

Outcome of patients with scleroderma admitted to intensive care unit. A report of nine cases

T. Shalev¹, Y. Haviv², E. Segal², M. Ehrenfeld³, R. Pauzner³, Y. Levy¹,
P. Langevitz³, Y. Shoenfeld¹

¹Department of Medicine "B" and The Center for Autoimmune Diseases;

²The General Intensive Care Unit; ³The Rheumatology Unit, The Chaim Sheba Medical Center, Tel Hashomer and The Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel.

Abstract Objective

Patients with systemic rheumatic disease constitute a small percentage of admissions to the medical intensive care units (ICUs). Systemic sclerosis (SSc) is one of the rheumatic diseases that together with secondary complications may lead to a critical illness requiring hospitalization in the ICU. We present the features, clinical course and outcome of critically ill patients with scleroderma that were admitted to the ICU.

Methods

The medical records of nine patients with diagnosis of scleroderma (8 female, 1 male), admitted to the intensive care unit of Sheba Medical Center during the 11-year interval between 1991 and 2002, were reviewed.

Results

The mean age of the patients at the time of admission to the ICU was 48 ± 13 [SD] years. The mean duration of SSc from diagnosis to the ICU admission was 8 ± 8 years. Six patients had diffuse SSc, two patients had limited SSc and one patient had juvenile diffuse morphea. The main reasons for admission to the ICU were: infection/ septic syndrome ($n = 4$), scleroderma renal crisis (SRC) with pulmonary congestion ($n = 2$), acute renal failure associated with diffuse alveolar hemorrhage namely scleroderma- pulmonary - renal syndrome (SPRS) ($n = 1$), iatrogenic pericardial tamponade ($n = 1$), mesenteric ischemia ($n = 1$). The patients had high severity illness score (mean APACHE II 25 ± 3).

Eight out of nine patients (89%) that were admitted to the ICU died during the hospitalization, six (66.6%) of them died in the ICU. Septic complications as the main cause of death were determined in five patients (62.5%), while four of them had pneumonia and acute respiratory failure along with underlying severe pulmonary fibrosis. Lungs and kidneys were the most common severely affected organs by SSc in our patients.

Conclusion

The outcome of scleroderma patients admitted to the ICU was extremely poor. Infectious complication was the most common cause of death in our patients. Although infections are treatable, the high mortality rate for this group of patients was dependent on the severity of the underlying visceral organ involvement, particularly severe pulmonary fibrosis. The severity of this involvement is a poor outcome predictor. An early diagnosis and an appropriate treatment of such complications may help to reduce the mortality in scleroderma patients.

Key words

Systemic sclerosis, scleroderma, systemic rheumatic disease, intensive care unit, mortality, scleroderma renal crisis, pulmonary fibrosis.

Tamar Shalev, MD; Yael Haviv, MD; Eran Segal, MD; Michael Ehrenfeld, MD; Rachel Pauzner, MD; Yair Levy, MD; Pnina Langevitz, MD; Yehuda Shoenfeld, MD, FRCP (Hon).

Please address correspondence and reprint requests to: Prof. Yehuda Shoenfeld MD, FRCP (Hon.) Department of Medicine "B", Sheba Medical Center, Tel-Hashomer 52621, Israel.

E-mail: Shoenfel@post.tau.ac.il

Received on April 6, 2005; accepted in revised form on April 10, 2006.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2006.

Introduction

SSc is an autoimmune disorder of unknown etiology characterized clinically by thickening of the skin and by involvement of visceral organs, including the gastrointestinal tract, lungs, heart, and kidneys. Clinically, SSc is very heterogeneous ranging from mild forms of skin sclerosis with minimal organ involvement to severe skin and multiple visceral organ fibrosis. The pathologic manifestations of the disease are excessive deposition of collagen in skin and internal organs along with vascular lesions of small arteries (1, 2). Organ failure is generally considered as the major cause of death in these patients. Life-threatening complications of SSc necessitating ICU admission entail decompensated pulmonary hypertension, acute pulmonary aspiration, alveolar hemorrhage, renal crisis, and, occasionally, symptomatic pericardial and bowel involvement (3). Patients with SSc often have baseline organ dysfunction before developing acute illness requiring admission to ICU (4-8). It is difficult to confirm whether it is the underlying illness by itself or the severity of the complications unrelated to SSc requiring admission to ICU that influence these patients' outcome. In the following study are examined presenting features, clinical courses and outcomes of critical illness requiring admission to ICU in patients with SSc. Few studies have evaluated the outcome of rheumatic patients in ICU including SSc patients but, to the best of our knowledge, this is the first report dealing specifically with SSc patients.

