Sclérodermie systémique et réanimation: état des lieux et perspectives

Luc Mouthon

Service de Médecine Interne, hôpital Cochin,

Centre de Référence Vascularites nécrosantes et sclérodermie systémique

Assistance Publique-Hôpitaux de Paris, Paris

Université Paris Descartes, Inserm U1016, Institut Cochin, Paris



Conflicts of interest

- Consultant: Actelion, CSL Behring, LFB Biotechnologies, Lilly, Pfizer, Octapharma
 - Financial support to ARMIIC
- > Investigator: Actelion, CSL Behring, Pfizer
- Financial support (grants to ARMIC): Actelion, CSL Behring, GSK, LFB Biotechnologies, Pfizer
- Invited conference: SOBI, Roche, Actelion, CSL Behring, Octapharma, GSK, LFB Biotechnologies, Pfizer, Lilly, UCB pharma

Introduction

- As of today, very few studies have specifically investigated the outcome of SSc patients and most data are derived form cohorts of critically ill patients with various systemic autoimmune diseases, of whom SSc patients represent a minority.
- Only very few studies focused on SSc in the ICU.
- These insufficient data make it impossible to draw any definitive conclusions.
- In this study we aimed to assess the features and the prognosis of patients with SSc that required ICU admission within a tertiary care center.

SYSTEMIC SCLEROSIS : EVOLUTION



Prevalence of visceral involvement in SSc

	Total	Missing data	IcSSc	dcSSc	
Number of patients, n (%)	1483 (100)	0 (0)	674 (45.5)	484 (32.7)	
Percentage of organ involvement by SSc subsets					
RP	94.4	0.1	96.3	94.2	
Skin involvement	87.8	0.3	91.5	97.6	
PAH	15.8	0.1	14.9	18.5	
Pulmonary fibrosis	34.5	0.1	20.8	56.1	
Oesophagus	60	0.1	59.2	69.3	
Stomach	14.2	0.2	15.3	15.6	
Intestine	5.7	0.2	6.1	5.3	
Kidney	10.5	0.2	9.1	15.9	
Heart	14.6	0.2	12	23	
Musculoskeletal system	47.5	1.4	44.9	56.6	
Nervous system	6.4	2.2	4.1	7.1	
Sicca-symptoms	39.5	2.5	43.5	39.7	
Masticatory organ	24.1	7.2	23.7	34.1	

Hunzelmann N, et al. Rheumatology 2008; 47:1185-92.

ScS diffuse et atteinte d'organe



Steen , Arthr Rheum 2000; 43: 2437-2444 2000

SYSTEMIC SCLEROSIS

- When major visceral involvement occurs in scleroderma, the outcome is poor
 - Lung fibrosis
 - Cardiac involvement
 - Renal insufficiency
 - Pulmonary hypertension



Ferri et al, Medicine, 2002

Changes in causes of Systemic Sclerosis related deaths between 1972 and 2001



Emergency states in patients with systemic sclerosis

Scleroderma renal crisis

- Renal insufficiency
- Malignant hypertension
- Left ventricular failure
- Seizure

Severe sepsis

Anemia

- Thrombotic microangiopathy
- Gastrointestinal hemorrhage

Shock

- Heart failure
- Pericarditis
- Severe sepsis
- Normotensive renal crisis
- Pulmonary embolism

Acute respiratory failure

- Pulmonary arterial hypertension
- Acute interstitial pneumonia
- Left ventricular insufficiency
- Pneumopathy
- Pulmonary embolism
- Pneumothorax

Digital ischemia

-Spontaneous -Related to the use of vasoactive drugs -Arterial catheterism

Gastrointestinal involvement

Occlusion Peritonitis (Pneumatosis)

Scleroderma renal crisis

Definition

- Rapidly progressive oliguric renal insufficiency with no other explanation
- and/or rapidly progressive hypertension occurring during the course of SSc
- Prevalence: 2-5% of SSc patients

Prognosis: 65% survival at 5 years





Penn et al. BMJ 2007 Teixeira et al Ann Rheum Dis 2008 Mouthon L et al Human Pathol 2010

