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Antibiotic use and associated factors in a large sample of hospitalised older people

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ABSTRACT

Objectives: The aims of this study were to assess (i) the prevalence of antibiotic use, (ii) factors associated with their use and (iii) the association with in-hospital mortality in a large sample of hospitalised older people in Italy.

Methods: Data were obtained from the 2010–2017 REPOSI register held in more than 100 internal medicine and geriatric wards in Italy. Patients aged ≥65 years with at least one antibiotic prescription during their hospitalisation were selected. Multivariable logistic regression models were used to determine factors associated with antibiotic use.

Results: A total of 5442 older patients were included in the analysis, of whom 2786 (51.2%) were prescribed antibiotics during their hospitalisation. The most frequently prescribed antibiotic class was β-lactams, accounting for 50% of the total prescriptions. Poor physical independence, corticosteroid use and being hospitalised in Northern Italy were factors associated with a higher likelihood of being prescribed antibiotics. Antibiotic use was associated with an increased risk of in-hospital mortality (odds ratio = 2.52, 95% confidence interval 1.82–3.48) also when accounting for factors associated with their use.

Conclusion: Hospitalised older people are often prescribed antibiotics. Factors related to poor physical independence and corticosteroid use are associated with increased antibiotic use. Being prescribed antibiotics is also associated with an increased risk of in-hospital death. These results demand the implementation of specific stewardship programmes to improve the correct use of antibiotics in hospital settings and to reduce the risk of antimicrobial resistance.

1. Introduction

The continuing emergence of antimicrobial resistance in bacteria is increasingly threatening the efficacy of antibiotics worldwide, with more and more antimicrobials losing their ability to cure infections [1]. Excessive and inappropriate use of antibiotics are key drivers of antimicrobial resistance. Many countries have implemented initiatives to control antimicrobial resistance and to improve the rational use of antibiotics [2]. Furthermore, describing and understanding the pattern of antibiotic use in different settings and specific populations may promote the implementation of interventions to improve prescribing. Older people are often hospitalised with multimorbidity and are exposed to the use of multiple concomitant drugs [3–6], thus representing a population at higher risk for infections and related adverse outcomes [7]. Antibiotics are indeed widely prescribed for this population both in the community and hospital settings, representing together with children the heaviest users [8–10]. Some studies have highlighted different antibiotic prescribing patterns by age and geographical area [8,11]; however, there are no data providing an overview on the overall prevalence

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of antibiotic use, associated factors and in- hospital mortality in older people hospitalised in internal medicine wards.

With this background and gaps of knowledge, the aims of this study were to assess (i) the prevalence of antibiotic use, (ii) factors associated with their use and (iii) the association with in-hospital mortality in a large sample of older people admitted to more than 100 internal medicine and geriatric wards in Italy participating in the REPOSI register (REgistro POliterapie SIMI — Società Italiana di Medicina Interna) from 2010–2017.

2. Methods

2.1. Data collection and setting

Data were obtained from the REPOSI register, an ongoing collaboration between the Italian Society of Internal Medicine (SIMI), Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico and the Istituto di Ricerche Farmacologiche Mario Negri IRCCS. REPOSI is a multicentre, prospective register started in 2008 collecting information on patients aged ≥65 years acutely admitted to internal medicine and geriatric wards in Italy during four index periods lasting 1 week during each season. Data collection was carried out in 2008, 2010, 2012, 2014 and then yearly since 2016 up to date. More details are available elsewhere [12,13] .

The data set included sociodemographic factors, clinical and laboratory parameters, performance in activities of daily living according to the Barthel Index [14], patterns of co-morbidities and their severity according to the Cumulative Illness Rating Scale [15], as well as the drugs prescribed at hospital admission, during hospital stay and at discharge. Cognition was assessed by means of the Short Blessed Test (SBT). Following discharge, additional data were collected at 3 months and 12 months follow-up by telephone. Participation was voluntary and all patients provided signed informed consent. REPOSI was approved by the ethics committees of the participating centres. The study was conducted according to Good Clinical Practice and the Declaration of Helsinki.

Data from patients enrolled in 2008 were excluded from the present analysis because the original case report form was largely incomplete, with many scales not assessed and follow-up information not available.

