ORIGINAL RESEARCH

Community acquired pneumonia among adult patients at an Egyptian university hospital: bacterial etiology, susceptibility profile and evaluation of the response to initial empiric antibiotic therapy

Rehab H El-Sokkary[1]
Raghdaa A Ramadan[1]
Mohamed El-Shabrawy[2]
Lobna A El-Korashi[1]
Abeer Elhawary[2]
Sameh Embarak[2]
Rehab M Elsaid Tash[1]
Neveen G Elantouny[3]

[1]Medical Microbiology and Immunology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt; [2]Chest Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt; [3]Internal Medicine Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt

Correspondence: Rehab H El-Sokkary
Medical Microbiology and Immunology Department, Faculty of Medicine, Zagazig University, 12 Abdaziz Ali Street, Zagazig Sharkeia, Egypt
Tel +20 100 565 0273
Fax +20 55 230 7830
Email rehab_elsokkary@yahoo.com

Background: Effective empirical antibiotic therapy for community acquired pneumonia (CAP), based on frequently updated data about the pattern of bacterial distribution and their antimicrobial susceptibilities, is mandatory.

Aim: To identify the bacterial etiology of CAP in adults and their antibiotic susceptibility patterns and to evaluate the response to initial empirical antibiotic therapy in an Egyptian university hospital.

Settings and design: A cross-sectional hospital-based study.

Patients and methods: CAP cases were selected by systemic random sampling from those admitted to the chest department. All were evaluated at admission and 4 days after starting empiric therapy. Typical bacteria were isolated, identified and tested for their antibiotic susceptibility. An indirect IF assay was used to diagnose atypical bacteria. Clinical response to initial empiric antibiotic therapy was clinically, laboratory and radiologically evaluated.

Results: Two hundred and seventy CAP patients were included. Bacteria represented 50.4% of them. *Klebsiella pneumoniae* was the most prevalent bacterium (10.37%) followed by *Streptococcus pneumoniae* and *P. aeruginosa* (7.78% each). Overall, 76.2% of isolates showed a multidrug resistant phenotype: 82.61% (19/23) *S. pneumoniae*, 89.66% (26/29) *K. pneumoniae*, 65.22% (15/23) *Pseudomonas aeruginosa*, 87.50% (7/8) *Escherichia coli* and 81.25% (13/16) *Staphylococcus aureus*. Broad spectrum β-lactams, especially carbapenems, and moxifloxacin showed in vitro efficacy on most of the tested isolates. Forty-three cases (15.9%) were nonresponders, 37 (86%) of them showed bacterial etiology. The highest rate of nonresponsiveness (30.43%) was observed in cases receiving antipseudomonal/antipneumococcal β-lactam plus a fluoroquinolone for suspected *P. aeruginosa* infection.

Conclusion: Multidrug resistance in bacteria causing CAP and high frequency of isolation of hospital pathogens are prominent features of this study. Azithromycin containing regimens were associated with the lowest rates of nonresponsiveness. Development and implementation of an antibiotic stewardship program are highly recommended for CAP management.

Keywords: pneumonia, atypical bacteria, respiratory infection, community, antibiotic stewardship, empirical therapy, infection control

Introduction

Community-acquired pneumonia (CAP) is an issue of public health concern, being a leading cause of morbidity that often requires hospitalization, and a significant cause

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of mortality, especially in severe cases presenting with sepsis or requiring assisted ventilation.[1] Multiple agents can give rise to CAP but a few are responsible for the majority of cases, with bacterial pathogens accounting for a significant percentage of the cases.[2] Despite the advances in management of CAP and the development of new diagnostic modalities, a definitive microbial etiology is not usually available for the first 3–4 days and clinical evaluation in the first two days is strongly recommended.[3]

In CAP, immediate initiation of effective antibiotic therapy is crucial for a favorable outcome, and empirical choice of initial antibiotic therapy is the mainstay of treatment. However, the rapid emergence and wide dissemination of microbial resistance have rendered most of the available antimicrobial agents ineffective.[4]

Evaluation of clinical response to initial treatment, ideally performed after 72 hours of starting treatment, is critical, as failure of such response carries a high risk of death. In this context, this study was conducted to identify the bacterial etiology of CAP in adults and their antibiotic susceptibility pattern and to evaluate the response to initial empiric antibiotic therapy in an Egyptian university hospital.

Methods
Study design and setting
This cross-sectional hospital-based study was conducted over a period of 27 months, from September 2015 to March 2018. It was carried out in Chest and Medical Microbiology and Immunology Departments, Zagazig University, Zagazig, Egypt.

Patient selection and empirical antibiotic regimens
This study included 270 patients diagnosed as having CAP, selected by systemic random sampling from those admitted to chest department. All were evaluated at admission and 4 days after starting empiric therapy.

