

SEVEN-DAY PROFILE PUBLICATION



# The Intensive Care Global Study on Severe Acute Respiratory Infection (IC-GLOSSARI): a multicenter, multinational, 14-day inception cohort study

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## Abstract

**Purpose:** In this prospective, multicenter, 14-day inception cohort study, we investigated the epidemiology, patterns of infections, and outcome in patients admitted to the intensive care unit (ICU) as a result of severe acute respiratory infections (SARIs).

**Methods:** All patients admitted to one of 206 participating ICUs during two study weeks, one in November 2013 and the other in January 2014, were screened. SARI was defined as possible, probable, or microbiologically confirmed respiratory tract infection with recent onset dyspnea and/or fever. The primary outcome parameter was in-hospital mortality within 60 days of admission to the ICU.

**Results:** Among the 5550 patients admitted during the study periods, 663 (11.9 %) had SARI. On admission to the ICU, Gram-positive and Gram-negative bacteria were found in 29.6 and 26.2 % of SARI patients but rarely atypical bacteria (1.0 %); viruses were present in 7.7 % of patients. Organ failure occurred in 74.7 % of patients in the ICU, mostly respiratory (53.8 %), cardiovascular (44.5 %), and renal (44.6 %). ICU and in-hospital mortality rates in patients with SARI were 20.2 and 27.2 %, respectively. In multivariable analysis, older age, greater severity scores at ICU admission, and hematologic malignancy or liver disease were independently associated with an increased risk of in-hospital death, whereas influenza vaccination prior to ICU admission and adequate antibiotic administration on ICU admission were associated with a lower risk.

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**Take-home message:** Admission to the ICU for SARI is common and associated with high morbidity and mortality rates. We identified several risk factors for in-hospital death that may be useful for risk stratification in these patients.

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A complete list of IC-GLOSSARI investigators is provided in the "Appendix" and in the electronic supplementary material (file ESM2).

**Conclusions:** Admission to the ICU for SARI is common and associated with high morbidity and mortality rates. We identified several risk factors for in-hospital death that may be useful for risk stratification in these patients.

**Keywords:** Severe acute respiratory infections, Pneumonia, Outcome, Intensive care

## Introduction

Recent outbreaks of severe acute respiratory syndrome (SARS) and H1N1 influenza infection [1–4] have stimulated an interest in the surveillance of patients with severe acute respiratory infection (SARI), defined by the World Health Organization as an acute respiratory illness of recent onset (within 7 days) that includes fever ( $\geq 38^\circ\text{C}$ ), cough, and dyspnea requiring overnight hospitalization [5]. Whereas this definition of SARI may prove practical for surveillance systems, it provides little information for intensive care physicians regarding the nature of infections, the spectrum of severity, or the diagnostic and treatment strategies used for the subset of these patients that ultimately requires intensive care unit (ICU) admission. Indeed, only a subset of the patients with SARI will require ICU admission for oxygen therapy or mechanical ventilation; a smaller subset will develop acute respiratory distress syndrome and sepsis and an even smaller proportion will require adjunctive treatments [6–8].

Obtaining accurate information on the epidemiology of critically ill patients with SARI and how these patients are currently diagnosed and treated should help intensive care practitioners to understand the factors associated with progression from acute respiratory infection to more severe critical illness. Such information may also help identify high-risk populations and guide healthcare providers in resource allocation. It is also required to identify patients for future interventional studies and provide a framework to facilitate a rapid response of the ICU community to emerging epidemics.

We conducted a prospective, observational, inception cohort study to investigate the epidemiology and microbiological profiles of ICU-SARI, to document commonly used treatment and monitoring strategies, to measure current outcomes, and to identify risk factors for poor outcome in these patients.

## Methods

The Intensive Care Global Study on Severe Acute Respiratory Infection (IC-GLOSSARI) study group was an initiative of the Trials Group of the European Society of Intensive Care Medicine (ESICM-TG). Participation was entirely voluntary, with no financial incentive. Institutional review board approval was obtained by the participating institutions according to local ethical regulations. Informed consent was not required because of the observational and anonymous nature of the data collection. A steering committee

was nominated by the ESICM-TG and was responsible for the scientific conduct and consistency of the project. A list of contributing centers is provided in the “Appendix” and the electronic supplementary material (file ESM1).

