ARTICLE

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National emergency department trends for endogenous endophthalmitis: an increasing public health challenge

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BACKGROUND/OBJECTIVE: To characterize incidence rates and identify risk factors for admission and mortality in patients with endogenous endophthalmitis (EE) in the United States (US).
SUBJECTS/METHODS: Patients with EE were identified using the Nationwide Emergency Department (NEDS) Database from 2006 to 2017 in this cross-sectional study. Subjects were required to have diagnoses of both endophthalmitis and septicaemia using contemporary International Classification of Diseases diagnosis codes. Incidence rates, mortality rates and demographics were evaluated. Risk factors for admission and mortality were identified using weighted logistic regression analysis.
RESULTS: A total of 6400 patients with EE were identified. Incidence increased from 0.10 (95% confidence interval [CI]: 0.07–0.12) per 100,000 in the US population in 2006 to 0.25 (95% CI: 0.21–0.30) in 2017 ($p < 0.05$). Most were female (55.4%), insured with Medicare (53.5%), were in the first income quartile earnings (29.3%) [bottom 25% income bracket], lived in the South (40.5%), and presented to metropolitan teaching hospitals (66.6%). Mortality increased from 8.6% (95% CI: 3.8–18.3%) in 2006 to 13.8% (95% CI: 9.7–19.2%) in 2017 ($p = 0.94$). Factors predicting admission included older age (odds ratio [OR] 32.59; [95% CI 2.95–359.78]) and intravenous drug use (OR 14.90 [95% CI: 1.67–133.16]). Factors associated with increased mortality included: human immunodeficiency virus infection/immune deficiencies (OR 2.58 [95% CI: 1.26–5.28]), heart failure (OR 2.12 [95% CI: 1.47–3.05]), and hepatic infections/cirrhosis (OR 1.89 [95% CI: 1.28–2.79]). Pneumonia and renal/urinary tract infections (UTI) were associated with both increased hospital admission [(pneumonia OR 9.64 (95% CI: 1.25–74.35, $p = 0.030$), renal/UTI OR 4.09 (95% CI: 1.77–9.48)] and mortality [(pneumonia OR 1.64 (95% CI: 1.17–2.29, $p = 0.030$), renal/UTI OR 1.87 (95% CI: 1.18–2.97)]. Patients with diabetes mellitus (DM) had decreased odds ratio for mortality (OR 0.49 [95% CI: 0.33–0.73]).
CONCLUSION: EE has increased in incidence throughout US. The two systemic factors that conferred both an increase in mortality and admission were pneumonia, and renal/UTI. Additional exploration of the potential protective association of DM with decreased mortality in this context is needed.

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INTRODUCTION

Endogenous endophthalmitis (EE) comprises approximately 2–8% of all cases of endophthalmitis [1]. The eye becomes a secondary site of inoculation with hematogenous spread of infection from elsewhere. Since it is relatively infrequent, there have been few large-scale studies evaluating EE. Furthermore, symptoms are non-specific, with blurred vision as the most common presenting ocular symptom [2]. The diagnosis is missed in a substantial number of cases, with reports citing numbers ranging from 16% to 63% [3, 4]. Meanwhile, EE can have a rapid, debilitating course resulting in profound visual impairment. Thus, universal routine screening paradigms have been introduced for patients with bloodstream infections as a means for early identification and treatment (e.g., *Candida* species), but without proven success [5, 6]. Clinical suspicion for EE in the appropriate context for patients with systemic infections needs to be high; awareness of demographics patterns, and admission and mortality trends may therefore help dictate clinical management and elucidate patient outcomes.

There have been several studies limited to single centres evaluating demographics and mortality trends in patients with EE [7–11]. However there are a paucity of other studies that have used national databases to study EE, and none have focused on admission or mortality data [12, 13]. The primary goal of our study is to characterize patients who present to the emergency department (ED) with EE and evaluate risk factors for admission and mortality by examining these characteristics using data from a national database of EDs in the United States (US). We also assessed demographics, incidence, and temporal trends.

