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Original Article

Community-acquired pneumonia-causing bacteria and antibiotic resistance rate among Syrian patients

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Abstract

Introduction: Antimicrobial resistance poses a critical global health concern, particularly in developing countries like Syria, and is responsible for the increased rates of infection and mortality associated with community-acquired pneumonia (CAP).

Methodology: This cross-sectional study determined the prevalence of bacteria that cause CAP and the rate of antibiotic resistance in a sample of patients who attended the Chest Department of Ibn Al-Nafis Hospital in Damascus, Syria from September 2022 to March 2023.

Results: Almost three-quarters of the 100 CAP cases were caused by 3 agents: *Streptococcus pneumonia* (41%), *Staphylococcus aureus* (16%), and *Klebsiella* sp. (14%). The study showed high resistance of bacteria to the usually recommended antibiotics, which presents a significant challenge in treating these infections. Specifically, in this sample, Gram-negative bacteria had a higher antibiotic resistance rate than Gram-positive bacteria. Gram-negative bacteria showed the highest resistance against nitrofurantoin, cefazolin, and cefoxitin (100%, 91.7%, and 91.3%, respectively). Gram-positive bacteria exhibited the highest resistance against erythromycin, cefoxitin, and oxacillin (91.37%, 91.22%, and 87.71%, respectively). Resistance to the commonly recommended amoxicillin, and amoxicillin + clavulanic acid, was higher than 80%, while the tested Gram-positive bacteria showed high sensitivity to other recommended options such as cefotaxime (71%) and ceftriaxone (81%).

Conclusions: These findings underscore the importance of being able to adapt the general World Health Organization recommendations according to local evidence. It is crucial to emphasize the need for continuous local monitoring, functioning and well-equipped laboratories, and well-trained specialists in infectious diseases in hospitals to be able to make these decisions.

Key words: antibiotic resistance; community-acquired pneumonia; Syria.

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Introduction

Community-acquired pneumonia (CAP) is an infectious disease of public health concern and a major cause of morbidity that often requires hospitalization [1,2]. Pneumonia is predominantly caused by bacteria; however, there are a wide variety of pathogens that can cause pneumonia. CAP results in approximately 7 million deaths each year [3,4]. The overall incidence of CAP is 16 to 23 cases per 1000 persons per year, and the rate increases with age [5]. Some of the risk factors for CAP include comorbidities such as chronic obstructive pulmonary disease (COPD), asthma, and heart failure [6,7]. Initiating an effective antibiotic therapy promptly is essential for a positive outcome in CAP [5,8]. However, the rapid spread of antimicrobial resistance (AMR) has made most available antibiotics less effective [9,10]. AMR is a global threat to public health and economic development, contributing to increased morbidity, mortality, and healthcare costs with a significant impact on health systems, and it is mostly linked to the inappropriate use of antimicrobials [11–13].

AMR is responsible for an estimated 700,000 deaths each year [11,12], and projections suggest that this number could rise to 10 million by 2050, if no action is taken [12]. Developing countries often bear a higher burden of infectious diseases, with AMR exacerbating morbidity and mortality rates [13]. Many healthcare systems in developing nations struggle with limited access to essential medicines, including effective antibiotics. Treatment options become even more restricted when resistance develops. The cost of newer antibiotics can be prohibitive, further limiting patients' treatment possibilities. Poor healthcare infrastructure, including inadequate laboratory capacity for diagnosing infections and monitoring resistance

patterns, hampers effective responses to AMR [13]. Additionally, many healthcare facilities lack basic sanitation and infection control measures, facilitating the spread of resistant pathogens. Regulation of antibiotics in developing countries is often weak, allowing for over-the-counter sales without prescriptions, which contributes to misuse. The burden of AMR strains already limits healthcare resources, diverting attention from other critical health initiatives [14]. Furthermore, there is often a lack of public awareness regarding AMR and its consequences. Educational campaigns are necessary to inform both healthcare providers and the general public about appropriate antibiotic use.

In 2019, Syria reported 1,700 deaths linked to AMR [14]. Syria also had the 96th highest age-standardized mortality rate per 100,000 population related to AMR across 204 countries [14]. The importance of AMR in Syria stems from the increasing prevalence of infections and inappropriate use of antibiotics, which contributes to the emergence of antibiotic-resistant strains [15]. This is due to the war that destroyed Syria for a long time [16]. Several factors have contributed to the emergence of AMR since the conflict began, including the destruction of public healthcare facilities, departure of thousands of healthcare workers and assistants from the country, and economic sanctions that have limited access to medical supplies and equipment [17,18].

