RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Antirheumatic treatment, disease activity and risk of *Staphylococcus aureus* bacteraemia in rheumatoid arthritis: a nationwide nested case–control study

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To cite: Dieperink SS, Mehnert F, Nørgaard M, *et al*. Antirheumatic treatment, disease activity and risk of *Staphylococcus aureus* bacteraemia in rheumatoid arthritis: a nationwide nested case–control study. *RMD Open* 2022;**8**:e002636. doi:10.1136/rmdopen-2022-002636

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/rmdopen-2022-002636).

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Received 1 August 2022
Accepted 17 October 2022

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ABSTRACT

Objectives To assess how biological disease-modifying antirheumatic drugs (bDMARDs), glucocorticoids and disease activity affect risk of *Staphylococcus aureus* bacteraemia (SAB) in patients with rheumatoid arthritis (RA).

Methods In a nationwide cohort of patients with RA from the DANBIO registry, we conducted a nested case–control study including first-time microbiologically verified SAB cases from 2010 to 2018 and incidence density matched controls (1:4 by sex, age). We interlinked Danish registries and identified antirheumatic treatments, RA-specific clinical characteristics, comorbidities and socioeconomic status. The relative risk of SAB was assessed by adjusted ORs with 95% CIs and number needed to harm (NNH) reflected the absolute risk.

Results Among 30 479 patients, we identified 180 SAB cases (incidence rate: 106.7/100 000 person-years) and matched 720 controls (57% women, median age 73 years, IQR: 65–80). Risk of SAB was increased in current (OR 1.8 (95% CI 1.1 to 3.2)) and former bDMARD users (OR 2.5 (95% CI 0.9 to 7.0)), and in current users of oral glucocorticoids ≤7.5 prednisolone-equivalent mg/day (OR 2.2 (95% CI 1.3 to 4.0) and >7.5 mg/day (OR 9.5 (95% CI 3.9 to 22.7)) (non-use as reference). ORs for moderate/high disease activity compared with remission were 1.6 (95% CI 0.8 to 3.3)/1.5 (95% CI 0.6 to 4.3). Risk was increased in patients with longstanding RA (>10 years vs ≤3 years, OR=2.4 (95% CI 1.1 to 5.3)). The NNH was 1172(95% CI 426 to 9374) for current use of bDMARDs and 110(95% CI 43 to 323) for glucocorticoids >7.5 mg/day.

Conclusion We identified a dose-dependent increased risk of SAB in patients with RA currently using oral glucocorticoids. Daily use of >7.5 mg appeared to be a clinically relevant risk factor, whereas the absolute risk was low for bDMARDs. No clear impact of disease activity was found.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ *Staphylococcus aureus* is a leading cause of bacteraemia (SAB) and patients with rheumatoid arthritis (RA) are at increased risk of this severe condition.
⇒ It remains unclear how treatment with biological disease-modifying antirheumatic drugs (bDMARDs), glucocorticoids, and RA disease activity affect SAB risk.

WHAT THIS STUDY ADDS

⇒ In this nationwide nested case–control study of patients with RA, we found a dose–response relationship between daily and cumulative dose of oral glucocorticoids and the relative risk of SAB.
⇒ Use of glucocorticoids >7.5 mg/day prednisolone was a clinically relevant risk factor for SAB, based on relatively low number needed to harm, whereas the absolute risk associated with use of bDMARDs was low.
⇒ No clear impact of disease activity was found.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study demonstrates that prednisolone-sparing treatment should be carefully considered when higher dose oral glucocorticoids is needed for disease control.

INTRODUCTION

Rheumatoid arthritis (RA) is an inflammatory joint disease treated with immunosuppressive agents such as biological disease-modifying antirheumatic drugs (bDMARDs) and glucocorticoids, especially when conventional synthetic DMARDs (csDMARDs) are insufficient or not tolerated.[1 2] *Staphylococcus aureus* is a leading cause of bacteraemia with ≈20% mortality and ≈30% risk of septic metastases

causing secondary infections, such as endocarditis, osteomyelitis and joint infections.[3–5] Risk factors include high age, male sex, comorbidities, implanted devices, surgical procedures and intravenous catheters.[6 7]

We have previously demonstrated an approximately doubled risk of *S. aureus* bacteraemia in Danish patients with RA compared with the general population and an up to fivefold increased risk for patients with RA with orthopaedic implants.[8] However, it remains unknown how antirheumatic treatments and disease activity affect the risk, with existing studies being few and contradictory.[9 10] One study found neither bDMARDs nor glucocorticoids to be associated with an increased risk in patients with RA, whereas another concluded that oral glucocorticoids increased the risk of *S. aureus* bacteraemia in the general population and in patients with various rheumatic diseases including RA.[9 10] These studies were hampered by lacking information on RA-specific clinical characteristics, such as disease activity and severity, which are associated with both general infection risk and the choice of antirheumatic treatment.[11 12] Thus, the impact of antirheumatic treatments on the risk of *S. aureus* bacteraemia may have been confounded by indication.

