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Original Article

Antibiotics use and its association with Multi-Drug Resistance in a Tertiary Care Geriatrics Hospital in Egypt

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Abstract

Introduction: Multi-Drug Resistance (MDR) is common in hospitalized geriatric patients. The study aims to investigate the pattern of antibiotic use and determine its association with MDR in hospitalized geriatric patients.

Methodology: A retrospective cohort study including 193 geriatric patients admitted to a Geriatric Intensive Care Unit (GICU) in a tertiary care Geriatrics hospital in Egypt, throughout a consecutive 6 months duration. A review of medical records was done to extract clinical, socio-demographic, and prescribing data on antibiotics throughout admission. The presence of MDR organisms (MDROs) was determined by reviewing culture and sensitivity reports. Descriptive statistics and logistic regression analysis were performed.

Results: 181 (93.8%) patients received at least 1 antibiotic. Cephalosporins were the most commonly consumed antibiotics (24%). MDROs were significantly associated with receiving ≥ 3 antibiotics. Longer hospital stay was a predictor of multiple antibiotics use (Odds Ratio of 1.075). MDROs were prevalent in 110 (57.0 %) patients. *Klebsiella* species were the most frequent MDROs (26%) with the highest susceptibility to amikacin.

Conclusions: The study provides a detailed description of both antibiotics use and MDR among hospitalized geriatric patients in Egypt. It gives a novel insight into the ongoing drug-pathogen combinations in acute healthcare settings of the aged. This data has a potential role in applying antimicrobial stewardship programs for hospitalized geriatric patients to mitigate antimicrobial resistance in similar settings.

Key words: Antibiotics; critically ill; geriatric patients; multi-drug resistance.

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Introduction

Geriatric patients are more liable to various infections that necessitate particular attention to antibiotics consumption [1]. Antibiotics are frequently utilized to treat infections, but unfortunately, they are increasingly less effective because of the ongoing antimicrobial resistance (AMR) [2]. Inappropriate use of antibiotics is frequent in frail geriatric patients [3]. Hence, special considerations on antibiotics use and selection among this vulnerable group of patients [1].

AMR is a major global health threat with the highest impact on the lower income countries because of the gaps in knowledge to understand the leading pathogen-drug combinations contributing to this problem [4]. Inappropriate and excessive use of antibiotics has major attributes to AMR with the subsequent high rate of mortality due to resistance to first-line antibiotics such as β-lactams and fluoroquinolones [5]. Accordingly, monitoring of antibiotics consumption at hospitals is important through different methods such as the World Health Organization-assigned defined daily dose (WHO-DDD) and Days of Therapy (DOT) methods [6].

There are several attempts to combat AMR including the development of an institutional Antimicrobial Stewardship Program (ASP) [7], and sticking to the WHO standards of antibiotics use including the AWaRe Classification of antibiotics which was developed in 2017 and updated in 2021 by an expert committee on use and selection of antimicrobials to support ASP at local, national and global levels. Antibiotics are classified into three groups; Access, Watch, and Reserve (AWaRe), taking into consideration the impact of different antibiotics on AMR [8].

Despite these facts, few pieces of literature were available on antibiotic use and its clinical impact on AMR in hospitalized geriatric patients. This study aims to investigate the pattern of antibiotic use and its

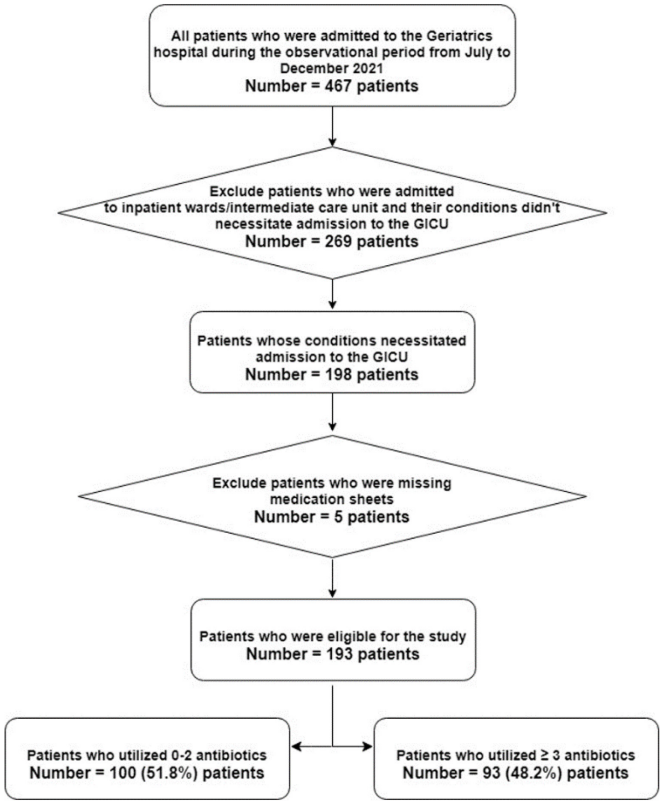
association with MDR among critically ill geriatric patients.