All patients were scrutinised to establish whether or not they were prescribed with at least one antibiotic [Anatomical Therapeutic Chemical (ATC) classification system codes: J01* (antibacterial for systemic use) and A07AA* (intestinal anti-inflammatory and anti-infective agents)]. Additional ATC codes referring to antibiotics (G01*, S01–03*) were not present in the REPOSI database. Additional drug categories were considered as potentially associated factors, such as proton pump inhibitors (PPIs) (ATC A02BC*), corticosteroids (ATC H02*, A07EA* and R01AD*) and antineoplastic and immunomodulating agents (ATC L*). Co-morbidities were defined through the International Classification of Diseases (ICD), 9th edition.

2.2. Statistical analysis

Data are summarised as frequency (%), mean ± standard deviation, or median (interquartile range). Multivariable logistic regression models were used to determine factors associated with the use of antibiotics during the hospital stay, as most of these drugs were acutely administered for events that occurred during hospitalisation. Because of the large amount of candidate predictor variables and the large number of missing data for some of them, separate multivariable models were built including clinically relevant variables according to the feature to be investigated.

(i) Patients' health status: including geographical area, living arrangement, body mass index (BMI), smoking and drinking habits, the Barthel Index, SBT score, previous hospitalisation, polypharmacy (five or more drugs) and number of co-morbidities.
(ii) Specific co-morbidities: including diabetes, anaemia, chronic kidney disease, anaemia, dementia, depression and tumours.
(iii) Specific co-administered drugs: including PPIs, corticosteroids, and antineoplastic and immunomodulating agents.

All statistically significant variables in these models were included in a final full model. All models were adjusted for sex and age.

In-hospital mortality was analysed by means of a logistic regression model accounting for antibiotic prescription during hospital stay, demographic characteristics and clinical risk factors associated with antibiotic prescription. Statistical analysis was performed using SAS software v.9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

A total of 5442 subjects enrolled in 115 Italian internal medicine and geriatric wards from 2010–2017 were included in the present analysis.

3.1. Prevalence of antibiotic use

Of the 5442 older patients included in the analysis, 2786 [51.2%; 95% confidence interval (CI) 49.9–52.6%] were prescribed at least one antibiotic during their hospitalisation. Fig. 1 shows the distribution of patients prescribed or not with antibiotics during the different phases of hospitalisation. Overall, 2621 patients (48.2%) were prescribed antibiotics during their hospital stay, with 2318 of them being newly prescribed. Among the 2621 patients, 56.6% were prescribed with only one antibiotic and 13.4% with three or more antibiotics (concomitant or not). The main characteristics of patients prescribed antibiotics during their hospital stay are shown in Table 1. The prevalence of antibiotic use was similar in males (1291/2673; 48.3%) and females (1330/2769; 48.0%). Patients prescribed antibiotics were slightly older than those not prescribed antibiotics, with those aged ≥85 years comprising 28.7%. Among patients enrolled in Northern Italy, the prevalence of those prescribed antibiotics was slightly higher (1609/3059; 52.6%) compared with those enrolled in the Centre or in the South (1012/2383; 42.5%) of Italy. No differences were observed between the different years of the REPOSI register. Fig. 2 shows the distribution of the most prescribed classes of antibiotics during the different hospitalisation periods. Most prescribed antibiotics at hospital admission were intestinal anti-infective agents (especially rifaximin), followed by fluoroquinolones (levofloxacin) and third- generation cephalosporins (ceftriaxone). Ceftriaxone was also the most commonly prescribed antibiotic during hospital stay, followed by levofloxacin, piperacillin and ciprofloxacin. Levofloxacin was the most commonly prescribed at hospital discharge, followed by amoxicillin and rifaximin, whereas ceftriaxone was less prescribed at hospital discharge.

At admission, 407 antibiotic prescriptions were made, including 106 for respiratory diseases, 72 for gastrointestinal diseases and 29 for genitourinary diseases. During hospital stay, there were 4313 prescriptions of antibiotics, including 1953 for respiratory diseases, 588 for genitourinary diseases, 260 for sepsis or septicaemia, 239 for gastrointestinal diseases and 149 for hepatobiliary diseases. At discharge, there were 353 prescriptions for respiratory diseases, 175 for genitourinary diseases, 119 for

