J Infect Chemother 25 (2019) 714–719

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Original Article

Impact of additional antibiotics on in-hospital mortality in tuberculosis isolated general bacteria: A propensity score analysis☆

Takamasa Kan [a, b, 1], Kosaku Komiya [a, b, *, 1], Kokoro Honjo [a, b, 1], Sonoe Uchida [a, b, 1], Akihiko Goto [a, b, 1], Hiroshi Kawano [a], Shuichi Takikawa [a], Tetsuyuki Yoshimatsu [a], Jun-ichi Kadota [b, 1]

[a] *Internal Medicine, National Hospital Organization Nishi-Beppu Hospital, 4548 Tsurumi, Beppu, Oita, 874-0840, Japan*
[b] *Respiratory Medicine and Infectious Diseases, Oita University Faculty of Medicine, 1-1 Idaigaoka, Hasama-machi, Yufu, Oita, 879-5593, Japan*

ARTICLE INFO

Article history:
Received 11 January 2019
Received in revised form
2 March 2019
Accepted 22 March 2019
Available online 11 April 2019

Keywords:
Antibiotics
Propensity score analysis
Pneumonia
Co-infection

ABSTRACT

Whether or not additional antibiotics with anti-tuberculosis agents are required to treat bacterial co-infection with pulmonary tuberculosis is unclear. We aimed to assess the impact of additional antibiotics on mortality in pulmonary tuberculosis patients whose sputum cultures were positive for general bacteria as a surrogate definition of bacterial pneumonia. This study was a single-center retrospective cohort using a propensity score analysis. We included patients who were admitted for pulmonary tuberculosis and whose sputum cultures were positive for general bacteria. The mortality of patients who received additional antibiotics was analyzed after adjusting for other variables, including the propensity score predicting treatment with additional antibiotics. We assessed 68 and 55 tuberculosis patients treated with and without general antibiotics, respectively. Additional antibiotics tended to be administered to patients with a high level of C-reactive protein and neutrophil count, poor performance status, hypoxemia and hypoalbuminemia (C-statistics of area under receiver operating characteristic curve to the propensity score; 0.884, $p < 0.001$). In the multivariate analysis, advanced age and not the use of additional antibiotics was associated with in-hospital mortality. Additional antibiotics with anti-tuberculosis agents may not improve the prognosis of pulmonary tuberculosis patients whose sputum cultures were positive for general bacteria. Isolation of general bacteria does not equate to complication with bacterial pneumonia, so physicians should not administer general antibiotics to TB patients based solely on the results of sputum culture for general bacteria. A prospective study is needed to verify these results using a more accurate definition of pulmonary tuberculosis complicated with bacterial pneumonia.

1. Introduction

While the overall prevalence of tuberculosis (TB) is significantly declining worldwide, its prevalence among older individuals remains high, even in high-income countries [1–3]. TB infection occurs in an estimated 30% of cases of close contact with people with active disease, and active primary TB develops in 5%–10% of those infected within 2 years [4,5]. However, over the course of an infected person's life, the risk that the dormant bacilli will progress to reactivation TB is around 5%. The main mechanism of TB development in elderly patients is thought to be endogenous reactivation of latent TB.

In most high- or middle-income countries, the proportion of the elderly population is gradually increasing [6]. These individuals are prone to pneumonia due to a poor immune system response and decreased swallowing function [7]. TB patients, especially those among older populations, have a risk of co-

Abbreviations: ATS, American Thoracic Society; CIs, confidence intervals; CRP, C-reactive protein; Hb, hemoglobin; IDSA, Infectious Diseases Society of America; MRSA, methicillin-resistant *Staphylococcus aureus*; PS, performance status; ROAG, revised oral assessment guide; TB, tuberculosis; TP, total protein.

☆ All authors meet the ICMJE authorship criteria.

* Corresponding author. Respiratory Medicine and Infectious Diseases, Oita University Faculty of Medicine, 1-1 Idaigaoka, Hasama-machi, Yufu, Oita, 879-5593, Japan.

E-mail address: komiyakh1@oita-u.ac.jp (K. Komiya).