CAP was defined as the presence of a new or progressive pulmonary infiltrate on chest radiograph, together with at least two of the following four criteria: fever (>38.5°C), cough, production of purulent sputum or leukocytosis over 10,000/mm³. Those criteria had to be present before or within 48 hours of admission. Patients were excluded if aged less than 18 years, were discharged from a hospital within the 2 weeks preceding admission, were receiving antimicrobial therapy and/or immunosuppressive therapy, had computed tomography (CT) chest radiographic examination suggesting

noninfectious causes such as pulmonary infarction, had acquired immunodeficiency syndrome or had leukemia.[5]

Initially, all patients received antibiotic therapy on their first day of admission on an empirical basis according to Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) 2007 guidelines: patients with severe CAP criteria were admitted to the intensive care unit (ICU), while others received ward care according to clinical evaluation in combination with patients' investigations, and severity scoring.[6]

The following antibiotic regimens were given for non-ICU patients: respiratory quinolones; levofloxacin or β-lactam (ampicillin-sulbactam [eg, IV q 6 hours]), cefotaxime (1 g IV q 8 hours) or ceftriaxone (1 g IV q 24 hours) combined with azithromycin (500 mg IV q 24 hours). For ICU admitted patients: intravenous combination of a potent antipneumococcal beta lactam (cefotaxime, ceftriaxone, or ampicillin sulbactam in full doses) plus an advanced macrolide (azithromycin) or plus respiratory fluoroquinolones (levofloxacin 750 mg IV q 24 hours). For suspected *Pseudomonas* infection (presence of structural lung abnormalities eg, bronchiectasis, chronic obstructive pulmonary disease and a history of previous frequent antimicrobials or corticosteroids use) the following regimens were used: combined antibiotic therapy with an anti-pseudomonal/antipneumococcal beta lactam antibiotic ; cefepime (2 g IV q 12 hours), piperacillin-tazobactam (4.5 g IV q 6 hours), imipenem (500 mg IV q 6 hours), or meropenem (1 g IV q 8 hours) plus an antipseudomonal fluoroquinolones (levofloxacin 750 mg IV q 24 hours) or an anti-pseudomonal/antipneumococcal beta lactam plus azithromycin (500 mg IV q 24 hours) and an aminoglycoside (gentamicin 7 mg/kg/day IV). Vancomycin (15 mg/kg IV q 12 hours) was added if methicillin resistant *Staphylococcus aureus* (MRSA) infection was suspected (either known MRSA colonization, or risk factors for it [eg, end stage renal disease, and injection drug users], presence of empyema, necrotizing or cavitary pneumonia, late flu like illness, or antimicrobial treatment, especially with fluoroquinolones, in the earlier three months).[5,7]

A minimum duration of treatment for non-ICU patients achieving an afebrile state for 48–72 hours was 5 days. Continuation of antibiotic therapy for longer duration was done if the initial treatment was not dynamic against the recognized pathogen or if the patient's condition was complicated by extra pulmonary infections. On the other hand, in patients admitted to ICU, the initial duration of antibiotic therapy was 7–10 days.

Patients' work-up

Clinical evaluation

Cases were clinically assessed within 48 hours of hospital admission with full history taking and full clinical examination. Case severity was determined according to CURB-65 severity rating score for CAP: [C, mental confusion; U, blood urea >7 mmol/L; R, respiratory rate ≥30/min; B, low blood pressure (diastolic ≤60 mmHg or systolic <90 mmHg); age ≥65 years]. All included cases fulfilled a score of more than 1. Patients with a score of 0 or 1 are at low risk of death and were considered for home treatment.[8]

Laboratory investigations

Complete blood count (Sysmex® x5 500; Kobe, Japan), kidney and liver function tests, serum electrolytes, C-reactive protein (COBAS INTEGRA® 400; Hoffman-La Roche Ltd., Basel, Switzerland), arterial blood gas analysis (RAPIDLab® 348EX; Siemens, Munich, Germany).

Radiological investigation

All patients received a posteroanterior view plain chest X-ray (RotaLiX SRT 32; Philips, Italy) at admission and for follow up. When indicated, conventional CT was done by Hi-speed spiral CT (GE Medical Microsystem, Xi'an, China).