Patients and methods

The study was conducted in the intensive care unit (ICU) of the Sheba Medical Center in Tel-Aviv, Israel. The discharge, hospitalization and outpatient clinic summaries of all the patients with the diagnosis of scleroderma admitted to this ICU over an 11-year period (1991-2002) were reviewed. The patients were identified by using the archive and the main computers of Sheba Medical Center.

Eight patients who fulfilled the American Rheumatism Association criteria

for classification of systemic sclerosis (9) and one patient with localized form of scleroderma were enrolled in the study. Patients with SSc were categorized into the following subgroups: limited cutaneous disease (lcSSc) and diffuse cutaneous scleroderma (dcSSc) based on the extent of skin involvement (10). Disease duration was determined from the time of diagnosis. All the available information about clinical and laboratory features in these patients was considered. The involvement of visceral organs was diagnosed according to clinical and laboratory evidence over time. Pulmonary fibrosis was defined as bibasilar interstitial fibrosis on chest radiogram, isolated carbon monoxide diffusion capacity of the lungs (DLCO) reduction ($\leq 80\%$ of predicted normal value) or restrictive syndrome on pulmonary function tests (11). Pulmonary hypertension (PHT) was defined as a mean estimated systolic pulmonary artery pressure > 30 mm Hg on Doppler echocardiography, reduced DLCO with preserved lung volumes on pulmonary function tests (DLCO $< 55\%$, forced vital capacity (FVC)/DLCO ratio > 1.4) and/or evidence of increased pulmonary artery pressure on right heart catheterization (> 30 mm Hg) (11). Patients with PHT related to pulmonary fibrosis were diagnosed as having a secondary PHT. Heart involvement was determined on the presence of symptomatic pericarditis, cardiomyopathy with a decrease in left ventricular ejection fraction and symptoms of congestive heart failure, or an arrhythmia attributable to scleroderma heart (12). Scleroderma renal crisis (SRC) was determined as the onset of accelerated arterial hypertension together with rapidly progressive renal failure (13). Gastrointestinal involvement included gastro-esophageal reflux disease (GERD) according to the findings of pH-manometry or barium swallow tests and diffuse bowel disease resulting in pseudoobstruction, bacterial overgrowth, or malabsorption (14). Raynaud's phenomenon was defined by at least 2 of 3 phases of color changes (white, blue, red), usually induced by cold exposure, and involving at least finger of both upper extremi-

ties. The following information was obtained: age, sex, type, duration of SSc, length of stay in hospital before ICU admission, length of stay in the ICU, and whether the admission was emergency or elective. Clinical, hematological, serological characteristics and previous treatment regimens before hospital admissions were recorded for each patient. Where the immunological profile, including anti-topoisomerase I and anti-centromere antibodies, was available, it was recorded. Major reasons for admission of SSc patients to the ICU were: a) hypotension or shock from any cause, defined by a systolic blood pressure of less than 90 mm Hg or the need of inotropic support to maintain arterial blood pressure above this level; b) acute respiratory failure, defined as a deterioration in the gas exchange and the need for an increase in inspired oxygen concentration or mechanical ventilation. Because of the small number of patients in this study the primary diagnosis at admission to the ICU as well as the "accompanying" diagnoses were recorded separately for each patient.