[1] Members of the Oita prefectural tuberculosis control project 2017–2020.

https://doi.org/10.1016/j.jiac.2019.03.022
1341-321X/

infection with general bacteria, and it may worsen their prognosis. Indeed, it was reported that 29.7% of elderly TB patients have bacterial respiratory infections [8]. Another study showed that 21 of 701 patients with healthcare-associated pneumonia had co-existing lung TB [9].

When TB patients have a severe respiratory condition or show markedly elevated biomarkers of inflammation, the administration of glucocorticoids or additional general antibiotics along with anti-tuberculosis medications is considered. While the effect of glucocorticoids in critically ill patients with lung TB has been discussed [10], the impact of additional general antibiotics has not been assessed. Some physicians advocate that anti-tuberculosis agents manage not only TB but also general bacteria, so additional antibiotics are unnecessary, even when patients are suspected of being complicated with general pneumonia. However, there is no evidence regarding whether or not additional general antibiotics are effective in these patients. Because it is challenging to determine whether or not a TB patient is complicated with general pneumonia, this study included TB patients with positive sputum cultures for general bacteria as a surrogate definition of bacterial pneumonia.

The aim of this study was to assess the impact of additional antibiotics on in-hospital mortality in patients with pulmonary TB whose sputum cultures are positive for general bacteria.

2. Patients and methods

2.1. Patients

This was a retrospective cohort study using a propensity score analysis conducted at National Hospital Organization Nishi-Beppu Hospital, the only hospital with the capacity to accept patients with smear-positive lung TB in Oita Prefecture, Japan. The number of samples was calculated using G*Power (2 trials, α error = 0.05, power = 0.8 and effect size = 0.5), and a total sample number of 128 patients including patients with additional antibiotics and patients without (1:1) was deemed necessary.

This study included patients who were admitted to the hospital for smear-positive pulmonary TB from January 2013 to December 2015 and whose sputum cultures were positive for general bacteria as a surrogate definition of general pneumonia. Patients found to have normal flora or *Candida species* only were excluded from this study. The study protocol was approved by the Institutional Ethics Committee (Approval Number 30-1; Approval Date 31 May 2018). Informed consent was waived by the Committee because of the retrospective design.

2.2. Definition of exposure and outcomes

Physicians decide whether or not additional general antibiotics are required for isolated general bacteria in patients with lung TB based on the patients' condition, such as their oxygenation status or laboratory findings, because it is quite difficult even for experts to judge whether these patients are complicated with bacterial pneumonia or simply have bacterial colonization. Therefore, we used propensity score based on the data of patients' background characteristics to reduce selection bias with respect to the decision to add general antibiotics.

We divided TB patients with isolated general bacteria in sputum culture into two groups: those who were administrated additional antibiotics with anti-TB agents within two weeks after admission and those who were treated with anti-TB agents only. Fluoroquinolones used to treat TB were regarded as additional antibiotics for general pneumonia because these agents are

