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Bacterial sepsis-induced rhabdomyolysis

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Abstract *Objective*: To describe the syndrome of rhabdomyolysis during bacterial sepsis with regard to incidence, blood bacteriology and complications and to examine the association between hyperosmolal state and rhabdomyolysis, evaluating the relationship between plasma osmolality (Posm) and serum creatine phosphokinase (CPK) levels.
Design: Prospective study including all patients admitted to the intensive care unit (ICU) for sepsis with positive blood culture and rhabdomyolysis over a 3-year period.
Setting: Seven-bed medical/surgical ICU of a teaching hospital.
Patients: 35 patients (group 1) with bacterial sepsis-induced rhabdomyolysis (15 males, 20 females; mean age 71 ± 13 years) and 122 (group 2) bacteraemic septic patients without rhabdomyolysis (49 males, 73 females; mean age 68 ± 15) were studied. Patients with rhabdomyolysis were divided into gram(+) and gram(–) subgroups according to the blood culture growth.
Results: From 491 patients recorded, 35 fulfilled the inclusion criteria for bacterial sepsis-induced rhabdomyolysis (7.1 %). Gram-positive bacteria predominated in group 1 (69 %), while gram-negative predominated (60 %) in group 2. There was a correlation between CPK and Posm levels in the rhabdomyolysis Group ($r = 0.52$, $R^2 = 0.27$, $p = 0.003$). There was a stronger correlation between these two variables ($r = 0.67$, $R^2 = 0.45$, $p = 0.001$) in the gram(+) subgroup. Acute renal failure (68.5 %) and electrolyte disorders such as hyperkalaemia (34 %) and hypocalcaemia (48.5 %) were the major complications in the rhabdomyolysis group. Sixteen (45.7 %) patients in group 1 and 49 (40 %) in group 2 died during their stay in the ICU from sepsis and multiple organ failure. Rhabdomyolysis was not considered a contributing factor to their death, as none of our patients died during or immediately after the syndrome.
Conclusion: Bacterial sepsis-induced rhabdomyolysis results from certain types of microorganisms, mainly gram-positive and to a lesser extent gram-negative. Hyperosmolality is a predisposing mechanism for rhabdomyolysis during bacteraemic sepsis from any type of bacterial microorganism.

Key words
Rhabdomyolysis · Bacterial sepsis · Plasma osmolality

Introduction

Rhabdomyolysis is a clinical and laboratory syndrome resulting from leakage of muscle cell contents into the plasma. Drugs, alcohol and coma are the most frequent causes of non-traumatic origin [1]. In the study by Gabow et al. [1], infectious causes of rhabdomyolysis, mainly viral and to a lesser extent bacterial, accounted for 5 % of the reported cases. During viral infections a direct muscle invasion has been proposed as the caus-

ative mechanism [2, 3]. In contrast, the mechanisms during bacterial sepsis are poorly understood and are likely to be multiple: anoxia, impaired metabolism, hyperosmolality, mediators such as tumour necrosis factor (TNF) and interleukins, toxins and direct bacterial invasion of muscle fibres, have all been implicated as causative mechanisms [4–6]. However, the role of specific microorganisms on the development of rhabdomyolysis during bacterial sepsis has not been clearly elucidated. Some reports have emphasized the role of gram-positive cocci, mainly *Streptococcus pneumoniae* and *Staphylococcus aureus*, on the development of rhabdomyolysis [7–9]. On the contrary, gram-negative bacilli, although they account for the majority of hospital-acquired septic episodes, are seldom reported as the causative agents. Of note are the limited reports on rhabdomyolysis from certain nosocomial strains (i.e. *Escherichia coli*) considering the frequency of bacteraemia caused by these strains [10–12].

The aim of our study was to describe the syndrome of rhabdomyolysis in bacteraemic septic patients with regard to incidence, the type of infective microorganism and complications. In addition, because of disorders in homoeostasis in septic patients, we examined the association between hyperosmolal state and rhabdomyolysis, evaluating the relationship between plasma osmolality (Posm) and serum creatine phosphokinase (CPK) levels.

