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ORIGINAL ARTICLE

Patients receiving a high burden of antibiotics in the community in Spain: a cross-sectional study

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Abstract

Some patients in the community receive a high burden of antibiotics. We aimed at describing the characteristics of these patients, antibiotics used, and conditions for which they received antibiotics. We carried out a cross-sectional study. Setting: Thirty Health Primary Care Areas from 12 regions in Spain, covering 5,960,191 inhabitants. Patients having at least 30 packages of antibacterials for systemic use dispensed in 2017 were

Abbreviations: ASP, antimicrobial stewardship programs; UTIs, urinary tract infections; COPD, chronic obstructive pulmonary disease.

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considered. Main outcome measures: Prevalence of antibiotic use, conditions for which antibiotics were prescribed, clinical characteristics of patients, comorbidities, concomitant treatments, and microbiological isolates. Patient's average age was 70 years; 52% were men; 60% smokers/ex-smokers; 54% obese. Overall, 93% of patients had, at least, one chronic condition, and four comorbidities on average. Most common comorbidities were cardiovascular and/or hypertension (67%), respiratory diseases (62%), neurological/mental conditions (32%), diabetes (23%), and urological diseases (21%); 29% were immunosuppressed, 10% were dead at the time of data collection. Patients received three antibiotic treatments per year, mainly fluoroquinolones (28%), macrolides (21%), penicillins (19%), or cephalosporins (12%). Most frequently treated conditions were lower respiratory tract (infections or prophylaxis) (48%), urinary (27%), and skin/soft tissue infections (11%). Thirty-five percent have been guided by a microbiological diagnosis, being *Pseudomonas aeruginosa* (30%) *and Escherichia coli* (16%) the most frequent isolates. In conclusion, high antibiotic consumers in the community were basically elder, with multimorbidity and polymedication. They frequently received broad-spectrum antibiotics for long periods of time. The approach to infections in high consumers should be differentiated from healthy patients receiving antibiotics occasionally.

KEYWORDS
ambulatory Care, antibiotic prescribing, antimicrobial stewardship programs, infection, outpatients

1 | INTRODUCTION

Antimicrobial resistance is a growing problem, widely recognized as a major threat to public health.[1-4] In general practice, there is a major concern that some common infections are becoming increasingly difficult to be treated, and those infections caused by antibiotic-resistant bacteria may take longer to be resolved.[5] Primary Care is responsible for most of the antibiotics prescriptions in human health.[6-9] There is a high prevalence of infectious diseases in this setting,[10] and two thirds of patients treated for infectious diseases receive antibiotic therapy.[2,6,7] This leads to 25-30% of the population receiving antibiotics annually.[11,12]

Not all patients in the community receive the same burden of antibiotics.[13,14] While some patients receive antibiotics occasionally, others receive antimicrobial treatments on a continuous or cyclic manner for prolonged periods of time, in the context of infectious diseases with indication of long-term treatments, recurrent infections or for prophylactic purposes.[13] These patients are more susceptible to infections by multidrug resistant bacteria,[15-17] leading to more frequent use of broad-spectrum antibiotics. This limits the possibility of treating future infections in the ambulatory setting.[18]

Improving the appropriate use of antibiotics has become an increasing priority for Health Services. The establishment of powerful interventions, preferably integrated into antimicrobial stewardship programs (ASP), is essential.[19,20] It is a priority to identify which patients receive a high burden of antibiotics in the community, and which of them could benefit from interventions aimed to improving the use of antibiotic. At this time, when global attention is focused on the SARS-CoV-2 pandemic, it is necessary not to forget the importance of maintaining ASP interventions since optimizing the use of antibiotics should not cease to be a priority.[21] Furthermore, given the higher rates of inpatient utilization of broad-spectrum antibiotics during the pandemic, a higher spread of bacterial resistance could be expected.[22]

The objective of this work was to characterize the patients who receive a high burden of antibiotics in the community, the antibiotics used, and clinical conditions for which patients are treated. Our results will serve to design interventions aimed at optimizing antibiotic prescribing in these patients.

