BMJ Open

Exposure to suppressive antibiotic therapy in women with recurrent urinary tract infections and severity of infections: a retrospective population-based cohort study

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To cite: Llor C, Ouchi D, Fernández-García S, *et al*. Exposure to suppressive antibiotic therapy in women with recurrent urinary tract infections and severity of infections: a retrospective population-based cohort study. *BMJ Open* 2025;**15**:e098371. doi:10.1136/bmjopen-2024-098371

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-098371).

Received 22 December 2024
Accepted 21 July 2025

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ABSTRACT

Background Women with recurrent urinary tract infections (UTIs) often undergo intensive antibiotic exposure, especially with suppressive therapies. Suppressive therapy is recommended for women with three UTIs in the past year or two in the last 6 months. However, the collateral long-term effects of this have been poorly studied.

Objectives To assess whether suppressive therapy for recurrent UTIs increases the incidence and severity of future infections compared with episodic UTI treatment.

Design Retrospective cohort study.

Setting and Participants The study was conducted using data from the Information System for Research in Primary Care database, including 5.8 million people in Catalonia. Two groups of women with recurrent UTIs (≥3 episodes/year) were compared: those on suppressive antibiotic therapy for ≥6 months and those treated episodically. Primary outcomes were hospitalisations due to pyelonephritis, septicaemia, COVID-19, influenza, pneumonia and mortality by these infections, over a 100-month follow-up period.

Results Among 36 170 women, 2898 (8%) were treated with continuous suppressive therapy. Overall, 6.9% of the population experienced severe infections, with a higher incidence in women on suppressive therapy (12.6%) compared with those without (6.4%), with a HR of 1.50 (95% CI 1.33 to 1.68). Pyelonephritis presented the greatest difference (HR, 1.95 (95% CI 1.64 to 2.33)), followed by septicaemia (HR, 1.34 (95% CI 1.13 to 1.59)) and COVID-19 (HR 1.23 (95% CI 1.01 to 1.50)).

Conclusions Suppressive antibiotic therapy in women with recurrent UTIs is associated with a higher incidence and severity of future infections. Future research should focus on clarifying causal relationships and identifying the potential mechanisms involved.

STRENGTHS AND LIMITATIONS OF THE STUDY

⇒ We analysed long-term antibiotic prescribing using a large database covering nearly 6 million patients in Catalonia.
⇒ To address confounding bias, we applied inverse probability of treatment weights based on propensity scores and conducted a bias analysis for unmeasured confounders. While we acknowledge selection bias due to eligibility criteria defined 6 months before treatment allocation, we believe its impact is minimal, as the observation period primarily ensured accurate treatment group assignment.
⇒ Some exclusions due to severe outcomes during this period may have introduced additional bias. An E-value analysis suggests the associations are robust to unmeasured confounding.
⇒ We classified exposure groups based on baseline treatment, without accounting for changes in therapy during follow-up. This may lead to exposure misclassification and biased estimates, which could be better addressed in a prospective or randomised study design.
⇒ Smoking and body mass index (BMI) data were limited; smoking was excluded, and obesity status was used for BMI, assuming those without BMI information were not obese. We expect minimal bias, which is unlikely to affect our conclusions.

INTRODUCTION

Gut microbiota is intrinsically involved in the development and appropriate function of the immune system. An eubiotic microbiota is crucial for facing infectious diseases more efficiently, with less aggressiveness and a better prognosis.[1] Antibiotics possess the ability to strongly disrupt normal flora and microbiota within the gastrointestinal tract and other organs and may counterintuitively serve as a potential factor for increased infection severity in patients with COVID-19 or other common infections.[2] It is postulated that the prescription of antibiotics in these instances could potentially induce greater harm than healing effects. This rationale is largely attributed to the

disruption of healthy microbiota, which may incidentally assist in impeding the process of viral clearance from the body.

