A4 inhibitors and colchicine should be avoided.

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CASE REPORT

Community-onset *Clostridium difficile*-associated diarrhoea not associated with antibiotic usage

Two case reports with review of the changing epidemiology of *Clostridium difficile*-associated diarrhoea

M.P. Bauer[1], A. Goorhuis[2], T. Koster[3], S.C. Numan-Ruberg[1], E.C. Hagen[4], S.B. Debast[5], E.J. Kuijper[2], J.T. van Dissel[1*]

Departments of [1]Infectious Diseases and [2]Medical Microbiology, Leiden University Medical Centre, Leiden, the Netherlands, [3]Department of Internal Medicine, Groene Hart Hospital, Gouda, the Netherlands, Departments of [4]Internal Medicine and [5]Medical Microbiology, Meander Medical Centre, Amersfoort, the Netherlands, [*]corresponding author: tel.: +31 (0)71-526 26 13, fax: +31 (0)71-526 67 58, e-mail: e.j.t.van_dissel@lumc.nl

ABSTRACT

The emergence of hypervirulent strains of *Clostridium difficile* causing outbreaks in hospitals and nursing homes may result in a greater than before spread of the bacterium in the community. By consequence, the incidence of community-onset cases of *Clostridium difficile*–associated diarrhoea (CDAD) may increase outside known risk groups that are currently characterised by prior hospitalisation, prior antibiotic usage, older age and significant comorbidity. Here, we describe two case histories of community-onset CDAD. The first concerns a previously healthy young female with community-acquired CDAD without recent hospitalisation or antibiotic usage. The second patient developed diarrhoea in the community after discharge from a hospital where – in retrospect – an outbreak of CDAD occurred. The cases illustrate that CDAD should be included in the differential diagnosis of patients seeking care for community-onset diarrhoea, even in those without characteristic risk factors for CDAD.

KEYWORDS

Clostridium difficile, community-acquired diarrhoea, passive immunotherapy

INTRODUCTION

Recently, outbreaks of diarrhoea due to *Clostridium difficile* PCR-ribotype 027 have been reported in Canada, the United States and Europe, including the Netherlands.[1-5] Typically, outbreaks occur in a hospital or nursing home and primarily affect elderly individuals who suffer significant underlying conditions that make them susceptible to acquiring *C. difficile*-associated diarrhoea (CDAD).[6] Among the predisposing conditions, exposure to antibiotics during an extended period of hospitalisation is regarded as most significant.[7] The severity of CDAD can range from transient, mild diarrhoea to fulminant colitis. A recently circulating strain of *C. difficile* characterised as toxinotype III, North American pulsed field type 1, restriction endonuclease analysis group BI and PCR ribotype 027 has been associated with enhanced virulence, apparently due to the production of higher amounts of toxins.[1,4,8]

As can be expected from the known risk factors of CDAD (i.e., hospitalisation, old age, antibiotic usage, underlying medical conditions, gastrointestinal surgery, nasogastric tubes, etc), most of the outbreak reports have dealt with nosocomial CDAD. There is an overall lack of information on community-onset CDAD. Here, we describe two such cases: a case of truly community-acquired CDAD without any known risk factors and a case of community-onset CDAD caused by an epidemic strain likely acquired during

a recent stay in hospital. The two cases illustrate various aspects of community-onset CDAD and indicate that physicians should be aware of the possibility of CDAD cases in the community, also in those who do not have known risk factors for CDAD. Moreover, such cases suggest that the epidemiology of CDAD may be changing, with a greater than before circulation of the bacterium in the community due to increased introduction of the bacterium from hospitals and institutions with outbreaks.

CASE REPORT

A 28-year-old female presented to the emergency department because of syncope and severe diarrhoea. Her prior medical history was unremarkable with the exception of two caesarean sections, performed years before the present admission. On presentation, she complained of cramping abdominal pain, nausea and vomiting of one day's duration, and passing of profuse watery stools mixed with blood. Soon after her symptoms began she noticed light-headedness and briefly lost consciousness during passage of stools. Because of the peracute nature and severity of her symptoms, her general practitioner referred her to the emergency room of the nearby hospital.

The patient was not taking any medication, nor had she recently used any. On physical examination, she did not appear severely ill. A blood pressure of 80/40 mmHg and a pulse of 60 beats/min were noted. Examination of heart and lungs was unremarkable, her abdomen was tender. Rectal examination revealed pink stools with some mucus.

Laboratory investigation revealed a leucocytosis of 12.9 x 10^9/l, with a neutrophil count of 11.2 x 10^9/l. The haemoglobin level was 8.5 mmol/l and the erythrocyte sedimentation rate (ESR) was 5 mm/h. Urea, creatinine, glucose, electrolyte and liver enzyme levels were within normal limits.

A diagnosis of vasovagal syncope due to a severe bout of gastroenteritis and mild dehydration was made. The patient was admitted for fluid resuscitation (3 litres in the first 24 h). Stool cultures were negative for *Salmonella, Shigella, Yersinia* and *Campylobacter* and stool examination did not reveal any parasites, such as *Gardia lamblia*. An enzyme-linked immunosorbent assay (ELFA, Biomerieux) for *C. difficile* toxin A on stool was positive. Her stools were not cultured for *C. difficile*. Treatment with oral metronidazole 500 mg three times daily for ten days was initiated, a regimen to which she responded favourably. After three days she was discharged and she completed her ten-day course of antibiotics at home. After completion of the antimicrobial regimen, she participated in an experimental protocol aimed at reducing the occurrence of relapses of CDAD and received a bovine immune milk preparation (anti-CD WPC) for two weeks. During a follow-up up to 60 days after start of the immune milk, the patient remained asymptomatic, and contact over one year later indicated that CDAD had not recurred.

Regarding the possible source of her *C. difficile* infection, an extensive history was taken. This revealed that three months previously the patient's two infant sons had been admitted to another hospital for two days because of a respiratory tract infection. The patient had spent one night in the hospital with her children during their admission. There had been no *C. difficile* outbreak in this hospital. Of note, neither the sons nor other family members had experienced diarrhoea. Moreover, after the diagnosis of CDAD had been made in the patient, stool cultures of her husband and two sons were taken but were negative for *C. difficile*. In conclusion, no plausible source of exposure could be established. It seems highly unlikely that the patient's episode of CDAD is related to her one-day stay in hospital three months earlier.

The second case concerns a 71-year-old male who was admitted with progressive diarrhoea. He had suffered a stroke in the past and had vascular dementia with secondary parkinsonism, chronic obstructive pulmonary disease, hypertension and chronic renal failure due to nephrosclerosis. One week before admission, he had been discharged from hospital where he was being examined for chronic watery stools with concomitant loss of an already compromised kidney function. Diarrhoea had been present for six months. At that admission, peripheral eosinophilia (0.7 x 10^9/l) was noted. A computed tomography scan of the abdomen showed extensive arterial wall abnormalities compatible with atherosclerosis and thickening of the sigmoid wall. Colonoscopy had not revealed abnormalities, whereas biopsies of the sigmoid showed mild inflammation with infiltration of eosinophils. Microbiological examination of stools including multiple tests for *C. difficile* toxin and extensive parasitological examination were negative. On the basis of these findings and especially the fact that repeatedly, no infectious agent could be demonstrated, a differential diagnosis of eosinophilic colitis or cholesterol embolism was made. Symptomatic treatment with loperamide and haemodialysis was started. Upon readmission the patient had a fever up to 39.1°C. His medication consisted of loperamide, aspirin, clopidogrel, atorvastatin, perindopril, metoprolol, temazepam, levodopa/carbidopa, alfacalcidol, epoetin beta iv during haemodialysis and ipratropium albuterol inhalations; he had not received antibiotics recently. The patient lived in a nursing home. Physical examination, including the abdomen, did not reveal abnormalities except for a mild tachycardia of 110 beats/min and increased bowel sounds. Laboratory investigation showed a leucocytosis of 15.6 x 10^9/l and an ESR of 48 mm/h. The eosinophilia had decreased. His C-reactive protein level was 322 mg/l. A rapid immunoassay for *C. difficile* toxin A (ELFA, BioMérieux) was positive. *C. difficile* was cultured from the stool as well; the strain was typed as ribotype 027. This case later on proved to be part of an epidemic due to ribotype 027

in this hospital. Treatment was started with oral vancomycin 250 mg four times a day for 14 days. After the antimicrobial regimen, the patient also participated in the experimental protocol and received a bovine immune milk preparation (anti-CD WPC) for two weeks. His condition improved and he was discharged from hospital; rapid stool tests for *C. difficile* toxins were repeatedly negative.

DISCUSSION

The cases presented here concern community-onset CDAD. The first case illustrates that CDAD can be acquired in the community in the absence of any of the known risk factors for this disease. The second case illustrates how exposure to *C. difficile* in a hospital in which CDAD is endemic can cause CDAD to spread into the community. It underlines once more that prior use of antibiotics is not a necessary factor for CDAD to develop.