## Study design

The study was performed over 4 weeks, from 3 to 17 November 2013 and from 13 to 26 January 2014. Each center included patients for two 1-week periods, one in November and the other in January. These dates were arbitrarily chosen to capture the expected peaks of admissions due to SARI. The same centers participated in both periods. All adult ( $\geq 18$  years) patients admitted to the participating ICUs during the study period (2 weeks per center) were screened. Patients admitted to the ICU due to SARI, defined as possible, probable, or microbiologically confirmed respiratory tract infection together with recent onset (within 7 days prior to ICU admission) dyspnea and/or fever ( $\geq 38^\circ\text{C}$ ), were included in the study. Patients were excluded if they (1) were less than 18 years of age; (2) had had symptoms for more than 7 days; (3) were receiving invasive mechanical ventilation prior to admission for any reason other than general anesthesia for surgical procedures; and (4) had previously been included in the study during the same study period. As a result of the lack of data from similar studies on this specific population, it was not possible to estimate the sample size prior to inclusion. The study was purely observational and there was no study protocol for patient diagnosis or therapy. Patients were followed up for 60 days after admission to the ICU for in-hospital mortality.

## Definitions

Infection was defined according to the definitions of the International Sepsis Forum (Table E1) [9]. Organ failure was defined as a sequential organ failure assessment (SOFA) score  $>2$  for the organ in question. Hospital-acquired SARI was defined as the development of SARI 48 h or more after hospital admission [10]. The definition of healthcare-related infections is provided in Table E1 [10]. Patients were classified as having community-acquired SARI if they did not fit the criteria for healthcare-related or hospital-acquired SARI.

Antibiotic therapy was considered adequate if the results of microbiology confirmed in vitro sensitivity and/or if clinical improvement occurred with no need to change or escalate the antibiotic regimen within 7 days of the onset of therapy.

### Data collection

Data were collected in individual centers on paper case record forms (CRFs) and were then transcribed by local investigators into a secure Internet-based platform. A minimal data set was recorded for all adult patients admitted to the participating ICUs during the two study weeks. This included the type of admission (surgical or not), use of mechanical ventilation on admission to the ICU and during the ICU stay, the ICU length of stay, and the ICU mortality. In patients with SARI, data collection on admission included demographic data, comorbid diseases, and the presenting signs and symptoms. Clinical and laboratory data to calculate the SAPS II score [11] were recorded as the worst values within 24 h after admission. Microbiologic and clinical infections were recorded daily as were the antibiotics administered. Organ function was evaluated daily using the SOFA score [12]. The daily data collection was performed for 28 days following admission to the ICU or until ICU discharge or death.

### Data management and quality control

Detailed instructions were available for all participants before starting data collection and throughout the study period. Plausibility checks were performed for each variable and between variables. Data were further reviewed by the primary investigator (YS) for plausibility and availability of outcome parameters, and any doubts were clarified with the center in question. Any file with more than 20 % missing data was excluded from the study. The reliability of data collection was further analyzed using Kappa statistics on a randomly selected 2 % of the collected comorbidity and mortality data. Discordance was clarified through direct contact with the investigators and corrected in the final database. The Kappa coefficient ranged from 0.84 to 1.00 denoting very good agreement between collected data and the randomly recollected sample.

For single missing values of the SOFA score, the mean value of the results on either side of the absent result was imputed. When first or last values were missing, the nearest value was carried backward or forward, respectively. When more than one consecutive result was missing, it was considered as a missing value in the analysis. Missing data represented 6.7 % of the collected data and 1.5 % were replaced.

### Outcome parameters

The primary outcome parameter in patients with SARI was in-hospital mortality within 60 days of admission to the ICU. Secondary outcome parameters included death in the ICU, ICU and hospital lengths of stay, and organ failure as assessed by the SOFA score.

### Statistical analyses

Data were analyzed using IBM® SPSS® Statistics software, version 22 for Windows, R software, version 3.2.2 (CRAN project), and MLwiN v.2.28. The Kolmogorov–Smirnov test was used to verify the normality assumption of continuous variables. Difference testing between groups was performed using analysis of variance (ANOVA), Student's *t* test, Mann–Whitney test, Chi square test, or Fisher's exact test, as appropriate.

To identify the independent risk factors for in-hospital death in patients with SARI we used a three-level multilevel technique with in-hospital outcome as the dependent variable (Table E2). The explanatory variables considered in the model were

- Individual-level factors: age, sex, ethnicity, SAPS II and SOFA scores on admission to the ICU, source of admission, comorbidities, mode of acquisition of SARI, prior vaccination against pneumococcus or influenza, antibiotic administration, adequacy and timing (in days) of the antibiotic therapy initiated on admission to the ICU, need for mechanical ventilation during the ICU stay, number of days in the hospital prior to ICU admission, and microorganisms retrieved at any time during the ICU stay
- Hospital-level factors: type of hospital, level of care, number of staffed ICU beds
- Country-level factors: for this level, a random intercept model was considered

Data are given as means with standard deviation, medians, and interquartile ranges (IQR), or numbers and percentages (*n*, %). All statistics were two-tailed and a *p* value less than 0.05 was considered as significant.