Table 1 Study inclusion and exclusion criteria (PO_2 partial pressure of oxygen, SaO_2 arterial oxygen saturation, HCO_3 bicarborate)

Inclusion criteria

1. Sepsis defined as:
   - A. Site of infection other than soft tissue or necrotizing fasciitis
   - B. Positive blood culture
   - C. Fever (> 38°C rectal) or hypothermia (< 35.5°C rectal)
   - D. Tachycardia (> 90 beats/min)
   - E. Tachypnoea (> 20 breaths/min, if mechanicaly ventilated, minute ventilation > 10 l/min)
2. Rhabdomyolysis defined as:
   - A. Elevated serum CPK > 2500 IU/l (10 times greater than the upper limit of normal) in the absence of MB fraction
   - B. Myoglobinaemia
   - C. Myoglobinuria defined by orthotoludine test positive for blood without gross haematuria[a]

Exclusion criteria

1. Shock (mean blood pressure < 70 mm Hg) or severe hypovolaemia defined by central venous pressure < 5 mm Hg
2. Drug overdose or alcohol abuse
3. Stupor, coma, hypothyroid state
4. Diabetic ketoacidosis or non-ketotic hyperosmolal coma
5. Malignant hyperthermia
6. Prolonged hypoxia (PO_2 < 50 mm Hg, SaO_2 < 75 %), severe acidosis (HCO_3 < 15 mEq/l)
7. Electrolyte disorders (hypokalaemia: K < 3 mEq/l, hypophosphataemia: P < 2 mg/dl, hypernatraemia: Na > 150 mEq/l or severe hyponatraemia: Na < 120 mEq/l)
8. Trauma or recent surgery
9. Patients with chronic obstructive pulmonary disease taking corticosteroids, status asthmaticus
10. Past medical history positive for hereditary disorder

[a] Not obligatory

Materials and methods

The study was approved by the Ethical Committee of our hospital, which did not require the patients to give individual written informed consent.

During a period of 36 months (January 1993 to January 1996), we prospectively evaluated all critically ill septic patients with positive blood cultures and elevated serum CPK, either on admission or during their stay in the hospital. Bacteraemic septic patients without rhabdomyolysis were the control group. The study was carried out in a seven-bed medical/surgical intensive care unit (ICU). The inclusion and exclusion criteria are listed in Table 1.

All patients were treated for sepsis in the ICU; the standard treatment included intravenous fluids (colloid or crystalloid), antibiotic therapy chosen empirically initially and then according to blood culture growth, mechanical ventilatory support when necessary and parenteral or enteral nutritional support within 24–48 h. Patients on mechanical ventilation were sedated with intermittent infusions of morphine and midazolam. Muscle relaxants were not used. Low doses of dopamine (1.5–2.5 μg/kg per min) were routinely given. Rhabdomyolysis was treated with adequate hydration and forced diuresis with frusemide or mannitol.

Fluid balance and volume status were estimated daily. Central venous and arterial catheters were routinely placed in each patient and central venous pressure (CVP), systolic, diastolic and mean intra-arterial pressure (MAP) were recorded continuously. Laboratory data were collected on admission to the ICU and daily thereafter. These included complete blood count, urea nitrogen, serum creatinine, serum electrolytes, calcium, phosphorus, chloride, albumin and total protein concentration, prothrombin and partial thromboplastin times and fibrin products, CPK and isoenzyme MB. Serum myoglobin was obtained on the day of entry to the study and Posm was estimated and recorded daily. Urine analysis was routinely performed and the presence of gross haematuria (red blood cells > 5 per power field) was recorded. The orthotoludine test by dipstick was performed on the day of entry. Cultures (blood, sputum, urine) were drawn on admission and thereafter when necessary. Blood gas analysis was routinely obtained twice daily and continuous monitoring of arterial saturation was performed. The Acute Physiology and Chronic Health Evaluation (APACHE II) score was calculated from data obtained on admission or on entry to the study [13].

Of 491 patients admitted, 35 fulfilled the inclusion criteria (group 1). The control group (group 2) consisted of 122 bacteraemic septic patients without rhabdomyolysis. Group 1 was divided into gram(+) and gram(–) subgroups according to blood culture growth.