Methodology

Study design, participants, and procedure

A retrospective cohort study was conducted in the Geriatrics Hospital of Ain Shams University, Egypt during the observational period from July to December 2021. 193 hospitalized older adults (aged ≥ 60 years) admitted to Geriatric Intensive Care Unit (GICU) were enrolled in the study. GICU is a specialized 20-bed unit at the Geriatrics hospital for acute management of older patients with major organ system failure necessitating hemodynamic monitoring including continuous monitoring of vital data such as heart rate, temperature, and blood pressure, electrocardiogram, peripheral oxygen saturation, central venous pressure, fluid charts, and arterial blood gas analysis. The management at GICU analysis provides mechanical ventilation and intravenous inotropic support and/or vasopressors. The inclusion criteria of the study mandated admission to GICU either directly from the emergency department or as a referral from in-patient wards or intermediate care unit at the Geriatrics hospital or other hospitals during the mentioned observational period. Exclusion criteria included those who did not need admission to GICU and those with missing medication sheets in the clinical record as described in Figure 1.

Figure 1. Eligibility criteria for this study.



Clinical, Demographic, and Laboratory data

Clinical records of the studied patients were reviewed and data were collected and recorded for further analysis. Clinical and demographic data included age, gender, length of hospital stay (LOS) in days, and the presence of comorbidities. Hospital LOS was determined by revising admission and discharge dates from the administrative data section at the hospital and defined as the number of days between admission and discharge dates. Laboratory data including the results of culture and antimicrobial susceptibility testing was retrieved from the central laboratory information system of Ain Shams University hospitals.

Data extraction for antibiotics consumption

A review of the medication sheets of each patient was conducted and antibiotics use throughout admission at GICU was determined and counted. According to the total number of antibiotics consumed by each patient, participants were classified into two groups, a group who received 0-2 antibiotics and the second group included all patients who received ≥ 3 antibiotics during their stay at the GICU. Antibiotics were classified according to anatomical therapeutic chemical classification (ATC) as pharmacological groups of systemic antibiotics (J01) [9]. Receiving any dose of a particular antibiotic was sufficient to count it. The DOT method was also used to estimate antibiotic consumption among participants. One DOT represented the intake of a single antibiotic on a given day regardless of its dose (number or strength). For example, patients who received 3 antibiotics per day had 3 DOTs, and so on [6].

Antibiotics did not have to belong to different antibiotic classes or generations for counting because of the differences in the antibacterial spectrum. Accordingly, switching between different antibiotics even within the same class or generation was counted separately. For example, the switch from ceftriaxone to ceftazidime was counted separately as two different antibiotics because ceftazidime has greater activity against *Pseudomonas aeruginosa* in comparison to the rest of the third-generation cephalosporins [10].

Laboratory sample processing and identification of pathogens

Different clinical specimens were collected from different patients according to the clinical presentation of each patient. Samples included blood, urine, sputum,

wound swabs, pus, central line tips, throat swabs, chest tubes, and ascetic fluid. These samples were collected by trained nursing staff. Collected samples were processed and examined microbiologically according to standard operating procedures. Samples were inoculated to suitable culture media. Isolates were identified by conventional methods including Gram-stained films, growth characters, and biochemical reactions. Some isolates were further identified by Vitek 2 System (Biomerieux, France) All culture media were routinely supplied by (Oxoid, UK).

Antimicrobial susceptibility testing

Antimicrobial susceptibility testing was done for all the isolated pathogens by the Kirby Bauer disk diffusion method. For isolated *Enterobacteriaceae,* ESBL production was detected by the double disk synergy test using a disc of amoxicillin-clavulanate (AMC-20/10 µg) along with cefotaxime (CTX-30 µg) and ceftazidime (CAZ-30 µg). For *Staphylococcus aureus* and *coagulase-negative staphylococcal (CoNS*) isolates, characterization of methicillin resistance was done using cefoxitin (30 µg) and oxacillin (1µg) discs, and vancomycin susceptibility was detected using vancomycin agar screen test performed on Brain Heart Infusion (BHI) agar supplemented with 6 µg/ml vancomycin. Results were confirmed by Vitek-2 system (Biomerieux, France). Antimicrobial susceptibility tests were performed and interpreted according to the Clinical and Laboratory Standards Institute (CLSI) 2021. Quality control strains *Staphylococcus aureus* ATCC 25923, *Pseudomonas aeruginosa* ATCC 27853, and *Escherichia coli* ATCC 25922 were used [11].