2 | MATERIALS AND METHODS

2.1 | Design

A descriptive cross-sectional study was carried out in Primary Care, covering a total population of 5 960 191 inhabitants. The study setting comprised 30 Healthcare Areas from 12 of the 17 regions in Spain (Table S1). The Spanish National Healthcare System is organized in Health Areas. A Health Area is an administrative district that clusters a group of Primary Care centers and professionals under its organizational and functional dependency. Primary Care provides essential care for the entire population. Furthermore, each Health Area has one or more referral hospitals for hospital care.

The unit of analysis was the patient, identified by the use of his personal social insurance system card number. Inclusion criteria for high consumers were as follows: all patients assigned to Primary Care centers from the study areas, having at least 30 packages of antibacterial agents for systemic use (J01, according to the WHO Anatomical Therapeutic Chemical classification system[23]) dispensed from January to December 2017.

2.2 | Data sources and outcomes

Patients were identified through databases from computerized pharmacy records of reimbursed and dispensed drugs, from their Regional Health Care Services. Individual clinical data, diagnoses, and microbiological tests from patients were collected from the Electronic medical records of Public Health Services maintained for routine health-care activities. Diagnoses and microbiological data were searched in consultation sheets, hospital admission or discharge records, laboratory data applications, etc. Diagnoses were classified into the following categories: upper respiratory tract, lower respiratory tract, urinary tract, skin and soft tissue, gastrointestinal, dental, and others. The missing data were counted as a lack of the value in some variables due to the lack of records in the Clinical History. Patients without any data available in the electronic medical records or those with private pharmacy were excluded. Population data were obtained from the Statistics National Institute.[24]

Data were collected between 1 June and 31 October 2018 by Primary Care Pharmacists from the Public Health Services. An electronic form with restricted online access to researchers was designed ad hoc for the data collection. The anonymity of participants was guaranteed by their identification in the electronic form through a numerical code. Data were stored securely in a data center with perimeter security.

The following variables, defined at the population level, were calculated: prevalence of antibiotic use (that is the percentage of the population that consumes antibiotics during the year), the average number of antibiotic prescriptions per patient, and the average number of days with antibiotic per patient. Variables collected at the patient level were as follows: age, gender, smoking behavior (smoke now or former smoker), obesity, or high body mass index (BMI; obesity: BMI>30 kg/m^2), residence in nursing home or in long-term care facilities, urinary incontinence, bedridden, number and type of underlying chronic health conditions (Table S2), condition that caused antimicrobial treatment, hospital admissions, death, type of antibiotic prescribed, number of antibiotic treatments received, antibiotic days, concomitant treatments (Table S3), prescriber medical specialty, type of sample for microbiological testing, and microbiological isolates.

2.3 | Statistical analysis

A descriptive analysis of the data was carried out to determine the prevalence and profile of high antibiotic consumers. Summary statistics were computed using frequencies and percentages for categorical variables and median (50th percentile), and interquartile range (25-75th percentiles) for continuous variables with asymmetric distribution. Confidence intervals were calculated at 95% (95% CI). STATA Corp. V12 was used for statistical analysis.

2.4 | Ethics statement

This research was conducted in accordance with the Declaration of Helsinki and national and institutional legislation in Spain regarding clinical research and personal data protection. It has been approved by Hospitals Virgen del Rocío and Virgen Macarena Ethics Committee on Health Research (Seville, Spain) (Code 0295-N-18). This project is registered in the clinical studies database of Spanish Medicines Agency and Health Products (EPA-OD code GTI-ANT-2018-01).

3 | RESULTS

3.1 | Study population

We have identified 1,876,927 patients with antibiotics prescribed during the study period. The prevalence of antibiotic use was 31%. Among these patients, 1,162 were high consumers according to the criteria established in this study, and 889 met the inclusion criteria. Characteristics of high consumers are described in Table 1. Median age was 70 (58-80) years; 52% were men; around 60% were smokers or ex-smokers; 54% were obese.