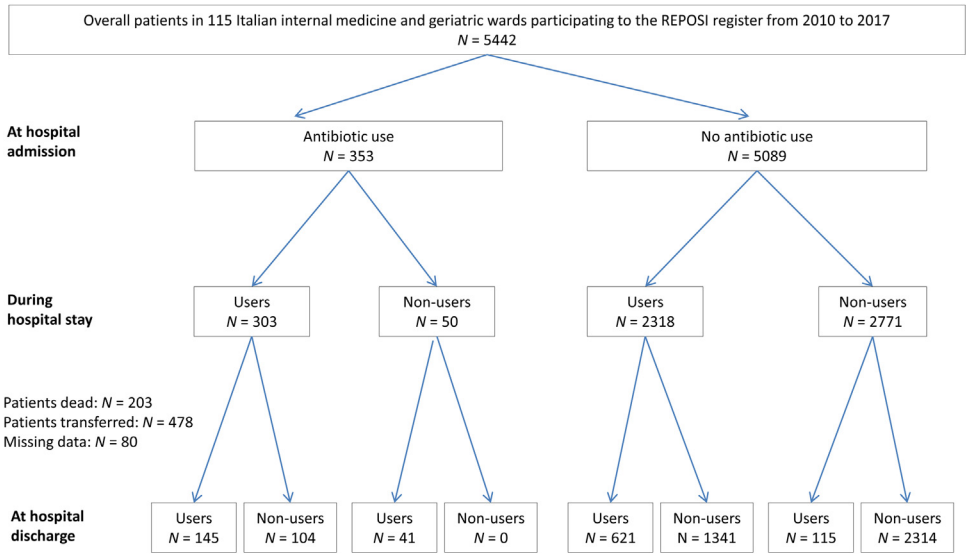

Fig. 1. Distribution of patients prescribed or not with antibiotics during hospitalisation.

gastrointestinal diseases, 51 for hepatobiliary diseases and 28 for sepsis or septicaemia.

3.2. Factors associated with antibiotic use

Results from the full multivariable logistic regression model are shown in Table 2. When investigating factors associated with antibiotic use, being unable to attend to bodily needs without assistance, i.e. mild disability to total dependence according to the Barthel Index, was the strongest predictor, with increasing odds ratios (ORs) for increasing disability from 1.25 (95% CI 1.05–1.48) to 2.36 (95% CI 1.88–2.97). Increasing age, being hospitalised in Northern Italy, increasing number of co-morbidities and being hospitalised in the previous 6 months were also statistically significant predictors of antibiotic use. Among the co-morbidities, none was significantly associated with antibiotic use. Being co-prescribed corticosteroids was associated with a higher probability of being prescribed antibiotics.

3.3. In-hospital mortality

Overall, 203 patients died, with 155 (76.4%) of them being prescribed antibiotics during their hospital stay. Being prescribed antibiotics was significantly associated with in-hospital mortality also in the adjusted regression model (OR = 2.52, 95% CI 1.82–3.48).

4. Discussion

This study describes antibiotic use in a large sample of older people hospitalised in internal medicine and geriatric wards in Italy from 2010–2017, revealing the following key findings: (i) more than one-half of patients were prescribed antibiotics during their hospital stay; (ii) the most frequently prescribed antibiotic class was β-lactams, accounting for 50% of the total prescriptions; (iii) among patients first prescribed antibiotics during their hospital stay, 35% of those discharged alive were still receiving antibiotics; (iv) increasing patient dependence in bodily needs, corticosteroids use and being hospitalised in Northern Italy were factors associated with an increased likelihood of being prescribed antibiotics; and (v) antibiotic use was associated with an increased risk of in-hospital mortality also after adjustment for patients' health status.

The prevalence of antibiotic use in the REPOSI setting confirms the very high use of antibiotic previously shown in Italy [16]. A recent report of the European Center for Disease Prevention and Control (ECDC) showed that hospital consumption of antibiotics for systemic use in Italy was among the highest of all European countries and more than double the European average hospital consumption. This was confirmed in an ECDC point prevalence survey which showed that, on any given day, 44% of patients in Italian acute-care hospitals received at least one antimicrobial agent, a significantly higher percentage than the European average (33%) [17]. In the current study, it was also found that 13.4% of hospitalised older people were prescribed with three or more antibiotics, confirming that the likelihood of being prescribed with more and different antibiotics increases with age [18].

β-Lactam antimicrobial agents are the most prescribed class during hospital stay, especially third-generation cephalosporins and particularly ceftriaxone. β-Lactam antibiotics indeed represent the most common treatment for bacterial infections in the hospital setting and their use continues to be the prominent worldwide cause of resistance of Gram-negative bacteria to these antibiotics [19,20] . Other studies previously showed that β-lactam drugs were also widely prescribed in community-dwelling older patients [8]. Amoxicillin was the most used antibiotic [8], being considered the first-choice drug for the most common respiratory infections, however in the current study its rate of prescription was lower than those of levofloxacin and ceftriaxone.

