Original Article

Differences in distribution and drug sensitivity of pathogens in lower respiratory tract infections between general wards and RICU

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Background: Lower respiratory tract infections (LRTIs) are common among patients in hospitals worldwide, especially in patients over the age of 60. This study investigates the differences in distribution and drug sensitivity of pathogens in LRTIs.

Methods: The clinical and laboratory data of 4,762 LRTI patients in the general ward and respiratory intensive care unit (RICU) of Xiangya Hospital (Changsha) were retrospectively analyzed.

Results: The infection rate of Gram-negative bacteria was significantly higher than that of Gram-positive bacteria in both the general ward and RICU (P<0.05). The incidence of Gram-negative bacteria infection was significantly higher in the RICU than in the general ward (P<0.05), whereas the incidence of Gram-positive bacteria infection is less in the RICU than in the general ward (P<0.05). In the general ward, the incidence of Gram-negative bacteria infection significantly increased (P<0.05) over time, whereas the incidence of Gram-positive bacteria infection significantly decreased from 1996 to 2011 (P<0.05). In the RICU, the incidence of Gram-positive bacteria infection decreased, while Gram-negative bacteria infections increased without statistical significance (P>0.05). *Staphylococcus pneumoniae* and *Staphylococcus aureus* were found to be the predominant Gram-positive strains in the general ward (34.70-41.18%) and RICU (41.66-54.87%), respectively (P>0.05). *Pseudomonas aeruginosa* and *Acinetobacter baumannii* were the predominant gram negative strains in the general ward (19.17-21.09%) and RICU (29.60-33.88%), respectively (P>0.05). *Streptococcus pneumoniae* is sensitive to most antibiotics with a sensitivity of more than 70%. *Staphylococcus aureus* is highly sensitive to vancomycin (100%), linezolid (100%), chloramphenicol (74.36-82.19%), doxycycline (69.57-77.33%), and sulfamethoprim (67.83-72.46%); however, its sensitivity to other antibiotics is low and decreased each year. Sensitivity of *Pseudomonas aeruginosa* to most β-lactam, aminoglycoside, and quinolone group antibiotics decreased each year.

Conclusions: The distribution and drug sensitivity of LRTI pathogens exhibit a high divergence between the general ward and RICU. *Streptococcus pneumoniae* may not be the predominant pathogen in LRTIs in some areas of China.

Keywords: Drug sensitivity; lower respiratory tract infections (LRTIs); respiratory intensive care unit (RICU); general ward; antibiotics

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Introduction

Lower respiratory tract infections (LRTIs) are common among patients in hospitals worldwide. LRTIs are associated with high overall mortality and account for 3% to 5% of deaths in adults, especially in patients over the age of 60 (1). Pneumonia is also the leading cause of death in children less than 5 years old (2). LRTIs are also the main cause of death in infants from infectious disease in America (3). LRTIs are classified as either community or hospital acquired. Hospital-acquired pneumonia (HAP) has an

attributable mortality rate of about 33% to 50% (4). LRTIs are usually treated with antibiotics, and management of LRTIs is made difficult by antibiotic resistance.

At present, therapy for community-acquired LRTIs is often empirical. Inappropriate antibiotics therapy, overuse of antibiotics, and misuse of antibiotics often occur, which may predispose patients to increased resistance to a class of antibiotics and may increase hospital mortality rate for patients in respiratory intensive care unit (RICUs) (5,6). Additionally, bacteria are constantly evolving and developing antibiotic-resistance. Therefore, effective selection and administration of antibiotics become a new challenge to clinicians. The knowledge of likely prevalent strains along with their resistance patterns will improve the management of LRTI patients. In China, over-the-counter antibiotics can be obtained easily. This antibiotic policy may increase the chance of bacteria developing drug resistance. Thus, a systemic investigation of the changes in various bacterial strains and their resistance to antibiotics in LRTI patients over a long period of time will benefit disease management.

