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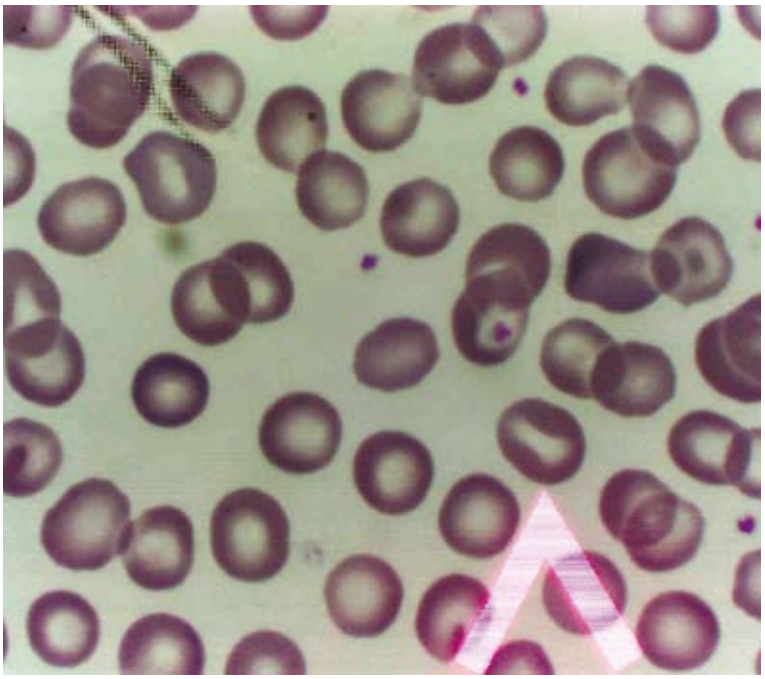

Haemolytic anaemia diagnosed after 30 years: what's your diagnosis?

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EDITORIAL

Early recognition of critically ill patients

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The field of intensive care medicine has moved forward with the implementation of several new therapies and strategies tested in numerous clinical trials. Implementation of new interventions in the daily practice of caring for critically ill patients, however, is a major challenge. Common factors associated with failure to implement new therapies and strategies in intensive care practice include simple translation problems ('we do not know how'), potentially biased expert opinions ('we do not believe it'), concerns about possible side effects ('we are afraid of doing harm'), costs associated with implementation ('we cannot afford it'), but maybe most of all problems with the (early) recognition of patients who might actually benefit from a new therapy or strategy ('we did not recognise it').

Simple interventions that have a high potential to benefit critically ill patients include, but are not restricted to, early infusion of sufficient amounts of fluids for sepsis[1] and lung-protective mechanical ventilation for acute lung injury/acute respiratory distress syndrome (ALI/ARDS).[2,3] Timing of fluid therapy for sepsis is crucial for its beneficial effects.[4] Indeed, the latest trial on fluid therapy showed that early optimisation of oxygen delivery (by means of early infusion of sufficient amounts of fluids) was able to decrease mortality in patients with septic shock.[1] *Early* therapy means *early* recognition. However, the location of patients in the early phase of their critical illness varies among institutions. Although most critically ill patients should be treated in the intensive care unit, a good many of them may spend a significant part of the early phase in the emergency department or the hospital ward. Obviously, early recognition of patients who may benefit from early fluid therapy should thus be done by physicians working outside the intensive care unit, and in most cases these physicians are the residents.

In this issue of the *Netherlands Journal of Medicine,* Tromp *et al.* report on the effects of a regional education programme on residents' knowledge about sepsis.[5] Their main finding was that residents level of knowledge about 'assessment of symptoms of sepsis' was less than about 'diagnosis and treatment'. Following education, knowledge about 'assessment of symptoms of sepsis' increased. This finding underlines the above-mentioned problem of under-recognition: residents are very aware of what to do, but do less well in recognising patients in whom they should act early. Continuous education may be warranted, since over time assessment of symptoms of sepsis tended to decline. Similar problems may exist with the early recognition of ALI/ARDS. Indeed, under-recognition of ALI/ARDS was (and continues to be) one of the most important barriers to the implementation of lung-protective mechanical ventilation.[6] Even physicians who are well trained in the field of intensive care medicine at times miss this important diagnosis, thereby possibly subjecting patients to mechanical ventilation strategies that may be harmful. But this problem may be even bigger: ALI/ARDS is rarely present at the time of hospital admission and it may be more important to be able to identify patients who may develop ALI/ARDS (instead of recognition of patients who already have ALI/ARDS). Indeed, subsequent ('second hit') hospital exposures modify the development and expression of this life-threatening syndrome in patients with predisposing conditions. Several studies suggest that early treatment of shock and infection[7] and avoidance of ventilator-related lung injury[8-10] and transfusion-related acute lung injury[11] may reduce the incidence of hospital-acquired ALI/ARDS. From this we may conclude that ALI/ARDS, at least in part, is a potentially preventable healthcare-acquired complication.

In this issue of the *Netherlands Journal of Medicine,* Ahmed *et al.*[12] report on progress on the early recognition of patients with or at risk of ALI/ARDS. Automated electronic screening tools and novel scoring systems may facilitate care of patients at risk for ALI/ARDS. 'ALI/ARDS sniffers' may be helpful in the early recognition of ALI/ARDS, and high-resolution monitoring may help in the timely identification of patients who develop ALI/ARDS during the course of their illness.

The interest of these two papers[5,12] lies in the possible combined effect of education and application of electronic

screening tools in the early recognition of the many disease states of critically ill patients. Many interventions should find their way into daily practice: implementation through education and early recognition of so-called bundles of care[13] have the potential to improve the outcome of these patients.[14]

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REVIEW

Early identification of patients with or at risk of acute lung injury

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ABSTRACT

Acute lung injury (ALI) and its more severe form, acute respiratory distress syndrome (ARDS), are important critical care syndromes for which the treatment options are limited once the condition is fully established. Enormous basic and clinical research efforts have led to improvements in supportive treatment, but surprisingly little has been done on the prevention of this devastating syndrome. The development and progression of ALI/ARDS may be triggered by various intrahospital exposures including but not limited to transfusion, aspiration, mechanical ventilation, certain medications and delayed treatment of shock and infection. Early recognition of patients with or at risk of ALI/ARDS is essential for designing novel prevention and treatment strategies. Automated electronic screening tools and novel scoring systems applied at the time of hospital admission may facilitate enrolment of patients into mechanistic and outcome studies, as well as future ALI/ARDS prevention trials.

KEYWORDS

Acute lung injury, acute respiratory distress syndrome, pneumonia

INTRODUCTION

Acute lung injury (ALI) and its more severe form, acute respiratory distress syndrome (ARDS), are important critical care syndromes for which the treatment options are limited once the condition is fully established. In fact, most recent data suggest that the poor prognosis of ALI/ARDS has remained essentially the same over the past 15 years.[1] Enormous basic and clinical research efforts have led to improvements in supportive treatment,[2,3] but surprisingly little has been done on the prevention of this devastating syndrome.

Insufficient understanding of the clinical development and progression of ALI precludes the design of preventive strategies at the present time. While some studies have suggested potentially important roles of several environmental risk modifiers,[4-12] the knowledge gap persists, with limited understanding of why some patients with septic shock, trauma or pneumonia do and others do not develop ALI.

Preclinical studies support a 'two hit' model of development of ALI/ARDS whereby different exposures modify the expression of ALI/ARDS in the primed or susceptible host.[13] For example, common critical care exposures such as mechanical ventilation[14] and transfusion[15] greatly influence the development of ALI in preclinical models, and the 'two hit' experiments are considered to more accurately represent the clinical setting.[13] Preliminary clinical data suggest that ALI/ARDS is rarely present at the time of hospital admission, but develops over a period of hours to days in subsets of patients with predisposing conditions, such as pneumonia, sepsis, trauma and shock and corresponding medical and surgical interventions.[16,17]

EARLY IDENTIFICATION OF PATIENTS WITH ALI/ARDS

Electronic surveillance for ALI/ARDS

Critical care syndromes such as ALI/ARDS are not routinely coded in hospital databases and are greatly under recognised by bedside providers. Although a standardised definition has existed for more than a decade,[18] efforts required for data collection and screening have significantly limited clinical studies in this area. In a recent study, only 27% of ALI episodes were documented by bedside providers.[19] The advancement of electronic medical records (EMR) provides the opportunity for electronic screening (syndrome surveillance) of ALI/ARDS and related syndromes. Our team has developed and validated a novel syndrome surveillance

tool (ALI 'sniffer') for the recognition of patients with ALI and ARDS (*figure 1*).[19] Electronic alert is triggered by the following combination of observations: the ratio of partial pressure of oxygen to inspired oxygen concentration (PaO_2/FIO_2) <300 and chest radiograph report (free text Boolean query containing trigger words: ('bilateral' AND 'infiltrate') OR 'edema'. With an excellent negative predictive value (0.99, 95% CI 0.98 to 1.00), ALI sniffer is optimised for screening patients with a high probability of ALI/ARDS. It has been continuously running since December 2005, allowing prospective identification of ALI/ARDS cases.

Azzam *et al.*[20] have recently reported similar results. Using the American European Consensus Conference (AECC) criteria,[18] excluding current or known history of congestive heart failure, the automated screening tool had a sensitivity of 87%, specificity of 89% and accuracy of 88% in capturing patients with ALI/ARDS.

Although currently limited to a minority of institutions, electronic screening has a very promising potential application in both clinical settings and research.

High-resolution monitoring of ALI/ARDS development

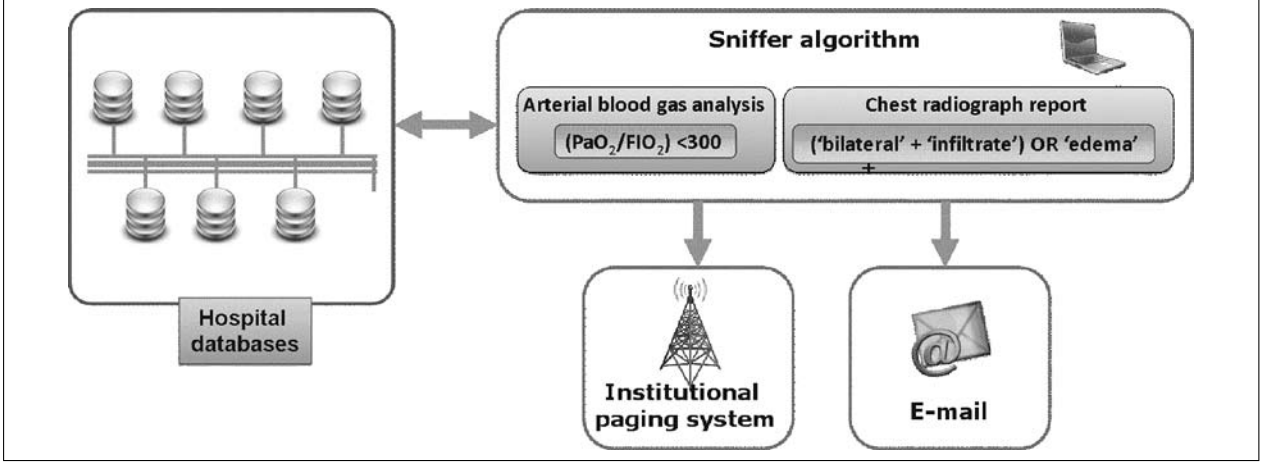
A standardised ALI assessment method based on the AECC definition[21] facilitated diagnosis of ALI/ARDS for clinical research and quality improvement projects in our institution.[22] The absence of left atrial hypertension as a primary explanation for pulmonary oedema is excluded by integrated clinical evaluation based on the combination of echocardiographic findings (E/E' <15), brain natriuretic peptide levels (BNP <250 pg/ml in the absence of renal failure), venous filling pressures (PAOP ≤18 cm H_2O or CVP <15 cm H_2O in the absence of pulmonary hypertension) and the response to therapy (brisk response to diuretics and positive pressure ventilation favours hydrostatic oedema). This process yielded good inter-observer agreement for differentiation between ALI and hydrostatic oedema (kappa values from 0.65 to 0.83).[22,23]

Since most clinical studies to date have been limited by a low temporal resolution ('today the patient does not have ALI and tomorrow he/she does'), it has been very difficult to distinguish between the cause and effect role of specific risk factors (effect-cause bias). High-resolution monitoring of hospitalised patients allows us to pinpoint the beginning of respiratory worsening based on the sustained changes in respiratory rate and the ratio of arterial oxygen saturation over inspired oxygen concentration (SpO_2/FIO_2) without being dependent on bedside providers ordering arterial blood gas (ABG) analysis. Rice *et al.*[24] recently validated SpO_2/FIO_2 thresholds against the gold standard of ABG. SpO_2/FIO_2 <315 corresponds to ALI (PaO_2/FIO_2 <300) and SpO_2/FIO_2 <235 corresponds to ARDS (PaO_2/FIO_2 <200). Hence, early identification of ALI/ARDS could be done without arterial blood gas confirmation which could cause delay in diagnosis and treatment as well as enrolment in clinical trials. In *figure 2* the black arrow points to a sustained decrease in oxygen saturation followed by an increase in oxygen supplementation at 1 AM suggesting the onset of respiratory worsening. The chest radiograph and blood gas analysis performed five hours later (6 AM) confirmed ALI, but only exposures occurring before 1 AM were considered in the analysis. This conservative approach minimises the effect-cause bias in this type of association study. Our group has used this approach to identify exposures of interest related to transfusions,[6] antibiotic management[25] and goal-directed resuscitation.[25]

IDENTIFICATION OF PATIENTS AT RISK OF DEVELOPING ALI AND ARDS

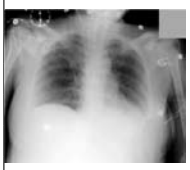
One of the principal barriers towards better understanding of clinical pathogenesis of ALI/ARDS and the design of effective ALI/ARDS preventive strategies is the fact that previous clinical studies focused exclusively on patients admitted to the ICU. While multiple studies around the world reported

Figure 1. *Electronic surveillance for acute lung injury (ALI 'sniffer')*

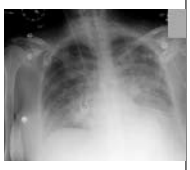


Ahmed, et al. Early identification of patients with or at risk of acute lung injury.

Figure 2. *High-resolution monitoring of acute lung injury development*



	20.00	21.00	22.00	23.00	00.00	01.00	02.00	03.00	04.00
Physiological parametres									
Real-time variables									
Heart rate	82	88	86	87	88	105	125	127	114
NIBP systolic	108	106	108	112	116	115	154	91	81
NIBP diastolic	58	52	52	56	58	75	81	48	39
Fresh-frozen plasma (ml)		226		245	269				
Medication infusions									
Vasopressin (unit/min)									
Crystalloid in									
0.9 NaCl (ml/h)	100	100	100	100	100	100	100	100	100
0.9 NaCl - fluid bolus (ml)								<	500
Ventilator settings									
Real-time variables									
Oxygen device #1	CFM					↓	CFM		CFM
Oxygen %/LMP #1	5.00						50%		50%
SpO_2	99	100	97	98	97	88	91	95	92



The black arrow points to a sustained decrease in oxygen saturation followed by an increase in oxygen supplementation at 01.00 AM suggesting the onset of respiratory worsening. The chest radiograph and blood gas analysis performed five hours later (06.00) confirmed ALI.

the risk factors for ALI/ARDS,[26-29] only a few prospectively followed patients with predisposing conditions to document the probability of developing ALI/ARDS. Landmark studies by Pepe *et al.*,[30] Fowler *et al.*[31] and Hudson *et al.*[32] were conducted in the early 1980s and 1990s, before the current definitions of ALI and ARDS, sepsis and pneumonia were established. Recent cohort studies used specific definitions but were still restricted to patients admitted to the ICU.[5,12,33-35,10,11,36]

The proportion of patients with risk factors who develop ALI/ARDS drops drastically when assessed at the time of hospital admission.[17] In a recent study by Ferguson *et al.*[17] only 7% of hospitalised patients with sepsis, 2% with pancreatitis, 10% with pneumonia and 15% with witnessed aspiration developed ALI.[17] Many patients with predisposing conditions never develop ALI/ARDS and are never admitted to the ICU[17] making the enrolment of non-selected patients into ALI/ARDS prevention studies neither practical nor efficient without a method to select high-risk patients.

To facilitate enrolment of patients into mechanistic and outcome studies as well as future ALI/ARDS prevention trials, our group has recently developed an ALI/ARDS prediction model,[37] (the Lung Injury Prediction Score: LIPS) which incorporates demographic, environmental and clinical characteristics at the time of, and before hospital admission. LIPS takes into consideration not only different incidences of ALI/ARDS depending on underlying risk factors (from 2% risk in patients with uncomplicated pancreatitis[17] up to 40% in those with septic shock[38]) but also the presence of significant risk modifiers (smoking,[39] alcohol,[10,40] diabetes mellitus,[11] chemotherapy,[38] hypoalbuminaemia,[41] and respiratory rate[5]). If prospectively validated and refined in relevant patient populations, this model could serve to define the patients at high risk of ALI/ARDS in whom future mechanistic studies and ALI/ARDS prevention trials will be conducted. By determining not only patients at high risk but also the attributable burden of ALI/ARDS in contemporary cohorts of patients at risk, the findings are expected to facilitate the prioritisation of preventive strategies and future clinical trials.

Another recent study[42] reported that patients who require high oxygen supplementation when in the emergency room (O_2 >2 l/min) are more likely to progress into ALI. In addition, the authors defined a clinical diagnosis of early ALI in patients who present at hospital admission with bilateral opacities on chest radiograph not exclusively due to left atrial hypertension and who initially required oxygen supplementation of >2 l/min (73% sensitive and 79% specific for progression to ALI with respiratory failure).

CONCLUSION

ALI/ARDS is rarely present at the time of hospital admission. Subsequent ('second hit') hospital exposures have modified the development and expression of the syndrome in patients with predisposing conditions. Therefore, ALI/ARDS may be viewed as a potentially preventable healthcare-acquired complication analogous to venous thromboembolism, stress ulcer bleeding or nosocomial infections. Preliminary studies suggest that early treatment of shock and infection[38] and avoidance of ventilator and transfusion-related lung injury[43] may reduce the incidence of hospital-acquired ALI/ARDS.[43] Electronic surveillance and novel scoring systems for early identification of patients with or at risk of ALI/ARDS will facilitate future mechanistic studies and ALI/ARDS prevention trials.

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REVIEW

Rhabdomyolysis: a review of the literature

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ABSTRACT

Rhabdomyolysis is a potentially life-threatening syndrome that can develop from a variety of causes; the classic findings of muscular aches, weakness and tea-coloured urine are non-specific and may not always be present. The diagnosis therefore rests upon the presence of a high level of suspicion of any abnormal laboratory values in the mind of the treating physician. An elevated plasma creatine kinase (CK) level is the most sensitive laboratory finding pertaining to muscle injury; whereas hyperkalaemia, acute renal failure and compartment syndrome represent the major life-threatening complications. The management of the condition includes prompt and aggressive fluid resuscitation, elimination of the causative agents and treatment and prevention of any complications that may ensue. The objective of this review is to describe the aetiological spectrum and pathophysiology of rhabdomyolysis, the clinical and biological consequences of this syndrome and to provide an appraisal of the current data available in order to facilitate the prevention, early diagnosis and prompt management of this condition.

KEYWORDS

Creatine kinase, rhabdomyolysis, muscle weakness, myoglobin, myoglobinuria

INTRODUCTION

Rhabdomyolysis is a potentially life-threatening syndrome characterised by the breakdown of skeletal muscle resulting in the subsequent release of intracellular contents into the circulatory system. These cell contents include enzymes such as creatine kinase (CK), glutamic oxalacetic transaminase, lactate dehydrogenase, aldolase, the haeme pigment myoglobin, electrolytes such as potassium and phosphates, and purines.[1-3] The development of rhabdomyolysis may be associated with a wide variety of diseases, injuries, medications and toxins. It ranges in severity from an asymptomatic elevation of CK levels in blood, to severe life-threatening cases associated with very high CK levels, myoglobinuria and acute renal failure.
Rhabdomyolysis was first reported in Germany in 1881, but it was Bywaters and Beall who described the syndrome in detail after the Battle of London, during the Second World War.[4]

PATHOPHYSIOLOGY

Although the causes of rhabdomyolysis are so diverse, the pathogenesis appears to follow a final common pathway, ultimately leading to myocyte destruction and release of muscle components into the circulation. In the normal myocyte, the sarcolemma, a thin membrane that encloses striated muscle fibres, contains numerous pumps that regulate cellular electrochemical gradients. The intercellular sodium concentration is normally maintained at 10 mEq/l by a sodium-potassium adenosine triphosphatase (Na/K-ATPase) pump located in the sarcolemma.[5] The Na/K-ATPase pump actively transports sodium from the interior of the cell to the exterior. As a result, the interior of the cell is more negatively charged than the exterior because positive charges are transported across the membrane. The gradient pulls sodium to the interior of the cell in exchange for calcium by a separate ion exchange channel. Moreover, low intracellular calcium levels are also maintained by an active calcium exchanger (Ca^{2+} ATPase pump) that promotes calcium entry into the sarcoplasmic reticulum and mitochondria.[6] The above processes depend on ATP as a source of energy. ATP depletion, which appears to be the end result of most causes of rhabdomyolysis, results in Na/K-ATPase and

Ca^{2+} ATPase pump dysfunction, the end result of which is an increased cellular permeability to sodium ions due to either plasma membrane disruption or reduced cellular energy (ATP) production.[7] Accumulation of sodium in the cytoplasm leads to an increase in intracellular calcium concentration (which is normally very low relative to the extracellular concentration). This excess calcium then increases the activity of intracellular proteolytic enzymes that degrade the muscle cell. As the myocyte degenerates, large quantities of potassium, aldolase, phosphate, myoglobin, CK, lactate dehydrogenase, aspartate transaminase and urate leak into the circulation.[5,7,8] Under physiological conditions, the plasma concentration of myoglobin is very low (0 to 0.003 mg per dl). If more than 100 g of skeletal muscle is damaged, the circulating myoglobin levels exceed the protein-binding capacity of the plasma and can precipitate in the glomerular filtrate. Excess myoglobin may thus cause renal tubular obstruction, direct nephrotoxicity, and acute renal failure.[9-11] *Figure 1* describes the mechanisms of rhabdomyolysis.

