

# New insight on antimicrobial therapy adjustment strategies for gram-negative bacterial infection

## A cohort study

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### Abstract

Gram-negative bacterial infections, especially multidrug-resistant (MDR) bacterial infection, are becoming a serious threat to public health. Although it is widely accepted that both appropriate initial empirical therapy and targeted therapy are important, but for patients needing therapy adjustment, few studies have explored whether adjustment strategy based on microbiologic susceptibility test (MST) brings better outcome compared with empirical adjustment.

A total of 320 patients with gram-negative bacterial infection (airway, blood, or pleural effusion) were selected and a prospective cohort study was conducted. Baseline characteristics and outcomes (microbiologic, clinical, and economic) were documented during follow-up.

MDR and nosocomial infections were common among MDR subjects. Initial therapies consistent with MST could result in reduced in-hospital mortality, treatment failure rate, infection-related death, percentages of patients needing therapy adjustment, and daily hospitalization cost with increased successful treatment rate compared with inconsistent with MST, and microbiologic outcomes were also better with appropriate therapies.

For patients needing therapy adjustment, relying on MST gained no significant benefit on mortality, clinical, or microbiologic outcomes compared with depending on clinical experience. But for patients with MDR infection, adjustment relying on MST gained more benefit than non-MDR infection.

Appropriate initial therapy significantly improved the prognosis of patients with gram-negative bacterial infections, but improvement was not that obvious for patients needing therapy adjustment which was based on MST compared with clinical experience, and more beneficial effects of adjustment relying on MST were obtained for patients with MDR bacterial infection.

**Abbreviations:** BALF = bronchoalveolar lavage fluid, CI = confidence interval, ICU = intensive care unit, MDR = multidrug resistant, MST = microbiologic susceptibility test, OR = odds ratio, SD = standard deviation.

**Keywords:** empirical therapy, gram-negative bacteria, microbiologic susceptibility test, multidrug resistance

## 1. Introduction

Infections caused by gram-negative bacteria has been drawing clinicians' attentions in the recent years as a result of increasingly

prevalence of multidrug resistance (MDR), difficulty of treatment, high morbidity and mortality, and heavy economic burden.<sup>[1-3]</sup> The most common infections potentially involving gram-negative bacteria include urinary tract infections, pneumonias, blood stream and central line-associated infections, intra-abdominal infections, skin and soft tissue infections, and acute exacerbations of chronic obstructive pulmonary disease,<sup>[2]</sup> of which pneumonias and blood stream infections especially central line-associated infections are probably critically severe and cause high mortality.<sup>[2,4]</sup>

The severity of gram-negative bacterial infection could be the results of many reasons, but the most important one might be the emergence of MDR and even pan-drug resistance, which means the pathogens are resistant to most or all existing antimicrobial drugs. The mechanisms of bacteria gaining drug resistance can be intrinsic, acquired, or adaptive, of which induction of lactamases such as extended-spectrum  $\beta$ -lactamases and carbapenemases, porin losses, and drug efflux pumps play important roles.<sup>[2,5]</sup> In addition to these molecular mechanisms, globalization, excessive use of antibiotics in animal husbandry and aquaculture, overuse of antibiotics in the communities and hospitals, and lack of good antimicrobial stewardship or good infection control practices also contribute to persistence and spread of MDR gram-negative bacteria,<sup>[2,6]</sup> leading to severe infections with limited antimicrobial agents to be selected.

To be faced with such challenge, guidelines and expert consensus have agreed that unnecessary antibiotic use should be

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avoided and if necessary, initial antimicrobial treatment should be selected based on patients' most likely pathogens and risk factors of MDR bacterial infections, followed by targeted treatment once microbiologic susceptibility test (MST) results are known.<sup>[5,7-12]</sup> This strategy is based on facts that delayed (e.g., starting treatment until culture results are obtained) or inappropriate initial antimicrobial therapy significantly leads to higher mortality and treatment failures,<sup>[13,14]</sup> and this strategy can lower both the risk of death and emergence of drug resistance.<sup>[14]</sup> However, for patients already starting initial antimicrobial therapy upon diagnosis of infections and seemingly gaining no benefit from initial therapy, clinicians often have to decide whether to wait until MST results are obtained or adjust treatment based on their own clinical experience. A few studies have found that for patients with inappropriate initial therapy, switching therapy based on culture results is not able to obtain beneficial effect on mortality,<sup>[15-17]</sup> indicating in some circumstances, adjusting therapy based on MST might not have beneficial effect on patients' prognosis.

Thus, it is important to make it clear which strategy is more appropriate for patients with bacterial infections, and what is the role of MST under this circumstance. In order to compare these two therapy adjustment strategies and verify the importance of MST, our research was conducted.

## 2. Methods

### 2.1. Subject selection and study design

Subjects were screened and selected from patients admitted to Ruijin hospital (one of the biggest tertiary-care hospital located in Shanghai, China) from January 2012 through December 2015. Patients were screened by identifying positive culture results of gram-negative bacteria from airway, blood, or pleural effusion samples because of their availability and prevalence.

Our inclusion criteria were: patient was infected by gram-negative bacterium, which was identified by the culture result from the sample according to history (e.g., previous infection, trauma, hematologic disease, and intravascular catheterization), symptoms (e.g., fever, cough, expectoration, dyspnea, and chest pain), signs (e.g., purulent secretion, rales, and cyanosis), imaging findings (e.g., lung infiltrates and pleural effusion), and laboratory tests (e.g., circulating leukocyte  $>10,000 \text{ mm}^{-3}$ ); patient was  $>14$  years old.