Hospitalized LRTI patients are placed in the respiratory general ward or the RICU depending on their condition. However, a study comparing the bacterial strains and their resistance to antibiotics in general wards and RICUs is currently unavailable. In this study, we analyzed bacterial strains isolated from the sputum or endotracheal aspiration samples from patients hospitalized in the general ward and RICU from January, 1996 to December, 2011 and further analyzed the antibiotic resistance of predominant strains of bacteria.

Methodology

Subjects

A total of 4,762 positive sputum or endotracheal aspiration samples collected from hospitalized patients who were diagnosed with LRTI at the Department of Pneumology, Xiangya Hospital, Central South University (Changsha) from January 1996 to December 2011 are included in this study. The diagnoses were based on the diagnostic criteria of community-acquired pneumonia (CAP) and HAP, established by the third national pulmonary infection and ILD conference in 1998 (7).

Sputum collection

The second sputum in the morning of the second day after admission was carefully collected into a sterile container by forcing a deep cough after brushing teeth, rinsing the mouth twice using sterile water, and discarding the first sputum. The sputum was collected for 3 continuous days and sent for bacterial culture within 2 hours of collection. In order to reduce the chance of contamination with resident flora in the oral cavity and nasopharynx, samples were excluded from this study if the sample had more than 10 squamous epithelial cells and less than 25 polymorphonuclear leukocytes or their ratio is higher than 1:2.5 under low magnification microscope in smear examination. The bronchial secretions obtained by bronchofibroscope endotracheal aspiration or a protected specimen brush were sent for bacterial culture within 10 minutes.

Pathogen diagnosis and drug-susceptibility test

Samples were inoculated on blood agar plate using the streak plate technique and incubated for 24-48 hours at 37 ℃. The pathogen was identified as the following: (I) the predominant bacterium in three morning sputum cultures was the same; (II) the concentration of pathogen from bronchofibroscope endotracheal aspiration and protected brush sample was no less than 10^5 CFU/mL (half quantitative); and (III) the pathogens were confirmed by a standard method routinely used in the clinical laboratory. All isolated bacterial strains were tested for drug susceptibility using the Kirby-Bauer method. The double-disc synergy method was used for drug susceptibility assay of extended-spectrum β-lactamases (ESBLs). Results were interpreted according to National Committee for Clinical Laboratory Standards (NCCLS) breakpoints.

Statistic analysis

Data were presented as percentages. All data were statistically analyzed using SPSS 13.0. χ^2 test or Fisher test was used to compare differences between groups. A $P<0.05$ was considered statistically significant.

Results

Distribution and changes in pathogen

From January 1996 to December 2011, 4,762 positive bacterial strains were isolated, of which 2,685 strains were isolated from the general ward and 2,077 strains from RICU. We divided these 16 years into four periods for analysis: 1996-1999, 2000-2003, 2004-2007 and 2008-2011.

Table 1 Distribution of 4,762 bacteria isolated from 1996 to 2011

Strain	1996-1999		2000-2003		2004-2007		2008-2011	
	Quantity	Percentage (%)	Quantity	Percentage (%)	Quantity	Percentage (%)	Quantity	Percentage (%)
G^+ bacteria	121	15.14	123	13.73	144	11.33	162	9.02
G^- bacteria	678	84.86	773	86.27	1,127	88.67	1,634	90.98
Total	799	100.00	896	100.00	1,271	100.00	1,796	100.00

Table 2 Distribution of bacteria isolated from general wards from 1996 to 2011

Strain	1996-1999		2000-2003		2004-2007		2008-2011	
	Quantity	Percentage (%)	Quantity	Percentage (%)	Quantity	Percentage (%)	Quantity	Percentage (%)
G^+ bacteria	109	16.47	106	14.87	68	12.62	49	6.36
G^- bacteria	553	83.53	607	85.13	471	87.38	722	93.64
Total	662	100.00	713	100.00	539	100.00	771	100.00

Table 3 Distribution of bacteria isolated from respiratory intensive care unit (RICU) from 1996.01 to 2011.12

Strain	1996-1999		2000-2003		2004-2007		2008-2011	
	Quantity	Percentage (%)	Quantity	Percentage (%)	Quantity	Percentage (%)	Quantity	Percentage (%)
G^+ bacteria	12	8.76	17	9.29	76	10.38	113	11.02
G^- bacteria	125	91.24	166	90.71	656	89.62	912	88.98
Total	137	100.00	183	100.00	732	100.00	1,025	100.00