CAUSES

The aetiological spectrum of rhabdomyolysis is extensive; in many cases, multiple muscle insults are usually needed to produce rhabdomyolysis unless an underlying myopathy is present.[12] The most common causes of rhabdomyolysis in adults are illicit drugs, alcohol abuse, medical drugs, muscle diseases, trauma, neuroleptic malignant syndrome (NMS), seizures and immobility.[12] Whereas in paediatric patients, the most common causes are viral myositis, trauma, connective tissue disorders, exercise, and drug overdose.[11] *Table 1* summarises the causes of rhabdomyolysis.

Drugs and toxins

Rhabdomyolysis may result from substance abuse, toxins, prescription and nonprescription medications. Substances that are commonly abused include ethanol, methanol and ethylene glycol,[13,14] heroin,[15] methadone,[16] barbiturates,[17] cocaine,[18] caffeine,[19] amphetamine,[20] lysergic acid diethylamide,[21] 3,4-methylenedioxymethamphetamine

Figure 1. *Mechanisms of rhabdomyolysis*

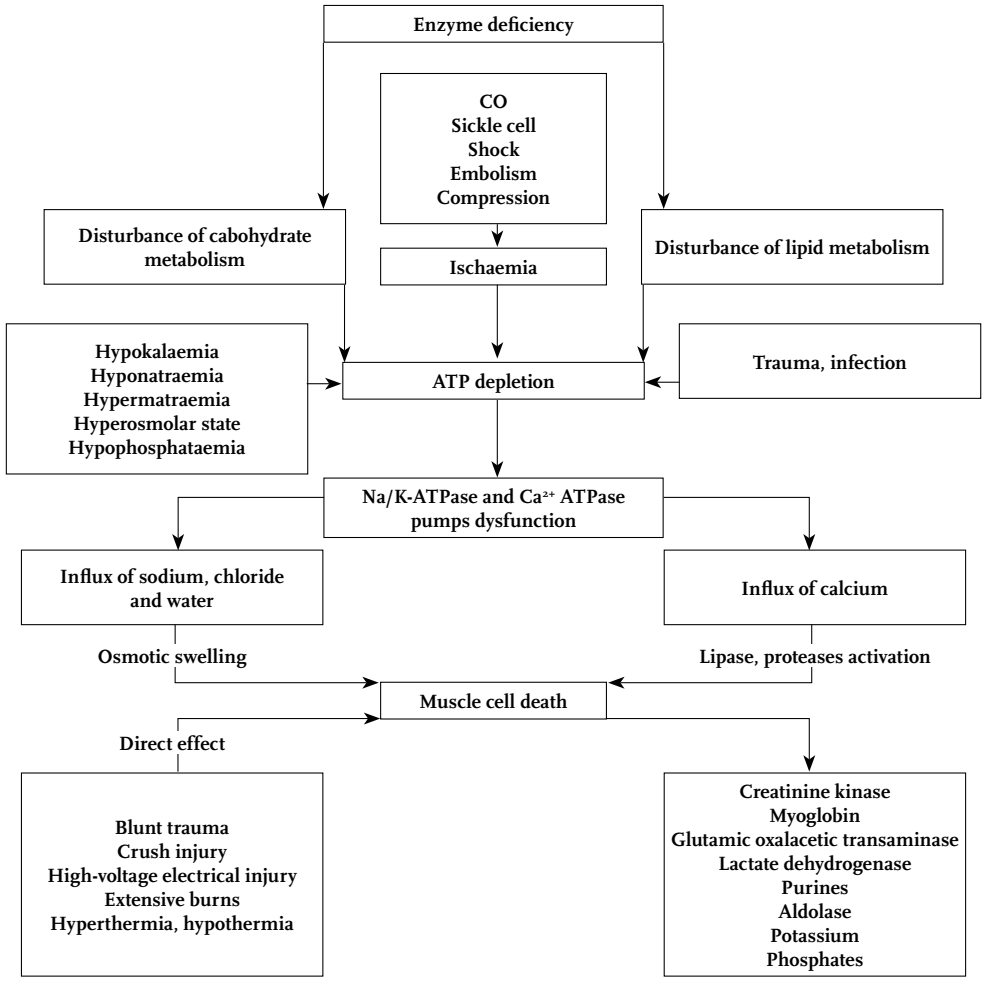

Table 1. *Causes of rhabdomyolysis*

Drugs and toxins
Trauma
Excessive muscular activity
Temperature extremes
Muscle ischaemia
Prolonged immobilisation
Infection
Electrolyte and endocrine abnormalities
Genetic disorders
Connective tissue disorders
Unknown

(MDMA, ecstasy),[22] phencyclidine,[23] benzodiazepines,[24] and toluene (from glue sniffing).[25]

Alcohol can induce rhabdomyolysis through a combination of mechanisms including immobilisation, direct myotoxicity and electrolyte abnormalities (hypokalaemia and hypophosphataemia).[9] Moreover cocaine-induced rhabdomyolysis may occur through multiple mechanisms: vasospasm with muscular ischaemia, seizures, hyperpyrexia, coma with muscle compression, and direct myofibrillar damage.[17]

Excessive use of barbiturates, benzodiazepines, and other sedative and hypnotics can cause depression of the central nervous system with prolonged immobilisation and muscle compression, resulting in muscle hypoxia and destruction.[26]

Other causes of toxin-induced rhabdomyolysis include carbon monoxide (CO),[27] hemlock herbs from quail,[9] snake bites,[28] spider venom (e.g., black widow spider),[29] and massive honey bee envenomations.[30] CO combines with haemoglobin to form carboxyhaemoglobin in the blood and prevents the binding of oxygen, so causing muscle hypoxia and rhabdomyolysis.

Rhabdomyolysis may also result from both prescribed and over-the-counter medications including[31] salicylates,[32], fibric acid derivatives (e.g., bezafibrate, clofibrate, fenofibrate, gemfibrozil),[33-36] neuroleptics,[37] anaesthetic and paralytic agents (the malignant hyperthermia syndrome),[38] quinine,[39] corticosteroids,[40] statins (e.g., atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, cerivastatin),[41-46] theophylline,[47] cyclic antidepressants, selective serotonin reuptake inhibitors (the serotonin syndrome),[48] aminocaproic acid,[49] phenylpropanolamine,[50] and propofol.[51]

Statin-induced rhabdomyolysis may result from a variety of mechanisms. Firstly an unstable skeletal muscle cell membrane due to a blockage in the synthetic pathway for cholesterol, which results subsequently in a low intra-membranous cholesterol content. Secondly, the presence of abnormal prenylated protein causes an imbalance in intracellular protein messenger. Thirdly, abnormal mitochondrial respiratory function occurs which is caused by coenzyme Q10 deficiency.[44]

Trauma

Rhabdomyolysis may also occur after traumatic events, including significant blunt trauma (caused by physical assault or sudden automobile deceleration) or crush injuries,[52] high-voltage electrical injury (from lightning strikes or electrocution by high-voltage power supplies),[53] and extensive third-degree burns.[1]

Crush injuries are associated with severe trauma and most commonly occur with multiple casualty disasters, such as bombings, earthquakes, building collapse, mine accidents, and train accidents.[54-57] Rhabdomyolysis is actually noted to occur only once the acute compression of the muscle is relieved during which the necrotic muscle is released into the circulation: for example, once the victims of collapsed buildings are excavated or the people crushed during car accidents are released. In high-voltage electrical injury and extensive third-degree burns, rhabdomyolysis occurs through the direct myofibrillar damage that results as a consequence of the electrical insult.

Excessive muscular activity

Other significant causes of rhabdomyolysis include excessive muscular activity,[58-61] such as sporadic strenuous exercise (e.g., marathons), status epilepticus, status asthmaticus, severe dystonia, acute psychosis, and military recruits in boot camp. The more strenuous or prolonged the exercise, the more damage is incurred. Excessive muscular activity results in a state in which ATP production cannot keep up with the demand, subsequently exhausting cellular energy supplies leading to a disruption of muscle cell membranes. Factors that increase the risk of exertional rhabdomyolysis are hypokalaemia (often resulting from excessive sweating), and sickle-cell trait (especially in combination with high altitude), extreme heat and humidity, exercise-induced asthma, or pre-exertion fatigue.[62] Noteworthy, rhabdomyolysis cases associated with low-intensity exercise have also been reported.[63] In these cases the mechanism remains unknown.

Temperature extremes

Excess heat, regardless of its cause, may result in muscle damage. The term *thermal maximum* was developed to measure the magnitude and duration of heat that cells can endure before becoming damaged. Human *thermal maximum* has been established as a core body temperature of approximately 42 °C (107.6 °F) for between 45 minutes and eight hours.[64] Cellular destruction occurs more quickly and completely at higher temperatures. Causes of excess heat include heat stroke,[65] neuroleptic malignant syndrome[66] and malignant hyperthermia syndrome.[67] Although rare, exposure to cold with or without hypothermia can lead to rhabdomyolysis,[12,68,69] due to direct muscle injury.[70]

Muscle ischaemia

Muscle ischaemia interferes with oxygen delivery to the cells, thereby limiting the production of ATP. If oxygen deprivation is maintained for prolonged periods this may result in muscle cell necrosis. Skeletal muscle ischaemia may result from either localised or generalised conditions. Localised causes include compression of blood vessels[71-73] (e.g., intraoperative use of tourniquets, tight dressings or casts, prolonged application of air splints or pneumatic antishock garments and clamping of vessels during surgery), thrombosis, embolism, compartment syndrome, CO and sickle cell trait.[74,75] On the other hand, generalised causes of muscle ischaemia include hypotension and shock states.

Prolonged immobilisation

Prolonged immobilisation (e.g., anaesthesia, coma, drug or alcohol-induced unconsciousness) has been reported to cause rhabdomyolysis due to unrelieved pressure on gravity-dependent body parts.[76] As reported by Szewczyk *et al.*,[77] the most common positions leading to rhabdomyolysis were the lateral decubitus, lithotomy, sitting, knee-to-chest and prone position. The primary mechanism is reperfusion of damaged tissue after a period of ischaemia, and the release of necrotic muscle material into the circulation after pressure is relieved.[76,77] The risk factors for position-related rhabdomyolysis were identified as body weight more than 30% above ideal body weight, duration of surgery more than five to six hours, extracellular volume depletion, pre-existing azotaemia, diabetes, and hypertension.[78]

Infections

The proposed mechanisms for infection-induced rhabdomyolysis include tissue hypoxia (caused by sepsis, hypoxia, dehydration, acidosis, electrolyte disturbances and hypophosphataemia), direct bacterial invasion of muscle, low oxidative and glycolytic enzyme activity, activation of lysosomal enzymes and mechanisms implicating endotoxins.[79-81]

Numerous bacterial, viral, fungal and protozoal infections can lead to rhabdomyolysis. Viral infections as a cause of rhabdomyolysis have been described in many reports worldwide, of which influenza types A and B[82,83] are the most common. Other viruses linked towww rhabdomyolysis include HIV,[84] coxsackievirus,[85] Ebstein-Barr virus,[86] echovirus,[87] cytomegalovirus,[88] herpes simplex virus,[89] varicella-zoster virus,[90] and West Nile virus.[9W1]

Bacterial infections including *Legionella* species are classically associated with rhabdomyolysis in adults.[92] Other bacterial agents that might cause rhabdomyolysis include *Salmonella* species,[93] *Streptococci* species,[94,95] *Francisella tularensis*,[96] *Staphylococcus aureus*[97] *Leptospira* species,[98] *Mycoplasma* species[99] and *Escherichia coli*.[100]

On the other hand, rhabdomyolysis has been reported in patients with fungal and malaria infections.[101-103]

Electrolyte and endocrine abnormalities

Severe electrolyte derangements, including hyponatraemia,[104] hypernatraemia,[105] hypokalaemia[106] and hypophosphataemia[107] may lead to rhabdomyolysis, with the proposed mechanism being cell membrane disruption as a result of deranged sodium-potassium-ATPase pump function.

Endocrine abnormalities such as hypothyroidism[108] or hyperthyroidism,[109] diabetic ketoacidosis,[110] and non-ketotic hyperosmolar diabetic coma[111] have been reported to cause rhabdomyolysis.

Genetic disorders

These disorders usually start during childhood; a history of recurrent episodes of rhabdomyolysis, a family history of attacks or episodes precipitated by mild exertion or starvation increases the probability of a genetically determined metabolic myopathy. Inherited disorders that may cause rhabdomyolysis include enzyme deficiencies (of carbohydrate or lipid metabolism)[112,113] and myopathies.[114] Abnormalities in glycogen or lipid metabolism result in a block of anaerobic glycolysis that predisposes to the loss of integrity of the sarcolemmal membrane and the liberation of myoglobin following exercise. *Table 2* describes the common genetic disorders that cause rhabdomyolysis.

Table 2. *Common genetic disorders that cause rhabdomyolysis*

Deficiencies of glyco(geno)lytic enzymes
Myophosphorylase (McArdle's disease)
Phosphorylase kinase
Phosphofructokinase (Tarui's disease)
Phosphoglycerate mutase
Phosphoglycerate kinase
Lactate dehydrogenase
Abnormal lipid metabolism
Carnitine palmitoyltranferase deficiency I and II
Carnitine deficiency
Other genetic disorders
Myoadenylate deaminase deficiency
Duchenne's muscular dystrophy
Malignant hyperthermia

Connective tissue disorders

Although considered rare, it is known that connective tissue disorders such as polymyositis, dermatomyositis and Sjögren's syndrowwwme may induce rhabdomyolysis.[115-117]

Unknown causes

In many cases the aetiology of rhabdomyolysis cannot be identified. Some of these cases present with recurrent myoglobinuria and are termed idiopathic paroxysmal myoglobinuria (Meyer-Betz disease). Whether such patients have a genetic defect requires further study.

CLINICAL FEATURES

The clinical presentation is extremely variable; due to the large range of causes of this condition, it may vary from subclinical to severe, depending upon the extent and severity of muscle damage. Tea-coloured urine is a classical manifestation of rhabdomyolysis.

In conscious patients, the main complaint may be muscle tenderness, swelling, stiffness and cramping, accompanied by weakness and loss of function in the involved muscle group(s).[2,3,8,9] Muscle swelling may not become apparent until after rehydration with intravenous fluids. Most frequently the involved muscle groups are the postural muscles of the thighs, calves and lower back.[118] Nonspecific systemic symptoms, such as malaise, fever, abdominal pain, and nausea and vomiting, may also be seen.[3,8,9] Changes in mental status occur occasionally, either secondary to urea-induced encephalopathy or related to the underlying aetiology (e.g. toxins, infections, electrolyte disturbance, drugs and trauma). In comatose patients, the finding of limb induration may suggest rhabdomyolysis. Skin changes due to ischaemic tissue injury (discoloration, blisters) may be present on the affected area; however, there may be no signs of muscle involvement.

Rhabdomyolysis may be an incidental finding during laboratory testing, in such cases efforts should be directed toward finding the underlying aetiology.

INVESTIGATIONS

Unless there is a high index of suspicion, rhabdomyolysis can be missed, since muscular pain, swelling, and tenderness may not be prominent features and may even be absent. Therefore, the definitive diagnosis of rhabdomyolysis should be made by laboratory tests including serum CK and urine myoglobin. In addition, skeletal muscle biopsy can be used to confirm the diagnosis.

Serum creatine kinase

Serum CK concentration, mainly the CK-MM subtype, is the most sensitive indicator of damage to muscles. Serum CK begins to rise approximately 2 to 12 hours after the onset of muscle injury, peaks within 24 to 72 hours, and then declines at the relatively constant rate of 39% of the previous day's value.[118] A persistently elevated CK level suggests continuing muscle injury or development of a compartment syndrome.[119] Although various values of CK have been postulated to define rhabdomyolysis, the magnitude of elevation is rather arbitrary; and there is no cut-off value that conclusively diagnoses rhabdomyolysis. A serum CK activity greater than five times the normal value (in the absence of heart or brain diseases) was accepted by many authors as a criterion for the diagnosis of rhabdomyolysis.[1,2] However, the Clinical Advisory on Statins defined statin-induced rhabdomyolysis as muscle symptoms with marked CK elevation typically substantially greater than 10 times the upper limit of normal, with a creatinine elevation consistent with pigment nephropathy and usually with brown urine with myoglobinuria.[120,121]

Serum and urine myoglobin

Myoglobin is normally bound to plasma globulins, and has a rapid renal clearance which maintains a low plasma level up to a certain serum concentration (0 to 0.003 mg/dl). After the occurrence of muscle damage the circulating myoglobin levels exceed the plasma protein binding capacity, reach the glomeruli and are eventually excreted in the urine. Myoglobinuria does not occur without rhabdomyolysis, but rhabdomyolysis does not necessarily lead to visible myoglobinuria (tea or cola coloured urine). Before the urine becomes discoloured by myoglobin the level of myoglobin in the urine must exceed 100 mg/dl.[122] Although elevated serum myoglobin and myoglobinuria are reliable parameters for rhabdomyolysis, their sensitivity and specificity are affected by many factors. Firstly, serum myoglobin usually increases before a rise in CK and drops more rapidly than does the decline in CK concentration (in one to six hours).[119] Moreover, myoglobinuria may not be visible or may resolve early in the course of rhabdomyolysis. These facts make this parameter less sensitive and therefore should not be relied upon to rule out the diagnosis of rhabdomyolysis. Secondly, myoglobinuria is detected by urine dipstick tests (orthotoluidine), which also react with the globin fragment of haemoglobin. Thus, in the presence of red blood cells or haemolysis, the specificity of this test is limited. Radioimmunoassay is more sensitive and specific than dipstick. However, this test is often not readily available, and it may take more than 24 hours to obtain results.

Muscle biopsy

The muscle biopsy is not necessary, although it can be used to confirm the diagnosis of rhabdomyolysis. The histopathological findings usually include loss of cell nucleus and muscular stria with the absence of inflammatory cells.[123]

Investigations for underlying abnormalities

Once the diagnosis of rhabdomyolysis is established, a search must be instituted for a cause. A careful history and physical examination may reveal the underlying aetiology of rhabdomyolysis or at least may help in the selection of the appropriate diagnostic workup. However, in many cases the history and clinical examination are not conclusive; in such cases the decision to select the appropriate test is not clear since there is no standard protocol for such a situation. Actually, the nature of the investigations depends on the disorder suspected; thus, toxicological screens should be

performed if drugs are a suspected causal agent, whereas appropriate cultures and serological studies should be performed if infections are suspected. Endocrine assay and blood chemistry may be necessary to confirm the suspected endocrine and metabolic disorders. Furthermore, genetic analysis, muscle biopsy, and the forearm ischaemic test[124] may be indicated in patients with suspected genetic disorders, whereas the susceptibility of any individual to malignant hyperthermia can be detected by performing the Caffeine Halothane Contracture Test (CHCT).[125] Magnetic resonance image (MRI) may be useful in distinguishing the various aetiologies of rhabdomyolysis.[126,127]

Other investigations

Arterial blood gas analysis is useful tool to evaluate acid-base balance, whereas ECG is helpful to evaluate for cardiac arrhythmias related to hyperkalaemia or hypocalcaemia. Complete blood count including haemoglobin, haematocrit and platelets, blood chemistry, liver function tests, prothrombin time (PT), activated partial thromboplastin time (aPTT), serum aldolase, and lactate dehydrogenase are other useful laboratory tests that should be included. MRI is very effective in localising rhabdomyolysis, especially when fasciotomy is considered as a treatment option. The sensitivity of MRI in the detection of muscle involvement is higher than that of either computed tomography or ultrasound.[128]

Investigations may show hyperkalaemia, hypocalcaemia, hyperphosphataemia, hyperuricaemia, metabolic acidosis and raised levels of other muscle enzymes including lactate dehydrogenase, aldolase, carbonic anhydrase III and aminotransferases.[113] An elevated aspartate aminotransferase (with a normal alanine aminotransferase) could be a clue that rhabdomyolysis is occurring. The hypercalcaemia observed in some patients during the recovery phase of acute renal failure is due to the mobilisation of calcium from their muscle deposits and because of secondary hyperparathyroidism which usually occurs.[129] Troponin I was found to be high in 50% of patients with rhabdomyolysis. Of these, 58% were ultimately found to be true positives, 33% were false positives, and 9% were indeterminate.[130] Serum creatinine may be disproportionately elevated in relation to blood urea nitrogen in the absence of prerenal azotaemia, because of the release of preformed creatine from damaged muscles and its spontaneous hydration to creatinine.