The calculated plasma osmolality was defined in mOsm/kgH_2O by the formula: Posm = $2 \times (Na^+)$ + Glu/18 + UN/2.8, where $[Na^+]$ is ionized sodium, Glu is glucose in mg/dl, and UN is urea nitrogen in mg/dl. The normal Posm ranges from 280–295 mOsm/kgH_2O. This method, calculated rather than measured osmolality, was selected because it provides more information about the stage of hydration in our patients [14]. Discrepancies between these two

Table 2 Clinical features and laboratory data for patients with (group 1) and without (group 2) rhabdomyolysis. Values are mean ± SD or per cent

	Group 1 (n = 35)	Group 2 (n = 122)
Clinical features		
Age (years)	71 ± 13	68 ± 15
Sex (male : female)	15 : 20	49 : 73
Blood culture (%)		
Gram (+)	69	40
Gram (–)	31	60
APACHE II score	17.4 ± 4.9	15.6 ± 4.7
MAP (mm Hg)	83.9 ± 7.6	85.8 ± 6.3
Hyperosmolal state (%)	85.7	67
Acute renal failure (%)	68.5	20
Disseminated intravascular coagulation (%)	11.4	13.3
Mechanical ventilation (%)	57	60
Laboratory data		
CPK (IU/l)	12 267 ± 8310	113 ± 93
Plasma osmolality ($mOsm/kgH_2O$)	317.3 ± 16.3	314.3 ± 25.1
Sodium (mEq/l)	144.1 ± 4.9	143.4 ± 6.0
Potassium (mEq/l)	5.1 ± 0.8	4.1 ± 0.6
Chloride (mEq/l)	105.7 ± 2.8	108.7 ± 7.4
Calcium (mg/dl)	7.1 ± 0.5	8.7 ± 0.9
Phosphate (mg/dl)	6.3 ± 2.0	3.7 ± 1.9
Albumin (g/dl)	3 ± 0.3	2.9 ± 0.5
Glucose (mg/dl)	203 ± 63.9	175 ± 72.7
Urea nitrogen (mg/dl)	50.1 ± 20.9	58.5 ± 48.3
Creatinine (mg/dl)	3.4 ± 2.05	1.8 ± 1.4
Ht (%) Haematocrit	39.6 ± 6.4	31.3 ± 6.5
White blood cells ($\times 10^6$/dl)	19 919 ± 4136	15 327 ± 7544

methods exist in cases of methanol, ethanol and ethylene glycol ingestion, which were excluded from our study.

A serum sodium concentration greater than 150 mEq/l and a calculated Posm greater than 340 $mOsm/kgH_2O$ were used as exclusion criteria. Values above these levels are clearly abnormal and reflect moderate to severe hypernatraemia and hyperosmolality, respectively, which are considered predisposing factors for rhabdomyolysis [15, 16].

The highest CPK, serum creatinine, potassium and phosphorus levels and the lowest calcium levels were used for analysis. Comparison of serum values and other variables between groups was carried out by using the unpaired t-test. Values are presented as means with standard deviation. To evaluate the association between two variables, the correlation coefficient was calculated with a significant limit at the level of 95%, and a scatter plot was drawn.

Results

Initially, 65 (13.2%) cases of bacterial sepsis-related rhabdomyolysis were examined: 7 patients were excluded because of severe electrolyte abnormalities prior to the event, 13 because of prolonged hypotension and tissue hypoxia, 2 due to extended seizure activity, 6 due to coma and 2 due to delirium tremens. The remaining 35 patients (7.1%) developed rhabdomyolysis due to bacterial sepsis.

Table 3 Clinical features and laboratory data on peak CPK day in the subgroups of patients with rhabdomyolysis (group 1). Values are mean ± SD

	Gram (+) (n = 24)	Gram (–) (n = 11)
Clinical features		
APACHE II score	17.5 ± 4.9	16.2 ± 4.0
MAP (mm Hg)	82.4 ± 6.8	87.3 ± 8.5
ARF	70.8 %	63.6 %
Laboratory data		
CPK (IU/l)	13 499 ± 9365	9577 ± 4634
Plasma osmolality ($mOsm/kgH_2O$)	316.9 ± 16.5	318.1 ± 16.6
Sodium (mEq/l)	144.2 ± 4.9	143.7 ± 5.2
Potassium (mEq/l)	4.9 ± 0.8	5.3 ± 0.9
Chloride (mEq/l)	105.5 ± 3.0	106.2 ± 2.4
Calcium (mg/dl)	7.04 ± 0.6	7.1 ± 0.4
Phosphate (mg/dl)	6.5 ± 2.3	5.8 ± 1.3
Albumin (g/dl)	2.9 ± 0.3	3 ± 0.4
Glucose (mg/dl)	191.5 ± 61.3	227.1 ± 65.4
Urea nitrogen (mg/dl)	49.3 ± 20.9	51.8 ± 21.6
Creatinine (mg/dl)	3.7 ± 2.3	2.7 ± 1.3
Ht (%) Haematocrit	40.3 ± 6.7	37.9 ± 5.8
White blood cells ($\times 10^6$/dl)	20 114 ± 4430	19 495 ± 3268