Antimicrobial stewardship (AMS) refers to coordinated interventions designed to improve the appropriate use of antimicrobials. The primary goal of AMS is to achieve the best clinical outcomes related to antimicrobial use while minimizing toxicity and other adverse events. Additionally, it aims to limit the selective pressure on bacterial populations that drives the emergence of antimicrobial-resistant strains. However, a good AMS program requires local data on resistance patterns, and antimicrobial use and misuse.

In this context, this study aims to identify the bacterial causes of CAP in adults in Syria, and assess their susceptibility to commonly used antibiotics. This research is the first of its kind in Syria; therefore, it will provide valuable insights into the spread of bacterial resistance to various antibiotics and help determine the effectiveness of different antibiotics for the design of AMS programs.

Methodology

Study design and patient selection

This cross-sectional hospital-based study was conducted from September 2022 to March 2023. The sample included 100 patients diagnosed with CAP and showing bacterial etiology. The patients were selected by systematic random sampling from those admitted to the Chest Department at Ibn Al-Nafis Hospital in Damascus, Syria.

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/mm^3 [19]. Exclusion criteria were: patients who had used antibiotics after having symptoms before hospitalization, patients with a history of human immunodeficiency virus (HIV) infection, and patients with tuberculosis or receiving treatment for tuberculosis.

Microbiological investigation

Bacterial culture data recorded in the period between September 2022 to March 2023 were extracted from the laboratory database at the Ibn Al-Nafis Hospital.

Respiratory culture samples were collected before starting antibiotic treatment. The samples included sputum, endotracheal aspirates (ETA), bronchoalveolar-lavage (BAL) specimens, and pleural fluid (PF) in some cases. The specimens were collected and transported under complete aseptic conditions.

A direct smear microscopy test (Gram staining and Ziehl-Neelsen [ZN] stains) was performed for the respiratory specimens.

Bacterial culture was done on blood agar, MacConkey agar, and chocolate agar media. Bacterial growth in the media was determined by its characteristic appearance, such as colony shape, Gram staining, and application of biochemical reactions using the standard methods. Members of the Enterobacteriaceae family and other Gram-negative bacteria were identified by indole, urease, H_2S and gas production, citrate utilization, motility test, lysine decarboxylase test in lysine iron agar (LIA), oxidase test, and carbohydrate fermentation reaction in Kligler iron agar (KIA). Blood coagulation tests, catalase, and optochin were used for Gram-positive bacteria [20]. No testing was done on atypical bacterial species.

All culture results from September 2022 to March 2023 were reviewed for each patient's diagnosis and prescribing information. Patient demographics, along with complete records of bacteriological cultures and resistance patterns, were obtained from the laboratory database and examined. Antimicrobial susceptibility testing was carried out using the disc diffusion methods

in accordance with the European Committee on Antimicrobial Susceptibility Testing (EUCAST guidelines) [21,22]. For the purposes of this study, AMR was defined as the presence of an organism that showed resistance to one or more antibiotics.

The antibiotics were categorized according to the World Health Organization (WHO) AWaRe classification into three groups (Table 1) [23]. A direct quotation is provided below:

1. The Access group includes antibiotics that are active against a wide range of commonly encountered susceptible pathogens while showing lower resistance potential than the antibiotics in the other groups. Selected Access group antibiotics are recommended as essential first- or second-choice empiric treatment options for infectious syndromes reviewed by the Essential Medicines List (EML) Expert Committee. They are listed as individual medicines on the Model Lists of Essential Medicines to improve access and promote appropriate use.
2. The Watch group includes antibiotic classes with higher resistance potential and most of the highest priority agents among the critically important antimicrobials for human medicine and/or antibiotics at relatively high risk of selection of bacterial resistance. Selected Watch group antibiotics are recommended as essential first or second-choice empiric treatment options for a limited number of specific infectious syndromes and are listed as individual medicines on the WHO Model Lists of Essential Medicines.
3. The Reserve group includes antibiotics and antibiotic classes that should be reserved for treatment of confirmed or suspected infections due to multi-drug-resistant organisms. The Reserve group antibiotics should be treated as "last resort" options.

Table 1. Antibiotics used in disk diffusion tests according to the WHO AWaRe classification and ATC codes.

AWaRe classification	Antibiotics	ATC
Access	Nitrofurantoin	J01XE01
	Cefazolin	J01DB04
	Tetracycline	J01AA07
	Amoxicillin	J01CA04
	Trimethoprim	J01EA01
	Ampicillin	J01CA01
	Amikacin	J01GB06
	Gentamicin	J01GB03
Watch	Cefoxitin	J01DC01
	Cefuroxime sodium	J01DC02
	Azithromycin	J01FA10
	Cefepime	J01DE01
	Levofloxacin	J01MA12
	Cefotaxime	J01DD01
	Ceftazidime	J01DD02
	Ceftriaxone	J01DD04
	Ciprofloxacin	J01MA02
	Tobramycin	J01GB01
	Imipenem	J01DH51
	Meropenem	J01DH02
	Piperacillin	J01CA12
Reserve	Aztreonam	J01DF01
	Linezolid	J01XX08
	Tigecycline	J01AA12

Statistical analysis

The data was coded, checked, entered, and analyzed using SPSS Statistics for Windows version 15 (SPSS Inc., Chicago, IL, US). Continuous variables were expressed as means and standard deviations (SD), while categorical variables were expressed as frequencies and percentages. The relationship between categorical variables was examined using Chi-square and Fisher's exact tests. A significance level of $p < 0.05$ was used for all tests.