Lower performance in self-attending to daily living activities (especially faecal and urinary incontinence and eating) and an increased need in the amount physical assistance were associated with a higher likelihood of being prescribed an antibiotic during hospital stay, likely due to the occurrence of infections.

Corticosteroid use was associated with an increased risk of being prescribed an antibiotic. This is in line with previous studies which established that the use of corticosteroids is associated with an increased risk of infection [21]. Corticosteroids are indeed frequently and chronically used in monotherapy or in combination to treat musculoskeletal diseases owing to their anti-inflammatory properties. On the other hand, corticosteroids present immunosuppressive characteristics that expose patients to a higher risk of infection occurrence.

Antibiotic use was also associated with an increased risk of in-hospital mortality, even after adjustment for patient age, physical condition and number of co-morbidities.

Table 1
Demographic and clinical characteristics of patients ($n = 5442$) according to antibiotic use during their hospital stay.

Variable	Antibiotic use [n (%)][a]		
	No	Yes	Missing
No. of patients	2821	2621	
Sex			
Male	1382 (49.0)	1291 (49.3)	
Female	1439 (51.0)	1330 (50.7)	
Age (years) (mean ± S.D.)	78.1 ± 7.4	79.7 ± 7.5	
Study year			
2010	760 (26.9)	620 (23.7)	
2012	691 (24.5)	632 (24.1)	
2014	530 (18.8)	513 (19.5)	
2016	381 (13.5)	361 (13.8)	
2017	459 (16.3)	495 (18.9)	
Geographical area			
North	1450 (51.4)	1609 (61.4)	
Centre	621 (22.0)	463 (17.7)	
South	750 (26.6)	549 (20.9)	
Marital status			173
Single	170 (6.2)	185 (7.3)	
Married	1553 (56.8)	1301 (51.3)	
Widow/divorced	1011 (37.0)	1049 (41.4)	
Living arrangement			225
Alone	605 (22.4)	581 (23.0)	
With family members	1773 (65.8)	1582 (62.7)	
Nursing home	162 (6.0)	156 (6.2)	
Other	155 (5.8)	203 (8.0)	
BMI (mean ± S.D.)	26.0 ± 5.0	25.8 ± 5.2	647
Barthel Index			111
Total dependence	172 (6.3)	334 (13.0)	
Severe dependence	137 (5.0)	235 (9.1)	
Moderate dependence	315 (11.4)	383 (14.9)	
Mild dependence	516 (18.8)	480 (18.6)	
No dependence	1612 (58.6)	1147 (44.5)	
Short Blessed Test			547
Normal status	1083 (42.4)	846 (36.1)	
Possible cognitive impairment	463 (18.1)	411 (17.5)	
Moderate cognitive impairment	762 (29.9)	745 (31.8)	
Severe cognitive impairment	244 (9.6)	341 (14.6)	
Previous hospital admission	847 (30.0)	990 (37.8)	
Smoking			150
Never	1490 (54.4)	1359 (53.2)	
Ex-smoker	996 (36.4)	996 (39.0)	
Smoker	252 (9.2)	199 (7.8)	
Drinking habit			174
Never	1366 (50.0)	1302 (51.4)	
Ex-drinker	157 (5.7)	152 (6.0)	
Drinker	503 (18.4)	448 (17.7)	
Social drinker	707 (25.9)	633 (25.0)	
Polypharmacy at hospital admission (≥5 drugs other than antibiotics)	1620 (57.4)	1627 (62.1)	
Specific drugs classes			
Corticosteroids	197 (7.0)	262 (10.0)	
Proton pump inhibitors	1341 (47.5)	1339 (51.1)	
Antineoplastic agents	112 (4.0)	116 (4.4)	
Diagnosis at hospital admission			
No. of diagnoses [median (IQR)]	5 (3–7)	6 (4–8)	
Diabetes	741 (26.3)	675 (25.8)	
Chronic kidney disease	538 (19.1)	549 (20.9)	
Anaemia	283 (10.0)	223 (8.5)	
Depression	320 (11.3)	277 (10.6)	
Dementia	187 (6.6)	259 (9.9)	
Tumours	426 (15.1)	463 (17.7)	
Laboratory values [median (IQR)]			
Haemoglobin (g/dL)	12.1 (10.4–13.5)	11.8 (10.2–13.2)	50
Platelets ($\times 10^3/\mu L$)	217 (171–277)	223 (165–295)	65
Leukocytes ($\times 10^3/\mu L$)	7.2 (5.8–9.1)	8.9 (6.7–12.3)	58
Creatinine clearance (mL/min)	62.7 (42.5–81.8)	58.1 (39.1–79.8)	77
Total cholesterol (mg/dL)	163 (134–192)	149 (120–181)	1518

S.D., standard deviation; BMI, body mass index; IQR, interquartile range.
[a] Data are n (%) unless otherwise stated.