A recent cohort study performed by our group was the first to confirm the presence of a significant correlation between previous antibiotic use and increased infection severity in COVID-19 patients. Interestingly, patients with recent antibiotic exposure, as well as those with a non-recent, but repeated history of antibiotic therapy, were statistically more prone to greater severity of symptoms during subsequent COVID-19 infection.[3] This association between prior intensive antibiotic exposure and increased COVID-19 severity has been replicated in later studies.[2 4–8] Intensive antibiotic exposure is thought to disrupt defensive immunity, which may increase the severity of both potential and existing viral infections.[9 10]

One of the groups in which exposure to antibiotics is very intense is women with recurrent urinary tract infections (UTI). We hypothesised that continuous prophylactic antibiotic therapy is associated with greater severity of certain infections. Suppressive therapy is recommended for women presenting with three UTI episodes in the previous year or two or more in the last 6 months.[11] Local guidelines recommend both continuous suppressive therapy and postcoital prophylaxis for a minimum of 6 months.[12 13] However, we chose continuous suppressive treatment for our study, as it involves more sustained exposure to antibiotics. We aimed to assess whether women with recurrent UTIs treated with suppressive therapies experience greater severity in any of the following five infections—acute pyelonephritis, COVID-19, septicaemia, influenza and pneumonia—compared with women who are treated for UTIs each time they occur.

MATERIAL AND METHODS

Study design

This retrospective population-based cohort study aimed to analyse two distinct groups of women with recurrent UTIs, defined as experiencing three or more UTIs in the preceding year. One cohort comprised women who underwent continuous daily suppressive antibiotic therapy for at least 6 months, while the other cohort consisted of women treated episodically for each UTI without suppressive therapy. The primary outcomes were the incidence of hospitalisation due to acute pyelonephritis, COVID-19, septicaemia, influenza and/or pneumonia, as well as mortality by these infectious complications. The follow-up period was 100 months (8 years and 4 months), using primary healthcare records from the Catalonia region, covering the years 2012–2021. This study was approved by the Clinical Research Ethics Committee of the Institut Universitari d'Investigació en Atenció Primària Jordi Gol, Barcelona, Spain, code 22/068-PCV. Figure 1 graphically depicts the design of this study.

Data collection

The study data source was the Information System for Research in Primary Care (SIDIAP; www.sidiap.org) database,[14] which collects clinical information of approximately 5.8 million people in Catalonia (around 80% of the Catalan population and is representative in geography, age and sex). This information is pseudonymised and originates from different data sources. The main source is from ECAP (electronic health records in primary care of the Catalan Health Institute); including sociodemographic characteristics, comorbidities registered as International Classification of Disease-10 codes, Clinical Modification,[15] specialist referrals, clinical parameters, toxic habits, date of death, laboratory test data and drug prescriptions issued in primary healthcare, registered

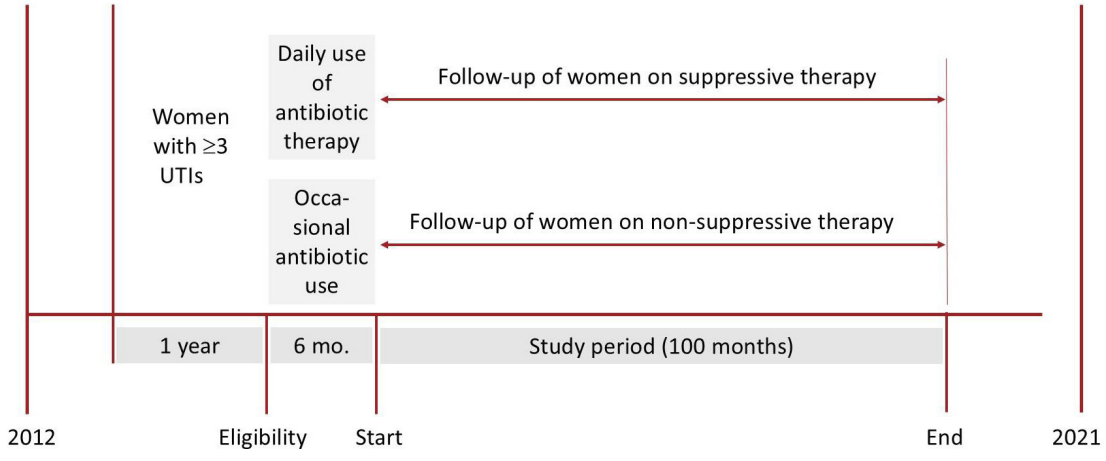

Figure 1 Study design.The starting point, referred to as time zero, marks the assignment of participants to each of the study cohorts. Eligibility is determined during the six months preceding this date. Participants were followed up for a maximum of 100 months (8 years and 4 months). Irrespective of the starting date, follow-up was censored at the end of 2021. UTI=Urinary tract infection

in the Anatomical Therapeutic Chemical classification system as J01 (systemic antibacterials).[16] The pharmacy invoice data corresponding to the primary healthcare drug prescriptions and the database of diagnoses at hospital discharge were also considered in this study.[17] The codes considered in this study are summarised in online supplemental tables 1,2.