Our exclusion criteria were as follow: subject was already included in our study; the cultured bacteria were considered as colonization or contamination clinically; and patients refused to take part in this study or had already taken part in other studies and clinical data could not be used in our study.

After selection, subjects' baseline characteristics were documented, including age, gender, specimen sources, cultured pathogens, MST results, time of hospital admission and infection diagnosis, initial therapy, whether used antibiotics in the past 72 hours or 90 days, whether admitted into intensive care unit (ICU), whether had comorbidities, whether had some infection risk factors such as malnutrition, severe trauma, mechanical ventilation  $>48$  hours, intravascular catheterization, dialysis in the past 30 days, hospitalization  $>2$  days in the past 90 days, and so on. Then the subjects were followed up prospectively until death or hospital discharge, additional information was collected such as whether patients' therapies were adjusted and their adjustment strategies (based on clinical experience or MST), and their outcomes were evaluated.

The primary measures of outcomes included in-hospital mortality, microbiologic and clinical outcomes in the end of treatment, hospitalization time after infection, and antibiotic cost. The secondary measures included the microbiologic and clinical outcomes after 72-hour treatment, therapy time after infection, total hospitalization time, and total and daily hospitalization cost. All subjects gave their written informed consent, and this study was approved by the ethics committee of Ruijin hospital.

### 2.2. Some important definitions

MDR bacteria were defined as follow in our study: for *Enterobacteriaceae*, resistant to any third or fourth generation of cephalosporins, or aztreonam, or any kind of carbapenems; for *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, resistant to  $\geq 3$  kinds of following antibiotics including cephalosporins, carbapenems, fluoroquinolones, aminoglycosides, and lactam + lactamase inhibitor combination agents; for other pathogens, resistant to  $\geq 3$  kinds of common antimicrobial drug classes.

Nosocomial infections were defined as infections which occurred and were diagnosed 48 hours after hospital admission.

Therapy adjustment strategies: if therapy was adjusted before MST result came out, we regarded this kind of adjustment as depending on clinical experience; and if therapy was adjusted after MST result came out and consistent with the latest MST, we regarded it as depending on MST.

Microbiologic outcomes at the evaluation time: if there was pathogen cultured from original infection site, it was considered persistency; if there were infection-related symptoms but no collected samples from original infection site to confirm, it was considered possible persistency; if other pathogens were cultured from original infection site, it was considered reinfection; if there was no infection-related symptom and no collected samples from original infection site to confirm, it was considered assumed clearance; and if there was no pathogen cultured from original infection site, it was considered clearance.

Clinical outcomes: if death was the result of the infection, it was named death because of infection; if death was not the result of the infection, it was named death because of other causes; if clinical manifestations and imaging findings continued or deteriorated, it was regarded as failure; if the clinical manifestations reoccurred after initial improvement, it was considered relapse; if the clinical manifestations were improved, it was considered improvement; if the clinical manifestations and imaging findings were improved without further deterioration, it was considered success; and if the clinical manifestations and imaging findings were not consistent, a discussion by all the authors and several experienced respiratory clinicians and further follow-up would be done to determine the patient's classification of outcome.

### 2.3. Statistical analysis

Data were summarized descriptively using frequencies and cross-tabulations for categorical variables or using descriptive statistics such as the mean and standard deviation (SD) for continuous variables. Continuous variables were evaluated using Student's *t* test and analysis of variance. The chi-square and Fisher's exact tests were used to assess categorical variables. In some circumstances, logistic regression analysis was performed to evaluate the relationship between infection risk factors and mortality or to

exclude confounding factors' effect, in which odds ratio (OR) and 95% confidence interval (95% CI) would be calculated. All analyses were performed using SPSS v20.0.0 and missing data were excluded from our analyses. A two-sided  $P$ -value  $<0.05$  was considered to be statistically significant.

### 3. Results

#### 3.1. Demographic characteristics of patients

A total of 1379 samples of positive culture results of gram-negative bacteria were screened and 320 subjects were finally included in this study, with 147 no therapy adjustment, 60 based on clinical experience, and 113 relying on MST when therapy was adjusted, and all of them completed the follow-up (mean  $\pm$  SD follow-up time,  $29.87 \pm 40.70$  days, detailed flow diagram can be seen in Fig. 1). Most of the specimens were from sputum, endotracheal intubation, and blood (35%, 11.3%, and 49.1%, respectively). Most common pathogens included *A baumannii*, *Klebsiella pneumoniae*, *Escherichia coli*, and *P aeruginosa* (20.3%, 22.5%, 23.1%, and 13.8%, respectively, more details in Table S1, <http://links.lww.com/MD/B623>). MDR and nosocomial infections were common among these patients (61.6% and 79.7%, respectively). There were 169 subjects whose initial therapy was consistent with MST, and initial consistency reduced the possibility of therapy adjustment (76.7% vs 41.4%, initial inconsistency and consistency, respectively; relative risk = 0.540, 95% CI = 0.441–0.661). For patients needing therapy change, relying on MST could bring better MST consistency (nearly 100% except for 1 patient whose pathogen was resistant to all the drugs tested and the most sensitive drug was used according to MST).

