MAYO CLINIC

ORIGINAL ARTICLE

Use of Glucocorticoids and Risk of Community-Acquired *Staphylococcus aureus* Bacteremia: A Population-Based Case-Control Study

Jesper Smit, MD; Achim J. Kaasch, MD, DMSc; Mette Søgaard, DVM, PhD; Reimar W. Thomsen, MD, PhD; Henrik Nielsen, MD, DMSc; Trine Frøslev, MSc; and Henrik C. Schønheyder, MD, DMSc

Abstract

Objective: To investigate whether the use of systemic glucocorticoids is a risk factor for community-acquired *Staphylococcus aureus* bacteremia (CA-SAB).

Patients and Methods: We used population-based medical registries in Northern Denmark to conduct a case-control study including all adults with first-time CA-SAB and matched population controls from January 1, 2000, through December 31, 2011. Glucocorticoid users were categorized as current users (new or long-term use), former users, and nonusers. Using conditional logistic regression, we computed odds ratios (ORs) of CA-SAB according to glucocorticoid exposure, overall and by 90-day prednisolone-equivalent cumulative dose.

Results: We identified 2638 patients with first-time CA-SAB and 26,379 matched population controls. Current glucocorticoid users experienced considerably increased risk of CA-SAB compared with nonusers (adjusted OR=2.48; 95% CI, 2.12-2.90). The adjusted OR was 2.73 (95% CI, 2.17-3.45) in new users, 2.31 (95% CI, 1.90-2.82) in long-term users, and much lower at 1.33 (95% CI, 0.98-1.81) in former users of glucocorticoids compared with nonusers. The risk of CA-SAB increased with higher 90-day cumulative doses. Compared with nonusers of glucocorticoids, the adjusted OR was 1.32 (95% CI, 1.01-1.72) for persons with a cumulative dose of 150 mg or less, 2.42 (95% CI, 1.76-3.33) for persons whose cumulative dose was greater than 500 to 1000 mg, and 6.25 (95% CI, 4.74-8.23) for persons with a cumulative dose greater than 1000 mg.

Conclusion: Glucocorticoid use was associated with a substantially increased risk of CA-SAB. The risk increased with higher cumulative dose, revealing a distinct dose-response relation.

 ■ Mayo Clin Proc. 2016;91(7):873-880

Staphylococcus aureus bacteremia (SAB) is a serious infection associated with high morbidity rates and 30-day mortality of 20% to 40%.[1,2] Systemic glucocorticoids are potent immunosuppressive drugs widely used in the treatment of acute and chronic conditions across almost all clinical specialties.[3] In Denmark, approximately 3.5% of the entire population redeem at least 1 glucocorticoid prescription each year.[4,5] Glucocorticoids exert inhibitory effects on multiple immune responses mediated by neutrophilic leukocytes as well as suppressive effects on macrophage function,[6-9] which may increase the risk of SAB in users. Older age and comorbidity associated with glucocorticoid use may further increase the risk of SAB.[1,2]

Nevertheless, few and conflicting data exist on the association between the use of glucocorticoids and the risk of SAB,[10,11] and, to our knowledge, no previous study has investigated the use of glucocorticoids as a risk factor for SAB as the primary objective. Previous investigations have been limited by restricted numbers of study participants and unavailability of detailed data on glucocorticoid use.[10,11] In addition, lack of adjustment for potential confounding factors, including age, sex, and comorbidity, may have further biased the studies' results.[10,11]

Considering the high prevalence of glucocorticoid use and the detrimental clinical effects of SAB, comprehensive population-based data are needed to elucidate the association between

From the Department of Clinical Microbiology (J.S., H.C.S.), Department of Infectious Diseases (J.S., H.N.), and Department of Clinical Medicine (H.N., H.C.S.), Aalborg University Hospital, Aalborg, Denmark; Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark (J.S., M.S., R.W.T., T.F.); and Institute for Medical Microbiology, Immunology, and Hygiene, University of Cologne, Cologne, Germany (A.J.K.).

glucocorticoid therapy and SAB risk. We, therefore, conducted a case-control study to investigate whether the use of systemic glucocorticoids is associated with an increased risk of community-acquired SAB (CA-SAB).

PATIENTS AND METHODS

Setting

We conducted this case-control study using routinely collected data from population-based medical registries in Northern Denmark (catchment population ~1.8 million inhabitants) between January 1, 2000, and December 31, 2011. Denmark has a tax-supported health care system that provides free medical care and partial reimbursement of the costs of most prescribed medications, including glucocorticoids. We linked medical registries and databases using the unique identification number (the civil registration number) assigned to all Danish citizens on birth or immigration.[12,13] According to Danish legislation, individual consent is not required for registry-based studies. The project was approved by the Danish Data Protection Agency.

Patients With SAB

Patients hospitalized with CA-SAB were identified using the databases of the departments of clinical microbiology in the catchment area from 1995 onward (information on blood culture practice and susceptibility testing is provided in Supplemental Appendix 1, available online at http://www.mayoclinicproceedings.org). We defined eligible cases as patients 15 years and older with 1 or more positive blood cultures with *S aureus* as the sole isolate. Patients with previous SAB are at increased risk for reinfection with SAB compared with the general population[14]; therefore, we limited the study to patients with incident CA-SAB, defined as no previous SAB diagnosis within at least 5 years of the current admission.

Community-acquired SAB was defined as SAB in patients in whom 1 or more positive blood cultures had been obtained within the first 2 days of the current admission. Patients with a first blood culture obtained more than 2 days after admission were excluded because we consider these infections to be hospital acquired. The subset of patients with CA-SAB and recent health care contacts before the current hospitalization were further classified as health care–associated SAB if 1 or more of the following criteria were met within 30 days of the current admission: an admission to the hospital, a visit to a hospital outpatient surgical clinic, and a visit to a hospital hematology, oncology, or nephrology clinic.[15]

We retrieved data on recent health care contacts from the Danish National Patient Registry, which holds data on all citizens admitted to Danish hospitals since 1977 and on all citizens who used Danish outpatient clinics since 1995.[16] Records include dates of hospital admission and discharge, up to 20 discharge diagnoses, and data on surgical procedures.

Selection of Population Controls

From the Danish Civil Registration System, which maintains daily updated records on demographic characteristics and vital status for all Danish residents,[12,13] we randomly selected 10 population controls matched to each CA-SAB case by age, sex, and residence. We applied the risk set sampling technique,[17] ie, eligible population controls had to be alive and at risk for a first hospitalization with CA-SAB on the date that the corresponding case was admitted. Population controls were assigned an index date identical to that of corresponding cases.

Use of Glucocorticoids

The Aarhus University Prescription Database (AUPD) keeps detailed information on all redeemed prescriptions in the study area since 1998.[18] Each record logs information about the type and quantity of medication dispensed according to the Anatomical Therapeutic Chemical (ATC) classification system and the prescription redemption date (ATC codes are available in Supplemental Appendix 2, available online at http://www.mayoclinicproceedings.org). Using this database, we identified all prescriptions redeemed for systemic glucocorticoid therapy by the study participants before their index date (prescriptions for inhaled glucocorticoids and glucocorticoids for topical application were excluded).

Based on the prescription information and methods used previously,[4,5] we defined current users as patients whose most recent prescription redemption was within 90 days before the index date. To account for differences in duration of

Mayo Clin Proc. ■ July 2016;91(7):873-880 ■ http://dx.doi.org/10.1016/j.mayocp.2016.04.023
www.mayoclinicproceedings.org