In this nationwide, nested case–control study of patients with RA, we linked data from a prospective RA cohort in the clinical DANBIO registry to virtually complete registries of microbiologically verified *S. aureus* bacteraemia cases, vital status, prescriptions, hospital contacts and educational level. We aimed to investigate the impact of bDMARDs, glucocorticoids and disease activity on the risk of *S. aureus* bacteraemia.

METHODS

Data sources

We identified patients with RA in the nationwide Danish rheumatological clinical database DANBIO.[13 14] The validity of the RA diagnosis (positive predictive value ≈95%) and coverage of patients with RA (completeness ≈90% compared with the Danish National Patient Registry, DNPR) in DANBIO are high.[14]

We enriched DANBIO data with data from other national registries by interlinkage on the individual level using the unique personal identification number issued at birth or immigration.[15] First-time cases of microbiologically verified *S. aureus* bacteraemia were retrieved in the Danish National *S. aureus* Bacteraemia Database (linked to personal identification numbers since 1992, completeness 94%–97%).[16 17] Through the Civil Registration System, we determined vital status.[15] In addition, we linked to the following virtually complete registries: the Population's Education Registry for highest attained educational level as a proxy for socioeconomic status[18–20]; the DNPR for history of comorbidities, surgeries/procedures and hospital contacts[21]; and the Register of Medicinal Products Statistics (hereafter 'the prescription registry') regarding redeemed prescriptions for glucocorticoids and glucose-lowering medication (for the identification of diabetes mellitus).[22] Information retrieved included anatomical therapeutical code, dose, formulation, package size and number of packages collected.[22]

Study population and nested case–control design

The DANBIO cohort consisted of adult (≥18 years) patients with RA without prior *S. aureus* bacteraemia, who were alive on 1 January 2010. Entry date was defined as the latest date of either RA diagnosis or first registered contact in DANBIO (online supplemental table S1) before 31 December 2018. We identified patients with a first occurrence of *S. aureus* bacteraemia (=case index event) between 1 January 2010 and 31 December 2018 (=study period).

For the nested case–control study, we matched four controls per case by sex and age (1-year intervals) at the date of the case index event (=index date). Controls had to be alive at the index date and still at risk of a first-time *S. aureus* bacteraemia, and one patient could serve as control for several cases (incidence density matching).[23]

Main exposures

The exposures of main interest were predefined and included treatment with bDMARDs and glucocorticoids as well as RA disease activity.[24]

Users of bDMARDs had received any bDMARD (according to DANBIO) 0–24 months prior to the index date, as opposed to non-users. We subcategorised users according to most recent bDMARD use into either current (0–3 months prior to the index date, 0–12 months for rituximab) or former users (>3 months prior to index date, >12 months for rituximab). We further grouped current use by mode of action into tumour necrosis factor inhibitors (TNFi) and others (non-TNFi). Targeted synthetic DMARDs were rarely used (≤3 users among both cases and controls) and were not included.

For glucocorticoids, we identified oral users based on prescriptions, and parenteral users either by prescriptions or by glucocorticoid injections registered in DANBIO (online supplemental table S1). We defined users (including current and former users) and non-users as described above for bDMARDs. Current oral use was subcategorised according to daily and cumulative prednisolone-equivalent dose, respectively. Daily dose was either the dose at the index date in DANBIO or was estimated from the latest prescription before the index date, in categories of low (≤7.5 mg) or higher dose (>7.5 mg).[25 26] Prescribed dose 0–6 months before the index date was summed up and categorised as ≤1000 mg, 1001–1500 mg or >1500 mg (online supplemental table S1).

Disease activity was estimated by the most recent Clinical Disease Activity Index (CDAI) score in DANBIO before index date and categorised as remission, low, moderate or high.[27]

Other covariates

Based on the literature, comorbidities potentially influencing *S. aureus* bacteraemia risk were defined a priori and identified in DNPR and the prescription registry (online supplemental table S1).[6 7 28] We further identified all surgical procedures performed 0–30 days before the index date.

In DANBIO, we identified body mass index, smoking status and RA-specific clinical characteristics, including disease duration, serostatus, functional status, erosive status and treatment with csDMARDs (categorised as non-user, user, former user and current user as described above, with current users subcategorised into monotherapy and csDMARD combination therapy) (online supplemental table S1).[29]

Statistics

The incidence rate (IR) of *S. aureus* bacteraemia was calculated by dividing the number of *S. aureus* bacteraemia cases with the total number of person-years of follow-up in the DANBIO cohort in the study period, that is, whichever came last of entry date or 1 January 2010 and until first-time *S. aureus* bacteraemia, death, or 31 December 2018, whichever came first.