Definition of multi-drug resistant organisms (MDROs)

MDROs were defined according to Magiorakos *et al.* as acquired non-susceptibility to at least one agent in three or more antimicrobial categories [12]. MDR was considered positive in the presence of MDR isolates in any clinical specimen. Accordingly, patients were categorized into those with and without MDR isolates. For the provision of a susceptibility pattern to different antibiotics, only, the first isolates per patient during this 6 months observational period were included without duplication. All bacterial isolates were not tested with all antibiotics mentioned in the study. The selection of antimicrobials tested against different bacterial isolates followed our laboratory's standard procedures. These procedures depend on guidelines mostly CLSI 2021, the site of infection, intrinsic resistance, and the method used. The automated susceptibility available in the laboratory is Vitek 2 system (Biomerieux, France), in which certain cards are available for each organism [11].

Statistical analysis

Values were presented as means ± SD or as numbers and percentages, as appropriate. The relations between patients who received 0-2 antibiotics or ≥ 3

Table 1. Participant's characteristics and their associations with receiving ≥ 3 antibiotics in critically ill geriatric patients.

Participant's characteristics	Total (N = 193) (100%)	Patients received 0-2 antibiotics (N = 100) (51.8%)	Patients received ≥ 3 antibiotics (N = 93) (48.2%)	Univariate analysis	
				OR (95% C.I.)	*p* value
Age	75.14 ± 8.755	74.71 ± 8.354	75.61 ± 9.189	1.012 (.979-1.046)	0.485
Hospital LOS (days)	15.63 ± 11.340	11.89 ± 8.478	19.20 ± 12.559	1.072 (1.035-1.111)	**< 0.001***
Number of MDROs isolates	1.47 ± 1.955	.85 ± 1.359	2.14 ± 2.263	1.579 (1.276-1.954)	**< 0.001***
Number of comorbidities	3.78 ± 1.715	3.38 ± 1.633	4.18 ± 1.708	1.336 (1.101-1.621)	**0.003***
Male/Female	77(39.9) / 116 (60.1)	40 (51.9) / 60 (51.7)	37 (48.1) /56 (48.3)	1.016 (0.570- 1.813)	0.956
Presence of MDROs isolate	110 (57.0)	41 (37.3)	69 (62.7)	4.137 (2.243-7.629)	**< 0.001***
Hypertension	94(48.7)	45 (47.9)	49 (52.1)	1.155 (0.619 - 2.156)	0.651
Cardiac disease	81(42.0)	37 (45.7)	44 (54.3)	1.346 (0.726- 2.496)	0.346
Diabetes Mellitus	73 (37.8)	30 (41.1)	43 (58.9)	1.792 (0.959- 3.346)	0.067
Chronic hepatic disease	38 (19.7)	14 (36.8)	24 (63.2)	1.918 (0.909- 4.047)	0.087
Chronic renal disease	37 (19.2)	17 (45.9)	20 (54.1)	1.176 (0.564- 2.453)	0.665
Old stroke/Transient Ischemic Attacks	35 (18.1)	15 (42.9)	20 (57.1)	1.398 (0.657- 2.973)	0.384
Malignancy	32 (16.6)	16 (50.0)	16 (50.0)	.970 (0.447- 2.102)	0.938
Dementia	26 (13.5)	15 (57.7)	11 (42.3)	.682 (0.292-1.590)	0.375
Chronic respiratory disease	24 (12.4)	10 (41.7)	14 (58.3)	1.420 (0.591- 3.414)	0.433

*Significant difference.

antibiotics and other variables were tested using odds ratio. Variables with p values < 0.05 in univariate analysis were introduced in a logistic regression model to detect independent predictors of patients receiving ≥ 3 antibiotics. Mann Whitney test was performed to compare medians of DOT of various antibiotics among participants. All tests were bilateral and a p value of 0.05 was the limit of statistical significance. Analysis was performed by statistical package software IBM-SPSS version 24.

Ethical considerations and approval

Both the ethical review board members at the Geriatrics hospital, Ain Shams University hospitals, and the Ethical Committee in the Faculty of Medicine at Ain Shams University have revised and approved the study protocol (Approval Code: FMASU R 57 / 2022). The ethical approval date was 30/3/2022. The study conforms to the provisions of the Declaration of Helsinki and preserves participants' confidentiality.

Results

A total of 193 critically ill geriatric patients with a mean age of 75.14 ± 8.755 years were included. A total of 181 (93.8%) patients used antibiotics. Among them, 93 (48.2%) patients utilized ≥ 3 antibiotics during their stay at the GICU. The two patients' groups were compared regarding different variables in univariate analysis using an odds ratio. Significant variables included hospital LOS in days, presence of MDROs isolates, number of comorbidities, and number of MDROs isolates. Having MDROs isolates would increase the odds of receiving ≥ 3 antibiotics by 4.137 times. By 95%, having MDROs infection would increase the odds of receiving ≥ 3 antibiotics from 2.243 to 7.629. Also, a one-day increase in hospital stay would increase the odds of receiving ≥ 3 antibiotics by 1.072. By 95%, the one-day increase in hospital stay would increase the odds of receiving ≥ 3 antibiotics from 1.035 to 1.111 (Table 1).