Variables and outcomes

Six months prior to the assignment of women with recurrent UTIs to either of the two study cohorts—continuous suppressive treatment or episodic treatment of each infection (time zero), the variables collected were as follows: gender, age, geographical area, socioeconomic and environmental inequalities, socioeconomic deprivation score including five discrete values,[18] the adjusted comorbidity group,[19] obesity defined as a body mass index (BMI) >30 kg/m^2, smoking habit and comorbidities of interest. The variables assessed in each cohort during follow-up were the diagnosis of hospital admission and mortality related to acute pyelonephritis, sepsis (septicaemia), pneumonia, influenza and COVID-19. The primary outcome was a composite endpoint of severity composed of hospitalisation and/or death due to any of these five infections. The risk of these events was analysed by comparing the two cohorts of women with recurrent UTIs.

Statistical analysis

Baseline characteristics of the study population were summarised using typical descriptive statistics, including mean, SD, median, IQR, frequencies and percentages. Given the substantial imbalance between groups, stabilised inverse probability of treatment weights (IPTW) were calculated using propensity scores estimated with logistic regression modelling the probability of being exposed versus not exposed, with the observed confounding factors corresponding to the variables in online supplemental table 3. Standardised mean differences (SMDs) for all confounders were assessed before and after application of IPTW to ensure successful adjustment (online supplemental figure 1), with an SMD <10% indicating an effective adjustment.

For both primary (any hospitalisation) and secondary outcomes (cause-specific hospitalisations and death within 30 days), we estimated 100-month cumulative incidence using competing risks analysis (accounting for all-cause mortality) and HRs via IPTW-weighted Cox models. Absolute between-group differences in cumulative incidence at month 100 were calculated, with 1000-iteration bootstrap resampling used to obtain 95% CIs. HRs were estimated using robust variance estimation for 95% CIs. Results are presented as cumulative incidence curves (with 12-month risk tables) and numerical HR estimates.

For the bias analysis, we used the E-value to quantify the minimum strength of association that unmeasured confounders would need to have with both the exposure and the outcome to eliminate the observed association.

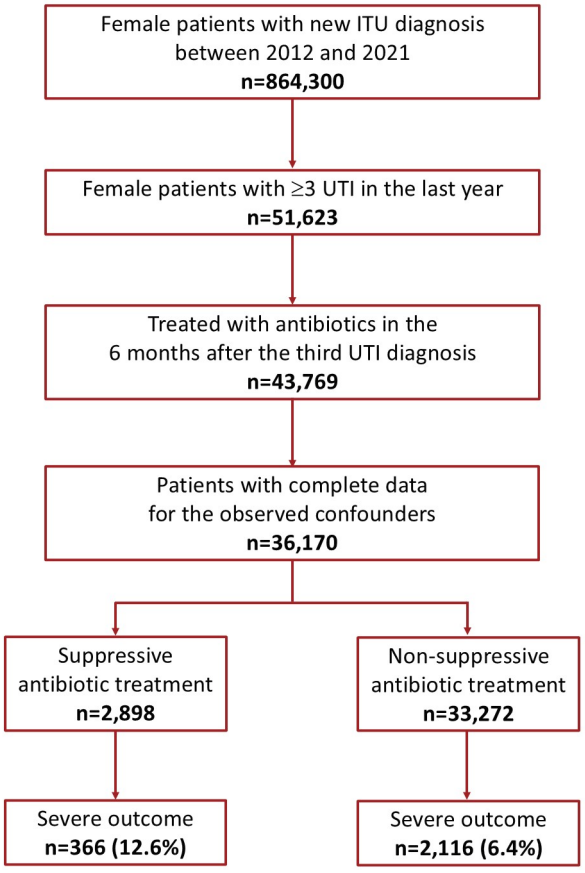

Figure 2 Patient selection process. UTI, urinary tract infection.

The E-value was calculated from the HR observed using the standard formula and assuming a prevalence among unexposed patients of 0.10. All statistical analyses were performed with R V.4.3.1.

