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Risk Factors for Unnecessary Antibiotic Therapy: A Major Role for Clinical Management

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Background. Assessment of antimicrobial use places an emphasis on therapeutic aspects of infected patients. Our aim was to determine the risk factors for unnecessary antibiotic therapy (UAT).

Methods. This was a prospective, multicenter study evaluating all curative antibiotic therapies prescribed over 2 consecutive days through the same electronic medical records. Each item that could participate in these prescriptions was collected from the computerized file (reason for hospitalization, comorbid conditions, suspected or definitive diagnosis of infection, microbial analyses). UAT was defined as the recognition of noninfectious sydromes (NIS), nonbacterial infections, use of redundant antimicrobials, and continuation of empirical broad-spectrum antimicrobials.

Results. Four hundred fifty-three antibiotic therapies were analyzed at 17 institutions. An infectious disease was the reason for hospitalization in 201 cases (44%). An unspecified diagnosis of infection was observed in 104 cases (23%). Microbial samples were taken in 296 cases (65%), allowing isolation of a pathogen in 156 cases (53%). Unspecified diagnosis was associated with the absence of a microbial sample compared to patients with a diagnosis: (56/104 [54%] vs 240/349 [69%]; $P = .005$). A total of 158 NIS were observed (35%). UAT was observed in 169 cases (37%), due to NIS in 106 cases. In multivariate analysis, the modifiable risk factors for UAT were unspecified diagnosis (adjusted odds ratio [AOR], 1.83; 95% confidence interval [CI], 1.04–3.20) and absence of a blood culture (AOR, 5.26; 95% CI, 2.56–10.00).

Conclusions. UAT is associated with an unspecified diagnosis and the absence of microbial testing. Antimicrobial stewardship programs should focus on diagnostic difficulties and microbial testing, the latter facilitating antibiotic reassessment and therapeutic interruption.

Keywords. antimicrobial stewardship; audit; antibiotic therapy; unnecessary; microbial testing.

The primary aim of antimicrobial stewardship programs (ASPs) is to prevent the emergence of multidrug-resistant bacteria by reduction of antibiotic use [1–3]. In the past 20 years, the implementation of ASPs has become a global task, involving both community and hospital settings [3, 4].

The current outcome of ASPs is controversial, and only moderate success has been observed in France despite the high level of involvement by the Ministry of Health, assessing the means for and the implementation of actions in healthcare institutions [5–8]. Within a few years, several tools were put in place such as computerized prescription records and restricted access to certain antibiotic compounds [5, 7, 8]. Moreover, internal guidelines for most infections observed in the hospital setting need to be made available and updated every 3 years [8, 9].

These tools should also facilitate large-scale audits when consensual definitions of antibiotic prescription quality are available. Proposed definitions of the terminology to describe a day of therapy with a particular antimicrobial agent were recently published [10]. Accordingly, it seems reasonable to define unnecessary antibiotic therapy (UAT) as the use of antimicrobials for noninfectious syndromes and/or the use of antimicrobials for nonbacterial infections, the use of redundant antimicrobials, or the absence of a reduction in the use of broad-spectrum antimicrobials [10].

Before delving further into the complexities of antibiotic use, it is important to consider that antibiotic prescriptions are the final result of several stages of the medical process, that at the very least include the medical history, the patient's condition, a physical examination, and microbial testing.

This past decade, by working in a multidisciplinary network in the southeast of France, we performed a number of multicenter audits that revealed large differences in clinical practices and patient outcomes, underlying the lack of consideration for the

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national ASP [11–13]. Moreover, several years ago, we reported that there was no link between the application of the national recommendations for antibiotic therapy and the quality of their prescription at the beside level [9]. As our network extended to a large group of private clinics, our aim was to analyze current antibiotic prescription quality according to newly proposed terminology and to determine the risk factors for UAT.

METHODS

This was a prospective, multicenter study involving several private clinics that had the same system of electronic patient records in common. The antibiotic audits were sponsored by the French National Health Agency, and the patients or their relatives provided their written consent for computerization of their personal data for hospitalization purposes and potential clinical research.

In this study, in every institution and over a period of 2 consecutive days, all patients receiving ongoing antibiotic therapies for curative purpose were included. To do so, electronic medical record software was used to select the individuals who were being prescribed antibiotics at each institution.