The clinical and laboratory data for the study population are shown in Tables 2 and 3. Group 1 consisted of 15 males and 20 females, mean age 71 ± 13 years, mean APACHE II score 17.4 ± 4.93 and mean MAP 84 ± 7.5 mmHg. The aetiology of sepsis was pneumonia (n = 12), urinary tract infection (n = 4), primary bacteraemia (n = 3), pancreatitis (n = 4), gall bladder infections (cholecystitis, cholangitis), catheter-related sepsis (n = 4), 1 patient with peritonitis and 1 with septic arthritis and inflammatory bowel disease. Serum myoglobin was measured in 33 patients (1329 ± 752 μg/dl); a positive orthotoludine test was observed in 27 (77%). Twenty patients (57%) were on mechanical ventilation and 22 patients (62.8%) received total parenteral nutrition (TPN) while rhabdomyolysis developed. Group 2 consisted of 49 males and 73 females, mean age 68 ± 15 years, mean APACHE II score 15.6 ± 4.70 and mean MAP 85.8 ± 6.3 mmHg. Pneumonia (42%), urinary tract infection (16%), catheter-related sepsis (12.5%) and cholangitis (6%) were the major causes of sepsis in this group.

Both groups and subgroups were similar with regard to age, APACHE II score and MAP (mean ± SD). The mean CPK levels and Posm values of subgroups are shown in Table 3. The difference in the mean CPK levels between the two subgroups of patients with rhabdomyolysis was not statistically significant (p = 0.065). There was a correlation between CPK and Posm levels for the study population (r = 0.52, R^2 = 0.27, p = 0.003)

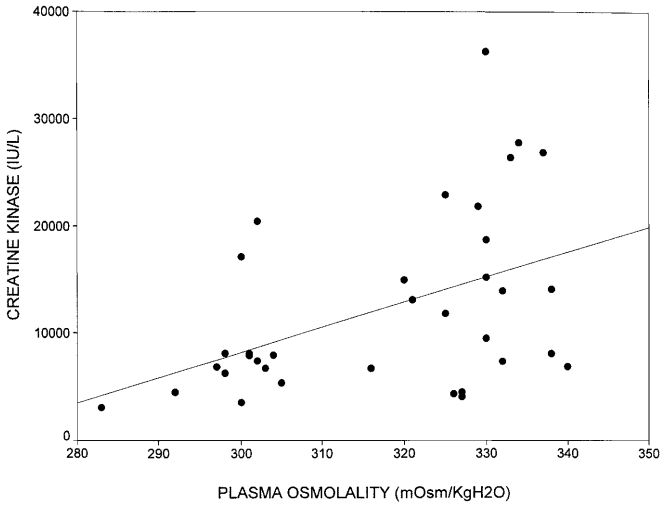

Fig. 1 Scatter plot of CPK levels vs plasma osmolality in patients with rhabdomyolysis ($r = 0.52$, $R^2 = 0.27$, $p = 0.003$)

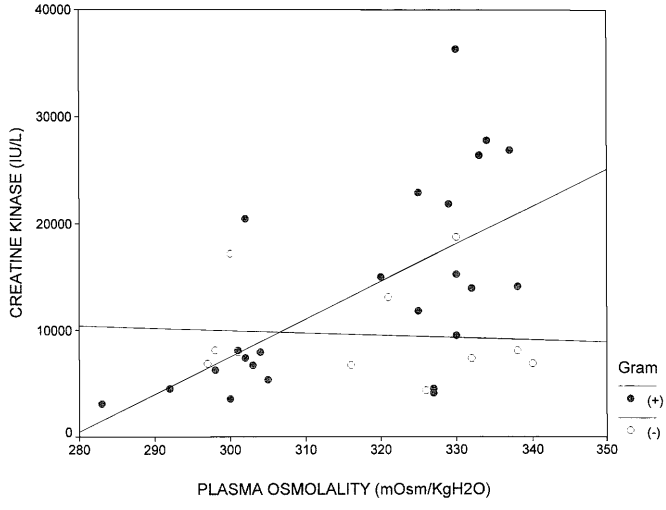

Fig. 2 Scatter plots of CPK vs Posm levels in gram(+) subgroup *solid circles* ($r = 0.67$, $R^2 = 0.45$, $p = 0.001$) and in gram(–) subgroup *open circles* ($r = 0.11$, $R^2 = 0.10$, NS)

(Fig. 1). These values correlated better in the patients with gram-positive sepsis and rhabdomyolysis (gram(+) group) ($r = 0.67$, $R^2 = 0.45$, $p = 0.001$), while there was no correlation in the gram(–) subgroup ($r = 0.11$, $R^2 = 0.10$, NS) (Fig. 2).