Patient and public involvement

No patients were involved in this study.

RESULTS

Study population

Of a total of 864 300 women with newly diagnosed UTI episodes between 2012 and 2021, 51 623 had three or more UTIs in the previous year, constituting the group eligible for daily suppressive antibiotic therapy (figure 2). Of these, 36 170 patients took antibiotics either continuously or sporadically during the following 6 months and had complete data for potential confounders. Among these women, 2898 (8%) underwent daily suppressive treatment, while the remainder took antibiotics only sporadically when they had episodes of UTI, defining the suppressive antibiotic therapy group and the non-suppressive antibiotic group, respectively. Fosfomycin was the most frequently prescribed antibiotic in both groups of women (online supplemental table 4).

The mean age of the entire population of women studied was 56.1 years (SD 21.2 years), with the suppressive

antibiotic therapy group being slightly older, although no statistically significant differences were observed. Smoking status, BMI and the percentage of obese patients were greater for those exposed to suppressive antibiotic therapy. As shown in table 1, the presence of the different comorbidities of interest was higher among patients exposed to suppressive antibiotic therapy compared with those who took antibiotics sporadically, being statistically significant for musculoskeletal problems.

Severity outcomes in the two groups of women

The cumulative incidence of severe outcomes in the two groups of women with recurrent UTIs was evaluated (table 2). A total of 2482 patients experienced the primary composite outcome of hospitalisation due to COVID-19, pyelonephritis, pneumonia, septicaemia and/or influenza infection, or death by these causes during the 100-month follow-up period (6.9%). This outcome occurred in 12.6% of women treated with suppressive prophylactic antibiotic therapy and 6.4% of those not treated with suppressive therapy. The cumulative incidence at 100 months was 0.16 (95% CI 0.14 to 1.18) and 0.12 (95% CI 9.12 to 0.13), respectively, with an absolute difference of cumulative incidence of 0.04 (95% CI 0.02 to 0.06). The HR for experiencing this severe outcome among those treated with suppressive therapy, compared with those not treated, was 1.50 (95% CI 1.33 to 1.68). Figure 3 shows the cumulative incidence of the primary severe outcome in the two groups of women.

The cumulative incidences of the various outcomes considered in this study are shown in online supplemental figure 2. The incidence of all endpoints was greater in the group of women treated with daily prophylactic suppressive antibiotic therapy compared with those treated occasionally. The most significant difference was observed in hospitalisations for pyelonephritis, which were statistically higher among women treated with suppressive therapy, with a HR of 1.95 (95% CI 1.64 to 2.33). This was followed by septicaemia (HR 1.34 (95% CI 1.13 to 1.59) and COVID-19 infection (HR 1.23 (95% CI 1.01 to 1.50)). Although the cumulative incidence of hospitalisation of pneumonia, influenza infection and death within the first month after these infections was higher in patients receiving daily continuous suppressive antibiotic therapy, no statistically significant differences were observed.

We calculated the E-value to assess the potential impact of unmeasured confounders on the HR observed (online supplemental figure 3). The calculated E-value for the HR observed for the main severity outcome was 2.36 (the lower limit of the 95% CI is 1.99). This suggests that an unmeasured confounder would need to be associated with both the exposure and outcome with an HR of at least 2.36 to fully explain the association observed.

DISCUSSION

Summary of main findings

A low number of women eligible for daily suppressive antibiotic therapy was detected in our study, as only 8% of women with three or more UTIs in the previous year were treated with this prophylactic therapy. The main findings of this study are the significantly greater incidence of severe infections during the 100-month follow-up among women taking suppressive therapy, including a higher incidence of severe pyelonephritis, septicaemia and COVID-19, compared with women not exposed to continuous suppressive therapy and who were only treated intermittently when they experienced symptoms of UTI. The association identified in this study may be influenced by confounding factors, as patients who used antibiotics continuously on a daily basis tended to be slightly older and had more comorbidities compared with women who took antibiotics intermittently, which could have heightened their susceptibility to infections and adverse clinical outcomes. However, all the main confounders were effectively adjusted in our study.