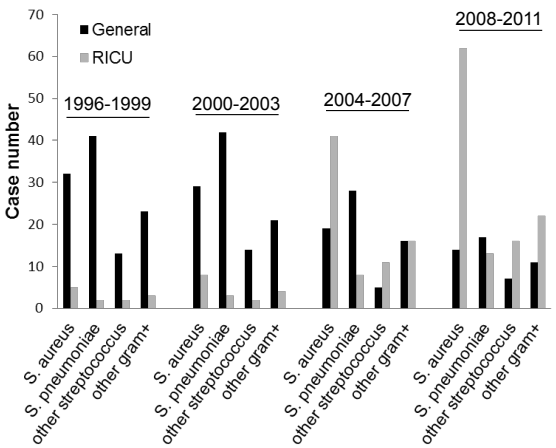

Figure 1 Distribution of specific Gram-positive bacteria in general wards and respiratory intensive care unit (RICU) from 1996 to 2011.

Distribution and changes in Gram-positive bacteria

During the four periods, the incidence of Gram-positive bacteria infection is lower than Gram-negative bacteria infection (P<0.05). The combined proportion of gram positive bacteria isolated from patients in the general ward and RICU decreased (P<0.05) (*Table 1*). The proportion of gram positive bacteria decreased in the general ward (P<0.05) (*Table 2*). In contrast, the proportion of gram positive bacteria increased in the RICU (8.76%, 9.29%, 10.38%, and 11.02%) without statistical significance (P>0.05) (*Table 3*). Among these isolated gram positive bacteria, *Streptococcus pneumoniae* is the most common bacterial strain in patients in the general ward throughout the four periods, while the second most common bacterial strain is *Staphylococcus aureus* (P>0.05) (*Figure 1*). In the RICU, *S. aureus* is the most common gram positive bacterium isolated from patients throughout those four periods with a tendency of increase each period (P>0.05) (*Figure 1*).

Distribution and changes in Gram-negative bacteria during the four periods

During the four periods, Gram-negative bacteria remained the major pathogen of hospital-acquired LRTIs (P<0.05). The combined proportion of gram negative bacteria isolated from patients in both the general ward and RICU increased (P<0.05) (*Table 1*). The proportion of gram negative bacteria increased in the general ward (P<0.05)

Table 4 Distribution of specific Gram-negative bacteria in general wards from 1996 to 2011

Strain	1996-1999		2000-2003		2004-2007		2008-2011	
	Quantity	Percentage (%)	Quantity	Percentage (%)	Quantity	Percentage (%)	Quantity	Percentage (%)
Pseudomonas aeruginosa	106	19.17	128	21.09	95	20.17	148	20.50
Acinetobacter baumannii	99	17.90	115	18.95	81	17.19	116	16.07
Klebsiella pneumoniae	83	15.01	85	14.00	76	16.14	82	11.36
Haemophilus parainfluenzae	89	16.09	104	17.13	85	18.05	122	16.89
Eschericia coli	56	10.13	55	9.06	49	10.40	58	8.03
Haemophilus influenzae	61	11.03	59	9.72	48	10.19	69	9.56
Other Gram-negative bacteria	59	10.67	61	10.05	37	7.86	127	17.59
Total	553	100.00	607	100.00	471	100.00	722	100.00

Table 5 Distribution of specific Gram-negative bacteria in RICU from 1996 to 2011

Strain	1996-1999		2000-2003		2004-2007		2008-2011	
	Quantity	Percentage (%)	Quantity	Percentage (%)	Quantity	Percentage (%)	Quantity	Percentage (%)
Pseudomonas aeruginosa	31	24.80	47	28.31	171	26.07	230	25.22
Acinetobacter baumannii	37	29.60	51	30.72	211	32.16	309	33.88
Klebsiella pneumoniae	12	9.60	19	11.45	66	10.06	67	7.35
Haemophilus parainfluenzae	7	5.60	10	6.02	26	3.96	39	4.27
Eschericia coli	11	8.80	19	11.45	54	8.23	67	7.35
Haemophilus influenzae	4	3.20	5	3.01	13	1.98	17	1.86
Other Gram-negative bacteria	23	18.40	15	9.04	115	17.54	183	20.07
Total	125	100.00	166	100.00	656	100.00	912	100.00