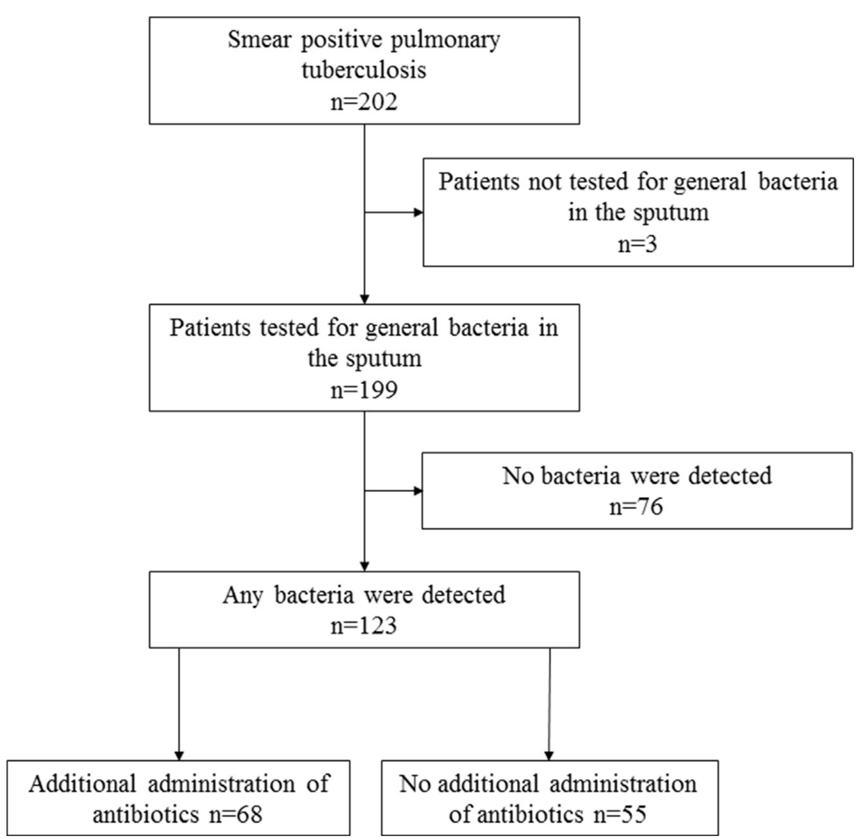

Fig. 1. A flow chart of the participants evaluated over the course of the study and the number of patients in each group.

recommended for the treatment of general pneumonia in the American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) guidelines for pneumonia [11]. We analyzed the impact of the additional antibiotics on in-hospital mortality as the main outcome and the length of the hospital stay as the secondary outcome. Patients' background characteristics, laboratory data and findings of chest X-ray were collected from medical records. Standard anti-TB treatment was defined as a regimen of rifampicin, isoniazid and ethambutol with or without pyrazinamide.

2.3. Statistical analyses

The statistical analyses were performed using the IBM SPSS statistics ver. 24 software package (IBM SPSS, Tokyo, Japan). The confidence intervals (CIs) in the 2-sided analyses were 95%. Statistical significance was defined as a p value < 0.05 for all of the analyses. Continuous variables were compared using the *t*-test or Mann-Whitney test, and the chi-squared test was applied to compare categorical variables. Propensity scores were used to reduce selection bias with respect to the decision to add general antibiotics to anti-tuberculosis medications and were estimated based on the performance status (PS) defined by the Eastern Cooperative Oncology Group, respiratory failure (SpO_2<90%), neutrophil count, concentration of hemoglobin (Hb), albumin, C-reactive protein (CRP), steroids use and standard anti-tuberculosis treatment. A Cox proportion hazards model was used for the patients treated with additional antibiotics after adjusting for other variables, including the propensity score, using the stepwise method.

3. Results

3.1. Patient characteristics

Two hundred and two patients with smear-positive TB were admitted to the hospital. Among them, 199 (98%) underwent general sputum examinations, and 123 were found to have general bacteria aside from their normal flora and *Candida species* in sputum culture, as shown in Fig. 1 and Table 1. Significantly more patients were positive for any general bacteria in the sputum than were negative for such findings.

We assessed 68 and 55 TB patients treated with and without general antibiotics, respectively. Hypoxemia; anemia; steroids use; a poor PS; revised oral assessment guide (ROAG) score [12]; elevation of the WBC count and/or neutrophil count, CRP, BUN and Gaffky number; and decreased levels of total protein (TP) and albumin were seen more frequently in patients administered additional antibiotics for treatment toward general bacteria than in those without additional antibiotics (Table 2). The mortality in the group with additional antibiotics was significantly higher than that in the group without additional antibiotics. The proportion of resistant TB and the length of the hospital stay showed no significant differences between the two groups. The propensity score for predicting treatment with additional antibiotics was calculated with the presence of hypoxemia, anemia, PS, CRP, standard anti-TB treatment, neutrophil count, steroids use and albumin and had a good C-statistic of the area under the receiver operating characteristic curve (0.884, 95% CI: 0.824–0.944, p < 0.001).

3.2. Sputum examination and additional antibiotics

A wide range of bacteria was identified from the sputum cultures of the 123 patients (Table 2). *Staphylococcus aureus*, including 36 cases of methicillin-resistant *Staphylococcus aureus* (MRSA), was most commonly detected in this study. Levofloxacin was most frequently used for treatment of general bacteria in 35 patients, followed by ceftazidime in 13, meropenem and ciprofloxacin in 8, cefozopran in 7, cefotiam in 6 and biapenem in 4. Antibiotics covering MRSA and *Pseudomonas aeruginosa* were used in 5 (7%) and 43 (63%) of the 68 cases, respectively.

Table 1
Baseline characteristics of patients who were positive or negative for any general bacteria in sputum.