COMPLICATIONS

The complications of rhabdomyolysis include hypovolaemia, compartment syndrome, arrhythmias, disseminated intravascular coagulation, hepatic dysfunction and acute renal failure. *Table 3* describes the complications of rhabdomyolysis.

Table 3. *Complications of rhabdomyolysis*

Hypovolaemia
Compartment syndrome
Arrhythmias and cardiac arrest
Disseminated intravascular coagulation
Hepatic dysfunction
Acidosis
Acute renal failure

Hypovolaemia

Necrosis along with inflammation results in the influx of fluid into the necrotic muscle and the accumulation of substantial amounts of fluid into the affected limbs (up to 10 litres per limb). The influx of extracellular fluids produces a 'third space' effect and as fluid is lost from the circulation, hypovolaemia and haemodynamic shock develop.[131]

Compartment syndrome

The ischaemic and oedematous muscle further raises intra-compartmental pressure potentiating a vicious cycle of continuing ischaemia.[122]

Most striated muscles are contained within rigid compartments formed by fasciae, bones, and other structures. High intra-compartmental pressure provokes additional damage and necrosis. This further muscle damage is manifested as the 'second wave phenomenon', the persistent elevation or rebound elevation in CK levels at 48 to 72 hours after the initial insult. Prolonged ischaemia and infarction of muscle tissue can result in replacement of muscle by inelastic fibrous tissue and severe contractures (Volkmann's contracture).[113]

The measurement of intramuscular pressure provides an objective parameter guiding the decision to perform fasciotomy. In non-hypotensive patients, this should be done when the intramuscular pressure exceeds 50 mmHg or if pressure values between 30 and 50 mmHg show no tendency to decrease after a maximum of six hours.[9]

Arrhythmias and cardiac arrest

One of the most characteristic electrolyte abnormalities induced by rhabdomyolysis is severe hyperkalaemia, especially in patients with acidaemia or oliguria. Hyperkalaemia can precipitate severe arrhythmias and cardiac arrest. Hypocalcaemia resulting from calcium deposition in necrotic muscle is another electrolyte disturbance that may lead to cardiac arrhythmias.[1,2] Moreover, hyperkalaemia coupled with hypocalcaemia can predispose to malignant cardiac arrhythmias.

Disseminated intravascular coagulation

Disseminated intravascular coagulation (DIC) may complicate severe rhabdomyolysis and can result in haemorrhagic complications.[118] It probably results from the

activation of the clotting cascade by components released from the damaged muscles.

Hepatic dysfunction

Hepatic dysfunction occurs in approximately 25% of patients with rhabdomyolysis. Proteases released from injured muscle may be implicated in hepatic inflammation.[132]

Acidosis

Sulphur-containing proteins released in large amounts can lead to hydrogen and sulphate loads that overwhelm renal excretory mechanisms, resulting in an anion gap acidosis, which may be severe. Other causes of acidosis in the setting of rhabdomyolysis include lactic acidosis from ischaemia and the acidosis of uraemia.

Acute renal failure

Acute renal failure (ARF) develops in 33% of patients and is the most serious complication in the days following the initial presentation.[122] Factors known to contribute to rhabdomyolysis-induced ARF include hypovolaemia, acidosis or aciduria, tubular obstruction, and the nephrotoxic effects of myoglobin.

ARF occurs as a result of decreased circulating plasma volume which potentiates renal hypoperfusion (via renal vasoconstriction) and in the presence of acidic urine, myoglobin and uric acid precipitates and forms obstructive casts. At urinary pH below 5.6, myoglobin dissociates into ferrihaemate and globin. Ferrihaemate has a direct nephrotoxic effect which potentiates acute tubular necrosis, a form of ARF. In the absence of hypovolaemia and acid urine, myoglobin has a less nephrotoxic effect.[6,9] Various clinical factors are used to predict the risk of ARF, including serum CK, creatinine, potassium, and Ca^{2+}, as well as the urine myoglobin level, but no single parameter has been established.[133]

MANAGEMENT

There is a lack of level I evidence from which the best management plans for rhabdomyolysis may be derived. In fact, no randomised controlled trials of treatment have been conducted, and most evidence is based on retrospective clinical studies, case reports and animal models. Nevertheless important aspects of management include prompt and aggressive fluid resuscitation, the elimination of causative agents and the management and prevention of any complications that may arise. *Table 4* summarises the management plan for rhabdomyolysis.

Prehospital care

Because hypovolaemia is often present, normal saline (NS) resuscitation should be initiated preferably at the site of injury, before extrication. It has been reported that early intervention has decreased the incidence of ARF.[134] Intravenous access should immediately be secured with a large-bore catheter and normal saline infusion should begin at a rate of 1.5 litres/hour to maintain a urine output of 200 to 300 ml/hour. Potassium- or lactate-containing solutions should be avoided because of the risk of rhabdomyolysis-associated hyperkalaemia and lactic acidosis.

Table 4. *Management plan for patients with rhabdomyolysis*

Prehospital care
- ABC assessment
- Intravenous access
- Consider the importance of early fluid administration in the field
- NS infusion at a rate of 1.5 litres /hour, to maintain a urine output of 200-300 ml/hour
- Avoid empirical administration of potassium and lactate-containing fluids

Inhospital care
- Aggressive intravenous rehydration
- A careful history and physical examination
- Closely monitor serum electrolyte and CK
- Monitor fluid intake and urinary output (urinary catheter insertion).
- Check limbs for compartment syndromes
- Haemodynamic monitoring (central venous pressure measurements).
- Administer mannitol and bicarbonate (for patients with crush injury): a 20% mannitol infusion at a dose of 0.5 g/kg is given over a 15-minute period and subsequently followed by an infusion at 0.1 g/kg/h. Adjustments are made to maintain urine output >200 ml/h. Sodium bicarbonate, one ampoule (44 mEq) added to 1 l of ½NS or two to three ampoules (88 to 132 mEq) in D5W to run at a rate of 100 ml/hour, has been recommended to maintain a urinary pH of ≤6.5 to prevent the development of ARF
- Intensive care monitoring (for critically ill patients)

Treatment of any reversible cause of muscle damage
- Correct electrolyte and metabolic abnormalities
- Treat hyperthermia and hypothermia
- Eliminate and detoxify drugs and toxins

Management and prevention of complications
- Hyperkalaemia may be fatal and should be corrected vigorously
- Hypocalcaemia should be corrected only if it causes symptoms
- Hypophosphataemia and hyperphosphataemia usually require no treatment; treat hyperphosphataemia with oral phosphate binders when serum levels exceed 7 mg/dl
- Compartment syndrome requires immediate orthopaedic consultation for fasciotomy
- DIC usually resolves spontaneously after several days if the underlying cause is corrected, but if haemorrhagic complications occur, therapy with platelets, vitamin K, and fresh frozen plasma may be necessary
- Hyperuricaemia and hyperphosphataemia are rarely of clinical significance and rarely require treatment
- Consider dialysis as a lifesaving procedure for patients with rising or elevated potassium level, persistent acidosis, or oliguric renal failure with fluid overload
- Consider continuing dialysis support until patients' kidney function has recovered

CK = creatine kinese; ½NS = half-normal saline; D5W = dextrose 5%; ARF = acute renal failure; DIC = disseminated intravascular coagulation.

Inhospital care

Once in hospital, aggressive intravenous rehydration should be continued in order to promote vigorous diuresis and to dilute the released toxic products:[135] An infusion of 1.5 litres of saline per hour is often required during the initial management, and 300 to 500 ml/h once haemodynamic stability has been achieved. In severe cases of rhabdomyolysis with crush injury, administration of both blood products and normal saline may be necessary for the effective treatment of hypovolaemia.

Concurrently, a careful history and physical examination should be attempted in order to identify and manage any underlying illnesses. Vital signs, urine output, serial electrolyte levels, and CK levels should be obtained as soon as possible. Intensive care monitoring may be required depending on the severity of the clinical scenario. A urinary catheter should be inserted and urine output should be monitored carefully. For patients with heart disease, comorbid conditions, preexisting renal disease or for elderly patients, haemodynamic monitoring may be necessary to avoid fluid overload. Although there is no standard protocol in the literature for the duration of fluid administration, IV fluid should be continued until the levels of CK in the plasma decrease to 1000 U/l or below.[2]

Although there are no randomised controlled trials supporting this, the addition of mannitol and bicarbonate after the initial resuscitation with saline has been recommended (especially in crush injury) by many experts[136,137] to prevent acute kidney injury.

Proposed benefits of mannitol include an increase in the renal blood flow and glomerular filtration rate which may help to prevent obstruction by myoglobin casts; osmotic diuretics draw fluid in from the interstitial compartment to the intravascular compartment which counteracts the hypovolaemia and acts to reduce muscle swelling and nerve compression, as well as the scavenging of free radicals.[6,134,138,139]

Mannitol should only be given after volume replacement and avoided in patients with oliguria. A 20% mannitol infusion at a dose of 0.5 g/kg is given over a 15-minute period and subsequently followed by an infusion at 0.1 g/kg/h. Adjustments are made to maintain urine output at >200 ml/h. Urinary and serum pH levels are monitored, with acetazolamide added if the serum pH is >7.45 or urinary pH remains <6.0.[133] The use of loop diuretics (e.g., furosemide) in rhabdomyolysis is controversial, with some researchers recommending their use and others opposing it because loop diuretics acidify the urine.[118]

Alkalinisation of urine (by sodium bicarbonate) is advocated for the purpose of decreasing cast formation, minimising the toxic effects of myoglobin on the renal tubules, inhibiting lipid peroxidation, and decreasing the risk for hyperkalaemia. Sodium bicarbonate, one ampoule (44 mEq) added to 1 litre of half-normal saline (½NS) or two to three ampoules (88 to 132 mEq) in dextrose 5% (D5W) to run at a rate of 100 ml/h, has been recommended to maintain a urine pH of ≥6.5 to prevent the development of ARF.[140]

Treatment of any reversible cause of muscle damage

In order to stop ongoing muscle destruction any underlying condition, such as trauma, infection, or toxins, must obviously be identified and treated as soon as possible. Treatment of hyperthermia is essential and can be achieved by using external cooling measures and by controlling for muscular hyperactivity with benzodiazepines. In malignant hyperthermia, anaesthetics should be discontinued, and the patient should be treated with dantrolene sodium; the usual initial dose is 2.5 to 4.0 mg/kg, followed by about 1 mg/kg every four hours for up to 48 hours to avoid recrudescence. Electrolyte and metabolic abnormalities that cause rhabdomyolysis (e.g., hyponatraemia, hypernatraemia, hyperglycaemia, hypercalcaemia, and decreased phosphorous) should be corrected promptly. Drugs and toxins should be eliminated and detoxified (e.g., gastric lavage, antidotes and/or haemodialysis) if possible, and hypoxia must be corrected.

Management and prevention of complications

Aggressive rehydration is considered the standard of care in preventing ARF in patients with rhabdomyolysis, while the role of mannitol and bicarbonate is controversial. In 1984, Ron *et al.*[141] published a review of seven patients treated for crush injuries suffered after the collapse of a building. Mannitol and sodium bicarbonate were used over the first five days. Visible myoglobinuria cleared at an average of 48 hours and at no time did patients have a creatinine of >1.5 mg/dl and none of the patient required haemodialysis. But lack of a control group is the major limitation of this study. In an experimental study conducted in 2005, Ozguc *et al.*[142] reported that the association of saline solution, sodium bicarbonate, and mannitol was more effective than hypertonic saline-dextran in decreasing oxidant injury in rhabdomyolysis; they also found that hypertonic saline-dextran increased metabolic acidosis that followed autologous muscle extract infusion. Other experimental studies by Zagar in 1992[143] suggested that mannitol may be protective due to the associated diuresis that minimises intratubular haeme pigment deposition.

In 1994, Knottenbelt[56] published a retrospective review of 200 patients with extensive soft tissue injuries from severe beatings, who received fluid loading with balanced salt solution (without mannitol or bicarbonate). He found that significantly increased rates of ARF and death were associated with injury-admission intervals of more than 12 hours, severe metabolic acidosis, low initial haemoglobin, heavy pigmenturia, and high serum CK levels. Accordingly, large-volume infusion of crystalloid alone creates a solute diuresis sufficient to alkalinise the urine.

In 1997, Homsi *et al.* performed a retrospective analysis of patients with rhabdomyolysis at risk for ARF; they compared groups receiving saline (n=9) *vs* saline, bicarbonate and mannitol (n=15). The authors concluded that progression to established renal failure can be totally avoided with prophylactic treatment, and that once appropriate saline expansion is provided, the association of mannitol and bicarbonate seems to be unnecessary.[144] In 2004, Brown *et al.* found that the use of sodium bicarbonate and mannitol in post-traumatic rhabdomyolysis does not prevent ARF, dialysis or mortality in patients with CK levels >5000 U/l.[145] The author advised to reevaluate the standard of administering bicarbonate and mannitol to patients with post-traumatic rhabdomyolysis.

Based on this literature review and taking into consideration that sodium bicarbonate can aggravate hypocalcaemia, as well as contributing to a hyperosmolar state,[133] it can be concluded that, in patients with rhabdomyolysis and a good urinary response to fluid administration, alkalinisation of the urine with sodium bicarbonate and diuresis with mannitol is unnecessary and needs to be re-evaluated.

In animal models, free-radical scavengers (e.g., antioxidants) and iron chelators (e.g., deferoxamine) have been observed to minimise the renal damage caused by free radicals as well as the direct toxic effects of myoglobin, but their potential role in preventing ARF in patients with rhabdomyolysis is under investigation.

Rhabdomyolysis-induced ARF may be oliguric (most common) or nonoliguric. The need for dialysis, serum potassium and calcium levels, and mortality rates appear to be similar for rhabdomyolysis-induced and non-rhabdomyolysis-induced ARF. Patients with rhabdomyolysis-induced ARF, however, have higher serum uric acid and anion gap levels.[118]

Hyperkalaemia is a potentially life-threatening complication of rhabdomyolysis especially when associated with ARF and hypocalcaemia. Treatment should be initiated to prevent cardiac complications. Traditional insulin and glucose therapy is recommended. Intravenous calcium may be ineffective as a treatment for hyperkalaemia if given to a patient with hyperphosphataemia. This is because calcium and phosphate can combine and precipitate removing them from the circulation.[3] The use of ion-exchange resins (e.g., sodium polystyrene sulphonate) is effective but will take many hours. If hyperkalaemia persists despite these treatments, emergent dialysis will become a pertinent option.

Hypocalcaemia observed early in rhabdomyolysis usually requires no treatment. Calcium should only be given to treat hyperkalaemia-induced cardiotoxicity or profound signs and symptoms of hypocalcaemia. In contrast, hypercalcaemia is frequently symptomatic and normally responds to saline diuresis and intravenous furosemide. Hyperphosphataemia should be treated with oral phosphate binders when serum levels exceed 7 mg/dl. Similarly, the hypophosphataemia, which may occur late in rhabdomyolysis, requires treatment only when the serum level is below 1 mg/dl.

Compartment syndrome requires immediate orthopaedic consultation for fasciotomy. DIC usually resolves spontaneously after several days if the underlying cause is corrected, but if haemorrhagic complications occur, therapy with platelets, vitamin K, and fresh frozen plasma may be necessary.

Hyperuricaemia and hyperphosphataemia are rarely of clinical significance and rarely require treatment.

Metabolic acidosis should be treated with aggressive intravenous fluid hydration. Bicarbonate administration may be detrimental, as metabolic alkalosis could worsen the hypocalcaemia.

Dialysis should be considered as a lifesaving procedure for patients with rising or elevated potassium level, persistent acidosis, or oliguric renal failure with fluid overload. Dialysis with supportive care effectively limits the morbidity and mortality from ARF associated with rhabdomyolysis.

PROGNOSIS

The prognosis of rhabdomyolysis is heavily dependent upon the underlying aetiology and the associated comorbidities. Despite the lack of any well-organised prospective studies, the available evidence from case reports and small retrospective studies suggests that rhabdomyolysis, when treated early and aggressively, has an excellent prognosis. Moreover, the prognosis for the recovery of full renal function is also excellent.

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REVIEW

A systematic review of selective and non-selective beta blockers for prevention of vascular events in patients with acute coronary syndrome or heart failure

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ABSTRACT

Background: To assess the influence of β2-receptor suppression on top of selective β1-receptor blockade on the occurrence of vascular events and on all-cause mortality in patients with acute coronary syndrome (ACS) or heart failure (HF).

Methods: Systematic review of studies published since 1980. Randomised controlled trials directly comparing β1 blockers with β1+2 blockers, or comparing the two β blockers with placebo, were included. Studies had a minimum treatment period of three months and total mortality or vascular events as their primary or secondary outcome.

Results: Of the included studies, five directly compared β blockers (3733 patients) and 28 compared β blockers with placebo (30,889 patients). These latter studies were heterogeneous in study population, dose and type of β blockers. In ACS, the only study directly comparing different β blockers was underpowered to detect a difference on mortality, while in HF β1+2 blockers significantly decreased mortality compared with β1 blockers (RR 0.86, 95% confidence interval 0.78 to 0.94). In ACS, β1 blockers in placebo-controlled trials non-significantly reduced total mortality (RR 0.82, 0.67 to 1.01) or vascular events (RR 0.68, 0.42 to 1.11), while β1+2 blockers were associated with a significant decrease in total mortality (RR 0.73, 0.64 to 0.82), and vascular events (RR 0.71, 0.59 to 0.84). In HF, β1 and β1+2 blockers reduced total mortality, while only β1+2 blockers decreased vascular events (RR 0.80, 0.64 to 1.00).

Conclusions: Additional β2-receptor blockade may be more effective than β1-receptor blockade alone in preventing total mortality and vascular events in patients with ACS or, to a lesser extent, HF. However, only a few studies directly compared β blockers, and indirect comparisons were subject to heterogeneity, which weakens firm conclusions.

KEYWORDS

Epidemiology, heart failure, myocardial infarction, pharmacology, prevention

INTRODUCTION

Beta-adrenergic receptor blocking agents (β blockers) are generally recommended for the treatment of patients with acute coronary syndrome (ACS) or heart failure (HF), because of their proven positive effects on life expectancy, risk of sudden cardiac death and left ventricular ejection fraction.[1-4] In patients with HF, β blockers inhibit the adverse effects of an increased sympathetic activity, which has been associated with increased mortality.[2,5]

Beta blockers can be classified as β blockers with a much higher affinity for β1- than for β2-adrenergic receptors (β1 blockers), and β blockers with both β1- and β2-adrenergic receptor blocking properties (β1+2 blockers).[6] Previous meta-analyses have suggested a better effect of β1+2 blockers on total mortality and cardiovascular morbidity in patients with ACS[7] and HF,[8,9] although these parameters were not the primary outcomes in these trials. Furthermore, in the large COMET trial, carvedilol (a β1+2 blocker) significantly

reduced cardiovascular mortality compared with the β1 blocker metoprolol in patients with HF.[10] Interestingly, the reduction in cardiovascular mortality was largely driven by a difference in vascular events.[11] The underlying mechanism of this effect is unclear. One hypothesis is that sympathetic activity may influence vascular events by increasing the prothrombotic activity.[12,13] This sympathetic activity may be reduced by a specific presynaptic β2-adrenergic inhibitory effect of β1+2 blockers,[14-16] resulting in less activation of platelets and clotting factors.[13] Since patients with HF have an increased sympathetic activation, β blockers with β2-adrenergic inhibitory effects could reduce the associated prothrombotic activity and, consequently, the number of vascular events.

We therefore performed a systematic review of all randomised studies assessing β blockers in patients with ACS and HF to test the hypothesis that suppression of the β2-adrenergic receptor in addition to the β1-adrenergic receptor is more effective in reducing vascular events than a more selective suppression of the β1 receptor.

METHODS

Study selection

To test our hypothesis we divided β blockers into β blockers that antagonise the β1 receptor more selectively (β1 blockers), and β blockers with both β1- and β2-adrenergic receptor blocking capacities (β1+2 blockers). The effects of β1 and β1+2 blockers for secondary prevention in patients with ACS or HF were analysed. The primary outcomes evaluated were 1) all-cause mortality and 2) vascular events, defined as fatal and non-fatal strokes, fatal and non-fatal myocardial infarctions and fatal pulmonary embolisms and other venous thromboembolic events.