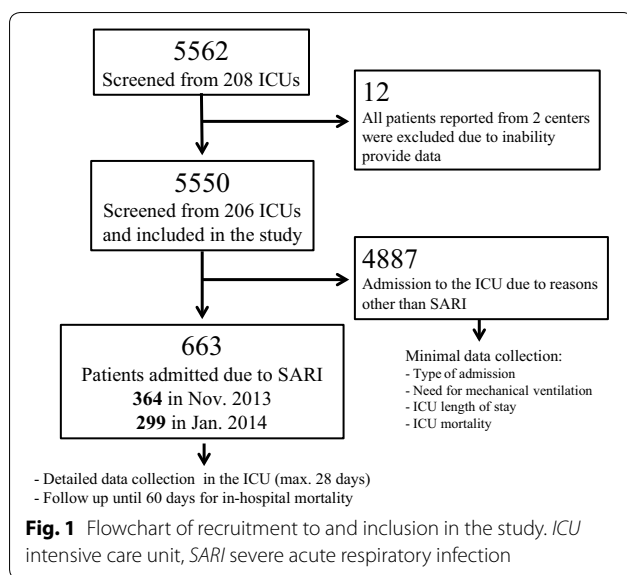
## Results

### Characteristics of study cohort

A total of 206 ICUs from 42 countries contributed to the study, mostly located in Western Europe (66.5 %, *n* = 137) (Table E3). During the study periods, 5550 patients were admitted to these units (Fig. 1). A total of 663 (11.9 %) patients were admitted because of SARI; 364 in the first and 299 in the second inclusion periods. The epidemiology of SARI in the different geographic regions is presented in Table E4.

SARI admissions were more likely to be non-surgical and to require mechanical ventilation on admission to the ICU and at any time during the ICU stay than those who were admitted for reasons other than SARI (Table E5).

The characteristics of patients with SARI on admission to the ICU are presented in Table 1; these admissions were most commonly community-acquired (68.8 %). The most common comorbidities in these patients were



systemic hypertension (51.3 %) and chronic obstructive pulmonary disease (COPD, 31.1 %) (Table E6).

#### Clinical manifestations, patterns of infection, and antimicrobial therapy in SARI patients

The first symptoms occurred at a median of 2 days (IQR 0–4) before admission to the ICU, most commonly dyspnea (92.8 %), cough (75.3 %), and fever (64.7 %). Less common symptoms included headache (18.3 %), nausea and vomiting (17.4 %), and diarrhea (7.3 %). A history of recent foreign travel was reported by 27 patients (4.1 %).

Prior antimicrobial therapy was initiated in 378 patients (57.0 %) (Table E7) and in 611 patients (96.5 %) a new antimicrobial agent was started on admission to the ICU, mostly empirically (88.6 %). The initial antimicrobial therapy was adequate in 80.6 % of cases. The antimicrobial regimen was changed in 209 patients (31.5 %) because of clinical deterioration (45.2 %), culture results (34.8 %), or in the context of de-escalation of therapy (19.9 %). Concomitant antimicrobials were used in 130 patients (19.6) for indications other than treatment of SARI.

Specimens were obtained for microbiological examination in 596 (89.9) patients and were positive for microorganisms in 62.7 % of patients (Table E8). Microbiological investigation on admission to the ICU revealed predominantly Gram-positive (29.6 %) or Gram-negative bacteria (26.2 %) but rarely atypical bacteria (1.0 %); 7.7 % of the microorganisms isolated on admission were viruses (Table 2). Overall, the most frequently isolated Gram-positive bacteria was *Streptococcus pneumoniae* (12.7 %); the most frequently isolated Gram-negative microorganism was *Pseudomonas aeruginosa* (14.4 %). Viruses were

isolated in 13.7 % of positive cultures, atypical bacteria in 2.9 %, and fungi in 27.6 % of cases. In patients with hospital-acquired SARI, Gram-negative microorganisms (33.3 vs. 26.5 %,  $p = 0.002$ ) and fungi (29.5 vs. 12.8 %,  $p = 0.001$ ) were more frequently and viral infections less frequently (3.9 vs. 9.9 %,  $p = 0.006$ ) isolated than in patients with community-acquired SARI (Fig. 2).

#### Morbidity and mortality

Organ failure was present on admission to the ICU in 427 (64.4 %) of the patients with SARI and occurred during the entire ICU stay in 495 (74.7 %). Respiratory, cardiovascular, and renal failures were the most common organ failures (Table 3). The ICU and hospital mortality rates were 20.2 and 27.2 %, respectively.

The overall ICU mortality in all patients admitted to the contributing centers ( $n = 5550$ ) was 13.1 % and the median ICU stay was 3 (IQR 2–8) days. Patients with SARI had higher ICU mortality (20.2 vs. 12.2 %,  $p < 0.001$ ) and longer ICU lengths of stay [5 (2–12) vs. 3 (2–8)] days,  $p < 0.001$ ) than those without SARI (Table E5).