Comorbidities especially sepsis were common among patients (57.2%), and infection risk factors including old age (41.6%), long time hospitalization (88.4%), previous hospitalization (hospitalization  $>2$  days in the past 90 days, 39.4%), mechanical

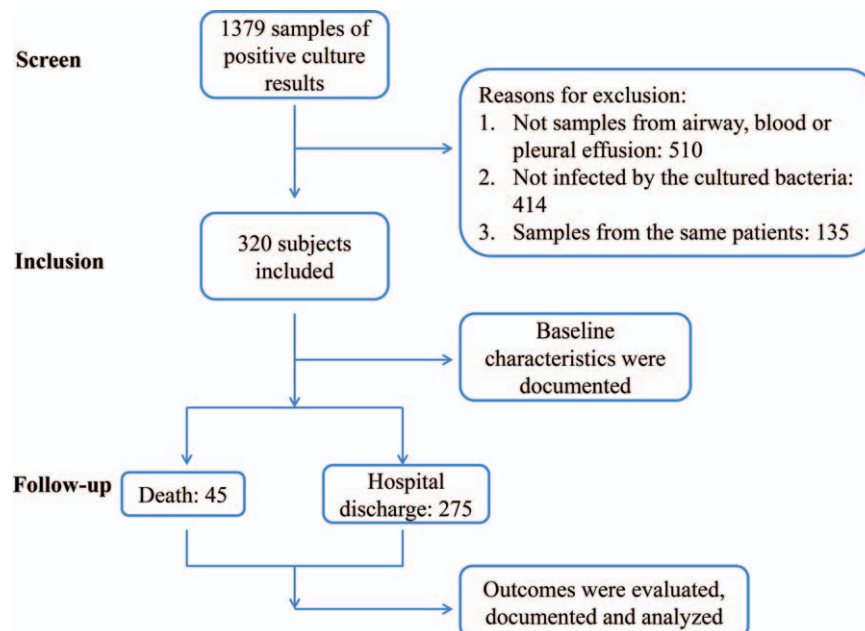
ventilation (31.6%), intravascular or retention catheterization (65.9% and 36.9%, respectively), endotracheal intubation (27.8%), blood transfusion (37.2%), total parental nutrition (26.3%), and intestinal wall destruction (20.3%) were also important features among these subjects. And logistic regression analysis indicated that previous hospitalization and mechanical ventilation were associated with increased mortality (OR = 2.151 and 2.198,  $P = 0.021$  and  $0.018$ , respectively). Detailed characteristics can be seen in Table 1.

#### 3.2. Initial therapies consistent with MST brought better outcome

Clinical practice guidelines have insisted on consistency of initial empiric therapy with MST,<sup>[7,10,12]</sup> and our research also revealed that consistency with MST could result in reduced treatment failure rate (43.8% vs 14.5%,  $P < 0.001$ , inconsistency vs consistency, respectively) and relapse rate (6.9% vs 1.8%,  $P < 0.05$ ) combined with increased improvement rate (41.5% vs 74.1%,  $P < 0.001$ , Fig. 2A) after 72-hour treatment. As for microbiologic outcomes, similar results could be found (persistence rate, 44.5% vs 18.8%,  $P < 0.001$ ; assumed clearance rate, 8.6% vs 34.9%,  $P < 0.001$ , Fig. 2B).

Meanwhile at the end of treatment decreased treatment failure rate (14.4% vs 2.4%,  $P < 0.001$ ) and infection-related death (7.2% vs 1.8%,  $P < 0.05$ ) and increased successful treatment rate (36.0% vs 67.9%,  $P < 0.001$ ) were found (Fig. 2C). Just like 72-hour outcomes, final microbiologic outcomes were also better if initial therapies were consistent with MST (persistence rate, 22.5% vs 4.5%,  $P < 0.001$ ; possible persistence rate, 26.7% vs 13.5%,  $P < 0.01$ ; assumed clearance rate, 25.0% vs 49.0%,  $P < 0.001$ , Fig. 2D).

Moreover, initial consistency with MST could reduce in-hospital mortality after infection (21.1% vs 8.3%,  $P = 0.001$ ), daily hospitalization cost ( $4834.06 \pm 3642.73$  vs  $3560.52 \pm 2794.37$  RMB,  $P = 0.002$ ; RMB is the currency used in China.



**Figure 1.** Flow diagram of screen, inclusion, and follow-up. Not infected by the cultured bacteria indicates that the patients were not infected by the cultured bacteria, which were considered as colonization or contamination.