We conducted a comprehensive literature search of Medline, EMBASE and the Cochrane Central Register of Controlled Trials library from 1981 to June 2009. In Medline text and Cochrane library keywords were "randomised controlled trial", "acute coronary syndrome" (in Cochrane "myocardial ischemia") or "congestive heart failure" and "adrenergic beta-antagonists", using Medical Subject Heading Terms. In EMBASE text keywords were "randomised controlled trial", and "heart muscle ischemia" or "heart failure", and "beta adrenergic receptor blocking agent". The results of the searches were limited to studies of humans and were not restricted to English language. In addition a review of references from primary or review articles was performed to identify any additional relevant studies.

The list of articles was reviewed by two authors, who independently evaluated all articles for possible inclusion. Disagreement was resolved by consensus and if necessary by the opinion of a third reviewer. When multiple papers for a single study had been published, we used the publication with the data that best corresponded to our objectives and supplemented it, if necessary, with data from the other publications. To assess the agreement between reviewers for study selection, we used the kappa (κ) statistic, which measures agreement beyond chance.[17]

We included randomised controlled or active controlled trials that directly compared β1 and β1+2 blockers. Since there were only a few trials comparing these compounds directly, we also assessed randomised placebo-controlled trials. Patients with systolic heart failure were included regardless of the underlying cause of heart failure or cardiac rhythm. Only studies with prespecified outcomes of mortality or vascular events were included. To assess the long-term effects of β-blocker treatment only studies with at least three months of treatment were considered. Studies assessing β-blockers with intrinsic sympathicomimetic, class-III antiarrhythmic or partial agonist activity, were excluded. The oldest trial with β1 blockers was published in 1981.[18] To facilitate a balanced comparison between the different β blockers, only studies published since that time were included.

Data extraction and quality assessment

Using a data extraction form, two authors independently extracted the following baseline characteristics for all included studies: first author, year of publication, source of publication, country of origin, study design, inclusion and exclusion criteria, type of β blocker used and dosage, concomitant medication, duration of follow-up, cause of heart failure, NYHA classification and left ventricular ejection fraction, number, mean age and gender of the study patients. The following outcomes were retrieved: all-cause mortality and number of strokes, myocardial (re)infarctions, or venous thromboembolic events (all fatal and non-fatal events). Since the numbers of reported events were relatively small, we analysed these events as a composite endpoint. For each study the number of patient-years was calculated by multiplying the total number of patients with the mean follow-up period.

Study quality was evaluated as described by Jadad *et al.*[19] Studies using adequate treatment allocation sequence, proper concealment, blinding of both patient and investigator, and completeness of follow-up, were considered to reflect higher methodological quality. Since not all studies provided information on these quality criteria, we also assessed the effect of including only trials with adequate concealment and loss to follow-up <20%.

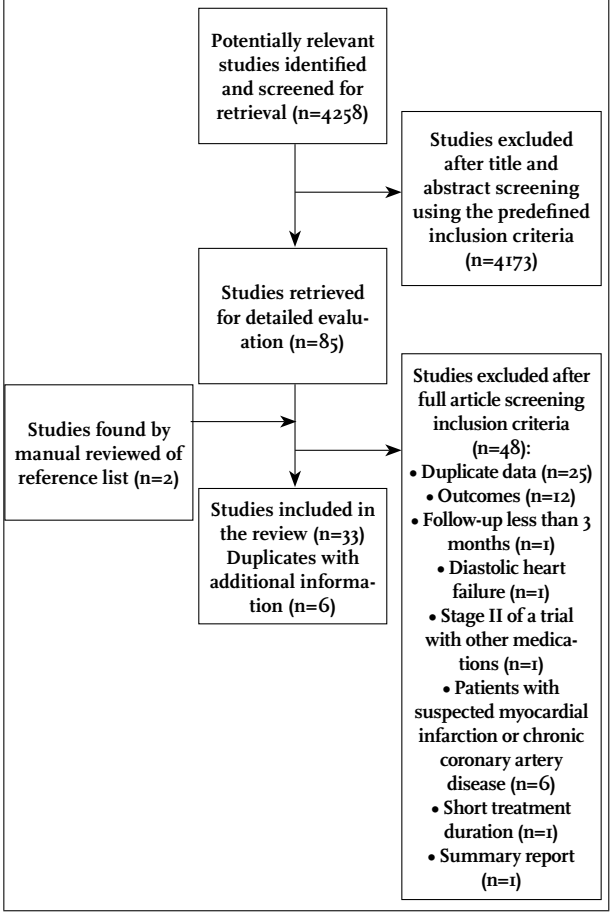
Statistical analysis

There were only a few studies that directly compared β1 and β1+2 blockers. Therefore, despite potential biases of comparisons between different studies, the effects of β1 and β1+2 blockers were indirectly analysed by pooling the results of placebo-controlled studies. Relative risks (RR)

and 95% confidence intervals (95% CI) were calculated using the DerSimonian and Laird random-effects model[20] with the Review Manager developed by the Cochrane Collaboration, version 4.2.10 for Windows. A random-effects model was chosen since results with this model are more conservative. Statistical heterogeneity between studies was evaluated using the χ^2 and I^2 test, for each of the outcomes separately, with a p value <0.05 considered as heterogeneous.

Sensitivity analyses were performed to evaluate the robustness of the results. First, we considered the effect of only including high-quality studies with a double-blind design and with a number of loss to follow-up less than 20%. In addition, the effect of excluding studies one at a time to identify those that may have a disproportionate influence on the summary treatment effect was evaluated. Publication bias was assessed using a funnel plot of effect size versus standard error.[21] In a final analysis the results were adjusted for number of patient-years to assess the influence of duration of study follow-up.

Figure 1. *Results of article search and selection*



RESULTS

Literature search

Figure 1 summarises the process of study selection. A total of 4258 relevant literature citations were identified, of which 4173 were excluded after scanning titles and abstracts, leaving 85 studies for detailed assessment. Two additional studies were identified through a manual review of study bibliographies.[22,23] Of these 87 retrieved articles, 48 were excluded for the following reasons: 12 because total mortality or vascular events were not a prespecified outcome of the study; one study because patients were followed up for less than three months; 25 because of duplicate data, substudies or commentaries; six studies were excluded because of inclusion of patients with suspected myocardial infarction or chronic coronary artery diseases, without documented ACS; one study because it included patients with diastolic heart failure; one because it was the summary report of four randomised trials with carvedilol; another because the treatment with β blockers was the second part of a trial with other medications; and one because treatment duration was only seven days. Hence, of the 39 remaining studies 33 were included in the present systematic review,[10,18,22-52] with a total of 34,360 patients (*table 1*). Six additional studies reported additional information.[11,53-57] The interobserver agreement for study selection was excellent (κ =0.98).

Study characteristics and quality

Table 1 shows the study characteristics of the 33 trials included. Five studies directly compared β1 with β1+2 blockers, one assessing patients with ACS[40] and four patients with HF.[10,37,41,44] Twenty-eight studies compared a β1 or β1+2 blocker with a control group, of which 11 studies enrolled patients with ACS[18,22,23,27,28,35,39,42,45,50,51] and 17 patients with HF.[24-26,29-34,36,38,43,46-49,52] The number of patients among the studies ranged from 50 to 3991. In one study with three treatment arms in different dosages;[29] we only included the group given the target dose used in most other studies. In another study the results from 326 of 764 subjects were excluded, since these patients had no acute myocardial infarction or HF.[23]

Various β blockers were studied: the β1 blockers included metoprolol, nebivolol, bisoprolol, atenolol and betaxol and the β1+2 blockers included carvedilol, bucindolol, propranolol and timolol. In trials that included information on concomitant treatment, on average 91% of the patients received angiotensin-converting enzyme (ACE) inhibitors, 91% diuretics, and 74% digitalis. No information was available on statin use. Twenty-seven studies were reported as double blind,[10,18,22,23,26-39,42-46,48-50,56] 13 had appropriate random allocation of treatment[10,26,30-32,35,38-40,43,49,51,52] and in ten studies information on concealment allocation was adequate.[10,26,30-32,35,38,43,49,51] A description of patient

Table 1. *Study and participant summary characteristics*

	Year	Total (n)	Mean age (years)	Male (%)	Participants	Treatment	Target dose	Main concomitant medication	Average follow-up in months	Patient-years
Patients with ACS; direct comparator β blocker										
CAMIS[40]	2005	232	61	78	Within 24 hours after AMI	Carvedilol/ Atenolol	25 mg bid/ 50 mg bid	Aspirin, statin, vasodilator	18	348
Patients with HF; direct comparator β blocker										
BETACAR[39]	2006	255	57	86	NYHA II-III, LVEF <35%	Carvedilol/ Betaxolol	25 mg bid/ 20 mg od	Vasodilator, diuretic, digitalis, nitrates	8	170
COMET[10]	2003	3029	62	80	NYHA II-IV, LVEF <35%	Carvedilol/ Metoprolol	25 mg bid/ 50 mg bid	Vasodilator, diuretic, digitalis	58	14640
Kukin[41]	1999	67	58	69	NYHA II-IV, LVEF <35%	Carvedilol/ Metoprolol	25 mg bid‡ / 25 mg bid‡	Vasodilator, diuretic, digitalis	6	34
Metra[44]	2000	150	57	91	NYHA II-IV, LVEF <35%	Carvedilol/ Metoprolol	25 mg bid†/ 50 mg bid†	Vasodilator, diuretic, digitalis	14	175
Patients with ACS; β1 blockers										
Goteborg[8]	1983	1395	66% <65 years	76	AMI	Metoprolol	100 mg bid	None reported	3	349
Lopressor[42]	1987	2395	58	83	5-15 days after AMI	Metoprolol	100 mg bid	None reported	12	2395
Manger Cats[22]	1983	553	100% <70 years	?	<1 year after AMI	Metoprolol	100 mg bid	None reported	12	553
Olsson[45]	1985	301	60	81	Within 2 days after AMI	Metoprolol	100 mg bid	Digitalis, diuretics	36	903
Salathia[23]	1985	474	6% <65 years	71	AMI	Metoprolol	100 mg bid	None reported	12	474
Patients with ACS; β1+2 blockers										
BEAT[51]	2002	343	69	83	Within 7 days after AMI, LVEF <35%	Bucindolol	50 mg bid†	Vasodilator, diuretic, digitalis	7.5	214
BHAT[28]	1982	3837	55	84	5-21 days after AMI	Propranolol	60-80 mg 3/day	None reported	25	7994
Basu[27]	1997	151	60	81	AMI	Carvedilol	25 mg bid	Aspirin, heparin, thrombolysis, nitrates	6	76
CAPRICORN[35]	2001	1959	63	74	3-21 days after AMI, LVEF <40%	Carvedilol	25 mg bid	Vasodilator, diuretics, aspirin	16	2612
Hansteen[55]	1982	560	58	85	4 days after AMI	Propranolol	40 mg 4/ day	None reported	12	560
Pedersen[57]	1983	1884	61% <65 years	62	6-27 days after AMI	Timolol	10 mg bid	Diuretics, digitalis	17	2669
Patients with HF; β1 blockers										
Anderson[24]	1985	50	51	66	LVEF <40%, idiopathic	Metoprolol	50 mg bid	Vasodilator, diuretic, digitalis, anticoagulant	19	79
CIBIS-I[31]	1994	641	60	83	NYHA III-IV, LVEF <40%	Bisoprolol	5 mg od	Vasodilator, diuretic, digitalis (in 56% of patients)	23	1229
CIBIS-II[30]	1999	2647	61	81	NYHA III-IV, LVEF <35%	Bisoprolol	10 mg od	Vasodilator, diuretic	16	3529
ENECA[36]	2005	260	72	73	NYHA II-IV, LVEF <35%	Nebivolol	10 mg od	Vasodilator, diuretic, digitalis	8	173
SENIORS[38]	2005	2128	76	63	LVEF <35%	Nebivolol	10 mg od	Vasodilator, diuretic	21	3724
MERIT-HF[43]	1999	3991	64	78	NYHA II-IV, LVEF <40%	Metoprolol*	200 mg od	Vasodilator, diuretic	12	3991
Waagstein[52]	1993	383	49	?	LVEF <40%, idiopathic dilated cardiomyopathy	Metoprolol	100-150 mg 2-3/day	Vasodilator, diuretic, digitalis	12	383

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Table 1. *Continued*

	Year	Total (n)	Mean age (years)	Male (%)	Participants	Treatment	Target dose	Main concomitant medication	Average follow-up in months	Patient-years
Patients with HF; β1+2 blockers										
Aranow[25]	1997	158	81	29	NYHA II-III, LVEF >40%, prior ACS	Propranolol	30 mg 3/ day	Vasodilator, diuretic, digitalis in AF	32	421
Austr/NZ HF[26]	1997	415	67	80	NYHA II-III, LVEF <45%, ischaemic cause	Carvedilol	25 mg bid	Vasodilator, diuretic, digitalis	19	657
BEST[49]	2001	2708	60	78	NYHA III-IV, LVEF <35%	Bucindolol	50-100 mg bid	Vasodilator, diuretic, digitalis	24	5416
CHRISTMAS[32]	2003	387	63	90	NYHA I-III, LVEF <40%, ischaemic cause	Carvedilol	25 mg bid	Vasodilator, diuretic	6	194
COPERNICUS[47]	2001	2289	63	80	LVEF <25%	Carvedilol	25 mg bid	Vasodilator, diuretic, digitalis	10	1908
Cohn[33]	1997	105	60	69	<150 meter on walking test, LVEF <35%	Carvedilol	25 mg bid	Vasodilator, diuretic, digitalis, nitrates	6	53
Colucci[34]	1996	366	54	85	425-550 meter on walking test, LVEF<35%	Carvedilol	25 mg bid‡	Vasodilator, diuretic, digitalis, nitrates	7	214
MOCHA[29]	1996	173	60	77	150-425 meter on walking test, LVEF <35%	Carvedilol	25 mg bid	Vasodilator, diuretic	6	87
Palazzuoli[48]	2005	58	71	66	NYHA III-IV, LVEF <40%	Carvedilol	25 mg bid	Vasodilator, diuretic, digitalis, anticoagulant	12	58
PRECISE[46]	1996	278	60	73	150-450 meter on walking test, LVEF <35%	Carvedilol	25 mg bid‡	Vasodilator, diuretics, digitalis	6	139

ACS = acute coronary syndrome; HF = heart failure; AMI = acute myocardial infarction; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; B = blinding of outcome measure; R = randomisation; bid = twice daily, od = once daily; P = one of our endpoints was a primary outcome. W = description of withdrawals. ‡If bodyweight >85 kg target dose was doubled. †If bodyweight >75 kg target dose was doubled. * Metoprolol CR/XL.

withdrawal was provided in all studies except two.[22,37] Based on Jadad's scale,[19] ten out of 33 (30.3%) studies were rated as high quality.[10,26,30-32,35,38,39,43,49]

Direct comparison of β1 and β1+2 blockers in patients with ACS and HF

For ACS, the only study with direct comparison of different β blockers (n=232) showed no difference on all-cause mortality (RR 0.39, 95% CI 0.08 to 1.95).[40] No data were available on vascular events.

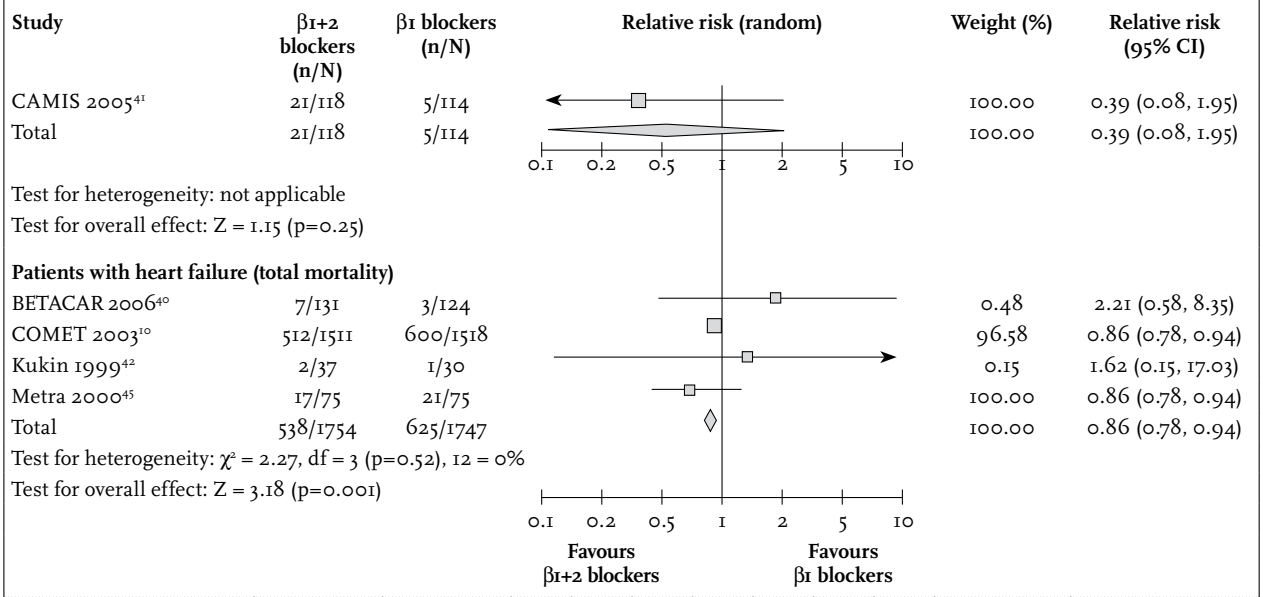
In four studies that directly compared the effects of β1 and β1+2 blockers on total mortality in patients with HF,[10,37,41,44] β1+2 blockers significantly decreased total mortality compared with β1 blockers (RR 0.86, 95% CI 0.78 to 0.94) (*figure 2*). It should be noted that the COMET trial[10] contributed to more than 96% of these results. Only the COMET trial reported vascular mortality and morbidity,[11] showing a significantly better effect of the β1+2 blocker carvedilol in reducing fatal and non-fatal myocardial infarction and death from stroke (HR 0.70, 95% CI 0.50 to 0.99, and HR 0.33, 95% CI 0.18 to 0.62, respectively).

Indirect comparison of β1 and β1+2 blockers in ACS

In the five studies on β1 blockers,[18,22,23,42,45] treatment resulted in a non-significant reduction of all-cause mortality compared with placebo (RR 0.82, 95% CI 0.67 to 1.01) (*figure 3*). Information on vascular events was available in three of the five studies.[18,42,45] Fifty-six of the 2047 (3%) patients with β1 blockers and 81 of 2044 (4%) patients in the control group had vascular complications, without a statistical significant difference between the two groups (RR 0.68, 95% CI 0.42 to 1.11) (*figure 3*). There was no clear heterogeneity across studies for both outcomes (I^2=31.4 %, p=0.20 and I^2=0 %, p=0.61, respectively).

Compared with placebo, β1+2 blockers reduced total mortality in patients with ACS, (RR 0.73, 95% CI 0.64 to 0.82).[27,28,35,39,50,51] In addition, β1+2 blockers also lowered the risk of vascular events by 29% (RR 0.71, 95% CI 0.59 to 0.84), occurring in 395 of 4361 (9%) patients with β blockers and in 545 of 4373 (12%) patients with placebo (*figure 3*). This effect was consistent in all studies except one.[39] There was no significant statistical heterogeneity among the studies (I^2=0%, p=0.79).

Figure 2. *Direct comparison of β1 and β1+2 blocker treatment on total mortality*



95% CI = 95% confidence interval; n = number of events; N = number of included patients.

Indirect comparison of β1 and β1+2 blockers in HF

In seven studies that assessed all-cause mortality in patients with heart failure,[24,30,31,36,38,43,52] 558 of 5057 patients (11%) who received β1 blockers died compared with 736 of 5043 patients (15%) in the control group, resulting in a reduction in mortality (RR 0.76, 95% CI 0.68 to 0.84) (*figure 4*). Data on vascular events were available in three placebo-controlled trials,[30,31,52] involving 3671 patients. In these studies, β1 blockers did not protect patients against vascular events, as compared with placebo (RR 1.33, 95% CI 0.86 to 2.04) (*figure 4*). There was no significant heterogeneity for both outcomes (I^2=0 %, p=0.38 and I^2=19.3 %, p=0.28, respectively) (*figure 4*).

For β1+2 blockers, ten trials assessed all-cause mortality,[25,26,29,32-34,46-49] 625 of 3546 (18%) HF patients who received β1+2 blockers died, compared with 762 of 3391 (22%) patients in the control group, with a statistically significant reduction in mortality (RR of 0.75, 95% CI 0.61 to 0.92) (*figure 4*). For this latter outcome there was some heterogeneity across the studies (I^2=41%, p=0.04).

Six trials reported vascular events in HF.[25,26,29,46,47,49] Compared with placebo, β1+2 blockers were associated with a 20% decrease in vascular events (RR 0.80, 95% CI 0.64 to 1.00).