The electronic patient records include the patient's entire medical history, their current medical file, all laboratory testing, radiological results, and successive treatments. They also include the nurses' comments and clinical parameters such as blood pressure, heart rate, and body temperature over the entire duration of their hospitalization.

The following parameters were recorded exclusively from the digital files; the specialty of the physician in charge of the patient, access to an antibiotic referent (a pharmacist, microbiologist, or any other physician who can devote work on an ASP), the availability of infectious disease (ID) advice, the indication for the hospitalization, the diagnosis of the infection, and all microbiological samples and their laboratory results. Therefore, for the audit, the same data were available to us and the prescribers.

An unspecified diagnosis was defined as the absence of an identified diagnosis or a suspected diagnosis of ID in the complete reading of the patient's electronic report.

Urinary colonization was defined as a positive urine culture without any sign of urine infection.

Healthcare-associated infections (HCAIs) were defined as 1 of the following: (1) a diagnosis established ≥48 hours after hospital admission; (2) when the infection was observed <1 month after surgery, and <1 year in case of insertion of a surgical device; or (3) when observed in association with an underlying urinary or venous catheterization. It should be noted that the diagnoses of HCAI were established during the audit, but not necessarily by the physicians in charge.

As the same electronic medical record including prescriptions was used in all of the institutions, we recorded details of successive antibiotic therapies, including the names of the drugs, the dosages, and the routes of administration in the same manner.

We defined UAT in accordance with recently published recommendations [10]: the use of antimicrobials for noninfectious syndromes and for nonbacterial infections, the use of redundant antimicrobials, or continuation of broad-spectrum antimicrobials over 5 days despite the availability of bacterial test results. We chose this delay because the timeframe in which microbial test results become available can vary depending on the institution.

Noninfectious syndromes were defined as an obvious other diagnosis that explained the clinical presentation and/or the associated inflammatory syndrome in conjunction with a concomitant absence of/or sterile microbiological test results. This included all progressive cancers, inflammatory diseases, acute thrombosis, ischemia, hematoma, drug allergies, and metabolic abnormalities.

We also recorded antibiotic therapies justified by the physician in charge based only on an increase in C-reactive protein (CRP) or procalcitonin (PCT).

As an audit over 2 days could not consider the duration of the antibiotic therapy, the item "days of therapy beyond the indicated duration of therapy without any clinical reason for a lengthened course" was not considered [10].

Inappropriate antibiotic therapy was defined as (1) the use of antimicrobials in the setting of an established infection to which the pathogen was resistant; or (2) antimicrobials not recommended in the treatment guidelines for the diagnosed infectious diseases [10]. Last, a suboptimal antibiotic therapy was defined as an inadequate drug choice or dosage. As unnecessary parenteral administration, depending on the perceived severity and/or supposed higher efficiency of parenteral therapy, may be a source of disagreement between physicians and/or ID specialists, we did not consider this last item.

As some of the patients could have already undergone treatment with antibiotics for several days at the time of the audit, we were able to determine the impact of antibiotic therapy. Accordingly, a favorable outcome was defined as resolution of the clinical symptoms and/or of the inflammatory syndrome. An adverse outcome was defined as the persistence or worsening of clinical symptoms over 3 days of therapy. When these 2 opposite situations were unclear at the time of the audit or when the audit occurred within the first 2 days of treatment, the impact of the antibiotic therapy was deemed to be "uncertain."

Consistency between the data collectors was ensured by the same ID physician, working as a coordinator of the ASP in the group of clinics, being present at all of the institutions that were audited successively.

The patients or their relatives provided written consent for computerization of their personal data for hospitalization purposes and clinical research.

Statistical Analysis

The data were analyzed with StatView software version 5.0, and statistical significance was established at α = .05. Continuous variables were compared with the Student *t* test or the Mann-Whitney nonparametric test. Proportions were compared with the χ^2 or Fisher exact test when appropriate. Logistic regression was used for multivariate analysis of the risk factors associated with UAT, and the results are presented as adjusted odds ratios with their 95% confidence intervals. Variables were selected for the multivariate analysis based on the level of significance of the univariate association with UAT ($P < .1$). Models were built up sequentially, starting with the variable most strongly associated with UAT and continuing until no other variable reached significance or altered the odds ratios of variables already in the model. When the final model was reached, each variable was dropped in turn to assess its effect.