We characterised cases and controls at the index date with respect to for example, sex, age, RA treatment, disease activity, comorbidities and the fraction of cases caused by methicillin-resistant *S. aureus* (MRSA). The relative risk of *S. aureus* bacteraemia was assessed by adjusted ORs with 95% CIs computed by multivariate conditional logistic regression analyses, comparing cases with controls. When using incidence density matching, ORs may be considered unbiased estimates of IR ratios.[30]

We estimated ORs of *S. aureus* bacteraemia for oral glucocorticoids and bDMARDs stratified according to exposure definitions described above (see the Main exposures section) with non-users as the reference group. Similarly, we estimated ORs for disease activity with remission as reference. OR estimates for the main exposures were presented both as adjusted for age and sex and fully adjusted for all predefined potential confounders. We did not adjust for comorbidities affecting few patients (n≤3 for both cases and controls). For comparisons including strata with≤10 patients, we only presented age and sex adjusted ORs. Likewise, we investigated how the risk was associated with seropositive RA, longstanding RA (>10 years), and poor functional status, by estimating fully adjusted ORs (online supplemental table S1).

We calculated the estimated number of persons needed to be exposed per year for one extra case to occur (the number needed to harm, NNH) and the number of excess cases of *S. aureus* bacteraemia per 10 000 exposed per year for treatment exposures if both the fully adjusted OR and the lower confidence limit were above one. NNH was the inverse of excess cases, which was calculated based on the fully adjusted ORs and the IR in the cohort ((IR*OR)-IR). Confidence limits were calculated likewise using the 95% CIs to the ORs.[31]

We tested for interactions between current use of oral glucocorticoids and bDMARDs, and with either of these and sex, age and orthopaedic implants at index date. Also, we tested for multicollinearity by the variance inflation factor. All analyses were performed using SAS V.9.4.

Sensitivity analyses

We investigated the risk of *S. aureus* bacteraemia associated with disease activity in the subgroup of patients with a recent CDAI registration (0–6 months before the index date, both cases and controls) using multivariate ordinary logistic regression. Similarly, we explored the impact of persistent remission/low disease activity, moderate/high disease activity and fluctuating disease activity on the risk of *S. aureus* bacteraemia, in the subset of patients with ≥3 CDAI registrations 0–3 years before the index date. Furthermore, we explored the impact of treatment exposures on the risk of non-hospital acquired *S. aureus* bacteraemia, defined as cases who were either not hospitalised at the index date or with index-date less than 2 days after hospitalisation.

Missing data

Missing values of CDAI, educational level, Health Assessment Questionnaire (HAQ), serostatus, erosive status, body mass index and smoking status were imputed by multiple imputation by chained equation (100 dataset) with all the main analysis variables, the matching variables and the outcome variable included in the model.[32]

Patient and public involvement

We included a patient research partner in the hypotheses generating phase, which led to the inclusion of RA disease duration as an exposure.

RESULTS

Characteristics of the DANBIO cohort

The cohort comprised 30 479 patients with RA contributing 168 729 person-years of follow-up. We observed 180 cases of first-time *S. aureus* bacteraemia corresponding an IR of 106.7/100 000 person-years.

For the nested case–control study, we included the 180 cases of *S. aureus* bacteraemia and identified 720 controls matched by age and sex. Patients with *S. aureus* bacteraemia were mainly women (57%) aged median 73 years (IQR 65–80). At index date, more cases had seropositive RA (76% vs 66% of controls), erosive disease (48% vs 39%), CDAI 'moderate' (29% vs 16%) or 'high' disease activity (10% vs 7%), HAQ score indicating 'severe to very severe disability' (28% vs 10%) and longer RA duration (years since diagnosis median 13.0 (IQR 6.2–21.4) vs 7.8 (IQR 3.5–14.4) for controls) (table 1). Furthermore, orthopaedic implants were more common among cases (53% vs 34%). HIV and history of solid-organ transplantation were rare. Cases often had recent surgery (38% vs 5%) (table 1). Previous comorbidities or recent surgery were present in 87% (n=157) of cases and 64% (n=458) of controls.