Three factors are thought to explain the classical risk profile for CDAD. First, the patient must be exposed to the pathogen. Although the bacterium is ubiquitous and can be isolated from many sources both inside and outside hospitals, CDAD is most frequently acquired in hospitals and care institutions where the bacterial load is likely high because host factors predispose the population admitted to these institutions to develop clinical disease.[6] Second, prior administration of antibiotics and consequent disruption of the resident bowel flora has always been considered important, if not necessary, for colonisation by *C. difficile*. In particular clindamycin, cephalosporins, fluoroquinolones (especially of the later generations) and less so macrolides and intravenous β-lactams with β-lactamase inhibitors have been associated with CDAD.[2,7,9-19] Lastly, a host factor appears to determine, at least in part, whether or not colonisation is followed by clinical manifestations of CDAD. Older age cohorts admitted for extended periods because of severe underlying disease are at highest risk for CDAD.[7,19-22] Presumably, in these individuals a lack of effective antitoxin humoral immunity is a decisive factor in developing CDAD, since long duration of disease and relapse has been associated with lower concentrations of circulating and faecal antibodies against *C. difficile* toxins A and B.[23-25]

Since early 2003, an increase in the incidence of CDAD has been reported in Canada and subsequently in the upper part of the United States of America and Europe. The CDAD cases in this outbreak were remarkable because they ran a more severe course.[19,26-28] The greater morbidity was associated with the emergence of PCR ribotype 027.[1,4,8] In just a few years, outbreaks of CDAD due to PCR ribotype 027 occurred in the Netherlands as well.[3,4,29-31] Of note, the outbreaks concerned hospitalised or institutionalised patients. One report already noted an increase in community-acquired cases of CDAD in a population not considered at risk but unfortunately only a few strains of *C. difficile* were available for typing and type 027 was not found.[32]

The rate of community-acquired (CA) CDAD, formerly a very rare entity, appears to be increasing.[19,33-35] *Table 1* summarises findings in the studies that have been published on this subject. Some of these cases may actually be hospital acquired, since definitions of CA-CDAD vary. However, some clearly do not fit the classical risk profile.[19,32,36] A systematic surveillance of CA-CDAD has not been performed until recently. Stool samples of 703 patients with diarrhoea submitted by general practitioners in an area of 3.6 million inhabitants in Germany were investigated for pathogens including *C. difficile* by culture and enzyme immunoassay for *C. difficile* toxin A/B. The *C. difficile*-toxin A/B assay was positive in 66 (9.3%) of the stool samples. Thirty-one (47%) of 66 patients had healthcare-associated diarrhoea (i.e., defined as an onset of symptoms within four weeks after hospital discharge) whereas 35 (53%) were truly community-acquired. Recent usage of antibiotics was reported by 34/66 (52%) patients, most frequently cephalosporins (33%) and fluoroquinolones (33%).[37]

If the incidence of CA-CDAD is indeed increasing, what could be the cause? The emergence of CDAD in hospital outbreaks undoubtedly leads to the spread of the pathogen among admitted patients, not all of whom will develop symptoms of CDAD during hospitalisation. As illustrated by the second case, some cases of CDAD can be expected to occur in the weeks or even months following discharge. In addition, the increased circulation of *C. difficile* within hospitals will increase the rate of asymptomatic *C. difficile* carriership within the population, due to temporary excretion of the pathogen by discharged patients and/or healthcare workers. Contact with such cases will in the end lead to some cases of community-acquired CDAD. Furthermore, it has been suggested that an animal reservoir may play a role in the emergence of community-acquired CDAD.[38] *C. difficile*-associated disease and carriage have been reported in pets and farm animals. In 1993, the role of pets as a reservoir was investigated comparing restriction endonuclease analysis types of *C. difficile* isolates from pets, veterinary clinics, humans and hospitals.[39] In that study, there was no correlation between isolates from pets and humans and therefore it was concluded that animals do not form an important reservoir for strains that cause human disease. However, *C. difficile* seems to have become more important as an animal pathogen[40] and a number of recent studies have found overlap between animal and human ribotypes, suggesting that there is interchange of strains between animals and humans.[41,42] Of note, *C. difficile* could be cultured from 20% of retail meat samples in a Canadian study, with a majority of the toxigenic isolates being *C. difficile* type 027.[43] Incidentally, neither of the patients we describe had had contact with any possible animal source.

The first patient recovered quickly after treatment with metronidazole. In the recent outbreaks, however, the relapse

Table 1. *Results of published studies concerning community-acquired CDAD*

Study	Country, year, setting	Overall incidence of CDAD (/100,000 py)*	Number of patients with CDAD	Definition of CDAD	Proportion of CA-CDAD (%)	Definition of CA-CDAD	Proportion of COHA-CDAD (%)	Proportion of noso-comial CDAD (%)	Proportion of CDAD with unknown location of onset
Karlström[35]	Sweden, 1995, GP/hospital	58	1888	Stool positive in any test for CD and CT+	28	CO, no hospitalisation preceding 4 weeks	15	52	5
Kyne[25]	Ireland, 1995, hospital	?	73	Diarrhoea and CT+	11	CO or onset in first 72 hours of admission without hospitalisation preceding 60 days	9.6	79.4	0
Wheeler[33]	UK, 1993-1996, community	160	6	Diarrhoea and CT+	100†	CO	?	0	0
Wheeler[33]	UK, 1993-1996, GP	20	17	Diarrhoea and CT+	100†	CO	?	0	0
Dial[19]	UK, 1994-2004, GP	<1 in 1994 to 22 in 2004	1672	Clinical diagnosis and/or CT+	74	CO without hospitalisation preceding year	26	0	0
Paltansing[34]	Netherlands, 2005, hospital	16/10,000 admissions	81	Diarrhoea and CT+	6§	CO	30§	61	3
Riley[49]	Australia, 1988 GP	5.5% of stool samples	16	Diarrhoea, CD cultured or CT+	100†	CO	?	0	0

CDAD = *Clostridium difficile*-associated diarrhoea; py = person years; CA-CDAD = community-acquired CDAD, COHA-CDAD = community onset healthcare-associated; GP = general practice; CD = *Clostridium difficile*; CT+ = cytotoxin test positive in stool; CO = community onset. *Unless otherwise specified. †CA-CDAD and COHA-CDAD were not separated. §Data partially through personal communication.

rate of CDAD has increased from about 20% to as high as 47% in cases caused by PCR ribotype 027. Unfortunately, besides increasing the dose or extending the course of antibiotics, switching metronidazole into oral vancomycin and using alternating or pulsed regimens, there is little one can do to prevent cycles of relapses and even the measures mentioned have not been proven to be efficacious. Also, the efficacy of strategies including probiotics, bacteriotherapy, toxin-absorbent resins and intravenous immunoglobulins is currently uncertain and not supported by evidence from clinical trials.[44,45] Previously, we reported on the use of passive immunotherapy with anti-*C. difficile* whey protein concentrate (40%; anti-CD-WPC) made from milk from cows immunised with inactivated *C. difficile* toxins and killed bacterial cells. Anti-CD-WPC neutralises the action of toxins *in vitro* and protects against CDAD in an animal model.[46] As a milk product, it was found safe for use in humans with CDAD[47] and in a first, uncontrolled trial an about 50% reduction in relapse rate was observed.[48] However, the efficacy of this treatment modality still has to be submitted to a dose-finding and placebo-controlled randomised trial.

In conclusion, the emergence of new strains of *C. difficile* causing outbreaks in hospitals and nursing homes in recent years may also forward the circulation of such strains in the general population, and increase the incidence of community-acquired cases of CDAD outside the well-known risk groups. The present case histories illustrate that CDAD should be included in the differential diagnosis of both acute and chronic community-onset diarrhoea, even when the patient has not recently taken antibiotics, is young and has no comorbidity. It also underscores that strict hygienic measures should be taken in all patients with diarrhoea to prevent spread of the pathogen.

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Netherlands
The Journal of Medicine

PHOTO QUIZ

Undulating blood pressure

I.M. Noppers, J.G. Zijlstra*

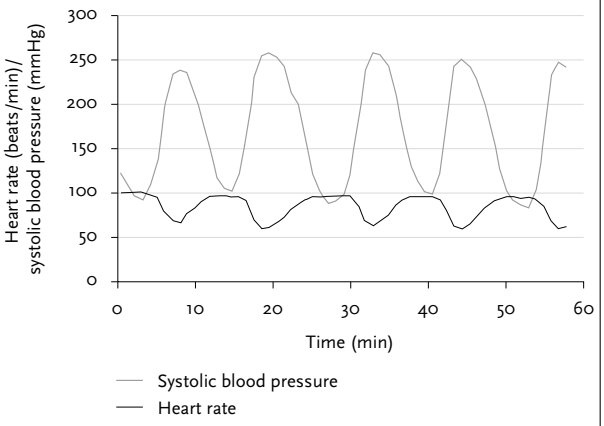
Department of Critical Care, University Medical Center Groningen, PO Box 30.001, 9700 RB Groningen, the Netherlands, *corresponding author: tel.: +31 (0)50-361 61 61, fax: +31 (0)50-361 32 16, e-mail: j.g.zijlstra@int.umcg.nl

CASE REPORT

A 58-year-old woman presented to another hospital with upper gastrointestinal bleeding. Her history was unremarkable except for hypertension, which was considered to be essential. Unexpectedly, upper gastrointestinal endoscopy revealed bleeding oesophageal varices. The patient stabilised but the blood pressure showed marked swings with hypotension and hypertension. After she developed abdominal symptoms, a laparotomy was performed. A small section of the jejunum had to be excised because of vena mesenterica thrombosis. Because of recurrent gastrointestinal bleeding she was referred to our hospital.