Microbiological investigation

Specimen collection

Before starting antibiotic treatment, blood and respiratory culture samples were collected. Blood culture samples were collected from all patients. Following careful alcohol skin disinfection, two samples of peripheral blood were drawn from two different venipuncture sites 30 minutes apart and were inoculated in blood culture bottles (Egyptian Diagnostic Media, Cairo, Egypt). Respiratory samples including sputum, endotracheal aspirates (ETA), bronchoalveolar-lavage (BAL) specimens, and pleural fluid (PF) were collected in some cases. In patients with productive cough, sputum samples were obtained at the time of initial clinical evaluation or within 24 hours of admission. If the patient was not able to expectorate sputum spontaneously, sputum was induced by 3% hypertonic saline nebulization. Regarding BAL specimens, around 20 mL of 0.9% saline solution were applied, during bronchoscopy under local anesthesia and collected through a fiber optic bronchoscope. An additional 5 mL of blood were drawn from each patient; sera were separated and stored at –20°C for serological detection of atypical bacteria. Specimens were collected and transported under complete aseptic condition.[8]

Identification of isolated bacteria

For respiratory samples, both direct smear microscopy (Gram and Ziehl-Neelsen [ZN] stains) and bacterial culture were performed. High quality sputum and ETA (ie, 10 epithelial cells/low power field [LPF] and 25 white blood cells/LPF) and BAL specimens with significant growth of potential pathogens by quantitative cultures (>10^4 colony forming units/mL) were included. Blood cultures were processed according to the standard methods.[8] Positive acid-fast bacilli by ZN stain in the presence of suggestive radiological findings were diagnostic for pulmonary tuberculosis. Identification of isolated bacteria was done by conventional biochemical reactions. For Gram positive cocci, catalase, coagulase, optochin sensitivity tests were used. For Gram negative bacilli (GNB), the analytical profile index (API) (bioMérieux, Craponne, France); API 20 E for enterobacteriacea and API 20NE for non-fermentative and oxidase tests were used.[9] Atypical bacterial infections were diagnosed by indirect immunofluorescent technique for the detection of specific IgM antibodies to *Mycoplasma pneumoniae, Chlamydophila pneumoniae, Legionella pneumophila* serotype 1 and *Coxiella burnetii* using Pneumoslide-M test (Vircell, Granada, Spain). As per the manufacturer's instruction, phosphate buffered saline (PBS) was used to dilute the sera 1:1. Antihuman IgG sorbent was added to the diluted sera and incubated for 90 minutes at 37°C with the antigen-containing wells on the slide. After washing the slide with PBS, a fluorescent secondary IgM antibody was added to it and incubated at 37°C for 30 minutes, then washed again with PBS and finally read using fluorescence microscope at 400× magnification.

Antibiotic susceptibility testing of isolated bacteria

This was done by the modified Kirby–Bauer disk diffusion method on Muller Hinton agar (MHA) for selected antibiotics, including those commonly used for empirical therapy.[10] Plates were incubated at 37° C for 16–18 hours. MHA supplemented with 5% sheep blood and *Haemophilus* test medium (HTM) were used for *Streptococci* and *Haemophilus influenzae*, respectively, and incubated in 5% CO_2. Cefoxitin was tested as a surrogate for oxacillin by disk diffusion method (cefoxitin disk 30 µg). As per CLSI recommendations,[10] E-test (bioMérieux) was used to test for vancomycin susceptibility in *Staphylococcus aureus* and *Streptococcus*. This test measures the minimal inhibitory concentration (MIC) of the tested antibiotic. Screening for beta-lactam resistance in *Streptococcus pneumoniae* was done with the oxacillin 1 µg disk; isolates with oxacillin

1 μg disk zone diameter ≥20 mm are considered susceptible to benzylpenicillin, ampicillin, amoxicillin and piperacillin (without and with beta-lactamase inhibitor), cefotaxime, ceftriaxone and cefepime in addition to all carbapenems, while isolates with oxacillin 1 μg disk zone diameter <20 mm were further tested for MIC determination of these β-lactams. Oral penicillin breakpoints for *S. pneumoniae* were used.[10]

S. aureus ATCC 25923, *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were used as quality control strains (American Type Culture Collection Global Bioresource Center, Manassas, VA, USA). Results of all susceptibility testing was interpreted according to CLSI guidelines.[10]

Non-susceptible isolates to at least one agent in three or more classes of antimicrobials were considered as multidrug resistant (MDR) isolates. MRSA is considered an MDR.[11] MDR *S. pneumoniae* was defined as *S. pneumoniae* isolates showing nonsusceptibility to penicillin (MIC, ≥0.12 μg/mL) and other ≥2 non–β-lactam antimicrobial classes.[12]

Clinical response to treatment

Clinical response to treatment was evaluated within 48–72 hours of hospital admission. It was monitored by febrile chart, hemodynamics and chest radiography. Characteristics of patients showing an early response to treatment (defined as a time to clinical stability ≤ 4 days) were compared with those of patients with failure of response to initial therapy.[13]

Statistical analysis

The data were coded, checked, entered and analyzed using SPSS version 15 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as mean and SD. Categorical variables are expressed as frequencies and percent. Chi-square and Fisher's exact tests were used to examine the relationship between categorical variables. A significance level of $P<0.05$ was used in all tests.