Comparison with existing research findings

Different population-based studies have shown similar results regarding COVID-19 infection. Our previous study demonstrated a greater incidence of severe COVID-19 infection, including death, hospitalisation and pneumonia, among patients who had taken antibiotics compared with those who had not. This association was even stronger with intensive antibiotic exposure, recent use of antibiotics and the use of broad-spectrum antibiotics.[3] A study of 3.16 million COVID-19 patients in England found that increased antibiotic use and diversity correlated with higher risks of severe outcomes. Patients with the highest antibiotic exposure had a significantly higher probability of having severe outcomes compared with those with the lowest exposure.[6 7] Other studies carried out in the last 2 years also observed similar findings. Two studies found that patients with severe COVID-19 manifestations were more likely to have been prescribed empirical antibiotics before their admittance to the hospital.[4 5] In Serbia, one study found that prior antibiotic use was associated with a longer duration of illness at admission among patients with COVID-19.[8]

One of the main results of this study is that intensive antibiotic therapy was not only associated with increased severity of COVID-19 infection but also with other severe viral and bacterial infectious diseases. We found that the cumulative incidence of hospitalisations due to all infections measured was greater among women taking suppressive treatment compared with those taking antibiotics occasionally. However, we observed statistically significant differences only for pyelonephritis, septicaemia and COVID-19, but not for influenza or mortality within the first month of disease.

The microbiota plays a crucial role in fostering and maintaining a stable, immunologically supportive environment in both the respiratory and gastrointestinal

Table 1 Demographic and clinical characteristics of the study population at baseline

	Total	Treated with suppressive therapy	Not treated with suppressive therapy	SMD*
n	36 170	2898	33 272	
Age,				
Mean, years, (SD)	56.1 (21.2)	60.7 (20.2)	55.7 (21.2)	0.24
Median, years, (IQR)	58.0 (39.0, 74.0)	65.0 (45.0, 77.0)	57.0 (38.0, 74.0)	
Age ≥60 years	16 857 (46.6)	1646 (56.8)	15 211 (45.7)	0.25
Rurality, n (%)				0.03
Rural	5987 (16.6)	470 (16.2)	5517 (16.6)	
Urban	26 432 (73.1)	2107 (72.7)	24 325 (73.1)	
Unknown	3751 (10.4)	321 (11.1)	3430 (10.3)	
Adjusted morbidity group				
Mean (SD)	10.4 (7.8)	12.9 (8.2)	10.2 (7.7)	0.34
GMA >5, n (%)	25 085 (69.4)	2310 (79.7)	22 775 (68.5)	0.26
Nursing home residents, n (%)	2278 (6.3)	278 (9.6)	2000 (6.0)	0.13
Follow-up				0.17
Mean, years, (SD)	4.6 (2.42)	5.0 (2.5)	4.5 (2.4)	
Median, years, (IQR)	4.4 (2.4, 6.5)	4.8 (2.9, 7.1)	4.4 (2.4, 6.5)	
Smoking, n (%)				0.04
Non-smokers	982 (2.7)	63 (2.2)	919 (2.8)	
Former smokers	1160 (3.2)	87 (3.0)	1073 (3.2)	
Smokers	1187 (3.3)	103 (3.6)	1084 (3.3)	
Missing data	32 841 (90.8)	2645 (91.2)	30 196 (90.1)	
Alcohol intake, n (%)				0.14
No risk	16 995 (47.0)	1551 (53.5)	15 444 (46.4)	
Moderate risk	5856 (16.2)	420 (14.5)	5436 (16.3)	
High risk	69 (0.2)	7 (0.2)	62 (0.2)	
Missing data	13 250 (36.6)	920 (31.8)	12 330 (37.1)	
Body mass index				
Mean, kg/m^2, (SD)	28.0 (5.8)	28.9 (6.0)	27.9 (5.8)	0.17
BMI >30 kg/m^2, n (%)	7395 (20.4)	772 (26.6)	6623 (19.9)	
Missing data, n (%)	13 745 (38.0)	968 (33.4)	12 777 (38.4)	0.17
Urine cultures, n (%)	14 659 (40.5)	1363 (47.0)	13 296 (40.0)	0.14
Indwelling catheters, n (%)	177 (0.5)	29 (1.0)	148 (0.4)	0.07
Referral to the specialist, n (%)	1686 (4.7)	202 (7.0)	1484 (4.5)	0.11
Comorbidities, n (%)				
Urinary lithiasis	1164 (3.2)	143 (4.9)	1021 (3.1)	0.09
Diabetes mellitus	2975 (8.2)	327 (11.3)	2648 (8.0)	0.11
Dyslipidaemia	5129 (14.2)	563 (19.4)	4566 (13.7)	0.15
Chronic kidney failure	1428 (3.9)	169 (5.8)	1259 (3.8)	0.1
Cerebrovascular disease	983 (2.7)	120 (4.1)	863 (2.6)	0.09
Neurological diseases	3632 (10.1)	437 (15.1)	3195 (9.6)	0.1
Musculoskeletal diseases	1177 (3.3)	97 (3.3)	1080 (3.2)	0.01
Digestive diseases	879 (2.4)	114 (3.9)	765 (2.3)	0.09