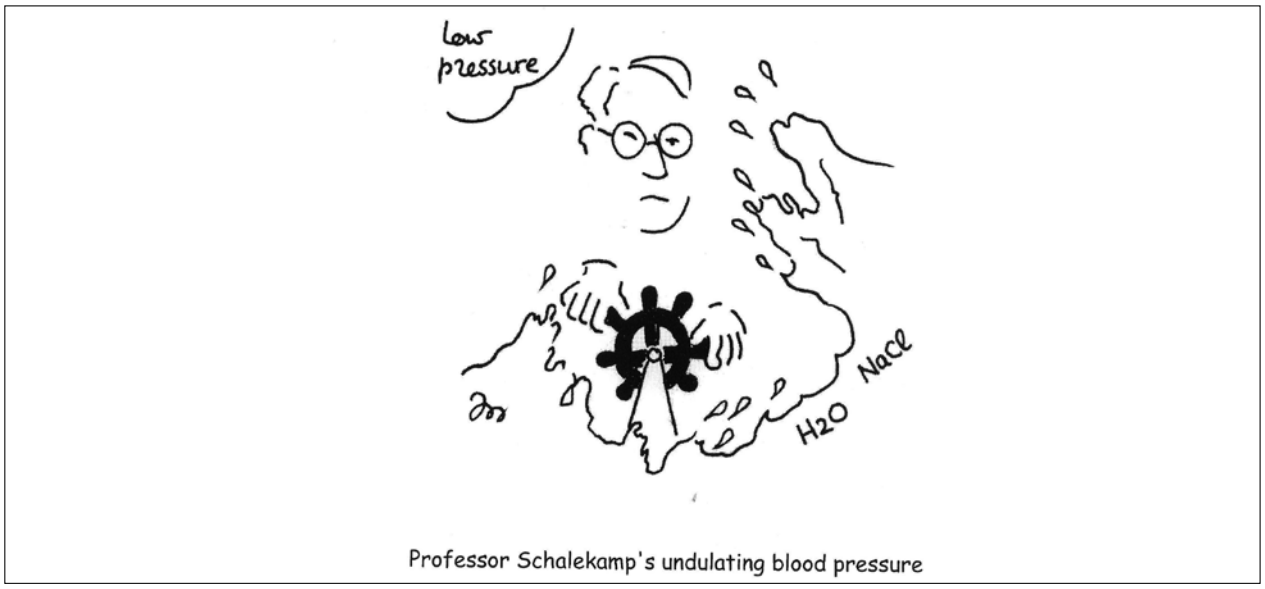
Endovascular volume was kept low to control bleeding. Blood pressure revealed cycles of 13 minutes of alternating hypertension and hypotension with bradycardia during hypertension (*figure 1*).

Figure 1. *Heart rate and systolic blood pressure*



WHAT IS YOUR DIAGNOSIS?

See page 214 for the answer to this photo quiz.



Professor Schalekamp's undulating blood pressure

Netherlands
The Journal of Medicine

PHOTO QUIZ

An unexpected finding in bacterial pneumonia

E. Anton*, M. Escalante

Department of Internal Medicine, Hospital of Zumarraga (OSAKIDETZA-SVS), Barrio Argixao s/n 20700-Zumarraga, Guipuzcoa, Spain, *corresponding author: tel.: +34 943-03 50 00, fax: +34 943-03 50 64, e-mail: ejaaranda@hotmail.com

CASE REPORT

An 83-year-old man presented with a one-week history of a cough productive of purulent sputum, diaphoresis, asthenia, and dyspnoea. Past medical history was relevant for chronic obstructive lung disease and diabetes mellitus. On examination, crackles and decreased breath sounds were present at both lung bases. Chest radiograph only showed right lung atelectasis. Therapy with oral cefuroxime was started. The patient initially had a pyrexia of 38°C for three days despite antibiotics. A thoracoabdominal computerised tomography scan was performed.

WHAT IS YOUR DIAGNOSIS?

See page 215 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (ON PAGE 212)

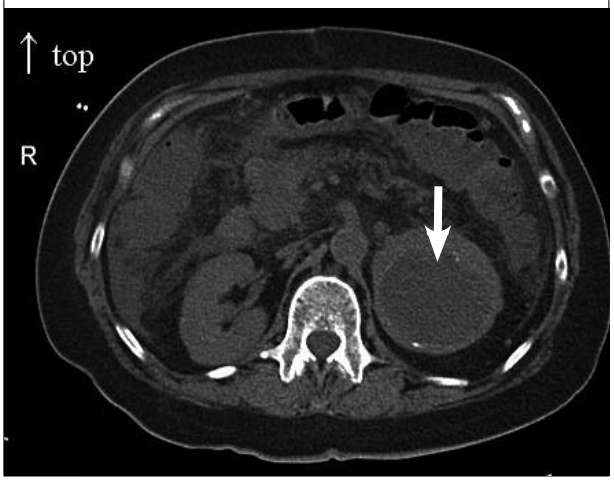
UNDULATING BLOOD PRESSURE

DIAGNOSIS

An abdominal computed tomography scan performed in the work-up of the abdominal symptoms revealed a mass cranial to the left kidney (*figure 2*). A phaeochromocytoma was considered and treatment with labetalol resulted in a more or less stable blood pressure. After ligation of the varices, the bleeding was controlled and volume was replenished. The cycling disappeared resulting in stable hypertension controlled with labetalol and phenoxybenzamine. Urine and serum analyses showed elevated catecholamines and products of catecholamine metabolism. A metaiodobenzylguanidine (MIBG) scan was compatible with a phaeochromocytoma in the left adrenal gland. Left adrenalectomy was performed and the diagnosis phaeochromocytoma was confirmed on histology. After surgery, she remained normotensive without medication except for anticoagulation with coumarin. She is without symptoms to date.

The varices were due to thrombosis of the portal vein without liver cirrhosis, probably related to a JAK-2 mutation. This also explained the thrombosis of the mesenteric vein.

Figure 2. *Upper abdominal CT scan with a mass in the left adrenal region (arrow)*



Hypotension and hypertension alternating with this amplitude and frequency is very rare and is described almost exclusively in patients with phaeochromocytoma.[1,2] The mechanism is not clear.[3] Alternating release and changing proportions of adrenaline, noradrenaline and dopamine has been suggested but is hard to prove. A returning phenomenon in all case reports is that patients showing this type of blood pressure cycling are hypovolaemic. All patients with phaeochromocytoma tend to be hypovolaemic but the described patients had an additional cause of volume depletion. In our patient it was bleeding and intentional fluid restriction. In all described patients blood pressure could be controlled after administration of fluids. The high vascular tone due to the catecholamines is probably exaggerated by the hypovolaemia resulting in low vascular compliance. This might render the patients extremely sensitive to additional changes in volume and vasoactive substances.

In patients with this type of blood pressure cycling, phaeochromocytoma should be considered and treatment is usually unsuccessful unless volume is repleted.

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ANSWER TO PHOTO QUIZ (ON PAGE 213)

AN UNEXPECTED FINDING IN BACTERIAL PNEUMONIA

DIAGNOSIS

The computerised tomography scan showed a condensation in the lower lobe of left lung, a transdiaphragmatic fistula, and a small abscess in the left iliopsoas muscle (*figures 1-3*, arrows). *Staphylococcus aureus* grew in the blood and sputum cultures. Intravenous ceftriaxone and cloxacilline were given for two and four weeks respectively. Two weeks later, the abnormalities had disappeared. The patient improved and was discharged. He was well one month later.

Case reports of transdiaphragmatic fistulas connecting subphrenic collections and the lower airway are very uncommon.

The erosion of a lower pneumonia through the diaphragm seems extremely rare, and has been described sporadically in thoracic actinomycosis.[1-3] *S. aureus*, an important cause of bacteraemia both in community and hospital settings, could spread from the primary entrance route to multiple localisations, mainly endocardium, bone, muscle, and joints.[4] So, pyogenic psoas abscess resulting from haematogenous spread has rarely been reported following a prior pneumonia caused by *S. aureus*.[5]

However, a transphrenic involvement such as contiguity dissemination mechanism remains, to the best of our knowledge, unreported in *S. aureus* pneumonia.

The diagnosis is iliopsoas abscess following a transdiaphragmatic fistula due to *Staphylococcus aureus* pneumonia.

