Journal of Microbiology, Immunology and Infection (2016) 49, 654–662

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

ORIGINAL ARTICLE

Risk factors for slowly resolving pneumonia in the intensive care unit

Meiling Li [a,c], Jialin Liu [b,**], Ruoming Tan [a], Zhaojun Liu [a], Jianyong Yin [a], Hongping Qu [a,*,c]

[a] *Department of Critical Care Medicine and Respiratory Intensive Care Unit, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China*
[b] *Department of Pulmonary Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China*

Received 18 September 2013; received in revised form 2 June 2014; accepted 6 November 2014
Available online 22 November 2014

KEYWORDS
antibiotic therapy;
critically ill;
pneumonia;
radiographic infiltrations;
resolution;
risk factors

Background: Slowly resolving pneumonia (SRP) poses early challenges for identification and medical expense for clinicians in intensive care units (ICUs); to date, the literature has been very limited in this regard.
Methods: This was a retrospective and cohort-based study in the ICU of a university-affiliated hospital in Shanghai. Medical records of pneumonia patients in the ICU between April 2008 and February 2011were reviewed retrospectively to evaluate the risk factors for SRP.
Results: In all, 106 pneumonia patients in the ICU were identified as immune-competent with a diagnosis of bacterial pneumonia. There were 62 (58.49%) patients who showed SRP and their radiographic infiltrations were completely resolved between 5 weeks and 8 weeks. Multivariate logistic regression analysis demonstrated that initial treatment with an inappropriate antibiotic, multilobar infiltration, and a high CURB-65 score were independent risk factors for SRP, with odds ratio (OR) values of 8.338 [95% confidence interval (CI) 2.117–32.848], 11.184 (95% CI 2.526–49.514), and 2.329 (95% CI 1.172–4.626), respectively. The length of the ICU stay in the SRP group was twice as long as that of the normally resolving pneumonia (NRP) group (62.27 ± 73.73 vs. 32.25 ± 23, $p = 0.002$). The 28-day and 60-day mortality rates in the SRP group were 17.74% and 25.81%, respectively. In addition, the 60-day mortality rate was significantly higher in the SRP group than the NRP group (25.81% vs. 6.82%, respectively; $p = 0.012$). Moreover, SRP was an independent risk factor for 60-day mortality (OR 5.687, 95% CI 1.334–24.240).

* Corresponding author. Department of Critical Care Medicine and Respiratory Intensive Care Unit, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, 197 Rui-Jin Er Road, Boulevard 36, Shanghai 200025, China.
** Corresponding author.
E-mail addresses: fillelibra@hotmail.com (J. Liu), hongping_qu0412@hotmail.com (H. Qu).
[c] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.jmii.2014.11.005

Conclusion: Treatment with an inappropriate antibiotic, multilobar infiltration, and a high CURB-65 score were independent risk factors for SRP.

Introduction

The unapparent resolution of pulmonary infiltrates in both nonresolving and slowly resolving pneumonia (SRP) poses diagnostic and treatment challenges for clinicians as a common consultation problem.[1,2] Nonresolving pneumonia often represents a noninfectious process that mimics an infectious process.[3,4] SRP is usually associated with host- or treatment-related factors.[5,6] Advances in procedures used to diagnose pneumonia have led to a declining incidence of nonresolving pneumonia, while the incidence of SRP is definitely rising with multiple supporting methods.[7,8] Kirtland and Winterbauer[9] first proposed a definition of SRP that referred to immune-competent patients who exhibited improved clinical symptoms with antibiotic therapy and chest radiographs with less than 50% clearing by 2 weeks or less than complete clearing at 4 weeks.[10] To date, the literature concerning the evaluation and treatment of SRP has been limited. Although the precise incidence of SRP is not well established, early studies reported that 25—67% of the pulmonary infiltration of pneumonia patients showed delayed resolution along with high mortality,[11] prolonged hospital stays, and high treatment costs.[8] Some studies on critically ill patients found that as many as 47% of pneumonia cases showed delayed resolution.[12] Due to its high incidence and poor outcome, the recognition and resolution of SRP in intensive care units (ICUs) deserve more attention from clinicians.

The objective of this study was to investigate the incidence, length of ICU stay, outcome, and risk factors associated with SRP in critically ill patients to promote the identification of high-risk patients.

Methods

Ethical statement

The extent of our involvement with participants was limited to the evaluation of radiographic resolution and analysis of the participants' clinical features. We promised to hold all the information of participants in a confidential manner. The study protocol and consent procedure with waiver of written consent was approved by the Shanghai Jiao Tong University School of Medicine and affiliated to the Ruijin Hospital Ethics Committee.

Study population

The study group was sampled from patients who were admitted to the ICU of a 1300-bed university-affiliated hospital with a diagnosis of pneumonia between April 2008 and February 2011. {Pneumonia was defined as a new or progressive infiltrate as seen on a chest radiograph or computed tomography (CT) scan along with a high clinical suspicion of pneumonia, defined by at least one of the following: fever ($>38^{\circ}C$); leucopenia [$<$ 4000 white blood cells (WBC)/mm^3] or leukocytosis ($>$ 12,000 WBC/mm^3); altered mental status with no other recognized cause (for adults older than 70 years); and at least two of the following: (a) new onset of purulent sputum, change in characteristics of sputum, increased respiratory secretions, or increased suctioning requirements, (b) new onset or worsening cough, dyspnea, or increased ventilation demand.}