Treatment of scleroderma renal crisis: 1st week IEC inhibitors, increase to maximal dose within 48 hours Insufficient results at 72 h: add calcium channel blockers Insufficient results: prostacyclin, intravenous α -/ β blockers and/or minoxidil **Oliguric renal insufficiency: Early dialysis** Add anti-endothelin 1 receptor antagonists ? Teixeira et al 2007 Ann N Y Acad Sci:

Teixeira et al 2007 Ann N Y Acad Sci; Mouthon et al. Clin Rev Allerg Immunol 2009 Penn et al. QJM 2012

Interstitial lung disease

Non specific interstitial pneumonia



Usual interstitial pneumonia

- -More frequent in diffuse SSc and anti-topoisomerase 1 Abs
- -Prevalence: 16-100%
- Asymptomatic, then crackles, dyspnea
- May be responsible for respiratory insufficiency, death
- PFTs every year, HRCT every 2 years

Interstitial Lung Disease in Systemic Sclerosis A Simple Staging System Goh NSL, AJRCCM 2008



Acute respiratory insufficiency in a patient with SSc-ILD (I)

- Make sure that there is nothing more !!!
 - Left ventricular insufficiency
 - Pulmonary arterial hypertension
 - Pulmonary embolism
 - Infection, either expected or unexpected (mycobacteria, *Pneumocystis jiroveci*)
 - Pneumothorax (pulmonary fibrosis and emphysema syndrome) (Cottin et al, Arthritis Rheum 2010)

Acute respiratory insufficiency in a patient with SSc-ILD (II)

Treatment
Corticosteroids (dose to be discussed, up to 1 mg/kg/d)
➢ Pulse cyclophosphamide
➢ Treat an infection



Avoid intubation (mouth aperture limitation, difficulties at the time of extubation)
 Propose non invasive ventilation

Pulmonary hypertension

Definition

Mean pulmonary artery pressure of ≥ 25 mmHg associated with a normal pulmonary artery wedge pressure ≤ of 15 mmHg

Simonneau, G., N. Galiè, et al. (2004). "Clinical classification of pulmonary hypertension." J Am Coll Cardiol 43(12 Suppl S): 5S-12S

Rubin, L. J. (1997). "Primary pulmonary hypertension." N Engl J Med 336(2): 111-117.



Causes of death in SSc patients

TABLE 2. Causes of death observed in the total population

Causes of death, n (%)	All patients (n=546)
Total number of deaths	47 (8.6)
Scleroderma-related causes of death	24 (4.4)
PAH	17
Pulmonary fibrosis	2
Gastrointestinal	2
Renal crisis	3
Non-scleroderma-related causes of death	23 (4.2)
Cancer	8
Infection	4
Cardiovascular or cerebrovascular atherosclerosis	2
Other cause	2
Unknown cause	7

Acute respiratory insufficiency in a patient with SSc-PAH

- Make sure that there is nothing more (right heart cath) !!!
 - Left ventricular insufficiency
 - Pulmonary embolism
 - Pericarditis
 - Veno-occlusive disease
- Treatment
 - Oxygen
 - Diuretics
 - Dobutamine
 - Epoprostenol (tritherapy)
 - DIscuss emergency transplantation
 - If improved, combined therapy

Pulmonary Veno-Occlusive Disease

- Pulmonary oedema occurring shortly after the start of vasodilators in a patient with PAH
- Under-recognized cause of PAH in SSc patients.

(Montani D et al. Eur Respir J 2009;33:189-200)

- Difficult to treat
 - Diuretics
 - Low dose vasodilators (epoprostenol)
 - Lung transplantation





Dorfmuller P et al. Hum Pathol 2007

Digital ischemia





Favoured

- hypotension, shock
- vasoactive drugs
- ciclosporin (transplantation)
- Past history of digital ischemia
- radial/ulnar artery occlusion

Management

- Analgesia (grade III)
- Antibiotics
- Prostacyclin (sildenafil)
- Heparin
- Surgery (differed)

Gastro-intestinal tract involvement (I)

- Hemorrhage
 - Oesophagitis
 - Gastric antral vascular ectasia
 - Colonic telengiectasias
- Treatment:
 - High dose proton pump inhibitors
 - Transfusion (if necessary)
 - Laser
 - Surgery if necessary