*An SMD >0.1 is considered unbalanced between groups.
BMI, body mass index; GMA, adjusted morbidity group; SMD, standardised mean difference.

Table 2 Competing risk cumulative incidence at month 100 of the primary outcomes, absolute between-group differences in cumulative incidence and HR between patients exposed to suppressive antibiotic therapy and those not exposed

Outcome	Exposed to suppressive antibiotic treatment (n=2898)	Not exposed to suppressive antibiotic treatment (n=33 272)	Cumulative incidence at 100 months*		Absolute difference of cumulative incidence (95% CI)†	HR (95% CI)*
			Exposed to suppressive antibiotic treatment	Not exposed to suppressive antibiotic treatment		
Main severity outcome	366 (12.6)	2116 (6.4)	0.161 (0.141 to 0.179)	0.123 (0.116 to 0.130)	0.0371 (0.0169 to 0.0588)	1.50 (1.33 to 1.68)
Hospitalised for:						
COVID-19 infection	127 (4.4)	818 (2.5)	0.0704 (0.05 to 0.0865)	0.0588 (0.0532 to 0.0644)	0.0116 (8.23e-04 to 0.0336)	1.23 (1.01 to 1.50)
Pyelonephritis	17 (0.6)	119 (0.4)	0.0713 (0.0594 to 0.08)	0.0454 (0.04 to 0.0496)	0.0259 (0.0135 to 0.039)	1.95 (1.64 to 2.33)
Septicaemia	173 (6.0)	832 (2.5)	0.0855 (0.0682 to 0.102)	0.0672 (0.0614 to 0.0729)	0.0183 (3.28e-03 to 0.0386)	1.34 (1.13 to 1.59)
Influenza infection	71 (2.4)	417 (1.3)	0.0071 (0.0032 to 0.0109)	0.00627 (0.0048 to 0.00774)	7.81e-04 (–3.5e-03 to 0.00606)	1.17 (0.681 to 2.02)
Pneumonia	167 (5.8)	989 (3.0)	0.03 (0.0213 to 0.0387)	0.0226 (0.0198 to 0.0254)	0.00738 (–1.44e-03 to 0.0156)	1.28 (0.982 to 1.66)
Death <30 days after hospitalisation	5 (0.2)	20 (0.1)	0.0024 (1.28e-04 to 0.00467)	0.00143 (6.37e-04 to 0.00222)	9.73e-04 (1.25e-03 to 0.0036)	1.47 (0.546 to 3.93)

*Adjusted using inverse probability of treatment weights. CI derived from the robust standard errors.
†Adjusted using inverse probability of treatment weights. CI derived from the bootstrap method.

tracts.[20 21] The upper respiratory tract microbiota is known to be a gatekeeper of respiratory health, preventing or resisting the intrusion of invasive respiratory pathogens,[22] such as *Streptococcus pneumoniae* or *Haemophilus influenzae*, which may exist as harmless commensals or as highly invasive and deadly pathogens.[23 24] While, on one hand, the advantage of the intake of antibiotics during a viral respiratory infection, such as COVID-19 or influenza infection, is that individuals can protect themselves against secondary bacterial infection by inhibiting the