**Table 1****Baseline characteristics of the subjects.**

Characteristics	Therapy adjustment based on MST	Therapy adjustment based on clinical experience	Subjects without therapy adjustment	P value
Number	113	60	147	
Age, mean ± SD, y	58.95 ± 16.34	63.12 ± 17.68	60.43 ± 17.67	0.318*
Sex				0.985
Male	78 (69.0)	41 (68.3)	100 (68.0)	
Female	35 (31.0)	19 (31.7)	47 (32.0)	
Specimen sources				0.042†
Sputum	40 (35.4)	19 (31.7)	53 (36.1)	
Blood	50 (44.2)	26 (43.3)	81 (55.1)	
BALF	4 (3.5)	4 (6.7)	2 (1.4)	
Endotracheal intubation	16 (14.2)	9 (15.0)	11 (7.5)	
Pleural effusion	1 (0.9)	2 (3.3)	/	
Others	2 (1.8)	/	/	
Pathogens				0.480
<i>Acinetobacter baumannii</i>	27 (23.9)	12 (20.0)	26 (17.7)	
<i>Klebsiella pneumoniae</i>	26 (23.0)	15 (25.0)	31 (21.1)	
<i>Escherichia coli</i>	22 (19.5)	9 (15.0)	43 (29.3)	
<i>Pseudomonas aeruginosa</i>	15 (13.3)	11 (18.3)	18 (12.2)	
Others	23 (20.3)	13 (21.7)	29 (19.7)	
MDR bacterial infection	70 (61.9)	40 (66.7)	87 (59.2)	0.601
Nosocomial infection	92 (81.4)	44 (73.3)	119 (84.4)	0.184
MST consistency of initial therapy	46 (41.1)	24 (40.0)	99 (76.2)	0.000
MST consistency after adjustment	112 (99.1)	32 (54.2)	–	0.000
Corticosteroid use	20 (17.7)	12 (20.0)	15 (10.2)	0.125
Antibiotics use in the past 72 hours	56 (49.6)	36 (60.0)	63 (42.9)	0.078
Antibiotics use in the past 90 days	73 (68.2)	37 (63.8)	98 (71.0)	0.606
ICU admission	33 (29.2)	12 (20.0)	27 (18.4)	0.102
Comorbidities				
Sepsis	70 (61.9)	30 (50.0)	83 (56.5)	0.310
Heart failure	11 (10.2)	8 (13.3)	13 (9.6)	0.730
Respiratory failure	41 (38.0)	16 (26.7)	27 (20.0)	0.008
Hepatic dysfunction	35 (32.4)	14 (23.3)	34 (25.2)	0.334
Renal dysfunction	25 (23.1)	10 (16.7)	17 (12.6)	0.095
Confusion	22 (20.4)	12 (20.0)	14 (10.4)	0.065
Hematologic diseases	45 (41.3)	13 (21.7)	46 (33.8)	0.036
Infection risk factors				
>65 years old	44 (38.9)	28 (46.7)	61 (41.5)	0.617
Malnutrition	8 (7.1)	2 (3.3)	7 (4.8)	0.581
Rheumatoid diseases	2 (1.8)	0 (0)	2 (1.4)	0.830†
Severe trauma	5 (4.4)	8 (13.3)	9 (6.1)	0.080
Mechanical ventilation >48 hours	45 (39.8)	22 (36.7)	34 (23.1)	0.010
Intravascular catheterization	77 (68.1)	52 (86.7)	82 (55.8)	0.000
Retention catheterization	48 (42.5)	23 (38.3)	47 (32.0)	0.213
Endotracheal intubation >48 hours	39 (34.5)	20 (33.3)	30 (20.4)	0.024
Dialysis in the past 30 days	6 (5.3)	2 (3.3)	3 (2.0)	0.364†
Blood transfusion	44 (38.9)	22 (36.7)	53 (36.1)	0.889
TPN	38 (33.6)	13 (21.7)	33 (22.4)	0.085
Chemical therapy	10 (8.8)	6 (10.0)	10 (6.8)	0.742
Granulocytopenia >10 days	3 (2.7)	4 (6.7)	10 (6.8)	0.294†
BMT	2 (1.8)	2 (3.3)	2 (1.4)	0.582†
Hospitalization >2 days in the past 90 days	39 (34.5)	32 (53.3)	55 (37.4)	0.044
Intestinal wall destruction	32 (28.3)	15 (25.0)	18 (12.2)	0.004

Data are presented as No. (%) unless otherwise indicated. Comparisons were made using Pearson  $\chi^2$  unless otherwise indicated.

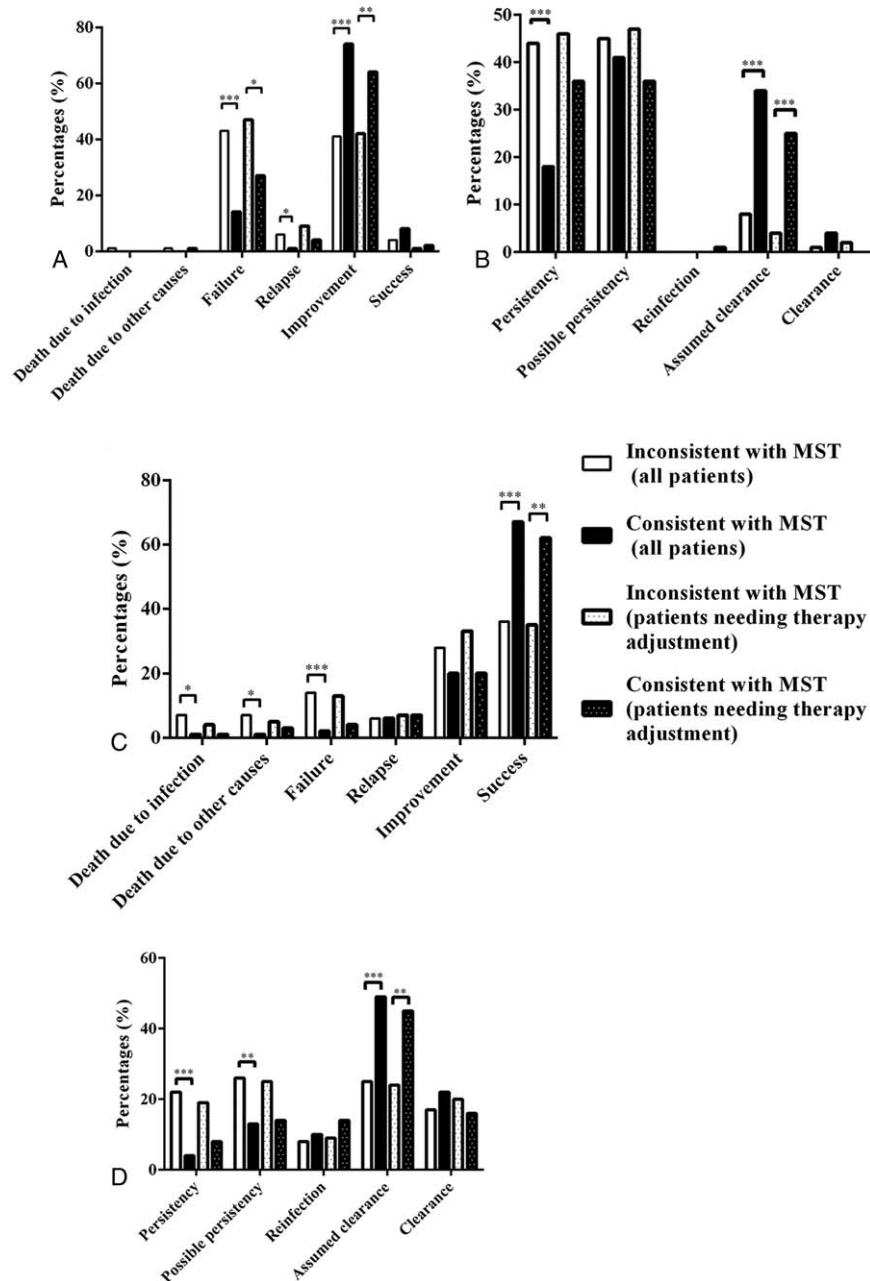
ANOVA = analysis of variance, BALF = bronchoalveolar lavage fluid, BMT = bone marrow transplantation, ICU = intensive care unit, MDR = multidrug resistant, MST = microbiologic susceptibility test, SD = standard deviation, TPN = total parental nutrition.

