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Growing Antibiotic Resistance in Fatal Cases of Staphylococcal Pneumonia in the Elderly

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Abstract

Older people are often especially susceptible to pneumonia and bacteria may develop resistance to antibiotics quicker in the elderly, whose immune systems gradually diminish. This study analyses, retrospectively, resistance to antibiotics in high-risk elderly patients with fatal pneumonia. Records of all patients aged over 65 who did not survive a bout with pneumonia were gathered from the records of the Department of Pneumology of HELIOS Clinic in Wuppertal, Germany from the period of 2004–2014. Susceptibility testing was executed for the study population, whose pneumonia was triggered by various kinds of bacteria. We detected 936 pneumonia patients of the overall mean age of 68.0 ± 13.6 years, with the following pneumonia types: 461 (49.3 %) community-acquired, 354 (37.8 %) nosocomial-acquired, and 121 (12.9 %) aspiration pneumonia. There were 631 (67.4 %) males and 305 (32.6 %) females there. We identified 672 (71.8 %) patients who had a high risk for pneumonia, especially staphylococcal pneumonia ($p < 0.0001$). The elderly patients had a higher risk of dying from pneumonia (2.9 odds ratio, 95 % confidence interval 1.8–4.6; $p < 0.0001$); of the 185 pneumonia-related deaths, 163 (88.1 %) were in the elderly. In those with fatal staphylococcal pneumonia, a high antibiotic resistance rate was found for piperacillin-tazobactam ($p = 0.044$), cefuroxime ($p = 0.026$), cefazolin ($p = 0.043$), levofloxacin ($p = 0.018$), erythromycin ($p = 0.004$), and clindamycin ($p = 0.025$). We conclude that elderly patients with staphylococcal pneumonia show resistance to common antibiotics. However, no significant antibiotic resistance could be ascribed for other types of pneumonia in these patients.

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Keywords
Antibiotics • Elderly • Mortality • Pneumonia • Sensitivity • Resistance

1 Introduction

Pneumonia is associated with an acute infection of the respiratory tissue, is usually of bacterial origin, and manifests with cough, fever, and shortness of breath. Young adults usually make a complete recovery from pneumonia. In older and inveterately unwell individuals, pneumonia can be lethal (Pepersack 2014; Chong and Street 2008). Community-acquired pneumonia in older people is commonly triggered by *Streptococcus pneumonia*, *Staphylococcus aureus*, *Enterobacteriaceae*, *Haemophilus influenzae*, *Pseudomonas aeruginosa,* or *Legionella* spp. (El-Solh et al. 2001). Pneumonia in the elderly is a major challenge for physicians due to a high frequency, variety of causes, atypical clinical presentation, and age-related factors. Despite the special management of pneumonia in the elderly, no specific recommendations for antimicrobial treatment are provided in the international guidelines (Petrosillo et al. 2015). With the increase in antibiotic resistance, questions about the clinical impact of pneumonia in the elderly have now been raised (Feikin et al. 2000). An increase in mortality in elderly pneumonia patients has been documented (Feldman 2001; Marrie 2000). Therefore, it is important to investigate antibiotic resistance in fatal pneumonia in the elderly, so that a timely antibiotic therapy can be initiated to shorten the patients' suffering and the duration of hospitalization, in addition to reduced mortality.

In the present study we set out to retrospectively identify antibiotic resistance in patients aged over 65 with fatal pneumonia over the last decade, according to the International Classification of Diseases (ICD) J15.0–J15.6 (WHO 2015).

2 Methods

The Ethics Committee of the Witten-Herdecke University in Germany approved the study, waiving the requirement for informed consent due to a retrospective nature of the study. The majority of patients' information was anonymized before investigation. This quality-control observational investigation retrospectively analyzed the resistance to antimicrobial agents commonly used in daily practice in patients over 65 years old with fatal community- or nosocomial-acquired pneumonia. Data were retrieved from clinical records at the Department of Pneumology of HELIOS Clinic, Witten/Herdecke University, in Wuppertal, Germany, during the period of 1 January 2004 to 20 September 2014. The underlying bacterial background was the following: group B *Streptococcus* (ICD J15.3), *Streptococcus pneumoniae* (ICD J15.4), *Staphylococcus* (ICD J15.2), *Pseudomonas* (ICD J15.1), *Escherichia coli* (ICD J15.5), Gram-negative bacteria (ICD J15.6), or *Klebsiella* (ICD J15.0). The study elderly population was compared with pneumonia inpatients less than 64 years of age with fatal outcomes, and with those over and under 65 years of age who survived (Table 1). All in patients with nosocomial-acquired pneumonia who were first treated for different medical reasons in different departments were enclosed in this trial. The elderly with acute infections, like urinary infections or gastroenteritis, were disqualified from this investigation as were the neurological inpatients due to a restricted access to their records.

The criteria were used for the designation of pneumonia were the infiltrations in X-ray examination, typical clinical symptoms, along with a minimum of two of the following: breathing difficulty, fever > 38 °C, sputum production, and coughing.

2.1 Antibiotics Examined

Sensitivity and resistance of *Streptococcus*, *Staphylococcus*, *Pseudomonas*, *Escherichia coli*, Gram-negative bacteria, and *Klebsiella* to penicillin, oxacillin, ampicillin, piperacillin, piperacillin-tazobactam, ampicillin-sulbactam, cefuroxime, cefazolin, cefepime, ceftazidime, cefotaxime, tetracyclin, meropenem, imipenem, ciprofloxacin, levofloxacin, erythromycin, co-trimoxazole, clindamycin, gentamicin, vancomycin, teicoplanin, linezolid, rifampicin, fosfomycin, fucidin, colistin, tigecycline, and amikacin were examined. The frequency of application of these antibiotics in the elderly patients with pneumonia in the clinical setting was noted. For bacterial susceptibility testing, diameter breakpoints in the inhibition zone were utilized according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI 2012), with a modification for European standards introduced by the European Committee on Antimicrobial Susceptibility Testing (EUCAST 2011).