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Figure 1. *CT scan of the abdomen showing a small abscess in the left iliopsoas muscle (black arrow)*

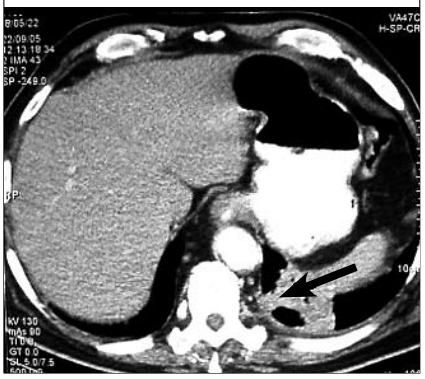


Figure 2. *CT scan of the abdomen showing a transdiaphragmatic fistula (black arrow)*

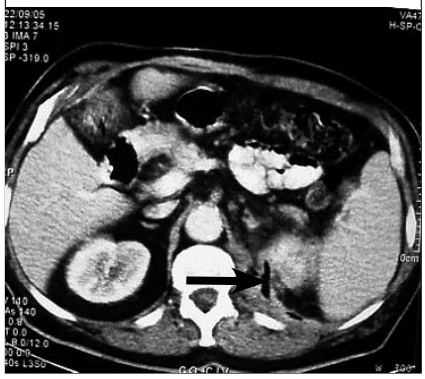
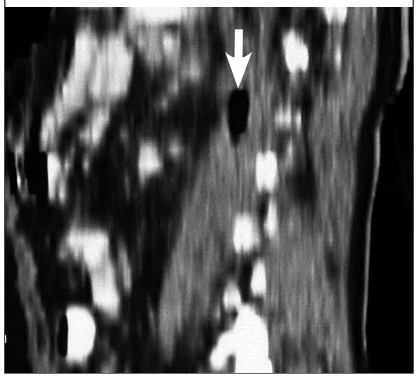


Figure 3. *CT scan of the abdomen (sagital view): air in transdiaphragmatic fistula (white arrow)*



LETTER TO THE EDITOR

Anaemia and haemolysis in pregnancy due to rapid folic acid and vitamin B12 depletion

Dear Editor,

Folic acid and vitamin B12 deficiencies can induce haemolysis, mimicking the HELLP syndrome.[1] None of the reported cases, however, record how fast such vitamin depletion can occur. Here we report rapid vitamin depletion in a 25-year-old pregnant vegetarian woman, without a history of anaemia.

CASE REPORT

A 25-year-old Moroccan gravida 2 was admitted at 35 weeks gestation with anaemia, haemolysis, thrombocytopenia and elevated transaminases without pre-eclamptic symptoms. Her first pregnancy was complicated by severe pre-eclampsia. At 31 weeks gestation she delivered a male infant (1260 grams), whom she breastfed for three weeks. At five months postpartum, investigations revealed mild to moderate hyperhomocysteinaemia, with normal vitamin concentrations (*table 1*).

Seven months later in a subsequent pregnancy, having not taken periconceptional folate supplements, she participated in a double-blind randomised study of folic acid (5 mg) versus placebo from 12 weeks gestation. Fasting serum folate and plasma homocysteine concentrations were measured at 20 and 28 weeks (*table 1*).

Low values of serum folate and vitamin B12 were demonstrated. Apparently the woman was taking placebo medication which was stopped and oral folic acid 5 mg/day and parenteral vitamin B12 was started.

Within three weeks, serum lactate dehydrogenase, the parameter which was used to define haemolysis, had normalised. The woman delivered a healthy male (3050 grams) at 39 weeks, without recurrence of pre-eclampsia. Follow-up investigation showed gastric parietal cell antibodies, so ongoing vitamin B12 therapy was maintained. Schilling's test was not performed. Haemoglobin electrophoresis was normal.

So we present rapid vitamin depletion during pregnancy resulting in haemolytic anaemia. Interestingly, this did not develop during her first pregnancy or while she was lactating. Possible explanations are that the well-grown foetus of the second pregnancy had a higher demand for vitamins than his elder growth-restricted sibling, that the pregnancy accelerated the onset of autoimmune gastritis and associated B12 deficiency, or that the time between

Table 1. *Laboratory findings before, during and after a second pregnancy complicated by haemolysis*

	Before	During						After
	4 months	10 weeks	20 weeks	28 weeks	33 weeks	35 weeks	37 weeks	39 weeks	9 months
Hb (7.5-10.0 mmol/l)	6.6	6.2	6.9	7.3	6.4	5.5	5.7	5.7	7.9
Ht (37-47%)	34	31	34	33	29	26	26	28	
MCV (80-100 fl)						99			
MCH (1700-2000 pmol/l)						2275			
MCHC (20-22.5 mmol/l)						23			
Thrombocytes (150-400 x 10^9/l)	339	398	241	153	150	130	129	354	
Serum ALAT (5-45 U/l)		15	9	17	18	28		11	
Serum ASAT (10-40 U/l)		24	18	28		52	22	30	
Serum LDH (150-400 U/l)				447	1009	1646	836	394	
Serum folate (>5.9 nmol/l)	9.5		7.8	3.3		3.9			
Serum vitamin B12 (156-672 pmol/l)	331					108			
Erythrocyte vitamin B6 (17-100 nmol/l)	33								
Plasma homocysteine fasting (6-15 µmol/l)	17.9		12	10.5					7.9
6 hrs post 100 mg/kg methionine loading (18-51 µmol/l)	52.6								

Hb = haemoglobin; Ht = haematocrit, MCV = mean corpuscular volume; MCH = mean corpuscular haemoglobin; MCHC = mean corpuscular haemoglobin concentration; ALAT = alanine aminotransferase; ASAT = aspatate aminotransferase; LDH = lactate dehydrogenase.

the two pregnancies was too short to recover from possible mild pre-existing deficiencies.

An average Western diet usually contains adequate vitamin B12 and folate above the recommended dietary allowance.[2,3]

More women, however, are becoming vegetarians, so more B12 deficiency can be expected in pregnant women.[4] On direct questioning, no recent changes in her diet were identified.

Thus, B12 and folate status should be investigated in cases of haemolytic anaemia in pregnant women who have not had a recent change in diet.

S.A. van Gellekom[1*], G. Lindauer-van der Werf[2], W.M. Hague[3], J.I.P. de Vries[1]

[1]Department of Obstetrics and Gynaecology, VU University Medical Centre, Amsterdam, the Netherlands, [2]Saint Lucas Andreas Hospital, Amsterdam, the Netherlands, [3]Women's and Children's Hospital, Adelaide, South Australia, [*]corresponding author: fax: +31 (0)20-444 29 54, e-mail: sgm200@student.vu.nl

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MONTHLY NJM ONLINE HITLIST

The table lists online hits for all articles published in the February issue of the *Netherlands Journal of Medicine* (available online on PubMed since 19 February 2008).

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LETTER TO THE EDITOR

Bacteraemia following rubber band ligation for non-bleeding oesophageal varices in a patient with alcoholic liver cirrhosis

Dear Editor,

Rubber band ligation (RBL) for the treatment of oesophageal varices is a common procedure with low morbidity and mortality.[1] Significant complications such as bacteraemia have been reported in less than 6% of patients treated with RBL for bleeding oesophageal varices.[2-4] Septic complications following RBL for non-bleeding varices are, however, very rare.[1,5] Although antibiotic prophylaxis is indicated for all patients with variceal bleeding, some experts suggest that the decision to use antibiotic prophylaxis in high-risk patients solely to prevent infectious complications should be individualised.[5,6] According to the guidelines antibiotic prophylaxis is not indicated for patients undergoing RBL for non-bleeding varices.[1,3]

We report a case of bacteraemia with *Aeromonas sobria* following RBL for non-bleeding oesophageal varices in a 68-year-old male, with documented Child-A alcoholic liver cirrhosis. He was treated with RBL for bleeding oesophageal varices four weeks previously and was admitted to our hospital because of fever. One day before admission he had undergone RBL because of non-bleeding oesophageal varices. No recurrent oesophageal varices bleeding was observed. On examination, he appeared ill with a rectal temperature of 40.3°C, his blood pressure was 98/60 mmHg, with a pulse rate of 90 beats/min and a respiration rate of 12 breaths/min. Further physical examination was unremarkable. Chest x-ray and urine sediment were normal. Laboratory investigation revealed elevated inflammatory indices. After taking blood cultures, he was empirically treated with augmentin and gentamicin for the presumed diagnosis of bacteraemia. Blood cultures grew *Aeromonas sobria* sensitive to cefotaxime. Then he was successfully treated with intravenous cefotaxime for ten days.

Based on these recommendations,[1,3] the patient's history of alcoholic liver cirrhosis is not considered as a high risk, and our patient was not given antibiotic prophylaxis prior to the RBL procedure.

Aeromonas sobria is a facultatively anaerobic, oxidase positive, Gram-negative rod found worldwide in soil and in tap and brackish water. It can cause soft-tissue infections, which usually occur in traumatic wounds, complicated by bacteraemia frequently after contact with tap/surface water or soil.[7,8] In this case, one may speculate that the RBL caused local oesophagus injury and that drinking tap water naturally containing this micro-organism may have caused local infection and bacteraemia. Whether antibiotic prophylaxis would have prevented bacteraemia in this patient is unclear. If bacteraemia after RBL for non-bleeding varices is also observed by others, antibiotic prophylaxis might be considered, at least in high-risk patients.