All trials reported fatal or non-fatal events of worsening heart failure; β1 and β1+2 blockers equally decreased these events (RR 0.77, 95% CI 0.61 to 0.97, and RR 0.82, 95% CI 0.70 to 0.95 respectively, data not shown).

Sensitivity analysis

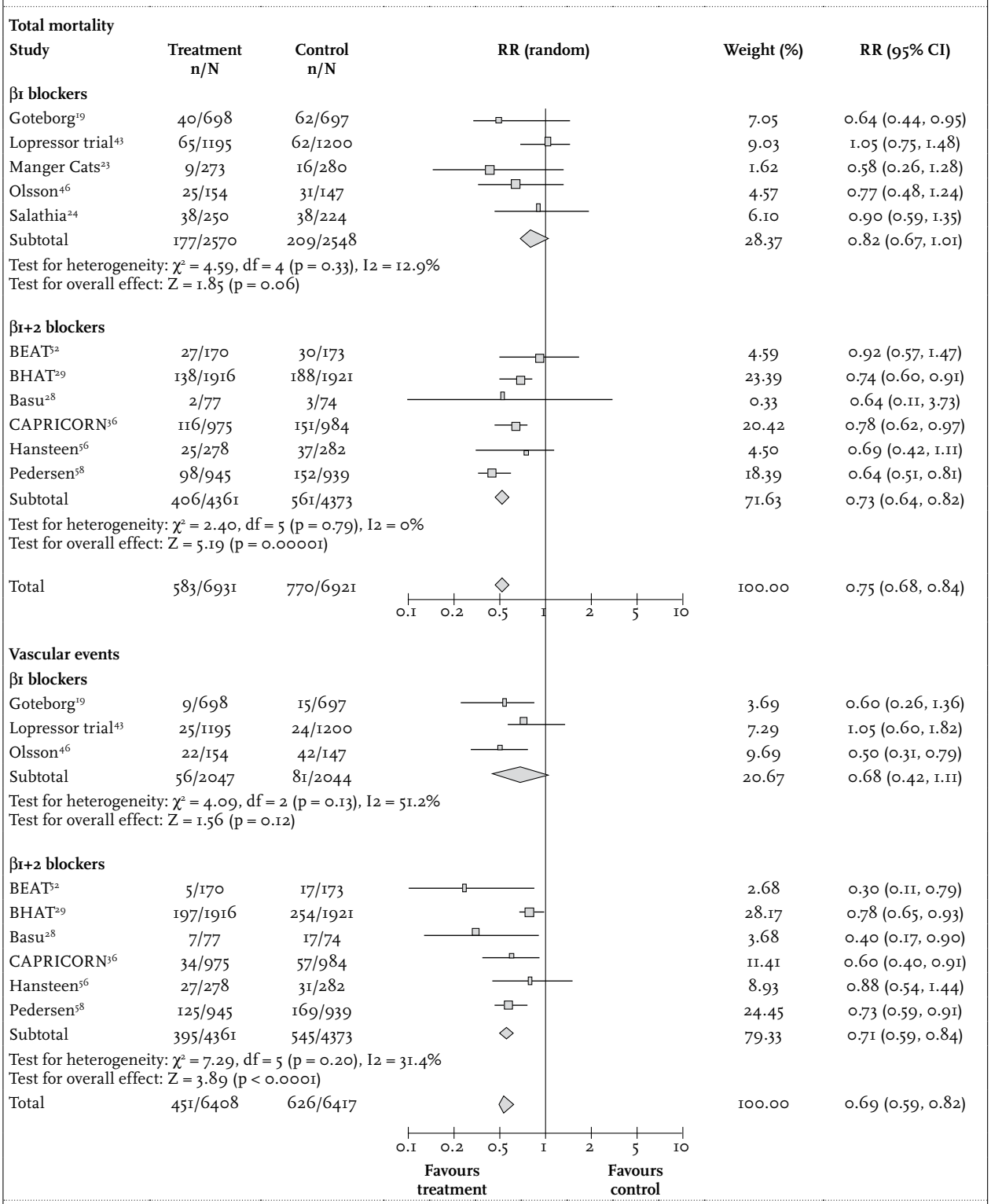
The results of our primary analyses were unaffected by removing individual studies one by one or by analysing the effect of different β blockers. Assessing various factors in Jadad's scale did not affect the significant associations in the results. Moreover, including only higher quality studies, results were virtually the same (*table 2*). When we analysed the long-term effects of β-blocker treatment among studies that had a follow-up of at least 12 months, the overall results on total mortality and on fatal and non-fatal vascular events did not change. Due to the low number of reported events, separate analysis for myocardial infarction and stroke was not possible.

The funnel plots for the studies with patients with ACS were symmetrical, indicating no publication bias. There was some asymmetry in the funnel plots for β blockers in patients with HF, indicating a possible publication bias. Because of its low power and relatively small number of included trials (maximum of ten included studies per group), we did not perform an Egger's regression analysis. Correcting the results for number of patient-years provided similar pooled relative risks for all figures (data not shown).

DISCUSSION

This systematic review confirms the beneficial effects of β blockers on total mortality, as reported previously.[8,9,58] We specifically assessed the beneficial effect of β2-adrenergic receptor blockade on vascular events in patients with ACS or HF. Beta blockers with β2-adrenergic inhibitory effects could reduce sympathetic activation and the associated prothrombotic activity, and, consequently, the number of vascular events. Indeed, our results suggest a somewhat

Figure 3. *Effects of β1 and β1+2 blocker treatment on total mortality and vascular events in patients with acute coronary syndrome*



RR = relative risk; 95% CI = 95% confidence interval; n = number of events; N = number of included patients.

Figure 4. *Effects of β1 and β1+2 blocker treatment on total mortality and vascular events in patients with heart failure*

Total mortality

Study	Treatment n/N	Control n/N	RR (random)	Weight (%)	RR 95% CI)
β1 blockers					
Anderson[25]	5/25	6/25		1.10	0.83 (0.29, 2.38)
CIBIS-I[32]	53/320	67/321		7.64	0.79 (0.57, 1.10)
CIBIS-II[31]	156/1327	228/1320		13.17	0.68 (0.56, 0.82)
ENECA[37]	7/134	7/126		1.16	0.94 (0.34, 2.61)
MERIT-HF[44]	145/1990	217/2001		12.57	0.67 (0.55, 0.82)
SENIORS[39]	169/1067	192/1061		13.19	0.88 (0.72, 1.06)
Waagstein[53]	23/194	19/189		3.27	1.18 (0.66, 2.09)
Subtotaal	558/5057	736/5043		52.11	0.76 (0.68, 0.87)
Test for heterogeneity: χ^2 = 7.44, df = 6 (p = 0.28), I2 = 19.3%					
Test for overall effect: Z = 4.24 (p = <0.0001)					
β1+2 blockers					
Aronow[26]	44/79	60/79ww		11.07	0.73 (0.58, 0.93)
Austr / NZ HF[27]	20/207	26/208		3.51	0.77 (0.45, 1.34)
BEST[50]	411/1354	448/1354		17.37	0.92 (0.82, 1.02)
CHRISTMAS[33]	8/193	6/194		1.12	1.34 (0.47, 3.79)
COPERNICUS[48]	130/1156	190/1133		12.24	0.67 (0.54, 0.83)
Cohn[34]	2/70	2/35		0.34	0.50 (0.07, 3.40)
Colucci[35]	2/232	5/134		0.47	0.23 (0.05, 1.17)
MOCHA[30]	1/89	13/84		0.31	0.07 (0.01, 0.54)
PRECISE[47]	6/133	11/145		1.28	0.59 (0.23, 1.56)
Palazzuoli[47]	1/33	1/25		0.17	0.76 (0.05, 11.53)
Subtotal	625/3456	762/3391		47.89	0.75 (0.61, 0.92)
Test for heterogeneity: χ^2 = 18.05, df = 9 (p = 0.03), I2 = 50.1%					
Test for overall effect: Z = 2.78 (p = 0.005)					
Total	1183/8603	1498/8434		100.00	0.77 (069, 0.86)
Test for heterogeneity: χ^2 = 1.95, df = 2 (p = 0.38), I2 = 0%					
Test for overall effect: Z = 1.29 (p = 0.20)					
			0.01 0.1 1 10 100		
Vascular events					
β_1 blockers					
CIBIS-I[32]	10/320	11/321		7.93	0.91 (0.39, 2.12)
CIBIS-II[31]	38/1327	24/1320		16.55	1.57 (0.95, 2.61)
Waagstein[53]	0/194	1/189		0.67	0.32 (0.01, 7.92)
Subtotal	48/1841	36/1830		23.15	1.33 (0.86, 2.04)
Test for heterogeneity: χ^2 = 5.45, df = 5 (p = 0.36), I2 = 8.2%					
Test for overall effect: Z = 1.98 (p = 005)					
Aranow[26]	3/79	5/79		3.27	0.60 (0.15, 2.43)
Austr / NZ HF[27]	25/207	34/208		17.64	0.74 (0.46, 1.19)
BEST[50]	79/1354	78/1354		27.15	1.01 (0.75, 1.37)
COPERNICUS[48]	52/1156	76/1133		24.68	0.67 (0.48, 0.95)
MOCHA[30]	1/89	3/84		1.33	0.31 (0.03, 2.97)
PRECISE[47]	0/133	3/145		0.78	016 (0.01, 299)
Subtotal	160/3018	199/3003		74.85	0.80 (0.64, 1.00)
Total	208/4859	235/4833		100.00	0.87 (0.67, 1.14)
			0.01 0.1 1 10 100		
			Favours treatment	**Favours control**	

RR = relative risk; 95% CI = 95% confidence interval; n = number of events; N = number of included patients.

Table 2. *Sensitivity analysis by methodological criteria, defined as double blind and loss to follow-up less than 20%*

Group of patients and outcomes	β1 blockers RR (95% CI)	β1+2 blockers RR (95% CI)
Acute coronary syndrome: total mortality	0.84 (0.67-1.05)	0.72 (0.63-0.81)
Acute coronary syndrome: vascular events	0.68 (0.42-1.11)	0.74 (0.66-0.84)
Heart failure: total mortality	0.75 (0.66-0.85)	0.74 (0.56-0.96)
Heart failure: vascular events	1.34 (0.82-2.18)	0.79 (0.61-1.03)

RR = relative risk; CI = confidence interval.

better, and at least a more consistent, reduction of vascular events and total mortality of additional β2-receptor blockade compared with β1-receptor blockade alone in patients with ACS. In patients with HF, β1 and β1+2 blockers both reduced total mortality, but only β1+2 blockers had an effect on vascular events.

Our analysis was hampered by the few trials that directly compared β1 and β1+2 blockers, including a limited number of patients. For ACS one trial directly compared β blockers, but was underpowered to detect a difference on mortality. For HF, four trials directly compared β blockers, but these results were dominated by the large COMET trial, in which the dosages and formulation of metoprolol tartrate have been heavily debated.[59] The remaining three trials included only 472 patients and were not powered to detect a difference on mortality. The results of the COMET trial point to beneficial effects of carvedilol on reducing vascular events, which could also be explained by antiadrenergic effects.[60]

Consequently, we extended our analysis to placebo-controlled trials assessing the efficacy of the different β blockers, a method prone to potential biases. These studies have different designs and are heterogeneous, which impairs comparing these studies. Different types and dosages of β blockers were assessed, the study subjects differed, and clinical outcomes were not clearly reported in every trial. In addition, the β1 blocker trials were in general older than the studies assessing the β1+2 blockers. However, β1+2 blockers studies showed far more consistency compared with β1 blockers, with a reduction of vascular events in all except one trial. Furthermore, the validity of our findings is supported by the absence of heterogeneity among studies for the major outcomes, and by the sensitivity analysis, where the better efficacy of β1+2 blockers remained in high-quality studies. In addition, removing individual trials or analysing different types of β blockers did not affect our main results. Five out of six studies that investigated the efficacy of β1+2 blockers in patients with ACS, including the three largest studies involving almost 8000 patients, found a reduction in vascular events.[28,35,57]

Our aim was to assess the influence of β2-receptor blockade in addition to β1-receptor blockade. We therefore compared β1 versus β1+2 blockers. Due to this classification we also included third-generation β blockers (such as carvedilol and nebivolol) in both groups. These third-generation β blockers have additional effects such as α-receptor blocking properties, antioxidative effects and NO-releasing capacities and have a more favourable metabolic profile.[61,62] These additional effects on our outcome parameters cannot be totally ruled out. However, the third-generation β1 blocker nebivolol showed no clear effect on mortality and vascular events. Furthermore, the beneficial effect of β1+2 blockers on vascular events could have been influenced by α1-receptor blocking properties of the β1+2 blockers carvedilol and bucindolol. However, propranolol and timolol,[28,55,57] not affecting the α1 receptor, also reduced all-cause mortality and vascular events in the ACS trials (RR 0.63, 95% CI 0.55 to 0.74, and RR 0.77, 95% CI 0.67 to 0.88, respectively). In addition, specific α1-receptor blockers are not effective in patients with HF, also when combined with β1 blockers.[63]

Previous studies have suggested that the release of norepinephrine is partly regulated by prejunctional β_2-adrenergic receptors. This implies that β1+2 blockers have a specific sympathoinhibitory effect that is less prominent in more selective β1 blockers. Indeed, β1+2 blockers reduce norepinephrine levels more effectively compared with selective β1 blockers.[14-16] Furthermore, increased (nor)epinephrine plasma levels enhance coagulation activity by increased platelet activity and thrombin generation,[13,64] and these prothrombotic effects can be blocked by the β1+2 blocker propranolol but not by metoprolol or phentolamine, which points to a specific β2-adrenergic receptor mediated effect.[13] Thus β1+2 blockers not only reduce sympathetic activity more effectively, but also the associated platelet activation and increments in coagulation factors.[13,64-66] The net result could be a reduced prothrombotic state, thereby reducing both arterial as venous thrombotic events.

In conclusion, this systematic review suggests that suppression of the β2-adrenergic receptor in addition to the β1 receptor may be more effective in reducing vascular events in patients with ACS and HF. The current literature is too heterogeneous to draw firm conclusions. Nevertheless, the presumed antithrombotic effect of β2-adrenergic receptor blockers may call for additional studies assessing the beneficial effect of β1+2 blockers in patients with ACS or HF.

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ORIGINAL ARTICLE

Heart failure as presenting manifestation of cardiac involvement in systemic lupus erythematosus

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ABSTRACT

Background: Heart failure in systemic lupus erythematosus (SLE) is rare, and its long-term outcome is unknown. The aim of this study was to analyse the long-term outcome of six SLE patients with heart failure as first manifestation of cardiac involvement and to review previously reported cases.

Methods: We conducted a retrospective chart review of SLE patients from two tertiary referral centres who presented between 1999 and 2004 with clinical and echocardiographic signs of heart failure as their first manifestation of cardiac involvement. Details of the clinical presentation and follow-up and serial findings at echocardiography were collected. A retrospective review of the literature was performed using the PubMed database.

Results: Six cases were identified who presented with heart failure, as confirmed by echocardiography (left ventricular ejection fraction (LVEF) ranging from 23 to 37%). Treatment with high-dose glucocorticoids, cytotoxic treatment (azathioprine in one patient, cyclophosphamide in five patients), intravenous immunoglobulins (in one patient) and temporary inotropic support (two patients) resulted in complete resolution of symptoms and improvement of LVEF, with a mean follow-up of 77 months (range 43 to 113). Twenty-one additional cases of heart failure as manifestation of cardiac involvement in SLE have been reported, most with favourable short-term outcome following institution of immunosuppressive therapy.

Conclusions: Heart failure is a rare but life-threatening manifestation of cardiac involvement in SLE. Long-term outcome can be excellent when aggressive treatment is instituted promptly.

KEYWORDS

Cardiac involvement, heart failure, systemic lupus erythematosus

INTRODUCTION

Heart failure is a rare but potentially life-threatening complication of myocarditis due to systemic lupus erythematosus (SLE).[1,2] With timely therapy almost full recovery of cardiac function can be achieved. Post-mortem studies from the 1950s and 1960s found an average prevalence of myocarditis in 57%, but after the introduction of corticosteroid therapy this percentage decreased to 7%. The pathogenesis is thought to be mediated by immune complex formation and complement activation.[3] Granular deposits of complement and immunoglobulin have been demonstrated in myocardial blood vessel walls and along muscle bundles. Focal interstitial plasma cell and lymphocyte infiltrates are seen with fibrinoid degeneration of collagen fibres and small foci of myocardial fibrosis, possibly leading to cardiac dysfunction. The diagnosis depends largely on clinical suspicion and echocardiography. Myocarditis may present clinically with fever, dyspnoea, palpitations, nonexertional chest pain, resting tachycardia that is disproportionate to the patient's temperature, gallop rhythms, new cardiac murmurs, cardiomegaly and peripheral oedema. Sinus tachycardia and nonspecific ST-T segment changes are frequently noted on the electrocardiogram. With echocardiography, left ventricular (LV) dysfunction can be observed, reflected by global or regional wall motion abnormalities, a decrease in LV ejection fraction (LVEF) and an increase in LV volumes

(indicating LV dilatation or remodelling).[4-6] Apart from systolic LV dysfunction, diastolic dysfunction has been reported as well.[7] Echocardiography is also essential to detect valvular lesions and pericardial effusion, which can occur in conjunction with myocarditis.[8] Endomyocardial biopsy may distinguish between acute myocarditis and other causes of cardiomyopathy, although its sensitivity and specificity for the diagnosis of lupus myocarditis are not known.[9] Current treatment strategies are empirical rather than based on clinical trials, and long-term outcome data are lacking. In the present study, we describe six patients from two tertiary referral centres who presented with life-threatening heart failure as a first cardiac manifestation of SLE, but experienced a good clinical response after immunosuppressive therapy with a mean follow-up of 77 months (range 43 to 113 months).

PATIENTS AND METHODS

We identified six patients by retrospective chart review who presented with heart failure secondary to myocardial involvement of SLE between January 1999 and November 2004 at Leiden University Medical Center, the Netherlands (patients 1-4), and University of Crete Medical Center, Greece (patients 5, 6), both tertiary referral centres. SLE was defined according to the 1997 American College of Rheumatology classification criteria.[10] Demographic data, duration of disease, relevant clinical features, immunological data, 2D echocardiographic data and response to therapy were recorded. The diagnosis of SLE myocarditis was based on a clinical presentation of heart failure, confirmed by echocardiography. All patients were treated with supportive therapy (diuretics, oxygen, inotropics when required) and intravenous methylprednisolone pulse therapy (1000 mg on three consecutive days), followed by oral prednisone. Five out of six patients also received intravenous cyclophosphamide pulse therapy (750 mg/m^2 or less in case of kidney dysfunction). The response to therapy was assessed clinically and by echocardiography with a mean follow-up of 77 months.

RESULTS

All patients had severe heart failure with LV ejection fraction below 40% (range 23 to 37%). In addition, mild to moderate mitral regurgitation was observed in all patients on echocardiography . Two patients were treated on the intensive care unit with inotropic therapy and mechanical ventilation, one patient also received intra-aortic balloon pump counterpulsation (IABP) and another patient needed continuous veno-venous haemofiltration (CVVH). Five patients had an elevated serum creatinine and proteinuria, while patients 1, 2 and 4 also had dysmorphic erythrocytes. Five patients had detectable antiphospholipid and/or anticardiolipin antibodies.