Acute renal failure (ARF) (serum creatinine > 2 mg/dl) was observed in 24 (68.5 %) patients in group 1 vs 25 (20 %) in group 2 ($p < 0.01$). Haemodialysis was performed in three of the rhabdomyolysis group. The patients in this group who developed ARF were older (mean age 75 ± 8.5 vs 67 ± 16), had higher CPK (14481 ± 9051 vs 7436 ± 2989, $p = 0{,}002$), Na and Posm (144.7 ± 4.9 vs 142.6 ± 4.9, $p = 0.25$ and 322.6 ± 14.4 vs 305.8 ± 14.3, NS, respectively) and lower albumin levels (2.8 ± 0.3 vs 3.3 ± 0.4, $p = 0.02$) in comparison with patients with normal renal function. Twelve patients (34 %) developed hyperkalaemia (K > 5.5 mEq/dl) and 16 (48.5 %) had hypocalcaemia (Ca < 7.0 mg/dl) in the rhabdomyolysis group. Disseminated intravascular coagulation, as defined by thrombocytopenia (platelets < 100 000/mm^3), prolonged prothrombin time and/or prolonged activated thromboplastin time attributed to rhabdomyolysis was observed in 4 (11.4 %) patients in group 1 vs 16 (13.3 %) in group 2.

Table 4 Microorganisms responsible for sepsis in the study population

Microorganisms	Frequency (%)
Group 1	
Gram (+)	
Staphylococcus aureus	25.7
Staphylococcus epidermidis	5.7
Streptococcus pneumoniae	14.2
Streptococcus faecalis	22.8
Gram (–)	
Pseudomonas aeruginosa	20
Escherichia coli	8.5
Klebsiella pneumoniae	2.8
Group 2	
Gram (+)	
Staphylococcus aureus	13.5
Staphylococcus epidermidis	6.5
Streptococcus faecalis	20
Gram (–)	
Acinetobacter	18
Escherichia coli	15
Proteus mirabilis	1.5
Pseudomonas aeruginosa	20
Klebsiella pneumoniae	5.5

The causative microorganisms responsible for sepsis are listed in Table 4. Staphylococcal and streptococcal species were the major organisms in group 1, while *enterobacteriaceae* predominate in group 2.

Sixteen (45.7 %) patients from group 1 and 49 (40 %) from group 2 died during their stay in the ICU from sepsis and multiple organ failure. Rhabdomyolysis was not considered a contributing factor to their death as none of our patients died during or immediately after the syndrome.

Discussion

Critically ill patients with systemic infections often reveal increased levels of muscle enzymes, particularly CPK. These levels, in excess of three to five times the upper limit of normal, are usually attributed to non-specific causes such as fever, rigors and prolonged immobilization [17]. More specific causes such as low

blood pressure, electrolyte abnormalities and hypophosphataemia, tissue hypoperfusion, hyperthermia, hypoxia, dehydration and acidosis, are known to induce rhabdomyolysis in any patient in a critical condition [18]. Data on the occurrence of rhabdomyolysis during bacterial sepsis are incomplete. Only a few large series have been reported in the literature in English [1, 19]. In the study of Gabow et al. [1], sepsis accounted for 2% of cases of rhabdomyolysis but the bacterial agents involved were not identified. In addition, the presence of the above-mentioned predisposing factors was not elucidated. In another study, "septicemia" accounted for 4.3% of cases of severe rhabdomyolysis (CPK levels > 40 times the upper limit of normal), but the causative microorganisms were also not reported [19].