S. Rasoul[1*], J. Vecht[2], P.H.P. Groeneveld[1]
Departments of [1]Internal Medicine and [2]Gastroenterology, Isala Clinics, location Sophia, Zwolle, the Netherlands, [*]corresponding author: tel.: +31 (0)38-424 40 41, fax: +31 (038)-424 76 45, e-mail: s.rasoul@isala.nl

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LETTER TO THE EDITOR

Current problems in the diagnosis of Henoch-Schönlein purpura according to the ACR or EULAR/PReS criteria

Dear Editor,

We read with interest the article 'A patient with abdominal pain and a rash' by van Laarhoven *et al.*[1] They made the diagnosis of Henoch-Schönlein purpura (HSP) in their patient using the American College of Rheumatology (ACR) criteria.[2] Recently, however, the diagnostic criteria of HSP were modified by EULAR/PReS (the European League against Rheumatism/ Paediatric Rheumatology European Society)[3] to overcome the weak points of the ACR criteria. In these new criteria, the age criterion was deleted, 'predominant IgA deposition' was included in the definition of the criterion describing 'biopsy', and arthritis and renal involvement were added to the group of criteria. Nevertheless, there are some problems in the correct diagnosis of HSP.[3]

Firstly, the ACR or EULAR/PReS criteria cannot detect the atypical presentation (e.g. delayed appearance of purpura) of HSP,[4] leading to unnecessary procedures, such as appendectomy, or unfavorable outcome, such as death. Therefore, Kaneko *et al.* reported that measurement of plasma factor XIII (fibrin stabilising factor) might be useful for the early diagnosis of HSP, because it is decreased even without the purpuric rash, although not a diagnostic criterion of HSP.[5]

Secondly, skin biopsy cannot exactly differentiate HSP from hypersensitivity vasculitis, because IgA deposits may not be stained according to the biopsy site or various factors (e.g. phagocytosis with time) even in HSP.[6]

Thirdly, polyangiitis overlap syndrome can be missed even though a patient presenting with the features of HSP shows IgA deposits on biopsy specimens.[7] Therefore, if a patient has an atypical presentation or a progressive course, the overlap of other vasculitis should also be examined to prevent unexpected fatal situations.

In the future, further studies should be performed to elucidate the epidemiology and natural course of HSP based on the new EULAR/PReS criteria as well as the usefulness of the criteria.

J.I. Shin, J. Seung Lee*
Department of Paediatrics, The Institute of Kidney Disease, Yonsei University College of Medicine, Severance Children's Hospital, Seoul, Korea, *corresponding author: tel.: +82-2-2228 20 54, fax: +82-2-393 91 18, e-mail: jsyonse@yumc.yonsei.ac.kr

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SPECIAL REPORT

Aldosterone-to-renin ratio as a screening test for primary aldosteronism – The Dutch ARRAT Study

P.M. Jansen*, F. Boomsma, A.H. van den Meiracker, the Dutch ARRAT investigators

Department of Internal Medicine, Division of Vascular Pharmacology and Metabolism, Erasmus Medical Centre, 's Gravendijkwal 230, 3015 CE Rotterdam, the Netherlands, *corresponding author: e-mail: p.jansen.1@erasmusmc.nl

ABSTRACT

Since the introduction of the aldosterone-to-renin ratio (ARR) as a screening tool for primary aldosteronism (PA), there has been a marked increase in the reported prevalence of this condition among hypertensive subjects. A meta-analysis from the literature shows a PA prevalence of almost 8% among hypertensive patients, with a twofold higher prevalence in referred patients as compared with primary care patients (9.0 *vs* 4.3%). However, the usefulness of the ARR remains subject of debate, because of doubts on its validity, and the many factors affecting the ARR, including posture, time of day of blood sampling, and use of antihypertensive medication. Furthermore, there is no clear cut-off value and it is unknown what population should be screened. Recently, The Dutch ARRAT Study was initiated. This is a multicentre, prospective trial aiming to evaluate the test characteristics of the ARR within a Dutch population of therapy-resistant hypertensive patients. The effect of antihypertensive medication on the ARR will be studied. Furthermore, from this study the prevalence of PA in this population will follow. Last, the blood pressure response to the selective aldosterone-receptor-antagonist eplerenone will be evaluated. The Dutch ARRAT Study will run until the end of 2009 and will contribute to the formulation of uniform guidelines for the screening for PA in the Netherlands.

KEYWORDS

Aldosterone-to-renin ratio, hypertension, primary aldosteronism

BACKGROUND

Primary aldosteronism (PA) has been a well-known cause of hypertension since the 1950s when Jerôme Conn described a disease state characterised by severe hypertension and hypokalaemia. The cause turned out to be an aldosterone-producing adrenal tumour.[1] Albeit a well-known cause of hypertension, PA was considered to be extremely rare with an estimated prevalence ranging from 0.05 to 2%. This was partly due to the lack of reliable screening tests. The suspicion of PA was mainly raised in the presence of resistant hypertension and hypokalaemia.[2]

Since the introduction of the aldosterone-to-renin ratio (ARR) in 1981,[3] the reported prevalence of PA has increased considerably,[4] and it is nowadays considered a major cause of hypertension by many investigators.

Prevalence studies

Since the introduction of the ARR numerous studies have investigated the prevalence of PA.[5-27] These studies differ in the population that was screened, the screening test that was used and the applied cut-off values of abnormality. Also, there were differences in the diagnostic workup, as will be discussed later. An overview of these studies is given in *table 1,* subdivided into primary care patients (*table 1A*), referred patients with moderate to severe, often poorly controlled hypertension (*table 1B*), and special subgroups (*table 1*C).

The prevalence of an elevated ARR in the reported studies ranged from 0 to 37%, with a weighed mean value of 19%. The prevalence of confirmed PA ranged from 0.7 to 27% with a weighed mean value of 7.8%. The prevalence of PA is highly dependent on the studied population. Rossi *et al.* found an increase in prevalence of PA with increasing severity of hypertension. The mean prevalence in this

Table 1A. *Overview of studies on the prevalence of primary aldosteronism based on aldosterone-to-renin ratio and formal confirmation testing in primary care patients*

Ref.	Population	N	Region	Medication protocol	Screening test	Units	Cut-off values	P(ARR) (%)	Confirmation test	P(PA) (%)	Hypokalaemia (%)	APA (%)
5	Drug trial volunteers with hypertension	52	Australia	Cessation of diuretics	PAC/PRA (3x)	PAC: ng dl^{-1} PRA: ng ml^{-1} hr^{-1}	30	12	FST	12	0	33
9	Primary care clinic hypertensive patients	350	Singapore	Unchanged antihypertensive regimen	PAC/PRA	PAC: ng dl^{-1} PRA: ng ml^{-1} hr^{-1}	PAC/PRA>20 PAC>15	18	Iv SLT	4.6	38	50
14	Primary care clinic hypertensive patients	609	Chili	Cessation of β-blockers, ACE-I, ARB, diuretics, spironolactone and aspirin	SA/PRA	SA: ng dl^{-1} PRA: ng ml^{-1} hr^{-1}	25	10	FST	6.1	2.7	5.4
16	Patients with essential hypertension	118	USA	Unchanged antihypertensive regimen	PAC/PRA	PAC: ng dl^{-1} PRA: ng ml^{-1} hr^{-1}	12.4 (ROC curve)	32	Oral SLT	13	NA	0
20	Mild to moderate, normokalaemic hypertensive patients	347	USA	Cessation of all antihypertensive medication	SA/PRA + elevated SA	SA: ng dl^{-1} PRA: ng ml^{-1} hr^{-1}	SA/PRA > 25 SA > 8	7.5	Oral SLT	3.2	0 (per definition)	NA
22	Primary care hypertensive patients	200	Sweden	Cessation of all antihypertensive medication except calcium blockers	SA/PRC	SA: pmol l^{-1} PRC: ng l^{-1}	100	25	FST	8.5	NA	6.3
25	Randomly selected, primary care hypertensive patients	287	Italy	Cessation of antihypertensive medication except doxazosin and verapamil	PAC/DAR	PAC: pg ml^{-1} DAR: pg ml^{-1}	32	32	-	NA	NA	NA
26	Unselected primary care hypertensive patients	846	UK	Unchanged antihypertensive regimen	PAC/PRA	PAC: pmol l^{-1} PRA: pmol ml^{-1} hr^{-1}	800	14	PAC/PRA >800 + PAC >400 and adrenal adenoma or ΔSBP >20 mmHg on spironolactone	0.7	17	17
Mean								*16*		*4.3*	*12*	*15*

ARR = aldosterone-to-renin ratio; PA = primary aldosteronism; P(ARR) = prevalence of an elevated ARR; P(PA) = prevalence of PA; PAC = plasma aldosterone concentration; SA = serum aldosterone concentration; PRA = plasma renin activity; APA = aldosterone-producing adenoma; DAR = direct active renin; FST = fludrocortisone suppression test; SLT = salt loading test; LDF-score = logistic discriminant function – score; ACE-I = angiotension converting enzyme inhibitors; ARB = angiotensin II receptor blocker; NA = not available; ND = not done. PAC = to convert ng/dl to pmol/l multiply by 27.7. *In patients with an elevated ARR. **The LDF score is explained in Rossi *et al.* (1998).[42] Weighed means for the prevalence of an increased ARR and of PA are based on the total number of cases divided by the total number of patients in the reported studies. Mean percentages of hypokalaemia and APA are weighed for the total number of PA cases in the reported studies.