Significant variables were entered in a logistic regression model to detect the significant predictors for receiving multiple (≥ 3) antibiotics. Only hospital LOS was found to be a significant predictor for receiving ≥ 3 antibiotics. The model was able to correctly predict receiving ≥ 3 antibiotics by 71.7%. It was able to explain 28.3% of the variability of receiving ≥ 3 antibiotics as indicated by the Nagelkerke R Square value. The results showed that a one-day increase in hospital stay would increase the odds of receiving ≥ 3 antibiotics by 1.075. The 95 CI means that by 95% we are confident that a one-day increase in hospital stay would increase the odds of receiving ≥ 3 antibiotics from 1.029 to 1.123 (Table 2).

Figure 2. Frequency of antibiotics use in critically ill geriatric patients (**A**) Frequency of different classes of antibiotics; (**B**) Frequency of individual antibiotics.

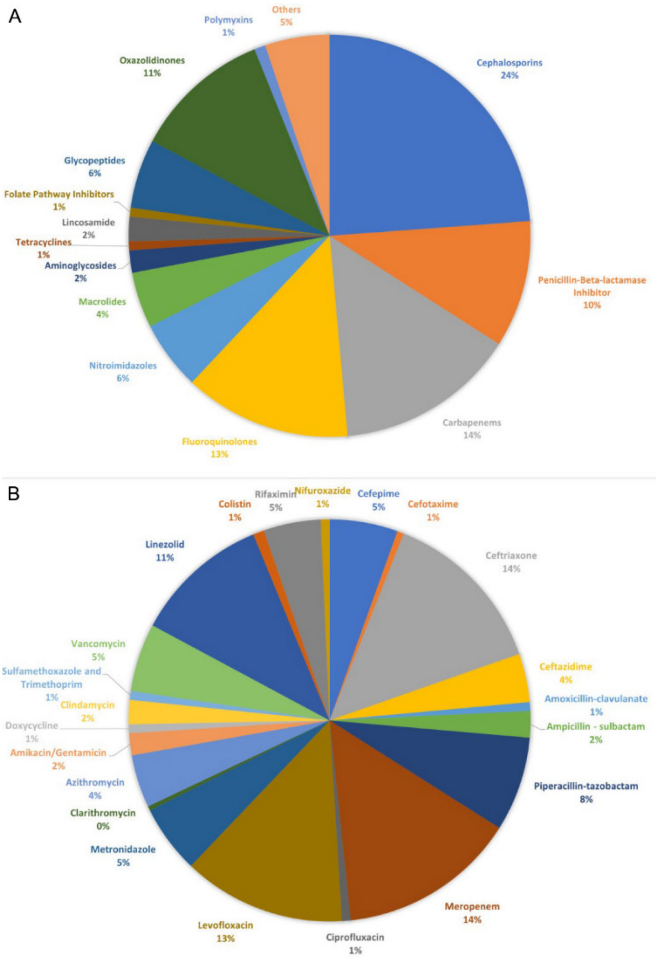


Table 2. Multivariate analysis of significant factors associated with multiple antibiotics use among participants.

Risk factors of multiple antibiotics use	Multivariate analysis	
	OR (95% C.I.)	p value
Presence of MDROs isolates	2.180 (0.735- 6.469)	0.160
Number of MDROs isolates	1.129 (0.808- 1.578)	0.477
Hospital LOS (days)	1.075 (1.029-1.123)	**0.001***
Number of comorbidities	1.173 (0.926-1.486)	0.186

*Significant difference.

Table 3. Antibiotics consumption as expressed by the Duration of Therapy (DOT) of each antibiotic among participants.