The study was approved by the institutional review board (IRB) no 4759/5-8-2018, Faculty of medicine, Zagazig University. An informed written consent was obtained from all participants at time of recruitment. This study was conducted in accordance with the Declaration of Helsinki.

Results
Patient characteristics

Demographic, clinical, laboratory data and comorbidities of participants at admission are listed in Table 1.

Table 1 Characteristics of study participants (n=270)

Characteristics	n	%
Demographic data		
Age in years (mean ± SD)	56.7±16.3	
Sex		
Female	90	33.33
Male	180	66.67
Habit		
Nonsmoker	128	47.41
Cigarette smoking	80	29.63
Goza smoking	62	22.96
Drug and/or alcohol	32	11.85
Clinical data		
Fever	222	82.22
Dyspnea	182	67.41
Cough	214	79.26
Expectoration	190	70.37
Hemoptysis	80	29.63
Chest pain	115	42.59
Laboratory data		
CRP, mg/dL	176.43±3.46	
WBC count, ×10⁹/L	15.0±12.1	
Platelet count, ×10⁹/L	234±24.5	
CURB-65 severity rate score		
CURB 2	185	68.52
CURB 3–5	85	31.48
Comorbidities	(N=108)	40.00
Diabetes mellitus	34	31.48
Hypertension	28	25.93
Ischemic heart disease	18	16.67
Liver diseases	8	7.40
COPD	20	18.52

Notes: Values are mean ± SD or n (%).
Abbreviations: CRP, C reactive protein; CURB-65 severity score [C, mental confusion; U, blood urea >7 mmol/L; R, respiratory rate ≥30/min; B, low blood pressure (diastolic ≤60mmHg or systolic <90mmHg); age ≥65 years]; WBC, white blood cells.

Bacterial etiology

Out of 270 enrolled cases, 136 cases (50.4%) showed bacterial etiology. Dual bacterial pathogens were identified in 9 cases (3.33%), Table 2.

Antibiotic susceptibility testing

Table 3 shows the antibiotic susceptibility pattern of 104 isolated bacterial agents. The single *Streptococcus pyogenes* isolate was susceptible to penicillin, and thus it was considered susceptible to amoxicillin-clavulanate, ampicillin-sulbactam, cefepime, cefotaxime, ceftriaxone, cefuroxime, imipenem and meropenem. The MDR phenotype was revealed in 76.19% (80/105) of tested bacteria, distributed as follows: 82.61% (19/23) *S. pneumoniae*, 89.66% (26/29) *Klebsiella pneumoniae*, 65.22% (15/23) *P. aeruginosa*, 87.50% (7/8) *E. coli* and 81.25% (13/16) *S. aureus* isolates were MRSA.

Table 2 Bacterial etiology of CAP

Bacterial etiology	n	%	Blood culture	Respiratory specimens	Serum[a]
Single bacterial agent	127	47.04			
K. pneumoniae	28	10.37	12	16	–
S. pneumoniae	21	7.78	12	9	–
P. aeruginosa	21	7.78	0	21	–
M. pneumoniae	15	5.56	–	–	15
S. aureus	11	4.07	4	7	–
L. pneumophila	10	3.70	–	–	10
E. coli	8	2.96	1	7	–
H. influenzae	5	1.85	0	5	–
C. pneumoniae	4	1.48	–	–	4
M. tuberculosis	4	1.48	–	4	–
Mixed bacterial agents	9	3.33			
M. pneumoniae + S. aureus	4	1.48	2	2	4[b]
M. pneumoniae + S. pneumoniae	1	0.37	1	–	1[b]
K. pneumoniae + S. aureus	1	0.37	1	1	
L. pneumophilia + P. aeruginosa	1	0.37	–	1	1[b]
L. pneumophilia + S. pyogenes	1	0.37	–	1	1[b]
S. pneumoniae+ P. aeruginosa	1	0.37	1	1	

Notes: [a]Serology testing was done for detection of atypical bacteria from serum. [b]Atypical bacteria; *M. pneumonia, L. pneumophilia*.
Abbreviation: CAP, community acquired pneumonia; *K. pneumoniae, Klebsiella pneumoniae*; *S. Pneumoniae; Streptococcus pneumoniae*; *P. aeruginosa, Pseudomonas aeruginosa*; *M. pneumoniae, Mycoplasma pneumoniae*; *S. aureus, Staphylococcus aureus*; *L. pneumophila, Legionella pneumophila*; *E. coli, Escherichia coli*; *H. influenzae, Haemophilus influenzae*; *C. pneumoniae, Chlamydophila pneumoniae*; *M. tuberculosis, Mycobacterium tuberculosis*; *S. pyogenes, Streptococcus pyogenes*.