Table 1B. *Overview of studies on the prevalence of primary aldosteronism based on aldosterone-to-renin ratio and formal confirmation testing in referred patients*

Ref.	Population	N	Region	Medication protocol	Screening test	Units	Cut-off values	P(ARR) (%)	Confirmation test	P(PA) (%)	Hypokalaemia (%)	APA (%)
6	Referred, normokalaemic hypertensive patients	199	Australia	None	PAC/PRA (3x)	PAC: ng dl^{-1} PRA: ng ml^{-1} hr^{-1}	30	11	FST	8.5	0 (per definition)	29
7	Unselected hypertension clinic population	465	UK	Cessation of antihypertensive treatment if possible (60 %)	PAC/PRA	PAC: pmol l^{-1} PRA: ng ml^{-1} hr^{-1}	750	17	FST	9.2	4.7	12
8	Hypertension clinic population	305	Chili	No antihypertensive treatment	SA/PRA (2x)	SA: ng dl^{-1} PRA: ng ml^{-1} hr^{-1}	25	14	FST	9.5	0	3.4
10	Referred patients with poorly controlled hypertension	90	USA	Continuation of antihypertensive treatment	PAC/PRA	PAC: ng dl^{-1} PRA: ng ml^{-1} hr^{-1}	100	17	ND	NA	40*	67*
11	Referred hypertensive patients	1065	Italy	Cessation of antihypertensive treatment except α-blockers	Post-captopril (50 mg) PAC/PRA	PAC: ng dl^{-1} PRA: ng ml^{-1} hr^{-1}	35	13	iv SLT	6.3	39	24
12	Moderate to severe hypertensive patients	402	Czech Rep.	Cessation of antihypertensive treatment except α-blockers	PAC/PRA	PAC: ng dl^{-1} PRA: ng ml^{-1} hr^{-1}	50	22	iv SLT	19	70	36
13	Referred hypertensive patients	300	Australia	Cessation of diuretics, β-blockers, central antihypertensive agents and dihydropyridine calcium blockers	PAC/PRA	PAC: ng dl^{-1} PRA: ng ml^{-1} hr^{-1}	30	20	FST	18	13	31
15	White subjects with resistant hypertension	150	USA	Cessation of spironolactone, triamterene, or amiloride	PAC/PRA	PAC: ng dl^{-1} PRA: ng ml^{-1} hr^{-1}	20	32	Oral SLT	20	15	NA
15	African Americans with resistant hypertension	115	USA	Cessation of spironolactone, triamterene, or amiloride	PAC/PRA	PAC: ng dl^{-1} PRA: ng ml^{-1} hr^{-1}	20	28	Oral SLT	24		NA
17	Consecutive referred hypertensive patients	1125	Italy	Cessation of antihypertensive medication except calcium blockers and/or doxazosin	SA/PRA	SA: pg ml^{-1} PRA: ng ml^{-1} hr^{-1}	40	19	ARR baseline ≥40 + ARR post captopril ≥30 and/or LDF score ≥50%**	11	30	43
18	Unselected referred hypertensive patients	122	UK	Continuation of antihypertensive treatment	PAC/PRA	PAC: pmol l^{-1} PRA: ng ml^{-1} hr^{-1}	750	16	ND	NA	25*	NA
23	Unselected, consecutive hypertensive patients	3000	Italy	Cessation of all antihypertensive medication and other interfering medication	SA/PRA	SA: ng dl^{-1} PRA: ng ml^{-1} hr^{-1}	25	23	iv SLT	5.9	25	30
Mean								20		9.0	29	30

Table 1C. *Overview of studies on the prevalence of primary aldosteronism based on aldosterone-to-renin ratio and formal confirmation testing in special subgroups*

Ref.	Population	N	Region	Medication protocol	Screening test	Units	Cut-off values	P(ARR) (%)	Confirmation test	P(PA) (%)	Hypokalaemia (%)	APA (%)
8	Normotensive control subjects	205	Chili	No antihypertensive treatment	SA/PRA (2x)	SA: ng dl^{-1} PRA: ng ml^{-1} hr^{-1}	25	1.5	FST	1.5	0	0
19	Diabetic patients with hypertension	61	USA	Cessation of spironolactone	PAC/PRA	PAC: ng dl^{-1} PRA: ng dl^{-1} hr^{-1}	30	0	ND	NA	NA	NA
21	Patients with type 2 DM and resistant hypertension	100	USA	None	PAC/PRA	PAC: ng dl^{-1} PRA: ng ml^{-1} hr^{-1}	30	34	Oral SLT (11 %) iv SLT (89 %)	14	NA	NA
24	Normokalaemic hypertensive patients with adrenal incidentalomas	90	Italy	Cessation of antihypertensive medication	PAC/PRA	PAC: ng dl^{-1} PRA: ng ml^{-1} hr^{-1}	112	8.8	iv SLT captopril suppression test	5.6	0 (per definition)	40
27	Patients with residual hypertension after successful endovascular treatment of renal artery disease	24	Italy	None	PAC/DAR	PAC: pg ml^{-1} DAR: pg ml^{-1}	23	33.3	iv SLT	27	NA	29

referred population was 11.2%. However, the prevalence ranged from 6.6% in patients with grade I to 19% in grade III hypertension.[17] A similar trend was observed by Mosso *et al*. who found a prevalence of 2.0% in grade I, rising to 13.2% in grade III hypertension.[14] When the mean reported prevalence of PA in primary care patients is compared with referred patients it is clear that it is twice as high in referred patients, who are expected to have more severe hypertension (*figure 1B*). Remarkably, the prevalence of an elevated ARR is almost as high in primary care as in referred patients (*figure 1A*), indicating the higher percentage of false-positive values when applied in a primary care setting. Even in normotensive subjects a small subset appears to have PA, with reported prevalences of around 1.5%.[8,14]

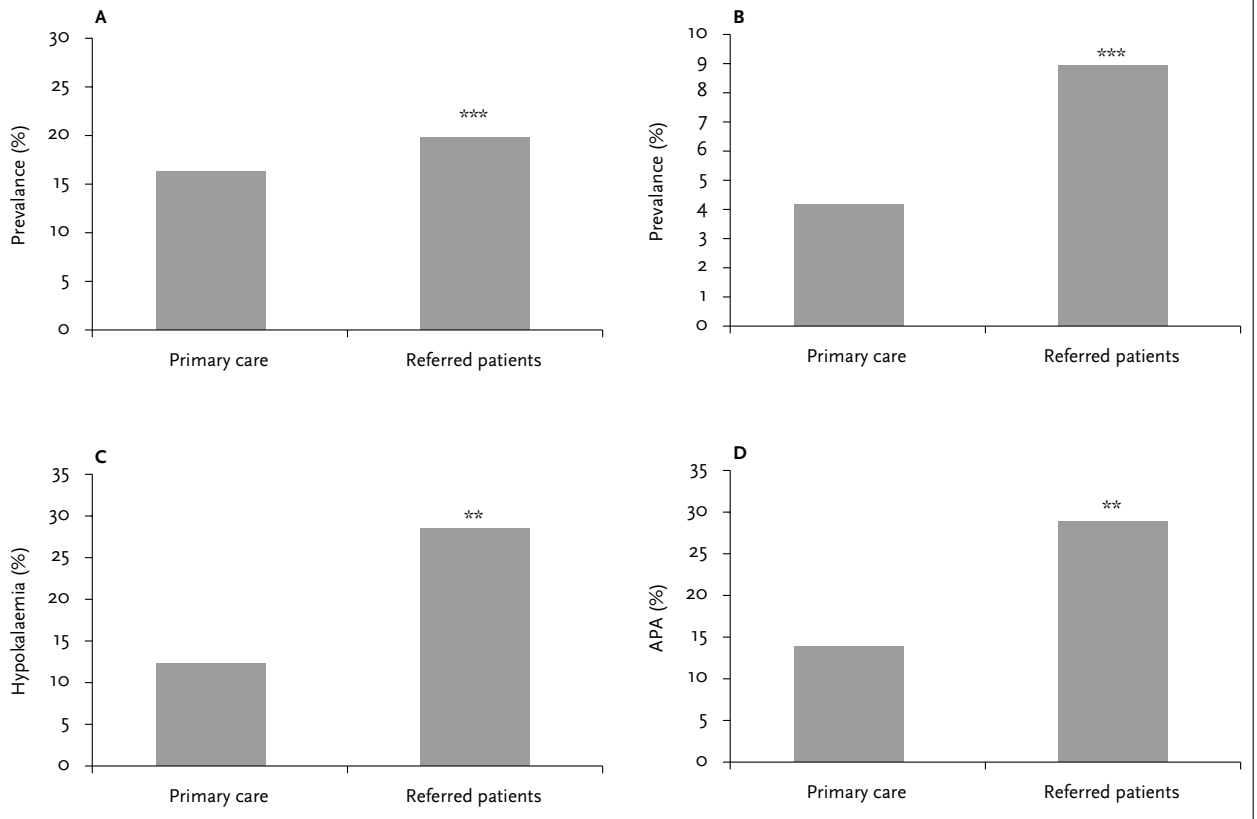
In contrast to former beliefs, many patients with PA present without hypokalaemia, with percentages ranging from 0 to 70%.[5,8-14,17,23,28] In some studies only normokalaemic patients were included.[6,20,24] A retrospective evaluation from centres in five continents showed that between 9 and 37% of patients were hypokalaemic.[4] In the reported studies the percentage of hypokalaemic patients among PA cases was higher in referred patients than in primary care patients (*figure 1C*). Also, the reported numbers of aldosterone-producing adenomas were higher in this group (*figure 1D*). It seems reasonable to conclude that referred patients more frequently have an APA reflected by a more severe phenotype of higher blood pressure levels and lower serum potassium values.