Ethical clearance

Ethical approval for the study was obtained from the International University of Science and Technology, College of Pharmacy and Medical Sciences Research Committee Office (approval code: MD-190822-3, approval date: 19/8/2022). Informed consent was obtained from the participants.

Results

Demographic and clinical characteristics

The study sample consisted of 100 patients diagnosed with CAP. The demographics and comorbidities of the participants at admission are listed in Table 2. Of the 100 patients, 55 were females and 45

Table 2. Characteristics of the 100 patients with community-acquired pneumonia included in the study.

Data	Characteristics		Frequency	%
Demographic data	Age in years (mean ± SD)		65 ± 3.5	
	Age group	< 60 years old	15	15%
		≥ 60 years old	85	85%
	Gender	Female	55	55%
		Male	45	45%
	Habit	Cigarette smoking	70	70%
		Alcohol	10	10%
Clinical data	Fever		90	90%
	Dyspnea		70	70%
	Cough		82	82%
	Expectoration		73	73%
	Hemoptysis		20	20%
	Chest pain		50	50%
Comorbidities	Diabetes mellitus		32	32%
	Hypertension		25	25%
	Ischemic heart disease		15	15%
	Liver diseases		5	5%
	Chronic obstructive pulmonary disease		19	19%

Table 3. Bacterial etiology of the 100 cases of community-acquired pneumonia included in this study.

Gram positive / negative	Bacteria species	N = %	Age (years)		Patients with diabetes (n = 32)
			> 60 (n = 85)	< 60 (n = 15)	
G+	*Streptococcus pneumoniae*	41%	31	10	10
	Staphylococcus aureus	16%	13	3	3
	Subtotal	57%	44	13	13
G–	*Klebsiella pneumoniae*	14%	13	1	6
	Enterobacter cloacae	9%	9	0	3
	Escherichia coli	9%	8	1	5
	Acinetobacter baumannii	8%	8	0	3
	Pseudomonas aeruginosa	3%	3	0	2
	Subtotal	43%	41	2	19
Total		**100%**	**100**	**100**	**100**

were males (p = 0.145), with an overall gender distribution ratio of 1:1.22. The age ranged between 22 years and 75 years, with a median age of 62 years and a mean ± SD of 65 ± 3.5 years.

It should be noted that 70% of the patients smoked, but only 19% had COPD. Diabetes (32%) and hypertension (25%) were the two most frequent comorbidities of the patients in the study sample (Table 2).

Fever, cough, expectoration, and dyspnea were the most frequent clinical symptoms present in more than 70% of the included patients, and only 20% had hemoptysis.

Bacterial etiology of CAP

It is important to note that all CAP cases were monobacterial. Table 3 summarizes the distribution of the bacteria identified in the study sample. The 3 most common bacteria causing infection in this sample were *Streptococcus pneumoniae* (41% of patients), *Staphylococcus aureus* (16%), and *Klebsiella* spp. (14%).

CAP was most prevalent in the age group above 60 years (85% of the sample), with a statistically significant difference in the incidence rate compared to the age group under 60 years (p = 0.001). There was no difference in the presence of Gram-negative and Gram-positive bacteria in this group (p = 0.165). The results indicated that patients over the age of 60 years exhibited greater resistance to antibiotics than those who were less than 60 years old (p = 0.003). Additionally, patients who smoked demonstrated higher antibiotic resistance compared to non-smokers (p = 0.002).

Resistance patterns of the isolated bacteria

The bacteria were classified into Gram positive and Gram negative to understand the pattern of AMR.

Table 4. Susceptibility testing of the Gram-negative bacteria identified in the samples of patients with community acquired pneumonia.