Gastro-intestinal tract involvement (II)

- Occlusion
 - After ruling out a surgical issue
 - Gastric aspiration
 - Octreotide: 50 µg/d
 subcutaneous (Soudah et al. NEJM 1991)
- Cystic pneumatosis (Quiroz et al. Am J Med Sci 1995)
 - Sub-mucosal cysts
 - May lead to :
 - Peritonitis (perforation)
 - Occlusion (compression)





Systemic sclerosis patients in Intensive care Unit

- 145 patients with systemic autoimmune diseases were hospitalised (1996-2006) in the ICU at Cochin
- 12 had SSc (2 males), mean age 63 years [54; 69]
- The diagnosis upon admission in ICU was
 - infections (n=5); pneumopathy (n=4) and urine infection (n=1)
 - Disease flare (n=5), mainly pulmonary fibrosis
 - PAH (n=1)
 - Cardiac arrest (n=1)
- 8 died
 - 4 in ICU (2 infections and 2 end stage pulmonary fibrosis)
 - 4 other died during hospitalisation after ICU
- Patients with SSc had the worse prognosis among other systemic autoimmune diseases

Bouldouyre M et al. Unpublished. Collaborative work with Pr JD Chiche

Outcome of Patients with Systemic Sclerosis in the Intensive Care Unit

Frédéric Pène, Tarik Hissem, Alice Bérezné, Yannick Allanore, Guillaume Geri, Julien Charpentier, Jérôme Avouac, Loïc Guillevin, Alain Cariou, Jean-Daniel Chiche, Jean-Paul Mira, and Luc Mouthon



Patients

- 24-bed medical ICU at Cochin (average 1500 admissions per year).
- All patients with SSc (Internal Medicine, Rheumatology) admitted to the ICU from November 2006 to December 2010 were eligible for inclusion.
- Patients admitted for management of risky procedures, venous access adjustment or intermittent hemodialysis for chronic renal failure were excluded.
- ICU admission decisions were taken on by both the ICU physician and the referring physician throughout the study period.
- End-of-life decisions to withhold or withdraw life support were taken on collectively
- For patients who were admitted more than once to the ICU, only the first episode was analysed.

Data collection (I)

Demographic and underlying disease-related data were collected:

- age, gender, functional status prior to ICU admission as assessed by the Knaus scale (A, prior good health, no functional limitation; B, mild to moderate limitation of activity because of a chronic disease; C, serious but not incapacitating restriction of activity; D, severe restriction of activity, including bedridden or institutionalized persons)
- characteristics of underlying SSc (organ involvement, treatments including corticosteroids and/or immunosuppressive drugs).
- Pulmonary hypertension: defined by right heart catheterisation with a mean PAP > 25 mmHg or by echo (sPAP > 50 mmHg).
- Pulmonary fibrosis was defined as predicted FVC < 55% or a DLCO < 55%, with fibrosis confirmed on high-resolution CTscan.

Data collection (II)

- Data related to the ICU stay included clinical and biological data at the time of ICU admission and requirements for organ failure supports.
- The Simplified Acute Physiology Score 2 (SAPS II) (age, comorbid conditions, physiologic and biological variables within the first 24 h in the ICU) provides a probability of in-hospital mortality (first day in ICU).
- The Sequential Organ Failure Assessment (SOFA) score: restricted to organ failure assessments. (first day in ICU).
- Patients with acute respiratory failure were eligible for noninvasive ventilation in the absence of emergency intubation requirement.
- Endotracheal intubation and mechanical ventilation were performed in case of refractory hypoxemia, respiratory arrest, dependance to non-invasive ventilation, unstable circulatory condition or deterioration of neurologic status.

Data collection (III)

- Intubated patients were mechanically ventilated using a protective strategy with low tidal volume of 6 mL/kg and limitation of plateau pressure to 30 cm H₂O whenever possible.
- Patients with severe sepsis or septic shock were treated according to the Surviving Sepsis Campaign guidelines.
- Endpoints were short-term (in-ICU and in-hospital) and long-term survival.
- The long-term follow-up was obtained for all patients by using the reference center registry or individual medical files.