Other subgroups that have been studied for the prevalence of PA include African American patients with resistant hypertension,[15] patients with type 2 diabetes mellitus (DM) and resistant hypertension[21] and hypertensive patients with adrenal incidentalomas.[24] Black subjects generally have lower plasma renin levels than white subjects.[29] However, neither ARR levels nor the prevalence of PA in black and white patients with resistant hypertension were statistically different (24% in African Americans and 20% in white patients).[15,30] In a group of 100 patients with type 2 DM and poorly controlled hypertension a 14% prevalence of PA was reported. This was independent of glycaemic control. This prevalence is similar to reported prevalences in other populations.[21] Patients with adrenal incidentalomas form another group potentially at risk for having PA. Bernini *et al*. screened 90 normokalaemic subjects with an adrenal incidentaloma with hypertension and 35 subjects without hypertension for the presence of PA. Of the subjects with hypertension, 5.6% had PA, whereas no cases were found in the normotensive subgroup, indicating that an adrenal incidentaloma *per se* should not be an indication for screening for PA, unless hypertension is present.[24]

Differences in diagnostic protocols

There are important differences in the diagnostic protocols that were used in the reported studies. The ARR is widely

Figure 1. *Prevalence of A) an elevated aldosterone-to-renin ratio (ARR), B) primary aldosteronism (PA), C) percentage of hypokalaemia and D) aldosterone-producing adenomas (APA) among PA cases in primary care and referred patients*



**p<0.01. ***p<0.001. Figures are based on weighed mean values for the studies reported in *table 1*. The differences are tested using χ^2 testing.

used for screening purposes, but there are variations in the reported cut-off values, depending on the units, and on locally established reference values (*table 1*). Furthermore, in some studies the ARR had to be raised on more occasions for the test to be positive.[5,6,8] Rossi *et al.* assessed ARR after acute administration of captopril, to raise specificity,[11] while other groups included an elevated aldosterone level in the screening test for this purpose.[9,20] In most studies renin was assessed as plasma renin activity (PRA),[5-21,23,24,26] while other studies used plasma renin concentration (PRC).[22,25,27]

Many factors are known to influence the ARR, such as the time of blood sampling and the position of the patient [31,32] and even under standardised conditions biological variability is considerable.[33] These factors account for the wide variation in reported cut-off values making it difficult to formulate a uniform cut-off value.[32] For a correct interpretation of the ARR, sampling conditions should be standardised within and between centres in the same diagnostic setting, using locally established reference values.[32,34]

Some antihypertensive drugs are known to affect aldosterone and renin levels. Beta-blockers cause a decrease in plasma renin levels, thereby leading to an overestimation of the number of positive cases (false-positivity),[35,36] whereas angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers can lead to false-negative results by increasing plasma renin levels.[36] Some protocols required cessation of all antihypertensive drugs[8,20,23,24] whereas other studies allowed the use of certain specific combinations of antihypertensive medications (*table 1*). In some studies no alterations in antihypertensive treatment were made,[9,10,18,21,27] especially when discontinuation of antihypertensive treatment was considered dangerous.[21,27] The most frequently allowed combination of antihypertensive drugs was doxazosin and/or calcium channel blockers.[11-14,17,22,25] Possibly, other factors can be of influence on the ARR as well, for instance the use of non-steroidal anti-inflammatory drugs.[34]

Debate on the ARR as a screening test for PA

Some authors dispute the usefulness of the ARR as a screening test for PA because of the many influencing factors, poor reproducibility, and low sensitivity and specificity.[34,37,38] Furthermore, an elevated ARR may be merely a reflection of low renin levels without indicating

whether there is indeed autonomous secretion of aldosterone, or whether it is mainly a case of 'regular' low-renin hypertension.[31,37,39,40] Also, the clinical relevance of an increased ARR remains unclear.[41] The application of the ARR in an unselected hypertensive population could therefore lead to an enormous increase in costs.[38]

The discussion on the validity of the ARR as a screening test has led to the evaluation of alternative screening methods. Rossi *et al.* have developed a logistic multivariate model in which the probability of PA is calculated based on parameters such as PRA, serum potassium and plasma aldosterone.[42]. Seiler *et al.* have simplified this model to the (serum aldosterone)^2-to-PRA ratio which supposedly has a better diagnostic value than the conventional ARR.[35] However, the validity of this test has not been prospectively evaluated.

Confirmation tests and subtyping

Most authors agree that the ARR should only be used as a screening test and that patients with an elevated ARR should be subjected to a confirmation test to establish the diagnosis. The most frequently applied confirmation tests are the intravenous or oral salt loading test and the fludrocortisone-suppression test.[43]

Most studies include subtyping after establishing the diagnosis of PA. The most important subgroups of PA are aldosterone-producing adenomas (APA) and idiopathic primary aldosteronism (IPA). Glucocorticoid-remediable aldosteronism (GRA) is a genetic form of PA in which crossing-over of the CYP11B1 and CYP11B2 genes leads to a hybrid gene, coding for aldosterone synthase, but under main regulation by ACTH instead of angiotensin II.[44]

In most studies, subtyping was performed using computed tomography (CT) or magnetic resonance imaging (MRI) techniques to visualise any adrenal abnormalities.[5,7,8,10-14,16,23] In some cases adrenal venous sampling (AVS) was used to assess lateralisation of aldosterone production.[5,6,9,12,13] Gallay *et al.* and Rossi *et al.* utilised scintigraphic techniques to detect any functional tumours.[10,11] GRA was mostly detected using a dexamethasone-suppression test or genetic testing. The prevalence of APAs among PA cases is given in *table 1* and ranged from 0 to 67%.

Mulatero *et al.* showed that widespread screening for PA has led to a shift in the proportion of bilateral hyperplasia as a cause of PA, with this subtype now comprising the majority of cases. Interestingly, the detection rate of APAs appears to be mainly dependent on the availability of AVS, with higher proportions found in centres where AVS was available.[4,17] This supports the superiority of AVS to detect lateralised aldosterone production over CT or MRI. This has been confirmed by Stowasser *et al.* who found a large incoherence between the findings in radiological imaging *vs* AVS.[13]

CONCLUSION

PA appears to be a relatively frequent cause of hypertension, with prevalences ranging up to more than 20%, depending on the population subjected to screening. Most cases present without hypokalaemia. Furthermore, diagnostic protocols vary in their individual steps and methods. Several known and unknown factors can influence the ARR.

Diagnosing PA as a cause of hypertension is important. First, because patients with PA have more cardiovascular events than patients with essential hypertension, independent of blood pressure, stressing the need for early detection to prevent complications.[45] Second, because specific treatment is available: adrenalectomy in case of an adrenal adenoma and treatment with an aldosterone-receptor-antagonist in case of bilateral adrenal hyperplasia.[46,47]

The Dutch ARRAT Study

Because of the discussion concerning the correct diagnostic pathway for the screening for PA, a study on the diagnostic value of the ARR for the Dutch situation is needed. This has led to the design of The Dutch ARRAT Study.

The Dutch ARRAT Study is a prospective, multicentre study, in which the diagnostic value of the ARR and the prevalence of PA will be evaluated within a Dutch population of therapy-resistant hypertensive patients. Furthermore, the effect of add-on therapy with an aldosterone-receptor antagonist on blood pressure will be studied.

The objectives of The Dutch ARRAT Study are outlined in *table 2*.

The inclusion and exclusion criteria for the study population are given in *table 3*. It is planned to include a total of 500 patients over a period of three years. Nineteen centres will participate.

