Outcome of patients with systemic diseases admitted to the medical intensive care unit of a tertiary referral hospital: a single-centre retrospective study

T Heijnen¹, A Wilmer², D Blockmans³, L Henckaerts³

KU Leuven - University of Leuven, Belgium, ¹Department of Anaesthesiology, ²Department of Microbiology and Immunology (University Hospitals, Medical Intensive Care Unit), and ³Department of Microbiology and Immunology (University Hospitals, General Internal Medicine), Leuven, Belgium

Objectives: Systemic diseases form a rare heterogeneous group of diseases, with important morbidity caused by disease evolution and/or treatment. We describe the clinical features and outcome of patients with these diseases admitted to a referral hospital intensive care unit (ICU).

Method: We conducted a retrospective case review of all patients with systemic diseases (n = 86) admitted to the medical ICU of Leuven University Hospital between May 2007 and September 2012.

Results: The most frequent diagnoses were systemic vasculitis (n = 31), sarcoidosis (n = 15), systemic sclerosis (n = 9), and systemic lupus erythematosus (SLE) (n = 7). The main reason for admission was infection (60%), followed by disease-related organ failure (48%). Respiratory failure was the most common organ dysfunction. The mean APACHE II (Acute Physiology and Chronic Health Evaluation II) score was 28 ± 10. Mortality was 19% during ICU admission, 39% during hospital stay, and 58% at the end of follow-up. Death was caused by infection in the majority of cases (56%), and by evolution of the underlying disease in 32%. Only age and APACHE II score were associated with mortality.

Conclusions: The mortality of patients with systemic diseases admitted to an ICU is high, both during their stay in the ICU and afterwards. Age and APACHE II score, but not infection or immunosuppressive therapy, were associated with mortality.

Systemic diseases comprise a heterogeneous group of rare disorders with substantial morbidity and mortality (1). The estimated prevalence of these diseases approaches 0.5%. Studies have shown that 10–25% of these patients require a hospital admission in the course of their disease and that an estimated 30% of these patients would need intensive care (2, 3). Early diagnostics and treatment are fundamental to reducing mortality but can be extremely difficult because of the marked diversity in the clinical presentation of these diseases.

Reasons for admission to an intensive care unit (ICU) can be divided into three categories: (i) manifestations of the systemic disease (e.g. an exacerbation, a new manifestation, or even the diagnosis of the disease); (ii) infections (often associated with immunosuppressive treatment); and (iii) acute, non-disease-related serious illnesses that can be aggravated by the underlying disease.

In this study we describe the clinical presentation and the outcome of patients with systemic diseases admitted to the ICU of a tertiary referral hospital in Belgium.

Method

A single-centre retrospective case-series review was conducted for all patients with a systemic disease admitted to the medical ICU of Leuven University Hospitals (Leuven, Belgium) from 1 May 2007 to 30 September 2012. Patients with a diagnosis of rheumatoid arthritis were not included. Detailed information on patient selection, data collection, and statistical analysis can be found in the online Supporting Information.

Ethical approval

This study was approved by the Ethics Board of our institution. Because of the retrospective study design, the need for informed consent was waived according to the guidelines of the Board.

Results

Baseline patient characteristics

Baseline patient characteristics are listed in Table 1. The main diagnostic subgroup comprised patients with vasculitides (n = 31, 36%), followed those with sarcoidosis (n = 15, 17%). The lungs were the most
Table 1. Clinical characteristics of the 86 patients with systemic autoimmune diseases prior to ICU admission.