Survivors were younger, more likely to be female, less likely to be admitted to the ICU from a hospital ward, had lower severity scores on admission to the ICU, and had a lower incidence of organ failure during the ICU stay (Tables E9, E10) than non-survivors. Survivors were more likely to have received pneumococcal or influenza vaccines than non-survivors. Arrhythmias, chronic renal failure, cancer, asthma, hematologic malignancies, organ or bone marrow transplantation, liver disease, immunosuppression, or chemotherapy prior to ICU admission were more frequent in non-survivors than in survivors (Table E7). The most common primary causes of in-hospital death were multiorgan failure (43.6 %) and pneumonia (31.9 %) (Table E11).

In multivariable analysis, older age, greater severity scores on admission to the ICU, hematologic malignancy, and liver disease were independently associated with an increased risk of in-hospital death. Influenza vaccination prior to ICU admission, and adequate antibiotic administration on admission to the ICU were associated with a lower risk of in-hospital death (Table E2).

#### Discussion

The main findings of our study were that (1) SARI was a common cause of admission to the ICU and was associated with considerable morbidity and high mortality rates; (2) these infections were predominantly due to Gram-positive or Gram-negative bacteria and rarely due to atypical bacteria or viruses; and (3) older age, greater severity scores, and comorbid conditions were independently associated with an increased risk of in-hospital death in these patients, whereas prior influenza

**Table 1 Characteristics of patients with severe acute respiratory infections (SARI) on admission to the ICU, stratified according to the inclusion periods**

	All patients	Inclusion period		p value
		November 2013	January 2014	
N	663	364	299	
Age, years, mean $\pm$ SD	63.9 $\pm$ 16	64.5 $\pm$ 15.9	63.1 $\pm$ 16.2	0.226
Male, n (%)	386 (58.7)	216 (59.8)	170 (57.2)	0.501
Healthcare worker, n (%)	11 (1.7)	5 (1.4)	6 (2.0)	0.798
Ethnicity, n (%)				
White/Caucasian	441 (67.7)	246 (69.5)	195 (71.3)	0.392
Asian	49 (7.5)	22 (6.2)	27 (9.1)	
Latin American	46 (6.9)	24 (6.8)	22 (7.4)	
South Asian <sup>a</sup>	41 (6.2)	23 (6.5)	18 (6.1)	
Arab	34 (5.2)	19 (4.9)	15 (5.1)	
Black	24 (3.6)	15 (4.2)	9 (3.0)	
Others	16 (2.5)	5 (1.4)	11 (3.7)	
Source of admission, n (%)				
Community	194 (29.4)	108 (29.9)	36 (22.1)	0.847
Hospital ward	183 (27.8)	99 (27.4)	64 (39.3)	
Emergency room	165 (25.0)	93 (25.8)	34 (20.9)	
Other hospital	58 (8.8)	33 (9.1)	25 (8.4)	
Long-term facility	24 (3.6)	10 (2.8)	14 (4.7)	
Other ICU	13 (2.0)	2 (0.6)	11 (3.7)	
Step-down/-up	14 (2.1)	10 (2.8)	4 (1.3)	
Others	8 (1.2)	6 (1.7)	2 (0.7)	
Severity scores				
SAPS II, mean $\pm$ SD	50.4 $\pm$ 19.0	49.3 $\pm$ 18.2	51.7 $\pm$ 19.8	0.178
SOFA score, median (IQR)	5 (2–9)	5 (2–9)	5 (2–9)	0.727
Mode of acquisition, n (%)				
Community-acquired	452 (68.2)	246 (68.3)	206 (69.4)	0.059
Healthcare-related	76 (11.5)	37 (10.3)	39 (13.1)	
Nosocomial-acquired	129 (19.5)	77 (21.4)	39 (17.5)	
Mechanical ventilation on admission to the ICU				
Invasive	385 (58.1)	208 (57.1)	177 (59.2)	0.594
Non-invasive	46 (6.9)	28 (7.7)	18 (6.0)	0.399
Influenza vaccine, n (%)	67 (10.2)	43 (11.9)	24 (8.1)	0.751
Pneumococcal vaccine, n (%)	49 (7.4)	31 (8.6)	18 (6.0)	0.692

Missing values  $n = 2-12$  (max 1.8 %), valid percentages are presented after exclusion of missing values

ICU intensive care unit, SAPS simplified acute physiology score, IQR interquartile range, SOFA sequential organ failure assessment score

<sup>a</sup> India, Pakistan, and Sri Lanka

vaccination and adequate initial antibiotic administration were associated with a lower risk.

Repeated outbreaks of SARI-related epidemics represent a major healthcare problem [1–4]. Several studies have investigated the epidemiology and clinical characteristics of SARI, with a special emphasis on viral etiology [13–17] or on the subset of patients admitted to the ICU with severe community-acquired pneumonia [17–22]. To the best of our knowledge, our study is the first to investigate this issue in a large prospective, multinational cohort

of critically ill patients with SARI, providing a global view of this condition worldwide.