AWaRe	Antibiotic	R %	S %	I %
A	Nitrofurantoin	100%	0%	0%
A	Cefazolin	91.7%	8.0%	0%
W	Cefoxitin	91.3%	4.3%	4.3%
W	Cefuroxime	90.9%	0%	9%
W	Azithromycin	83.3%	0%	16.6%
A	Amoxycillin	82%	0%	18%
A	Tetracycline	78.6%	7.1%	14.3%
A	Amoxicillin/ clavulanic acid.	75%	0%	25%
W	Cefepime	75%	25%	0%
W	Levofloxacin	75%	25%	0%
W	Cefotaxime	75%	20%	5%
W	Ceftazidime	75%	25%	0%
A	Trimethoprim	72.5%	20%	7.5%
R	Aztreonam	69.2%	15.4%	15.4%
A	Ampicillin	63.6%	36.4%	0%
W	Ceftriaxone	62.5%	37.5%	0%
W	Ciprofloxacin	61.5%	38.5%	0%
R	Linezolid	50%	0%	50%
A	Amikacin	50%	20%	30%
W	Tobramycin	45%	47.5%	7.5%
W	Imipenem	38.7%	54.8%	6.5%
A	Gentamicin	38.5%	46.1%	15.4%
W	Meropenem	37.5%	57.5%	5%
R	Tigecycline	35.8%	23%	41%
W	Piperacillin	30.8%	23%	46.2%
R	Colistin	0%	100%	0%

R: resistant; S: susceptible; I: intermediate. AWaRe: A: Aware; Wa: Watch; Re: Reserve.

AMR pattern in Gram-negative bacteria

The Gram-negative bacteria strains showed significant resistance to many Access and Watch antibiotics (Table 4). The highest resistance was observed for nitrofurantoin (100%) and cefazolin (91.7%) (both, Access), followed by the Watch antibiotics cefoxitin (91.3%), cefotaxime (90.9%), and azithromycin (83.3%). However, the Gram-negative bacteria showed high susceptibility to the Reserve antibiotic colistin (100% sensitivity in all tested samples) but lower susceptibility to another Reserve antibiotic, tigecycline (23%). Additionally, Gram-negative bacteria exhibited moderate susceptibility to many Watch antibiotics, such as tobramycin (47.5%), imipenem (54.8%), and meropenem (57.5%). (Figure 1)

Acinetobacter sp. showed the highest rate of resistance to most antibiotics compared to other Gram-negative bacteria ($p = 0.001$). *K. pneumoniae* exhibited a high prevalence of resistance to nitrofurantoin, tetracycline and azithromycin (100%), followed by clindamycin (71.9%), and tetracycline (78.1%). *K. pneumoniae* were 100% susceptible to ceftriaxone and colistin. *Enterobacter cloacae* exhibited a high prevalence of resistance to all antibiotics (100%) except colistin. *Escherichia coli* exhibited a high prevalence of resistance to nitrofurantoin, levofloxacin, cefotaxime, ceftriaxone, azithromycin, cefazolin, and ceftazidime (100%); but it was susceptible to colistin (100%) and meropenem (87.5%) (Table 5).

AMR pattern in Gram-positive bacteria

Resistance and susceptibility were also tested for the Gram-positive bacteria strains isolated from the study sample (Table 6). The bacteria exhibited significant resistance to several antibiotics in the Access and Watch groups. The highest resistance was observed in the case of erythromycin at 91.2%, followed by cefoxitin at 90.6% (both Watch), and oxacillin at 87.7% (Access). Unlike in the case of Gram-negative bacteria, many antibiotics were highly effective against the identified Gram-positive bacteria. There was a susceptibility of 97.8% to imipenem, 92.9% to vancomycin, 91.2% to meropenem, 89% to tigecycline, 87.7% to linezolid, 87.5% to gentamicin, and 84.21% to rifampin (Figure 2).

Figure 1. Antimicrobial susceptibility pattern of all Gram-negative (G–) bacteria identified in the present sample of patients with community-acquired pneumonia.

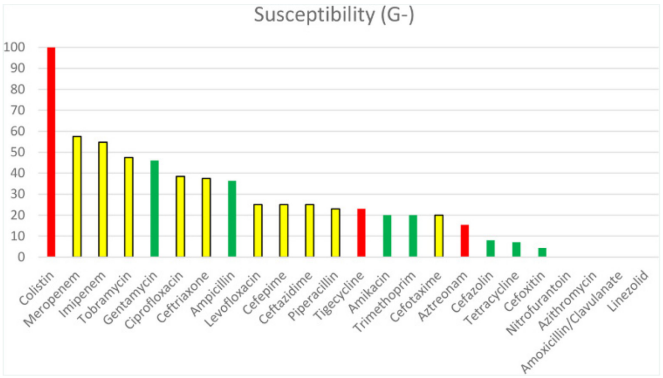

Figure 2. Antimicrobial susceptibility pattern of all Gram-positive (G+) bacteria identified in the present sample of patients with community-acquired pneumonia.