2.2 Susceptibility Testing

Streptococcus and *Staphylococcus* were identified based on growth on Columbia blood agar and chocolate agar (Becton Dickinson; Heidelberg, Germany) after 18–48 h at 37 °C using 5 % carbon dioxide and MALDI-TOF-MS (Bruker; Bremen, Germany). *H. influenzae* and Gram-negative bacteria were identified based on growth on chocolate agar with bacitracin (Becton Dickinson; Heidelberg, Germany). Gram-negative isolates and *H. influenzae* were further confirmed by use of the API NH system (biochemical reactions) for the identification of *Neisseria* and *Haemophilus* (bioMérieux; Marcy-l'Étoile, France). The panel selected to perform the evaluation for Gram-negative bacteria was NMIC/ID-76. BBL™ CHROMagar™ Orientation medium (Becton Dickinson; Heidelberg, Germany) was utilized to identify *Enterobacteriaceae*. The analyzed *Enterobacteriaceae* were *Escherichia coli*, *Enterobacter* spp., *Klebsiella*, *Proteus mirabilis*, *Citrobacter* spp., *Shigella*, *Serratia marcescens*, and *Yersinia*.

E. coli was grown on Columbia blood agar and MacConkey agar (Becton Dickinson; Heidelberg). The detection of *E. coli* by MALDI-TOF MS was executed on a Microflex LT device with FlexControl software (Bruker Daltonik; Bremen, Germany) for the automatic acquisition of mass spectra in the linear positive mode within a range of 2–20 kDa. The antimicrobial susceptibility testing was achieved using the programed system BD PHOENIX (Becton Dickinson; Heidelberg, Germany). The measurement of the minimum inhibitory concentration (MIC) was executed by E-test for the antibiotics which showed resistances to carbapenems.

BD™ Pseudosel™ Agar was used for detection of *P. aeruginosa* from clinical specimens. The agar contains cetrimide, which is a selective agent against alternative microbial flora. Cetrimide also enhances the production of white pyocyanin and fluorescein pigments of *Pseudomonas*, which exhibit characteristic blue-green and yellow-green colors. *P. aeruginosa* colonies from agar plates were suspended in Phoenix ID broth (Becton Dickinson; Heidelberg, Germany) to a 0.5–0.6 McFarland standard. The identification was executed by either BD Phoenix™ automated system or by MALDI-TOF MS (Bruker Daltonik; Bremen, Germany). A BD Phoenix™ mechanized microbiology technique (Becton-Dickinson Diagnostic Systems; Sparks, MD) was used, equipped with software suitable for the interpretation of susceptibility testing. Fungi were grown and detected on BD™ Sabouraud Agar (Becton Dickinson; Heidelberg, Germany). Susceptibility testing was executed on Mueller-Hinton agar (BD, Heidelberg, Germany) by means of McFarland 0.5 from overnight cultures, followed by incubation at 35 °C for 16–18 h.

A disc diffusion method established by Bauer et al. (1996) was also used for susceptibility testing for screening purposes and in cases

when carbapenemase activity was ruled out, e.g., imipenem, meropenem, or ceftazidime resistance. A synergy testing or metallo-beta-lactamase E-test was performed when phenotypic metallo-beta-lactamase-producing Gram-negative bacteria were suspected.

2.3 Microbiology

The expectoration from the oropharyngeal space and windpipe was acquired in a number of ways, such as bronchial lavage, tracheal secretion, or throat smear. To perform bronchial lavage, approximately 20 mL of 0.9 % salt-water solution were infused following the administration of a local anesthetic and sucked back by means of the fiber-optic bronchoscope. Bronchial fluid was then deposited in three separate, sterilized 40-mL sample containers. Tracheal secretions were recovered also using flexible fiber-optic bronchoscopy by suctioning into aseptic 40-mL specimen traps (Argyle^{TM}, Covidien, Neustadt/Donau, Germany). The throat-smear was taken by applying slight turning pressure on the pharyngeal cotton swab, using a commercially available cotton throat-swab system (MEUS Srl, Piove di Sacco, Italy). Expectoration was collected by having the patients cough into 30-mL antiseptic sputum containers (Salivette®, SARSTEDT, Nümbrecht, Germany), which was later examined microbiologically.

A microscopic investigation was performed after Gram staining at magnification of 80–1000x in a minimum five viewing fields, according to the standards of Bartlett (1987). Adhering to the morphological and bacteriological standards actually produced higher than expected doubts in the microbiological assessment of bacteria.

For blood cultures, 20 mL of blood was taken through venipuncture and transferred into the BACTEC plus aerobic and anaerobic/F media (Becton, Dickinson and Company; Heidelberg, Germany). The samples were then incubated at body temperature and checked if positive for growing microorganisms after 5 days. Negative vials were discarded.

2.4 Statistical Analysis

Categorical variables were expressed as proportions, while continuous variables were given as means ± SD. 95 % confidence intervals (CI) were calculated. Odds ratios (OR) were calculated for the mortality in different age-groups and for the risk of pneumonia triggered by different types of bacteria in patients over 65 years old compared with younger patients. Antibiotics used in each kind of pneumonia were compared with a 4×2 chi-squared test, where samples were categorized as sensitive or resistant after evaluating the outcome of the antibiotic susceptibility testing. In cases where the number of samples was greater than 120, Fisher's exact probability test was used to classify an antibiotic as sensitive or resistant in the contingency table. Types of pneumonia were compared with a 4×3 chi-squared test. One-way analysis of variance ANOVA for independent samples was performed to compare various agents causing pneumonia. Two-tailed tests were performed, and $p < 0.05$ was taken as an indicator of significant differences.

Additionally, the number of deaths during hospital stay was calculated in pneumonia patients. Thereafter, survival probabilities were determined by means of the Kaplan-Meier method.

3 Results

Overall, 936 pneumonia cases were detected out of the total of 6,932 patients. One hundred and eighty five (19.8 %) patients of all age died from pneumonia (Table 1). The male patients older than 65 years were more likely to come down with pneumonia (Table 2). In addition, patients older than 65 years had an increased risk of dying from pneumonia, which was gender independent (Table 2). Pneumonia in the elderly was mostly of staphylococcal origin. Interestingly, fewer pre-senile patients suffered from pneumonia and they were not significantly more likely to die from pneumonia. In the elderly patients with fatal pneumonia, antibiotic resistance was not found in streptococcus pneumonia (Table 3).

However, increased antibiotic resistance was found in those who died from staphylococcal pneumonia. The resistance concerned in this case the following antibiotics: piperacillin-tazobactam, cefuroxime, cefazolin, levofloxacin, erythromycin, and clindamycin (Table 4). Some antibiotic resistance could be seen for pneumonia caused by *Pseudomonas* (Table 5). No appreciable resistance was detected for pneumonia caused by *E. coli* (Table 6), Gram-negative bacteria (Table 7), *Haemophilus* (Table 8), or *Klebsiella* (Table 9). The elderly were more likely to develop community-acquired pneumonia (Table 10). The bacteria were mainly discovered in the tracheal and bronchial secretions (Table 11). There were 163 (17.4 %, 95 % CI 15.0–19.8 %) deaths related to pneumonia in the elderly patients. Consequently, the survival rate in hospitalized patients with pneumonia in this investigation was 82.6 % (95 % CI 79.9–85.3 %).