	Positive (n = 123)	Negative (n = 76)	*P*-value
Gender (female)	58 (47)	40 (52)	0.453
Age (years)	82.0 (77.0–88.5)	79.0 (64.5–84.0)	<0.001
BMI (kg/m^2)	18.3 (16.3–20.4)	19.9 (17.9–21.5)	0.001
PS	3 (2–4)	2 (1–3)	<0.001
ROAG score	10 (8.0–14.0)	8 (8.0–9.0)	<0.001
WBC (10^3/μl)	6.6 (5.1–9.0)	6.8 (5.1–8.5)	0.868
Neutrophil count (10^3/μl)	5.0 (3.6–7.8)	5.1 (3.6–6.6)	0.344
Hb (g/dl)	11.0 (9.9–12.1)	12.3 (10.8–13.4)	0.002
CRP (mg/dl)	5.2 (1.2–10.2)	1.61 (0.49–3.76)	<0.001
TP (g/dl)	6.2 (5.6–6.8)	6.9 (6.3–7.4)	0.003
Alb (g/dl)	2.5 (2.1–3.2)	3.2 (2.6–3.6)	<0.001
AST (IU)	28 (22–41)	21 (17–28)	0.014
BUN (mg/dl)	16.7 (13.8–25.0)	15.2 (11.3–19.6)	0.069
Cre (mg/dl)	0.71 (0.50–0.91)	0.75 (0.59–0.87)	0.504
COPD	8 (6)	4 (5)	0.721
Cardiac diseases	21 (17)	9 (11)	0.305
Cerebrovascular diseases	22 (17)	10 (13)	0.378
DM	21 (17)	16 (21)	0.483
Respiratory failure	46 (37)	9 (13)	<0.001
In-hospital death	35 (28)	7 (9)	0.001
Tuberculosis related death	15 (13)	3 (2)	0.049
Standard anti-tuberculosis	76 (62)	54 (71)	0.182
Additional antibiotics	68 (55)	15 (19)	<0.001
Steroid use	35 (28)	7 (9)	<0.001
Gaffky number	2 (1–4)	2 (1–3)	0.149
Resistant tuberculosis	8 (6)	9 (11)	0.191
Duration of hospital stay	103 (62–151)	90 (54.5–132)	0.035
Cavitation on chest X-ray	60 (49)	39 (51)	0.728

Data are presented as the number (%) or median (interquartile range).
Alb: albumin, ALT: alanine transaminase, AST: aspartate transaminase, BMI: body mass index, BUN: blood urea nitrogen, COPD: chronic obstructive pulmonary disease, Cre: creatinine, CRP: C-reactive protein, DM: diabetes mellitus, Hb: hemoglobin, PS: performance status, ROAG: revised oral assessment guide, TP: total protein.

3.3. Impact of additional antibiotics on in-hospital mortality and length of hospital stay

Thirty-five patients (28%) died during their hospital stay, as shown in Table 3. Thirty-one of the 35 patients (89%) died from TB-related causes according to death certificate. Other causes of death were cardiac and hepatic failure in one patient each and cerebral infarction in one patient. Twenty-nine of the 35 dead patients (82%) were treated with additional antibiotics along with anti-TB agents. While the rate of cases treated with additional antibiotics in the dead group was significantly greater than that in the surviving group, no significance was seen in the multivariate analysis after adjusting for the propensity score and other variables. The model demonstrated that only age was significantly associated with in-hospital mortality.

The administration of additional antibiotics was not associated with the duration of the hospital stay (HR = 0.929, 95% CI: 0.372–2.318, p = 0.874). Furthermore, there were no marked difference in the in-hospital mortality between patients who were administered fluoroquinolone only and those who were treated with other additional antibiotics (9/20 [45%] vs. 20/48 [41%], p = 0.401).

Table 2
Characteristics of patients treated with or without additional antibiotics.