Patient 1

A 19-year-old woman with a history of arthralgias, was admitted in October 2004 because of pancytopenia (haemoglobin (Hb) 4.8 mmol/l, leucocytes 1.2 x 10^9, thrombocytes 32 x 10^9), and fever. Bone marrow analysis was inconclusive. On admission, she reported no specific complaints. Physical examination was unremarkable except for bradyphrenia, a temperature of 38.6°C and two small cervical lymph nodes. Laboratory results showed normal serum creatinine, folic acid, vitamin B12, thyroid function, slightly elevated liver enzymes and on urinanalysis 2+ proteinuria and erythrocyturia; antinuclear antibody (ANA) was positive. A repeat bone marrow examination was slightly hypocellular. Aplastic anaemia, myelodysplastic syndrome or acute myeloid leukaemia were excluded. Bacterial and viral cultures of serum and cerebral spinal fluid remained negative and computed tomography (CT) and magnetic resonance imaging (MRI) of the cerebrum were unremarkable. She recovered spontaneously and was discharged 12 days later. Ten days after discharge she was readmitted because of fever 39°C, nausea and vomiting, dyspnoea without palpitations or thoracic pain. On examination, her mental state was normal. Her blood pressure was 120/85 mmHg, heart rate 110 beats/min, temperature 37.3°C, her central venous pressure was normal and respiration frequency 14/min. On cardiac auscultation a gallop rhythm was heard without murmurs. On examination of the lungs no bibasilar breath sounds could be heard, on percussion there was a dullness in the lower lung fields, there were no rales. Mild peripheral oedema was observed. She had no signs of arthritis. Laboratory results showed an erythrocyte sedimentation rate (ESR) of 134 mm/1st hour, Hb 5.3 mmol/l, mean cell volume (MCV) 91 fl, reticulocytes 9‰, leucocytes 1.7 x 10^9/l (74% granulocytes), thrombocytes 90 x 10^9/l, creatinine 93 µmol/l, albumin 24 g/l, creatine phosphokinase (CPK) and troponin T were normal (50 U/l and < 0.01 µg/l respectively). Antibodies against double-stranded (ds) DNA, Smith (Sm) antibodies and immunoglobulin M and G (IgM and IgG) anticardiolipin (aCL) antibodies were positive, lupus anticoagulans was negative and complement levels were very low. Dysmorphic erythrocytes were present at urinanalysis and a proteinuria of 11 g/24 h was measured. Renal biopsy was not performed because of thrombocytopenia. Chest X-ray showed cardiomegaly and some pleural effusion. Echocardiography showed diffuse hypokinesia of the left ventricle, 3 cm pericardial effusion with systolic collapse of the right atrium, diastolic collapse of the right ventricle and mitral valve inflow variation >30%. Drainage of 700 ml pericardial fluid was performed. Examination of the pericardial fluid revealed 0-5 leucocytes/ power field, no malignant cells

were found. Cultures remained negative (bacterial, fungal, tuberculosis). She was treated with furosemide, perindopril, carvedilol, acenocoumarol, intravenous methylprednisolone (1000 mg for three days) and cyclophosphamide 1350 mg (750 mg/m^2). Culture-negative fever persisted and cardiac function deteriorated, necessitating inotropic therapy on the intensive care unit. Upon intravenous treatment with ten pulses of cyclophosphamide, two courses of high-dose methylprednisolone for three days and three courses of immunoglobulins (36 g/day, four days) her cardiac function gradually improved with LVEF increasing from 25 to 50%. At the time of last follow-up (September 2008) her cardiac function was stable and her renal function normal without proteinuria.

Patient 2

A 37-year-old woman with a history of ANA-positive, anti-ds DNA negative, rheumatoid factor negative, non-erosive polyarthritis for 11 years, treated with hydroxychloroquine, presented in July 1999 with exertional dyspnoea, fever and rash. The diagnosis of active SLE was made on the basis of ANA positivity, positive antiphospholipid antibodies, biopsy-proven glomerulonephritis (interstitial necrotising vasculitis with thrombosis and full house immunofluorescence, but with insufficient glomeruli for classification), pleuritis, and focal vasculitis in a skin biopsy, while other causes of pleuritis and nephritis were excluded. Antibodies against dsDNA, SSA and SSB were negative, while anti-ENA, anti-Jo and ribonucleoprotein (RNP) were weakly positive. IgM and IgG aCL were strongly positive. At echocardiography, diffuse hypokinesia was found, the LVEF measured 27% and mild mitral regurgitation was observed. CPK was normal (13 U/l). Following treatment with furosemide, enalapril, nifedipine, ascal, prednisolone 60 mg, and intravenous cyclophosphamide pulse therapy (12 x 1250 mg) she made a full recovery and went into remission in 2001. In November 2005 echocardiography showed an LVEF of 42% with normal dimensions. At the last follow-up in January 2007 she was still in remission on enalapril 10 mg daily and acetylsalicylic acid 100 mg daily.

Patient 3

A 40-year-old woman with a history of deep venous thrombosis, was admitted in October 2000 because of dyspnoea, alopecia, weight loss, muscle weakness, rash and disturbed vision. She developed cardiogenic shock and also had positive blood cultures with *Staphylococcus aureus* due to phlebitis but heart failure persisted after treatment with antibiotics (flucloxacillin). Echocardiographic examination demonstrated severe LV dysfunction (LVEF 23%) with moderate mitral regurgitation. Significant coronary artery stenosis was excluded on invasive coronary angiography. Endomyocardial biopsy of the left ventricle showed no signs of vasculitis, immunofluorescence on immunoglobulins and complement was negative. CPK was normal (59 U/l). Findings of renal biopsy were compatible with lupus nephritis World Health Organisation (WHO) classification II. MRI of her cerebrum showed abnormalities compatible with SLE and she had retinal cotton wool spots as signs of vasculitis. Mild autoimmune thyroiditis was present, for which she received substitution with thyroxin. She was ANA, ENA, RNP, Sm positive, SSA, SSB and anti-dsDNA negative, and strongly positive for IgM and IgG aCL. She experienced no improvement after treatment with intravenous methylprednisolone pulses (1000 mg on three consecutive days) and azathioprine for 20 days. Impressive improvement was seen, however, after several intravenous pulses of cyclophosphamide (1185 to 1500 mg, 750 mg/m^2). After treatment with eight pulses of cyclophosphamide her SLE went into remission with gradual normalisation of her heart function (LVEF 52% and 63% in December 2002 and June 2006 respectively). At the last follow-up in June 2008 she was doing well, on thyroxin 75 µg daily, enalapril 20 mg twice daily, hydroxychloroquine 200 mg twice daily, and acenocoumarol.

Patient 4

A 22-year-old woman, had been treated successfully for chronic myeloid leukaemia (CML) with hydroxyurea and α-interferon when she presented in November 1998 with polyarthritis, fever 39°C, purple skin lesions and myalgia. A diagnosis of SLE was made on the basis of leukopenia, positive ANA, antibodies against dsDNA and antiphospholipids, positive aCL, low complement levels, pleural effusion and leuocytoclastic vasculitis. Treatment with 60 mg prednisolone and azathioprine was initiated, and α-interferon discontinued. Two months later she was readmitted because of dyspnoea. Perfusion scintigraphy revealed a perfusion/ventilation mismatch in the right lung, for which anticoagulant therapy was started. Nevertheless, she remained dyspnoeic and fatigued, and was readmitted in February 1999. CPK was slightly elevated (101 U/l, normal up to 55 U/l). She was treated with intravenous methylprednisolone pulses 3 x 1000 mg, and switched to oral prednisolone in conjunction with azathioprine 125 mg daily. She was treated with mechanical ventilation and inotropic therapy and also with CVVH for renal failure as a result of lupus nephritis (WHO IIIA) and acute tubulus necrosis (ATN) after hypotension. Echocardiography demonstrated a severely depressed LV function (LVEF 25% in February 1999) with mild mitral regurgitation. Azathioprine was replaced by cyclophosphamide 65 mg daily (1 mg/kg iv), which was switched to intravenous cyclophosphamide pulse therapy (1300 mg, 750 mg/m^2) two weeks later. On recent echocardiography LVEF was 51% without mitral regurgitation. In May 2001 a relapse of CML was

diagnosed, and imatinib 400 mg daily was started, upon which the CML went into remission. In June 2008 her CML and SLE were still in remission.

Patient 5

A 38-year-old woman, was diagnosed with SLE in March 2003 on the basis of photosensitivity, malar rash, arthritis, oral ulcers, and Raynaud's phenomenon. ANA, anti-dsDNA antibodies and aCL were negative. Her disease was well controlled with hydroxychloroquine 400 mg once daily when she was admitted in October 2004 for surgical treatment of haemorrhoids under regional anaesthesia. Approximately three hours after surgery she presented with dyspnoea, tachypnoea, chest pain, bloody sputum, hypotension and tachycardia. An ECG showed inverted T waves in various leads. Serum troponin was positive (9.8 ng/ml, normal <1.5). Echocardiography revealed a depressed LVEF (37%) with global hypokinesia, but no pericarditis. No evidence of lupus nephritis was present. On the basis of these findings a working diagnosis of lupus myocarditis was made and treatment instituted with intravenous methylprednisolone pulses (1 g on three sequential days), followed by oral prednisone (30 mg daily), azathioprine (150 mg daily) and hydroxychloroquine (400 mg daily), which led to a complete recovery. Follow-up echocardiography in November 2004 showed normalisation of LVEF (60%). She was still doing well at the last follow-up visit in May 2008.

Patient 6

A 37-year-old woman, was diagnosed with SLE in June 1984 on the basis of a malar rash, photosensitivity, arthritis, chorea, positive ANA, anti-dsDNA antibodies and aCL. She was successfully treated for lupus nephritis (WHO class III) and secondary antiphospholipid syndrome in October 1994. In December 2001 she was admitted for surgical drainage of a left salpingo-ovary abscess. She was on prednisolone (4 mg/day), hydroxychloroquine (400 mg/day) and acetylsalicylic acid (100 mg/day). On the fourth postoperative day she developed left common femoral vein thrombosis. On the ninth postoperative day the patient abruptly became dyspnoeic. The ECG showed inverted T waves in various leads. Serum troponin and CPK were within the normal range. Echocardiography revealed a depressed LVEF (30%) with diffuse hypokinesia and mild mitral valve regurgitation, but no evidence of myocardial infarction or pulmonary embolism. On the basis of these findings lupus myocarditis was diagnosed. No evidence of active nephritis was found. She was treated with intravenous methylprednisolone pulses (1 g on three sequential days) and an intravenous pulse of cyclophosphamide (1300 mg, 750 mg/m^2) once a month for seven months, from December 2001 until June 2002. Her symptoms improved dramatically. Follow-up echocardiography in March 2002 and March 2008 showed an LVEF of 55 and 45%, respectively. She has been in remission ever since with a last follow-up in March 2008.

DISCUSSION

We describe six patients with severe heart failure due to SLE (summarised in *table 1*). Echocardiography was essential in confirming the clinical diagnosis of myocarditis and monitoring its activity over time, and excluding other causes of heart failure. Patient 1 also had significant pericardial effusion, but drainage did not result in improvement of heart failure. Five patients had evidence of lupus nephritis and a good response to immunosuppressive therapy with (methyl)prednisolone and cyclophosphamide. One patient was also treated with intravenous immunoglobulins; the contribution of this adjunct therapy to recovery was not clear. Cardiac function recovered in all patients within six months and remained normal over a mean follow-up period of 77 months. To our knowledge the present study is the first to describe clinical and echocardiographic data of cardiac function in this context with a long follow-up.

Various case reports demonstrated that severe myocardial dysfunction may potentially be reversible in SLE patients (*table 2*). Glucocorticoids are commonly used. Treatment with both glucocorticoids and cyclophosphamide has been reported to be superior to glucocorticoids alone, although controlled clinical trials to support this are lacking.[11-14] Severe myocarditis as a presentation of SLE is rare. Several authors described patients who presented with severe heart failure as initial presentation without classical clinical stigmata of lupus, similar to some of the patients in the present report.[15-18] Busteed *et al.* reported on a patient who experienced a remission of myocarditis after treatment with methylprednisolone and six pulses of cyclophosphamide, but died 14 months later of lupus nephritis and cerebral vasculitis.[13] The authors suggested that myocarditis carries a poor prognosis despite initial clinical remission. Disla *et al.* described a patient who was treated with intravenous immunoglobulins as well, because after pulse treatment with methylprednisolone 2 g and cyclophosphamide 500 mg/m^2 she still needed maximum doses of inotropic therapy and IABP was installed.[19] Following treatment, full recovery was observed. In a few patients (patient 1, 2, 3, 6, and 14, *table 2*) histological evidence of lupus myocarditis was obtained. Endomyocardial biopsy is generally recommended in unexplained heart failure but can be complicated in critically ill patients by (fatal) rhythm disturbances.[9] A negative biopsy does not rule out myocarditis and sensitivity and specificity are unknown. MRI has not yet been systematically evaluated in lupus patients with heart disease, although a preliminary report did reveal cardiac

Table 1. *Characteristics of patients in present study*

Patient no. Age/sex	Disease duration	SLE manifestations before onset of heart involvement	Antibodies	LVEF (%) pre/post therapy	Nephritis yes/no	CPK	Therapy	Outcome	Follow-up (months)
1. 19/F	1 month	Pancytopenia, fever	ANA+ Anti-dsDNA+ Anti-Sm+ Anti-CL+	25/50	Yes	N	MP pulse CYC pulse IVIg	Improvement	47
2. 37/F	11 years	Polyarthritis	ANA+ Anti-dsDNA- Anti-SSA-SSB- Anti-CL+	27/42	Yes	N	Prednisolone 60 mg CYC pulse	Improvement	90
3. 40/F	0 year	None	ANA+ Anti-dsDNA+ Anti-PL+ Anti-CL+	23/63	Yes	N	MP pulse AZA CYC pulse	Improvement	92
4. 22/F	4 months	Fever, polyarthritis, skin lesions, leukopenia	ANA+ Anti-dsDNA- Anti-SSA+	25/51	Yes	↑	Prednisolone 60 mg AZA CYC pulse	Improvement	113
5. 38/F	1.5 year	Photosensitivity, malar rash, arthritis, oral ulcers, Raynauds	ANA- Anti-dsDNA- Anti-CL-	37/60	No	NA	MP pulse AZA HCQ	Improvement	43
6. 37/F	7.5 years	Photosensitivity, malar rash, arthritis, chorea	ANA+ Anti-dsDNA+ Anti-CL+	30/45	No	N	MP pulse CYC pulse	Improvement	75

MP = methylprednisolone; CYC = cyclophosphamide; IVIg = intravenous immunoglobulins; AZA = azathioprine; HCQ = hydroxychloroquine; NA = not available, N = normal, ↑ = increased.

abnormalities in patients with active disease.[20] Serum CPK levels were normal, except in patient 13 who was successfully resuscitated, patient 17 had mild elevation of CPK and troponin I (326 IU and 5.6 µg/l respectively, normal <160 IU and <0.2 µg/l) while having a flare of SLE myocarditis. In this patient cardiac catheterisation revealed normal coronary arteries.

Of note, five out of the six patients in our series had detectable anticardiolipin and/or antiphospholipid antibodies. It is unclear whether these antibodies are just a marker of underlying disease activity, are involved in the development of heart failure in lupus patients, or contribute to secondary intracavitary thrombus formation.[21-23] A recent large registry study involving 200 SLE patients, 42 of whom tested positive for antiphospholipid antibodies, showed an association with mitral valve nodules and mitral regurgitation but no association with other vascular abnormalities including systolic dysfunction.[24]

The differential diagnosis of heart failure due to lupus myocarditis includes viral myocarditis related to the use of immunosuppressive drugs, ischaemic heart disease, and toxic myocarditis related to the use of antimalarial drugs. Severe cardiotoxicity may develop following prolonged use of antimalarials with both conduction disturbances and congestive heart failure.[25] These cardiotoxic effects have been reported with chloroquine and less frequently with hydrochloroquine use alone. Clinical and echocardiographic presentations of antimalarial-induced cardiomyopathy often include a restrictive pattern and biventricular hypertrophy that can mimic amyloidosis.

CONCLUSION

Heart failure due to myocarditis can be the presenting (cardiac) manifestation of SLE, which requires prompt action. Echocardiography is an essential diagnostic tool. We report on six patients with a good clinical response on immunosuppressive therapy with a relatively long follow-up, including echocardiography. In our opinion therapy with pulses of methylprednisolone and intravenous cyclophosphamide is the therapy of choice given its rapid mode of action. Therapy should be started without delay. High-dose glucocorticoids plus an initial cycle of six monthly pulses of cyclophosphamide 750 mg/m^2, followed by a repeat cycle if LVEF has not completely normalised, is relatively well tolerated and effective. In our patients heart failure did not recur after successful treatment.

Table 2. *Characteristics of patients in case reports*

Patient no. Age/sex	Disease duration	SLE manifestations before onset of heart involvement	Antibodies	LVEF (%) pre/post therapy	Nephritis yes/no	CPK	Therapy	Outcome	Ref.
1. 34/F	2 years	NA	ANA+Anti-dsDNA+	NA	NA	NA	Prednisolone 40 mg CYC 100 mg p.o.	Improvement	27
2. 33/F	NA	NA	ANA+Anti-dsDNA-	NA	Yes	NA	Prednisolone 80 mg AZA	Improvement	27
3. 62/F	15 years	NA	NA	10/NA	NA	NA	Prednisolone 60 mg	Improvement	27
4. 46/F	0 months	Lymphopenia, anaemia, fever	ANA+Anti-dsDNA- Anti-SSA+	NA	No	NA	MP 80 mg i.v.	Recovery cardiac function (follow-up 1.5 years)	15
5. 28/F	1 years	Arthritis, fever, lymphopenia, lymphadenopathy	ANA+Anti-dsDNA+ Anti-Sm+	NA	NA	NA	MP pulse CYC pulse IVIg	Functional recovery	19
6. 38/M	0 months	Oral ulcers, haemolytic anaemia	ANA+Anti-dsDNA+	45/65	No	N	Prednisolone 1 mg/kg	Resolution of myocardial damage	16
7. 30/F	6 months	Rash, alopecia, arthritis, pleuritis, oral ulcers	ANA+Anti-dsDNA-	34/55	No	N	MP pulse AZA	Recovery cardiac function	11
8. 55/M	6 months	Proximal weakness, arthritis	ANA+Anti-dsDNA+	19/25	No	N	AZA, (prednisolone 40 mg)	Improvement	11
9. 20/F	1 years	Vasculitis, pericarditis, arthritis	ANA+Anti-dsDNA+	20/46	No	N	CYC pulse (prednisolone 80 mg)	Improvement	11
10. 32/F	2 years	Rash, arthritis, pleuritis, oral ulcers, nephritis	Anti-dsDNA+	20/45	Yes	N	MP pulse CYC pulse	Improvement	11
11. 45/F	10 years	Rash, arthritis, vasculitis, interstitial lung disease	NA	11/38	No	N	Prednisolone 60 mg CYC pulse	Improvement	11
12. 48/F	3 years	Alopecia, arthritis, rash, photosensitivity	ANA+	11/30	No	N	MP pulse CYC pulse	Improvement	11
13. 59/F	Several years	Arthritis, pleuritis, sec. myelofibrosis	ANA+Anti-dsDNA-	20/50	NA	↑*	IVIg (prednisolone 40 mg)	Recovery cardiac function	28
14. 20/F	3 years	Discoid rash, oral ulcers, seizure, myositis, leucopenia	ANA+ Anti-dsDNA+ Anti-SSA+	19/63	Yes	N	CYC pulse Prednisolone 50 mg	Recovery myocarditis, nephritis no complete remission (follow-up 2 years)	12
15. 23/F	7 years	Malar rash, arthralgia	ANA+Anti-dsDNA+	40/55	No	N	MP pulse CYC pulse	Recovery myocarditis death: nephritis, cerebral vasculitis(after 14 m)	13
16. 43/F	1.5 years	Raynaud, arthritis, myositis	ANA+Anti-dsDNA- Anti-RNP+Anti-Sm+	29/34	No	N	Prednisolone 20 mg	Only mild improvement after 1 year	29
17. 15/F	1 years	Arthritis	ANA+Anti-dsDNA+	30/50 40/55§	No	N ↑	MP pulse, MP pulse IVIg†	Marked improvement	29
18. 22/M	4 years	Autoimmune thrombopenia arthritis, nephritis	Anti-dsDNA+Anti-RNP+	24/53	Yes		MP pulse CYC pulse‡	Improvement	29
19. 36/F	0 months	Serositis	ANA+Anti-dsDNA+	35/46			MP pulse	Functional recovery	17
20. 16/F	0 months	Serositis, lymphopenia, nephritis	Anti-dsDNA+	28/NA	Yes	N	MP pulse	Recovery cardiac function renal: haemodialysis	18
21. 45/M	NA	Photodermatitis, nephritis	ANF+Anti-dsDNA+ Anti-Sm+	27/NA	Yes		CYC pulse Prednisolone, HCQ	Recovery cardiac function	14

*After resuscitation; †treatment for bicytopenia; ‡treatment for lupus nephritis; §recurrence of severe myocarditis in same patient after 6 years. MP = methylprednisolone; CYC = cyclophosphamide; IVIg = intravenous immunoglobulins; AZA = azathioprine; HCQ = hydroxychloroquine; NA = not available; N = normal. ↑ = increased.

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CASE REPORT

Complete remission of severe idiopathic cold urticaria on interleukin-1 receptor antagonist (anakinra)

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ABSTRACT

A 62-year-old patient had suffered from severe cold intolerance with an urticarial rash and oropharyngeal angio-oedema upon cold exposure since early childhood. This could be provoked by the ice cube test and by exposure in a cold room. Her family history was negative, and she did not carry any mutations in the *NRLP3* gene. Treatment with IL-1 receptor antagonist anakinra resulted in complete resolution of these symptoms, with a radical beneficial change in her quality of life. In recent years this patient had developed progressive neurological symptoms leading to a diagnosis of amyotrophic lateral sclerosis (ALS), which seems unrelated to the idiopathic cold urticaria. The neurological symptoms did not respond to anakinra treatment and were eventually fatal.

Conclusion: We describe the first case of IL-1RA treatment in idiopathic cold urticaria with good response. Anakinra had no effect on the progression of her symptoms of ALS.

KEYWORDS

Amyotrophic lateral sclerosis, interleukin-1, interleukin 1 receptor antagonist protein, urticaria

INTRODUCTION

Cold urticaria/urticaria-like syndromes are rare disorders, characterised by intolerance to cold. Upon cold exposure, patients develop an urticarial rash, which is described as itchy or burning, often accompanied by fever and chills, recurrent arthralgia, and conjunctivitis.[1] Acquired cold urticaria can be idiopathic or secondary to e.g. cryoglobulinaemia or infectious diseases.