Overall, 93% of patients had at least one of the analyzed comorbidities while 92% were receiving concomitant chronic treatments (Table 1). Most common comorbid conditions were chronic respiratory disease, cardiovascular (60%; 67% considering those with hypertension), neurological/mental, diabetes, urological disease, and 29% were immunosuppressed. High consumers had four chronic conditions on average, 53% were admitted, at least once, during the year of the study, and 10% were dead at the time of data collection (Table 1).

For their pathologies, patients received a median of five concomitant chronic treatments (Table 1). Treatments most commonly prescribed were proton pump inhibitors (PPI), corticoids, antihypertensives, bronchodilators, analgesics, benzodiazepines, lipid-lowering agents, antidepressants, and antidiabetics.

3.2 | Antibiotic treatments and infectious diseases

Patients received a total of 3,226 antibiotic treatments during the study period. Half of the patients (51%) received antibiotics for the entire annual period: 24% received them in a single antibiotic course and 76% received several courses (18% received two courses; 17% received three courses; 13% received four courses, and 28%

TABLE 1 Descriptive analysis of patients

	Number of patients (N, %) or median	95% Confidence interval or interquartile range
Total	**889 (100)**	
Age (years), median	70	[58-80]
Gender (% women)	423 (48)	44-51
Smokers or ex-smokers[a]	375 (59)	55-62
Obesity[b]	279 (54)	49-58
Urinary incontinence	129 (15)	12-17
Bedridden[c]	62 (8)	6-10
Residence in nursing homes or long-term care facilities[d]	58 (7)	6-9
Number of comorbidities, median	4	[2-5]
Comorbid conditions:		
Hypertension, heart disease, cerebrovascular disease	593 (67)	64-70
Arterial hypertension	515 (58)	55-61
Heart failure	99 (11)	9-13
Peripheral arterial disease	51 (6)	4-8
Stable coronary heart disease	45 (5)	4-7
Stroke	43 (5)	4-7
Acute myocardial infarction	34 (4)	3-5
Transient ischemic attack	29 (3)	2-5
Angina pectoris	20 (2)	1-4
Other	144 (16)	14-19
Respiratory tract chronic conditions	553 (62)	59-65
Asthma	480 (54)	51-57
Chronic Obstructive Pulmonary Disease	302 (34)	31-37
Bronchiectasis	262 (30)	27-33
Chronic bronchitis	34 (4)	3-5
Cystic fibrosis	25 (3)	2-4
Tuberculosis (previous or latent)	22 (3)	2-4
Chronic respiratory failure	9 (1)	1-2
Emphysema	3 (0)	0-1
Chronic neurological or mental diseases	285 (32)	29-35
Depression	228 (26)	23-29
Dementia	79 (9)	7-11
Alzheimer	28 (3)	2-5
Parkinson	21 (2)	2-4
Schizophrenia	17 (2)	1-3
Situation that leads to immunosuppression	254 (29)	26-32
Malignancies	147 (17)	14-19
Transplant	53 (6)	5-8
Prolonged use of corticoids	26 (3)	2-4
Human immunodeficiency virus infection (VIH)	14 (2)	1-3
Other	53 (6)	5-8
Urological diseases	186 (21)	18-24
Chronic renal failure	109 (13)	10-15
Benign prostate hyperplasia	97 (11)	9-13
Obstructive uropathy	15 (2)	1-3
Other conditions		
Diabetes	202 (23)	20-26
Dermatitis	52 (6)	4-8
Liver failure	31 (4)	2-5
Psoriasis	11 (1)	1-2
Number of chronic treatments (median)	5	[3-7]
Type of concomitant treatment		
Proton pump inhibitors	572 (64)	61-68
Corticoids:	533 (60)	57-63
Inhaled	307 (35)	31-38
Systemic	226 (25)	23-28
Antihypertensives	498 (56)	53-59
Bronchodilators	473 (53)	50-54
Analgesics	417 (47)	44-50
Benzodiazepines	342 (39)	35-42
Lipid-lowering agents	297 (33)	30-37
Antidepressants	228 (26)	23-29
Antidiabetics	199 (22)	20-26
NSAIDs	192 (22)	19-25
Antiplatelet drugs	185 (21)	18-24
Anticoagulants	136 (15)	13-18
Antihistamines	91 (10)	8-12
Other immunosuppressive agents	72 (8)	6-10
Antipsychotics	71 (8)	6-10
Mucolytics	44 (5)	4-7
Cough suppressants	8 (1)	0-2
Patients with hospital admissions[e]	383 (53)	50-57
Exitus[f]	82 (10)	8-12