4 Discussion

This observational study, which covered a 10-year period, shows that pneumonia had an overall mortality rate of 19.8 % in all age groups. Pneumonia continues to be feared by clinicians due to its high mortality rate for all ages, ranging between 10 and 25 %. Fatal outcomes from pneumonia are related, among other factors, to the advanced age of patients (Pachon et al. 1990). A high frequency of pneumonia in the elderly has been shown in several studies (Feldman 2001; Marrie 2000). Pneumonia in the elderly could be categorized for scientific reasons as community-acquired pneumonia, nursing home-acquired pneumonia, or hospital-acquired pneumonia (Watkins and Lemonovich 2011; Niederman et al. 2001; Marik 2001). Although this classification was not considered in this study, community-acquired pneumonia was the most frequent form of pneumonia in the elderly.

In contrast, aspiration pneumonia was found in all age groups in the present study. Aspiration pneumonia is characterized as the misrouting of gastric content into the lungs (Dikensoy et al. 2002). While initial clinical reports focused on aspiration pneumonia resulting from accidental foreign-body aspiration (Riquelme et al. 2008), the number of studies concerning aspiration pneumonia in the elderly has increased with aging populations in recent decades (Donowitz and Cox 2007; Gutiérrez et al. 2006). Since the definition of aspiration pneumonia remains imprecise, a confusion may arise in clinical reports.

There are sex differences in pneumonia caused by different bacteria. The incidence rate of pneumonia observed in the present study was higher in males and was higher than that reported in other studies (Millett et al. 2013; El-Solh et al. 2001). The male sex has been defined as a risk factor for pneumonia among nursing home residents (Cunha 2001). We found that the elderly was suffering predominantly from staphylococcal pneumonia. The frequency of different bacteriological causes of pneumonia in the elderly varied by the region. These observations are in line with those reported in some previous studies (Hashemi et al. 2010; Schito 2006).

S. aureus is frequently resistant to beta-lactams and also to beta-lactamase-resistant penicillins (Gin et al. 2007). Although piperacillin and tazobactam have a very broad spectrum of activity in both the Gram-positive and Gram-negative bacteria (Skov et al. 2002), an increased resistance to this beta-lactam combination was unraveled in this present study. The increased antibiotic resistance of staphylococci was mainly present in the elderly pneumonia patients. Increased resistance of staphylococci to cefuroxime, a second-generation cephalosporin, was also observed in the elderly whose illness was fatal. Cefuroxime has a broad spectrum of activity and it is used to combat pneumonia in clinical practice. In the Gram-positive range, cefuroxime acts against staphylococci, streptococci, and pneumococci, and others (Shoji et al. 2014; Jalil et al. 2008). Additionally, resistance to cefazolin, a first-generation cephalosporin, was found in the elderly who died from pneumonia. Cefazolin is effective against staphylococci (Mukae et al. 2014). According to the results of the present study, special care

Table 1 Number (%) of pneumonia cases caused by various bacteria according to age-group

	Streptococcus	*Staphylococcus*	*Pseudomonas*	*Escherichia coli*	Gram-negative bacteria	*Haemophilus*	*Klebsiella*	Total no. of cases (%)
Male	45 (67.2)	168 (64.4)	113 (67.3)	92 (68.1)	46 (62.2)	60 (73.2)	107 (71.8)	631 (67.4)
Female	22 (32.8)	93 (35.6)	55 (32.7)	43 (31.9)	28 (37.8)	22 (26.8)	42 (28.2)	305 (32.6)
No. of cases	**67 (7.2)**	**261 (27.9)**	**168 (17.9)**	**135 (14.4)**	**74 (7.9)**	**82 (8.8)**	**149 (15.9)**	**936 (100)**
Age (years)								
18–60	22 (32.8)	46 (17.6)	39 (23.2)	18 (13.3)	21 (28.4)	26 (31.7)	30 (20.1)	202 (21.6)
60–64	7 (10.4)	17 (6.5)	8 (4.8)	6 (4.4)	9 (12.2)	7 (8.5)	8 (5.4)	62 (6.6)
65–69	10 (14.9)	38 (14.6)	26 (15.5)	23 (17.0)	9 (12.2)	12 (14.6)	15 (10.1)	133 (14.2)
70–79	17 (25.4)	86 (33.0)	70 (41.7)	50 (37.0)	25 (33.8)	28 (34.1)	61 (40.9)	337 (36.0)
80–89	10 (14.9)	70 (26.8)	25 (14.9)	33 (24.4)	10 (13.5)	9 (11.0)	35 (23.5)	192 (20.5)
>90	1 (1.5)	4 (1.5)	0	5 (3.7)	0	0	0	10 (1.1)

Table 2 Mortality rate of pneumonia caused by various bacteria according to age-group; number of cases (%)

	Streptococcus	*Staphylococcus*	*Pseudomonas*	*Escherichia coli*	Gram-negative bacteria	*Haemophilus*	*Klebsiella*	Total no. of patients (%)	ORa	95 % CI	p
Age (years)											
18–60	1 (14.3)	5 (7.6)	2 (6.1)	2 (7.4)	4 (26.7)	0	2 (7.4)	16 (8.6)	0.1	0.1–0.2	<0.0001
60–64	1 (14.3)	3 (4.5)	0	1 (3.7)	1 (6.7)	0	0	6 (3.2)	1.2	0.5–3.3	0.662
65–69	4 (57.1)	9 (13.6)	6 (18.2)	6 (22.2)	2 (13.3)	2 (20.0)	2 (7.4)	31 (16.8)	3.5	1.8–6.8	0.0001
70–79	0	25 (37.9)	18 (54.5)	12 (44.4)	5 (33.3)	6 (60.0)	16 (59.3)	82 (44.3)	3.7	2.1–6.6	<0.0001
80–89	1 (14.3)	21 (31.8)	7 (21.2)	4 (14.8)	3 (20.0)	2 (20.0)	7 (25.9)	45 (24.3)	3.6	1.9–6.6	<0.0001
>90	0	3 (4.5)	0	2 (7.4)	0	0	0	5 (2.7)	11.6	3.0–44.4	0.0003
No. of fatal cases	**7 (3.8)**	**66 (35.7)**	**33 (17.8)**	**27 (14.6)**	**15 (8.1)**	**10 (5.4)**	**27 (14.6)**	**185 (100)**			
Male	5 (71.4)	45 (68.2)	16 (48.5)	19 (70.4)	8 (53.3)	8 (80.0)	20 (74.1)	121 (65.4)	0.9	0.6–1.3	0.515
Female	2 (28.6)	21 (31.8)	17 (51.5)	8 (29.6)	7 (46.7)	2 (20.0)	7 (25.9)	64 (34.6)	0.9	0.6–1.3	0.515
ORs	0.5	2.1	1.2	1.2	1.1	0.6	1	–	–	–	–
95 % CI	0.2–1.1	1.5–3.0	0.8–1.8	0.7–1.8	0.6–2.0	0.3–1.2	0.7–1.6	–	–	–	–
p	0.077	<0.0001	0.412	0.493	0.733	0.127	0.872	–	–	–	–