The Acute Physiology and Chronic Health Evaluation (APACHE II) score was used to determine the severity of illness in the first 24 hours on admission to the ICU (15). APACHE II scores were calculated from the ICU charts and records retrospectively. The management during the patient hospitalization in the ICU was recorded, including the requirement for mechanical ventilation, hemodialysis, inotropic support and the duration of their use. Special attention was given to the use of various treatment regimens prior to admission to ICU and thereafter. The causes of death were determined on the basis of clinical data and, where available, postmortem examination was reviewed. Patients were divided into three categories: those who died in the ICU, those who died in hospital, and those discharged from hospital.

Results

Patient characteristics

A total of 9 patients were admitted to our ICU between January 1991 and

December 2001 with diagnosis of scleroderma. Eight patients were female and one was a male. Mean age at the time of admission to the ICU was 48 ± 13 years (range 32–78 years). The mean disease duration from diagnosis to the ICU admission was 8 ± 8 years (range 6 months–26 years). Six patients had diffuse SSc (dcSSc), two patients were with limited cutaneous SSc (lcSSc), and one with juvenile diffuse morphea. One of the patients had an overlap syndrome and APS, who further developed to a full-blown rapidly progressive dcSSc, and another one was diagnosed as mixed connective tissue disease (MCTD) and developed lcSSc thereafter. The major clinical and laboratory characteristics of patients are shown in Table I. Four patients had pulmonary fibrosis with subsequent secondary pulmonary hypertension, proven by pulmonary function tests, chest x-ray and echocardiography (Table I). Only four patients had gastrointestinal tract involvement (GERD), while one of them had GERD as part of CREST (Table I). None of them had renal involvement at the time of diagnosis. One patient had cardiomyopathy with a moderate decrease in left ventricular ejection fraction on echocardiography and symptoms of congestive heart failure. During the course of SSc one patient was treated by IV IG for rapidly progressive skin involvement (Table I). Two patients were treated by iloprost: one patient was treated for severe digital ischemic skin ulcers with gangrena (Patient 4) and another one for severe pulmonary hypertension secondary to pulmonary fibrosis (Patient 8). The following serological findings were identified in our patients: positive antinuclear antibodies with speckled pattern in all patients, anti-topoisomerase I (Scl-70) in one and no patient of the 4 tested had anti-centromere antibodies. Anti-U1RNP antibodies were negative examined only in two patients (Table I). Neither p-ANCA nor anti-GBM antibodies were present in two patients with acute renal failure (Patient 1 and Patient 3). Patient 1 was diagnosed with SRC and patient 3 with scleroderma - pulmonary - renal syndrome. Kidney biopsy in both of them showed

changes compatible with scleroderma kidney without signs of vasculitis.

ICU course and outcome

The reasons for admission to the ICU varied (Table II). Four patients on admission had acute renal failure, while three of them were diagnosed with SRC. Three patients were with dcSSc and one with lcSSc. Two patients (Table I) were diagnosed with dcSSc several months previously and had normal renal function tests at presentation. A few weeks prior to the admission they had high blood pressure with elevated creatinine. Patient 1 was not treated with ACE-inhibitor previously. Patient 2 was treated with ACE-inhibitor which was discontinued because of rapidly deteriorating renal function tests. Both of them were admitted for SRC with malignant hypertension and pulmonary edema. High-dose ACE inhibitors with urgent hemodialysis were instituted. Patient 1 was discharged from the hospital and hemodialysis was discontinued three years later. Patient 2 was discharged from the ICU, but died in the internal medicine ward with sepsis and pneumonia few days later. Patient 4 had a rapidly progressive dcSSc of 12-months duration with APS, severe Raynaud's phenomenon with digital skin ulcers and bibasilar pulmonary fibrosis. During the treatment with intravenous iloprost for severe digital skin ulcers with gangrena, over the period of one month the patient developed rapidly progressive renal failure with SRC along with microangiopathic hemolytic anemia. She was also treated with ACE inhibitors and hemodialysis. She died in the ICU as a result of iatrogenic pericardial tamponade, complicated by sepsis after Tenkoff catheter insertion for dialysis. Patient 3 developed diffuse alveolar hemorrhage along with normotensive acute renal failure, also known as pulmonary-renal syndrome. Corticosteroids prior to the development of SRC were administered to two patients (Table I): to Patient 3 only for few weeks and to Patient 4 in a dose of 5 mg/day. All these 4 patients were treated with D-penicillamine for various periods of time. Only patient 1 out

Table I. Clinical and laboratory characteristics of scleroderma patients.