The inclusion criteria included pneumonia patients who reached clinical stability due to treatment in the ICU with a complete resolution or resolution of infiltrate differentiated from chronic changes. [Clinical stability was defined as a temperature $\leq 37.8^{\circ}C$, a heart rate $\leq$ 100 beats/min, a respiratory rate $\leq$ 24 breaths/min, systolic blood pressure $\geq$ 90 mmHg, arterial oxygen saturation $\geq$ 90% or $PaO_2 \geq$ 60 mmHg in room air, the ability to maintain oral intake, and a normal mental status.[10]]

The exclusion criteria included patients with immunodepression, interstitial pneumonia, pulmonary tumor, pulmonary tuberculosis, influenza A virus subtype H1N1 or another respiratory tract virus, legionnaires pneumonia, mycoplasma pneumonia, chlamydia pneumonia, and acute respiratory distress syndrome. [Immunodepression was defined as a recent history of neutropenia ($< 0.5 \times 10^9$ neutrophils/L for 110 days); the receipt of an allogeneic stem cell transplant; the prolonged use of corticosteroids (a mean minimum dose of 0.3 mg of prednisone equivalent/kg/day for 13 weeks); treatment with another recognized T cell suppressant such as cyclosporine, tumor necrosis factor-alpha (TNF-α) blockers, specific monoclonal antibodies, or nucleoside analogs during the past 90 days; or inherited severe immunodeficiency (such as chronic granulomatous disease or severe combined immunodeficiency).[13]]

Study methodology

Every eligible patient had pre-pneumonia radiography as basic radiographic data and a CT scan performed to identify pulmonary destruction and multilobar infiltration. Each pneumonia patient was evaluated once a week in the ICU by bedside X-ray examination or CT scan if possible until the pulmonary infiltrates were completely resolved or their radiological signs normalized to previous levels. Two specialized radiography colleagues who were blinded to clinical status evaluated the radiographic infiltrates. The patients with SRP reached clinical stability but exhibited either persistent pulmonary infiltrates 4 weeks after an initial pneumonia-like syndrome or demonstrated less than 50% clearing on chest radiographs taken 2 weeks after starting antibiotic therapy. The normally resolving

pneumonia (NRP) cases were completely resolved or normalized to previous levels within 4 weeks.

In our ICU, we usually did the sputum or endotracheal aspiration culture weekly or twice a week if needed as a routine procedure. Each pneumonia patient was examined for *Mycobacterium tuberculosis*, influenza virus, or other atypical pathogen to rule out pulmonary tuberculosis (TB), H1N1, or other atypical pneumonia. We also performed a Gram stain on sputum or endotracheal aspiration, and measured procalcitonin (PCT) and C-reactive protein (CRP) to identify colonization or infection.

Data collection

We collected clinical data from the participants, including their sex, age, aspiration history, pulmonary radiography, underlying diseases, CURB-65 score (a severity score including confusion, uremia, respiratory rate, blood pressure and age), Acute Physiology And Chronic Health Evaluation (APACHE) II score, PCT level, CRP level, microorganism from sputum sample or endotracheal aspiration, antibiotic susceptibility test, anti-infection treatments, steroid applications, need for an artificial airway, time required for radiographic clearing, and 28-day and 60-day mortality rates.

Definitions of risk factors

Initial treatment with an inappropriate antibiotic was defined as the first administration of an antimicrobial agent to which at least one causative microorganism was resistant or the lack of antimicrobial therapy for a known causative pathogen.[14–16]

High-dose steroid application was defined as the application of more than 2 mg intravenous methylprednisolone/kg/day for at least 14 days.[17,18]

The continued isolation of pathogen was defined as the elimination of the original pathogen from sputum cultures less than twice.[19]

Delayed clinical stability referred to a pneumonia patient who required more than 6 days to reach clinical stability.[10]

Statistical analysis

SPSS software (version 17.0; SPSS Inc., Chicago, IL, USA) was used for data analysis. The qualitative variables were expressed as frequency (%), while the quantitative variables were expressed as the mean ± standard deviation (SD). The SRP group was compared with the NRP group using the χ^2 test, the continuity correction χ^2 inspection, or Fisher's exact test for the qualitative variables (sex, type of pneumonia, aspiration history, radiographic characteristics, underlying diseases, microorganism and antibiotic susceptibility test results, anti-infection treatments, steroid applications, need for an artificial airway, 28-day and 60-day mortality rates) and a *t* test for the quantitative variables (age, CURB-65 score, APACHE II score, PCT level, CRP level). The data without a normal distribution were analyzed by the rank sum test. Univariate and multivariate analyses were performed to determine the risk factors associated with SRP. The Kaplan–Meier method was used for the survival function.

Results

Characteristics of the patients

There were 154 pneumonia patients admitted to the ICU between April 2008 and February 2011. A total of 106 pneumonia patients were eligible for inclusion in the study, and 62 pneumonia patients met the criteria for SRP, exhibiting radiographic infiltration that was completely resolved within 5–8 weeks. The incidence of SRP was 58.49% (Fig. 1). As part of our study methodology, we ruled out two cases of pulmonary tuberculosis and five cases of H1N1 influenza. We found that 90.9% of single-lobe pneumonia cases completely resolve in 4 weeks, while 56% of multilobar pneumonia cases required 5–8 weeks to completely resolve.