Antibiotic	Whole patients		Patients received 0-2 antibiotics		Patients received ≥ 3 antibiotics		*p* value*
	Total number of use	Median of Antibiotics' DOT (Minimum-Maximum)	Total number of use	Median of Antibiotics' DOT (Minimum-Maximum)	Total number of use	Median of Antibiotics' DOT (Minimum-Maximum)	
Cefepime	31	5.00 (1 - 16)	7	3.00 (1-6)	24	5.50 (1-16)	-----
Cefotaxime	3	5.00 (4 - 6)	1	4.00 (4-4)	2	5.50 (5-6)	-----
Ceftriaxone	77	3.00 (1-15)	39	3.00 (1-14)	38	3.00 (1-15)	0.556
Ceftazidime	27	4.00 (1-13)	8	4.50 (1-9)	19	4.00 (1-13)	-----
Amoxicillin-clavulanate	4	7.50 (3-15)	-----	-----	4	7.50 (3-15)	-----
Ampicillin - sulbactam	12	4.50 (1-12)	3	4.00 (2-5)	9	6.00 (1-12)	-----
Piperacillin-tazobactam	40	5.00 (2-18)	8	4.50 (4-7)	32	6.00 (2-18)	-----
Meropenem	80	6.00 (1-16)	25	5.00 (1-13)	55	7.00 (1-16)	0.056
Ciprofluxacin	4	3.50 (1-10)	1	1.00 (1-1)	3	5.00 (2-10)	-----
Levofloxacin	76	4.00 (1-25)	19	4.00 (1-9)	57	4.00 (1-25)	0.526
Metronidazole	29	4.00 (1-14)	7	2.00 (1-4)	22	5.50 (1-14)	-----
Clarithromycin	2	10.50 (7-14)	-----	-----	2	10.50 (7-14)	-----
Azithromycin	24	3.00 (1- 8)	9	3.00 (1-5)	15	3.00 (2-8)	-----
Amikacin/Gentamicin	11	5.00 (1-16)	1	9.00 (9-9)	10	4.50 (1-16)	-----
Doxycycline	3	3.00 (2-14)	-----	-----	3	3.00 (2-14)	-----
Clindamycin	11	3.00 (1-7)	2	2.50 (2-3)	9	4.00 (1-7)	-----
Sulfamethoxazole and Trimethoprim	2	7.00 (3-11)	-----	-----	2	7.00 (3-11)	-----
Vancomycin	28	5.00 (1-13)	6	3.50 (3-13)	22	6.00 (1-12)	-----
Linezolid	58	5.00 (1-18)	15	4.00 (1-10)	43	6.00 (1-18)	0.059
Colistin	4	4.00 (2-11)	-----	-----	4	4.00 (2-11)	-----
Rifaximin	26	4.00 (1-14)	6	4.00 (3-9)	20	4.00 (1-14)	-----
Nifuroxazide	5	3.00 (1-4)	-----	-----	5	3.00 (1-4)	-----

Mann-Whitney test* was performed as data were not normally distributed. It was not applicable for those counting less than 10.

Table 4. Comparison between percentages of MDR isolates in each sample to the total number of MDR isolates and percentages of each sample to the total studied samples.

Sample type	Number (%) of each sample to total number of samples (Total = 597)	Number (%) of MDR Isolates in each sample to the total number of MDR isolates (Total = 286)
Sputum	102 (17.08%)	76 (26.57%)
Blood	236 (39.53%)	92 (32.1%)
Urine	174 (29.14%)	75 (26.2%)
Wound	16 (2.68%)	19 (6.6%)
Pus	5 (0.84%)	5 (1.7%)
Central line	11 (1.8%)	12 (4.2%)
Throat	1 (0.16%)	1 (0.34%)
Chest tube	2 (0.33)	2 (0.69%)
Ascetic fluid	18 (3.01%)	4 (1.4%)
Pleural fluid	24 (4%)	0 (0%)
Stool	4 (0.67%)	0 (0%)
Pericardial fluid	2 (0.33%)	0 (0%)
CSF	2 (0.33%)	0 (0%)
Total	597	286

Table 5. Distribution of multi-drug resistant organisms among different specimens (Numbers and percentages represent number of isolates and their percentages in each specimen).

	Gram-negative pathogens								Gram-positive pathogens					
	Klebsiella species	*Acinetobacter species*	*E. coli*	*Pseudomonas*	*ESBL Kebsiella*	*ESBL E. coli*	*Proteus species*	*ESBL Proteus*	*CoNS*	*MRSA*	*Enterococci*	*Non-hemolutic streptococci*	*Strept. viridans*	Total
Sputum	28 (36.8%)	32 (42.1%)	4 (5.3%)	7 (9.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (6.6%)	0 (0%)	0 (0%)	0 (0%)	76 (100%)
Blood	14 (15.2%)	13 (14.1%)	5 (5.4%)	3 (3.3%)	1 (1.1%)	1 (1.1%)	0 (0%)	1 (1.1%)	45 (48.9%)	5 (5.4%)	3 (3.3%)	0 (0%)	1 (1.1%)	92 (100%)
Urine	18 (24%)	5 (6.7%)	18 (24%)	5 (6.7%)	6 (8%)	5 (6.7%)	3 (4%)	0 (0%)	9 (12%)	1 (1.3%)	3 (4%)	2 (2.7%)	0 (0%)	75 (100%)
Wound	6 (31.6%)	8 (42.1%)	1 (5.3%)	2 (10.5%)	1 (5.3%)	0 (0%)	1 (5.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	19 (100%)
Pus	3 (60%)	2 (40%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (100%)
Central line	4 (33.3%)	3 (25%)	0 (0%)	1 (8.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (33.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	12 (100%)
Throat	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
Chest tube	1 (50%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (50%)	0 (0%)	0 (0%)	2 (100%)
Ascetic fluid	0 (0%)	1 (25%)	1 (25%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (25%)	0 (0%)	1 (25%)	0 (0%)	0 (0%)	4 (100%)
Total	74	64	29	18	8	6	5	1	59	11	8	2	1	286

E. coli: Escherichia coli; ESBL: extended spectrum beta-lactamase; CoNS: Coagulase negative Staphylococci; S. aureus: Staphylococcus aureus; MRSA: methicillin resistant Staphylococcus aureus.