Table 1 Characteristics of Danish patients with rheumatoid arthritis (RA) and *Staphylococcus aureus* bacteraemia (cases) from 2010 to 2018 and matched controls

Characteristics	Cases n=180	Controls n=720
Women*	103 (57%)	412 (57%)
Median (IQR) age in years*	73 (65–80)	73 (65–80)
Median (IQR) time since entry into the cohort (years)	5.1 (2.4–8.4)	4.3 (2.1–7.1)
Median (IQR) time since diagnosis (years)	13.0 (6.2–21.4)	7.8 (3.5–14.4)
Serostatus by diagnosis code		
Seropositive RA	136 (76%)	476 (66%)
Seronegative RA	36 (20%)	210 (29%)
Missing	8 (4%)	34 (5%)
Bone erosions†		
Erosive disease	87 (48%)	278 (39%)
Non-erosive disease	31 (17%)	236 (33%)
Missing	62 (34%)	206 (29%)
Disease activity (CDAI score)‡		
Remission (0.0–2.8)	34 (19%)	212 (29%)
Low activity (2.9–10.0)	67 (37%)	313 (44%)
Moderate activity (10.1–22.0)	52 (29%)	115 (16%)
High disease activity (22.1–76.0)	18 (10%)	47 (7%)
Missing	9 (5%)	33 (5%)
Functional status (HAQ score)§		
Mild to moderate difficulty (0.0–0.875)	71 (39%)	429 (60%)
Moderate to severe disability (1.0–1.875)	51 (28%)	196 (27%)
Severe to very severe disability (2.0–3.0)	50 (28%)	74 (10%)
Missing	8 (4%)	21 (3%)
csDMARD use[ß]		
Non-user	49 (27%)	108 (15%)
Former user	22 (6%)	41 (6%)
Current user, monotherapy	90 (50%)	453 (63%)
Current user, combination therapy	19 (11%)	118 (17%)
Comorbidities		
Orthopaedic implant	96 (53%)	241 (34%)
Cancer	42 (23%)	118 (16%)
Diabetes mellitus	38 (21%)	88 (12%)
Chronic obstructive pulmonary disease	30 (17%)	83 (12%)
Chronic heart failure	28 (16%)	51 (7%)
Vascular device or pacemaker	17 (9%)	53 (7%)
Chronic liver disease	12 (7%)	18 (3%)
Chronic dialysis treatment	5 (3%)	≤3
Solid organ transplantation	≤3	≤3
HIV-positive	≤3	≤3
Recent surgery	69 (38%)	37 (5%)
≥1 inpatient procedure	48 (27%)	≤3
Highest attained educational level		
Basic school (<10 years)	82 (46%)	306 (42%)
Upper secondary school	5 (3%)	10 (1%)

Continued

Table 1 Continued

Characteristics	Cases n=180	Controls n=720
Vocational education	63 (35%)	260 (36%)
Short or medium length higher education	21 (12%)	110 (15%)
Long-term higher education or research	9 (5%)	25 (4%)
Missing	0 (0%)	9 (1%)
Smoking status		
Never smoker	40 (22%)	184 (26%)
Ever smoker	80 (44%)	319 (44%)
Missing	60 (33%)	217 (30%)
BMI level$^{\Sigma}$		
Below normal (15.0–22.9 kg/m^2)	27 (15%)	93 (13%)
Normal (23.0–29.9 kg/m^2)	45 (25%)	224 (31%)
Above normal (30.0–50.0 kg/m^2)	25 (14%)	74 (10%)
Missing	83 (46%)	329 (46%)

Cases comprised all patients with RA in DANBIO with a first-time *S. aureus* bacteraemia and controls were matched by age and sex. See figure 1 for information on biological antirheumatic treatment and glucocorticoids.
All presented values are n (%) unless stated otherwise. Exact numbers are not shown when n≤3 for discretion reasons. Methicillin-resistant *S. aureus* caused <1.7% (n≤3) of cases.
online supplemental table S1
*Matching variables.
†Erosive status was registered median 1 year before index (IQR 0–3 years before).
‡CDAI registered median 5 months before index (IQR 2–12 months).
§HAQ registered median 4 months before index (IQR 2–11 months).
¶Irrespective of concomitant use of biological antirheumatic drugs and glucocorticoids
**∑BMI cut-offs based on survival curves for elderly individuals, for details on BMI levels see online supplemental table S1).
BMI, body mass index; CDAI, Clinical Disease Activity Index; csDMARDs, conventional synthetic disease-modifying antirheumatic drug; HAQ, Health Assessment Questionnaire.

Use of bDMARDs, glucocorticoids and risk of *S. aureus* bacteraemia

Use of bDMARDs 0–2 years before the index date was more frequent among cases compared with controls (38% vs 23%) (figure 1). Most were current users at the index date, however, more cases than controls had stopped treatment and former users constituted 20% of users (14/69) among cases vs 11% (18/162) for controls. In the fully adjusted analysis, current use of bDMARDs was associated with increased risk of *S. aureus* bacteraemia compared with non-use (OR 1.8 (95% CI 1.1 to 3.2)). Former users were also at increased risk, although the CI was wide and included one (OR 2.5 (0.9 to 7.0)). The risk did not vary substantially by mode of action (figure 1).

