Risk Factors Predictive of Endogenous Endophthalmitis Among Hospitalized Patients With Hematogenous Infections in the United States

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• PURPOSE: To identify potential risk factors associated with endogenous endophthalmitis among hospitalized patients with hematogenous infections.
• DESIGN: Retrospective cross-sectional study.
• METHODS: MarketScan Commercial Claims and Encounters, and Medicare Supplemental and Coordination of Benefit inpatient databases from the years 2007-2011 were obtained. Utilizing ICD-9 codes, logistic regression was used to identify potential predictors/comorbidities for developing endophthalmitis in patients with hematogenous infections.
• RESULTS: Among inpatients with hematogenous infections, the overall incidence rate of presumed endogenous endophthalmitis was 0.05%-0.4% among patients with fungemia and 0.04% among patients with bacteremia. Comorbid human immunodeficiency virus infection/acquired immunodeficiency syndrome (HIV/AIDS) (OR = 4.27; CI, 1.55-11.8; $P = .005$), tuberculosis (OR = 8.5; CI, 1.2-61.5; $P = .03$), endocarditis (OR = 8.3; CI, 4.9-13.9; $P < .0001$), bacterial meningitis (OR = 3.8; CI, 1.2-12.0; $P = .023$), fungal meningitis (OR = 59.1; CI, 14.1-247.8; $P < .0001$), internal organ abscess (OR = 2.9; CI, 1.2-6.4; $P = .02$), lymphoma/leukemia (OR = 2.9; CI, 1.6-5.3; $P < .0001$), skin abscess/cellulitis (OR = 1.75; CI, 1.1-2.8; $P = .02$), pyogenic arthritis (OR = 4.2; CI, 1.8-9.6; $P = .001$), diabetes with ophthalmic manifestations (OR = 7.0; CI, 1.7-28.3; $P = .006$), and urinary tract infection (OR = 0.04; CI, 0.3-0.9; $P = .023$) were each significantly associated with a diagnosis of endogenous endophthalmitis. Patients aged 0-17 years (OR = 2.61; CI, 1.2-5.7; $P = .02$), 45-54 years (OR = 3.4; CI, 2.0-5.4; $P < .0001$), and 55-64 years (OR = 2.9; CI, 1.8-4.8; $P < .0001$); those having length of stay of 3-10 days (OR = 1.9; CI, 1.1-3.3; $P = .01$), 11-30 days (OR = 3.1; CI, 1.8-5.5; $P < .0001$), and 31+ days (OR = 5.3; CI, 2.7-10.4; $P < .0001$); and those with intensive care unit/neonatal intensive care unit (ICU/NICU) admissions (OR = 1.5; CI, 1.4-1.6; $P < .0001$) were all more likely to be diagnosed with endogenous endophthalmitis.
• CONCLUSIONS: Endogenous endophthalmitis is rare among hospitalized patients in the United States. Among patients with hematogenous infections, odds of endogenous endophthalmitis were higher for children and middle-aged patients, and for patients with endocarditis, bacterial meningitis, lymphoma/leukemia, HIV/AIDS, internal organ abscess, diabetes with ophthalmic manifestations, skin cellulitis/abscess, pyogenic arthritis, tuberculosis, longer hospital stays, and/or ICU/NICU admission. (Am J Ophthalmol 2015;159:498–504. Published by Elsevier Inc.)

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ENDOGENOUS ENDOPHTHALMITIS IS A RARE BUT potentially devastating ocular disease involving infectious (bacterial and/or fungal) inflammation of intraocular spaces, caused by hematogenous spread of pathogens from distant infectious loci in the body.[1] The leading cause of bacterial endogenous endophthalmitis is gram-positive species in western countries (gram-negative species in Asian countries), and the leading cause of fungal endogenous endophthalmitis is *Candida* (followed by aspergillosis).[2–6]

Endogenous endophthalmitis associated with hematogenous infections has been recognized for over a century,[7] more commonly among patients with fungemia than bacteremia,[8,9] but with wide variation in reported incidence rates—ranging from 12% to 26% incidence of retinal lesions in bacteremic patients[10–12] and from 0 to 78% incidence of chorioretinitis or endophthalmitis in patients with candidemia[13–18]—in studies with tens to hundreds of patients with hematogenous infections.[6] Clinical signs include infiltrative chorioretinitis and overlying vitritis (classic for candida endophthalmitis, though uncommon), as well as nonspecific findings such

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as cotton-wool spots, retinal hemorrhages, and white-centered Roth spot hemorrhages. These findings may also be independently attributable to other comorbidities, including diabetes, hypertension, anemia, and leukemia.[7]