Nonresponders

Forty-three cases were diagnosed as nonresponders at a rate of (15.9%); their characteristics are presented in Table 4. Mortality rate among responders was 11/227 (4.85%), and 7/43 (16.3%) among nonresponders.

Discussion

This study included 270 adult patients diagnosed with CAP. Smokers represented (52.5%) of cases. Smoking is a reported risk factor for CAP. It increases the susceptibility to respiratory infection through disturbance of the host defense mechanisms. The association between smoking habits and CAP development was confirmed in previous studies.[14] Co-morbid conditions were present in 40% of patients. Diabetes mellitus was the most common comorbidity followed by hypertension and ischemic heart diseases. Similar co-morbidities were previously reported.[15] This highlights chronic debilitating conditions, particularly diabetes, as risk factors in CAP.

Bacterial etiology was identified in 50.4% of enrolled cases. *K. pneumoniae* showed the highest rate of isolation (10.37%) followed by *S. pneumoniae* and *P. aeruginosa* (7.78% each) and atypical bacteria were the etiology of 36 cases (13.3%). These rates differ from those previously reported by another Egyptian study on CAP in 2013 which reported *S. pneumoniae* as the most common bacterium (36.4%), followed by *S. aureus* (7%); *K. pneumoniae*, *P. aerug*inosa and *E. coli* at rates of 4.8, 2.1 and 1.6%, respectively.[16] Another Egyptian study in Upper Egypt reported

S. pneumoniae followed by atypical bacteria (*C. pneumoniae* and *M. pneumoniae*), then *K. pneumoniae* as the causative bacteria of adult CAP at rates of 36%, 30% and 10%, respectively.[17] Low rates of *S. pneumoniae* in our isolates may be a true reduction due to increased awareness of pneumococcal vaccine by susceptible population or due to lower sensitivity of the used conventional methods.

CAP has long been known to be caused by pathogens such as *S. pneumoniae*, *H. influenzae* and atypical pathogens that are sensitive to the majority of the first-line antibiotics. Recently, GNB that used to dominate the hospital environment, such as *P. aeruginosa*, *K. pneumoniae* and *E. coli*, have emerged as causes of CAP with an estimated prevalence ranging from 2% to 30%.[18] Our findings are in line with this perspective, where GNB account for around 21% of CAP cases. The appreciation of GNB role in CAP that has elevated over the past few decades is probably due to an increase in the number of old CAP patients who are usually harboring colonizers of GNB, in addition to the reported high severity of illness caused by GNB that usually require hospital, and mostly ICU admission.[19]

K. pneumoniae, the commonly isolated bacterium in this study, showed high resistance to penicillin/β-lactamase inhibitors, except for piperacillin/tazobactam. Resistance rates to third and fourth generation cephalosporins ranged from 65.5% to 37.9%. Conversely, carbapenems showed the highest susceptibility among the tested β-lactams. Of *K. pneumoniae* isolates 41.4% and 34.5% were resistant

Table 3 Frequency of antibiotic resistance in bacterial isolates (n=104)

	S. pneumoniae (n=23)	*K. pneumoniae* (n=29)	*P. aeruginosa* (n=23)	*S. aureus* (n=16)	*E. coli* (n=8)	*H. influenzae* (n=5)
	n %	n %	n %	n %	n %	n %
OXA	19 82.60	–	–	13[a, b] 81.25	–	–
AMC	5[c] 21.74	28 96.55	–	–	6 75	0 0
AMP/SAM	5 21.74	27 93.10	–	–	6 75	0 0
TZP	5[c] 21.74	1 3.45	11 47.83	–	4 50	–
CXM	9 39.13	26 87.7	–	–	6 75	1 20
CTX	5 21.73	19 65.52	–	–	5 62.5	0 0
CRO	5 21.73	11 37.93	–	–	5 62.5	0 0
CAZ	–	12 41.38	7 30.43	–	3 37.5	0 0
FEP	3 13.04	11 37.93	8 34.78	–	4 50	0 0
ETP	1 4.35	1 3.45	–	–	0 0	0 0
MEM	2 8.70	2 6.90	6 26.09	–	0 0	0 0
IPM	1 4.35	6 20.70	1 4.35	–	0 0	0 0
VAN[d]	7 30.43	–	–	0 0	–	–
AMK	–	8 27.59	9 39.13	8 50	1 12.5	–
CIP	15 65.22	12 41.38	11 47.83	10 62.5	2 25	0 0
LVX	3 13.04	10 34.48	13 56.52	5 31.25	3 37.5	0 0
MOX	0 0	–	–	1 6.25	–	0
AZM	11 47.83	–	–	9 56.25	–	1 20
CLI	20 86.96	–	–	11 68.75	–	–
SXT	23 100	26 89.66	–	8 50	5 62.5	2 40