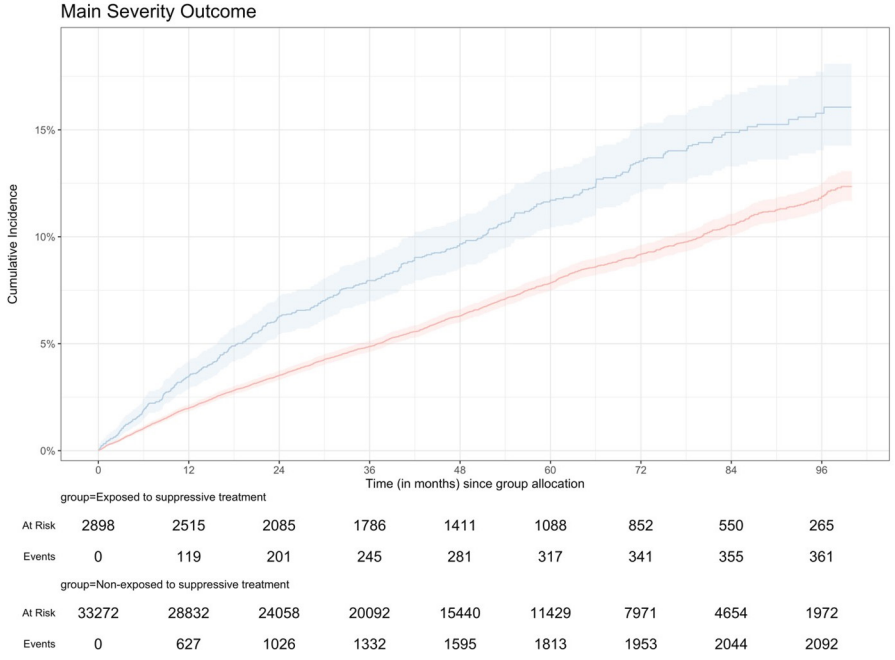

Figure 3 Cumulative incidence of the main severity outcome in the two groups. The blue curve represents exposed participants, while the red curve represents non-exposed participants. The gray shading indicates 95% confidence intervals. Follow-up time is displayed in months from time zero.

growth of opportunistic pathogens, on the other hand, antibiotic intake may cause microbiome dysbiosis by repressing health-associated species and allowing the emergence of antibiotic-resistant pathogens.[25] Antibiotics are believed to induce acute gut dysbiosis and impact resilience to disturbances by reducing the diversity and richness of bacterial populations and altering the antibiotic resistance genes within the gut microbiota.[26] This might explain why the severity of new infections is increased in patients taking antibiotics intensively. This association between antibiotic exposure and other adverse outcomes has also been observed in conditions beyond infections. In a population-based study, Sultan *et al*[27] identified a correlation between the frequency of antibiotic exposure and the risk of developing rheumatoid arthritis.

This dysbiosis caused by antibiotics has not only been studied in patients with COVID-19 but also in other respiratory tract infections. Due to increased antibiotic resistance, COVID-19 patients may be more susceptible to secondary bacterial infections, complicating treatment.[28] Additionally, COVID-19 patients tend to have microbiota dysbiosis, characterised by a microbiome that is usually less diverse compared with patients without the infection.[29] It is also suggested that respiratory infections are associated with an imbalance in nasopharyngeal microbiota, with pneumonia resulting from the overgrowth of a single species in the upper respiratory tract and the absence of distinct anaerobic bacteria.[30]

The result for pyelonephritis is, however, surprising. Previous meta-analyses have shown that antibiotic prophylaxis confers a reduction in the relative risk of women experiencing a microbiologically confirmed UTI compared with placebo.[31 32] However, evidence about preventing upper UTIs is lacking. This benefit of prophylactic suppressive therapy is clearly stated in clinical guidelines. A recent systematic review including nine guidelines on the management of recurrent UTIs showed that all guidelines recommended prophylactic antibiotic use, both continuous and post-coital regimens, for patients with at least three UTIs in the previous year.[33] This poses a dilemma for general practitioners and urologists, as the recommendation to prescribe suppressive antibiotic treatment for more than 6 months to women with recurrent UTIs is not without potential risks, as shown in the present study. Based on our results, patients exposed to suppressive therapy not only experience more side effects from antibiotics but also have a greater incidence of pyelonephritis. There is limited evidence to support the idea that continuous antibiotic exposure effectively reduces infection-related complications.[34] Moreover, a systematic review indicated that individuals prescribed antibiotics in primary care for respiratory or urinary infections are more likely to develop bacterial resistance to those antibiotics.[35] Therefore, the practice of prescribing prophylactic antibiotic therapy for recurrent UTIs must be reevaluated or restricted to women presenting a much higher number of UTIs.