Current use of oral glucocorticoids was more frequent in cases compared with controls (41% vs 19%) and, in the fully adjusted analysis, OR for current users compared with non-users was 3.2 (95% CI 1.9 to 5.3) (figure 1). Most current users of glucocorticoids received doses ≤7.5 mg prednisolone per day. Higher dose (>7.5 mg/day) was more common for cases compared with controls and fully adjusted ORs increased in a dose-dependent manner from 2.2 (95% CI 1.3 to 4.0) for ≤7.5 mg/day to 9.5 (95% CI 3.9 to 22.7) for >7.5 mg/day. Similarly, for cumulative dose, from 2.0 (95% CI 1.1 to 3.8) for ≤1000 mg to 7.5 (95% CI 3.1 to 18.4) for >1500 mg. (figure 1).

Parenteral glucocorticoids were used infrequently and with similar frequency among cases and controls with no clear sign of increased risk in the adjusted analysis (figure 1).

The NNH associated with current use of >7.5 mg/day oral glucocorticoids was 110 (95% CI 43 to 323) and the number of excess cases/10 000 patients/year was 91 (95% CI 31 to 231) (table 2). The NNH estimates for current bDMARD use were approximately ten times higher than those for higher dose oral glucocorticoids.

Disease activity and risk of *S. aureus* bacteraemia

In the analysis adjusted for sex and age, high and moderate disease activity were associated with increased risk when compared with remission, however, OR estimates decreased in the fully adjusted analysis and CIs included one (table 3).

Other RA-specific clinical characteristics and risk of *S. aureus* bacteraemia

Patients with longstanding RA (>10 years) were at increased risk compared with those with early RA (≤3 years, OR 2.4 (95% CI 1.1 to 5.3). Erosive disease, poor functional status and seropositive RA appeared to be associated with increased risk, but CIs were wide and included one (table 4).