(*Table 2*), but decreased in the RICU without statistical significance (P>0.05) (*Table 3*). In the general ward, *Pseudomonas aeruginosa* was the most common pathogen throughout the four periods. *Acinetobacter baumannii* was the second most common bacterium, followed by *Haemophilus parainfluenzae*, *Klebsiella pneumonia*, *Haemophilus influenza*, and *Escherichia coli* (P<0.05) (*Table 4*). In the RICU, Acinetobacter baumannii is the most common bacterium isolated from patients throughout those four periods with a tendency of increase each period, followed by *P. aeruginosa*, *K. pneumonia*, *E. coli*, *H. parainfluenzae*, and *H. influenza* (P>0.05) (*Table 5*).

Comparison of pathogens involved in LRTIs between the general ward and RICU

Gram-negative bacteria are the main pathogens of LRTI in both the RICU and general ward, while the total infection

Table 6 Changes in drug-susceptibility of major Gram-positive bacteria to routine antibacterials (%)

Antibacterials	Staphylococcus aureus				Streptococcus pneumoniae			
	1996-1999	2000-2003	2004-2007	2008-2011	1996-1999	2000-2003	2004-2007	2008-2011
Meropenem	48.14	43.05	36.79	19.38	85.82	90.69	83.26	84.42
Imipenem	72.35	65.67	41.18	23.31	96.03	84.22	89.65	87.14
Cefepime	67.27	58.41	33.84	17.95	84.36	79.28	81.99	81.47
Cefoperazone/sulbactam	69.43	54.34	38.27	20.75	81.62	85.78	80.30	81.04
Ceftazidime	52.29	41.07	29.55	18.41	73.52	82.63	76.97	78.80
Ceftriaxone	56.47	37.36	26.54	11.44	79.22	73.58	81.79	76.54
Cefotaxime	44.02	32.45	15.73	9.98	80.33	79.05	75.29	74.37
Cephazolin	–	–	–	–	69.04	83.22	74.32	77.14
Piperacillin/tazobactam	34.15	35.26	21.39	12.72	82.66	68.35	76.47	73.81
Ampicillin/sulbactam	–	–	–	–	66.28	70.15	69.61	71.13
Mezolicillin	–	–	–	–	64.72	68.51	73.19	75.34
Levofloxacin	52.37	43.21	34.55	21.62	77.06	81.14	78.23	80.11
Chloramphenicol	74.36	82.19	75.34	79.01	87.64	80.77	84.41	83.25
Vancomycin	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
Linezolid	–	–	–	100.00	–	–	–	100.00
Doxycycline	69.57	77.33	74.61	73.53	84.22	88.16	91.35	89.23
Sulfamethoprim	72.46	67.83	70.92	68.45	79.52	75.61	80.44	76.37

–, means no report of this bacterium.

rate was higher in the RICU than in the general ward (P<0.05). The total incidence of Gram-positive bacteria infection was higher in the RICU than in the general ward during the periods of 1996-1999 and 2000-2003 (P<0.05), but there were no significant differences during the period of 2004-2007 (P>0.05). The incidence of Gram-negative bacteria infection was higher in the general ward than in RICU during the period of 2008-2011 (P<0.05). Infections of four major kinds of Gram-positive bacteria exhibited significant differences between the two wards (P<0.05). However, there were no significant differences during the periods of 1996-1999 and 2000-2003 (P>0.05). Incidences of seven main types of Gram-negative bacteria infection were significantly different between the RICU and general ward in four periods (P<0.05).