Statistical analysis

- Results are reported as median (25th-75th percentile) or number (%) as appropriate.
- Categorical variables were compared with χ^2 or Fisher exact tests, and continuous variables were compared with the Mann-Whitney U test.
- Survival curves were obtained using the Kaplan-Meier method and compared using the log-rank test.

Outcome of Patients with Systemic Sclerosis in the Intensive Care Unit (I)

Variable	All Patients, $n = 41$	Survived, n = 25	Died, n = 16	p*
Age, yrs	50 (40-65)	47 (38–58)	59 (42–69)	0.10
Female	33 (80.5)	18 (72)	15 (93.7)	0.12
BMI, kg/m ²	23 (18.8–25.8)	23 (17.4–26.4)	22.9 (19.4-25)	0.66
Non-SSc significant comorbidities	s 10 (24.4)	6 (24)	4 (25)	0.94
Cardiovascular diseases	7 (17)	5 (20)	2 (12.5)	
Others**	3 (7.3)	1 (4)	2 (12.5)	
Features of SSc				
Time since diagnosis, mos , $n =$	40 78 (34–128)	72 (45–105)	97 (21-187)	0.68
Type of SSc, $n = 40$				0.27
Diffuse cutaneous	29 (72.5)	20 (80)	9 (56.2)	
Limited cutaneous	11 (27.5)	5 (20)	6 (37.5)	
mRSS, $n = 35$	19 (5-30)	20 (7-30)	19 (3–28)	0.60

Outcome of Patients with Systemic Sclerosis in the Intensive Care Unit (II)

Variable	All Patients, $n = 41$	Survived, n = 25	Died, $n = 16$	p*
Digestive involvement	39 (95)	25 (100)	14 (87.5)	0.14
Pulmonary involvement				
NYHA stage $3-4$, n = 37	20 (48.7)	11 (44)	9 (56.2)	0.59
Pulmonary fibrosis on CT sc	an,			
n = 39	28 (71.7)	17 (68)	11 (68.7)	0.48
DLCO, %, n = 35	41 (25–52)	40 (23-50)	45 (30–55)	0.37
< 70%	32 (91.4)	20 (80)	12 (75)	0.32
< 55%	30 (85.7)	19 (76)	11 (68.7)	0.62
FVC, $\%$, n = 36	62 (48-77)	59 (47-75)	71 (38-81)	0.58
< 70%	21 (58.3)	15 (60)	6 (37.5)	0.49
< 55%	14 (42.4)	10 (40)	4 (25)	0.72
PAH, n = 38	12 (31.5)	7 (28)	5 (31.2)	0.72
Renal involvement				
Serum creatinine level, μ mol	/1,			
n = 39	84 (63–105)	77 (52-89)	90 (85–118)	0.009
Creatinine clearance, ml/min	,			
n = 39	69.7 (54.6–97.7)	89 (61-125)	61.4 (42-73.6)	0.03

Outcome of Patients with Systemic Sclerosis in the Intensive Care Unit (III)

Variable	All Patients, $n = 41$	Survived, n = 25	Died, n = 16	p*
Immunological features				
ANA, n = 38	38 (100)	25 (100)	13 (81.2)	0.19
ACA, n = 38	5 (13.1)	2 (8)	3 (18.7)	0.31
Antitopoisomerase 1 antibodie	s,			
n = 38	13 (34.2)	7 (28)	6 (37.5)	0.32
Anti-RNP antibodies, $n = 36$	5 (13.8)	4 (16)	1 (6.2)	0.64
Anti-PM/Scl antibodies, $n = 37$	7 1 (2.7)	1 (4)	0(0)	1
Anti-RNA Pol III antibodies, n	1 = 36 1 (2.7)	1 (4)	0(0)	1
Current immunosuppressive treat	ment			
Glucocorticoids	27 (65.8)	16 (64)	11 (68.7)	0.75
Immunosuppressive drugs [†]	12 (29.2)	7 (28)	5 (31.2)	1

Short-term and longterm vital status



*One additional patient lost to followup. **Three additional patients lost to followup. ICU: intensive care unit.

Survival according to the requirement of endotracheal intubation and mechanical ventilation.