Patient no	Age/sex ‡	Disease duration (months)	Disease pattern	RP	GI tract	Heart disease	PHT	Lung disease	SRC	Previous treatment	Serum autoantibodies
1	32/F	9	dcSSc	Yes	No	No	No	No	SRC	DPCN diltiazem	ANF + ACA - NA anti-topo I - NA
2	42/M	8	dcSSc	No	Yes	No	No	Yes	SRC	DPCN colchicin IV IG	ANF + ACA - Anti-topo I - NA
3	44/F	96	lcSSc	Yes	Yes	Yes	No	Yes	SRC and SPRS	DPCN losartan diltiazem furosemid CS	ANF + Anti U1RNP - ACA -Anti-topo I -
4	42/F	12	dcSSc, APS and overlap syndrome	Yes	Yes	No	Secondary to ILD	Yes	SRC	DPCN CS diltiazem Iloprost- IV	ANF+ AntiU1RNP – ACA - NA Anti-topo I - NA
5	52/F	144	lcSSc and MCTD	Yes	Yes	No	No	No	No	CS DPCN	ANF + ACA – NA Anti-topo I - NA
6	55/F	60	dcSSc	Yes	No	No	Secondary to ILD	Yes	No	CS Azathioprine CTX	ANF + ACA - NA Anti-topo I - NA
7	40/F	312	Diffuse morphea	No	No	No	No	No	No	Phototherapy, penicilline	ANF+ ACA - NA Anti-topo I - NA
8	49/F	168	dcSSc	Yes	No	No	Secondary to ILD	Yes	No	CS Iloprost-Inh. sildenafil	ANF + ACA - Anti-topo I +
9	78/F	72	dcSSc	Yes	No	No	No	No	No	DPCN	ANF + ACA - Anti-topo I -

F: female; M: male; SSc: systemic sclerosis; dcSSc: diffuse cutaneous systemic sclerosis; lcSSc: limited cutaneous systemic sclerosis; MCTD: mixed connective tissue disease; RP: Raynaud's phenomenon; GERD: gastroesophageal reflux disease; PHT: pulmonary hypertension; ILD: interstitial lung disease; SRC: scleroderma renal crisis; SPRS: scleroderma-pulmonary –renal syndrome; DPCN: d-penicillamine ; CS: corticosteroids; ANF: antinuclear antibody; ACA: anticentromere antibody; Anti-U1RNP: anti-U1ribonucleoprotein antibody; Anti-topo I: anti-topoisomerase 1; IV: intravenous; Inh: inhalation; NA: not available. ‡ Age (years) at admission to ICU.

of these 4 patients survived.

Infectious complications in the ICU appeared in five patients (Table II). Three patients had pneumonia along with pulmonary fibrosis, one patient had bacteremia related to an orthopedic device and one had infection from undifferentiated site. One patient had *Pseudomonas aeruginosa* in BAL with further CMV pneumonitis (Patient 6), two patients had growth of *Staphylococcus aureus* (Patients 7, 8) and one had a growth of *Acinetobacter spp.* in the sputum (Patient 5). The main causes of death with “accompanying” diagnoses are shown in Table II. Septic complication as the main cause of death was determined in five patients. Three patients died in the ICU while the remaining two patients died later in the departments of medicine. One patient died from severe respiratory failure secondary to alveolar hemorrhage

along with acute renal failure. One patient died from an iatrogenic pericardial tamponade, complicated by sepsis in later course of the disease and the remaining one female patient of 78 years of age died because of mesenteric event.

The mean APACHE II score at admission for all patients was 25 ± 3 (range 20-30).

Table III shows the management of the patients during their stay in the ICU.