[a]Data from 641 patients.
[b]Data from 520 patients.
[c]Data from 775 patients.
[d]Data from 805 patients.
[e]Data from 717 patients.
[f]Data from 818 patients.

(Continues)

received ≥5 courses). On average, patients received three antibiotics treatments per year [p25-p75: 2-5].

Regarding the therapeutic group, fluoroquinolones was the most prescribed antibiotic group, followed by macrolides, penicillins, and cephalosporins (Table 2). When analyzed by antibiotic agents, azithromycin, amoxicillin-clavulanate, levofloxacin, and ciprofloxacin were the most prescribed antibiotics (Table 2).

TABLE 2 Frequency of antibiotic prescribing

	Number of antibiotic treatments (N, %)	95% Confidence interval
Total	**3,226 (100)**	
Fluoroquinolones	913 28)	27-30
Levofloxacin	398 (12)	11-14
Ciprofloxacin	373 (12)	11-13
Moxifloxacin	103 (3)	3-4
Norfloxacin	34 (1)	1-2
Other	5 (0)	0-0
Macrolides and lincosamides	674 (21)	20-22
Azithromycin	574 (18)	17-19
Clindamycin	55 (2)	1-2
Clarithromycin	40 (1)	1-2
Other	5 (0)	0-0
Penicillins	605 (19)	18-20
Amoxicillin-clavulanate	401 (12)	11-14
Amoxicillin	112 (4)	3-4
Beta-lactamase sensitive penicillins	32 (1)	1-1
Cloxacillin	32 (1)	1-1
Ampicillin	25 (1)	0-1
Other	3 (0)	0-0
Cephalosporins	377 (12)	11-13
Cefuroxime	192 (6)	5-7
Cefditoren	88 (3)	2-3
Cefixime	59 (2)	1-2
Ceftriaxone	15 (1)	0-1
Other	23 (1)	1-1
Aminoglycosides	130 (4)	3-5
Gentamicin	77 (2)	2-3
Tobramycin	40 (1)	1-2
Amikacin	13 (0)	0-1
Tetracyclines	49 (2)	1-2
Doxycycline	32 (01)	1-1
Minocycline	17 (1)	0-1
Other antibiotics		
Fosfomycin	255 (8)	7-9
Co-trimoxazole	176 (6)	5-6
Nitrofurantoin	49 (2)	1-2

The absence of a diagnosis in clinical records was detected for 4% of antibiotic prescriptions: 3,095 treatments were linked to some information about the type of infection or prophylaxis, and 2,786 treatments were linked to a specific diagnosis. The distribution by site of infection was as follows:

- 48% of use for lower respiratory tract conditions (33% infections, 12% prophylaxis),
- 27% of use for urinary tract conditions (23% infections, 3% prophylaxis),
- 11% of use for skin and soft tissue infections,
- 4% of use for upper respiratory tract infections.

Based on records, antibiotics were mainly used to treat infections, with 21% treatments used with prophylactic purposes. Prophylaxis of lower respiratory infections accounted for 69% of all established prophylaxis.

Specific diagnosis for which antibiotics were used can be observed in Table 3. Lower urinary tract infections (UTIs) were the most treated condition (21%), followed by chronic obstructive pulmonary disease (COPD) exacerbations (11%), and overinfected bronchiectasis (11%) (Table 3).