One in ten patients with SARI was treated empirically without any microbiologic sampling. Increased awareness of sepsis should be expected to improve compliance with early microbiologic sampling [23]. Nevertheless, the low index of suspicion in the absence of an ongoing epidemic may explain the relatively low rate of investigations aimed at detecting a viral etiology. In agreement with previous large epidemiologic

**Table 2 Isolated microorganisms (out of 416 patients with positive results)**

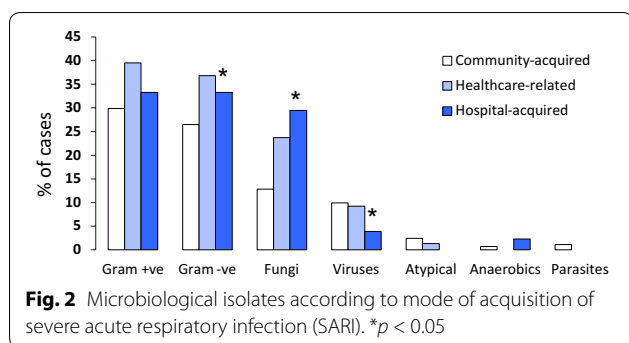
	On admission to the ICU	After admission	Any time in the ICU <sup>a</sup>
Gram-positive, n (%)	123 (29.6)	123 (29.6)	205 (49.3)
<i>Streptococcus pneumoniae</i>	41 (9.9)	23 (5.5)	53 (12.7)
<i>Staphylococcus aureus</i> sensitive to methicillin	23 (5.5)	27 (6.5)	42 (10.1)
Staph. coag. neg. sensitive to methicillin	15 (3.6)	34 (8.2)	45 (10.8)
<i>S. aureus</i> resistant to methicillin	14 (3.4)	13 (3.1)	26 (6.3)
Staph. coag. neg. resistant to methicillin	7 (1.7)	14 (3.4)	20 (4.8)
<i>Streptococcus</i> A, B, C, G group	7 (1.7)	5 (1.2)	12 (2.9)
<i>Streptococcus</i> , others	14 (3.3)	26 (6.3)	36 (8.6)
Other Gram-positive	10 (2.4)	16 (3.8)	26 (6.3)
Gram-negative, n (%)	109 (26.2)	127 (30.5)	201 (48.3)
<i>Pseudomonas aeruginosa</i>	29 (7.0)	40 (9.6)	60 (14.4)
<i>Klebsiella</i> species	27 (6.5)	36 (8.7)	57 (13.7)
<i>Escherichia coli</i>	23 (5.5)	26 (6.3)	43 (10.3)
<i>Acinetobacter</i> species	15 (3.6)	25 (6.0)	34 (8.2)
<i>Enterobacter</i> species	10 (2.4)	11 (2.6)	21 (5.0)
<i>Proteus</i> species	5 (1.2)	7 (1.7)	10 (2.4)
<i>Citrobacter</i> species	5 (1.2)	2 (0.5)	6 (1.4)
<i>Serratia</i> species	1 (0.2)	5 (1.2)	6 (1.4)
<i>Stenotrophomonas maltophilia</i>	3 (0.7)	5 (1.2)	7 (1.7)
<i>Haemophilus</i> species	7 (1.7)	11 (2.6)	18 (4.3)
Other Gram-negative	4 (1.0)	7 (1.7)	11 (2.6)
Anaerobic, n (%)	4 (1.0)	3 (0.7)	7 (1.7)
<i>Clostridium</i> species	2 (0.5)	3 (0.7)	5 (1.2)
Bacteroides	1 (0.2)	0 (0.0)	1 (0.2)
Anaerobe, others	1 (0.2)	0 (0.0)	1 (0.2)
Atypical bacteria, (%)	4 (1.0)	8 (1.9)	12 (2.9)
Mycobacteria	1 (0.2)	1 (0.2)	2 (0.5)
<i>Chlamydia</i> species	0 (0.0)	3 (0.7)	3 (0.7)
Mycoplasma	0 (0.0)	4 (1.0)	4 (1.0)
<i>Legionella pneumophila</i>	3 (0.7)	2 (0.5)	5 (1.2)
Fungi, n (%)	45 (10.8)	83 (20.0)	115 (27.6)
<i>Candida albicans</i>	36 (8.7)	61 (14.7)	87 (20.9)
<i>Candida</i> non- <i>albicans</i>	7 (1.7)	22 (5.3)	28 (6.7)
<i>Aspergillus</i> species	3 (0.7)	7 (1.7)	9 (2.2)
Other	2 (0.5)	9 (2.2)	11 (2.6)
Viruses, n (%)	32 (7.7)	27 (6.5)	57 (13.7)
Influenza A	23 (5.5)	16 (3.8)	38 (9.1)
Influenza B	3 (0.7)	0 (0.0)	3 (0.7)
HSV I or II	0 (0.0)	1 (0.2)	1 (0.2)
CMV	2 (0.5)	5 (1.2)	6 (1.4)
Other	5 (1.2)	6 (1.4)	11 (2.6)
Parasites, n (%)	2 (0.5)	3 (0.7)	5 (1.2)