\* Comparison made by one-way ANOVA.

† Comparison made by Fisher's exact test.

1 RMB=0.1456 dollars), and percentages of patients needing therapy adjustment (76.7% vs 41.4%,  $P < 0.001$ ). Therapy and hospitalization time after infection, hospitalization cost, and antibiotic cost were seemingly reduced with initial MST consistency, but there was no statistical significance (Table 2).

As patients needing therapy adjustment seemed to be more heavily ill and might influence the effect of appropriate initial therapy on infected patients, same analyses of these patients were conducted, and similar results could be seen (Table 2 and Fig. 2).



**Figure 2.** Initial therapy consistent with MST results led to better clinical and microbiologic outcomes. (A) Clinical outcomes after 72-hour treatment. (B) Microbiologic outcomes after 72-hour treatment. (C) Clinical outcomes at the end of treatment. (D) Microbiologic outcomes at the end of treatment. \* $P < 0.05$ , \*\* $P < 0.01$ , and \*\*\* $P < 0.001$ . MST = microbiologic susceptibility test.

**3.3. Antibiotic adjustment based on MST could bring more significant improvement of microbiologic outcomes than clinical outcomes but extended hospitalization time for gram-negative bacterial infection patients**

MST has been regarded as an important tool to guide antibiotic use in infectious diseases, and adjusting antibiotics based on MST during infection treatment has been self-evident which can also reduce the possibility of production of antibiotic-resistant organisms,<sup>[2,3,5,7]</sup> but studies evaluating prognosis of these patients were lacking. In our study, clinical and microbiologic outcomes were almost the same after 72-hour treatment between

patients whose therapies were adjusted based on MST or clinical experience (Fig. 3A and B) but the percentage of patients having adjusted therapy at this time was lower if based on MST (36.7% vs 13.7%,  $P = 0.001$ , based on experience and MST, respectively, Table 3).

Besides, if in-hospital mortality was evaluated between these two groups, we could find that there was no significant difference (21.7% and 12.4%,  $P > 0.05$ ). To exclude possible effects of some confounding factors (including respiratory failure, hematologic disease, intravascular catheterization, and hospitalization >2 days in the past 90 days), which had significant different baseline values between two groups, logistic regression analysis

**Table 2****Outcomes of patients with initial therapy consistent with MST or not.**

Outcomes	Initial therapy consistent with MST	Initial therapy inconsistent with MST	P value
In-hospital mortality, No. (%)			
Of all the patients	14 (8.3)	28 (21.1)	0.001*
Of patients needing adjustment	9 (12.9)	17 (16.7)	0.493*
Therapy time after infection, mean $\pm$ SD, days			
Of all the patients	15.17 $\pm$ 10.33	17.55 $\pm$ 18.62	0.218
Of patients needing adjustment	19.99 $\pm$ 11.29	23.30 $\pm$ 26.50	0.269
Hospitalization time after infection, mean $\pm$ SD, days			
Of all the patients	26.72 $\pm$ 25.84	33.58 $\pm$ 54.59	0.190
Of patients needing adjustment	29.23 $\pm$ 23.87	37.57 $\pm$ 57.96	0.202
Total hospitalization time, mean $\pm$ SD, days			
Of all the patients	71.14 $\pm$ 161.46	50.04 $\pm$ 61.96	0.147
Of patients needing adjustment	80.88 $\pm$ 183.22	52.41 $\pm$ 65.63	0.232
Hospitalization cost, mean $\pm$ SD, RMB <sup>†</sup>			
Of all the patients	192,318.68 $\pm$ 243,783.32	224,124.77 $\pm$ 258,879.34	0.307
Of patients needing adjustment	203,463.72 $\pm$ 232,849.35	227,616.93 $\pm$ 250,807.16	0.542
Daily hospitalization cost, mean $\pm$ SD, RMB			
Of all the patients	3560.52 $\pm$ 2794.37	4834.06 $\pm$ 3642.73	0.002
Of patients needing adjustment	3668.83 $\pm$ 2972.43	4760.54 $\pm$ 3632.39	0.048
Antibiotic cost, mean $\pm$ SD, RMB			
Of all the patients	24,760.70 $\pm$ 28,720.17	32,766.82 $\pm$ 40,746.49	0.075
Of patients needing adjustment	24,589.33 $\pm$ 24,991.28	36,165.73 $\pm$ 42,846.93	0.038
Patients needing therapy adjustment (%)	41.4	76.7	<0.001*