ORa odds ratio of age-group mortality, *ORs* odds ratio of species-related mortality, *CI* confidence intervals

Table 3 Susceptibility testing of common antibiotics in streptococcal pneumonia

		>65 deceased (n = 163)		<64 deceased (n = 22)		>65 survivor (n = 509)		<64 survivor (n = 242)		
Drug groups	Active substance	No. using antibiotics	Sensitive/ resistant	No. using antibiotics	Sensitive/ resistant	No. using antibiotics	Sensitive/ resistant	No. using antibiotics	Sensitive/ resistant	p
Penicillins	Penicillin	0	5/0	0	2/0	1	32/0	0	27/0	1.0
	Ampicillin	0	5/0	0	2/0	1	32/0	0	27/0	1.0
	Piperacillin	0	5/0	0	2/0	0	31/0	0	27/0	1.0
Penicillin + beta-lactamase inhibitors	Ampicillin + Sulbactam	0	5/0	0	2/0	11	32/0	9	27/0	1.0
	Piperacillin + Tazobactam	4	5/0	2	2/0	12	32/0	12	27/0	1.0
Cephalosporins	Cefuroxime	0	5/0	0	2/0	5	31/0	3	27/0	1.0
	Cefotaxime	0	5/0	0	2/0	0	32/0	0	27/0	1.0
Gyrase inhibitors	Ciprofloxacin	0	0/0	0	0/0	0	0/0	2	0/1	1.0
	Levofloxacin	0	1/0	1	0/0	0	11/0	1	5/1	0.389
Macrolide	Erythromycin	0	5/0	0	2/0	3	28/1	0	22/5	0.622
Trimethoprim + Sulfonamide	Co-trimoxazole	0	1/0	0	1/0	0	7/1	0	4/1	0.999
Lincosamide	Clindamycin	0	5/0	1	1/1	3	29/0	1	24/2	0.049
Aminoglycosides	Gentamicin	0	0/0	0	0/0	0	0/6	0	0/2	1.0
Glycopeptide	Vancomycin	0	5/0	0	2/0	0	32/0	0	27/0	1.0

Table 4 Susceptibility testing of common antibiotics in pneumonia caused by *Staphylococcus*

		>65 deceased (n = 163)		<64 deceased (n = 22)		>65 survivor (n = 509)		<64 survivor (n = 242)		
Drug groups	Active substance	No. using antibiotics	Sensitive/ resistant	No. using antibiotics	Sensitive/ resistant	No. using antibiotics	Sensitive/ resistant	No. using antibiotics	Sensitive/ resistant	p
Penicillins	Penicillin	0	5/51	0	1/7	0	21/115	0	12/42	0.398
	Oxacillin	0	25/31	0	6/2	1	84/54	0	38/15	0.025
	Ampicillin	0	6/49	0	0/7	0	23/115	0	11/43	0.356
	Piperacillin	1	5/30	0	1/5	1	11/87	0	7/29	0.666
Penicillin + beta-lactamase inhibitors	Ampicillin + Sulbactam	2	25/31	1	5/2	21	69/55	8	33/16	0.104
	Piperacillin + Tazobactam	33	26/31	6	6/2	79	83/54	26	38/16	0.044
Cephalosporins	Cefuroxime	7	25/32	0	6/2	23	83/54	11	38/16	0.026
	Cefotaxime	0	8/15	0	2/1	1	23/27	0	11/6	0.258
	Cefazolin	0	22/28	0	3/2	2	70/48	0	36/14	0.043
	Cefepime	0	5/10	0	2/0	1	20/13	0	7/3	0.121
Tetracycline	Tetracyclin	0	34/2	0	3/0	0	79/1	0	26/0	0.386
Gyrase inhibitors	Ciprofloxacin	3	2/34	2	0/4	5	4/60	5	2/17	0.840
	Levofloxacin	1	15/29	0	3/4	4	58/43	3	27/14	0.018
Macrolide	Erythromycin	4	22/34	0	7/1	3	80/57	3	37/17	0.004
Trimethoprim + Sulfonamide	Co-trimoxazole	1	54/3	0	8/0	0	130/7	2	49/3	0.923
Lincosamide	Clindamycin	1	26/30	0	7/1	3	85/53	1	38/16	0.025
Aminoglycosides	Gentamicin	2	48/9	0	7/1	4	127/10	5	50/4	0.285
	Tobramycin	0	8/11	0	2/0	0	47/18	0	15/5	0.054
Glycopeptide	Vancomycin	19	57/0	1	8/0	30	137/0	8	53/0	1.0
	Teicoplanin	0	11/1	0	2/0	0	36/0	0	10/1	0.203
Oxazolidinone	Linezolid	1	27/0	0	1/0	5	47/0	1	16/0	1.0
Rifamycin	Rifampicin	9	47/3	0	8/0	18	120/1	3	49/0	0.077
Epoxid	Fosfomycin	1	46/4	0	8/0	0	106/12	0	42/2	0.550
Fusidic acid	Fucidin	0	43/2	0	7/0	0	92/1	0	38/1	0.615

Table 5 Susceptibility testing of common antibiotics in pneumonia caused by *Pseudomonas*