A hereditary form, familial cold autoinflammatory syndrome (FCAS, previously known as familial cold urticaria), is caused by mutations in the gene for cryopyrin (syn., NLRP3, NALP3, PYPAF1).[2] Cryopyrin forms part of an inflammasome, a protein complex crucial in the activation of interleukin-1β (IL-1β).[3] Inhibition of IL-1β signalling by recombinant interleukin-1 receptor antagonist (rIL-1RA, anakinra) is an effective treatment of FCAS.[4]

There are no data available on response to anakinra in acquired or idiopathic cold urticaria. Most patients respond to oral antihistamine treatment but this is often a partial response and avoidance of cold exposure can be greatly disabling.[5]

Recently, we saw a patient with severe sporadic cold urticaria, in whom we evaluated the effect of anakinra treatment. This patient also developed neurological symptoms.

CASE REPORT

A 62-year-old Caucasian woman suffered from severe cold intolerance with an urticarial rash and oropharyngeal angio-oedema upon cold exposure since early childhood. She had never been able to go out in the snow, go ice skating or drink cold drinks in the summer. Even at ambient temperatures slightly lower than 20°C she was at risk of developing symptoms. Family history was negative. Physical examination at that time showed an increased breathing frequency of 18/min and an urticarial rash on her arms

that lasted for 30 minutes. The ice cube test (application of ice cube to patient's forearm for five minutes) resulted in a localised urticarial rash after three minutes, still visible 24 hours later (*figure 1*). Exposure to generalised cold in a cold room (4°C, with only regular indoor clothing) was only tolerated for five minutes; this caused general malaise with difficulties in swallowing and dyspnoea. Symptoms were not accompanied by an acute phase response.

In the past she had been investigated by several physicians, and no evidence for an underlying disease (e.g., infection, cryoglobulinaemia) was found. Hence and because of the life-long history, the diagnosis of idiopathic cold urticaria had been made. We sequenced the *CIAS1* gene, the causative gene in FCAS which encodes for cryopyrin, but no mutations were found. Previous treatment by oral antihistamines and steroids had been ineffective.

In the year before presentation, she had gradually developed neurological symptoms, which consisted chiefly of difficulties with speech and swallowing. On examination there was pseudobulbar dysarthria, slight right-sided anterior tibial weakness, elevated arm reflexes and knee jerks, subclonic Achilles tendon jerks and plantar responses in extensor. Extensive ancillary investigations yielded a tentative diagnosis of primary lateral sclerosis.

We studied cytokine production by peripheral blood mononuclear cells (PBMCs). Cells isolated from the patient and two healthy volunteers were stimulated for 24 hours at 37°C with lipopolysaccharide (LPS); supernatant concentrations of IL-1β, TNFα and IL-10 were measured by ELISA. This revealed no increased cytokine production by patient cells; rather, a trend towards less IL-1β production (*figure 2*). Incubation of the cells at a lower temperature (20°C) blocked cytokine production almost completely in both volunteers and patient. There was also no difference in cytokine production by patient cells isolated while symptomatic or symptom-free (data not shown). Serum IL-1α and IL-1β concentrations were not increased.

Figure 1. *Patient's right forearm, 24 hours after five-minute ice cube application, still showing a localised urticarial rash*

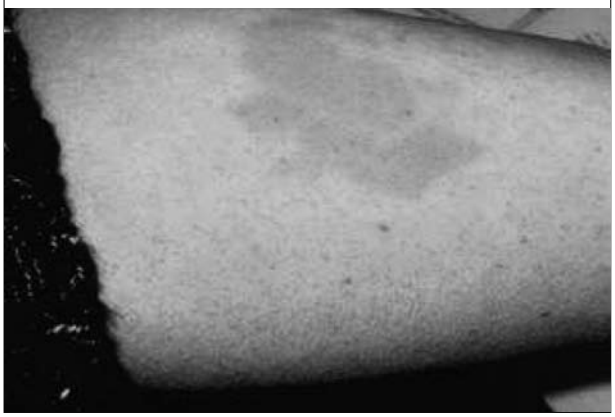
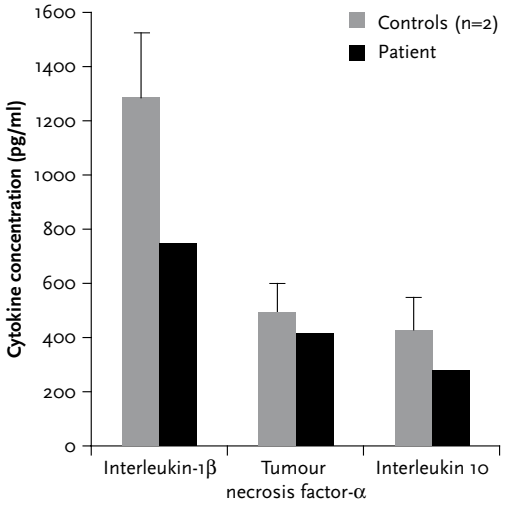


Figure 2. *Cytokine production by lipopolysaccharide (LPS)-stimulated peripheral blood mononuclear cells of two controls and the patient during the asymptomatic phase*



We decided to treat the patient with anakinra because of the severe, debilitating, cold urticaria, which clinically resembled FCAS. Anakinra treatment 100 mg subcutaneously a day had an immediate effect on the cold tolerance. After two doses, she was able to tolerate cold exposure in the cold room for at least 15 minutes (as long as the investigator, EB), without symptoms. The ice cube test did not lead to an urticarial rash (*table 1*). She was able to drink cold drinks without any symptoms. There was an impressive improvement in general well-being and activity. During follow-up of more than two years on daily anakinra, there was no recurrence of the cold urticaria and cold intolerance.

However, the response of the neurological symptoms was only subjective and temporary. After three weeks of anakinra treatment the patient reported greatly improved swallowing and greater speech facility, but speech analysis did not reveal a clear improvement. Over the ensuing months the neurological signs progressed and electromyographic examination showed signs of spontaneous muscle fibre activity and reinnervation in the thoracic and lumbosacral regions consistent with a diagnosis of ALS. The last examination in June 2008 showed nearly complete loss of the motor ability that enables speech, dropped head, inability to cough voluntarily, generalised weakness of the legs and she admitted to suffering from forced yawning. We decided to try a series of intravenous anakinra 300 mg infusions, but this did not result in any neurological improvement after ten injections. The side effects of anakinra were limited to transient skin lesions at the injection site during the first month; the high dose of intravenous anakinra was well tolerated. The patient recently died from complications of her neurological disease.

Table 1. *Patient characteristics with and without anakinra treatment*

Condition	Untreated	Anakinra 100 mg/day
CRP (mg/l)	<5	<5
Ice cube test	Localised urticarial rash	Asymptomatic
Cold room 4°C	Urticarial rash, dyspnoea	Asymptomatic
Outside temperature <20°C	Urticarial rash, dyspnoea	Asymptomatic
Cold drinks	Angio-oedema	Asymptomatic

DISCUSSION

We describe a patient with idiopathic lifelong cold intolerance with urticaria, who had a remarkable response to the interleukin-1 antagonist anakinra, which enabled her to restore her social life. Treatment of sporadic or idiopathic cold urticaria with anakinra has not been reported before, perhaps because many patients can be managed with antihistaminic drugs and occasional steroids.[5,6] However, in a severe case like this, anakinra seems to be a beneficial treatment with relatively few side effects. It was recently pointed out that the quality of life is severely hampered in patients with FCAS;[7] the severe cold intolerance in our patient had a similar impact.

From the effect of selective IL-1 inhibition, as is established by anakinra, it can be inferred that the symptoms in our patient were mediated by interleukin-1. This is, however, not mirrored by the cytokine studies, which did not demonstrate any increased serum concentrations of IL-1β and IL-1α, and no significant differences in production of cytokines (IL-1β, TNFα and IL-10) between patient and controls (*figure 2*). Interestingly, the IL-1β production by the cells of the patient tended to be lower than that of the controls, where one might have expected higher production. It is not an unusual observation, however, that mononuclear cells from blood do not show relevant cytokine changes, even in clinical situations that are assumed to be cytokine driven (e.g., rheumatoid arthritis, familial Mediterranean fever, and infections such as typhoid fever.)[8-10]

The combination of cold urticaria and neurological symptoms is found in the two other clinical syndromes that form part of the spectrum of cryopyrin-associated periodic syndromes (CAPS): in Muckle-Wells syndrome, sensorineuronal hearing loss can develop, and in CINCA/NOMID (abbreviations for chronic infantile neurological cutaneous and articular syndrome or neonatal-onset multisystem inflammatory disease, two names for the same disease), there is often severe neurological involvement which can include chronic meningitis (headache, seizures and spasticity of the lower extremities), cerebral atrophy, and sensorineuronal hearing loss.[11,12] These neurological complications also respond, at least partially, to anakinra treatment.[13] Our patient had neither a positive family history nor a CIAS1 gene mutation, but in about a third of patients who receive a clinical diagnosis of CINCA/NOMID no gene mutation can be found, and they still respond to anakinra.[10] However, the neurological phenotype of our patient did not closely resemble that of CINCA/NOMID, and there was no objective improvement or reversal of the gradual deterioration on anakinra treatment, even in a higher intravenous dose.

In the end, a definite, concomitant diagnosis of ALS was reached. We are not aware of any connection between urticaria and ALS. There have been a number of studies, mostly in mouse models of ALS, pointing to a role for IL-1β and caspase-1, the converting enzyme necessary for activation of pro-IL-1β in the pathogenesis of ALS.[14-18] Inhibition of caspase-1, either by pharmacological means[16] or by crossing the ALS mouse with a mouse with a dominant negative form of caspase-1 expressed in neuronal tissue,[18] had a positive effect on morbidity and mortality. We saw no improvement in our patient despite a high intravenous dose of anakinra. It can be argued that the drug is rapidly cleared from the body and may not reach adequate concentrations at the level of the central nervous system.

Anakinra has been found to be effective in a number of autoinflammatory syndromes in recent years, including familial Mediterranean fever (FMF),[19] Schnitzler syndrome,[20] hyper-IgD syndrome (HIDS),[21,22] and TNF-receptor associated periodic syndrome.[23]

In conclusion, this patient with severe idiopathic cold intolerance and urticaria unequivocally responded to IL-1RA, and daily injections gave her a normalised social life. The patient showed progressive neurological deterioration which turned out to be ALS, which did not respond to anakinra treatment.

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PHOTO QUIZ

A 72-year-old man with a rapidly progressive sepsis caused by a rare but life-threatening infection

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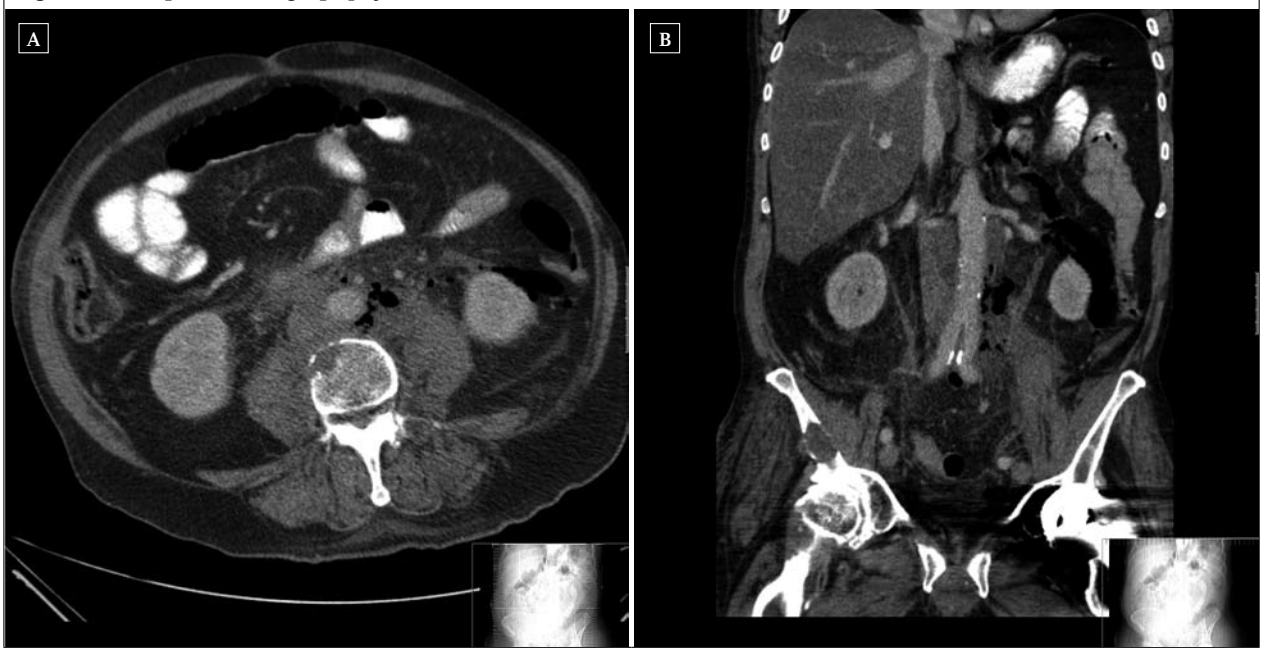
CASE REPORT

A 72-year-old man with a history of colon cancer presented to the emergency department with fever and abdominal pain. He had received his third course of oxaliplatin, capecitabine and bevacizumab one week before presentation. Physical examination revealed a slightly tender lower abdomen and a suprapubic catheter. Laboratory studies showed a white cell count of 19/mm^3 and a C-reactive protein level of 2.94 mg/dl. He was treated with ceftazidime under the clinical suspicion of a urinary tract infection. Shortly after admission he deteriorated clinically and went into a septic shock. A computed tomography of the abdomen was requested which showed extensive retroperitoneal gas formation (*Figure 1A* and *B*).

WHAT IS YOUR DIAGNOSIS?

See page 307 for the answer to this photo quiz.

Figure 1. *Computed tomography of the abdomen*



ANSWER TO PHOTO QUIZ (PAGE 306)

A 72-YEAR-OLD MAN WITH A RAPIDLY PROGRESSIVE SEPSIS CAUSED BY A RARE BUT LIFE-THREATENING INFECTION

DIAGNOSIS

The diagnosis of spontaneous abdominal gas gangrene was made in this patient. Multiple fluid boluses, tazocin and clindamycin were given. Blood cultures grew *Clostridium perfringens,* after which hyperbaric oxygen therapy was started. After six courses of hyperbaric oxygen therapy and antibiotics the patient recovered and survived.

Clostridial gas gangrene is a rare but rapidly progressive, life-threatening infection. *Clostridium* species are spore-forming, gram-positive bacteria found in soil and the gastrointestinal and genitourinary tract of humans and animals. They require an anaerobic environment to grow and therefore occur most frequently after trauma or surgery. In a minority of cases, however, a spontaneous infection occurs which is known to be associated with the highest mortality risk.[1] Various risk factors for spontaneous gas gangrene have been identified, including diabetes, liver cirrhosis, delivery and malignancy.[1-3] Of these, genitourinary and gastrointestinal malignancies are most commonly associated with spontaneous gas gangrene.[3,4] These cases are thought to be due to haematogenous spread from devitalised tissue.[4] In the case presented here, the angiogenesis inhibitor bevacizumab may have formed a risk factor as well. By inhibiting the growth of blood vessels, bevacizumab creates the required anaerobic environment for the *Clostridium* species to grow. In addition, bevacizumab is known to be associated with an increased thromboembolic risk and may thereby further contribute to an anaerobic environment.[5]

Spontaneous gas gangrene associated with malignancies is most commonly caused by *Clostridium septicum*, although the most commonly encountered *Clostridium* species overall is *Clostridium perfringens*.[1,6,7] *Clostridium septicum* is relatively aerotolerant which may have therapeutic consequences.[7]

Normally, the mainstay of treatment is surgical decompression combined with antibiotics. In the case of an extensive abdominal infection, surgical decompression is difficult and hyperbaric oxygen therapy is worth considering. Hyperbaric oxygen decreases clostridial toxin production and creates a less anaerobic environment for the bacteria to grow. It has been shown to be of benefit when used in conjunction with antibiotics and surgery, although these findings are not based on randomised controlled trials.[8-10] Based on the relative aerotolerancy of *Clostridium septicum*, hyperbaric oxygen therapy would in theory be less effective for gas gangrene caused by *Clostridium septicum* than for *Clostridium perfringens*.

In conclusion, spontaneous abdominal gas gangrene associated with a gastrointestinal malignancy is a rare but serious disorder which requires timely recognition in order to initiate an early and specific therapy to prevent death.

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PHOTO QUIZ

A woman with a swollen neck

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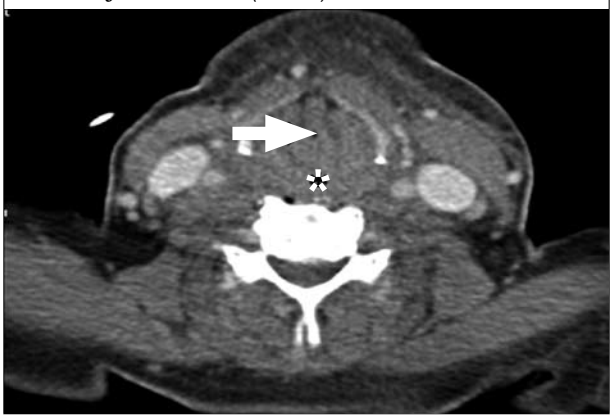
CASE REPORT

A 70-year-old female was admitted to the emergency department because of a mild stridor, a sore throat for the last 24 hours and difficulty in swallowing. She also reported difficulty in breathing at rest. Two months ago she underwent a dental extraction because of an abscess.

On physical examination, she was not in respiratory distress, but was uncomfortable because of pain. Her vital parameters were normal, but there was a mild stridor. Examination of the neck revealed a diffuse warm and tender bilateral swelling, which appeared more prominent on the left side. It was localised particularly in the submandibular space. Laboratory investigations showed a leukocytosis of 17.2 10^9/l (reference value 4 to 10 10^9/l) and neutrophilia, an elevated normal C-reactive protein level of 262 mg/l (reference value 0 to 6 mg/l), but were otherwise normal. A CT scan was performed (*figure 1*).

Figure 1. *CT scan: diffuse soft tissue swelling of the retropharyngeal space (asterisk) resulted in a pinpoint stenosis of the trachea (arrow)*



WHAT IS YOUR DIAGNOSIS?

See page 309 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 308)

A WOMAN WITH A SWOLLEN NECK

DIAGNOSIS

Ludwig's angina was diagnosed based upon the classical description. The infection is always bilateral. Both the submandibular and sublingual spaces are involved.[1,2] The infection is a rapidly spreading cellulitis without abscess formation or lymphatic involvement. The CT scan showed diffuse soft tissue swelling of the retropharyngeal space. Our diagnosis was confirmed after surgical exploration of the area. The stridor in combination with the severe airway compression on CT scan were indications for subsequent urgent maintenance of the airway. Because of diffuse swelling of the airway, we considered it unsafe and impossible to intubate the patient. A surgical airway (trachea cannula) was inserted. The patient was treated with cefuroxime and metronidazole. After seven days of treatment the trachea cannula could be removed. The patient recovered uneventfully.

Ludwig's angina is a rapidly spreading cellulitis, starting in the floor of the mouth involving the submandibular space, caused predominantly by anaerobes and Gram negative rods. A total of 70 to 85% of cases of Ludwig's angina follow infection of the second or third mandibular molar teeth. Once established, infection evolves rapidly. The tongue may enlarge to two or three times and distend into the hypopharynx, against the palate and out of the mouth. Extension of the process could involve the epiglottis, the parapharyngeal and retropharyngeal space and finally extend into the superior mediastinum.[1] Stridor and cyanosis are considered ominous signs. Radiographic views of the teeth may indicate the source of infection, and lateral views of the neck will demonstrate the degree of soft tissue swelling around the airway and possible submandibular gas.