	With additional antibiotics (n = 68)	Without additional antibiotics (n = 55)	*P*-value
Gender (female)	31 (45)	27 (47)	0.832
Age (years)	81.5 (74.7–88.0)	85.0 (79.0–90.0)	0.363
BMI (kg/m^2)	18.6 (16.1–20.5)	17.6 (16.6–19.0)	0.155
PS	3 (3,4)	3 (1.5–3)	<0.001
ROAG score	13 (9–16)	8 (8–10)	<0.001
WBC (10^3/μl)	7.1 (5.2–10.1)	6.2 (4.6–8.0)	0.009
Neutrophil count (10^3/μl)	6.0 (4.1–9.4)	4.2 (3.2–5.8)	<0.001
Hb (g/dl)	10.2 (9.6–11.6)	11.9 (10.3–12.6)	0.002
CRP (mg/dl)	7.75 (2.56–12.2)	2.61 (1.08–6.18)	<0.001
Alb (g/dl)	2.3 (1.9–2.9)	3.0 (2.4–3.4)	<0.001
AST (IU)	32 (23–58)	26 (22–38)	0.056
BUN (mg/dl)	20.1 (14.3–30.3)	15.7 (12.8–22.7)	0.023
Cre (mg/dl)	0.65 (0.44–0.96)	0.78 (0.59–0.91)	0.474
COPD	6 (9)	2 (3)	0.220
Cardiac diseases	14 (21)	7 (13)	0.220
Cerebrovascular diseases	10 (15)	12 (21)	0.369
DM	11 (16)	10 (18)	0.687
Respiratory failure	39 (57)	7 (13)	<0.001
In-hospital death	29 (43)	6 (11)	<0.001
Steroid use	30 (44)	5 (9)	<0.001
Gaffky number	3 (1–5)	1 (1–4)	0.032
Resistant tuberculosis	5 (7)	3 (5)	0.849
Duration of hospital stay	139 (104–176)	100 (70.5–145)	0.477
Cavitation on chest X-ray	38 (55)	22 (40)	0.080
MRSA	29 (42)	7 (12)	<0.001
MSSA	7 (10)	6 (10)	0.912
P. aeruginosa	9 (13)	3 (5)	0.148
S. haemolyticus	7 (10)	9 (16)	0.320
S. epidermidis	1 (1)	7 (12)	0.012
K. pneumoniae	8 (11)	10 (18)	0.317
S. maltophilia	6 (8)	1 (1)	0.095
E. cloacae	5 (7)	7 (12)	0.318

Data are presented as the number (%) or median (interquartile range).
Alb: albumin, ALT: alanine transaminase, AST: aspartate transaminase, BMI: body mass index, BUN: blood urea nitrogen, COPD: chronic obstructive pulmonary disease, Cre: creatinine, CRP: C-reactive protein, DM: diabetes mellitus, Hb: hemoglobin, MRSA: Methicillin-resistant *Staphylococcus aureus*, MSSA: Methicillin-susceptible *Staphylococcus aureus*, PS: performance status, ROAG: revised oral assessment guide, TP: total protein.

4. Discussion

This study demonstrated that the administration of additional antibiotics was not associated with in-hospital mortality and the duration of the hospital stay in TB patients whose sputum cultures were positive for general bacteria.

Several reasons why the addition of general antibiotics did not improve the prognosis in these TB patients can be considered. First, the additional antimicrobial agent might not have covered the causative bacteria. Levofloxacin or cephem antibiotics were frequently used as additional antibacterial drugs, but these antibiotics do not cover MRSA, which was most frequently isolated in this study. About half of MRSA bacteria isolated from sputum in patients with pneumonia were thought to be evidence of colonization [13]. However, only 5 of 39 patients found to have MRSA were given anti-MRSA drugs so it is still uncertain whether these isolations were an infection or colonization. The detection accuracy for the causative bacteria is related to the quality of the collected sputum [14]. Therefore, the quality of the sputum may not have been sufficient to evaluate the causal pathogens in our study accurately.

Second, the delayed timing of antibiotics administration may underlie the lack of an effect on the prognosis. Starting treatment with antibiotics within 1 h after the diagnosis of sepsis significantly reduces the mortality rate [15], and in cases of community-acquired pneumonia, the mortality rate was reportedly decreased by administering antibiotics within 4 h after hospital arrival [16]. Even in TB patients, if complication with general pneumonia is suspected, it may be desirable to administer appropriate antibiotics as early as possible. In the present study, we were unable to analyze the interval from the onset to the start of treatment for pneumonia because some patients had already been started on antibiotics treatment for general pneumonia by their primary physicians before they were referred to respiratory physicians for the treatment of lung TB.