Study limitations

In our study, we implemented IPTW based on propensity scores to address confounding bias, alongside a bias analysis to assess the potential impact of unmeasured confounders. However, we acknowledge the presence of selection bias as our eligibility criteria were defined 6 months prior to treatment allocation. This approach required patients to be followed for treatment exposure within this period, resulting in assignment at a delayed time point and potentially introducing a prevalent user bias. However, we believe that this bias is likely to have a minimal effect on our results. This is because the 6-month observation period was primarily used to ensure accurate treatment group allocation, or the baseline risk factors used to calculate the propensity scores. Some patients were excluded because they experienced severe outcomes during these 6 months, which could have introduced selection bias. In addition, the E-value analysis provides some assurance that the observed associations are robust to unmeasured confounding. Although this is a limitation, we expect any resulting bias to be relatively small and unlikely to significantly alter our primary conclusions.

Another limitation of our study is the classification of patients into exposure groups based solely on treatment at the time of cohort entry. Women with recurrent UTIs were assigned to either the continuous or episodic therapy group based on their management following ≥3 UTIs in the preceding year. However, treatment patterns may have changed during the follow-up period, with some women potentially switching between therapy types. These changes introduce the risk of exposure misclassification and may lead to biased estimates if not accounted for. Our current analysis does not incorporate time-varying exposure and therefore does not capture these shifts in management. A prospective cohort or randomised controlled design would offer more robust control over exposure status and follow-up. Another limitation is the presence of missing data for two important clinical variables: smoking habit and BMI. The smoking habit variable has a particularly high percentage of missing data because records were not captured at the index date. In cases in which the descriptive data suggest a potential imbalance between groups for this variable, we usually perform a sensitivity analysis by carrying forward the most recent value. However, as this imbalance was not observed in our study, we excluded smoking habits from the association analysis. On the other hand, nearly 40% of the BMI data were missing. To account for this, we created an 'obesity' variable by combining obesity diagnoses and BMI values above 30 kg/m^2, assuming that those without BMI information were not obese, which is standard clinical practice.

A strength of this study was its capacity to analyse long-term antibiotic prescribing using the large SIDIAP database, which integrates multiple data sources and encompasses nearly 6 million patients in Catalonia, providing comprehensive healthcare information.

Implications for clinical practice

Since a trial randomising patients to different antibiotic histories cannot be conducted, the interpretation of the findings of this observational study should take into account broader evidence regarding both the benefits and adverse effects of daily and continuous antibiotic exposure. There is limited evidence to indicate that continuous antibiotic exposure is more effective in reducing long-term infection-related complications compared with intermittent antibiotic use.

These findings suggest a potential link between continuous suppressive antibiotic use among women with recurrent UTIs and the risk of severe infections, such as pyelonephritis, COVID-19 and septicaemia. This highlights the need for more judicious antibiotic prescribing in primary care, especially for women at higher risk of UTI recurrences. Such an approach may better offset the potential adverse effects of continuous daily suppressive antibiotic use by treating UTIs as soon as urinary tract symptoms appear and being more restrictive in the use of suppressive therapies.

CONCLUSION

Our study reveals an association between continuous daily suppressive antibiotic therapy and an increased risk of severe infections among women with recurrent UTIs. Despite adjustments for key confounders, the findings suggest that intensive, prolonged antibiotic exposure may have unintended adverse effects. These results question the widespread application of long-term prophylactic antibiotics, especially given the absence of clear evidence supporting their effectiveness in preventing severe outcomes beyond lower UTIs. The increased risk of hospitalisation and severe infections supports a more cautious, individualised approach, favouring intermittent, symptom-driven treatment and reserving suppressive therapy for select high-risk patients.

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Contributors Concept and design: CL, AM and RM. DO performed the statistical analysis. Drafting of the manuscript: CL and DO. Administrative, technical or material support: SF-G and MG-S. DO and RM had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to and approved the final manuscript. The corresponding author affirms that all listed authors meet authorship criteria. RM is the guarantor.

Funding This research was funded by the Strategic Research and Innovation Plan for Health (Pla Estratègic de Recerca i Innovació en Salut) 2022-2024 grant for the financing of research projects in the field of primary health care, grant number SLT021/21/000022.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data are available upon reasonable request. If there is a reasonable request, deidentified participant data used in the research are available via emailing the corresponding author after publication.

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