Surgical drainage will reduce the risk of spread to the parapharyngeal space and the superior mediastinum. If cellulitis and swelling continue to advance or if dyspnoea occurs, artificial airway control should be gained immediately. Intubation of these patients must be regarded as a potentially difficult procedure. We prefer intubation in monitored conditions with all the equipment for the intubation of a compromised airway and a prepared team capable of performing an immediate coniotomy or tracheotomy.[3]

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PHOTO QUIZ

A patient with haemolytic anaemia diagnosed after thirty years

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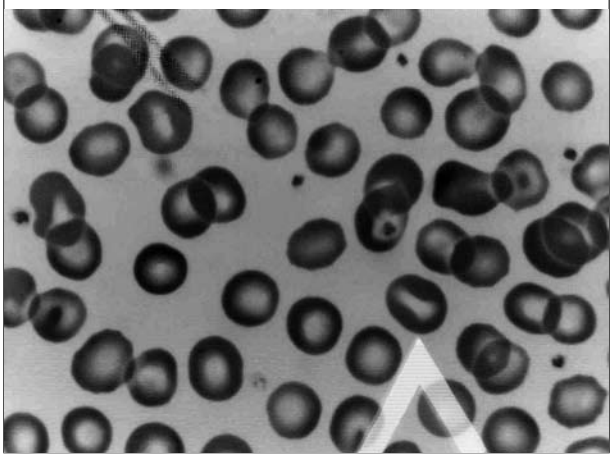
CASE REPORT

Since 1977, a 37-year-old woman had been treated for mild non-autoimmune haemolytic anaemia (haemoglobin 6.2 mmol/l (normal 7.2 to 9.5)) with a ^{51}Cr red cell half-life of less than 10 days (24 to 32 days). Mean corpuscular volume was 115 fl (80 to 100), mean cell haemoglobin concentration (MCHC) was 21.9 mmol/l (20.8 to 22.2), the reticulocytes fluctuated between 5.0 and 15.0% (0.3 to 2.0), unconjugated bilirubin was mildly elevated with normal lactate dehydrogenase. Splenectomy failed to restore the anaemia. Since splenectomy was also performed in her father and daughter because of anaemia, a hereditary disorder was suspected. The red cell spectrin content, the α and β haemoglobin chains and the activity of 13 intracellular-erythrocytic enzymes, however, were normal. The osmotic fragility was decreased with 50% lysis at 95.5 mOsmol/kg (127 to 159). On the blood smear (*figure 1*) a sporadic stomatocyte (arrow) was noted.

Figure 1. *The blood smear*



WHAT IS YOUR DIAGNOSIS?

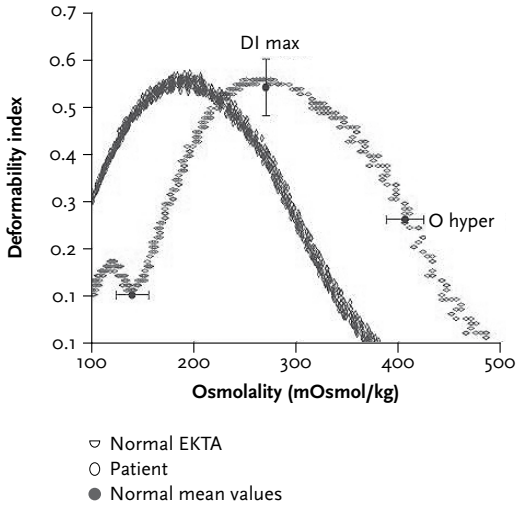
See page 311 for the answer to this photo quiz.

DIAGNOSIS

The combination of mild familial haemolytic anaemia, macrocytosis, high MCHC and decreased osmotic fragility with sporadic stomatocytes on the (wet) blood smear is suggestive for hereditary dehydrated stomatocytosis (DHSt). In mild cases the morphological features may be overlooked for many years as in this patient.[1-3] The clinical course is usually mild. Splenectomy is not advocated in view of the minimal effects on the anaemia and the high incidence of thrombotic events. Despite the mild anaemia, in this patient the DHSt was complicated by biopsy-proven intrathoracic and abdominal sites of extramedullary haematopoiesis, which is a well-known event in red cell membrane disorders such as spherocytosis.

The pathogenesis of this autosomal disorder is not fully understood and involves a net loss of intracellular potassium content that is not fully compensated by increased sodium influx, leading to a state of dehydration. DHSt may be diagnosed by demonstrating these mild cation shifts within the erythrocytes. In this case DHSt was diagnosed by the characteristic left-shifted curve on ektacytometry with normal deformability index. Ektacytometry examines the deformability of the erythrocytes in various osmotic conditions under constant shear stress.[4] The deformability, reflected by the deformability index (DI), is assessed by optical laser diffraction. As shown in *figure 2*, the deformability of normal erythrocytes is maximal (DI max) at the physiological osmolality of 290 mOsmol/kg. Under these physiological conditions the DI of the patient's erythrocytes is decreased and the normal maximal DI is reached at a lower osmolality of 200 mOsmol/kg. These parameters indicate a dehydrated state of the patient's erythrocytes under physiological osmolality. Ektacytometry may be a diagnostic tool in patients with haemolytic anaemia especially caused by red cell membrane abnormalities.

Figure 2. *Ektacytometer osmolality curves of erythrocytes*



The curve in grey resembles a normal curve. The black curve is the patient's curve. DI max = the maximal deformability index; O hyper = the osmolality at which 1/2 DI max is reached at the right site of the curve.

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SPECIAL REPORT

Internal medicine residents' knowledge about sepsis: effects of a teaching intervention

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ABSTRACT

The short- and long-term effects of a single teaching intervention for internal medicine residents are not known. Since sepsis is a prevalent and important disease and both therapeutic and diagnostic interventions have been protocolised, we investigated the effects of a sepsis-based single teaching intervention.

A prospective before-and-after education study was performed among residents who attended a regional professional training for internal medicine. All residents who participated were invited to complete a questionnaire about the assessment of symptoms and the diagnosis and treatment of sepsis. The questionnaire was filled out before, directly after, and four to six months after the teaching intervention. The overall questionnaire score was expressed on a 0 to 10 scale.

A total of 253 questionnaires from 109 training-grade doctors were collected. At baseline, the 'assessment of symptoms of sepsis' score was significantly lower than the 'diagnosis and treatment' score. Following the education session, training-grade doctors' knowledge about sepsis definitions and diagnosis and treatment of sepsis increased from (mean ± SD) 6.1 ± 1.6 to 8.2 ± 1.2 ($p<0.0001$). Moreover, four to six months after the teaching intervention, this effect was sustained ($p<0.0001$ compared with test 1), resulting in a mean score of 7.6 ± 1.1.

Our single teaching intervention resulted in improved and sustained knowledge on the assessment of symptoms, diagnosis and treatment of sepsis.

KEYWORDS

Education, internal medicine residents, knowledge, surviving sepsis campaign

INTRODUCTION

In 2004, the Central College of Medical Specialities (CCMS) of the Royal Dutch Medical Association presented guidelines for modernisation of all postgraduate speciality training programmes and since 2006 all these programmes should be based on these guidelines. To assess residents' competencies, several methods of evaluation can be applied.[1] Although the organised education for internal medicine residents is substantial, still little is known about its short- and long-term benefits.[2]

Over the last few years, several studies have shown that rapid diagnosis and management of sepsis is critical for successful treatment.[3-6] The Surviving Sepsis Campaign (SSC) provides helpful tools to improve the diagnosis and management of sepsis, especially for patients with severe sepsis and septic shock. However, implementation of these guidelines in daily practice appears to be troublesome.[7-9] As a result, about 30 to 40% of patients do not receive care according to the present scientific evidence and about 20 to 25% of the care provided is not needed or potentially harmful.[10,11]

Use of the SSC tools may be hindered by a variety of barriers to guideline adherence: lack of familiarity, lack of awareness, lack of agreement, lack of outcome expectancy, lack of self-efficacy, lack of motivation/inertia of previous practice and external barriers.[12] Previous studies have demonstrated that an important reason for not following the SSC guidelines is that the identification of patients with sepsis can be difficult, resulting in treatment delay.[13,14] Only about 30% of physicians correctly identified the diagnostic criteria for Systemic Inflammatory Response Syndrome (SIRS).[15] Even after active implementation of a sepsis teaching programme, only 48 and 67% of the training-grade doctors could define severe sepsis and septic shock, respectively.[16]

Another reason for not following the SSC guidelines is the lack of knowledge about the management of patients with sepsis.[13,14] Therefore, extensive knowledge about sepsis is an important condition for early identification and management of patients with sepsis. In addition, none of the previous studies have evaluated the knowledge deficiency for different sepsis topics and the short- and long-term effectiveness of a teaching intervention aimed at improving physicians' knowledge about sepsis. We performed the present study in which the potential variety in residents' knowledge about the identification and management of sepsis and the short- and long-term effectiveness of a brief and single teaching intervention were examined.

MATERIALS AND METHODS

Study design and population

We performed a prospective before-and-after education study among internal medicine residents who visited the regional professional training for internal medicine (RODIN) about sepsis. RODIN is part of the training programme for internal medicine residents[17] and is organised five times a year at the Radboud University Nijmegen Medical Centre (RUNMC). RODIN is attended by residents from the RUNMC or one of the six affiliated regional community hospitals.

During a brief educational intervention based on the SSC guidelines, an internist-intensivist (PP) gave a lecture about the SSC, diagnosis and the management of sepsis.

Development of the questionnaire

The questionnaire was based on the two topics of the SSC-based teaching intervention and included ten multiple choice questions: five questions covering assessment of the symptoms of sepsis (topic 1) and five questions about diagnosis and treatment of sepsis (topic 2). In the questionnaire, respondents were presented with short case descriptions. Examples of two questions are shown in *table 1* (the complete questionnaire is available on request).

Data collection and variables

All data were collected in three periods: immediately before, three hours after the education session about sepsis, and four to six months following the teaching intervention. Before and directly after the lecture, the residents were asked to fill out the first two questionnaires. All respondents were approached by mail and asked to fill out the third questionnaire. Non-responders received two reminders, including the questionnaire, by e-mail. Relevant respondent characteristics included gender, and year of training.

Table 1. *Questionnaire with five questions covering assessment of the symptoms of sepsis (topic 1) and five questions about diagnosis and treatment of sepsis (topic 2), examples of two questions*

Topic 1: Assessment of symptoms

Which of the following criteria are SIRS criteria?

- Temperature >38°C or <36°C, cold chills, heart rate >90 beats/min, respiratory rate >20 breaths/min, altered mental status, $PaCO_2$ <4.3 kPa (32 mmHg), white blood cell count >12 x 10^9/l, <4 x 10^9/l or >10% immature (band)forms.
- Temperature >38°C or <36°C, heart rate >90 beats/min, respiratory rate >20 breaths/min, $PaCO_2$ <4.3 kPa (32 mmHg) or respiration, white blood cell count >12 x 10^9/l, <4 x 10^9/l or >10% immature (band)forms.
- Temperature >38°C or <36°C, heart rate >90 beats/min, respiratory rate >20 breaths/min, $PaCO_2$ <4.3 kPa (32 mmHg), white blood cell count >12 x 10^9/l, <4 x 10^9/l or >10% immature (band)forms, hyperglycaemia in the absence of diabetes (glucose >6.8 mmol/l)

Topic 2: Diagnosis and treatment of sepsis

When patient's blood pressure and/or organ perfusion does not respond to fluid challenges, you have to start with vasopressor therapy. Which proprostion(s) is/are correct?
Proposition I: In case of hypotension in patients with septic shock, norepinephrine or dopamine is first choice vasopressor therapy.
Proposition II: To offer protection to the kidneys, a low dose of dopamine can be used in the treatment of severe sepsis.

- Proposition I as well as proposition II are correct
- Proposition I is correct, proposition II is incorrect
- Proposition I is incorrect, proposition II is correct
- Proposition I and proposition II are both incorrect

Statistical analysis

Descriptive statistics included frequencies, percentages, means and standard deviations. All questions were given an equal weight of one point per question. The overall questionnaire score was expressed on a 0-10 scale. Potential differences in the total questionnaire scores between the three tests were analysed using a random-effects model with random-factor respondent and fixed-factor test. In a secondary analysis, gender and year of experience were added as covariates to investigate whether gender and experience had an impact on the scores. Finally, we investigated whether these factors influenced the learning, by adding the interaction terms with the test to the model.

RESULTS

A total of 253 questionnaires were collected. Seven of these questionnaires were excluded: four questionnaires could not be linked to follow-up tests and three residents only filled out the questionnaire before or immediately after the education. We used 246 questionnaires for further analysis.

Respondents

A total of 109 internal medicine residents participated, 91 of whom (84%) completed the questionnaire before and

immediately after the education. Of these participants 39% were male and 45% had more than two years training experience. The set of all three questionnaires was completed by 64 participants (70%), 33% were male and 42% had a training experience of more than two years.

Questionnaire data

Figure 1 illustrates the mean overall questionnaire scores and the mean scores per topic for all participants in the study. At test I and test II the mean overall questionnaire scores are comparable with the mean scores of the 64 respondents who filled out all three questionnaires: 6.1 ± 1.5 for test I and 8.3 ± 1.1 for test II.

In the subgroup of residents who filled out all three questionnaires, the baseline score of 6.1 ± 1.6 increased to 8.2 ± 1.2 after the lecture (p<0.0001). Moreover, four to six months after the teaching intervention this improvement was sustained (p<0.0001 compared with test 1), resulting in a mean score of 7.6 ± 1.1.

At baseline, questions concerning 'diagnosis and treatment' scored significantly better than 'assessment of symptoms' (*table 1*). As a result, only the score of 'assessment of symptoms' improved significantly (p<0.0001).

There were no significant differences between male and female residents in baseline score (data not shown). The mean scores for the years of training experience are summarised in *figure 2*. After adding gender and experience as covariates to the analysis, we found that there was no significant difference between scores or increase in score per gender or year of training (all p>0.05).

Figure 1. *Overall score per test and topic*

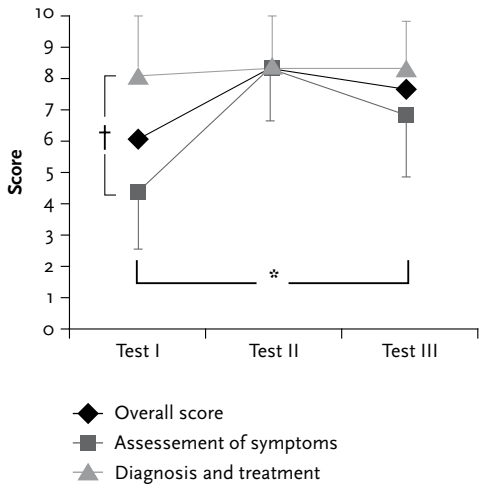
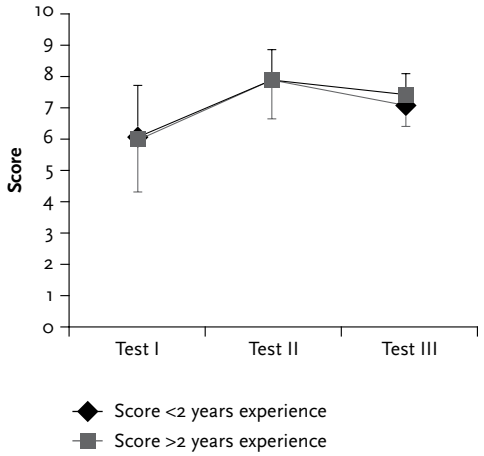


Figure 2. *Scores per years of training experience*



***Significant improvemet between mean score for test I (6.1 ± 1.6) *vs* mean score for test II (8.2 ± 1.2), and test I *vs* test III (7.6 ± 1.1), respectively (both p<0.0001). †Significant difference between mean score for assessment of symptoms (4.4 ± 1.8) and diagnosis and treatment (8.0 ± 1.9) at baseline (p<.0001).**

DISCUSSION

Identification of patients with sepsis is essential for early diagnosis and treatment. In managing sepsis, delays can be life-threatening.[3-5] Lack of adherence to recommended SSC guidelines is in part caused by lack of knowledge of these guidelines. Through the education of residents about the SSC guidelines, both diagnosis and treatment of sepsis may improve.[18]

We demonstrated that following an educational intervention about sepsis, residents' knowledge about assessment of symptoms of sepsis improved significantly. One of the main findings of this study is that apart from the short-term effects, the improved test results were sustained after four to six months. In the first (baseline) questionnaire, the issues relating to the symptoms of sepsis scored significantly lower than those related to the diagnosis and treatment. This might be related to the fact that the SIRS criteria described by Bone[19] demonstrate a high sensitivity, but low specificity for sepsis and may not equal the residents' clinical perception of a septic patient. Interestingly, a previous study showed that a majority of physicians believe that other physicians within their speciality define sepsis differently from themselves: not more than 17% agreed on any one definition.[20] This may explain why we found no association between years of experience and knowledge level at baseline or increase following an education session. Importantly, only the Bone criteria are acknowledged and it remains important that everyone uses these sepsis definitions correctly. In addition, this finding emphasises our view that the effectiveness of educational activities and progression

of knowledge during the training of residents should be monitored more frequently and more closely.
The issues concerning the treatment of sepsis scored significantly higher at baseline, resulting in the fact that a further increase did not reach statistical significance.

Only a few previous studies have described physicians' and nurses' knowledge about sepsis.[14-16,20] In accordance with our study, these studies showed an inadequate level of knowledge of the signs and symptoms of sepsis. It was demonstrated in one study that knowledge levels increased over time, when a group of residents in 1999 were compared with a different group of residents in 2003.[16] However, it is unclear whether or not this effect is linked to an unidentified more active teaching programme as mentioned by the authors, or by other unknown time-dependent factors.
A possible limitation of our study is the fact that we used a questionnaire that, although based on the SSC guidelines, was not formally validated. In addition, repeated use of the same questionnaire may have positively influenced the overall questionnaire score. However, this does not seem likely on account of the decreased overall score four to six months after the teaching intervention. Interestingly, compliance to the SSC guidelines in the emergency department significantly improved from 3.0 to 4.2 on a 0-6 scale (number of recommendations that were correctly performed). However, several other implementation strategies were conducted at the same time, and these results cannot be associated with the education of the residents alone.

CONCLUSION

Our teaching intervention resulted in a sustained improved knowledge on symptoms, diagnosis and treatment of sepsis. Short- and long-term quantitative determinations concerning the efficiency of educational activities should be performed more often.

ACKNOWLEDGEMENTS

We thank the internal medicine residents who visited RODIN, for taking the time to complete the questionnaires.

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LETTER TO THE EDITOR

Microscopic colitis and endoscopy

Dear Editor,

I read with great interest the review of microscopic colitis by Van der Wouden *et al* .[1] The authors gave a detailed account of the entity and its treatment based on four cases they had encountered in practice.

Van der Wouden *et al*. mentioned that endoscopic investigations may show 'minimal oedema and a few atypical ulcers of the mucosa'. This is true for more than 80% of patients. The rest present with erythema and ulcers but we should not forget that mucosal fractures or scar-like ridges are becoming more readily recognised nowadays, as the number of reports in the literature has increased since their initial description in 1993.[2,3] Mucosal tears are considered to be the effect of air insufflation-induced barotrauma of a less distensible colon (due to the collagen band deposition).

Both NSAIDs and proton pump inhibitors (more specifically lansoprazole) are associated with microscopic colitis and discontinuation of these medications is highly advised. There is no consensus for discontinuation of statins but in practice all of us will try a trial of withdrawal and re-challenge. It is worth pointing out the connection between microscopic colitis and coeliac disease. As serology for coeliac disease is readily available, it should be excluded in every new case of collagenous/microscopic colitis.

The use of cholestyramine is one more treatment (on the basis of contemplated pathogenetic mechanism) used for moderately severe colitis, while oral low-dose methotrexate has been tried, alongside azathioprine and cyclosporine, in refractory collagenous colitis.[4]

Finally, just to put things right, Linstrom described collagenous colitis; lymphocytic colitis was described by Lazanby *et al*. in 1989.[5]

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LETTER TO THE EDITOR

Unexpected cause of iron deficiency detected by capsule endoscopy

Dear Editor,

Flierman *et al.* present a case of ascariasis as an unexpected cause of microcytic anaemia.[1] Although the finding of *Ascaris lumbricoides* by video capsule endoscopy was certainly unexpected, we disagree with the conclusion that the infection with *Ascaris* had caused the iron deficiency. In contrast to some other helminths, *A. lumbricoides* does not feed on blood and does not cause mucosal damage severe enough to result in significant chronic faecal blood loss. The worm infections most commonly associated with iron deficiency anaemia are: hookworm (i.e. *Necator americanus* or *Ancylostoma duodenale*), *Schistosoma mansoni,* and *Trichuris trichiura*.[2] For example, a daily blood loss of 0.25 ml per adult worm of *A. duodenale* has been described. Anaemia is mostly associated with high worm loads and these heavy infections in particular can be readily diagnosed by demonstrating the eggs by microscopic stool examination. Treatment with mebendazole is effective, not only against ascariasis, but also against hookworm infections and trichuriasis. It would be interesting to know the origin and travel history of athe patient and the results of microscopical examination of the stool.

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RESPONSE TO LETTER TO THE EDITOR

Dear Editor,

We would like to thank Dr. Visser and Dr. Lieshout for their comments. The patient was born in the Dutch Antilles, but had not been there for several years. Her recent travel history was unremarkable. Her stool examination was negative. The suggestion that the anaemia was caused by other worm infections then the observed *Ascaris* could be a possible explanation of the effect of the mebendazole treatment. However, we would like to point out that similar case reports to ours have been reported before in the literature.[1] Furthermore a study in school children in Zanzibar identified the presence of *A. lumbricoides* as an independent explanatory factor of iron deficiency anaemia in a multivariate analysis including the presence of hookworm infections, suggesting that *A. lumbricoidis* itself could indeed be the causative factor.[2]

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