All nine patients required mechanical ventilation, while one patient (Patient 6) required prolonged mechanical ventilation (for more than two weeks). Two patients were treated with pulse methylprednisolone and one patient continued high dose prednisolone treatment along with cyclosporine after lung transplantation (Patient 6). None of them were treated with other immunosuppressive drugs during or

close to ICU hospitalization. Four patients required urgent hemodialysis. These patients had scleroderma kidney crisis and 3 out of these 4 underwent renal biopsy that confirmed scleroderma kidney vascular changes in all of them (Patients 1, 2 and 3).

The mean length of stay in the ICU was 8 ± 9 days (range 1- 30 days) and the mean in-hospital stay was 34 ± 36 days (range 7- 120 days). Eight out of the nine patients admitted to the ICU died during hospitalization (Table II). Six patients died in the ICU and two others in various departments of the hospital during the same hospitalization. One patient who was discharged survived until 2001. Her condition was quite stable during all those years.

Discussion

Our results show an unfavorable outcome in patients with scleroderma

Table II. ICU course and outcome of scleroderma patients.

Patient no	Age/sex	Disease type	Reason for admission to ICU	APACHE II at admission	LOS in ICU(days)	LOS in hospital (total/days)	Outcome	Cause of death
1	32/F	dcSSc	Pulmonary edema; SRC	24	2	7	Survived	
2	42/M	dcSSc	Pulmonary edema; SRC	25	1	10	Died in hospital	Sepsis
3	44/F	lcSSc	Alveolar hemorrhage; acute renal failure (SPRS)	26	16	28	Died in ICU	SPRS
4	42/F	dcSSc, APS and overlap syndrome	Cardiogenic shock due to iatrogenic pericardial tamponade	30	3	34	Died in ICU	Iatrogenic pericardial tamponade with shock, sepsis
5	52/F	lcSSc and MCTD	Septic shock, pneumonia, MOF	28	4	9	Died in ICU	Septic shock, MOF
6	55/F	dcSSc	Acute respiratory failure, pneumonia	20	30	90	Died in hospital	ARDS, pneumonia
7	40/F	Pansclerotic morphea	Sepsis, osteomyelitis	22	5	100	Died in ICU	Septic shock, S.aureus bacteremia with osteomyelitis
8	46/F	dcSSc	Acute respiratory failure; severe pulmonary fibrosis	24	10	14	Died in ICU	Respiratory failure, S.aureus pneumonia.
9	78/F	dcSSc	Acute abdomen; mesenteric event	28	4	14	Died in ICU	Mesenteric event
Total	Mean age 48 ± 13 8F/1M	6 dcSSc 2 lcSSc 1 morphea		Mean 25 ± 3	Mean 8 ± 9	Mean 34 ± 36	6 ICU deaths; 2 in-hospital deaths; one survivor	

F: female; M: male; SSc: systemic sclerosis; dcSSc: diffuse cutaneous systemic sclerosis; lcSSc: limited cutaneous systemic sclerosis; APS: antiphospholipid syndrome; MCTD: mixed connective tissue disease; SRC: scleroderma renal crisis; SPRS: scleroderma - pulmonary – renal syndrome; LOS of stay in ICU: length of stay in ICU; LOS of stay in - hospital: length of stay in hospital; MOF: multiorgan failure; ARDS: adult respiratory distress syndrome; prolonged MV: prolonged mechanical ventilation; S. aureus: Staphylococcus aureus; ±: standard deviation.

admitted to the ICU with an overall hospital mortality of 89% (8/9 patients) and ICU mortality of 66.6% (6/9 patients). Godeau *et al.* (16) also reported high mortality rate for SSc patients requiring admission to the ICU. In their study the mortality rate for SSc patients was the highest among all rheumatic patients (8/13 patients). The reported mortality rate of patients with systemic rheumatic disease in ICU ranges between 16-54% and is higher than in nonrheumatic ICU admissions (16-22). The mortality rate of our scleroderma patients was found to be significantly higher than the overall mortality rate in our ICU (30-40%). Infectious complications were the most common causes of death in our patients (62.5%- 5/8 patients). The association between the high mortality rate in ICU for rheumatic patients and infectious