Drug-susceptibility of major LRTI pathogens to routine antibiotics

Among the gram positive bacteria, *S. pneumonia* was sensitive to most antibiotics with a sensitivity of more than 70%. As the predominant bacterium in the RICU, *S. aureus* is highly sensitive (>70%) to vancomycin, linezolid, chloramphenicol, doxycycline, and sulfamethoprim without a tendency of decrease in its antibiotic sensitivity during these 16 years. However, its sensitivity to other antibiotics, such as meropenem, imipenem, cefepime, cefperazone/sulbactam, ceftazidime, ceftriaxone, cefotaxime, piperacillin/tazobactam and levofloxacin was relative low (<25%) and decreased yearly (*Table 6*).

Among the gram negative bacteria, *P. aeruginosa* and *A. baumannii* had a high infection rate in both the general ward and RICU. P. aeruginosa remained highly sensitive to meropenem, cefperazone/sulbactam, amikacin, moderately sensitive to imipenem, cefepime, ceftazidime, levofloxacin, ciprofloxacin, and mildly sensitive (<30%) to other antibacterials. However, its sensitivity decreased progressively (*Table* 7).

A. baumanni was highly sensitive to amikacin and levofloxacin without a tendency of decrease, but its sensitivity to meropenem, imipenem, cefepime, cefperazone/sulbactam, ceftazidime, ceftriaxone, cefotaxime, piperacillin/tazobactam and ampicilin/sulbactam decreased (*Table* 7). *S. aureus* was highly sensitive to routinely used antibiotics in this hospital. Therefore, its drug-susceptibility was not analyzed.

Table 7 Changes in drug-susceptibility of major Gram-negative bacteria to routine antibacterials (%)

Antibacterials	Pseudomonas aeruginosa				Acinetobacter baumannii			
	1996-1999	2000-2003	2004-2007	2008-2011	1996-1999	2000-2003	2004-2007	2008-2011
Meropenem	95.16	94.24	93.05	86.36	87.44	88.21	77.35	68.42
Imipenem	88.37	83.41	72.55	64.70	84.29	76.40	65.22	41.38
Cefepime	69.25	63.47	59.32	56.61	75.30	66.57	48.65	34.54
Cefoperazone/sulbactam	87.22	87.16	84.43	84.27	96.13	96.06	92.24	51.41
Ceftazidime	76.55	73.46	74.62	54.28	68.30	80.53	71.35	43.65
Ceftriaxone	60.02	51.66	45.87	26.91	77.15	83.26	71.54	37.49
Cefotaxime	42.23	41.08	40.72	23.61	85.35	87.32	70.67	31.51
Piperacillin/tazobactam	–	–	69.08	32.46	–	–	76.30	44.23
Ampicillin/sulbactam	73.14	37.26	34.72	21.63	92.07	93.11	86.35	38.29
Mezolicillin	–	–	32.56	18.69	–	–	40.64	19.87
Aztreonam	76.25	68.19	67.33	34.35	46.23	48.60	51.45	27.94
Levofloxacin	74.66	60.84	53.76	57.29	68.55	82.30	73.51	77.02
Ciprofloxacin	83.11	51.63	64.32	44.05	76.20	34.74	48.33	–
Amikacin	93.03	90.21	79.18	79.04	87.11	88.06	77.41	83.58
Tobramycin	–	–	–	11.95	–	–	–	15.73
Gentamicin	–	–	–	21.84	–	–	–	22.77

–, means no report of this bacterium.

Discussion

LRTI is a major disease in China, affecting 12% to 16% of hospitalized patients (8). Studies on the distribution and drug sensitivity of LRTI pathogens have been conducted in some areas of China with variable observation periods. However, there is still a lack of a longer period of observation in LRTI patients in southern China, and a comparative analysis between general wards and RICU has not been performed previously. This study analyzed the distribution and drug sensitivity of bacterial strains isolated from 2,685 patients in the general ward and 2,077 patients in the RICU for 16 years. We found that the proportion of gram positive bacteria decreased in the general ward, but increased in the RICU yearly. In contrast, the proportion of gram negative bacteria in the general ward increased, but decreased in the RICU yearly. *S. pneumoniae* was the predominant gram positive bacterium, while *P. aeruginosa* was the predominant gram negative bacterium in the general ward. *S. aureus* was the predominant gram positive bacterium, while *A. baumannii* was the predominant gram negative bacterium in the RICU. Among the gram positive bacteria, *S. pneumoniae* and *S. aureus* were sensitive to most antibiotics though resistance was widely observed. Among the gram negative bacteria, *P. aeruginosa* remained highly to moderately sensitive to most antibiotics, but its sensitivity decreased progressively. Our findings will benefit disease management in this area and help reform the antibiotic policy worldwide.