Comparisons were made using the Student *t* test unless otherwise indicated.

MST = microbiologic susceptibility test, SD = standard deviation.

\* Comparison made by Pearson  $\chi^2$  test.

<sup>†</sup> RMB is the currency used in China. 1 RMB = 0.1456 dollars.

was conducted and similar result was obtained (OR = 0.406, 95% CI = 0.158–1.044).

However, on the other hand, relying on MST would significantly improve the microbiologic outcomes at the end of treatment. The persistency rate and possible persistency rate were obviously reduced, whereas the clearance rate was increased if relying on MST (persistency rate, 23.3% vs 11.0%,  $P < 0.05$ ; possible persistency rate, 30.0% vs 15.0%,  $P < 0.05$ ; clearance rate, 8.3% vs 25.0%,  $P < 0.01$ , Fig. 3D). Additionally, treatment failure rate was also reduced if based on MST (17.2% vs 5.7%,  $P < 0.05$ , Fig. 3C), but other clinical outcomes such as death rate, relapse rate, improvement rate, and successful treatment rate had no significant difference.

Adjusting therapy based on MST was possibly more important for patients with MDR bacterial infections.

As MDR bacterial infection would influence the efficacy of empiric therapy,<sup>[2]</sup> and MST could help clinicians choose more appropriate antibiotics, which suggested MDR infection might have different effect on empiric therapy and therapy based on MST, and then subgroup analysis based on MDR infection or not was conducted. At the first evaluation time point (72 hours after treatment), similar clinical and microbiologic outcomes could be seen both in MDR and non-MDR groups. However, for patients whose therapy adjustment was based on MST, MDR infection could increase the possible persistency rate (30.0% vs 51.5%,  $P < 0.05$ , non-MDR and MDR infection, respectively) and decrease the assumed clearance rate (25.0% vs 9.1%,  $P < 0.05$ , Fig. 3E and F).

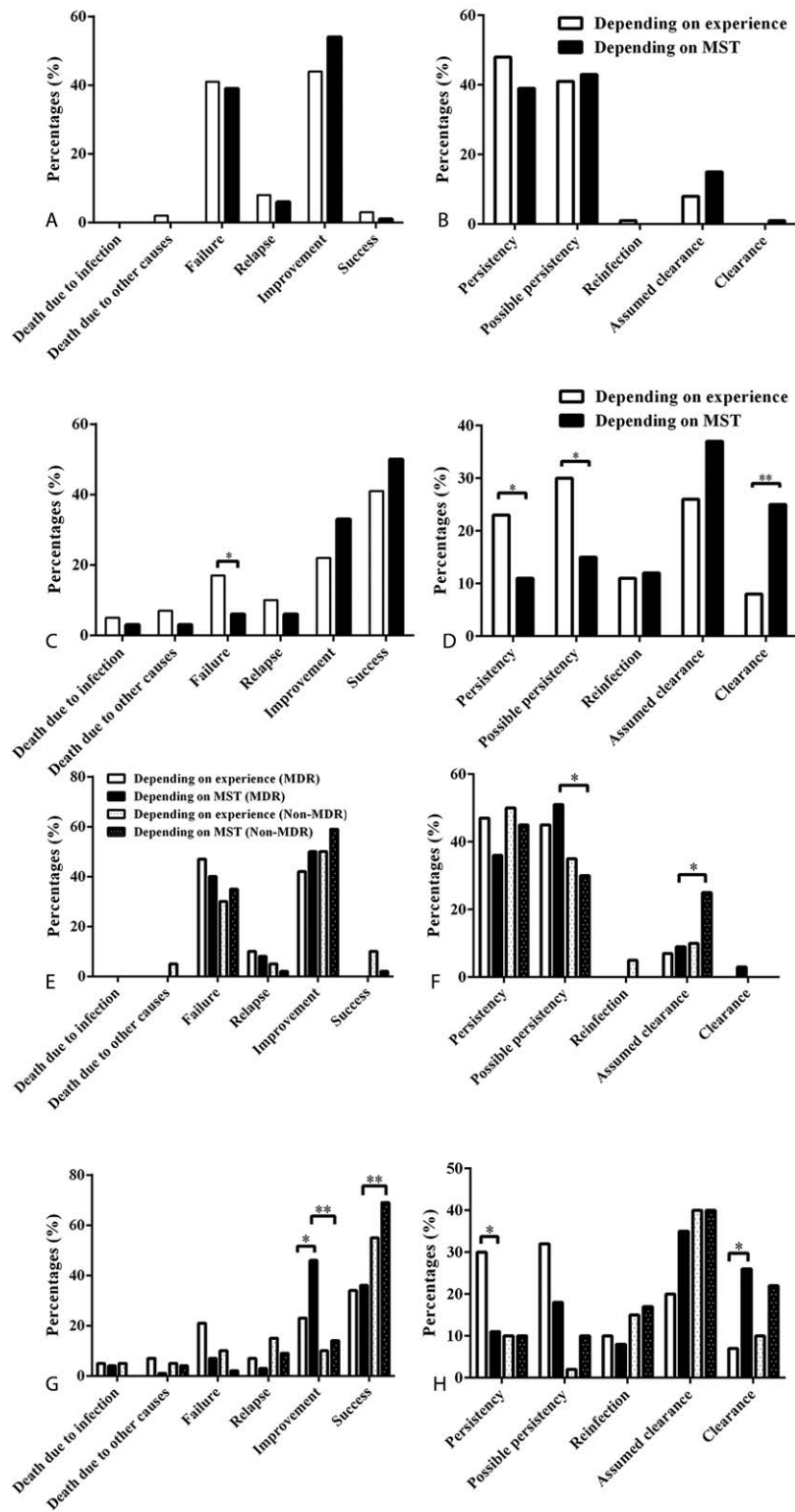
At the end of treatment, MDR infection would significantly influence the effect of therapy adjustment strategy on clinical and microbiologic outcomes. For MDR infection patients, strategy depending on MST significantly increased the improvement rate (23.7% vs 46.0%,  $P < 0.05$ , depending on experience and MST, respectively) but for non-MDR infection patients there was no such effect (10.0% vs 14.3%,  $P > 0.05$ ). Besides, although MDR