Since pathogens need to gain access to the blood stream and cross the blood-ocular barrier, immunosuppressed states and conditions that facilitate bacteremia and fungemia are thought to predispose to endogenous endophthalmitis. Several case series and case reports have collectively shown a high prevalence of human immunodeficiency virus infection/acquired immunodeficiency syndrome (HIV/AIDS), diabetes mellitus, end-stage renal disease/renal failure, malignancy, intravenous drug use, urinary tract infections/indwelling catheters, organ abscesses, liver transplant, and gastrointestinal infections in patients with endogenous endophthalmitis.[3,4,6,19–22]

Studies have provided descriptive analyses of comorbidities present in endogenous endophthalmitis patients. However, while these reports do give a basic idea of important comorbidities or predictors, they do not tell us relative importance or statistical significance in predicting risk of endogenous endophthalmitis. In this study we aimed to identify the leading causes of bacterial and fungal endophthalmitis in a large, nationally representative patient sample and quantify clinical comorbidities conferring high relative odds of endogenous endophthalmitis among patients with hematogenous infections. That is, what clinical factors are associated with an increased prevalence of endogenous endophthalmitis in hospitalized patients with bacteremia or fungemia? We hypothesized that sicker patients (measured by length of hospital stay and intensive care unit or neonatal intensive care unit admission) and immunocompromised patients would have higher odds of developing endogenous endophthalmitis.

METHODS

• **DATA SOURCE:** We performed a retrospective population-based cohort study utilizing the MarketScan Commercial Claims and Encounters, and the Medicare Supplemental and Coordination of Benefit inpatient databases from the years 2007 through 2011 (the most recent year the database was available). The MarketScan family of databases comprises the largest convenience-based proprietary database in the United States, annually encompassing approximately 40-50 million patients with employer-sponsored or supplemental insurance. These databases consist of de-identified, individual-level health records (inpatient and outpatient) obtained from large employers, hospitals, and Medicare programs. The inpatient databases include the hospitalization records of approximately 3 million employees, dependents, and retirees annually and these data are contributed by 150 employers and 21 health plans. Additional details regarding the MarketScan databases, sampling methodologies, and limitations are described elsewhere.[23] As the MarketScan database contains de-identified and anonymized records and complies with the privacy requirements of the Health Information Portability and Accountability Act of 1996, Institutional Review Board approval was not required.

The inpatient admission claims database contains demographic, insurance, and cost-related information, as well as 1 principal diagnosis code (coded using the International Classification of Disease, ICD-9) and up to 15 secondary ICD-9 codes along with 1 primary procedure code (coded using the Current Procedural Terminology, CPT) and up to 15 secondary CPT codes.

• **STUDY SAMPLE AND PROTOCOL:** Using International Classification of Disease (ICD9) codes, we identified patients who were hospitalized between January 2007 and December 2011 with a diagnosis of bacteremia, septicemia, and/or fungemia. If multiple hospitalizations for a given unique patient were observed over the study period, only the first hospitalization was included in our analysis. Patients were included in this study regardless of their age, sex, or any other demographic characteristics. We further divided our selected sample population into 2 groups based on whether a co-diagnosis of endophthalmitis was also recorded in the same admission record. Positive blood cultures in a patient with endophthalmitis are regarded as the most reliable method of confirming endogenous endophthalmitis[2,20]; since hematogenous infection and endophthalmitis from another cause (postoperative or traumatic) are unlikely to occur at the same time, we considered simultaneous endophthalmitis and bacteremia (or fungemia) to be a reliable indicator of endogenous endophthalmitis in hospitalized patients. For the purposes of our study, patients with ICD-9 codes for both hematogenous infection and endophthalmitis were considered to have endogenous endophthalmitis.

• **STATISTICAL ANALYSIS:** All statistical analysis was performed with SPSS (version 22; SPSS Inc, Chicago, Illinois, USA). We used descriptive statistics and cross-tabulations to calculate the prevalence estimates, and we used logistic regression to identify predictors of endophthalmitis in patients with hematogenous infections. Patients with hematogenous infections who did not develop endophthalmitis were regarded as the control group (base case). All logistic regression analyses for identifying and evaluating these potential risk factors were controlled for age and sex to minimize confounding effects. Odds ratios (OR) and their 95% confidence intervals (CI) were calculated for all potential endogenous endophthalmitis risk factors that were included in our analysis. *P* values were also calculated with a statistical significance cut-off level of $<.05$. All *P* values, odds ratios, and 95% confidence intervals were derived from logistic regression analyses.