| Characteristic                                      | Value                        |
|-----------------------------------------------------|------------------------------|
| Age at diagnosis of underlying disease (years)       | 52 ± 18 (10–84)              |
| Age on ICU admission (years)                         | 60 ± 16 (16–87)              |
| Female patients, n (%)                               | 43 (50)                      |
| Body mass index (BMI) (kg/m²), median (IQR) (range)  | 23 (19–25) (13–34)           |
| Total disease duration (years), mean ± sd (range)    | 8 ± 9 (0–36)                 |
| Time between diagnosis and ICU admission (years)      | 3.7 (0.25–14)                |
| Diagnosis during ICU admission, n (%)                | 10 (12)                      |
| Diagnosis within 1 month prior to ICU admission, n (%)| 6 (7)                        |
| Type of underlying autoimmune disease, n (%)         | 86 (100)                     |
| Systemic vasculitis                                  |                              |
| Large vessel vasculitis                              |                              |
| Giant cell arteritis                                 | 4 (5)                        |
| Large vessel vasculitis (not specified)              | 2 (2)                        |
| Takayasu arteritis                                   | 1 (1)                        |
| ANCA-related vasculitis                              |                              |
| Granulomatosis with polyangiitis (GPA)               | 10 (12)                      |
| Microscopic polyangiitis (MPA)                       | 5 (6)                        |
| ANCA-related vasculitis (not specified)              | 3 (3)                        |
| Cerebral vasculitis                                  | 1 (1)                        |
| IgA-related vasculitis                               | 5 (6)                        |
| Cryoglobulaemic vasculitis                           | 1 (1)                        |
| Polymyalgia rheumatic                                | 2 (2)                        |
| Systemic sclerosis                                   | 9 (10)                       |
| Systemic lupus erythematosus (SLE)                   | 7 (8)                        |
| Antiphospholipid syndrome                            | 3 (3)                        |
| Primary Sjögren’s syndrome                           | 3 (3)                        |
| Mixed connective tissue disease (MCTD)               | 2 (2)                        |
| Inflammatory myopathies                              |                              |
| Dermatomyositis                                      | 4 (5)                        |
| Polymyositis                                         | 2 (2)                        |
| Other                                                |                              |
| Relapsing polychondritis                             | 3 (3)                        |
| Amyloidosis                                          |                              |
| Primary amyloidosis                                  | 1 (1)                        |
| Secondary amyloidosis (FMF)                          | 2 (2)                        |
| Sarcoidosis                                          | 15 (17)                      |
| Retroperitoneal fibrosis                             | 1 (1)                        |
| Organ involvement in the course of the disease       |                              |
| Lungs                                                | 41 (48)                      |
| Skin                                                 | 22 (26)                      |
| Joints                                               | 11 (13)                      |
| Muscles                                              | 8 (9)                        |
| Central nervous system                               | 7 (8)                        |
| Gastrointestinal tract/liver                         | 7 (8)                        |
| Ear, nose, throat (ENT)                              | 6 (7)                        |
| Heart                                                | 5 (6)                        |
| Comorbidities                                        |                              |
| Chronic renal failure                                | 35 (41)                      |
| Chronic haemodialysis                                | 4 (5)                        |
| Diabetes                                             | 18 (21)                      |
| Insulin dependent                                    | 10 (12)                      |
| Not insulin dependent                                | 8 (9)                        |
| Malignancy                                           | 13 (15)                      |
| Active                                               | 4 (5)                        |
| Cured (> 5 years)                                    | 9 (10)                       |
| Relevant immunosuppression (last 3 months)           | 49 (57)                      |
| Organ transplant, n (%)                              | 11 (13)                      |
| Lung                                                 | 4 (5)                        |
| Kidney                                               | 3 (3)                        |
| Bone marrow                                          | 1 (1)                        |
| Cornea                                               | 1 (1)                        |
| Heart                                                | 1 (1)                        |
| Stem cell                                            | 1 (1)                        |

ICU, Intensive care unit; FMF, familial Mediterranean fever; IQR, interquartile range; sd, standard deviation.
frequently involved organ during the disease course before ICU admission (n = 41, 47%). Fifty-seven percent of the patients received a relevant dose of immunosuppressive drugs during the 3 months prior to the ICU admission. Comorbidities included diabetes mellitus (n = 18, 21%, of whom 10 were on insulin therapy), chronic renal failure (n = 35, 40%, of whom four were on chronic haemodialysis), and history of malignancy (n = 13, 15%, with active disease in four patients). Eleven patients (13%) had undergone an organ transplant in their past medical history; one patient was admitted to the ICU for reasons directly related to the transplantation.

Characteristics of the ICU stay

Characteristics of the ICU stay for the cohort are summarized in Table 2. The main reason for ICU admission in this group was infection (n = 52, 60%), followed by disease-related organ failure (n = 41, 48%) and non-infectious, non-disease-related causes (n = 31, 36%). Most patients required combinations of different life-saving interventions, including mechanical ventilation (n = 51; 59%), antibiotic therapy (n = 77; 90%), vasopressors (n = 36; 42%), renal replacement therapy (n = 25; 29%), and surgical intervention (n = 6, 7%).