The distribution of antibiotics by condition is described in Figure 1.

Regarding the most widely used antibiotics: fluoroquinolones were the most prescribed in lower respiratory tract infections. They were also frequently prescribed for the treatment of skin and soft tissue infections, upper respiratory tract infections, and UTIs. Macrolides accounted for the 83% of the of lower respiratory tract infection prophylaxis, and were also frequently used in the treatment of upper respiratory tract infections. Fosfomycin was the most widely used antibiotic in the treatment of UTIs and UTIs prophylaxis. Penicillins were mainly used in the treatment of upper respiratory tract infections, skin and soft tissue infections, UTIs, and UTI prophylaxis. Finally, cephalosporins have had a smaller use than previous groups, although we have stated a relative high use in the treatment of UTIs, lower respiratory tract infections, and skin and soft tissue infections.

Clinicians who made the prescriptions were specialists in Family and Community Medicine (50% of the total), followed by specialists in Pneumology (25%), Internal Medicine (8%), and Urology (6%). These four professional groups accounted for 88% of prescriptions.

3.3 | Microbiological data

A total of 1,074 samples were recorded for microbiological assessment, that is, 35% of antibiotic treatments would have been guided by a microbiological diagnosis: 49% corresponded to bronchial exudates, followed by urine cultures (32%), and skin exudates (13%) (Table 4). In 84% of cases, the identification of one or several etiological agents was recorded. *Pseudomonas aeruginosa* (30%), *Escherichia coli* (16%), *Staphylococcus aureus* (6%), and *Klebsiella pneumoniae* (4%)

TABLE 3 Conditions treated with antibiotics

	Number of antibiotic treatments linked to specific diagnosis (N, %)	95% Confidence interval
Total	**3,095 (100)**	
Lower respiratory tract conditions	1,494 (48)	47-50
Exacerbation of COPD	351 (11)	10-13
Overinfected bronchiectasis	326 (11)	10-12
Overinfected bronchiectasis prophylaxis	194 (6)	5-7
Exacerbation of COPD prophylaxis	182 (6)	5-7
Acute bronchitis	117 (4)	3-5
Chronic bronchitis	80 (3)	2-3
Pneumonia	56 (2)	1-2
Other	80 (3)	2-3
Urinary tract conditions	833 (27)	25-29
Lower urinary tract infection	661 (21)	20-23
Lower urinary tract infection prophylaxis	95 (3)	3-4
Prostatitis	17 (1)	0-1
Pyelonephritis	15 (1)	0-1
Other	8 (0)	0-1
Skin and soft tissue conditions	348 (11)	10-12
Diabetic foot	49 (2)	1-2
Boil/abscess	46 (2)	1-2
Cellulitis	35 (1)	1-2
Pressure ulcer infection	33 (1)	1-2
Fistula	20 (1)	0-1
Other	33 (1)	1-2
Upper respiratory tract infections	126 (4)	3-5
Sore throat/pharyngotonsillitis	44 (1)	1-2
Recurrent pharyngotonsillitis	33 (1)	1-2
Acute otitis media	10 (0)	0-1
Other	15 (1)	0-1
Bone infection (osteomyelitis)	39 (1)	1-2
Periprosthetic infection	37 (1)	1-2
Gastrointestinal infection	27 (1)	1-1
Dental infection	24 (1)	0-1

were the most frequent isolates. According to the records, 29% of *Staphylococcus aureus*, 14% of *Escherichia coli*, and 11% *Klebsiella pneumoniae* were multidrug resistant. The identification of the ethiological agent by microbiological sample is detailed in Table 4.

4 | DISCUSSION

This observational study shows that patients who receive a high burden of antimicrobials in the community are, basically, older adults with multiple chronic conditions and polymedication. The studied population had a high prevalence of comorbidities, a high management from hospital care and hospital admissions (53% patients), as well as a high risk of dying (10% *exitus*).