S. pneumoniae remains the primary cause of severe CAP and a leading cause of death worldwide. It accounts for two-thirds of bacteremic pneumonias (9) and is the most common cause of pneumonia leading to hospitalization in all age groups (10). In this study, we found that *S. pneumoniae* was the predominant gram positive bacteria and accounts for 34.7-39.6% of bacteria in the general ward and 10.5-17.6% of bacteria in the RICU. However, gram positive bacteria account for a smaller proportion of LRTI bacteria with a decreasing tendency during the investigated 16 years (15% to 9%). In contrast, gram negative bacteria account for a bigger proportion of LRTI bacteria with an increasing tendency during the 16 years when the pathogen distribution was analyzed in hospitalized LRTI patients as a whole (85% to 91%). However, this tendency is not consistent with previous investigations in other areas of China (11,12). Notably, *S. pneumonia* was sensitive to most antibiotics with a sensitivity of more than 70%. Thus, *S. pneumoniae* is not the major cause of LRTI at this particular hospital.

A novel finding in this study is the difference in distribution between patients in the general ward and RICU.

In the general ward, *S. pneumoniae* was the predominant gram positive bacteria, followed by *S. aureus*, and their combined infection rate was more than 66%. However, infection rates of these bacteria did not change over 16 years. In the RICU, *S. aureus* was the predominant gram positive bacterium with an infection rate of about 50%. However, the infection rate increased during each period. This might be associated with an increase in invasive operations performed in the RICU. As for the infection rate of gram negative bacteria, *P. aeruginosa* was the predominant gram negative bacterium in the general ward with no change in infection rate over 16 years. In the RICU, *A. baumannii* was the predominant bacterium, but the infection rate increased during each period. The difference in distribution of pathogens between the general ward and RICU provides valuable insight for the use of antibiotics in treating patients with LRTIs.

The most common treatment of LRTIs is antibiotics, which have varying adverse effects and effectiveness (13). Our study demonstrated that *S. pneumoniae* was sensitive to most antibiotics without a tendency to decrease in sensitivity, while *S. aureus* was highly sensitive to vancomycin, linezolid, chloramphenicol, doxycycline and sulfamethoprim. However, the sensitivity of *S. aureus* to other antibacterials especially β-lactam antibiotics is low and decreased during each period. This phenomenon may be caused by overuse of broad-spectrum antibiotics. Fortunately, no vancomycin and linezolid resistant strains of *S. aureus* were found until now. Consistent with previous findings in *P. Aeruginosa* (14-16), this strain can easily develop drug resistance. The drug sensitivity of *P. aeruginosa* to most β-lactam, aminoglycoside and quinolone antibacterials decreased. The sensitivity of *A. baumannii* is similar to that of *P. aeruginosa*, showing decreased sensitivity to most β-lactam antibacterials. Since the *A. baumannii* infection rate is increasing, especially in the RICU, there is an urgent need to switch to other kinds of antibiotics. The differences mentioned above indicate that routine antibiotic treatment can achieve satisfactory curative effect on gram positive bacteria in general wards, but poor curative effect in the RICU. In the RICU, vancomycin, linezolid, chloramphenicol, doxycycline and sulfamethoprim should be used as soon as possible to prevent patient conditions from worsening due to bacteria developing resistance to currently administered antibiotics.

Conclusions

In conclusion, the distribution and drug sensitivity of LRTI pathogens exhibit a characteristic of high divergence between different areas in China and even between the general ward and RICU of the same hospital. The guideline for antibiotic use should match the local pathogen distribution and drug sensitivity. *S. pneumoniae* may not be the major cause of LRTIs in other areas. Moreover, overuse of broad-spectrum antibiotics should be avoided.

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