Log-rank test p < 0.001. ICU: intensive care unit.

Intensive care management of patients with SSc, including inhospital survivors and those who died.

Variable	All Patients, $n = 41$	Survived, n = 25	Died, $n = 16$	p*
Time from hospital to ICU admission, day	ys 1 (0–4)	1 (0-2)	1 (0–11)	0.58
Reasons for ICU admission				0.42
Acute respiratory failure	27 (65.8)	16 (64)	11 (68.7)	
Acute renal failure	6 (14.6)	5 (20)	1 (6.2)	
Others	8 (19.5)	4 (16)	4 (25)	
Main diagnosis				0.07
Pulmonary infection**	14 (34.1)	7 (28)	7 (43.7)	
Cardiovascular complications [†]	8 (19.5)	3 (12)	5 (31.2)	
Scleroderma renal crisis	7 (17)	5 (20)	2 (12.5)	
Others [‡]	12 (29.2)	10 (40)	2 (12.5)	

Intensive care management of patients with SSc, including in-hospital survivors and those who died.

Variable	All Patients, $n = 41$	Survived, n = 25	Died, $n = 16$	p *
Admission characteristics				
Admission characteristics				
Mean arterial pressure	88 (77–104)	92 (81–105)	79 (71–98)	0.03
Glasgow coma scale	15 (15–15)	15 (15–15)	14 (7–15)	0.01
Serum protein level, g/l	69 (59–73)	70 (63–76)	59 (52-68)	0.002
Serum creatinine level, μ mol/l	88 (56-160)	72 (52-204)	101 (90-170)	0.10
Serum bilirubin level, μ mol/l	7.5 (4–11.7)	6 (3–9)	12 (5-27)	0.007
Admission severity scores				
SAPS2, points	38 (23-53)	26 (22-36)	55 (41-89)	< 0.001
SOFA, points	4 (4–7)	4 (2–5)	7 (5–11)	< 0.001

Intensive care management of patients with SSc, including in-hospital survivors and those who died.

Variable	All Patients, $n = 41$	Survived, n = 25	Died, $n = 16$	\mathbf{p}^*
Life-sustaining interventions				
Noninvasive ventilation	13 (31.7)	6 (24)	7 (43.7)	0.30
Invasive mechanical ventilation	13 (31.7)	2 (8)	11 (68.7)	< 0.001
Vasopressors	13 (31.7)	1 (4)	12 (75)	< 0.001
Renal replacement therapy	12 (29.2)	3 (12)	9 (56.2)	0.002
In-ICU length of stay, days	3 (2–7)	2 (2–3)	5 (3–11)	0.005

Discussion (I)

- We report here a large cohort of critically ill patients with SSc in the ICU
- SSc is is responsible for multiple organ involvements that may result in organ failure requiring life-sustaining organ supports in the ICU.
- Although the treatment of the disease remains challenging, the overall outcome has been improved over time.
- In our study, the main cause of admission in ICU was acute respiratory failure.
- Outcome of PAH associated SSc and scleroderma renal crisis is poor.

Discussion (II)

- Our study has several limitations.
- The number of patients remains limited owing to the rarity of the disease.
- The design was retrospective
- Patients admitted to the ICU were probably carefully selected upstream, despite we did not assess whether patients with end-stage disease were declined ICU admission by their referring physicians.
- The study was carried out in a single center

Perspectives

- Communiquer autour de la prise en charge des sclérodermies systémiques en réanimation
 - Auprès des réanimateurs
 - Auprès des spécialités impliquées dans la prise en charge des sclérodermies systémiques
- Discuter très précocement des patients qhez qui un transfert en réanimation est envisagé
- Ne pas baisser les bras si un patient n'est pas transféré en réanimation
- Mener des études multicentriques

Conclusion

- There are a number of emergency states in patients with systemic sclerosis
- More frequently encountered in patients with diffuse SSc and/or lung involvement (PAH/pulmonary fibrosis)
- Infections may be favoured by corticosteroids and immunosuppressants
- Bad prognosis of SSc patients in ICU
- Sometimes it is better not to transfer the patient in ICU and give symptomatic treatment
- These patients should be managed by trained teams