The demographic data including age, sex, and underlying diseases were equivalent for both the SRP group ($n = 62$) and the NRP group ($n = 44$). There were no differences in aspiration history ($n = 28$) and mechanical ventilation ($n = 49$) between the two groups. The radiographic study revealed no significant differences in the destruction of the pulmonary structure and pleural effusion between the two groups (Table 1). The PCT level (2.08 ± 3.74 vs. 0.86 ± 1.42, $p = 0.040$) and the CRP level (8.75 ± 10.65 vs. 5.49 ± 5.54, $p = 0.074$) at admission were statistically higher in the SRP group than that in the NRP group.

SRP group risk factors

A correlation analysis between quantitative variables such as age, the number of underlying diseases, PCT, CRP, the

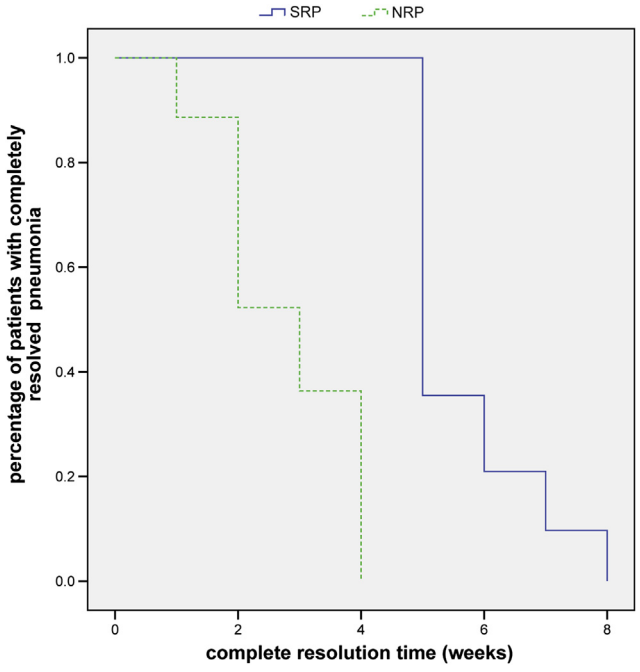

Figure 1. The complete radiographic resolution time for the two groups. The green line shows that the radiographic infiltration in the normally resolving pneumonia (NRP) patients completely resolved within 4 weeks, while the slowly resolving pneumonia (SRP) patients (blue line) required 5–8 weeks for complete resolution.

Table 1 The baseline characteristics of the patients

Characteristics	Total (n = 106)	SRP (n = 62)	NRP (n = 44)	p
Age[a]	70.56 ± 12.60	70.16 ± 12.97	68.78 ± 13.72	0.588
Sex: male/female	64/42	34/28	30/14	0.1664
Underlying disease				
Heart failure[b]	35 (32.7%)	24 (38.71%)	11 (25.00%)	0.1392
Chronic obstructive pulmonary disease[b]	26 (24.3%)	16 (25.81%)	10 (22.73%)	0.7166
Central nervous system disease[b]	30 (28.0%)	19 (30.65%)	11 (25.00%)	0.5249
Diabetes mellitus[b]	20 (18.7%)	15 (24.19%)	5 (11.36%)	0.0962
Renal insufficiency[b]	18 (16.98%)	13 (20.97%)	5 (11.36%)	0.1944
Hepatic insufficiency[b]	10 (9.43%)	8 (12.90%)	2 (4.55%)	0.2656
Radiographic feature				
Multilobar infiltration[b]	34 (32.08%)	31 (50.00%)	4 (9.09%)	< 0.0001
Pleural effusion[b]	52 (49.06%)	33 (53.23%)	19 (43.18%)	0.3081
Destruction of pulmonary structure[b]	40 (37.74%)	21 (33.87%)	19 (43.18%)	0.3298
Biomarker				
PCT[a]		2.08 ± 3.74	0.86 ± 1.42	0.040
CRP[a]		8.75 ± 10.65	5.49 ± 5.54	0.074

[a] Values are given as the mean ± standard deviation (SD).
[b] Values are given as number (%).
CRP = C-reactive protein; NRP = normally resolving pneumonia; PCT = procalcitonin; SRP = slowly resolving pneumonia.

CURB-65 score, the APACHE II score, and complete radiographic resolution time was performed. This analysis showed that the CURB-65 and APACHE II scores correlated with the radiographic resolution time. The correlation coefficients for the CURB-65 and APACHE II scores were 0.2432 (p = 0.012) and 0.2259 (p = 0.0199), respectively. The qualitative variables, which included central nervous system disease, chronic obstructive pulmonary disease, heart failure, diabetes mellitus, aspiration history, pulmonary structure, pleural effusion, multilobar infiltration, initial treatment with an inappropriate antibiotic, delayed clinical stability, continued isolation of pathogen, multidrug-resistant bacteria, artificial airway, and the application of high-dose steroids, were statistically analyzed by a univariate analysis. The univariate analysis identified treatment with an inappropriate antibiotic, multilobar infiltration, the lack of microbiological eradication, delayed clinical stability, and the application of high-dose corticosteroids as risk factors for SRP (Table 2).

Table 2 Risk factors for slowly resolving pneumonia (SRP), as identified by univariate analysis

Risk factor	p	RR value	95% CI	
Inappropriate initial antibiotic therapy	0.0004	1.7940	1.3639	2.3598
Multilobar infiltration	< 0.0001	2.0286	1.5182	2.7105
Continued isolation of pathogen	0.0443	1.3846	1.0097	1.8988
Delayed clinical stability	0.0104	1.5553	1.0848	2.2298
High-dose corticosteroid application	0.0053	1.8462	1.5359	2.2191

CI = confidence interval; RR = relative risk.