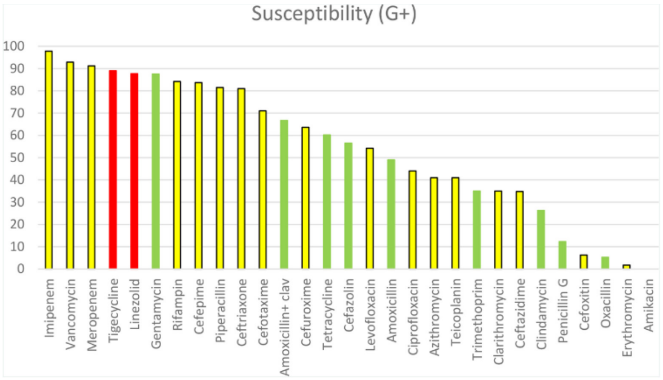

Table 5. Frequency of antibiotic susceptibility in Gram-negative bacteria isolates. (Susceptible (S), %).

Gram-negative bacteria	Cefepime (S %)	Cefotaxime (S %)	Cefoxitin (S %)	Ceftriaxone (S %)	Imipenem (S %)	Levofloxacin (S %)	Linezolid (S %)	Meropenem (S %)	Trimethoprim (S %)	Tigecycline (S %)	Amikacin (S %)	Aztreonam (S %)	Tobramycin (S %)	Colistin (S %)	Amoxicillin/ Clavule (S %)	Ampicillin (S %)	Azithromycin (S %)	Cefazolin (S %)	Ceftazidime (S %)	Cefuroxime (S %)	Ciprofloxacin (S %)	Gentamicin (S %)	Nitrofurantoin (S %)	Piperacillin (S %)	Tetracycline (S %)
Klebsiella	33.3	36.3	50	100	57	33.3	0	57	25	41.6	8.3	33.3	66.6	100	0	66.6	0	33.3	66.6	0	50	66.6	0	0	0
Acinetobacter	0	0	0	0	0	0	0	0	0	0	0	0	0	100	0	0	0	0	0	0	0	0	0	0	0
E. coli	11.1	0	0	0	0	0	0	87.5	0	33.3	44.4	0	55.5	100	0	25	0	0	0	0	0	25	0	33.3	0
Enterobacter	55.5	44.4	12.5	62.5	77.7	66.6	0	87.5	66.6	50	55.5	25	77.7	100	0	0	0	0	20	0	66.6	66.6	0	50	14.2
Pseudomonas	33.3	33.3	0	66.6	66.6	33.3	0	66.6	0	0	0	66.6	66.6	100	0	0	0	33.3	66.6	0	33.3	33.3	0	33.3	0

Table 6. Susceptibility testing of the Gram-positive bacteria identified in the samples of patients with community acquired pneumonia (CAP).

AWaRe	Antibiotic	R %	S %	I %
W	Erythromycin	91.2%	1.8%	7%
W	Cefoxitin	90.6%	6.3%	3.1%
A	Oxacillin	87.7%	5.3%	7%
A	Penicillin G	77.2%	12.3%	10.5%
A	Clindamycin	63.2%	26.3%	10.5%
W	Ceftazidime	47.8%	34.8%	17.4%
W	Teicoplanin	43%	41%	16%
W	Ciprofloxacin	40%	44%	16%
W	Clarithromycin	38.6%	35%	26.4%
W	Azithromycin	36.4%	41%	22.6%
A	Tetracycline	31.8%	60.2%	8%
A	Cefazolin	30.43%	56.5%	13%
A	Amoxycillin	27%	49%	24%
A	Trimethoprim	28%	35%	36.84%
W	Cefuroxime sodium	18.2%	63.6%	18.2%
W	Levofloxacin	15.8%	54.2%	30%
A	Amoxicillin/Clavulanate	14.3%	66.7%	19%
W	Cefotaxime	12%	71%	17%
W	Cefepime	9%	83.7%	7.3%
W	Piperacillin	7.4%	81.5%	11.1%
R	Linezolid	5.3%	87.7%	7%
W	Meropenem	%3.5	91.2%	5.3%
W	Rifampin	3.5%	84.2%	12.3%
W	Ceftriaxone	2.7%	81%	16.3%
W	Imipenem	2.2%	97.8%	0%
W	Vancomycin	0%	92.9%	7.1%
R	Tigecycline	0%	89%	11%
A	Gentamicin	0%	87.5%	12.5%
A	Amikacin	0%	0%	100%

R: resistant; S: susceptible; I: intermediate.

Staphylococcus aureus exhibited a high level of resistance to erythromycin, cefoxitin, and oxacillin (93%, 80%, and 75%, respectively), but was susceptible to gentamicin, imipenem, linezolid, and vancomycin (100%, 93%, 87.5%, and 86.5% respectively). *Streptococcus* exhibited a high level of resistance to oxacillin, cefoxitin, erythromycin, and penicillin G (95%, 94%, 90%, and 80%, respectively), but was susceptible to imipenem, meropenem, vancomycin, and linezolid (100%, 97%, 95%, and 87% respectively) (Table 7). The resistance rates in Gram negative bacteria were higher than in Gram positive bacteria ($p = 0.005$).