		>65 deceased (n = 163)		<64 deceased (n = 22)		>65 survivor (n = 509)		<64 survivor (n = 242)		
Drug groups	Active substance	No. using antibiotics	Sensitive/ resistant	No. using antibiotics	Sensitive/ resistant	No. using anti-biotics	Sensitive/ resistant	No. using antibiotics	Sensitive/ resistant	p
Penicillins	Ampicillin	0	0/17	0	0/0	1	0/40	0	0/26	1.0
	Piperacillin	0	24/6	0	1/1	33	62/2	2	28/15	0.0001
Penicillin + beta-lactamase inhibitors	Ampicillin + Sulbactam	1	0/30	0	0/2	12	1/88	4	0/45	0.833
	Piperacillin + Tazobactam	13	25/6	1	2/0	40	65/23	29	29/14	0.501
Cephalosporins	Cefuroxime	3	0/23	0	0/1	3	0/61	2	0/34	1.0
	Cefotaxime	0	0/3	0	0/0	0	1/10	0	0/4	1.0
	Cefepime	0	22/5	0	2/0	3	75/11	0	33/11	0.317
	Ceftazidime	1	23/4	1	1/0	5	62/17	4	28/12	0.468
Carbapenem	Imipenem	4	25/6	0	1/1	16	67/22	3	26/19	0.091
	Meropenem	1	23/4	0	1/1	5	65/17	1	26/11	0.384
Gyrase inhibitors	Ciprofloxacin	4	22/8	0	2/0	0	60/28	6	30/14	0.755
	Levofloxacin	0	9/8	0	1/0	5	30/23	1	13/10	1.0
Trimethoprim + Sulfonamide	Co-trimoxazole	0	0/23	0	0/1	0	0/60	0	0/33	1.0
Aminoglycosides	Gentamicin	1	20/6	0	2/0	4	66/19	1	27/12	0.633
	Tobramycin	0	21/5	0	1/0	0	56/16	1	26/10	0.801
	Amikacin	0	17/1	0	2/0	0	41/4	0	23/5	0.244
Tetracycline	Tigecycline	0	0/5	0	0/1	0	1//22	0	0/8	1.0
Others	Fosfomycin	0	2//5	0	0/0	0	0/21	0	1/7	0.036
	Colistin	0	1/0	0	1/0	0	3/0	0	4/0	1.0
	Rifampicin	0	0/6	0	0/1	0	0/22	0	0/9	1.0

Table 6 Susceptibility testing of common antibiotics in pneumonia caused by *Escherichia coli*

		>65 deceased (n = 163)		<64 deceased (n = 22)		>65 survivor (n = 509)		<64 survivor (n = 242)		
Drug groups	Active substance	No. using antibiotics	Sensitive/ resistant	No. using antibiotics	Sensitive/ resistant	No. using antibiotics	Sensitive/ resistant	No. using antibiotics	Sensitive/ resistant	p
Penicillins	Ampicillin	0	7/17	0	0/3	0	35/50	0	8/12	0.387
	Piperacillin	0	8/15	0	0/3	1	39/47	0	10/11	0.352
Penicillin + beta-lactamase inhibitors	Ampicillin + Sulbactam	6	10/11	0	0/3	16	45/37	5	12/9	0.293
	Piperacillin + Tazobactam	11	17/4	2	1/1	48	68/12	14	15/2	0.538
Cephalosporins	Cefepime	0	14/4	0	1/2	0	66/9	0	13/4	0.058
	Cefotaxime	0	19/5	0	1/2	0	76/9	1	15/5	0.026
	Ceftazidime	1	18/4	0	1/2	1	75/9	0	15/4	0.030
	Cefuroxime	4	16/5	0	1/2	8	68/13	0	15/5	0.146
Glycylcycline	Tetracycline	0	3/3	1	0/0	0	6/7	0	1/0	1.0
	Tigecycline	0	10/0	0	2/0	0	26/0	0	6/0	1.0
Carbapenem	Imipenem	4	24/0	2	3/0	12	87/0	3	21/0	1.0
	Meropenem	0	19/1	0	2/1	1	80/0	2	18/0	<0.0001
Gyraseinhibitors	Ciprofloxacin	3	17/7	0	2/1	6	69/17	0	18/3	0.593
	Levofloxacin	1	15/5	0	2/1	2	64/18	0	16/3	0.859
Aminoglycosides	Amikacin	0	15/1	0	2/0	0	60/0	0	17/0	0.189
	Gentamicin	0	20/4	0	2/1	0	81/6	0	21/0	0.075
	Tobramycin	0	13/2	0	2/0	0	56/6	0	17/0	0.453
Tri-methoprim + Sulfamethoxazole	Co-trimoxazole	0	15/8	0	2/1	0	63/22	0	17/4	0.682
Polymyxin	Colistin	0	1/0	0	0/0	0	2/0	0	0/0	1.0
Others	Fosfomycin	0	12/0	0	2/0	0	58/1	0	12/2	0.180

Table 7 Susceptibility testing of common antibiotics in pneumonia caused by Gram-negative bacteria

		>65 deceased (n = 163)		<64 deceased (n = 22)		>65 survivor (n = 509)		<64 survivor (n = 242)		
Drug groups	Active substance	No. using antibiotics	Sensitive/ resistant	No. using antibiotics	Sensitive/ resistant	No. using antibiotics	Sensitive/ resistant	No. using antibiotics	Sensitive/ resistant	p
Penicillins	Ampicillin	0	2/5	0	0/5	0	2/31	0	0/5	0.202
	Piperacillin	1	5/3	0	3/2	1	23/8	0	3/2	0.737
Penicillin + beta-lactamase inhibitors	Ampicillin + Sulbactam	1	2/6	0	1/4	3	4/26	1	1/4	0.693
	Piperacillin + Tazo-bactam	6	6/3	3	3/1	15	26/6	3	3/1	0.778
Cephalosporins	Cefepime	0	6/0	0	5/0	0	27/1	0	5/0	1.0
	Cefotaxime	0	6/2	0	3/2	0	27/7	0	3/2	0.657
	Ceftazidime	0	6/3	0	4/0	2	25/4	0	4/0	0.449
	Cefuroxime	0	2/5	0	0/5	2	7/26	0	0/5	0.579
Glycylcycline	Tetracycline	0	0/5	0	1/2	0	1/2	0	1/2	0.382
	Tigecycline	0	1/0	0	0/0	1	2/1	0	0/0	1.0
Carbapenem	Imipenem	3	6/2	0	5/0	4	30/3	0	5/0	0.400
	Meropenem	1	8/2	0	5/0	1	30/2	0	5/0	0.318
Gyrase inhibitors	Ciprofloxacin	2	8/2	1	4/1	4	29/4	1	4/1	0.631
	Levofloxacin	0	6/1	0	1/1	6	20/3	0	1/1	0.170
Aminoglycosides	Amikacin	0	3/2	0	4/0	0	15/1	0	4/0	0.217
	Gentamicin	0	7/2	0	4/1	2	28/5	0	4/1	0.932
	Tobramycin	0	2/4	0	3/0	0	13/6	0	3/0	0.118
Trimethoprim + Sulfamethoxazole	Co-trimoxazole	0	9/1	0	4/1	1	28/5	0	4/1	0.999
Polymyxin	Colistin	0	2/0	0	0/0	0	2/0	0	0/0	1.0
Others	Fosfomycin	0	2/2	0	2/0	0	11/1	0	2/0	0.175