The microbiology results and initial antibiotic use of all patients were summarized in Table 3. There was no difference in the culture-negative rates between SRP and NRP groups (14.52% vs. 25%, p = 0.17). There were no statistically significant differences in the bacterial species and drug susceptibility testing present in the SRP and NRP groups; however, multidrug-resistant bacteria appeared at a higher rate in the SRP group (59.09%).The incidence of inappropriate initial antibiotic use in the entire study population was 27.36%—this was evident by the value in the SRP group that was fourfold higher than that of the NRP group (p = 0.0004). The multivariate logistic regression analysis demonstrated that treatment with an inappropriate antibiotic, multilobar infiltration, and high CURB-65 score were independent risk factors for SRP (Table 4).

Prognosis and survey

The length of the ICU stay for the SRP group was twofold longer than that of the NRP group (62.27 ± 73.73 vs. 32.25 ± 23, p = 0.002). The 28-day and 60-day mortality rates in the SRP group were 17.74% and 25.81%, respectively. In addition, the 60-day mortality rate was significantly higher in the SRP group than the NRP group (25.81% vs. 6.82%, respectively; p = 0.012) (Fig. 2). The multivariate logistic regression analysis showed that SRP was an independent risk factor for 60-day mortality [odds ratio (OR) 5.687, 95% confidence interval (CI) 1.334—24.240].

Discussion

SRP exhibits a high incidence in critically ill patients and causes prolonged ICU stays and expensive medical costs. Our study showed that the presence of SRP is an independent risk factor for 60-day mortality in the ICU. It is unlikely that this definition could be used clinically to diagnose

Table 3 The microbiology results of all patients

No.	Group	Pathogen[a]	Culture site	Initial antibiotics	Inappropriate initial antibiotic use
1	SRP	*Acinetobacter baumannii*	Sputum	Imipenem/cilastatin sodium	N
2	SRP	*Acinetobacter baumannii* (MDR)	Tracheal aspirate	Cefoperazone/sulbactam, minocycline	N
3	SRP	MRSA	Sputum	Cefepime	Y
4	SRP	*Acinetobacter baumannii* (PDR)	Tracheal aspirate	Linezolid, ceftriaxone	Y
5	SRP	Negative	Tracheal aspirate	Piperacillin/tazobactam	N
6	SRP	*Staphylococcus epidermidis*	Tracheal aspirate	Imipenem/cilastatin sodium	Y
7	SRP	*Enterobacteria*	Tracheal aspirate	Imipenem/cilastatin sodium	N
8	SRP	*Klebsiella pneumoniae*	Sputum	Piperacillin/tazobactam	N
9	SRP	*Escherichia coli* (ESBL)	Sputum	Levofloxacin	Y
10	SRP	*Enterobacter cloacae*	Tracheal aspirate	Vancomycin	Y
11	SRP	*Flavobacterium indologenes*	Tracheal aspirate	Piperacillin/tazobactam	N
12	SRP	*Escherichia coli*	Tracheal aspirate	Imipenem/cilastatin sodium	N
13	SRP	MRSA	Sputum	Linezolid	N
14	SRP	MSSA	Tracheal aspirate	Cefoperazone/sulbactam	Y
15	SRP	MRSA	Tracheal aspirate	Moxifloxacin	Y
16	SRP	*Acinetobacter baumannii*	Sputum	Imipenem/cilastatin sodium	N
17	SRP	*Acinetobacter baumannii*	Tracheal aspirate	Imipenem/cilastatin sodium	N
18	SRP	*Staphylococcus capitis*	Tracheal aspirate	Imipenem/cilastatin sodium	Y
19	SRP	Negative	Sputum	Imipenem/cilastatin, fucidin	N
20	SRP	*Klebsiella pneumoniae*	Sputum	Imipenem/cilastatin sodium	N
21	SRP	*Acinetobacter baumannii*	Tracheal aspirate	Cefoperazone/sulbactam, minocycline	N
22	SRP	*Acinetobacter baumannii* (MDR)	Tracheal aspirate	Teicoplanin	Y
23	SRP	Negative	Tracheal aspirate	Piperacillin/tazobactam	N
24	SRP	MRSA	Tracheal aspirate	Piperacillin/tazobactam	Y
25	SRP	*Pseudomonas aeruginosa*	Tracheal aspirate	Meropenem	N
26	SRP	MRSA	Tracheal aspirate	Imipenem/cilastatin sodium	Y
27	SRP	Negative	Sputum	Imipenem/cilastatin sodium	N
28	SRP	*Klebsiella pneumoniae*	Tracheal aspirate	Imipenem/cilastatin sodium	N
29	SRP	*Acinetobacter baumannii*	Sputum	Levofloxacin	Y
30	SRP	*Acinetobacter baumannii* (MDR)	Tracheal aspirate	Clindamycinum	Y
31	SRP	MRSA	Tracheal aspirate	Vancomycin	N
32	SRP	*Pseudomonas aeruginosa* (MDR)	Tracheal aspirate	Cefepime	N
33	SRP	*Acinetobacter baumannii*	Sputum	Meropenem	N
34	SRP	*Acinetobacter baumannii*	Tracheal aspirate	Imipenem/cilastatin sodium	N
35	SRP	Negative	Tracheal aspirate	Imipenem/cilastatin sodium	N
36	SRP	*Acinetobacter baumannii*	Tracheal aspirate	Imipenem/cilastatin sodium	N
37	SRP	*Burkholderia cepacia*	Tracheal aspirate	Vancomycin	Y
38	SRP	*Acinetobacter baumannii* (PDR)	Tracheal aspirate	Meropenem, linezolid	Y
39	SRP	*Acinetobacter baumannii* (PDR)	Sputum	Imipenem/cilastatin sodium	N
40	SRP	*Enterococcus faecalis*	Sputum	Imipenem/cilastatin sodium	Y
41	SRP	*Klebsiella pneumoniae*	Tracheal aspirate	Imipenem/cilastatin sodium	N
42	SRP	Negative	Sputum	Imipenem/cilastatin sodium, teicoplanin	N
43	SRP	*Acinetobacter baumannii* (MDR)	Sputum	Azithromycin	Y
44	SRP	*Pseudomonas aeruginosa*	Sputum	Imipenem/cilastatin sodium	N
45	SRP	*Acinetobacter baumannii* (PDR)	Sputum	Azithromycin	Y
46	SRP	*Klebsiella pneumoniae*	Sputum	Imipenem/cilastatin sodium	N
47	SRP	*Acinetobacter baumannii* (PDR)	Sputum	Cefuroxime	Y
48	SRP	*Acinetobacter baumannii*	Sputum	Imipenem/cilastatin sodium	N
49	SRP	*Acinetobacter baumannii*	Tracheal aspirate	Levofloxacin	Y
50	SRP	*Acinetobacter baumannii*	Tracheal aspirate	Levofloxacin	Y
51	SRP	*Enterococcus faecium*	Sputum	Vancomycin	N
52	SRP	*Acinetobacter baumannii*	Sputum	Levofloxacin	Y
53	SRP	Negative	Tracheal aspirate	Imipenem/cilastatin sodium, vancomycin	N
54	SRP	MRSA	Sputum	Ceftazidime	Y
55	SRP	*Klebsiella pneumoniae* (ESBL)	Sputum	Cefoxitin	Y
56	SRP	*Klebsiella pneumoniae*	Sputum	Imipenem/cilastatin sodium	N