Based on the calculated DOT of each antibiotic, the Mann-Whitney test was performed as data were not normally distributed to compare between medians of DOT of various antibiotics among participants. Accordingly, antibiotics consumption among participants was expressed by the DOT of each antibiotic as described in (Table 3).

The frequency of antibiotics use among participants showed that cephalosporins were the most frequently consumed class of antibiotics (24%), while meropenem and ceftriaxone were the most frequently utilized individual antibiotics (14% each) (Figure 2).

The proportion of MDROs in different samples was compared to the number of different sample types taken (Table 4). Among participants, 110 (57.0 %) patients had at least one MDROs isolate, MDR *Klebsiella* species were the most frequent MDROs (26%) among participants. The frequency of different MDROs and their distribution in different specimens among participants is described in Table 5, and Figure 3. MDR *Acinetobacter and Klebsiella* species were the most common isolates in sputum (42.1% and 36.8% of sputum isolates respectively), while *CoNS* represented the most common isolates from blood and central line cultures (48.9% and 33.3% respectively). From the urine samples, *E.coli* and *Klebsiella* species represented together 48% of isolated pathogens (24% each).

Susceptibility patterns of various bacterial species to different antibiotics are described in Figure 4. *Methicillin-resistant Staphylococcus aureus* (*MRSA*), *CoNS*, and *Enterococci* showed the highest percentage of sensitivity to vancomycin and linezolid. *MRSA* was

Figure 3. Frequency of multi-drug resistant organisms among participants.

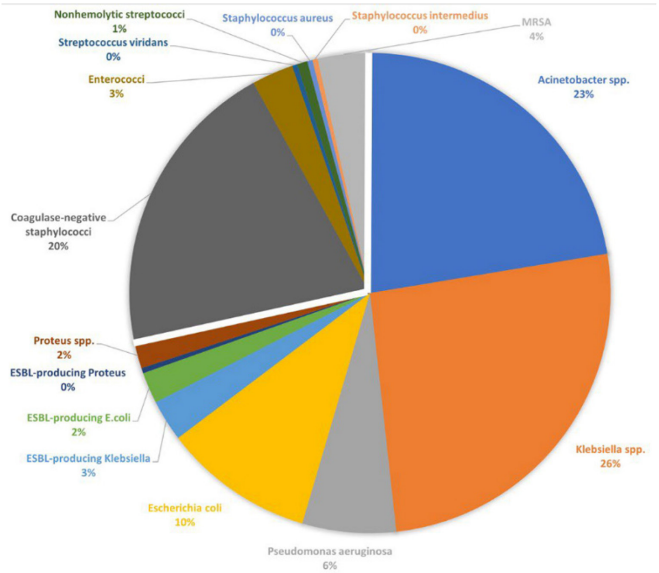
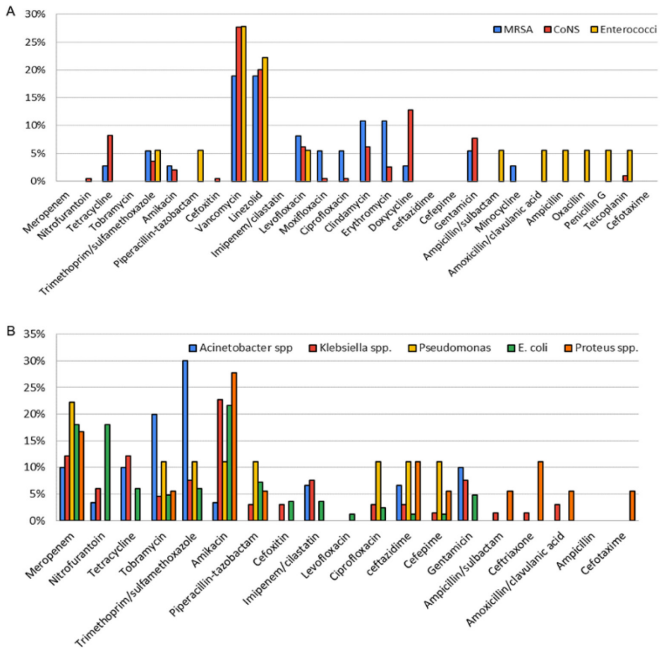


Figure 4. Antimicrobials susceptibility patterns of multi-drug resistant organisms among participants. (**A**) Antimicrobials susceptibility patterns of MDR-Gram-positive bacteria; (**B**) Antimicrobials susceptibility patterns of MDR-Gram-negative bacteria.



sensitive to a lesser extent to erythromycin and clindamycin followed by the 3 fluoroquinolones (levofloxacin, moxifloxacin, and ciprofloxacin). Following vancomycin and linezolid, CoNS revealed sensitivity to doxycycline, tetracycline, and clindamycin. Regarding *Enterococci*, they showed about 5% sensitivity to ampicillin/sulbactam, amoxicillin/clavulonic acid, oxacillin, teichoplanin, trimethoprim/sulfamethoxazole, and piperacillin/tazobactam.