In our study, prevalence of hypertension, asthma, CODP, neurological and mental disorders, diabetes, malignancies, or chronic renal failure were more frequent than that reported for general population receiving antibiotics in the community.[11,23] COPD and asthma were about 10 times more frequent in the study patients than in general population receiving antibiotics in the community

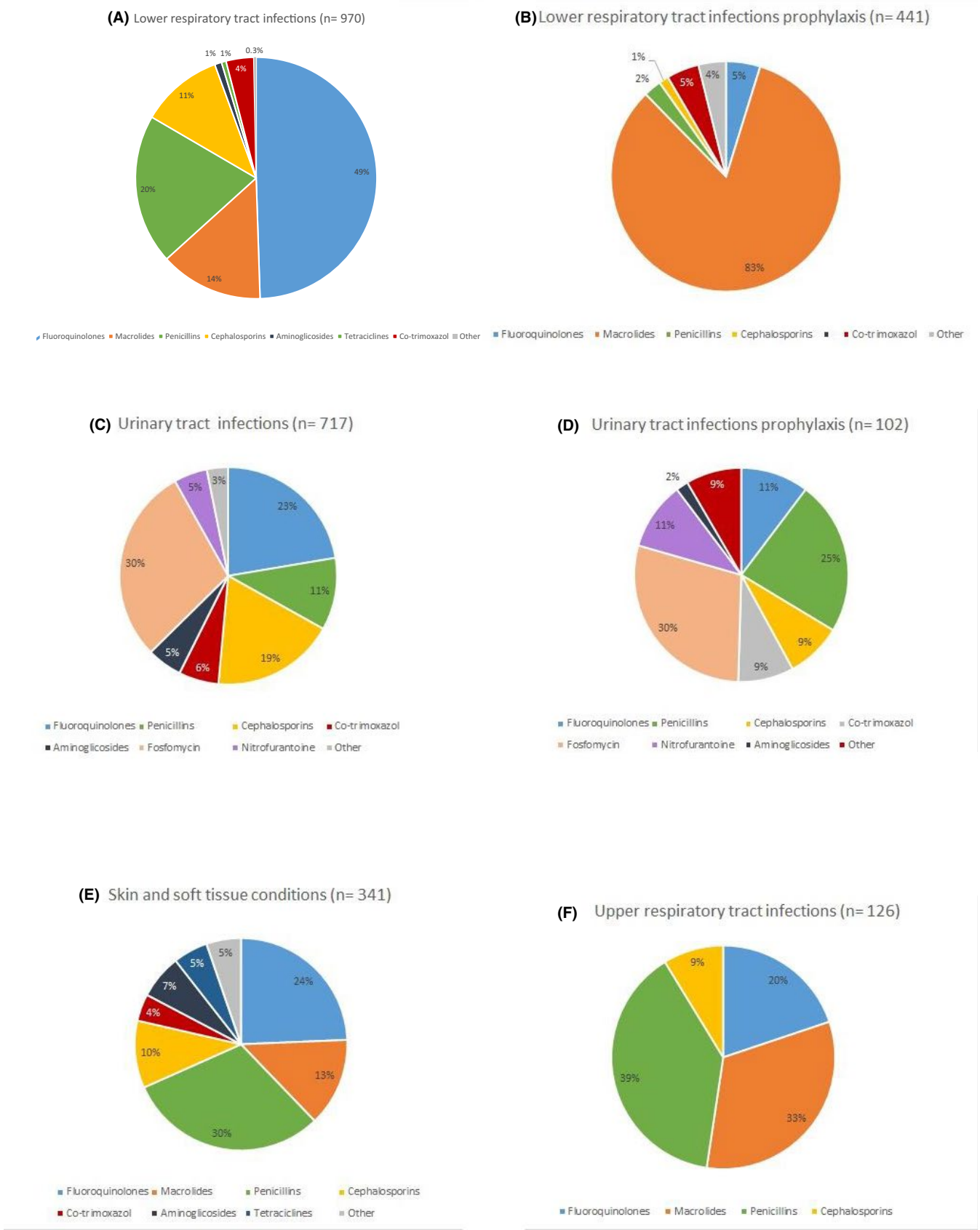

FIGURE 1 Distribution of antibiotics by condition: (A) lower respiratory tract infections, (B) lower respiratory tract prophylaxis, (C) urinary tract infections, (D) urinary tract infections prophylaxis, (E) skin and soft tissue conditions, and (F) upper respiratory tract infections