complication has been previously described by other investigators and was around 60% as the cause of death in those reports (16, 18, 19). One possible explanation for the high rate of infection might be that a significant number of our patients, in whom an infection was determined as the main cause of death, had interstitial lung fibrosis. As a result these patients were prone to severe respiratory failure even with mild pulmonary infections. It is known that pulmonary fibrosis and pulmonary hypertension have a poor prognosis and in last years are thought as the leading causes of death in patients with SSc (7, 8, 23). Steen and Medsger (24) found a 9-year cumulative survival rate of 38% in patients with severe pulmonary involvement. Hubbard *et al.* (25) reported on the median survival in patients with fibrosing alveolitis in

association with a connective tissue disease as less than 3 years. Thus, our results are not surprising in their adverse outcome. It should be noted that one patient out of those who died because of infectious complications had lung transplantation due to severe pulmonary fibrosis and secondary pulmonary hypertension of five-year duration. Kubo *et al.* (26) reported a high mortality rate close to transplantation due to a bacterial pneumonia in patients with scleroderma undergoing lung transplantation. These data raises the possibility that early detection, newer and aggressive treatments of interstitial lung disease in SSc patients may lead to improvement in the outcome (27, 28).

The survival was dismal prior to the vigorous treatment of hypertension and the use of ACE inhibitors in patients

Table III. Management during ICU hospitalization.

Patient no	Mechanical ventilation	Dialysis	Inotropic support	Antimicrobial treatment	Surgical intervention	Immunosuppressive treatment
1	Yes	Yes	No	No	No	No
2	Yes	Yes	No	No	No	No
3	Yes	Yes	Yes	Yes	No	Pulse methylprednisolone
4	Yes	Yes	Yes	Yes	No	No
5	Yes	No	Yes	Yes	Yes	Pulse methylprednisolone
6	Yes	No	No	Yes	No	High dose prednisone, cyclosporin
7	Yes	No	Yes	Yes	No	No
8	Yes	No	No	Yes	No	No
9	Yes	No	Yes	Yes	Yes	No
Total	9/9	4/9	5/9	7/9	2/9	3/9

with SSc developing SRC (29, 30). In our study four out of the nine patients (44%) developed acute renal failure where in three SRC was confirmed and one was diagnosed with pulmonary-renal syndrome. For two patients the SRC was the major reason for admission to ICU. Despite the high overall mortality of our patients, one patient with SRC who did not develop secondary complications survived. Two other patients died from iatrogenic cause and hospital acquired pneumonia associated with severe pulmonary fibrosis respectively. Based on our results SRC was not related directly to the high mortality rate in our patients. One patient was admitted to the ICU because he developed scleroderma-pulmonary-renal syndrome (SPRS) manifested as a fulminant course of acute normotensive renal failure associated with diffuse alveolar hemorrhage. Pulmonary-renal syndrome is a rare complication in SSc with a poor prognosis. Bar *et al.* (31) reviewed the histories of 11 patients including the patient described in our study with SPRS and found that all 11 patients (100%) died within 12 months of admission.

One 78-year-old patient died as a result of mesenteric ischemia. Small-vessel and intraluminal arterial involvement is present in SSc and can lead to intestinal wall edema, as well as present as severe abdominal colic or paralytic ileus (32). Many of these complications can be debilitating and even life-threatening (33). Severe comorbidity as diffuse SSc with severe organ involvement diagnosed at the age of 72 with

intestinal ischemia led to her fatal outcome.

The high mortality rate of the patients in our study was also predicted by a relatively high APACHE II score (median of 25.4) on admission to ICU. Kollef *et al.* (17) in a study of 48 ICU admissions of 36 patients with rheumatic diseases found that the mean APACHE II scores were significantly higher for non-survivors (27.5) compared to survivors (14.8). In other studies the mortality rate in patients with rheumatic disease exceeds that predicted by the APACHE II score and was higher than in non-rheumatic ICU admissions (16, 20).