Discussion

CAP remains a significant cause of morbidity and mortality [24,25]. It is often misdiagnosed and treated inappropriately [26,27]. Treatment with antibiotics should begin as soon as possible, especially for those who need to be hospitalized [15]. However, in most cases, the physician does not know for sure which pathogen is causing the infection, and the rising rate of antibiotic resistance has led to more severe cases [28,29].

This study involved 100 adult patients diagnosed with CAP. The incidence rate for patients over the age of 60 years was 85%. Smokers accounted for 70% of the cases, highlighting smoking as a known risk factor for CAP [7]. Smoking increases susceptibility to

Table 7. Frequency of antibiotic susceptibility in Gram-positive bacteria isolates. (Susceptible (S), %).

Gram-positive bacteria	Cefepime (S %)	Cefotaxime (S %)	Cefoxitin (S %)	Ceftriaxone (S %)	Clarithromycin (S %)	Clindamycin (S %)	Erythromycin (S %)	Imipenem (S %)	Levofloxacin (S %)	Linezolid (S %)	Meropenem (S %)	Oxacillin (S %)	Penicillin G (S %)	Rifampin (S %)	Teicoplanin (S %)	trimethoprim (S %)	Tygacycline (S %)	Vancomycin (S %)	Amikacin (S %)	Amoxicillin (S %)	Ampicillin (S %)	Azithromycin (S %)	Cefazolin (S %)	Ceftazidime (S %)	Cefuroxime sodium (S %)	Ciprofloxacin (S %)	Gentamicin (S %)	Nitrofurantoin (S %)	Piperacillin (S %)
Streptococcus pneumoniae	90.2	80.4	4.3	85.1	36.5	21.9	2.4	100	63.4	87.8	97.5	5	12.1	85.3	46.3	21.9	95	95	0	56.9	69.2	38.2	46.3	35.7	61.5	46.6	68.4	100	94.
Staphylococcus aureus	62.5	43.7	10	63.6	37.5	27.7	0	93.7	31.2	87.5	80	6.2	12.5	50	20	58.7	73.3	87.5	0	50	66.6	44.4	55.5	33.3	66.6	40	100	100	60

respiratory infections by disrupting the host's defense mechanisms [7]. Previous studies have confirmed the link between smoking habits and the development of CAP [7,27]. The most common comorbidity among the patients was diabetes mellitus, followed by hypertension and COPD [7,27]. Similar comorbidities have been reported in previous research, emphasizing that chronic conditions, particularly diabetes, are significant risk factors for CAP [26,27].

This study analyzed 100 samples from patients diagnosed with CAP admitted at a third-level hospital in Damascus, Syria. Interestingly, all samples were obtained before patients started any antimicrobial therapy; otherwise, patients were excluded. The bacteria that caused 90% of the cases of pneumonia in the study sample were *Streptococcus pneumoniae* (41%), *Staphylococcus aureus* (16%), *Klebsiella* sp. (14%), and *Enterobacter* sp. and *Escherichia coli* (9% each). These isolation rates differ from those reported by an Egyptian study on CAP where the authors isolated *Klebsiella pneumoniae* (10.4%), and *Streptococcus pneumoniae* and *Pseudomonas aeruginosa* (7.8% each); atypical bacteria were isolated in 36 patients (13.3%) [19]. Another study conducted in Vietnam reported *Streptococcus pneumonia* (12.6% of cases), *Klebsiella pneumoniae* (12.2%), and *Pseudomonas aeruginosa* (8.3%) [30]. In a study among Indian adolescents and adults with CAP, pathogenic bacteria included *Klebsiella pneumoniae* (1.6–24.0%), *Staphylococcus aureus* (1.0–12.8%), *Pseudomonas aeruginosa* (0.83–11.6%), *Escherichia coli* (0.83–8.57%), *Acinetobacter* spp. (0.83–5.0%), and *Enterobacter* spp. (0.83–4.0%) [31]. In the current study, the high rates of *Streptococcus pneumoniae* isolated may be due to low awareness of the pneumococcal vaccine by susceptible populations or low access to it. These findings are good examples of the importance of local studies to understand the etiology of infectious diseases, and the importance of following vaccination recommendations as a way to reduce certain types of infection; and thus, indirectly, reduce the use of antimicrobials to help contain AMR.