infection could reduce successful treatment rate for patients using either strategy, this reduction was more significant for patients using adjustment strategy based on MST (based on clinical experience, 55.0% vs 34.2%,  $P > 0.05$ , non-MDR and MDR infection, respectively; based on MST, 69.0% vs 36.5%,  $P < 0.05$ ). As for microbiologic outcomes, patients with MDR infection had decreased persistency rate (30.0% vs 11.7%,  $P < 0.05$ , based on experience and MST, respectively) and increased clearance rate (7.5% vs 26.7%,  $P < 0.05$ ) if adjustment was based on MST but for patients with non-MDR infection there was no such effect (Fig. 3G and H).

Additionally, therapy adjustment strategy could not significantly influence in-hospital mortality, therapy time after infection, total hospitalization time, hospitalization cost, daily hospitalization cost, and antibiotic cost for patients with MDR or non-MDR infection. However, percentage of patients with therapy adjustment during the first 72 hours since starting treatment was decreased and hospitalization time after infection increased if adjusting therapy was based on MST for patients with MDR infection but there was no significant difference for patients with non-MDR infection (Table 3).

#### 4. Discussion

In the recent years, bacterial infections especially MDR gram-negative bacterial infections have become a serious threat to global public health, with few novel agents produced for antimicrobial therapy.<sup>[2]</sup> To overcome this challenge, researchers and clinicians have presented many suggestions and strategies in order to improve patients' outcomes and avoid more production and spread of MDR bacteria, but sometimes these two objects are conflicting and we need to find a strategy to balance them based on our knowledge about advantages and disadvantages of each suggestion or strategy.



**Figure 3.** Therapy adjustment based on MST led to limited improvement of clinical outcomes but apparent microbiologic outcomes compared with adjustment based on clinical experience, and the improvement of therapy adjustment based on MST was more significant for patients with MDR gram-negative bacterial infections. (A) Clinical outcomes after 72-hour treatment for all patients. (B) Microbiologic outcomes after 72-hour treatment for all patients. (C) Clinical outcomes at the end of treatment for all patients. (D) Microbiologic outcomes at the end of treatment for all patients. (E)–(H) Subgroup analysis of clinical outcomes after 72-hour treatment (E), microbiologic outcomes after 72-hour treatment (F), clinical outcomes at the end of treatment (G), and microbiologic outcomes at the end of treatment (H) for patients with MDR or non-MDR bacterial infections. \* $P < 0.05$  and \*\* $P < 0.01$ . MDR = multidrug resistance, MST = microbiologic susceptibility test.