In summary, the outcome of patients with scleroderma requiring admission to the ICU was extremely poor. Infectious complication was the most common cause of death in our patients.

Patients with scleroderma may be admitted to the ICU because of an acute infection. They may have acute unrelated disorder along with worsening of, or development of a new complication of the disease that may become life-threatening and fatal because of the underlying systemic sclerosis with severe visceral organ involvement.

Therefore, it seems that despite recent advances in the management of SSc, patients with SSc admitted to the ICU have generally severe organ involvement accompanied by a high death rate with multifactorial reasons for admission and a poor initial prognosis, particularly in the presence of pulmonary complications. However, limitations due to the small study size and design

does not allow us to draw a definitive conclusion about the outcome of SSc patients admitted to the ICU and to delineate a subgroup of patients with a reasonable chance of recovery.

References

- DERK CT, JIMENEZ SA: Systemic sclerosis: current views of its pathogenesis. *Autoimmunity reviews* 2003; 2: 181-91.
- COSSIO M, MENON Y, WILSON W, DE BOIS-BLANC BP: Life-threatening complications of systemic sclerosis. *Crit Care Clin* 2002; 18: 819-39.
- JANSSEN NM, KARNAD DR, GUNTIPALLI KK: Rheumatologic diseases in the intensive care unit: epidemiology, clinical approach, management, and outcome. *Crit Care Clin* 2002; 18: 729-48.
- SCUSSEL-LONZETTI L, JOYAL F, RAYNAULD JP *et al.*: Predicting mortality in systemic sclerosis: analysis of a cohort of 309 French Canadian patients with emphasis on features at diagnosis as predictive factors for survival. *Medicine (Baltimore)* 2002; 81: 154-67.
- FERRI C, VALENTINI G, COZZI F *et al.*: Systemic Sclerosis Study Group of the Italian Society of Rheumatology (SIR- GSSSc). Systemic sclerosis: demographic, clinical, and serologic features and survival in 1,012 Italian patients. *Medicine (Baltimore)* 2002; 81: 139-53.
- JACOBSEN S, ULLMAN S, SHEN GQ, WIJK A, HALBERG P: Influence of clinical features, serum antinuclear antibodies, and lung function on survival of patients with systemic sclerosis. *J Rheumatol* 2001; 28: 2454-9.
- SIMEON CP, ARMADANS L, FONOLLOSA V: Survival, prognostic factors and markers of morbidity in Spanish patients with systemic sclerosis. *Ann Rheum Dis* 1997; 56: 723-8.
- HESELSTRAND R, SCHEJA A, AKESSON A: Mortality and causes of death in a Swedish series of systemic sclerosis patients. *Ann Rheum Dis* 1998; 57: 682-6.
- SUBCOMMITTEE FOR SCLERODERMA CRITERIA OF THE AMERICAN RHEUMATISM ASSOCIATION DIAGNOSTIC AND THERAPEUTIC CRITERIA COMMITTEE: Preliminary criteria for the classification of systemic sclerosis (scleroderma). *Arthritis Rheum* 1980; 23: 581-90.
- LEROY EC, BLACK CM, FLEISHMAJER R *et al.*: Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 1988; 15: 202-5.
- MATUCCI-CERINIC M, D'ANGELO S, DENTON CP, VLACHOYIANNPOULOS P, SILVER R: Assessment of lung involvement. *Clin Exp Rheumatol* 2003; 21 (Suppl.29): S19-23.
- COGLAN JG, MUKERJEE D: The heart and pulmonary vasculature in scleroderma: clinical features and pathobiology. *Curr Opin Rheumatol* 2001; 13: 495-9.
- STEEN VD, MAYES MD, MERKEL PA: Assessment of kidney involvement. *Clin Exp Rheumatol* 2003; 21 (Suppl. 29): S29-31.
- CLEMENTS PJ, BECVAR R, DROSOS AA, GHATTAS L, GABRIELLI A: Assessment of gastrointestinal involvement. *Clin Exp Rheumatol* 2003; 21 (Suppl. 29): S8-15.