Notes: [a]Cefoxitin is tested as a surrogate for oxacillin. [b]Oxacillin (cefoxitin)-resistant staphylococci are resistant to all tested β-lactam antimicrobial agents, Oxacillin (cefoxitin)-susceptible staphylococci can be considered susceptible to β-lactam/β-lactamase inhibitor combinations, oral and parenteral cephems including cephalosporins I, II, III, and IV and carbapenems. [c]Susceptibility inferred from the MIC of ampicillin. [d]*S. aureus* isolates were tested for vancomycin susceptibility by E-test.
Abbreviations: AMC, amoxicillin/clavulanate; AMK, amikacin; AMP/SAM, ampicillin + sulbactam; AZM, azithromycin; CAZ, ceftazidime; CLI, clindamycin; CIP, ciprofloxacin; CRO, ceftriaxone; CTX, cefotaxime; CXM, cefuroxime; ETP, ertapenem; FEP, cefepime; IMP, imipenem; LVX, levofloxacin; MEM, meropnem; MOX, moxifloxacin; OXA, oxacillin; SXT, trimethoprim –sulfamethoxazole; TZP, piperacillin/tazobactam; VAN, vancomycin; *S. Pneumoniae*; *Streptococcus pneumoniae*; *K. pneumoniae*, *Klebsiella pneumoniae*; *P. aeruginosa*, *Pseudomonas aeruginosa*; *S. aureus*, *Staphylococcus aureus*; *E. coli*, *Escherichia coli*; *H. influenzae*, *Haemophilus influenzae*.

to ciprofloxacin and levofloxacin, respectively. Resistance rates in *K. pneumoniae* for quinolones and β-lactams were higher than those reported for *K. pneumoniae* CAP isolates in Egypt.[17] Lin et al[20] and Sikarwar and Barta[21] published analogous data.

High rates of antibiotic resistance were detected among *S. pneumoniae*, where 82.6% of *S. pneumoniae* isolates were recorded as resistant to oxacillin; all showed penicillin MIC values > 0.12 μg/mL, and 47.83% were resistant to azithromycin. This is in accordance with the Egyptian as

Table 4 Comparison of responders' and nonresponders' characteristics

Characteristics	Nonresponders (n=43)		Responders (n=227)		P-value
	n	%	n	%	
Age in years (mean ± SD)	53.4±13		58.8±14.2		0.02*
Gender					
Male (n=180)	28	15.56	152	84.44	0.81
Female (n=90)	15	16.67	75	83.33	
Smokers (n=142)	23	16.20	119	83.8	0.89
Comorbidities (n=108)	21	19.44	87	80.56	0.2
Diabetes mellitus (n=34)	15	44.11	19	55.89	<0.001*
Hypertension (n=28)	9	32.14	19	67.86	0.01*
Ischemic heart disease (n=18)	7	38.88	11	61.12	0.006*
Liver disease (n=8)	4	50	4	50	0.008*
COPD (n=20)	7	35	13	65	0.015*
Initial empiric antimicrobial treatment					
-Levofloxacin (n=33)	7	21.21	26	78.79	0.38
-Antipneumococcal β-lactam+ azithromycin (n=87)	4	4.60	83	95.40	<0.001*
-Antipneumococcal β-lactam+ levofloxacin (n=67)	11	16.41	50	83.59	0.61
-Anti-MRSA coverage (n=31)[a]	5	16.12	26	83.87	0.97
-Anti-pseudomonal coverage					
Anti-pseudomonal/anti-pneumoccocal β-lactam + amikacin + azithromycin (n=29)	3	10.34	26	89.66	0.38
Anti-pseudomonal/anti-pneumoccocal β-lactam + ciprofloxacin/levofloxacin (n=23)	7	30.43	16	69.57	0.05
Bacterial agent identified/case[b]					
Cases with no bacteria identified (n=134)	6	4.48	128	95.52	<0.001*
Cases with single bacterial agent (n=127**)**					
S. pneumoniae (n=21)	4	19.05	17	80.95	0.7
K. pneumoniae (n=28)	10	35.71	18	64.29	0.003*
P. aeruginosa (n=21)	9	42.86	12	57.14	<0.001*
S.aureus (n=11)	5	45.45	6	54.55	0.006*
Mixed bacteria (n=9)	5	55.56	4	44.44	<0.001*
M. tuberculosis (n=4)	4	100	0	0	<0.001*
CURB-65 severity score					
Class 2 (n=185)	25	13.51	160	86.49	0.11
Classes 3–5 (n=85)	18	21.18	67	78.82	
Complications					
Suppurative complications[d] (n=47)	9	19.15	38	80.85	0.77
Shock (n=25)	4	16	21	84	
Respiratory failure (n=25)	6	24	19	76	