Table 3 (*continued*)

No.	Group	Pathogen[a]	Culture site	Initial antibiotics	Inappropriate initial antibiotic use
57	SRP	*Acinetobacter baumannii* (PDR)	Tracheal aspirate	Cefoxitin	Y
58	SRP	Negative	Sputum	Imipenem/cilastatin sodium, vancomycin	N
59	SRP	*Acinetobacter baumannii*	Sputum	Imipenem/cilastatin sodium	N
60	SRP	Negative	Sputum	Imipenem/cilastatin sodium	N
61	SRP	*Acinetobacter baumannii* (MDR)	Sputum	Moxifloxacin	Y
62	SRP	*Staphylococcus epidermidis*	Sputum	Vancomycin	N
1	NRP	*Acinetobacter baumannii*	Sputum	Ceftazidime	N
2	NRP	*Acinetobacter baumannii*	Tracheal aspirate	Imipenem/cilastatin sodium	N
3	NRP	*Pseudomonas aeruginosa*	Sputum	Imipenem/cilastatin sodium	N
4	NRP	*Acinetobacter junii*	Sputum	Piperacillin/tazobactam, minocycline	N
5	NRP	Negative	Sputum	Ceftazidime	N
6	NRP	*Klebsiella pneumoniae*	Sputum	Meropenem	N
7	NRP	*MRSA*	Sputum	Vancomycin	N
8	NRP	*Staphylococcus epidermidis*	Sputum	Vancomycin	N
9	NRP	*Acinetobacter baumannii* (MDR)	Sputum	Cefoperazone/sulbactam, minocycline	N
10	NRP	Negative	Tracheal aspirate	Piperacillin/tazobactam	N
11	NRP	MRSA	Tracheal aspirate	Vancomycin	N
12	NRP	Negative	Sputum	Piperacillin/tazobactam	N
13	NRP	Negative	Tracheal aspirate	Meropenem, teicoplanin	N
14	NRP	*Enterococcus faecium*	Tracheal aspirate	Vancomycin	N
15	NRP	Negative	Sputum	Piperacillin/tazobactam	N
16	NRP	*Acinetobacter baumannii*	Tracheal aspirate	Cefoperazone/sulbactam	N
17	NRP	MRSA	Tracheal aspirate	Vancomycin	N
18	NRP	*Acinetobacter baumannii* (MDR)	Sputum	Levofloxacin	Y
19	NRP	*Acinetobacter baumannii*	Sputum	Ceftazidime	N
20	NRP	Negative	Tracheal aspirate	Imipenem/cilastatin sodium	N
21	NRP	*Acinetobacter baumannii*	Tracheal aspirate	Imipenem/cilastatin sodium	N
22	NRP	*Pseudomonas aeruginosa*	Sputum	Ceftazidime	N
23	NRP	*Acinetobacter baumannii*	Sputum	Cefoperazone/sulbactam, minocycline	N
24	NRP	*Pseudomonas aeruginosa*	Tracheal aspirate	Cefoperazone/sulbactam	N
25	NRP	*Enterobacter aerogenes*	Sputum	Cefoxitin	N
26	NRP	*Acinetobacter baumannii*	Tracheal aspirate	Cefoperazone/sulbactam	N
27	NRP	*Staphylococcus aureus*	Sputum	Vancomycin	N
28	NRP	*Klebsiella pneumoniae*	Sputum	Clindamycin	Y
29	NRP	Negative	Tracheal aspirate	Maxipime	N
30	NRP	*Acinetobacter junii*	Sputum	Piperacillin/tazobactam	N
31	NRP	Negative	Sputum	Meropenem, teicoplanin	N
32	NRP	*Acinetobacter baumannii* (PDR)	Tracheal aspirate	Imipenem/cilastatin sodium	N
33	NRP	Negative	Sputum	Piperacillin/tazobactam	N
34	NRP	*Acinetobacter baumannii* (PDR)	Tracheal aspirate	Vancomycin	Y
35	NRP	*Burkholderia cepacia*	Tracheal aspirate	Cefoperazone	N
36	NRP	*Klebsiella pneumoniae* (ESBL)	Tracheal aspirate	Meropenem	N
37	NRP	*Klebsiella pneumoniae*	Sputum	Ceftazidime	N
38	NRP	*Enterococcus faecalis*	Sputum	Vancomycin	N
39	NRP	Negative	Sputum	Ceftazidime	N
40	NRP	*Burkholderia cepacia*	Sputum	Ceftazidime	N
41	NRP	*Klebsiella pneumoniae*	Tracheal aspirate	Ceftazidime	N
42	NRP	Negative	Sputum	Moxifloxacin	N
43	NRP	*Staphylococcus epidermidis*	Sputum	Teicoplanin	N
44	NRP	*Enterobacter cloacae*	Sputum	Ceftazidime	N