Regarding MDR Gram-negative isolates, *Acinetobacter* species had the highest sensitivity rate to trimethoprim/sulfamethoxazole followed by tobramycin, meropenem, and tetracycline, with no sensitivity to fluoroquinolones and most beta-lactams. Regarding *E. coli* and *Klebsiella* species they showed the highest rate of sensitivity to amikacin followed by meropenem. *Pseudomonas* species was most susceptible to meropenem. Similarly, *Proteus* species had the highest susceptibility to amikacin followed by meropenem.

Discussion

There is a general scarcity of data regarding AMR and antibiotic use among geriatric patients, especially in low-income countries [13]. This retrospective study aimed to investigate the pattern of antibiotic use and

ascertain its association with the presence of MDROs among hospitalized geriatric patients. The present study revealed important findings; First frequency, distribution, and predictors of antibiotics use among geriatric patients in a tertiary care university hospital in Egypt. Second, the provision of an antimicrobial susceptibility pattern for the most frequently encountered MDROs. Third, the prevalence and distribution of MDROs in acute care settings specialized for the aged.

Overall, 181 (93.8) patients utilized antibiotics, out of which 93 (48.2) patients received ≥ 3 antibiotics during the mentioned observational period at GICU. This study showed the most frequently prescribed classes of antibiotics including cephalosporins, carbapenems, and fluoroquinolones representing 24%, 14%, and 13% respectively. While, the most frequently prescribed individual antibiotics were meropenem ceftriaxone, and levofloxacin representing 14%, 14%, and 13% respectively of the total antibiotic prescriptions. This finding correlates with a previous prospective observational study including an analysis of 206 prescriptions of geriatric patients revealing that cephalosporins were the most commonly consumed antibiotics (33.2%), specifically cefotaxime (14.6%) and ceftriaxone (12.6%) [1]. This finding supports the documented frequent empirical prescribing of broad-spectrum antibiotics, which have a high potential to develop AMR. These data contradict the recently reported guidance of WHO for antibiotics use which listed meropenem, third-generation cephalosporins, and quinolones as watch antibiotics because of their higher potential to develop AMR [8], which makes these antimicrobials the top priority in the monitoring of ASP [8].

In our study, we used the DOT method to express antibiotics use among participants including the two studied groups of patients. The WHO-DDD was inconvenient for our analysis because of the inclusion of a special population with critical illnesses that necessitated frequent dose adjustments during the same admission because of the associated changes in the pharmacokinetics of antibiotics [6,14]. On the contrary, the DOT method is not affected by the changing dose of antibiotics or the WHO-DDD. So, it is currently the most preferable and accurate measure of antibiotic consumption and is used by National Healthcare Safety Network and Centers for Disease Control and Prevention [6].

The study showed factors significantly associated with receiving ≥ 3 antibiotics including the presence of MDR isolates, number of MDR isolates, hospital LOS and number of comorbidities. However, longer hospital LOS was the only significant predictor of receiving ≥ 3 antibiotics coinciding with previous studies reporting that patients with longer hospital stays are more likely to utilize more medications including a higher load of antimicrobials with a subsequent higher risk of getting resistant pathogens [1,15-16].

The current study tried to fill the gap of knowledge regarding drug-pathogen combinations through analysis of both antimicrobial susceptibility and the most frequently encountered MDROs in acute care settings of older adults. The study showed important information about the frequency and distribution of different MDROs in the acute care setting of geriatric patients. MDR isolates were reported in 110 (57%) patients. It confirms the high prevalence of MDR in critically ill older patients and coincides with the findings of other studies [17]. Gram-negative bacteria (GNB) comprised the majority, representing 72% of total MDR isolates. It supports the frequently reported higher risk of resistance among GNB because of their distinctive structure, making these bacteria at the most critical priority list of WHO for resistant pathogens with a particular threat at hospitals and nursing homes [18,19].

Various studies showed different frequencies of MDR among different microorganisms in various healthcare settings. In the present study, *Klebsiella* species were the most frequent MDROs representing (*26%)* followed by *Acinetobacter* species (23%) of the whole MDR isolates in the study. It supports the reported high prevalence of carbapenemase-producing *Klebsiella pneumoniae* in another prospective multinational study involving hospitals in 36 countries [20]. These data confirm the increasing resistance to carbapenems as stated in antibiotic resistance threats in the United States, 2019 as it considered carbapenem-resistant *Enterobacteriaceae* and carbapenem-resistant *Acinetobacter* as urgent threats necessitating intrusive actions [21].