Table 8 Susceptibility testing of common antibiotics in pneumonia caused by *Haemophilus*

		>65 deceased (n = 163)		<64 deceased (n = 22)		>65 survivor (n = 509)		<64 survivor (n = 242)		
Drug groups	Active substance	No. using antibiotics	Sensitive/ resistant	No. using antibiotics	Sensitive/ resistant	No. using antibiotics	Sensitive/ resistant	No. using antibiotics	Sensitive/ resistant	p
Penicillins	Ampicillin	0	8/2	0	0/0	1	27/11	0	26/7	0.767
	Piperacillin	1	4/1	0	0/0	0	9/3	0	6/1	0.999
Penicillin + beta-lactamase inhibitors	Ampicillin + Sulbactam	1	9/1	0	0/0	14	36/3	13	29/2	0.999
	Piperacillin + Sulbactam	2	5/0	0	0/0	3	11/0	3	6/1	0.522
	Piperacillin + Tazobactam	5	10/0	0	0/0	12	37/1	7	30/1	0.999
Cephalosporins	Cefuroxime	0	9/1	0	0/0	2	35/2	1	29/4	0.543
	Cefotaxime	0	10/0	0	0/0	0	37/1	0	31/1	0.999
Gyrase inhibitors	Ciprofloxacin	2	9/0	0	0/0	0	39/0	3	33/0	1.0
	Levofloxacin	0	5/0	0	0/0	2	32/1	2	25/0	0.999
Macrolide	Erythromycin	0	5/4	0	0/0	1	21/15	0	17/12	1.0

Table 9 Susceptibility testing of common antibiotics in pneumonia caused by *Klebsiella*

		>65 deceased (n = 163)		<64 deceased (n = 22)		>65 survivor (n = 509)		<64 survivor (n = 242)		
Drug groups	Active substance	No. using anti-biotics	Sensitive/ resistant	No. using anti-biotics	Sensitive/ resistant	No. using antibiotics	Sensitive/ resistant	No. using antibiotics	Sensitive/ resistant	p
Penicillins	Ampicillin	0	0/25	0	0/2	0	0/85	0	0/36	1.0
	Piperacillin	0	1/16	0	0/0	0	4/64	0	0/32	0.419
Penicillin + beta-lactamase inhibitors	Ampicillin + Sulbactam	1	13/11	0	2/0	13	56/27	6	23/13	0.466
	Piperacillin + Tazobactam	14	17/8	1	2/0	47	60/17	19	26/9	0.641
Cephalosporins	Cefuroxime	0	19/6	0	2/0	10	58/23	3	26/10	0.816
	Cefotaxime	0	19/6	0	2/0	0	69/15	0	28/8	0.775
	Cefepime	0	17/6	0	2/0	0	59/11	0	27/8	0.566
	Ceftazidime	1	16/6	0	2/0	1	60/12	1	27/8	0.591
Carbapenem	Imipenem	2	25/0	1	2/0	0	85/0	4	36/0	1.0
	Meropenem	1	25/0	0	2/0	0	77/0	0	36/0	1.0
Gyrase inhibitors	Ciprofloxacin	0	19/6	0	1/0	6	63/20	0	28/8	0.948
	Levofloxacin	0	13/5	0	2/0	1	48/17	0	25/6	0.860
Trimethoprim + Sulfo-namide	Co-trimoxazole	0	19/5	0	2/0	0	70/11	0	29/7	0.692
Aminoglycosides	Gentamicin	1	23/2	0	2/0	2	74/8	1	34/2	0.857
	Tobramycin	0	12/1	0	0/0	0	42/4	0	17/2	1.0
	Amikacin	0	11/0	0	0/0	0	42/1	0	18/0	0.999
Tetracycline	Tigecycline	0	2/0	0	0/0	0	14/1	0	7/0	0.999
	Tetracycline	0	8/3	0	1/0	0	24/5	0	13/2	0.773
Others	Fosfomycin	1	9/2	0	0/0	0	31/5	1	15/3	0.902

Table 10 Type of pneumonia according to age-group and mortality

	>65 deceased	<64 deceased	>65 survivor	<64 survivor	p
Community-acquired	73 (44.8)	9 (40.9)	242 (47.5)	137 (56.6)	
Nosocomial-acquired	65 (39.9)	5 (22.7)	213 (41.8)	71 (29.3)	
Aspiration	25 (15.3)	8 (36.4)	54 (10.6)	34 (14.0)	
Total no. of patients (%)	**163 (17.4)**	**22 (2.4)**	**509 (54.4)**	**242 (25.9)**	**0.0004**

Table 11 Specimen collection and bacterial species in patients with pneumonia; number (%) of patients