Third, the patients' severely ill condition might have attenuated the effect of additional antibiotics, even if the agents covered the causal pathogens. The administration of antimicrobial drugs to critically ill patients, even agents that address the causative bacteria, may not improve the prognosis of pneumonia [17,18]. This fact indicates that host factors greatly influence the prognosis, especially in elderly patients. Indeed, when the mortality rate was adjusted for the propensity score for deciding on the administration of additional antibiotics in our study, age was the only significant poor prognosis factor. In recent years, it has been shown that the risk of aspiration has a great influence as a host factor on the prognosis of pneumonia [18–20]. Elderly patients constituted a substantial portion of our study sample. Although we were unable to assess the swallowing function rigorously due to the retrospective design of our study, the existence of swallowing dysfunction may have also attenuated the clinical effectiveness of antimicrobial drugs.

Finally, the anti-TB agent rifampicin has antibacterial activities not only to *Mycobacterium tuberculosis* but also to other bacterial species, such as meningococcus, legionella and chlamydia [21]. Furthermore, rifampicin has been proposed for the treatment of MRSA infections in combination with other anti-MRSA drugs in the United States [22]. In the UK, rifampicin is indicated for the treatment of Legionella, severe staphylococcal infection, meningitis caused by *Neisseria meningitidis*, *Haemophilus influenzae*, etc. Streptomycin has also been confirmed to have activities against staphylococci, pneumococci, meningococcus and streptococci [23]. These anti-tuberculosis agents can be effective against general pneumonia complicated with lung TB and might have attenuated the effect of additional antibiotics in TB patients complicated by bacterial pneumonia.

No study has yet investigated the impact of additional general antibiotics in TB patients complicated with pneumonia. We examined the role of antibiotics administered in addition to anti-TB agents in TB patients whose sputum was positive for general bacteria using the propensity score to reduce the selection bias incurred when physicians decided to administer general antibiotics. The results suggested that additional antibiotics had no marked effect of improving the prognosis of patients complicated with general pneumonia. If this is true, physicians need not consider administering additional antibiotics to these TB patients. This may help reduce the costs and side effects associated with administering extra antibiotics. However, even after adjusting for the selection bias incurred when deciding to administer additional antibiotics with a propensity score, some unavoidable bias may have persisted due to the retrospective nature of the study. For example, we were unable to obtain certain detailed information, such as the accuracy of the sputum quality, which made it impossible to evaluate whether or not the detected bacteria were colonized or causative bacteria. Of further note, we included TB patients whose sputum cultures were positive for general bacteria, which is still a surrogate definition of complication with bacterial pneumonia and does not necessarily confirm actual bacterial pneumonia.

Table 3
Association of the measured parameters and in-hospital death.