**Table 3**  
**Outcomes of patients adjusting therapy depending on experience or MST.**

Outcomes	Depending on experience	Depending on MST	P value
In-hospital mortality, No. (%)			
MDR	11 (27.5)	9 (12.9)	0.055*
Non-MDR	2 (10.0)	5 (11.6)	1.000 <sup>†</sup>
All patients	13 (21.7)	14 (12.4)	0.110*
Percentages of patients with therapy adjustment during the first 72 hours since starting treatment, No. (%)			
MDR	13 (32.5)	4 (7.3)	0.002*
Non-MDR	9 (45.0)	9 (22.5)	0.073*
All patients	22 (36.7)	13 (13.7)	0.001*
Therapy time after infection, mean ± SD, days			
MDR	18.63 ± 14.63	21.56 ± 14.00	0.324
Non-MDR	14.10 ± 8.22	17.68 ± 10.32	0.183
All patients	17.12 ± 12.96	19.93 ± 12.67	0.185
Hospitalization time after infection, mean ± SD, days			
MDR	27.48 ± 24.76	48.51 ± 67.79	0.024
Non-MDR	20.60 ± 15.76	25.93 ± 23.43	0.366
All patients	25.18 ± 22.50	39.81 ± 56.03	0.018
Total hospitalization time, mean ± SD, days			
MDR	54.8 ± 69.2	61.7 ± 75.3	0.650
Non-MDR	78.2 ± 187.1	71.6 ± 191.1	0.898
All patients	62.60 ± 120.71	65.89 ± 136.28	0.879
Hospitalization cost, mean ± SD, RMB <sup>‡</sup>			
MDR	241,328.47 ± 260,406.89	257,473.01 ± 273,166.63	0.771
Non-MDR	214,014.63 ± 217,132.68	139,801.62 ± 172,438.50	0.192
All patients	232,223.86 ± 245,308.21	207,927.16 ± 242,105.22	0.546
Daily hospitalization cost, mean ± SD, RMB			
MDR	5017.80 ± 3945.36	4720.01 ± 3830.67	0.713
Non-MDR	4335.46 ± 2677.78	2970.21 ± 1920.14	0.051
All patients	4790.35 ± 3564.22	3983.26 ± 3273.18	0.151
Antibiotic cost, mean ± SD, RMB			
MDR	41,050.66 ± 42,974.56	39,603.23 ± 42,291.03	0.871
Non-MDR	14,705.21 ± 16,731.80	18,144.44 ± 18,400.86	0.487
All patients	32,120.00 ± 38,208.59	30,700.12 ± 35,914.32	0.817

Comparisons were made using the Student *t* test unless otherwise indicated.

MDR = multidrug resistant, MST = microbiologic susceptibility test, SD = standard deviation.

\* Comparison made by Pearson  $\chi^2$ .

<sup>†</sup> Comparison made by Fisher's exact test.

<sup>‡</sup> RMB is the currency used in China. 1 RMB = 0.1456 dollars.

The most commonly accepted strategy for infection control is immediately starting antimicrobial therapy upon diagnosis of infection, followed by targeted antimicrobial therapy based on culture results obtained later. This strategy is based on a fact that inappropriate or delayed treatment significantly worsens patients' outcomes, and how to choose proper initial antimicrobial therapy based on patients' characteristics and community or hospital's antibiotic resistance data has extensively been discussed in previous studies.<sup>[2,5,7,10,11,18]</sup> However, the value of different adjustment strategies has not been discussed but in some circumstances clinicians have to decide whether to adjust therapy before culture results are available. Thus, in our study, apart from confirmation of importance of appropriate initial therapy, we discuss this question and found that for patients needing therapy adjustment, a strategy based on MST had no significant effect on mortality, accompanied with longer hospitalization time, delayed therapy adjustment, and unobvious clinical outcome improvement, compared with strategy based on clinicians' experience. However, the microbiologic outcomes were significantly improved based on MST, and for patients with MDR bacterial infection, strategy based on MST had more positive effect both on clinical and microbiologic outcomes.

In terms of critical role of appropriate initial therapy, lots of studies have verified it in patients with blood stream infections or

pneumonia,<sup>[4,12,14,18,19]</sup> and many strategies aimed at early appropriate therapy have been explored.<sup>[11,20–24]</sup> In our study, we also confirmed it in patients with gram-negative bacterial infection. Previous studies mostly focus on its beneficial effect on mortality, but in our study, we also explored its effect on microbiologic and economic effects, in which significantly decreased pathogen persistency rate, daily hospitalization cost, and increased pathogen clearance rate were found.

Besides, we also discussed the effect of different therapy adjustment strategy on patients' outcomes. As to therapy adjustment, a few studies have already found that if initial empirical therapy was not appropriate or adequate, subsequent adjustment based on culture results or MST could not reverse the worsened outcomes especially mortality,<sup>[15–17]</sup> and delayed therapy was also associated with higher mortality, longer hospitalization, and increased health care costs.<sup>[25,26]</sup> The results from these studies have been important basis of our current antimicrobial therapy strategy, in which prompt initiation of appropriate therapy and subsequent targeted therapy were suggested, but sometimes culture results were not available because of several negative results before a positive one, long culture time, or delayed report (in our study, the mean time from diagnosis to positive culture results was 6.66 [±8.40] days). Under this circumstance combined with seemingly not effective



initial therapy, clinicians had to decide whether to change therapy or wait until positive culture results. As beneficial effect of adjustment based on MST was not absolutely apparent, and delayed appropriate therapy could increase patients' mortality rate, adjustment based on clinicians' experience before emergence of culture results might benefit. So, in our study we compared these two strategies and found that strategy based on MST resulted in longer hospitalization time, delayed therapy adjustment, decreased treatment failure rate, and improved microbiologic outcomes, accompanied with insignificant reduced mortality rate and hospitalization cost, indicating the limited benefit from this strategy among patients with gram-negative bacterial infection. However, if identified pathogens were MDR, the clinical benefit from this strategy seemed to be more obvious despite of still existing delayed therapy adjustment and longer hospitalization time, indicating that for patients with MDR infection, adjustment strategy based on MST might benefit more than based on clinical experience.

There were still some limitations in our study, which mostly were because of the characteristics of a cohort study. Confounding factors could not be ignored in our study although statistical methods were used to partially control them. And relative small sample of these patients also limited the extension of our results.

In conclusion, our study has insisted again on the importance of early appropriate initial antimicrobial therapy for patients with gram-negative bacterial infection, and we also found that therapy adjustment based on clinicians' experience was accepted under some circumstances, but for patients with MDR bacterial infection, waiting until culture results might obtain more clinical benefits even if longer hospitalization time was anticipated.

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