Notes: [a]Vancomycin was added. [b]The following bacteria are not presented in the table because all of them were isolated from responding cases: *E. coli* (8 cases), *H. influenzae* (5 cases), *M. pneumoniae* (15 cases), *L. pneumophilia* (10 cases), *C. pneumoniae* (4 cases). [c]Empyema or abscess, *P<0.05 indicates significant relation. Values are mean ± SD, or n (%).
Abbreviations: CURB-65 severity score [C, mental confusion; U, blood urea >7 mmol/L; R, respiratory rate ≥30/min; B, low blood pressure (diastolic ≤60mmHg or systolic <90 mmHg); age ≥65 years] MRSA, amethicillin resistant *Staphylococcus aureus*; *S. Pneumoniae*; *Streptococcus pneumoniae*; *K. pneumoniae*, *Klebsiella pneumoniae*; *P. aeruginosa*, *Pseudomonas aeruginosa*; *S. aureus*, *Staphylococcus aureus*; *E. coli*, *Escherichia coli*; *H. influenzae*, *Haemophilus influenzae*; *M. pneumoniae*, *Mycoplasma pneumoniae*; *L. pneumophila*, *Legionella pneumophila*; *C. pneumoniae*, *Chlamydophila pneumoniae*; *M. tuberculosis*, *Mycobacterium tuberculosis*.

well as the global trend of increasing resistance of *S. pneumoniae* to β-lactams and macrolides; Bahy et al[22] in a recent Egyptian study reported high rates of resistance to penicillin (80% and 82%) and macrolides (73% and 78%) in the two predominant *S. pneumoniae* serotypes 6A/B and 19 F which exceeded those reported from older Egyptian studies.[17,23] A nearly similar pattern was reported by Mohammed et al.[24] As for quinolones, 65.2% and 13.04% of *S. pneumoniae* isolates were resistant to ciprofloxacin and levofloxacin, respectively, while all (100%) retained susceptibility to moxifloxacin. This

is explained by the fact that the older second generation fluoroquinolones (ciprofloxacin and levofloxacin) target only the ParC subunit of the enzyme topoisomerase IV, and prolonged exposure to these agents selected for resistant strains with mutated ParC region. Moxifloxacin, however, retains activity on such mutant strains by the virtue of its additional effect on the unaltered GyrA subunit of DNA gyrase. In clinical practice, the ideal pharmacodynamics and adequate tissue penetration are additional advantages of moxifloxacin over levofloxacin in pneumococcal CAP.[25,26]

P. aeruginosa showed considerable resistance rates to antibiotics with anti-pseudomonal activity. They showed the least susceptibility to ciprofloxacin, levofloxacin and piperacillin/tazobactam. Carbapenems (imipenem and meropenem) showed the highest susceptibility rates (95.65% and 73.91%, respectively), while resistance to amikacin was detected in 39.13%. This is consistent with large-scale surveillance results[27,28] and Egyptian studies[23,29] except for the higher rates of quinolones and amikacin resistance in the latter.

Treatment of *P. aeruginosa* infections is to some extent difficult owing to its low outer membrane permeability. Moreover, it has the capability of acquiring resistance to most antibiotics. A variety of mechanisms may be implicated; eg, production of efflux pumps, use of selective porins, and possessing inducible beta-lactamases. So, *P. aeruginosa* therapy is better guided by the results of the susceptibility reports of individual strains.[30]

Our results pointed out that 81.25% of isolated *S. aureus* were MRSA. Previous Egyptian studies showed that MRSA represented 71%[22] and 79.3%[17] of *S. aureus* isolates. Vancomycin and moxifloxacin showed the highest susceptibility rates.

The MDR phenotype was a common finding among our isolates, where 76.2% of tested bacteria were MDR. In 2015, Mohamed et al[24] reported MDR of 73.3% among *S. pneumonia*e in Egypt. Researchers from other countries reported comparable results; Li et al[31] reported that 40% of *P. aeruginosa*, 62% of *E. coli* and 36% *of K. pneumoniae* were MDR. Cillóniz et al[32] found that 32% of *P. aeruginosa* isolates were MDR. These results highlight the antibiotic resistance in the community as a problem which calls for strenuous efforts to rationalize antibiotic use and eliminate over-the-counter antibiotic dispensing and self-medication especially in developing countries. Moreover, it emphasizes a lack of antimicrobial stewardship and defective infection control practices.