15. KNAUS WA, DRAPER EA, WAGNER DP, ZIMMERMAN JE: APACHE II: A severity of disease classification system. *Crit Care Med* 1985; 13: 818-28.
16. GODEAU B, MORTIER E, ROY PM *et al.*: Short and longterm outcomes for patients with systemic rheumatic diseases admitted to intensive care units: a prognostic study of 181 patients. *J Rheumatol* 1997; 24: 1317-23.
17. KOLLEF MH, ENZENAUER RJ: Predicting outcome from intensive care for patients with rheumatologic diseases. *J Rheumatol* 1992; 19: 1260-2.
18. POURRAT O, BUREAU JM, HIRA M *et al.*: Outcome of patients with systemic rheumatic diseases admitted to intensive care units: a retrospective study of 39 cases. *Rev Med Interne* 2000; 21: 147-51.
19. THONG BY, TAI DY, GOH SK, JOHAN A: An audit of patients with rheumatic diseases requiring medical intensive care. *Ann Acad Med Singapore* 2001; 30: 254-9.
20. ANSELL SM, BEDHESI S, RUFF B *et al.*: Study of critically ill patients with systemic lupus erythematosus. *Crit Care Med* 1996; 24: 981-4.
21. ALZEER AH, AL-ARFAJ A, BASHA SJ *et al.*: Outcome of patients with systemic lupus erythematosus in intensive care unit. *Lupus* 2004; 13: 537-42.
22. CAMARGO JF, TOBON GJ, FONSECA N *et al.*: Autoimmune rheumatic diseases in the intensive care unit: experience from a tertiary referral hospital and review of the literature. *Lupus* 2005; 14: 315-20.
23. LEE P, LANGEVITZ P, ALDERDICE CA *et al.*: Mortality in systemic sclerosis. *QJM* 1992; 298: 139-48.
24. STEEN VD, MEDSGER TA JR: Severe organ involvement in systemic sclerosis with diffuse scleroderma. *Arthritis Rheum* 2000; 43: 2437-44.
25. HUBBARD R, VENN A: The impact of coexisting connective tissue disease on survival in patients with fibrosing alveolitis. *Rheumatology* 2002; 41: 676-9.
26. KUBO M, VENSACK J, DAUBER J, KEENAN R, GRIFFITH B, MC CURRY K: Lung transplantation in patients with scleroderma. *The Journal of Heart and Lung Transplantation* 2001; 20: 174-5.
27. NAGY Z, CZIRJAK L: Increased levels of amino terminal propeptide of type III procollagen are an unfavorable predictor of survival in systemic sclerosis. *Clin Exp Rheumatol* 2005; 23: 165-72.
28. DANIELI AP, PARRINELLO G, ANTONIOLI CM *et al.*: Intravenous cyclophosphamide therapy for systemic sclerosis. A single-center experience and review of the literature with pooled analysis of lung function test results. *Clin Exp Rheumatol* 2004; 22: 551-2.
29. STEEN VD, MEDSGER TA JR: Long-term outcomes of scleroderma renal crisis. *Ann Intern Med* 2000; 133: 600-3.
30. LANGEVITZ P, BUSKILA D, LEE P, HERCZ G: Scleroderma hypertensive renal crisis and the changing pattern of mortality in systemic sclerosis (scleroderma). *Nephron* 1991; 57: 111-2.
31. BAR J, EHRENFELD M, ROZENMAN J, PERELMAN M, SIDI Y, GUR H: Pulmonary-renal syndrome in systemic sclerosis. *Semin Arthritis Rheum* 2001; 30: 403-10.
32. HAQUE U, YARDLEY J, TALAMINI M *et al.*: Colon stricture and volvulus in a patient with scleroderma. *J Rheumatol* 1999; 26: 2268-72.
33. JAOVISIDHA K, CSUKA ME, ALMAGRO UA, SOERGEL KH: Severe gastrointestinal involvement in systemic sclerosis: report of five cases and review of the literature. *Semin Arthritis Rheum* 2004; 34: 689-702.