This study revealed high resistance to antibiotics. Gram-negative bacteria showed the highest resistance against nitrofurantoin, cefazolin, and cefoxitin. On the other hand, Gram-positive bacteria exhibited the highest resistance against erythromycin, cefoxitin, and oxacillin. These findings suggest that the prevalence of resistance to commonly used antibiotics in Syria is concerning. The most susceptible Access antibiotic for Gram-negative bacteria was gentamycin (around 50% susceptibility), while gentamycin had almost 90% susceptibility for the Gram-positive bacteria tested.

This high percentage of resistance could be attributed to the widespread use of these antibiotics without proper prescriptions, their accessibility in pharmacies, and their low cost [32]. Additionally, incomplete courses of antibiotic treatment and excessive use may contribute to bacteria developing resistance against them [33]. Bacteria have developed various mechanisms to resist the effects of antibiotics. Some bacteria modify the adenine residues in the 23S rRNA component of the 50S ribosomal subunit, which decreases the binding affinity of erythromycin [32]. Additionally, some bacteria possess efflux pumps that actively transport erythromycin out of the cell, thereby reducing its intracellular concentration [32]. Many bacteria produce beta-lactamases that hydrolyze the beta-lactam ring of cefoxitin and cefazolin, making the antibiotic ineffective. Some bacteria can also modify penicillin-binding proteins (PBPs) so that cefoxitin cannot bind effectively, leading to resistance [32]. Changes in outer membrane proteins can further reduce the uptake of cefoxitin and cefazolin in Gram-negative bacteria. Similarly, bacteria may use efflux pumps to expel oxacillin from the cell. Furthermore, some bacteria may have mutations that diminish the activation of nitrofurantoin by bacterial nitrofuran reductases, resulting in decreased effectiveness. Bacteria can also use efflux pumps to remove nitrofurantoin from their cells. Polymerase chain reaction (PCR) testing for resistance genes could not be conducted in this study due to limited capabilities.

The effectiveness of antibiotic therapy and the susceptibility of bacteria to antibiotics vary from country to country [13]. For example, the findings of this study on the resistance of Gram-negative bacteria differ from those found in a study conducted in Mexico, where there was high resistance to ampicillin (95.6%), cefuroxime (84.2%), and piperacillin (82.9%) [34]. In a cross-sectional study of 426 samples of Enterobacteria isolated in Addis Ababa, the highest resistance was reported for the fixed-dose combination sulfamethoxazole + trimethoprim (77%), followed by the combination of amoxicillin + clavulanic acid (71.6%), cefotaxime (62.2%), cefepime (60.3%), ceftazidime (60.8%), and norfloxacin (58.8%) [35]. A similar study was conducted in Egypt where the results indicated that *Klebsiella pneumoniae*, the bacterium most commonly isolated in this research, exhibited a high resistance to penicillin and β-lactamase inhibitors, with the exception of piperacillin/tazobactam. The resistance rates to third and fourth-generation cephalosporins ranged from 65.5% to 37.9% [19].

The World Health Organization (WHO) published the AWaRe antibiotic guidelines in 2023 [13], which provide general recommendations for over 50 common conditions, including CAP. The first choice of antibiotic recommended by WHO for mild to moderate cases of CAP is amoxicillin or phenoxymethylpenicillin, and the second choice is amoxicillin + clavulanic acid. However, this research showed that amoxicillin was ineffective against Gram-negative bacteria, with a 0% susceptibility, although it showed a 49% susceptibility against Gram-positive bacteria. Similarly, the combination of amoxicillin + clavulanic acid had no effect on Gram-negative bacteria, while it exhibited a 66.7% susceptibility against Gram-positive bacteria. Additionally, the WHO AWaRe antibiotic guidelines have recommendations for managing severe cases of CAP; specifically, it recommends cefotaxime or ceftriaxone as a first choice, and amoxicillin + clavulanic acid as a second choice. It should be noted that in this study Gram-negative bacteria had low susceptibility to cefotaxime (20%) and ceftriaxone (37.5%), while Gram positive bacteria had a much higher susceptibility to these antibiotics (cefotaxime 71% and ceftriaxone 81%).

These discrepancies reinforce the need to conduct local sensibility testing. To achieve this objective, there is the need to train microbiologists and have well-prepared and operative microbiology laboratories because resistance patterns evolve quickly from one place to another, and good guidance should be adapted with updated information. This is the best way to avoid prescribing antimicrobials that are no longer effective against certain bacteria. For example, the data analyzed in the present study have shown that the specific recommendation to manage CAP caused by Gram-negative bacteria would be ineffective in patients like those in the study sample. In contrast, the recommendations would effectively treat CAP caused by Gram-positive bacteria. These discrepancies also help understand the underlying spirit of recommendations provided at a global level: to be used as a model or guidance that can be adopted or adapted when local evidence suggests a different approach.