CMV cytomegalovirus, HSV herpes simplex virus

<sup>a</sup> Microorganisms isolated both on admission to the ICU and during the ICU stay are counted once

studies in ICU patients with infections [24–26], pathogenic microorganisms were identified in only 62.7 % of patients. Lack of testing for all possible microorganisms during microbiological investigations, the relatively

high rates of prior antibiotic administration with possible interference with culture results, and inappropriate sampling techniques may hinder microorganism identification.



**Table 3** Morbidity and mortality in patients with SARI ( $n = 663$ )

Organ failure on admission to the ICU, $n$ (%) <sup>a</sup>	
Respiratory	205 (30.9)
Cardiovascular	217 (32.7)
Renal	180 (27.1)
CNS	138 (20.8)
Hematologic	54 (8.1)
Hepatic	29 (4.4)
Organ failure at any time in the ICU, $n$ (%) <sup>a</sup>	
Respiratory	357 (53.8)
Cardiovascular	295 (44.5)
Renal	296 (44.6)
CNS	216 (32.6)
Hematologic	133 (20.1)
Hepatic	50 (7.5)
Mortality rates, $n$ (%)	
ICU	123 (20.2)
In-hospital	163 (27.2)
Length of stay, days, median (IQR)	
ICU	5 (2–12)
Hospital	12 (7–23)
Limitation of therapy in-hospital, $n$ (%)	
DNR	72 (11.9)
WH/WD	57 (9.4)

Missing values: 53 and 64 for ICU and hospital mortality, respectively. Valid percentages are displayed after exclusion of the missing values

CNS central nervous system, DNR do not resuscitate order, ICU intensive care unit, LOS length of stay, WD withdrawal of life-sustaining therapy (vasopressors, mechanical ventilation, and renal replacement therapy), WH withholding of life-sustaining measures

<sup>a</sup> Defined as a SOFA score >2 for the corresponding organ

Despite the relatively small number of microbiological investigations performed, antimicrobial agents were used generously in our cohort. Interestingly, antiviral and antifungal agents were initiated without microbiological evidence of these microorganisms in 6.9 and 4.0 % of cases, respectively. The relatively high incidence of comorbid

conditions in our cohort, especially those related to immunosuppression, and the high predominance of life-threatening organ failure in these patients may explain the high use of antimicrobial agents.

The most commonly identified microorganisms were Gram-positive and Gram-negative bacteria. The reported microorganisms may have included, however, some non-pathogenic organisms that are not responsible for SARI. Interestingly, atypical microorganisms were less frequently identified. This observation raises questions regarding the frequent empirical use of macrolides in these patients. However, macrolides have been reported to have additional benefits in patients with community-acquired pneumonia, irrespective of their antimicrobial effects [27]. Moreover, diagnosis of infections with atypical bacteria is a considerable challenge, such that the occurrence of these infections may be underestimated [28].

Community-acquired infections were common in our cohort, explaining the frequent occurrence of infections with *S. pneumoniae*. The patterns of microbiologic isolates in our study may be useful to guide empirical antimicrobial therapy in patients with ICU-SARI. Although fungi were frequently isolated, only a small proportion of these patients received antifungal agents. This finding supports the common perception that fungal etiologies may not be relevant in all critically ill patients with respiratory infections [29].

Our data underscore the poor prognosis of critically ill patients with SARI. These patients had considerably higher mortality rates and longer lengths of stay compared to patients without SARI. The in-hospital mortality rate in our cohort was similar to rates reported in patients with severe community-acquired pneumonia in previous studies [17, 20, 30]. This can be explained by the frequent occurrence of organ failure in these patients.

We identified several risk factors for in-hospital mortality in the current cohort. These patterns may be useful in identifying patients at risk of poor prognosis. In agreement with the results of a meta-analysis of 70 large observational studies including 21,338 patients with sepsis [31], we found that adequate initial antibiotic administration was protective in terms of low risk of in-hospital death. This supports the early rigorous empiric use of wide-spectrum antibiotics in these patients, pending the results of microbiological investigations. Nonetheless, since the definition of appropriate antibiotic administration in the current study was based on both positive microbiologic isolates and clinical improvement, we cannot exclude a possible bias in patients who were judged only on the basis of clinical improvement.