Contrary to the dominance of carbapenemase-producing GNB, only 11 isolates of MRSA were detected in our study (4%). It coincides with the declining tendency of *MRSA* from 69.0% in 2005 to 35.3% in 2017 according to the China Antimicrobial Surveillance Network [22] Also, ESBL-producing *Enterobacteriaceae* represented about 5% of MDROs in our study, contrary to a recent review study in Asia reporting their high prevalence up to 71.6% [23]. The variability in the prevalence of MDROs could be explained by the different patients' populations and

antimicrobial susceptibility patterns in different healthcare settings.

The top three sites of MDR isolates were blood (92 specimens), sputum (79 specimens), and urine (75 specimens). MDR-GNB organisms were mostly present in sputum specimens rather than other ones, contrary to the predominant presence of Gram-positive organisms in blood specimens. It is important to note that the current study couldn't differentiate between bacteremia and contamination regarding positive blood cultures, especially for *CoNS* isolates which mandated specific procedures such as double culture check or time to positivity assessment [24], and both were missing in our analysis. Also, it is worth reporting that we compared the proportion of MDROs in different samples to the number of different sample types taken. It revealed the predominance of blood, sputum and urine samples, which could explain the expected predominant presence of MDR isolates among these samples.

The study revealed data regarding antimicrobial susceptibility patterns to guide selection and mitigate misuse of antibiotics at acute care settings of geriatric patients. Based on our analysis, vancomycin and linezolid represented the most effective ones for targeting MDR-Gram-positive bacteria including *MRSA*. While, antimicrobial susceptibility varied among MDR-GNB, for example, amikacin and tetracycline were the most effective in suppressing the growth of 23%, and 12% of MDR *Klebsiella* isolates respectively. Amikacin, meropenem, and nitrofurantoin were effective for 22%, 18%, and 18% of MDR *E. coli* isolates respectively. Trimethoprim/sulfamethoxazole, tobramycin, tetracycline, and meropenem were effective for 30%, 20%, 10%, and 10% of MDR *Acinetobacter* isolates respectively, while, meropenem was effective for 22% for MDR *Pseudomonas* isolates. Apart from *ESBL-producing E. coli*, none of MDR-GNB was sensitive to levofloxacin. Similarly, in a study of patients having a malignant disease, investigators found that MDR-GNB isolates were primarily sensitive to amikacin, imipenem, and meropenem, while they were primarily resistant to fluoroquinolones and cephalosporins. Contrary to the susceptibility patterns among 575 younger patients in the rehabilitation ward of a general hospital in China [25]. This diversity could be attributed to differences in susceptibility profiles among different patient populations in different settings [26].

The current study supports the ongoing AMR especially among GNB for carbapenems, with a subsequent higher risk of mortality [27]. Zhu *et al.* stated that exposure to carbapenems is one of the factors (Odds Ratio 4.16) associated with carbapenem-resistant *Klebsiella pneumoniae* infection [28]. Therefore, it is wise to restrict the empirical use of carbapenems to reduce the ongoing emergence of MDROs [25]. In addition, it is advisable to shift the tendency of prescribing broad-spectrum antibiotics to narrow-spectrum ones and prescribe antibiotics in accordance with the WHO guidance for antibiotics use and based on patient susceptibility reports to limit and restrict the emergence of MDROs at clinical settings of geriatric patients [1].

Limitations and Strengths

To the best of our knowledge, it is the first study investigating antimicrobial use among critically ill geriatric patients with the provision of a detailed description of its association with MDROs in a trial to expose the deficient practice in antimicrobials use and its attributes to AMR. In addition, the study provided a summary of MDR isolates and their susceptibility to different antibiotics. These data have a potential benefit for establishing ASP for geriatric patients at hospitals. The main limitations of the study include the following: First, the inability to discriminate between colonization and infection because of the retrospective design and absence of supporting serological, radiological, and/or clinical data of infection. Second, antibiotic therapy in this study couldn't be determined whether it was prophylactic, empirical, or definitive to ascertain its appropriateness for use. The study also lacks calculation of DOT per 1000 patient days [6] to express antibiotics consumption. Third, it is a single-institute study including a relatively small sample size. Thus, it seems difficult to generalize the findings. Further longitudinal multicenter studies are recommended to ascertain the current situation of AMR and provide new effective treatment options to combat MDROs among hospitalized geriatric patients.

Conclusions

The present study confirms the common misuse of antimicrobials and the ongoing increase of MDR at geriatric healthcare settings worldwide, including Egypt. A strict antibiotic selection policy is urgently needed. ASP and infection control protocols in clinical settings for older adults are important to enhance rational antibiotics use among frail older patients.

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Authors' Contributions

All authors have substantial contributions to the study through study design, data analysis, data interpretation, and manuscript writing. Khalid Elsayed Elsorady has also contributed to study conceptualization, participants' selection, data collection/entry, and manuscript drafting. Dalia Hosni Abdelhamid has also contributed to the laboratory part of data collection. All authors read and approved the final manuscript.

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