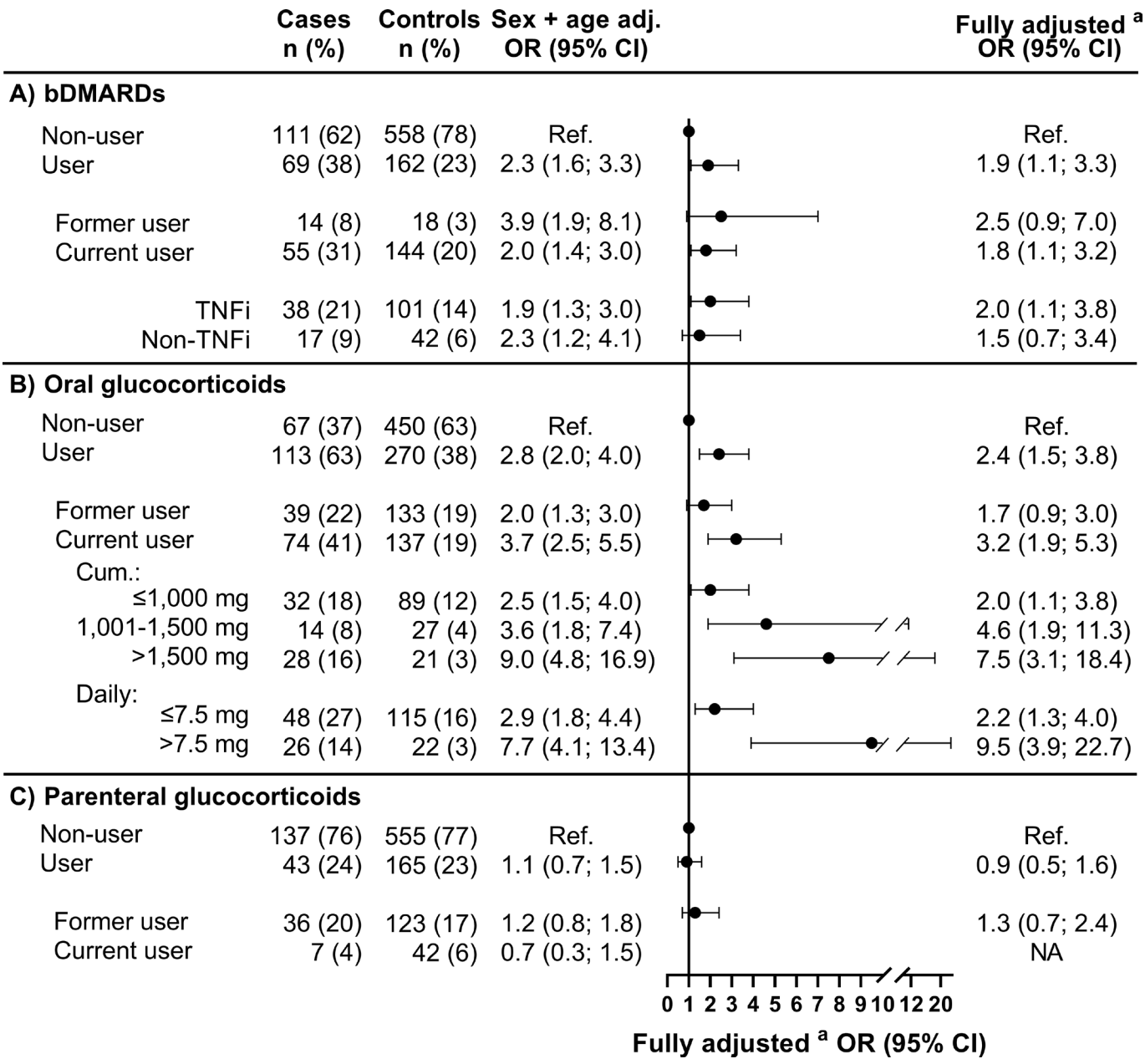

Figure 1 Antirheumatic treatment and risk of *Staphylococcus aureus* bacteraemia in Danish rheumatoid arthritis patients from 2010 to 2018. [a] Age, sex, diabetes mellitus, cancer, chronic heart failure, chronic dialysis treatment, chronic obstructive pulmonary disease, orthopaedic implant, vascular prosthesis, pacemaker or other device, recent surgery, disease duration, years since entry, csDMARD use, treatments in other panels of the figure, with imputed data: disease activity, highest attained educational level, serostatus, erosive status, functional status, body mass index and smoking status. bDMARD, biological disease-modifying antirheumatic drug; csDMARD, conventional synthetic DMARDs; NA, not applicable; TNFi, tumour necrosis factor inhibitors.

Model control and sensitivity analyses

The p value for the interaction term between sex and bDMARD use was 0.0110, however, in stratified analysis, adjusted ORs for current users versus non-users (men and women, respectively) were almost identical (online supplemental table S2). Former users differed but strata were too small for adjusted analysis. We found no sign of multicollinearity between covariates as assessed by estimated variance inflation factors.

The analysis of risk associated with disease activity restricted to patients with a recent registration of CDAI (0–6 months before index event) resulted in similar estimates to the main model, although high disease activity was rare and CIs were wide (online supplemental table S3). The OR estimates were slightly higher when comparing persistent moderate/high (OR 3.0 (95% CI 1.0 to 9.1)) and fluctuating disease activity (OR 1.4 (95% CI 0.8 to 2.6)) with persistent remission/low disease activity, however, the CIs for the fully adjusted OR estimates included one (online supplemental table S4).

The association between antirheumatic treatments and risk of non-hospital-acquired *S. aureus* bacteraemia

Table 2 Number needed to harm and excess cases of *Staphylococcus aureus* bacteraemia associated with drug exposures

Treatment exposure	NNH (95% CI)	Excess cases per 10 000 (95% CI)
bDMARDs		
User	1030 (408 to 6695)	10 (1 to 25)
Current user	1172 (426 to 9374)	9 (1 to 23)
Current TNFi	937 (335 to 9374)	11 (1 to 30)
Oral glucocorticoids		
User	665 (334 to 1769)	15 (6 to 30)
Current user	426 (216 to 1090)	23 (9 to 46)
Cumulative dose (mg)		
≤1000	956 (341 to 9374)	10 (1 to 29)
1001–1500	259 (91 to 1065)	39 (9 to 110)
>1500	144 (54 to 451)	70 (22 to 185)
Daily dose (mg)		
≤7.5	781 (312 to 3125)	13 (3 to 32)
>7.5	110 (43 to 323)	91 (31 to 231)

Risk associated with 1 year of exposure to biological antirheumatic treatment and oral glucocorticoids in Danish patients with rheumatoid arthritis from 2010 to 2018.
All estimates are based on the incidence rate and the fully adjusted ORs from figure 1 if both the OR and the lower confidence limit are above 1 (non-use as reference).
bDMARDs, biological disease-modifying antirheumatic drugs; NNH, number needed to harm; TNFi, tumour necrosis factor alpha inhibitor.

(n=146 of 180=81%) was comparable to the main model (online supplemental table S5).

DISCUSSION

In this nationwide study of patients with RA, current use of oral glucocorticoids in doses higher than 7.5 mg/day resulted in a 9.5-fold higher risk of *S. aureus* bacteraemia, even after adjusting for potential confounders including disease activity. Use of bDMARDs was associated with a doubled relative risk, however, the absolute risk was low, based on the NNH. Risk was increased in patients with longstanding RA, whereas no clear impact of disease activity was found.