Based on the results of this study, Gram-negative bacteria were susceptible to only a few parenteral antibiotics that are usually reserved for critically ill hospitalized patients (for example, imipenem [54.8% susceptibility], meropenem [57%], or colistin [100%]). Colistin is considered a reserve antibiotic and a last-resort option [36]. The study also revealed that Gram-negative bacteria have a higher antibiotic resistance rate than Gram-positive bacteria. This is due to the outer membrane of the Gram-negative bacteria, which enables them to be more resistant by altering their hydrophobic properties, mutating porins, and other factors [37]. In contrast, Gram-positive bacteria lack this outer membrane layer, making them less resistant to antibiotics than Gram-negative bacteria [32,38].

It is essential to prescribe antibiotics cautiously, and follow the recommendations and AWaRe categorization. However, when faced with susceptibility data, the healthcare professionals are faced with an important question: what would be an acceptable susceptibility threshold to trust in one antibiotic and prescribe it to a patient? The acceptable susceptibility threshold for confidence in an antibiotic can vary depending on several factors, including the specific antibiotic in question, the type and severity of the infection being treated, and local resistance patterns. This requires extensive research and follow-up to determine the relationship between treatment and death based on the type of bacteria, infection, location, and severity [39]. This underscores the role of microbiologists and specialists in infectious diseases in hospitals. These professionals can help make informed decisions based on the best available evidence.

The study by Danneman *et al.* indicated that even a threshold of antibiotic resistance of only 25% could lead to significantly higher rates of infection and death due to inappropriate antibiotic use [40]. Based on the CLSI guidance, an empiric antibiotic susceptibility threshold of ≥ 90% was deemed optimal [41]. Therefore, in clinical practice, a commonly used threshold is a susceptibility rate of 90% or higher for the specific antibiotic against the particular pathogen within the local population. If less than 90% of isolates are susceptible, the antibiotic may not be reliable for empirical treatment. This study focused on patients with severe pneumonia requiring hospitalization and found that antibiotic resistance was particularly high in Gram-negative infections. A susceptibility threshold (≥ 90%) was associated with shifts to narrower therapy, potentially resulting in colistin being used in 100% of patients with Gram-negative bacteria, and this depicts a bad situation As resistance increases in Gram-positive bacteria, treatment options become limited to meropenem, imipenem, and vancomycin, complicating future therapeutic choices.

This study has certain limitations that must be considered. The study only considers patients admitted to a single hospital in Damascus; hence, this information could differ from that of CAP patients admitted to other centers. In spite of the limitation, the present study was useful to identify a particular

situation which requires planning to determine how international reference recommendations can be adapted to the Syrian reality. It is not possible to discard the role of the conflict and post-conflict situation in the country as one of the possible explanations for the disparity in resistance results, as the management of infectious diseases was probably not ideal in recent years for different reasons, including the excessive use of certain wide-spectrum antibiotics due to lack of access to other alternatives.

The results of the present study should also serve as the basis for additional studies in the country to confirm or deny this susceptibility pattern and for AMS interventions in the study hospital and other Syrian hospitals.

This study had a small sample size because only the patients who did not take antibiotics before hospitalization were included. Therefore, future studies with larger sample sizes are recommended.

Conclusions

This study found that *Streptococcus pneumoniae* is the main cause of CAP. The results indicated that Gram-negative bacteria have a higher antibiotic resistance rate than Gram-positive bacteria. Gram-negative bacteria showed high resistance to nitrofurantoin, cefazolin, and cefoxitin. On the other hand, resistance in Gram-positive bacteria was highest against erythromycin, cefoxitin, and oxacillin. Vancomycin, colistin, rifampin, and imipenem were the most effective antibiotics according to the results in this sample. These medications are administered as injections and are reserved for hospitalized patients in critical condition, requiring a prescription. This study showed high resistance of bacteria to antibiotics, which presents a significant challenge in treating the infections they cause. This study shows discrepancies between some WHO recommendations and the antibiotics that should be used in practice in this specific hospital according to local sensitivity data.

In summary, this research highlights the need to (1) adapt general recommendations according to local evidence, (2) have functional microbiology laboratories and well-trained specialists in infectious diseases in hospitals, and (3) continue active campaigns to improve the smart use of antibiotics through AMS interventions tailored to the results of AMR and antimicrobial use surveillance. This research is a good example to reflect on the need for countries to be able to test AMR and monitor antimicrobial use continuously as the first step to adapting general recommendations and guidance according to local evidence. This can help to improve the smart use of antibiotics, thus contributing to resistance containment.

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Authors' contributions

RH: conceptualization, methodology, data collection, analysis and interpretation, writing—original draft; KJ: analysis, writing—review and editing; LC: data collection; KHA: data collection; HH: data collection; HA: writing—review and editing; AF: supervision, writing—review and editing. All authors have read and approved the final version of this manuscript.

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Conflict of interest

No conflict of interest is declared.

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