Specimen	>65 deceased	<64 deceased	>65 survivor	<64 survivor	p
Sputum	12 (7.4)	0	71 (13.9)	31 (12.8)	
Throat swab	3 (1.8)	1 (4.5)	3 (0.6)	2 (0.8)	
Tracheal secretion	92 (56.4)	14 (63.6)	231 (45.4)	116 (47.9)	
Bronchial secretion	40 (24.5)	4 (18.2)	136 (26.7)	61 (25.2)	
Arterial blood culture	2 (1.2)	0	6 (1.2)	4 (1.7)	
Venous blood culture	11 (6.7)	3 (13.6)	58 (11.4)	27 (11.2)	
Secretion drainage	3 (1.8)	0	4 (0.8)	1 (0.4)	0.110
Species					
Streptococcus pneumoniae	5 (3.1)	2 (9.1)	33 (6.5)	27 (11.2)	
Staphylococcus aureus	25 (15.3)	5 (22.7)	84 (16.5)	37 (15.3)	
Staphylococcus epidermidis	2 (1.2)	0	6 (1.2)	1 (0.4)	
Coagulase-negative staphylococci	3 (1.8)	0	5 (1.0)	4 (1.7)	
Staphylococcus haemolyticus	1 (0.6)	0	1 (0.2)	0	
Methicillin-resistant *Staphylococcus aureus* (MRSA)	27 (16.6)	3 (13.6)	40 (7.9)	11 (4.5)	
Staphylococcus capitis	0	0	3 (0.6)	0	
Staphylococcus hominis	0	0	1 (0.2)	1 (0.4)	
Staphylococcus warneri	0	0	0	1 (0.4)	
Pseudomonas aeruginosa	31 (19.0)	2 (9.1)	90 (17.7)	45 (18.6)	
Escherichia coli	24 (14.7)	3 (13.6)	87 (17.1)	21 (8.7)	
Enterobacter cloacae	1 (0.6)	1 (4.5)	3 (0.6)	1 (0.4)	
Serratia marcescens	4 (2.5)	3 (13.6)	16 (3.1)	12 (5.0)	
Proteus mirabilis	1 (0.6)	1 (4.5)	7 (1.4)	6 (2.5)	
Acinetobacter baumannii	2 (1.2)	0	2 (0.4)	0	
Stenotrophomonas maltophilia	1 (0.6)	0	2 (0.4)	3 (1.2)	
Citrobacter koseri	1 (0.6)	0	0	0	
Prevotella buccae	0	0	1 (0.2)	1 (0.4)	
Enterobacter aerogenes	0	0	1 (0.2)	2 (0.8)	
Proteus vulgaris	0	0	1 (0.2)	0	
Serratia plymuthica	0	0	1 (0.2)	0	
Haemophilus influenzae	7 (4.3)	0	21 (4.1)	18 (7.4)	
Haemophilus parainfluenzae	3 (1.8)	0	18 (3.5)	15 (6.2)	
Klebsiella pneumoniae	25 (15.3)	2 (9.1)	66 (13.0)	28 (11.6)	
Klebsiella ozaenae	0	0	1 (0.2)	1 (0.4)	
Klebsiella oxytoca	0	0	17 (3.3)	7 (2.9)	
Klebsiella granulomatis	0	0	2 (0.4)	0	
Total no. of patients (%)	**163 (17.4)**	**22 (2.4)**	**509 (54.4)**	**242 (25.9)**	

is required in the application of cefazolin for the treatment of pneumonia in the elderly.

The elderly patients with staphylococcal pneumonia in the present study also had high antibiotic resistance to levofloxacin, a gyrase inhibitor. Gyrase inhibitors have emerged as an important class of antibiotics in the treatment of pneumonia (Nasiri et al. 2013). A secondary development of resistance in staphylococci is possible during treatment with levofloxacin in pneumonia patients (Hidalgo et al. 2008). Another study demonstrates a very high rate of fluoroquinolone resistance in *S. aureus*, reaching almost 100 % in methicillin resistant isolates (Kim et al. 2004). Therefore, close monitoring of antimicrobial resistance is necessary during treatment with levofloxacin.

As a result of unnecessary application of macrolides, resistance to these antibiotics is frequently encountered. Erythromycin acts against a broad spectrum of Gram-positive bacteria, but its activity against staphylococci may be reduced due to the occurrence of resistance (Piątkowska et al. 2012). A past study shows this previously unidentified process of *S. aureus* resistance to erythromycin (Ying and Tang 2010). The present study confirmed a high frequency of resistance of staphylococci to erythromycin in the elderly pneumonia patients with a fatal outcome.

Resistance to antibiotics among staphylococci is a growing problem in everyday practice of treating pneumonia. This has prompted a renewed interest in the use of lincosamide antiinfection agents to treat *S. aureus* pneumonia (Guay 2007). Clindamycin is a clinically relevant representative of this group of antibiotics, which is usually effective against staphylococci (Prabhu et al. 2011). However, the extensive use of the antibiotics of this class has escalated staphylococci resistance to them (Colakoğlu et al. 2008; Yilmaz et al. 2007; Kader et al. 2005). The increased resistance to clindamycin was also demonstrated by the susceptibility testing in the present study, mainly in the elderly pneumonia patients who failed to survive. Since the primary clindamycin-resistant staphylococci may occur, sensitivity of staphylococci to clindamycin must be evidenced *in vitro* before the onset of pneumonia treatment.

A limitation of this study is that it was performed in a single university hospital. Since bacterial resistance to antibiotics may be regional, the results of this study may not be widely applicable and ought to be considered mostly for comparison with other studies in different regions. Also, after completion of the present study, it turned out that the antibiotics were not always evenly distributed in susceptibility testing.

In conclusion, bacterial resistance to antibiotics is a widespread problem. The emergence of resistance to piperacillin-tazobactam, cefuroxime, cefazolin, levofloxacin, erythromycin, and clindamycin in staphylococci pneumonia in the elderly may contribute to fatal outcomes. For that reason, close clinical and microbial monitoring of antibiotic resistance must be carried out during the treatment of pneumonia in patients over 65 years of age.

Conflicts of Interests The authors declare no competing financial or otherwise interests in relation to this study.

References

Barlett JG (1987) Diagnosis of bacterial infections of the lung. Clin Chest Med 8:119–134

Bauer AW, Kirby WM, Sherris JC, Turck M (1996) Antibiotic susceptibility testing by a standardized single disk method. Am J Clin Pathol 45:493–496

Chong CP, Street PR (2008) Pneumonia in the elderly: a review of severity assessment, prognosis, mortality, prevention, and treatment. South Med J 101(11):1134–1140

CLSI (2012) Clinical and Laboratory Standards Institute (2012) Performance standards for antimicrobial susceptibility testing. CLSI M100-S22. http://clsi.org/blog/2012/01/13/clsi-publishes-2012-antimicrobial-susceptibility-testing-standards/. Accessed 14 July 2015

Colakoğlu S, Alişkan H, Turunç T, Demiroğlu YZ, Arslan H (2008) Prevalence of inducible clindamycin resistance in Staphylococcus aureus strains isolated from clinical samples. Mikrobiyol Bul 42(3):407–412 (Article in Turkish)

Cunha BA (2001) Pneumonia in the elderly. Clin Microbiol Infect 7(11):581–588

Dikensoy O, Usalan C, Filiz A (2002) Foreign body aspiration: clinical utility of flexible bronchoscopy. Postgrad Med J 78(921):399–403

Donowitz GR, Cox HL (2007) Bacterial community-acquired pneumonia in older patients. Clin Geriatr Med 23(3):515–534