Table 3 Risk of *Staphylococcus aureus* bacteraemia associated with disease activity in Danish patients with rheumatoid arthritis from 2010 to 2018

Disease activity (CDAI score)	Sex+age adjusted OR (95% CI)	Fully adjusted* OR (95% CI)
Remission (0.0–2.8)	Reference	Reference
Low (2.9–10.0)	1.3 (0.9 to 2.1)	1.0 (0.5 to 1.8)
Moderate (10.1–22.0)	2.7 (1.7 to 4.5)	1.6 (0.8 to 3.3)
High (22.1–76.0)	2.3 (1.2 to 4.5)	1.5 (0.6 to 4.3)

See table 1 for numbers of exposed individuals at each level. Missing CDAI (≈5%) was imputed by multiple imputation.
*Age (1-year intervals), sex, diabetes mellitus, cancer, chronic heart failure, chronic dialysis treatment, chronic obstructive pulmonary disease, orthopaedic implant, vascular prostheses, pacemakers or other cardiac devices, recent surgical procedure, years since rheumatoid arthritis diagnosis, years since entry, oral glucocorticoid, parenteral glucocorticoid, biological and conventional synthetic disease-modifying antirheumatic drug use, and with imputed data: highest attained educational level, serostatus, erosive status, functional status, body mass index and smoking status.
CDAI, Clinical Disease Activity Index.

Table 4 Risk of *Staphylococcus aureus* bacteraemia associated with rheumatoid arthritis (RA) characteristics

Characteristic	Fully adjusted* OR (95% CI)
Years since RA diagnosis	
≤3	Reference
3.1–10	1.6 (0.8 to 3.4)
>10	2.4 (1.1 to 5.3)
Functional status (HAQ)	
Mild to moderate difficulty (0.0–0.875)	Reference
Moderate to severe disability (1.0–1.875)	0.8 (0.4 to 1.4)
Severe to very severe disability (2.0–3.0)	1.2 (0.6 to 2.4)
Serostatus	
Seronegative RA	Reference
Seropositive RA	1.7 (0.9 to 3.1)
Erosive status	
Non-erosive disease	Reference
Erosive disease	1.6 (0.8 to 3.1)

ORs comparing Danish patients with RA and *S. aureus* bacteraemia from 2010 to 2018 and RA controls matched by age and sex.
*Age, sex, highest attained educational level, diabetes mellitus, chronic heart failure, cancer, chronic liver disease, chronic obstructive pulmonary disease, chronic dialysis treatment, orthopaedic implants, vascular device or pacemakers, disease activity, body mass index, smoking status, years since entry, use of biological and of conventional synthetic disease-modifying antirheumatic drugs, of oral and of parenteral glucocorticoids, and all other variables in this table besides the one in question. Missing values for disease activity educational level, HAQ, serostatus, erosive status, body mass index and smoking status were imputed by multiple imputation.
HAQ, Health Assessment Questionnaire.

We have previously reported increased incidence of *S. aureus* bacteraemia in patients with RA compared with the general population with the highest absolute risk in men >70 years of age and the highest relative risk among women aged <60 years.[33] Risk factors for *S. aureus* bacteraemia in patients with RA have been sparsely studied.[9 10] The apparent negative impact of oral glucocorticoid use reported in this study was strengthened by the dose–response relationship and by the fact that both cumulative dose in the preceding 6 months and the current daily dose increased the risk of *S. aureus* bacteraemia. Our results contradict a previous study finding no such association.[9] However, patients with RA with non-*S. aureus*-related hospital admissions served as controls, which could have biased the impact of treatment towards no association. Another study reported an OR of 2.1 (95% CI 1.4 to 3.2) among patients with rheumatic diseases who currently used oral glucocorticoids, which is somewhat lower than ours.[10] Possible explanations include the pooling of different rheumatic diseases in that study and

lack of adjustment for concomitant antirheumatic treatments, disease activity and severity.

In contrast to previous findings, we identified an increased risk associated with current use of bDMARDs as compared with non-use in the preceding 2 years.[9] However, former bDMARD use was associated with a similarly increased risk (although the CI included one). This finding may appear unexpected, but likely reflects that individuals susceptible to infections are more prone to terminate bDMARD treatment due to infectious or other adverse events, leaving them with insufficiently controlled disease activity and probably higher dosages of glucocorticoids.[34]

Our findings of an increased risk associated with long-standing RA and the overall pattern of a slightly increased risk associated with moderate/high disease activity, low functional status, erosive disease and seropositivity are new, although previous studies have demonstrated associations between low functional status, high disease activity and infections in general.[12 35]

Cases of *S. aureus* bacteraemia acquired during hospitalisation are often associated with surgical procedures or intravenous catheters, thus inherent risk factors might be less influential in hospital-acquired *S. aureus* bacteraemia.[36] We found that the relative risk estimates of antirheumatic treatments were similar when analysing all *S. aureus* bacteraemia cases (ie, looking at hospital and non-hospital acquired cases together, main results), and when analysing non-hospital-acquired *S. aureus* bacteraemia cases separately (sensitivity analysis). This supports that the associations observed in our main results were not mediated by the cases acquired during hospitalisation.