RESULTS

The audit was performed from 1 April 2017 to the end of March 2018, a period during which 17 French private institutions participated successively. At most of the institutions, at the very least a binome was engaged to collect the data: ID physician plus pharmacist, ID physician plus antibiotic referent, or ID physician plus infection control specialist.

The median number of beds was 189 (range, 71–300). Nine of the institutions had an emergency unit and 4 had an intensive care unit (ICU), but 2 of the 4 ICUs did not have computerized prescriptions and their antibiotic therapies were not included in the audit.

Three of the institutions did not have an antibiotic referent, the latter being an ID specialist in 3 of these 14 institutions.

A total of 453 patients receiving an antibiotic treatment were analyzed according to consensual definitions (median, 27 range [19-38] per institution). These patients were in medical wards in 55% of the cases, in surgical wards in 41%, and ICUs in 4%. Of the 16 specialties, the 5 most represented ones were general medicine, including gerontology and oncology (30%), urology (15%), cardiology (10%), digestive surgery (10%), and orthopedics (9%). Obstetrics and emergency medicine were the least represented (<1%).

Ongoing cancer, notably those with locoregional extension and/or metastatic cancer, was a significant comorbid condition, irrespective of the specialty, being observed in 110 cases (24%), while other causes of fever and/or inflammatory states were observed in 39 cases (9%). Moreover, an increase in CRP and/or PCT was indicated in the medical files as the only reason for antibiotic prescriptions in 14 cases (3%). In all, 158 patients (35%) exhibited at least 1 potential cause of inflammatory noninfectious disease (Table 1).

The main diagnoses are indicated in Table 2: after urinary tract infections (n = 118 [26%]), unspecified diagnoses were in second position (n = 104 [23%]), ahead of pulmonary infections (n = 79 [17%]). An unspecified diagnosis occurred more often patients who exhibited a noninfectious syndrome compared to patients with a diagnosis (60/104 [58%] vs 98/349 [28%]; $P < .001$).

HCAIs were observed in 183 cases (40%), although they were nearly never specified in these terms in the patients' files by the physicians in charge. In 16% of the medical reports, an antibiotic referent's advice was indicated. Successive courses of antibiotic therapies, suggestive of treatment reassessment, were observed in 125 cases (28%).

As described in the Methods, the clinical outcome was assessed according to 3 categories: favorable (resolution of the symptoms) in 249 cases (55%), uncertain in 157 cases (35%), and adverse in 47 cases (10%). We observed a trend toward a favorable outcome when the antibiotic therapy was reassessed compared to patients who did not benefited of reassessment (77 of 249 [31%] vs 48 of 204 [23%]; $P = .079$).

Table 1 shows that UAT constituted the main category of antibiotic therapies (37%), for which the most common reason was noninfectious syndromes (23%). Most of the time, these comprised mixed cases of cancer and other inflammatory diseases. Other criteria for UAT accounted for 15% of all antibiotic courses.

The other categories of antibiotic therapy were inappropriate (34%), suboptimal (16%), and optimal (13%) therapy. The main reason for inappropriate antibiotic therapy was failure to follow the guidelines. The most frequent example of inappropriate antibiotic therapy (n = 66 [14%]) was the prescription of a fluoroquinolone as an empirical treatment for HCAI. It should be noted that several reasons for inappropriate or suboptimal antibiotic therapy were observed: A too-low dose of the considered antibiotic was noted in 95 cases (21%) (Table 1).

To determine the risk factors of UAT, these avoidable therapies were compared to required ones—that is, inappropriate plus suboptimal plus optimal. Table 2 shows the results of the univariate analysis, which indicated that several parameters are associated with UAT, including wards, specialized advice, noninfectious syndromes, unspecified diagnosis, results of microbial tests, and therapeutic modalities. Thus, we did not compare the clinics in terms of the UAT rate, because their medical and/or surgical activities, which were different, influenced the results.

The logistic regression revealed that medical wards, unspecified diagnosis, and lack of a blood culture were the risk factors for UAT. By contrast, 3 elements were associated with less UAT: an infection as an indication for hospitalization, diagnosis of a digestive (medical or surgical) infection, and the use of a parenteral route for antibiotic administration (Table 3). Finally, UAT was also more rarely associated with a favorable outcome (ie, resolution of the symptoms).