Interestingly, prior seasonal influenza vaccination was independently associated with a favorable in-hospital outcome. Ortiz and collaborators [32] estimated that

about 28,000 adults are hospitalized for influenza-associated critical illness in the USA annually. A recent bias-adjusted meta-analysis [33] confirmed that influenza vaccine was effective in preventing hospitalization from influenza and/or pneumonia and all-cause mortality in community-dwelling elderly. However, the evidence to support risk factors for influenza-related complications is still low and adequately powered studies are needed to address this issue [34, 35].

The study had several limitations. First, participation was voluntary and was concentrated in some countries in Western Europe, so that the results in this report may not be extrapolated to all ICU patients worldwide. Second, regional and seasonal differences may also occur and cannot be captured from our data. Third, some of the reported microorganisms may have represented respiratory colonization rather than infection. Fourth, the definitions of infection were not based on only the presence of microorganisms and we did not differentiate between possible and probable clinical infections. Nonetheless, defining infection according to the isolation of a pathogenic microorganism may also be subject to a certain bias because of possible interference from prior antibiotic administration, availability and the diagnostic performance of the serologic tests, and local practice concerning microbiologic investigations. Fifth, our data may not be extrapolated to all hospitalized patients with SARI. Finally, the study was purely observational and we did not apply standard protocols for diagnosis and therapy in patients with SARI; however, our aim was to report current practice in these patients.

## Conclusions

SARI is a common cause of admission to the ICU and has associated high morbidity and mortality rates. Our data describe the current patterns of infections and therapy of this serious healthcare problem. This information may be particularly useful in resource allocation and risk stratification for clinical and research purposes.

## Author details

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## Compliance with ethical standards

## Conflicts of interest

The authors declare that they do not have any conflict of interest in relation to the subject of this manuscript. Funding

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## Appendix 1. Alphabetical list of participating centers by region & country

### Study coordinator

*The trials group of the European Society of Intensive Care (ESICM):* (G Francois)

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*Austria:* General Hospital, Braunau (J Auer, G Schatzl); Krankenhaus Oberwart, Oberwart (K Mach, H Gruber)

*Belgium:* Ziekenhuis Oost-Limburg, Genk (E Schreurs, M Vander Laenen); Universitair Ziekenhuis, Leuven (H Ceunen, J Wauters); CHU Saint-Pierre, Brussels (P Deschamps); Cliniques Universitaires Saint-Luc UCL, Brussels (D Castanares); CHU Brugmann, Brussels (D Debels, C Pierrakos); Erasme University Hospital, Brussels (JL Vincent, F Taccone (*national coordinator*))

*Czech Republic:* University Hospital Motol, Prague (T Vymazal)

*Croatia:* University Hospital Centre Zagreb, Zagreb (I Gornik, A Vujiaklija Brajkovic)

*Denmark:* Holbaek Sygehus, Holbaek (R Medici); Rigshospitalet, Copenhagen (J Nielsen); Glostrup Sygehus, Glostrup (A Bendtsen, H Siegel)

*Finland:* Meilahti Hospital, Helsinki (T Suonsyrjä)

*France:* CHU Nord, Marseille (S Hraech), Hôpital Cochin, Paris (J-D Chiche, F Daviaux); CHRU Strasbourg-Hôpital de Hautepierre, Strasbourg (M Guillot, V Castelain); CHRU Nancy- Hôpital Brabois- Réanimation et soins continus chirurgicaux, Vandoeuvre-Les-Nancy (R-R Losser), CHRU Nancy- Hôpital Brabois- Réanimation médicale, Vandoeuvre-Les-Nancy (E Novy); Hôpital Bichat, Paris (J-F Timsit (*national coordinator*), L Bouadma); Groupe Hospitalier Paris Saint-Joseph, Paris (B Misset, F Philippart); Centre Hospitalier Dr Schaffner, Lens (J Mallat); CHU Amiens, Amiens (E Zogheib, M Miclo) Hôpital Bicêtre, Le Kremlin-Bicêtre Paris (J-L Teboul, N Anguel); CHU Saint-Etienne, Saint-Etienne (M Darmon); Hôpital Tenon, Paris (T Pham); CH Mulhouse-Hôpital



Emile Muller, Mulhouse (G Barberet); Hôpital Victor Dupouy, Argenteuil (G Plantefevé); Hôpital Edouard Herriot, Hospices Civils de Lyon, Lyon (B Floccard)

*Georgia:* Georgian Critical Care Medicine Institute, Tbilissi (Z Kheladze)