This case–control study nested in a well-defined contemporary cohort of patients with RA allowed us to explore how *S. aureus* bacteraemia risk was associated with time-varying factors such as antirheumatic treatment and disease activity. Strengths include access to and linking at the individual level of (1) prospectively collected information regarding antirheumatic treatments (including glucocorticoids) and disease activity, (2) microbiologically ascertained cases of *S. aureus* bacteraemia with high completeness and validity, and (3) other virtually complete national registries. Discrepancies between actual drug use and drugs listed in electronic records challenge assessment of drug exposures.[37] In this study, we combined information from prescriptions and DANBIO registrations to better capture users and the daily doses.

Limitations include the lack of power when estimating the impact of disease activity on the risk of *S. aureus* bacteraemia. Furthermore, median time elapsed since latest CDAI was 5 months, which could have caused an underestimation of the risk associated with higher disease activity and overestimation of risk associated with treatment. Reassuringly, we arrived at similar/marginally higher estimates both in the sensitivity analysis restricted to patients with a recent single registration of CDAI and in the analysis of persistent moderate/high disease activity restricted to patients with repetitive measurements. Similarly, functional status (HAQ) and erosive status may have changed in the time span from registration until the index date, however most will likely be unchanged, since median time elapsed since registrations were 4 months and 1 year, respectively. Furthermore, we may have underestimated risk associated with current use of antirheumatic treatments, since most current users had been using the drug for >3 months, which may have introduced a healthy user bias.[38 39] However, the study was not powered to stratify according to new and continuing use. Patients with *S. aureus* bacteraemia prior to 1992 may have been included in the study, however, we expect only few such patients because of the long time span combined with the high age and high mortality of most patients with this infection.[40] Few patients had MRSA bacteraemia, and the results may not be generalisable to populations with high MRSA prevalence. We observed that cases and controls differed in several aspects, and residual confounding caused by unmeasured differences may occur. Also, as in any study based on real-world data collected for administrative and clinical use, misclassification bias cannot be ruled out.

In conclusion, oral glucocorticoid use increased the risk of *S. aureus* bacteraemia in a dose-dependent manner in patients with RA. Especially daily use of >7.5 mg seemed to be a clinically relevant risk factor, whereas the absolute risk for bDMARD users appeared low. No clear impact of disease activity was found. Our findings demonstrate that prednisolone-sparing treatment should be carefully considered when higher dose oral glucocorticoid is needed for disease control.

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Acknowledgements We wish to thank patient research partner Pia Lüchau Pedersen for her assistance; Kristina Laugesen, MD, PhD, for scientific discussions on calculating estimated daily dose of oral glucocorticoids; statisticians Thomas Bøjer Rasmussen and Trine Frøslev for guidance; and we thank Gigtforeningen and Beckett-Fonden for their financial support for the study.

Contributors SSD had full access to all data in the study and take responsibility for the accuracy of the data analysis and for the overall content as the guarantor. Study concept and design: SSD, MLH, BG, MN and CT-P. Analysis and interpretation of data: all authors. Drafting of the manuscript: SSD. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: SSD and FM.

Funding This study was supported by The Danish Rheumatism Association (grant numbers R163-A5715 and R188-A6548) and Beckett-Fonden (reference number 19-2-5090).

Competing interests SSD has received grants related to the submitted work from The Danish Rheumatism Association and Beckett-fonden. FM, MN, LBO and AP reports no disclosures. All outside the submitted work: TB reports grants from Novo Nordisk Foundation, Simonsen Foundation, Lundbeck Foundation, Kai Hansen Foundation, Erik and Susanna Olesen's Charitable Fund; grants and personal fees from GSK, Pfizer, Gilead; and personal fees from Boehringer Ingelheim, MSD, Astra Zeneca, Janssen, Pentabase ApS; CT-P reports grants from Novo Nordisk and Bayer; BG reports grants from Pfizer, BMS, Sandoz, and chairs the steering committee of the Danish Rheumatology Quality Registry (DANBIO), which receives public funding from the hospital owners and funding from pharmaceutical companies, and; and Merete Hetland reports grants from Abbvie, Biogen, BMS, Celltrion, Eli Lilly, Janssen Biologics B.V, Lundbeck Fonden, MSD, Pfizer, Roche, Samsung Biopies, Sandoz, Novartis; co-chairs EuroSpA, which generates real-world evidence of treatment of psoriatic arthritis and axial spondylarthritis based on secondary data and is partly funded by Novartis.

Patient consent for publication Not applicable.

Ethics approval The study was registered and approved by the Capital Region of Denmark (approval number RH-2015-209), ensuring that data were handled in accordance to the General Data Protection Regulation (EU) 2016/679. Data from DANBIO were obtained through the Danish Rheumatologic Quality Registry (DRQ). Personal information was pseudonymised. No ethical approval is needed for register-based studies in Denmark.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. According to Danish legislation, none of the original data can be shared.

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