[a] Pathogens were yielded from a sputum sample or endotracheal aspiration. A second appropriate antibiotic was used in individual patients according to their microorganism results.

ESBL = extended-spectrum β-lactamases; MDR = multiple drug resistance; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*; N = no; NRP = normally resolving pneumonia; PDR = pandrug-resistant; SRP = slowly resolving pneumonia; Y = yes.

Table 4 Independent risk factors for slowly resolving pneumonia (SRP)

Risk factor	*p*	OR	95% CI	
Inappropriate initial antibiotic therapy	0.0024	8.338	2.117	32.848
Multilobar infiltration	0.0015	11.184	2.526	49.514
CURB-65 score	0.0158	2.329	1.172	4.626
Delayed clinical stability	0.3131	1.775	0.582	5.414

CI = confidence interval; OR = odds ratio.

patients with SRP at an early time point. Therefore, further investigation is required to identify the risk factors for SRP for early identification. From a list of possible factors including host-related factors, pulmonary radiographic features, microorganism characteristics, and treatment-related factors,[8,11,20,21] our study suggested that the extent of pulmonary infiltration, pneumonia severity, and initial antibiotic therapy have important effects on the resolution of pneumonia in critically ill patients.

We found that 90.9% of single-lobe pneumonia cases completely resolve in 4 weeks, while 56% of multilobar pneumonia cases require 5—8 weeks to completely resolve as demonstrated in a *Pneumococcus* pneumonia study.[22] However, several previous studies in heterogeneous

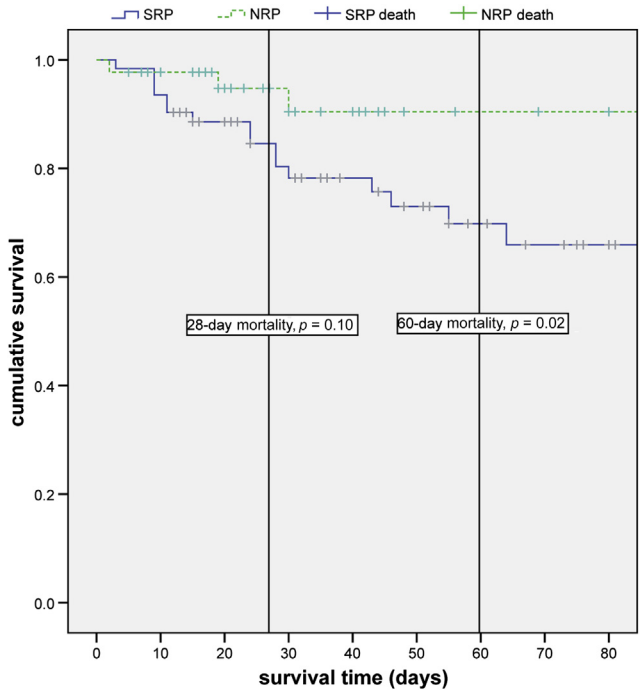

Figure 2. The survival functions of the two groups. The 28-day mortality rate was higher in the slowly resolving pneumonia (SRP) group than the normally resolving pneumonia (NRP) group, but this difference was not statistically significant ($p = 0.10$). By contrast, the 60-day mortality rate was significantly higher in the SRP group than the NRP group ($p = 0.02$). The gap between the two lines illustrates the relationship between the length of the intensive care unit (ICU) stay and the mortality rate in the two groups.

populations have suggested that the extent of pulmonary infiltration has an impact on pneumonia resolution.[22,23] In critically ill patients, our study showed that the incidence of multilobar infiltration is much higher in the SRP group than the NRP group and is an independent risk factor for SRP. Therefore, we recommend that pneumonia cases in the ICU receive an immediate radiographic evaluation to determine the extent of infiltration and assess the possibility of SRP.

Both the extent of pulmonary infiltration and pneumonia severity had an impact on SRP. Several disease severity indicators are used in the ICU, including CURB-65 scores,[24] APACHE II scores, and biomarkers such as PCT and CRP. Current studies suggest that advanced age, a fast respiratory rate, low blood pressure, and underlying diseases are risk factors for SRP.[21] The CURB-65 score is a synthetic index that includes age, confusion, uremia, respiratory rate, and blood pressure. Our study showed that the CURB-65 score instead of the APACHE II score was not only positively correlated with pneumonia resolution time but also an independent risk factor for SRP.