DISCUSSION

Our study found that UAT still amounts to a substantial portion (37%) of antibiotic prescriptions and, to our knowledge, showed

Table 1. Appropriateness of 453 Antibiotic Therapies at 17 Private Clinics According to the Proposed Definitions

Appropriateness of Therapy	Criteria	Cases
Unnecessary: n = 169 (37%) Including insufficient drug doses, n = 20 (4%)	Noninfectious syndromes[a]: n = 106 (23%), comprised cases mixing any clinical or biological element for ongoing infection (n = 62 [14%]), active cancer (n = 47 [10%]), and other causes of fever (n = 19 [4%]). We also observed 8 cases of isolated increase of CRP and/or PCT (2%).	Other causes of fever: hematoma (n = 6), thromboembolism (n = 3), necrosis (n = 3), vessel inflammation due to peripheral catheter (n = 2), inflammatory bowel diseases (n = 2), drug intolerance (n = 1), hemorrhagic pleurisy (n = 1), noninfectious arthritis (n = 1)
	Nonbacterial infections: n = 40 (9%)	28 urinary colonizations; 7 COPD[c], 5 bronchitis.
	Redundant antimicrobial: n = 13 (3%)	Amoxicillin + clavulanic acid + imidazole, n = 11; imipenem + imidazole, n = 2;
	Continuation of empirical broad-spectrum antimicrobials[b]: n = 11 (2%)	imipenem, n = 4; ceftriaxone + gentamicin, n = 5; piperacillin-tazobactam, n = 2
Inappropriate: n = 154 (34%) Including insufficient drug doses, n = 36 (8%)		Use of antimicrobials in the setting of a resistant pathogen, n = 29 (6%)
Suboptimal: n = 71 (16%) Including insufficient drug doses, n = 39 (9%) Useless parenteral therapy: not determined		
Optimal: n = 59 (13%)		

Source: Spivak et al [10].

As the audit was carried out on 2 consecutive days, we did not measure the duration of the antibiotic therapy, which is included in the definition of unnecessary antimicrobial treatment in case of a lengthened course.

Abbreviations: COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; PCT, procalcitonin.

[a]Noninfectious syndromes included all progressive cancers, inflammatory diseases, acute thrombosis, ischemia, hematoma, drug allergies, and metabolic abnormalities.

[b]One patient was associated with several criteria of unnecessary antibiotic therapy.

[c]COPD for which ≥2 antibiotic courses were prescribed without efficiency.

for the first time that noninfectious syndromes were the most predominant (23%) reason for a treatment to be designated as a UAT, while other criteria accounted for 15% of the treatments. Noninfectious syndromes were associated with unspecified diagnosis of infectious disease, and fewer microbial tests overall.

Logistic regression revealed the risk factors for UAT—that is, an unspecified diagnosis and the absence of microbial testing, which ultimately resulted in less frequent resolution of symptoms. By contrast, digestive infectious diseases frequently involved "required antibiotic therapy."

The limitations of our study stemmed from our method: Because it was a real-time prospective audit of antibiotic therapies for hospitalized patients using computerised medical reports, we could not assess the duration of the antibiotic treatment, which is another criterion for UAT. Moreover, the 2-day duration may have led to microbiological testing being considered to be noncontributing due to a lack of overview. This was, however, the actual way of practice for the physician at the time of prescription. Yet, the proposed terminology was made for the description of a day of therapy [12]. Finally, the physicians in charge may have had the correct diagnosis without this being recorded in the medical file. However, we believe that doctors usually provide a written record of their diagnosis when it is well established.

The high rate of inappropriate antibiotic therapies reported in our work (34%) is in accordance with recently published studies, even though the definitions that were used are quite different [14, 15]. In a prospective multicenter study, Braykov et al [14] also found that one-third of the patients who received a broad-spectrum empirical therapy did not exhibit a fever or an inflammatory response. In another study, the diagnosis was incorrect in 156 of 500 cases (31%) [15]. In a recent multicenter audit of patients with bacteremia in emergency departments, 12% of the patients did not have a precise diagnosis at the time of antibiotic prescription [13]. Thus, this is the first large-scale study of antimicrobial stewardship in private hospitals in France, and the results indicate that the level of UAT is quite similar to what has been observed in public institutions [5–9].