Patients will be followed-up for a period of 35 weeks. Before inclusion β-blocking agents and potassium-sparing diuretics are stopped. In the first stage reproducibility of the ARR will be studied. As gold standard for the presence or absence of PA an intravenous salt loading test will be performed. Also, an oral salt loading test will be done to assess the validity of this less cumbersome test. During the intravenous salt loading test plasma aldosterone levels

Table 2. *Objectives of The Dutch ARRAT Study*

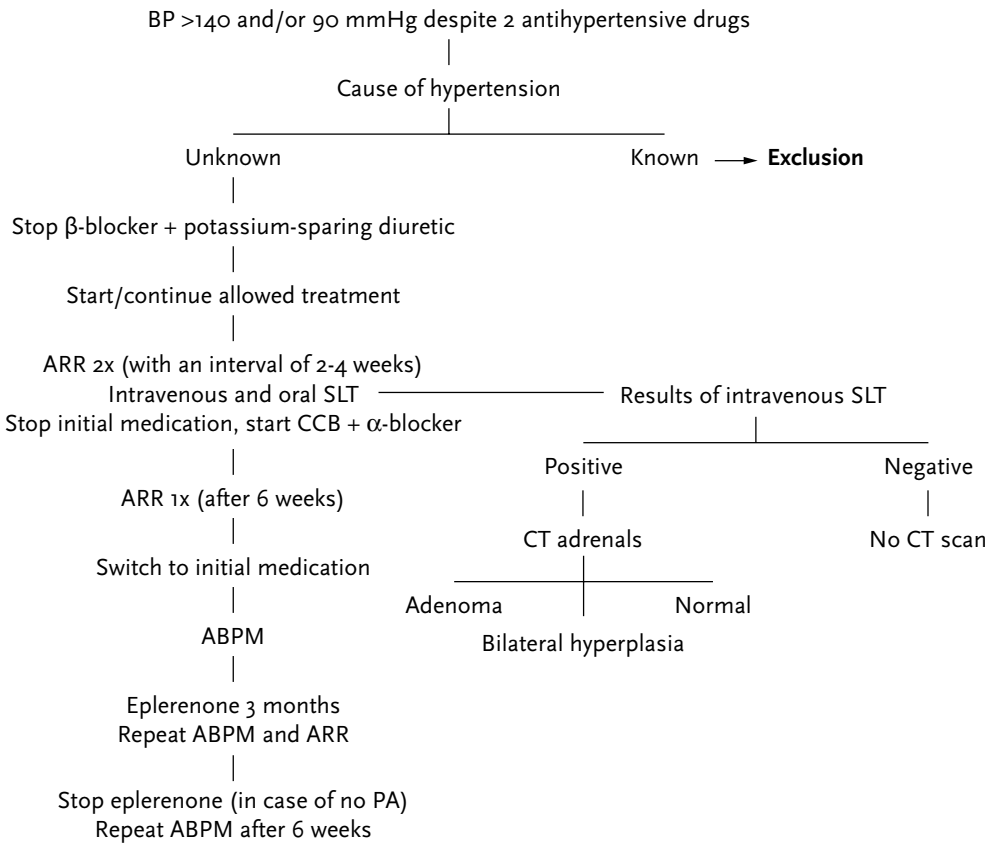
Evaluation of the test characteristics of the aldosterone-to-renin ratio
Evaluation of the effect of antihypertensive medication on the aldosterone-to-renin ratio
Assessment of the prevalence of primary aldosteronism in a Dutch population of patients with therapy-resistant hypertension
Evaluation of the clinical response to an aldosterone-receptor antagonist in this population

Table 3. *Inclusion and exclusion criteria of The Dutch ARRAT Study*

Inclusion criteria
Age 18-65 years
Office blood pressure >140 mmHg systolic and/or >90 mmHg diastolic or ambulant blood pressure >135 mmHg systolic and/or >85 mmHg diastolic
Use of an effective combination of at least two antihypertensive drugs
Exclusion criteria
Known cause of hypertension
White-coat hypertension
Serum creatinine level >200 µmol/l
Body mass index >32 kg/m^2
Poorly regulated diabetes mellitus (HbA_1C >8.0%)
Heart failure
Stroke, transient ischaemic attack or myocardial infarction in the past 6 months
Angina pectoris
Pregnancy
Neoplastic disease in the past 5 years
Alcohol abuse

will be assessed before and after a four-hour infusion of two litres of physiological salt solution. During the oral salt loading test the 24-hour urinary aldosterone excretion will be assessed while the patient is on a sodium-rich diet. In both tests an insufficient suppression of aldosterone is diagnostic of PA. For the intravenous salt loading test this is defined as a post-infusion plasma aldosterone exceeding 85 pg/ml and for the oral salt loading test as a 24-hour urinary aldosterone excretion exceeding 12 µg. Then, in all patients their original antihypertensive medications will be replaced by standardised medication consisting of doxazosin and amlodipine. After six weeks the ARR will be tested again. After restarting their own antihypertensive drugs, the effect of add-on therapy with eplerenone, a selective aldosterone-receptor-antagonist, on blood pressure and ARR will be evaluated. The blood pressure response will be evaluated with 24-hour ambulant blood pressure monitoring devices (ABPM). If the salt loading test is indicative for PA, a CT scan of the adrenal glands will be performed to assess the subtype of PA (adrenal adenoma or bilateral adrenal hyperplasia). The protocol is summarised in *figure 2*.

Figure 2. *Flowchart of The Dutch ARRAT Study*



BP = blood pressure; ARR = aldosterone-to-renin ratio; SLT = salt loading test; CCB = calcium-channel blocker; ABPM = ambulant blood pressure measurement; CT = computed tomography; PA = primary aldosteronism.

Time schedule

The inclusion started in December 2006. At the moment of writing, 50 patients have been included in the study protocol. Most centres have not yet started inclusion. Data collection will run until the end of 2009.

Expected outcomes

The Dutch ARRAT Study will provide data on the test characteristics and determinants of the ARR, the prevalence of PA in therapy-resistant hypertensive patients from the Dutch population and determinants of the clinical response to an aldosterone-receptor antagonist in this selected population. These data will ultimately contribute to the formulation of uniform guidelines for the diagnosis of primary aldosteronism in the Netherlands.

For more information about the study the authors can be contacted, also if you are interested in participating. If you have a patient meeting the criteria for inclusion, referral to one of the participating centres can be considered.

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SPECIAL REPORT

The Netherlands Journal of Medicine: the Utrecht years

G.H. Blijham

Chairman of the Board, University Medical Centre Utrecht, Utrecht, the Netherlands
Editor-in-Chief, Netherlands Journal of Medicine 1996-1998

A NEW START

The eighties and nineties of the last century were witness to major changes in the practice of internal medicine in the Netherlands. For decades, the approach towards internal medicine had been a generalistic one. Subspecialities were considered to be mainly relevant for academic medicine; in community hospitals internists were expected to be experts in every aspect of internal medicine. Now this was changing. New subspecialities were developing, such as infectious diseases and medical oncology and in the traditional subspecialities major scientific developments were being translated into new methods of patient care. Internal medicine became a family of disciplines, each with their own body of knowledge and expertise. Internists had to find ways to adapt to this new reality and to establish a new equilibrium between the generalistic approach of the past and the differentiated internal medicine of the future.

They did that in various ways, the most important one being the formation of large group practices which allowed individual members to subspecialise without losing the ability to cover the general aspects of the other subspecialities. It was only in academic medicine that subspecialists could develop full independence. In other words, differentiation on the individual level, as a group responsible for the generalistic approach: that became the major paradigm of the practice of internal medicine in the majority of Dutch hospitals. As a consequence, virtually all subspecialities, such as nephrology, haematology, medical oncology, infectious diseases, intensive care and endocrinology, have never been transferred into official medical specialities; they have remained subspecialities within the one official medical speciality of internal medicine.

So in the last two decades of the 20th century, two opposite developments were taking place at the same time: the fragmentation of internal medicine into subspecialities and the resurrection of internal medicine as a binding force between those subspecialists. The progress of science dictated the first one, the need for efficient and coherent patient care pushed the second one. In many countries the fragmentation took place earlier; internal medicine virtually disappeared. In the Netherlands it remained alive and well and so did its Journal, the Netherlands Journal of Medicine.

I have described these developments because they constitute the landscape in which the Journal had to find a new position. In short, more than in the past, we had to accommodate for what had happened in the subspecialities but we had to do that in a manner that was of interest to internists who would still not be full-blown subspecialists. The Journal had to become a journal covering all subspecialities without becoming a subspeciality journal. Of course, at the same time traditional aspects of general internal medicine including areas such as clinical epidemiology and medical ethics also had to be addressed.

The new Utrecht editorial team started this endeavour with enthusiasm and determination. Its composition was already a reflection of the new direction: a mixture of academic subspecialists and community hospital internists. We quickly found each other on the principles I have described and set out to put these principles into practice: soliciting of subspecialist articles with original data with relevance for the practice of internal medicine, inviting experts to give comments on new scientific findings in the context of their impact on medical practice, expanding the scope of book reviews to the full spectrum of internal medicine. We tried to increase the quality of the contributions by increasing the number of international reviewers; good quality papers will attract good quality papers and the success of this approach could be seen in a steady increase in the impact factor.

After four years, I was asked to become the President of my institution, the University Medical Centre Utrecht. That position soon appeared to be too challenging to be compatible with the chief editorship of the Netherlands Journal of Medicine. It was decided to keep the Journal's editorial office in Utrecht to continue with the changes that were initiated and appeared to be successful. With some regret but also with great thrust I descended in favour of the new editor-in-chief, Professor Andy Hoepelman. I am still very grateful that I had the privilege to lead the Journal in such an exciting time in the history of internal medicine in the Netherlands. Fortunately, the Utrecht years would continue in good hands.

Blijham. The Netherlands Journal of Medicine: the Utrecht years.

Aims and scope
The Netherlands Journal of Medicine publishes papers in all relevant fields of internal medicine. In addition to reports of original clinical and experimental studies, reviews on topics of interest or importance, case reports, book reviews and letters to the editor are welcomed.

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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.

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