TABLE 4 Type of microbiological sample and isolates

Microbiological sample and isolates	Number of samples (N, %)	Number of isolates (N, %)
Total	1,074 (100)	906 (100)
Bronchial exudate	527 (49)	436 (48)
Pseudomonas aeruginosa		201 (46)
Mycobacterium intracellulare, M. avium		47 (11)
Haemophilus influenzae		27 (6)
Staphylococcus aureus		19 (4)
Stenotrophomonas maltophilia		17 (4)
Serratia marcescens		14 (3)
Urine	348 (32)	264 (29)
Escherichia coli		120 (46)
Klebsiella pneumoniae		34 (13)
Pseudomonas aeruginosa		34 (13)
Enterococcus faecalis		27 (10)
Proteus mirabilis		26 (10)
Skin exudate	135 (13)	120 (13)
Pseudomonas aeruginosa		32 (27)
Staphylococcus aureus		26 (22)
Escherichia coli		16 (13)
Proteus mirabilis		11 (9)
Other	64 (6)	86 (10)

in Spain,[11] and the prevalence of hypertension, heart diseases, and diabetes was three times higher.[11] It should be emphasized the high percentage of patients with chronic renal failure among high consumers (12%).

Other aspects besides comorbidities such as smoking behavior, overweight/obesity, or polypharmacy, common conditions in patients in our study, might be associated with antibiotic prescribing decisions. In relation to concomitant medication, PPI, NSAIDs, or corticosteroids which may contribute to increase susceptibility to infections were frequently used by the study patients. Around 60% of high antibiotic consumers in our study received corticosteroids. This has been previously shown to be a better predictor of antibiotic prescribing than comorbidities themselves.[13]

Lower respiratory tract, urinary tract, and skin and soft tissue infections or prophylaxis justified most antibiotic treatments in high consumers. However, there are great differences between the conditions in these patients and those treated in general population: antibiotic use for the treatment of exacerbations of COPD and bronchiectasis, which represent a 2% of the use of antibiotics by general population in the community,[25] accounted for 34% of treatments in high consumers. By contrast, upper respiratory tract infections, which represent the 53% of infections treated with antibiotics in the ambulatory setting,[25] represented a 4% of infections treated in high consumers. In addition, prophylactic treatments, very scarce in healthy population, accounted for 21% of all treatments in high consumers, and expose these patients to antibiotics for prolonged periods of time, in a continuous or a cyclic manner.

Regarding the antibiotics prescribed, fluoroquinolones, macrolides, cephalosporins, or co-trimoxazole which represent a low prescription in the community in Spain (10%, 6%, 3%, and 0.3%, respectively)[25] accounted for 28%, 21%, 12%, and 5%, respectively, in high consumers (Table 2). The profile of antibiotic use was very heterogeneous by condition (Figure 1). The most notorious result was the relatively high use of fluoroquinolones and cephalosporins, two groups of antibiotics associated with the selection for resistant bacteria, for the treatment of all kind of infectious diseases, and the wide use of macrolides for the prophylaxis of lower respiratory tract infections.

The high prevalence of *Pseudomonas aeruginosa* and multidrug-resistant bacteria in these patients would justify these treatments, but at the same time, this makes the patients increasingly susceptible to infections by multidrug-resistant microorganisms.[15,17] In addition, the use of long-term macrolides for immunomodulatory purposes is a common practice,[26] although the appropriateness of both the indication and the duration of treatments should be tested.