Our study shows that noninfectious inflammatory diseases were the main source of UAT, greatly exceeding the other causes defined in the consensual terminology [10]. This is not surprising in light of the absence of specificity of fever and other clinical and biological signs of inflammation. Accordingly, we have reported that of 12 597 hospitalizations in an ID department, there were 1879 patients (14.9%) with a noninfectious disorder as the final diagnosis [16]. Yet, a meta-analysis has shown that inflammatory states are very common with active cancers [17]. The numerous antibiotic prescriptions for these noninfectious inflammatory syndromes, which were also associated with unspecified diagnosis of infection, were probably because the physicians in charge thought that "it is possible that an infectious disease is actually causing inflammation." However, no microbial investigation was performed, antibiotic reassessment was not done, and treatment was not stopped.

Table 2. Main Characteristics of Unnecessary Antibiotic Therapy Compared to Required Therapy, Which Was the Sum of Inappropriate Plus Suboptimal Plus Optimal Antibiotic Therapies: Univariate Analysis

Characteristic	Required Therapy (n = 284 [63%])	UAT (n = 169 [37%])	*P* Value	All (N = 453)
Ward				
Medicine	137 (48)	112 (66)	<.001	249 (55)
Surgery	130 (46)	56 (33)	.008	186 (41)
Intensive care	17 (6)	1 (1)	.009	18 (4)
Antibiotic referent[a] at the institution	249 (88)	132 (78)	.007	381 (84)
Antibiotic referent advice	30 (11)	7 (4)	.015	37 (8)
ID specialist at the institution	59 (21)	33 (20)	.749	92 (20)
ID specialist advice	17 (6)	3 (2)	.060	20 (4)
Age, y, mean ± SD	72 ± 16	72 ± 16	.447	72 ± 16
Sex ratio (male:female)	1.41	1.21	.425	1.33
Noninfectious syndromes				
Active cancer	63 (22)	47 (28)	.176	110 (24)
Other putative causes of fever	20 (7)	19 (11)	.123	39 (9)
Increase in CRP and/or PCT	6 (2)[b]	8 (5)	.200	14 (3)
At least 1 cause of inflammation	87 (31)	71 (42)	.014	158 (35)
Infection as a reason for hospitalization	161 (56)	40 (24)	<.001	201 (44)
Suspected or definitive diagnosis[c]				
Urinary tract infections	77 (27)	41 (24)	.503	118 (26)
Respiratory infections	48 (16)	28 (16)	.926	76 (16)
Gastrointestinal infections	57 (20)	9 (5)	<.001	66 (15)
Cutaneous infections	26 (9)	19 (11)	.472	45 (10)
Osteoarticular infections	23 (8)	4 (2)	.023	27 (6)
Endocarditis	11 (4)	6 (4)	.876	17 (4)
Unspecified	42 (15)	62 (37)	<.001	104 (23)
Healthcare-associated infections	123 (43)	60 (37)	.118	183 (40)
≥1 microbial test	207 (73)	89 (53)	<.001	296 (65)
Blood cultures	99 (35)	15 (9)	<.001	114 (25)
Urine cultures	133 (47)	79 (47)	.985	212 (47)
Any positive microbial test result	113/207 (55)	43/89 (45)	.321	156 (53)
Antibiotic therapy				
Parenteral administration	213 (75)	74 (44)	<.001	287 (63)
Antibiotic combination	125 (44)	35 (21)	<.001	165 (30)
Third-generation cephalosporin	99 (35)	48 (29)	.175	147 (32)
Amoxicillin + clavulanic acid	98 (34)	52 (31)	.453	150 (33)
Fluoroquinolones	92 (32)	49 (29)	.489	140 (31)
Vancomycin	29 (10)	4 (2)	.001	33 (7)
Aminoglycoside	52 (7)	12 (18)	<.001	64 (14)
Effective antibiotic reassessment	93 (33)	28 (17)	<.001	121 (27)
Insufficient drug dose	75 (26)	20 (12)	<.001	95 (21)
Clinical outcome				
Favorable	183 (64)	66 (39)	<.001	249 (55)
Uncertain	75 (27)	82 (49)	<.001	157 (35)
Adverse	26 (9)	21 (12)	.269	47 (10)
Nonbacterial infections				
Urinary colonization	14 (5)	28 (16)	<.001	42 (9)
Others[d]	7 (2)	12 (7)	.017	19 (4)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CRP, C-reactive protein; ID, infectious disease; PCT, procalcitonin; SD, standard deviation; UAT, unnecessary antibiotic therapy.