A question that has been raised is whether bacterial sepsis-induced rhabdomyolysis is dependent on the type of organism involved or is the result of cellular and metabolic alterations that can occur during any septic episode. Singh and Scheld [20], in their recent review article concerning the infectious aetiologies of rhabdomyolysis, showed that from the reported bacterial population only a few nosocomial species, particularly gram-positive ones were mainly implicated. Neither *Pseudomonas* nor bacteraemia with a group of organisms usually associated with sepsis (*Acinetobacter*, *Serratia*, *Proteus*) were found to be causative agents. It is well known that certain microorganisms produce muscle injury by direct bacterial invasion [21], whereas others produce myotoxins (i.e. *Clostridium*) or substances with similar effects (pyrogenic toxin A of streptococcal and staphylococcal species) [22]. Other microorganisms secrete several substances known as cytolysins, which under certain circumstances have the ability to cause plasma membrane destruction, either by direct digestion of its components, or acting by a variety of mechanisms, including activity of phospholipases resulting in membrane damage from the cell exterior and pore formation, leading to osmotic lysis [23–25].

On the other hand, several investigators have focused on the role of endotoxins and other mediators such as interleukin-1 or TNF in muscle breakdown during sepsis [26, 27]. The harmful effects of these cytokines on muscle membrane potential and Na^+/K^+ pump activity have been clearly demonstrated in experimental and human studies [28, 29]. It is well known that the adequacy of Na^+/K^+ pump is crucial for calcium homoeostasis and subsequent membrane cell integrity [30]. The endotoxin theory can certainly explain the increased muscle wasting commonly observed in long-standing critical septic illness [26, 31], but cannot entirely elucidate the acute onset of rhabdomyolysis during bacterial sepsis unless specific toxic properties of the involved microorganism exist. It is possible that under the effects of endotoxin, muscle cell membranes become vulnerable to toxin activity. This view also clarifies the increased incidence of rhabdomyolysis from certain toxin-producing bacteria [7, 32].

We found an increased incidence of gram-positive vs gram-negative sepsis-induced rhabdomyolysis despite the majority of gram-negative septic insults in our ICU. *Streptococcus pneumoniae* and *Staphylococcus aureus* are the commonest gram-positive bacteria known to induce rhabdomyolysis [7, 8, 33]. Direct bacterial invasion as well as impairment of the oxidative-glycolytic enzyme activity have been proposed as the pathogenetic mechanisms [21]. Of interest is the increased incidence of enterococcus (*Streptococcus faecalis*)- and *Pseudomonas aeruginosa*-associated rhabdomyolysis in our series. There is only one report in English where enterococcus is implicated for rhabdomyolysis during polymicrobial sepsis [34].

The other aim of the study was to investigate the relationship between plasma osmolality (Posm) and CPK levels during sepsis. The relationship between these variables has been clearly determined in diabetic but not in septic patients [4, 35]. These patients are often in a hyperosmolal state due to several factors such as TPN, hypertonic saline, hyperglycaemia and dehydration [36]. The relationship between Posm and CPK levels was proved in our study (Fig. 1). Rhabdomyolysis can be explained by the hyperosmolal state, however, by only 27% ($R^2 = 27\%$, $p = 0.003$) and we believe that several other factors may be operating. Sepsis from gram-positive bacteria plays an important role in the development of rhabdomyolysis as the correlation between Posm and CPK was statistically significant ($R^2 = 45\%$, $p = 0.001$), which was not the case with gram-negative sepsis. It is not clear, however, whether the higher CPK levels in the gram-positive subgroup and the small sample of the gram-negative subgroup are the sole explanation of this divergence, or whether the activity of different toxins' between the two subgroups may contribute. The latest requires further study.

Acute renal failure (ARF) is a common complication during severe rhabdomyolysis [1, 15]. Direct toxic effects of myoglobin or its decomposition products on renal tubules, renal ischemia due to release of vasoconstrictive mediators and decrease of glomerular perfusion rate have been proposed as causative agents [15]. The reported incidences vary from 16.5 to 67% according to the selected material [15, 37, 38]. The incidence of ARF in group 1 was significantly different than in group 2 (68.5 vs 20%, $p < 0.01$). Factors that interfere with the increased incidence of ARF in patients with rhabdomyolysis were the higher CPK and sodium levels and the lower albumin levels. The course to recovery of ARF was uncomplicated in all except three patients in group 1 who required haemodialysis.

In conclusion, our study supports the concept that bacterial sepsis-induced rhabdomyolysis results from certain types of microorganisms, mainly gram-positive and to a lesser extent gram-negative. Our data indicate that hyperosmolality predispose for rhabdomyolysis caused from any type of bacteria. Though multifactorial, further studies are needed in order to clarify the separate role of each agent on the development of rhabdomyolysis during bacterial sepsis.

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