ICU mortality

Sixteen patients (19%) died in the ICU. In univariate analysis, none of the documented patient characteristics were associated with death in the ICU (data not shown). In addition, in multivariable analysis, none of the included variables were significantly associated with outcome (Table 3). Infection was the most frequent cause of death in the ICU (n = 11) whereas evolution

Table 2. Characteristics and outcome of ICU stay.

| Reason for ICU admission, n (%) |      |
|---------------------------------|------|
| Infection                       | 52 (60) |
| Disease-related organ failure   | 41 (48) |
| Not infection related, not disease related | 31 (36) |
| Severity of condition           |      |
| APACHE II score, mean ± sd (range) | 28 ± 10 (5–49) |
| APACHE II score > 40, n (%)      | 8 (9) |
| Most important organ involvement on ICU admission, n (%) |      |
| Respiratory                     | 52 (60) |
| Cardiovascular                  | 13 (15) |
| Neurological                    | 9 (11) |
| Renal                           | 6 (7) |
| Gastrointestinal                | 4 (5) |
| Hepatic                         | 2 (2) |
| Intensive treatment during ICU stay |      |
| Mechanical ventilation, n (%)   | 51 (59) |
| Mechanical ventilation duration (days), median (IQR) | 6 (3–11) |
| Antibiotics, n (%)              | 77 (90) |
| Antibiotic duration (days), median (IQR) | 7 (3–10) |
| Vasopressor support, n (%)      | 36 (42) |
| Vasopressor duration (days), median (IQR) | 3 (1–7) |
| Dialysis, n (%)                 | 25 (29) |
| IHD; duration (days), median (IQR) | 2 (1–7) |
| CVVH; duration (days), median (IQR) | 4 (3–6) |
| Surgery, n (%)                  | 6 (7) |
| Duration of hospital stay, mean ± sd (range) in ICU (days) | 8 ± 8 (0–43) |
| Entire hospital stay (days)     | 37 ± 32 (4–156) |
| Outcome, n (%)                  |      |
| ICU mortality                   | 16 (19) |
| Total in-hospital mortality (ICU included) | 34 (39) |
| 28-day mortality                | 27 (31) |
| 90-day mortality                | 38 (45) |
| Mortality at end of follow-up   | 50 (58) |
| Duration of follow-up after first ICU admission (day 1) |      |
| Follow-up time survivors at end of follow-up (n = 36, 42%) (days), mean ± sd (range) | 1022 ± 527 (169–2060) |
| Age at death (years), mean ± sd | 65 ± 13 |

ICU, Intensive care unit; ANCA, anti-neutrophil cytoplasmic antibodies; IgA, immunoglobulin A; IQR, interquartile range; IHD, intermittent haemodialysis; CVVH, continuous veno-venous haemofiltration; sd, standard deviation.
of the underlying disease (n = 4) and unrelated causes (n = 1) were much less frequent. Mortality was higher in patients with respiratory failure (25%) compared to patients with other organ dysfunctions (9%) (p = 0.05).

In-hospital mortality

Thirty-four patients (40%) died during their hospital stay: 16 during ICU admission and 18 after discharge from the ICU. Mortality in the major subgroups was highest in systemic sclerosis (67%; 6/9), followed by 50% for the inflammatory myopathies (3/6); 47% for sarcoidosis (7/15); 41% for the total group of systemic vasculitides (13/32), and 14% for systemic lupus erythematosus (SLE) (1/7).

In univariate analysis, only age on ICU admission (p = 0.015) and APACHE II (Acute Physiology and Chronic Health Evaluation II) score (p = 0.003) were associated with in-hospital mortality. No other documented baseline patient characteristics in this study were associated with hospital mortality. We observed a non-significant trend for association with a history of malignancy.

We did not find any association between the duration of the underlying disease and the need for different life-saving interventions during the ICU stay. However, we did observe an expected association between the need for these life-saving interventions and mortality.

Although infection was the most important cause of in-hospital mortality (n = 19, 56%), it was not associated with increased mortality. Multivariable analysis (Table 3) showed that only the APACHE II score was independently associated with in-hospital mortality (p = 0.01).