[a]Antibiotic referent indicates a pharmacist or a microbiologist or any other physician who can devote a portion of their time to work on an antimicrobial stewardship program.

[b]Antibiotic therapy was required as we found clinical criteria of sepsis that had not been considered: 2 cases of pneumonia, 2 urinary infections, 1 endocarditis, and 1 intra-abdominal sepsis.

[c]Suspected or definitive diagnosis: depending on the level of proof, ie, the availability of the microbial testing and/or the other technical findings.

[d]Bronchitis and chronic obstructive pulmonary disease for which ≥2 antibiotic courses were prescribed without effectiveness.

Urine colonization, which is also a type of diagnostic error when treated with antibiotics, is usually perceived as a main cause of UAT in long-term care facilities [18, 19]. However, our study shows that it was only involved in 9% of the antibiotic prescriptions in the acute care settings. Accordingly, urine colonization was associated with elderly patients but not with

Table 3. Risk Factors for Unnecessary Antibiotic Therapy: Logistic Regression

Risk Factor	AOR (95% CI)	*P* Value
Hospitalization in a medical ward	2.11 (1.30–3.41)	.002
Infection as an indication for hospitalization	0.24 (.15–.41)	<.001
Gastrointestinal infections	0.23 (.10–.52)	<.001
Unspecified diagnosis	1.83 (1.04–3.20)	.033
Blood cultures not performed	5.26 (2.56–10.00)	<.001
Antibiotic administration via parenteral route	0.55 (.33–.90)	.018
Favorable clinical outcome[a]	0.36 (.23–.58)	<.001

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval.

[a]Resolution of the symptoms that may be related to treatments other than antibiotics, such as steroidal or antitumor drugs and/or resolution of nonbacterial infection.

medical or surgical specialties (data not shown). This high level of UAT due to diagnostic difficulties—that is, unspecified diagnosis plus urinary colonizations plus useless antibiotic treatment related to isolated inflammatory parameters—will not be reduced by the current ASPs, which are mostly only devoted to improvement of the prescription of antibiotics [4, 5, 9]. Our point of view is that to modify such diagnostic issues, only companionship, continuing training, and repeated audits made by the physicians themselves will work [6, 9, 14]. In all of the institutions, our data were provided to the prescribers without obvious disagreement. Accordingly, we have recently introduced the "accompanied self-antibiotic reassessment" to voluntary prescribers, which translated to reassessment sessions of 10–15 recent antibiotic prescriptions from a single practitioner, for their own patients, with the antibiotic referent and/or the ID specialist and/or the pharmacist. In these sessions we insist on the local bacteriological data (species and resistance) and the internal antibiotic guidelines.

Last, our results indicate that digestive infections were associated with a lower rate of UAT. This is in accordance with previous studies indicating a higher quality of antibiotic prescriptions in this context, as well as better outcomes [15, 20]. It seems reasonable to state that digestive infections, whether medical or surgical, are easier to diagnose and to prove, leading to antibiotic prescriptions that are warranted.

Another risk factor associated with UAT was the underuse of microbial testing, which could at least in part explain the rarity of 1 item of UAT—that is, the useless continuation of empirical broad-spectrum antimicrobials (2%; Table 2). Ultimately a poor outcome was the reflection of unspecified diagnoses. However, it is also possible that a putative benefit of antibiotics could be observed in noninfectious syndromes as other drugs such as steroids and/or cytotoxic compounds might be prescribed, or due to spontaneous resolution of the symptoms as result of nonbacterial infection. Once again, such primary associations have been reported in previous studies [2, 12, 13, 16, 20], but are not wholly taken into account in antimicrobial policies nor made widely available to the medical community.

In conclusion, UATs are related to noninfectious syndromes that are mainly observed in medical wards, being associated with unspecified diagnoses and the absence of microbial testing. Their reduction will require an intense collaborative medical approach in a multidisciplinary network.

Notes

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