Comorbidity is a main driver of prescribing in high consumers. The higher the comorbidity, the more antibiotic prescriptions patients received.[12,27,28] Rates of antibiotic prescribing to patients with asthma and COPD are 1.6- and 3-fold, respectively, higher than rates in general population, and patients with heart failure, peripheral arterial disease, diabetes, or coronary artery disease are prescribed 47-69% more antibiotics than individuals without these conditions.[12] Despite the great advances in the prevention, diagnosis, and treatment of infectious diseases, these continue to cause great morbidity and mortality in people with chronic conditions.

Guides on the management of infections in Primary Care recommend a restrictive use of antibiotics in this level of care, but justify the administration of prolonged or repeated course of antibiotics in some patients with chronic diseases such as diabetes, COPD, heart failure, or those with multiple pathologies.[12,27,28-31] The reason for this different management lies in the tendency of these patients to get more severe and recurrent infectious diseases, with worse prognosis, and with a higher probability of hospitalization and mortality than in healthy people.[12,28,31-34] Nonetheless, unnecessary antibiotic treatments, excessively long treatments, the unjustified use of broad-spectrum antibiotics, or injustified prophylaxis should be avoided in patients with comorbidities.

This study has several strengths. First, it includes a large representative sample of the national territory, including patients of all ages cared by the Public Health Care Services for all possible diagnoses. The use of individual patients as the unit of analysis is a major strength compared with studies conducted with aggregated data. Full information about patient's characteristics and underlying pathologies was collected. On the other hand, antibiotic prescriptions were linked to clinical information in 96% cases. The degree of underregistration of diagnoses in medical records was very low compared to other studies conducted in the Primary Care setting, which reported 30-60% diagnoses unknown.[25,35] All this enhances the generalizability of the results.

Several limitations of the study should be pointed out. First, antibiotic prescribing data were exclusively collected from the computerized pharmacy records of dispensed drugs from Regional Public Health Care Services. Hospital inpatient antibiotic use, private medicine, outpatient parenteral antibiotic therapy, or over-the-counter sales were not measured. Second, we were unable detect patient adherence, only dispensations made. We assumed a good therapeutic compliance, and that the actual consumption of drugs corresponded to the dispensations made. It could be to an overestimation of the total amount of antibiotics taken by patients actually. Third, we did not accessed to hospital records. Information about other treatments or infections may have been lost for not being registered in Primary Care Digital Health History.

Our results have several implications for practice: (a) It is crucial that antimicrobial guides include clear indications for patients with chronic conditions, to avoid unnecessary treatments or prophylaxis, to adjust the duration of treatments to the minimum effective, and to reserve broad-spectrum antibiotics to cases of failure or intolerance to narrow-spectrum antibiotics. (b) ASP should consider specific interventions for patients with comorbidities and frequent infections, with a different approach than healthy patients. (c) Since professionals from both care settings (Primary Care and Hospital) are involved in care of high consumers, coordination among them should be encouraged in relation to the establishment of antibiotherapy, especially if it is indicated in the long-term.

In conclusion, a high prevalence of aged patients with high-risk comorbidities among practices could account for legitimate medical reasons of higher antibiotic prescribing rates, and higher prescription of broad-spectrum antibiotics in the ambulatory setting. The approach to infections and antibiotic use by these patients should be carried out from both health-care settings, since these patients are with high management from hospital care and frequent hospital admissions. Further studies should be addressed to determine whether high consumers are prescribed antibiotics appropriately or whether the excessive antibiotic use by these patients could be decreased or avoided.

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DISCLOSURES

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AUTHOR'S CONTRIBUTIONS

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ETHICS APPROVAL STATEMENT

This research has been approved by Hospitals Virgen del Rocío and Virgen Macarena Ethics Committee on Health Research (Seville, Spain) (Code 0295-N-18). This project is registered in the clinical studies database of Spanish Medicines Agency and Health Products (EPA-OD code GTI-ANT-2018-01).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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