Effect of prior immunosuppressive treatment

Patients with relevant immunosuppressive therapy in the 3 months prior to ICU admission were more often admitted with an infection than other patients (73% vs. 43%, p = 0.004). There was no difference in duration of antibiotic treatment between patients with and without relevant immunosuppressive therapy. Furthermore, there was no association between the use of immunosuppressive therapy and mortality.

None of the studied parameters had any influence on the length of stay in the hospital. However, intensive treatments such as mechanical ventilation, dialysis, and inotropic therapy were associated with a longer stay in the ICU, as expected (data not shown).

Effect on length of hospital stay

Discussion

This study describes patient characteristics, clinical presentation, reasons for ICU admission, and outcome of a cohort of patients with systemic diseases. Only a limited number of comparable publications on this subject are available (3–13), and the different case-mix in the different studies makes adequate comparison difficult.

In agreement with previous studies, the heterogeneous group of vasculitides (n = 32, 37%) is the most frequent diagnosis in our study. Sarcoidosis (n = 15, 17%) takes second place, followed by scleroderma (n = 9, 10%) and SLE (n = 7, 8%). In older studies and not taking into account rheumatoid arthritis, SLE is the most frequent underlying condition (3–13). This may in part be explained by the differences in admission criteria in respective ICU wards. Because of the presence of a medium care ward in our hospital (with the possibility of providing intravenous therapy, haemodynamic monitoring, non-invasive ventilation, and dialysis), only the most severely ill patients were transferred to the ICU.

In agreement with previous studies (12), infection was the main reason for admission in our study, especially in patients treated with immunosuppressive drugs, followed by disease-related organ failure (6–8). Simultaneous infection and disease-related organ failure were commonly observed in our patients, contributing to the frequently difficult differential diagnosis in this population. Respiratory failure was the main organ dysfunction leading to ICU admission, again consistent with previous reports and with the general population admitted to the ICU.

In line with a previous study (8), we did not find a relationship between disease duration and the need for different therapies (e.g. invasive ventilation, dialysis, antibiotics) or between disease duration and mortality.
By contrast, two other small studies (4, 7) noted a better prognosis with a recent diagnosis.

The APACHE II score was independently associated with in-hospital mortality but not with ICU mortality. The most likely reason for this observation is that the APACHE II score is not well calibrated for this particular population and therefore does not discriminate well between ICU survivors and non-survivors. The most frequent cause of death was infection. Neither ICU mortality nor in-hospital mortality differed from the global mortality of patients in the same unit (data not shown). Nevertheless, mortality of patients with systemic diseases seemed to be exceptionally high during follow-up after their stay in the ICU. This suggests that, once the organ dysfunction warrants intensive care, a progressive decline in the patients’ health may be imminent.

The APACHE II score in our study population (mean 28, survivors 25, deaths 32) is very high compared to previous studies with a mixed population of multisystem rheumatic diseases, but comparable with previous studies in the same ICU (14). A possible explanation is a difference in case mix between studies. Moreover, as most of our patients suffered from chronic diseases, they obtained the maximum score for the ‘chronic health status’ parameter [which reflects chronic liver disease, heart failure, pulmonary disease, dialysis dependence, and immunosuppressive status (15)]. Our admission policy is also likely to play a role because the limited number of beds meant that only the extremely ill patients were referred to the ICU.

We are aware of the important limitations of our study, and all reported findings should be interpreted in the light of these limitations. The main limitation of this study is the retrospective design. In addition, the size of the study population was small and consisted of different diseases with great diversity. Moreover, there was considerable variation in severity of organ dysfunction among patients with the same disease. Finally, the study population was limited to a single centre so that the results are potentially affected by local policies.

We conclude that patients with systemic diseases admitted to an ICU have a high mortality rate during ICU admission and thereafter. These patients therefore require rapid and accurate diagnostics and prompt therapy. The most frequent reason for admission was infection and the most frequent organ failure was respiratory failure. To improve our knowledge of the contribution of the different variables that relate to mortality and to develop a prognostic model, a large prospective and multicentre study is required.

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Methods, Data collection and definitions, Statistical analysis, and Reference.

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