	Death (n = 35)	Survive (n = 88)	Crude HR	*P*-value	Adjusted with propensity score	*P*-value
Gender (female)	17 (47)	41 (46)	1.177 (0.598–2.314)	0.850		
Age (years)	86.0 (79.2–89.0)	82.0 (73.5–88.0)	1.056 (1.004–1.111)	0.035	1.065 (1.004–1.130)	0.036
BMI (kg/m^2)	17.4 (14.8–20.3)	18.6 (16.8–19.7)	0.938 (0.832–1.059)	0.301		
PS	4 (3,4)	3 (2,3)	2.436 (1.394–4.258)	0.002		
ROAG score	13 (9–17)	9 (8–13)	1.116 (1.021–1.220)	0.016		
WBC (/μl)	7.2 (4.7–9.8)	6.6 (5.3–8.6)	1.023 (0.924–1.133)	0.660		
Neutrophil count (10^3/μl)	5.9 (4.0–9.4)	4.9 (3.6–7.3)	1.000 (1.000–1.000)	0.221		
Hb (g/dl)	9.9 (9.1–11.0)	11.6 (10.1–12.6)	0.752 (0.622–0.908)	0.003		
CRP (mg/dl)	7.8 (2.3–12.7)	3.8 (1.1–9.2)	1.046 (0.997–1.097)	0.064		
Alb (g/dl)	2.1 (1–3)	2.9 (1–4)	0.288 (0.154–0.539)	<0.001		
AST (IU)	34 (22–60)	29 (22–47)	1.004 (0.999–1.009)	0.106		
BUN (mg/dl)	27.1 (16.0–40.5)	15.7 (12.8–23.2)	1.018 (1.002–1.034)	0.029	1.022 (0.996–1.049)	0.101
Cre (mg/dl)	0.89 (0.47–1.14)	0.73 (0.50–0.88)	1.889 (0.868–4.111)	0.109		
COPD	1 (2)	7 (7)	0.485 (0.066–3.558)	0.477		
Cardiac diseases	7 (20)	14 (15)	1.342 (0.584–3.085)	0.488		
Cerebrovascular diseases	6 (17)	16 (18)	1.080 (0.443–2.634)	0.865		
DM	7 (20)	13 (14)	1.378 (0.595–3.194)	0.455		
Respiratory failure	23 (65)	23 (26)	2.692 (1.322–5.480)	0.006		
Additional antibiotics	29 (82)	39 (44)	3.665 (1.516–8.864)	0.004	2.226 (0.737–6.725)	0.156
Steroid use	17 (54)	18 (25)	1.695 (0.855–3.360)	0.131		
Standard anti-tuberculosis	10 (28)	66 (75)	0.266 (0.127–0.559)	<0.001		
Gaffky number	2.5 (1.2–4.0)	2 (1–4)	1.006 (0.859–1.179)	0.937		
Resistant tuberculosis	2 (6)	6 (7)	0.934 (0.222–3.925)	0.926		
Cavitation on chest X-ray	19 (54)	41 (46)	0.980 (0.497–1.934)	0.955		
MRSA	16 (45)	20 (22)	1.744 (0.884–3.440)	0.109		
MSSA	5 (14)	8 (9)	2.283 (0.873–5.973)	0.092		
P. aeruginosa	6 (17)	6 (6)	2.189 (0.899–5.328)	0.084		
S. haemolyticus	4 (11)	12 (13)	1.138 (0.398–3.256)	0.809		
S. epidermidis	0 (0)	8 (9)	0.043 (0–10.213)	0.260		
K. pneumoniae	3 (8)	15 (17)	0.541 (0.165–1.772)	0.310		
S. maltophilia	2 (5)	5 (5)	0.720 (0.172–3.019)	0.653		
E. cloacae	1 (2)	11 (12)	0.313 (0.043–2.301)	0.254		

Data are presented as the number (%) or median (interquartile range).
Alb: albumin, ALT: alanine transaminase, AST: aspartate transaminase, BMI: body mass index, BUN: blood urea nitrogen, COPD: chronic obstructive pulmonary disease, Cre: creatinine, CRP: C-reactive protein, DM: diabetes mellitus, Hb: hemoglobin, MRSA: Methicillin-resistant *Staphylococcus aureus*, MSSA: Methicillin-susceptible *Staphylococcus aureus*, PS: performance status, ROAG: revised oral assessment guide, TP: total protein.

Our results do not completely deny the effectiveness of additional general antibiotics to pulmonary TB patients in whom general bacteria are detected due to the above-mentioned reasons. As long as the antibacterial spectrum of rifampicin is not perfect against causative pathogens for bacterial pneumonia, additional antibiotics with anti-TB agents may be beneficial to some TB patients complicated with bacterial pneumonia. Physicians should not add general antibiotics to TB patients based solely on the results of sputum culture for general bacteria. A large-scale prospective study will be required to valid our results using a more accurate definition of co-infection with general bacteria.

Conflicts of interest

All of the authors have stated explicitly that there are no conflicts of interest in connection with this article.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval

The study protocol was approved by the Institutional Ethics Committee of National Hospital Organization Nishi-Beppu Hospital, Oita, Japan (Approval Number 30-1; Approval Date 31 May 2018).

Authorship statement

T. K., K. K., S. U., A. G., and J. K. designed this study and drafted the manuscript. T. K., K.K. S. U., H. K., S. T. and T. Y. contributed to the data collection, data analysis and helped draft the manuscript.

Acknowledgements

The authors thank Mr. Hideyuki Kato, Dr. Tatsuya Otsu, Dr. Masahide Hara and Dr. Kazuya Goto (National Hospital Organization Nishi-beppu Hospital, Oita) for their advice and supports.