Some studies suggested that PCT and CRP levels could indicate pneumonia severity.[25,26] One study showed that a high CRP level was independently associated with the delayed resolution of radiographic abnormalities,[12] while Huang et al[26] showed that the PCT level provided little additional information over the CURB-65 score. Our results reflected no differences in the CRP levels of the SRP and NRP groups, whereas the PCT level was higher in the SRP group. However, our study further suggested that the CURB-65 score alone was an independent risk factor for SRP as a pneumonia severity indicator.

SRP was associated with both host-related factors and treatment-related factors. Treatment with an appropriate antibiotic plays an important role in pneumonia resolution.[19,27] A few reports have shown that the incidence of inappropriate antibiotic therapy was high in pneumonia patients, especially in ventilator-associated pneumonia patients (50%) in the ICU.[28] We found the incidence of inappropriate initial antibiotic use in the entire study population to be 27.36%, as shown by the fact that the value in the SRP group was fourfold higher than that of the NRP group ($p = 0.0004$). Initial treatment with an inappropriate antibiotic was independently associated with SRP, with the OR value for this variable adjusted to 8.338 by multivariate logistic regression analysis (Table 3).

Treatment with an inappropriate antibiotic is very important because it is the only SRP risk factor that can be modified to reduce SRP and improve patient outcomes.[29] The initial selection of an antimicrobial regimen for pneumonia must be guided by consideration of the local microbial ecology and the type of pneumonia to ensure effective antibiotic therapy.[30] There were no differences in the bacterial species and drug susceptibility testing present in the SRP and NRP groups; however, multiple drug resistance (MDR) bacteria appeared at a higher rate in the SRP group (59.09%). Some studies have suggested that both the bacterial species and possible drug resistance should be taken into account when choosing the antibiotic therapy for patients who are likely to be infected with MDR pathogens (including methicillin-resistant *Staphylococcus aureus*, MRSA).[31,32] It is better to identify the bacterial distribution

and drug resistance in the ICU before choosing the proper initial antibiotic therapy.

Different studies debate the use of steroids in pneumonia. Some studies found that corticosteroids exhibit anti-inflammatory effects in severe pneumonia and enable the rapid resolution of pneumonia.[33,34] Other studies suggested that steroids have adverse effects such as infection and neuromuscular disease, which could delay pneumonia resolution and increase mortality despite the use of an appropriate antibiotic.[35] In our study, in some patients the pneumonia induced acute respiratory distress syndrome, which required the administration of steroids to improve oxygenation. Our study suggested that the administration of high-dose steroids was related to SRP [relative risk (RR) 1.8462, 95% CI 1.5359—2.2191, $p = 0.0053$]. However, further investigation showed that the administration of high-dose steroids was not an independent risk factor for SRP, possibly because the sample size receiving high-dose steroids was too small for a valid statistical analysis.

Our study has some limitations. First, this was a single-center and retrospective study. A further prospective randomized comparative study is warranted to prove that the identification of high-risk patients can improve their treatment outcomes. Because this was a retrospective study, we had to analyze past information instead of adding more tests to identify the pathogen. Second, some of the trends observed might have reached statistical significance if the study sample size had been larger. Third, the average age of our population was 70.56 $\pm$ 12.60 years, preventing our results from properly reflecting the impact of age on SRP.

In conclusion, SRP in critically ill patients should receive more attention because of its high incidence, prolonged ICU stays, and poor outcome. Treatment with an inappropriate antibiotic, multilobar infiltration and a high CURB-65 score were independent risk factors for SRP. The use of appropriate antibiotics in high-risk patients should be taken into account to reduce the prevalence of SRP in the ICU.

Conflicts of interest

All authors declare that they have no financial or other potential conflicts of interest and have never submitted the manuscript, in whole or in part, to another journal.

Acknowledgments

We wish to thank Baisong Wang at Shanghai Jiaotong University for help with the statistical analysis.