*Germany:* Universitätsklinikum Jena, Jena (K Reinhart (*national coordinator*), Y Sakt, F Bloos); Klinikum Weiden, Weiden in der Oberpfalz (A Faltlhauser); Klinikum Luedenscheid, Luedenscheid (T Helmes); University Hospital Frankfurt, Frankfurt am (K Zacharowski, P Meybohm); Klinikum Saarbrücken, Saarbrücken (K Schwarzkopf); Klinikum Nürnberg, Dept. of Emergency and Critical Care Medicine, Nuremberg (M Christ, M Baumgaertel); Klinikum Nürnberg, Nephrologische Intensivstation BU13, Nuremberg (S John, J Nentwich); Universitätsmedizin-Charité, Berlin (M Deja, A Goldmann); Diakoniekrankenhaus Friederikenstift, Hannover (A Gottschalk, F Honig); University Medical Center Freiburg, Freiburg (B Siepe, U Goebel); Vivantes Humboldt-Klinikum, Berlin (J Lehmke, S Behrens); Oberschwabenklinik, Krankenhaus St. Elisabeth, Ravensburg (K Fiedler); Universitätsmedizin Mainz, Mainz (I Sagoschen); University Hospital, Tübingen (R Riesen, M Haap); University Hospital, Leipzig (Ph Simon, U Kaisers); Vivantes Klinikum Spandau, Berlin (S Behrens, M Niesen); Klinikum Augsburg, Augsburg (U Jaschinski); Universitätsklinikum des Saarlandes, Homburg (S Hoersch, A Jung); Robert-Bosch-Krankenhaus, Stuttgart (S Allgaeuer); Maria Hilf, Mönchengladbach (H Haake); Klinik Hennigsdorf der Oberhavel Kliniken, Hennigsdorf (A Lange)

*Greece:* Hippokrateion General Hospital, Athens (M Papanikolaou, M Balla); AHEPA University Hospital, Thessaloniki (M Giannakou, I Soultati); University Hospital of Ioannina, Ioannina (G Nikos, V Koulouras); Lamia General Hospital, Lamia (G Kyriazopoulos, D Gkika); General Hospital O Agios Dimitrios, Thessaloniki (G Vlachogianni, K Psaroulis); Hippokratio Hospital, Thessaloniki (E Mouloudi, E Massa)

*Ireland:* St Vincents University Hospital, Dublin (A Nichol, E Meany); Limerick University Hospital, Limerick (C Motherway)

*Italy:* San Gerardo Hospital, Monza (G Bellani); Pinategrande Private Hospital, Castelvoturno (V Pota, V Schiavone); University Hospital of Modena, Modena (M Girardis, S Busani); Azienda Ospedaliera Desenzano, Desenzano (N Petrucci, R Di Pasquale); Ospedale Sandro Pertini, Rome (P Mazzini); IRCCS San Martino-IST, Genova (A Molin, G Pellerano); Arispedale Sant'Anna Hospital, Ferrara (C Volta, S Spadaro); Azienda Ospedaliero Universitaria Pisana, Pisa (F Guarracino); Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Milan (M Savioli); Santa Maria degli Angeli

Hospital, Pordenone (T Pellis, N Chinellato); Ospedale Ceccarini, Riccione (A Gatta, F Cecchini); Policlinico P. Giaccone, Palermo (S.M. Raineri, A Cortegiani)

*Lithuania:* Vilnius University Hospital Santariskiu Clinics, Vilnius (G Kekstas, V Karosas)

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(M Alvarez); Hospital General Universitario de Albacete, Albacete (V Corcoles Gonzalez, J. M Gutierrez Rubio); Hospital Clínico Universitario Lozano Blesa, Zaragoza (R Montoiro Allue); Hospital Infanta Cristina, Badajoz (J Rubio Mateo-Sidron)

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#### **Middle East**

*Iran:* Nemazee Hospital (AACRC), Shiraz (F Zand, R Nikandish); Masih Daneshvari Hospital (NRITLD), Teheran (S Hashemian, H Jamaati);

*Qatar:* Hamad General Hospital, Doha (A.S. Alsheikhly)

*Saudi Arabia:* Prince Sultan Military Medical City (PSMMC), Riyadh (G Almekhlafi, M Albarrak); King Faisal Specialist Hospital, Riyadh (A Maghrabi, N Salahuiddin); King Fahad Hospital, Baha (T Aisa)

*Turkey:* Atasehir Memorial Hospital, Istanbul (H. K Atalan); Erciyes Universitesi Tip Fakultesi, Kayseri (M Sungur);

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*Colombia:* Clinica Universitaria Colombia, Bogota (D Molano, A Rojas); Clinica Medellín, Medellin (K Guerra)

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*Peru:* Hospital Nacional Dos de Mayo, Lima (R Quispe Sierra, R Ovalle Olmos); Hospital Regional Honorio Delgado, Arequipa (C Chavez)

*Venezuela:* Hospital Central Dr. Miguel Pérez Carreño, Caracas (I von Osten) ;

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**Philippines:** Chong Hua Hospital, Cebu (R Bigornia, Y Ikeda-Maquiling); The Medical City, Pasig (J Robles, J. E. Palo)

**Vietnam:** Bachmai Hospital, Hanoi (T Nguyen, C Dao)

### South Asia

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