References

[1] Mori T, Leung CC. Tuberculosis in the global aging population. Infect Dis Clin N Am 2010;24(3):751–68.
[2] Negin J, Abimbola S, Marais BJ. Tuberculosis among older adults–time to take notice. Int J Infect Dis 2015;32:135–7.
[3] Davies PD. TB in the elderly in industrialised countries. Int J Tuberc Lung Dis 2007;11(11):1157–9.
[4] Yoo JW, Jo KW, Park GY, Shim TS. Comparison of latent tuberculosis infection rate between contacts with active tuberculosis and non-contacts. Respir Med 2016;111:77–83.
[5] Augustynowicz-Kopec E, Jagielski T, Kozinska M, Kremer K, van Soolingen D, Bielecki J, et al. Transmission of tuberculosis within family-households. J Infect 2012;64(6):596–608.
[6] Deaton A. Income, health, and well-being around the world: evidence from the Gallup World Poll. J Econ Perspect 2008;22(2):53–72.
[7] Komiya K, Rubin BK, Kadota JI, Mukae H, Akaba T, Moro H, et al. Prognostic implications of aspiration pneumonia in patients with community acquired pneumonia: a systematic review with meta-analysis. Sci Rep 2016;6:38097.
[8] Lin GM, Chang FY, Chou CH, Lin YP, Ku CH. Characteristics and outcome of patients with dual pulmonary tuberculosis and non-mycobacterial respiratory infections. J Clin Med Res 2011;3(6):309–18.

[9] Feng JY, Fang WF, Wu CL, Yu CJ, Lin MC, Ku SC, et al. Concomitant pulmonary tuberculosis in hospitalized healthcare-associated pneumonia in a tuberculosis endemic area: a multi-center retrospective study. PLoS One 2012;7(5): e36832.
[10] Critchley JA, Young F, Orton L, Garner P. Corticosteroids for prevention of mortality in people with tuberculosis: a systematic review and meta-analysis. Lancet Infect Dis 2013;13(3):223–37.
[11] 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(2):S27–72.
[12] Andersson P, Hallberg IR, Renvert S. Inter-rater reliability of an oral assessment guide for elderly patients residing in a rehabilitation ward. Spec Care Dent 2002;22(5):181–6.
[13] McManus AT, Mason Jr AD, McManus WF, Pruitt Jr BA. What's in a name? Is methicillin-resistant Staphylococcus aureus just another S aureus when treated with vancomycin? Arch Surg 1989;124(12):1456–9.
[14] Geckler RW, Gremillion DH, McAllister CK, Ellenbogen C. Microscopic and bacteriological comparison of paired sputa and transtracheal aspirates. J Clin Microbiol 1977;6(4):396–9.
[15] Gaieski DF, Mikkelsen ME, Band RA, Pines JM, Massone R, Furia FF, et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. Crit Care Med 2010;38(4):1045–53.
[16] 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(6):637–44.
[17] Kett DH, Cano E, Quartin AA, Mangino JE, Zervos MJ, Peyrani P, et al. Implementation of guidelines for management of possible multidrug-resistant pneumonia in intensive care: an observational, multicentre cohort study. Lancet Infect Dis 2011;11(3):181–9.
[18] Ewig S, Welte T, Torres A. Is healthcare-associated pneumonia a distinct entity needing specific therapy? Curr Opin Infect Dis 2012;25(2):166–75.
[19] Rello J, Lujan M, Gallego M, Valles J, Belmonte Y, Fontanals D, et al. Why mortality is increased in health-care-associated pneumonia: lessons from pneumococcal bacteremic pneumonia. Chest 2010;137(5):1138–44.
[20] Komiya K, Ishii H, Umeki K, Mizunoe S, Okada F, Johkoh T, et al. Impact of aspiration pneumonia in patients with community-acquired pneumonia and healthcare-associated pneumonia: a multicenter retrospective cohort study. Respirology 2013;18(3):514–21.
[21] Thornsberry C, Hill BC, Swenson JM, McDougal LK. Rifampin: spectrum of antibacterial activity. Rev Infect Dis 1983;5(3):S412–7.
[22] Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical practice guidelines by the infectious diseases society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis 2011;52(3):e18–55.
[23] Murray R, Paine TF, Finland M. Streptomycin; bacteriologic and pharmacologic aspects. N Engl J Med 1947;236(19):701–12.