References

1. Kyprianou A, Hall CS, Shah R, Fein AM. The challenge of non-resolving pneumonia. Knowing the norms of radiographic resolution is key. *Postgrad Med* 2003;**113**:79—82. 85—8, 91—2.
2. Low DE, Mazzulli T, Marrie T. Progressive and nonresolving pneumonia. *Curr Opin Pulm Med* 2005;**11**:247—52.
3. Polverosi R, Zanellato E, Zanlungo P. Slow-resolution pneumonia: radiologic and tomodensitometric features. *Radiol Med* 1997;**93**:520—6.
4. Cunha BA. Slowly resolving and nonresolving pneumonias. *Drugs Today (Barc)* 2000;**36**:829—34.
5. Corley DE, Winterbauer RH. Infectious diseases that result in slowly resolving and chronic pneumonia. *Semin Respir Infect* 1993;**8**:3—13.
6. Luna CM, Niederman MS. What is the natural history of resolution of nosocomial pneumonia? *Semin Respir Crit Care Med* 2002;**23**:471—9.
7. Menendez R, Perpina M, Torres A. Evaluation of nonresolving and progressive pneumonia. *Semin Respir Infect* 2003;**18**:103—11.
8. Weyers CM, Leeper KV. Nonresolving pneumonia. *Clin Chest Med* 2005;**26**:143—58.
9. Kirtland SH, Winterbauer RH. Slowly resolving, chronic, and recurrent pneumonia. *Clin Chest Med* 1991;**12**:303—18.
10. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007;**44**(Suppl. 2):S27—72.
11. Kuru T, Lynch 3rd JP. Nonresolving or slowly resolving pneumonia. *Clin Chest Med* 1999;**20**:623—51.
12. Bruns AH, Oosterheert JJ, Prokop M, Lammers JW, Hak E, Hoepelman AI. Patterns of resolution of chest radiograph abnormalities in adults hospitalized with severe community-acquired pneumonia. *Clin Infect Dis* 2007;**45**:983—91.
13. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis* 2008;**46**:1813—21.
14. Harbarth S, Ferriere K, Hugonnet S, Ricou B, Suter P, Pittet D. Epidemiology and prognostic determinants of bloodstream infections in surgical intensive care. *Arch Surg* 2002;**137**:1353—9.
15. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006;**34**:1589—96.
16. Kumar A, Ellis P, Arabi Y, Roberts D, Light B, Parrillo JE, et al., Cooperative Antimicrobial Therapy of Septic Shock Database Research Group. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. *Chest* 2009;**136**:1237—48.
17. Tang BM, Craig JC, Eslick GD, Seppelt I, McLean AS. Use of corticosteroids in acute lung injury and acute respiratory distress syndrome: a systematic review and meta-analysis. *Crit Care Med* 2009;**37**:1594—603.
18. Lamontagne F, Briel M, Guyatt GH, Cook DJ, Bhatnagar N, Meade M. Corticosteroid therapy for acute lung injury, acute respiratory distress syndrome, and severe pneumonia: a meta-analysis of randomized controlled trials. *J Crit Care* 2010;**25**:420—35.
19. Niederman MS. Bronchoscopy in nonresolving nosocomial pneumonia. *Chest* 2000;**117**:212S—8S.
20. Cassiere H, Rodrigues JC, Fein AM. Delayed resolution of pneumonia. When is slow healing too slow? *Postgrad Med* 1996;**99**:151—4. 157—8.
21. Rome L, Murali G, Lippmann M. Nonresolving pneumonia and mimics of pneumonia. *Med Clin North Am* 2001;**85**:1511—30.
22. Van Metre Jr TE. Pneumococcal pneumonia treated with antibiotics: the prognostic significance of certain clinical findings. *N Engl J Med* 1954;**251**:1048—52.
23. Celis R, Torres A, Gatell JM, Almela M, Rodríguez-Roisin R, Agustí-Vidal A. Nosocomial pneumonia. A multivariate analysis of risk and prognosis. *Chest* 1988;**93**:318—24.

24. Myint PK, Sankaran P, Musonda P, Subramanian DN, Ruffell H, Smith AC, et al. Performance of CURB-65 and CURB-age in community-acquired pneumonia. *Int J Clin Pract* 2009;**63**:1345—50.
25. Povoa P, Coelho L, Almeida E, Fernandes A, Mealha R, Moreira P, et al. C-Reactive protein as a marker of infection in critically ill patients. *Clin Microbiol Infect* 2005;**11**:101—8.
26. Huang DT, Weissfeld LA, Kellum JA, Yealy DM, Kong L, Martino M, et al. Risk prediction with procalcitonin and clinical rules in community-acquired pneumonia. *Ann Emerg Med* 2008;**52**:48—58.
27. Scaglione F, Esposito S, Leone S, Lucini V, Pannacci M, Ma L, et al. Feedback dose alteration significantly affects probability of pathogen eradication in nosocomial pneumonia. *Eur Respir J* 2009;**34**:394—400.
28. Dupont H, Mentec H, Sollet JP, Bleichner G. Impact of appropriateness of initial antibiotic therapy on the outcome of ventilator-associated pneumonia. *Intensive Care Med* 2001;**27**:355—62.
29. Houck PM, Bratzler DW, Nsa W, Ma A, Bartlett JG. Timing of antibiotic administration and outcomes for Medicare patients hospitalized with community-acquired pneumonia. *Arch Intern Med* 2004;**164**:637—44.
30. Leone S, Fiore M, Felaco FM, Esposito S. Early and timely therapy: when to interrupt antibiotic therapy in nosocomial acquired pneumonia? *Infez Med* 2007;**15**:16—23.
31. Combes A, Luyt CE, Trouillet JL. Impact of antibiotic-resistant bacteria on the outcome of ventilator-associated pneumonia. *Semin Respir Crit Care Med* 2006;**27**:23—8.
32. Restrepo MI, Peterson J, Fernandez JF, Qin Z, Fisher AC, Nicholson SC. Comparison of the bacterial etiology of early-onset and late-onset ventilator-associated pneumonia in subjects enrolled in 2 large clinical studies. *Respir Care* 2013;**58**:1220—5.
33. Monton C, Ewig S, Torres A, El-Ebiary M, Filella X, Rañó A, et al. Role of glucocorticoids on inflammatory response in non-immunosuppressed patients with pneumonia: a pilot study. *Eur Respir J* 1999;**14**:218—20.
34. Confalonieri M, Urbino R, Potena A, Piattella M, Parigi P, Puccio G, et al. Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. *Am J Respir Crit Care Med* 2005;**171**:242—8.
35. Rodrigues J, Niederman MS, Fein AM, Pai PB. Nonresolving pneumonia in steroid-treated patients with obstructive lung disease. *Am J Med* 1992;**93**:29—34.