The main strength of this study is to give an overview of the overall use of antibiotics in a large cohort of older hospitalised patients, however some limitations must be mentioned. The REPOSI register minimum data set was lacking information regarding (i) specific pathogens causing the infection, (ii) susceptibility reports, (iii) biomarkers related to infection severity (e.g. C-reactive protein, procalcitonin, neutrophil–lymphocyte ratio), (iv) use as a prophylactic therapy and (v) dose and duration

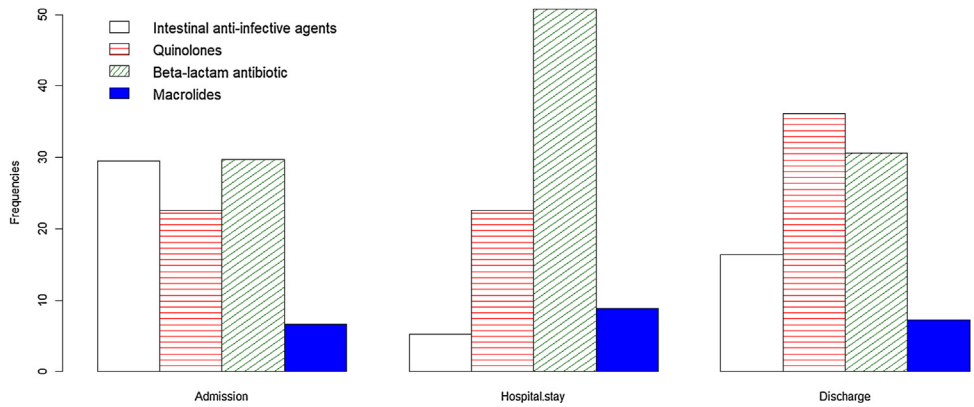

Fig. 2. Distribution of the most prescribed classes of antibiotics during hospitalisation.

Table 2
Multivariable logistic regression analysis of factors associated with antibiotic use.

Variable	OR (95% CI)	*P*-value
Sex (F vs. M)	0.92 (0.80–1.05)	0.213
Age (per 1-year increase)	1.01 (1.00–1.02)	0.006
Geographical area (South vs. North)	0.65 (0.46–0.92)	0.015
Geographical area (Centre vs. North)	0.70 (0.54–0.91)	0.007
Previous hospitalisation (yes vs. no)	1.26 (1.09–1.46)	0.002
Barthel Index (mild vs. no dependence)	1.25 (1.05–1.48)	<0.0001
Barthel Index (moderate vs. no dependence)	1.58 (1.28–1.96)	<0.0001
Barthel Index (severe vs. no dependence)	2.18 (1.72–2.76)	<0.0001
Barthel Index (total vs. no dependence)	2.36 (1.88–2.97)	<0.0001
Co-morbidities (per one disease increase)	1.05 (1.02–1.07)	0.0004
Dementia	0.98 (0.77–1.23)	0.839
Tumour	1.12 (0.96–1.30)	0.145
Corticosteroid use (no vs. yes)	1.35 (1.06–1.71)	0.013

OR, odds ratio; CI, confidence interval; F, female; M, male.

of antibiotic therapy, preventing an evaluation of the need and appropriateness of antibiotic use in this cohort of patients to be performed. Moreover, it was not possible to identify the different types of infection (such as community-acquired or healthcare-associated infections) owing to scant and insufficient information in the register data set.

5. Conclusions

This study showed that hospitalised older people in the years 2010–2017 were frequently prescribed antibiotics in internal medicine and geriatric wards in Italy. Poor physical independence and use of corticosteroids were associated with increased antibiotic use. Being prescribed antibiotics was also associated with an increased risk of death. Overall, these results suggest that the pharmacological management of infections in the hospitalised elderly remains challenging. Implementation of specific stewardship programmes to improve the correct use of antibiotics is needed, with the goal to decrease the risk of occurrence of antimicrobial resistance.

Funding

None.

Competing interests

None declared.

Ethical approval

Participation was voluntary and all patients provided signed informed consent. REPOSI was approved by the ethics committees of the participating centres. The study was conducted according to Good Clinical Practice and the Declaration of Helsinki.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jgar.2019.04.013.

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