Adequate antibiotic therapy usually results in some improvement in the patient's clinical course within 48–72 hours. If no improvement was observed, patients are considered nonresponders and are at high risk of in-hospital death.[33] Forty-three (15.9%) CAP patients in the current study were nonresponders. Many causes may lead to nonresponsiveness. Patient-related factors (including suppurative complications), medication-related factors and resistant bacteria are important causes.[34]

While investigating the response to each used empiric antibiotic regimen, the highest rate of nonresponsiveness was observed in cases receiving anti-pseudomonal/anti-pneumoccocal β-lactam plus ciprofloxacin/levofloxacin

30.43% (seven out of 23 cases received this regimen for anti-pseudomonal coverage) followed by those receiving an antipneumococcal β-lactam plus levofloxacin 11/67 (16.41%) and anti-MRSA 5/31 (16.12%) for severe CAP, but did not reach statistical significance. Meanwhile azithromycin containing regimens showed the lowest rates of nonresponsiveness (4.60%) and (10.34%) for antipneu-mococcal β-lactam plus azithromycin combination and antipseudomonal /anti-pneumoccocal β-lactam plus ami-kacin plus azithromycin combination, respectively. Several studies reported a benefit inferred by adding a macrolide to empiric combinations in treatment of CAP, even those caused by macrolide insensitive isolates, particularly in ICU admitted patients with sepsis.[35–37] This benefit stems from the anti-inflammatory properties of macrolides rather than the antimicrobial ones. Macrolides can decrease the chemotactic response of neutrophils, promote macrophage phagocytosis of apoptotic cells, enhance the release of anti-inflammatory cytokines, inhibit the synthesis of pro-inflammatory cytokines and reduce T-cell numbers and migration.[38,39] Although macrolide and fluoroquinolones containing combinations have been generally comparable in different clinical trials, many observational studies have reported better clinical outcomes with macrolide containing regimens for patients with severe CAP. Thus, these results should be interpreted with caution and need to be proven by well-designed clinical trials considering specific patient and disease characteristics.

Bacterial etiology was identified in 37 nonresponders (86%). *S. pneumoniae*, *K pneumoniae*, *P. aeruginosa*, *S. aureus*, mixed bacteria and *Mycobacteria* were the bacterial agents identified at rates comparable to Bodi et al.[40] Similarly, other researchers observed that nonresponding pneumonia was mostly due to organisms not covered by initial empirical antibiotic therapy; this applies to MDR organisms, atypical bacteria as well as mycobacterial tuberculosis.[18,39,41–44] Mixed bacterial etiology was another contributing factor to nonresponsiveness to initial empiric therapy, where a statistically significant difference was recorded, by the research team, between responders and nonresponders for the presence of mixed infection. Nonresponders in the current study showed a higher mortality rate (16.3%) compared to responders (4.85%). These findings were similar to a previous study, in which early nonresponse was identified in 8.4% of CAP patients, with mortality rate of 24%.[45] Another CAP cohort showed a nonresponder rate of 15.9% and an in-hospital mortality of 17.3% in nonresponders compared to 5.2% in responders.[46]

Conclusion

Local resistance statistics is very important to avoid the risk of inadequate therapy. Bacterial profile should be updated regularly as some nosocomial pathogens have emerged in the community causing pneumonia. The growing prevalence of MDR bacteria represents an important issue in choosing empiric antimicrobial management in seriously ill hospitalized patients. The widespread antibiotic-resistant microorganisms necessitate the implementation of antibiotic stewardship strategies, including de-escalation, shifting to oral therapy, rapid patient ambulation and discharge, and shorter duration of antibiotic therapy, which rely on evaluation of patient responses to initial empiric therapy. Factors related to bacterial agents, the antibiotic treatment, the host and their interactions may lead to failed treatment protocol. *P. aeruginosa*, tuberculosis and mixed agents should be considered in nonresponders. Broad spectrum β-lactams, especially carbapenems, and moxifloxacin showed in vitro efficacy on most of the tested isolates. Advanced macrolides (azithromycin) containing regimens showed the lowest rates of nonresponsiveness, have the advantage of atypical coverage and can spare fluoroquinolones as important second-line anti-tuberculous agents in patients at risk of TB especially MDR-TB. However, this result should be interpreted with caution and supported by further studies.

Recommendations

The antibiotic stewardship program is a necessity; further studies are needed to monitor its implementation. Future studies are needed to explore the molecular basis of the reported resistance patterns. The response to initial empiric treatment could be further investigated on a larger scale with each of the recorded associated comorbid conditions.

Limitations of the study

Antibiotic susceptibility testing for atypical bacteria was not feasible. Viral causes were not explored by this research, although the clinicians requested test for viral causes of CAP as a part of their diagnostic approach of the disease, which could be the objective of future studies with different scopes. The lack of antibiotic stewardship programs in the investigated hospital hinders proper stratification of patients. The shortage of national surveillance data limits the detailed interpretation of results.

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Disclosure

The authors report no conflicts of interest in this work.

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