El-Solh AA, Sikka P, Ramadan F, Davies J (2001) Etiology of severe pneumonia in the very elderly. Am J Respir Crit Care Med 163(3 Pt 1):645–651

EUCAST (2011) European Committee on antimicrobial susceptibility testing breakpoints 2011–2014. http://www.eucast.org. Accessed 14 July 2015

Feikin DR, Schuchat A, Kolczak M et al (2000) Mortality from invasive pneumococcal pneumonia in the era of antibiotic resistance, 1995–1997. Am J Public Health 90(2):223–229

Feldman C (2001) Pneumonia in the elderly. Med Clin North Am 85(6):1441–1459

Gin A, Dilay L, Karlowsky JA, Walkty A, Rubinstein E, Zhanel GG (2007) Piperacillin-tazobactam: a beta-lactam/beta-lactamase inhibitor combination. Expert Rev Anti Infect Ther 5(3):365–383

Guay D (2007) Update on clindamycin in the management of bacterial, fungal and protozoal infections. Expert Opin Pharmacother 8(14):2401–2444

Gutiérrez F, Masiá M, Mirete C, Soldán B, Rodríguez JC, Padilla S, Hernández I, Royo G, Martin-Hidalgo A (2006) The influence of age and gender on the population-based incidence of community-acquired pneumonia caused by different microbial pathogens. J Infect 53(3):166–174

Hashemi SH, Soozanchi G, Jamal-Omidi S, Yousefi-Mashouf R, Mamani M, Seif-Rabiei MA (2010) Bacterial aetiology and antimicrobial resistance of community-acquired pneumonia in the elderly and younger adults. Trop Doct 40(2):89–91

Hidalgo M, Reyes J, Cárdenas AM, Díaz L, Rincón S, Vanegas N, Díaz PL, Castañeda E, Arias CA (2008) Resistance profiles to fluoroquinolones in clinical isolates of Gram positive cocci. Biomedica 28 (2):284–294 (Article in Spanish)

Jalil A, Niazi ID, Khan SU (2008) Evaluation of restoration of sensitivities of resistant Staphylococcus aureus isolates by using cefuroxime and clavulanic acid in combination. J Ayub Med Coll Abbottabad 20 (2):28–30

Kader AA, Kumar A, Krishna A (2005) Induction of clindamycin resistance in erythromycin-resistant, clindamycin susceptible and methicillin-resistant clinical Staphylococcal isolates. Saudi Med J 26 (12):1914–1917

Kim HB, Lee B, Jang HC, Kim SH, Kang CI, Choi YJ, Park SW, Kim BS, Kim EC, Oh MD, Choe KW (2004) A high frequency of macrolide-lincosamide-streptogramin resistance determinants in Staphylococcus aureus isolated in South Korea. Microb Drug Resist 10(3):248–254

Marik PE (2001) Aspiration pneumonitis and aspiration pneumonia. N Engl J Med 344(9):665–671

Marrie TJ (2000) Community-acquired pneumonia in the elderly. Clin Infect Dis 31(4):1066–1078

Millett ER, Quint JK, Smeeth L, Daniel RM, Thomas SL (2013) Incidence of community-acquired lower respiratory tract infections and pneumonia among older adults in the United Kingdom: a population-based study. PLoS One 8(9), e75131

Mukae H, Kawanami T, Yatera K, Yanagihara K, Yamamoto Y, Kakeya H, Tokimatsu I, Kadota J, Kohno S (2014) Efficacy and safety of levofloxacin in patients with bacterial pneumonia evaluated according to the new "Clinical evaluation methods for new antimicrobial agents to treat respiratory infections (Second Version)". J Infect Chemother 20 (7):417–422

Nasiri MI, Naqvi SB, Zaidi AA, Saeed R, Raza G (2013) Comparative study on resistant pattern of clinical isolates against levofloxacin and cefepime. Pak J Pharm Sci 26(2):415–419

Niederman MS, Mandell LA, Anzueto A, Bass JB, Broughton WA, Campbell GD, Dean N et al (2001) Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med 163:1730–1754

Pachon J, Prados MD, Capote F, Cuello JA, Garnacho J, Verano A (1990) Severe community-acquired pneumonia. Etiology, prognosis, and treatment. Am Rev Respir Dis 142(2):369–373

Pepersack T (2014) Specificities of pneumonia in geriatrics. Rev Med Brux 35(4):368–374 (Article in French)

Petrosillo N, Cataldo MA, Pea F (2015) Treatment options for community-acquired pneumonia in the elderly people. Expert Rev Anti Infect Ther 13 (4):473–485

Piątkowska E, Piątkowski J, Przondo-Mordarska A (2012) The strongest resistance of Staphylococcus aureus to erythromycin is caused by decreasing uptake of the antibiotic into the cells. Cell Mol Biol Lett 17 (4):633–645

Prabhu K, Rao S, Rao V (2011) Inducible clindamycin resistance in Staphylococcus aureus isolated from clinical samples. J Lab Phys 3(1):25–27

Riquelme OR, Riquelme OM, Rioseco ZML, Gómez MV, Cárdenas G, Torres C (2008) Community-acquired pneumonia in the elderly: clinical and nutritional aspects. Rev Med Chil 136(5):587–593 (Article in Spanish)

Schito GC (2006) The importance of the development of antibiotic resistance in Staphylococcus aureus. Clin Microbiol Infect 12(Suppl 1):3–8

Shoji T, Hirai Y, Osawa M, Totsuka K (2014) Cefazolin therapy for methicillin-susceptible Staphylococcus aureus bacteremia in Japan. J Infect Chemother 20 (3):175–180

Skov R, Frimodt-Møller N, Espersen F (2002) In vitro susceptibility of Staphylococcus aureus towards amoxycillin-clavulanic acid, penicillin-clavulanic

acid, dicloxacillin and cefuroxime. APMIS 110 (7–8):559–564
Watkins RR, Lemonovich TL (2011) Diagnosis and management of community-acquired pneumonia in adults. Am Fam Physician 83:1299–1306
WHO (2015) International Classification of Diseases (ICD). http://www.who.int/classification/icd/en/. Accessed 6 June 2015
Yilmaz G, Aydin K, Iskender S, Caylan R, Koksal I (2007) Detection and prevalence of inducible clindamycin resistance in staphylococci. J Med Microbiol 56(Pt 3):342–345
Ying L, Tang D (2010) Recent advances in the medicinal chemistry of novel erythromycin-derivatized antibiotics. Curr Top Med Chem 10(14):1441–1449