MATERIALS/SUBJECTS AND METHODS
Data source
The Nationwide Emergency Department Sample (NEDS) is the largest all-payer ED database in the US, and was developed by the Healthcare Cost and Utilization Project to provide both regional and national estimates of ED care [14]. This database consolidates

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Table 1. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes.

ICD Definition	ICD-9 Code	ICD-10 Code
Endophthalmitis	360.00, 360.01, 360.02, 360.13, 360.19	H44.001, H44.002, H44.003, H44.009, H44.011, H44.012, H44.013, H44.019, H44.121, H44.122, H44.123, H44.129, H44.19
Septicaemia	00.31, 022.3, 038.0–038.9, 054.5, 659.3–659.33, 771.81, 785.52, 998.02, 995.92	R65.20, R65.21, A40.0-A40.9, A41.0-A41.9, A54.86, A02.1, A22.7, B00.7, O86.04, P36.0-P36.9, O85.0, O04.87, O07.37, O08.82, T81.44XA, T81.44XD, T81.44XS
Diabetes Mellitus	250.0–250.31	E08.0–E13.0
HIV/Immune Deficiency	H042.0-H044.9, 27.90–27.93	B20.0–B20.9, D80.0–D80.9
Heart Failure	428.0–428.9, 402.01, 402.11, 402.91	I50.0–I50.9
Pneumonia	011.61–011.66, 115.15, 115.95, 003.22, 011.60–011.66, 115.15, 115.95, 48.0–48.7, 99.731, 99.732	J09–J18, P23.0–P23.9, A01.03, A02.22, A54.84, B01.2, B06.81, B77.81, J82–J84, B05.2, J85.1, A37.9, A37.01, A37.11, A37.81
Endocarditis	036.42, 074.22, 093.20, 098.84, 112.91, 115.04, 115.94, 115.14, 42.1–42.49	I38, I39, M32.11, M32.82, A39.51, A52.03, B33.21, B37.6, I01.1, I33.0–I33.9
IV Drug Use	304.0–305.9	F10–F19
Gastrointestinal Comorbidities	52.0–56.0	K0.0–K6.0
Renal/Urinary Tract Infections	59.0–59.9	N0–N3
Hepatic Infections/Cirrhosis	57.0–57.39	K7–K8

the State Inpatient Databases and State Emergency Department Databases including both patients seen in the ED and subsequently admitted to the hospital, as well as visits that do not result in admission. The database contains roughly 145 million ED visits from 990 hospitals across 36 states nationwide, approximating a 20% stratified sample of hospital-owned EDs. NEDS uses discharge data and elements derived from International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and ICD, Tenth Revision, Clinical Modification (ICD-10-CM). This study was performed with the approval of the Johns Hopkins University School of Medicine Institutional Review Board and in accordance with the Declaration of Helsinki.

Study population
All cases with an ICD-9-CM and ICD-10-CM code corresponding to endophthalmitis were identified. Selection of cases also required septicaemia as a diagnosis for increasing rigor of capturing EE. These codes used for identification of EE are listed in Table 1.

Study measures
Secondary variables were also identified using ICD-9-CM and ICD-10-CM codes. Data related to patient, visit, institution, and outcomes were evaluated. Demographic variables consisted of age, gender, insurance status, and income quartile. Institution variables included region, metropolitan status, teaching designation, and trauma centre designation. Visit variables encompassed median cost adjusted for inflation and month. Outcome variables included admission status and mortality. The database only coded mortality if it occurred within the same visit as the presentation, including both death during ED stay or death occurring during the length of admission.

Data analysis
Nationwide estimates were determined using sample weights provided by NEDS. Weights were provided in the database using discharge level weights that are provided in the database to represent the relative proportion of the total US inpatient hospital population for each record, allowing for calculation of national estimates. Annual incidence of such visits was calculated using census data; the total number of EE cases during the study period

was divided by the total US population in the same period. Standard descriptive statistical methods were used for assessing demographics, and characteristics related to visit and institution. A univariate and multivariate weighted logistic regression model was used to determine demographic and visit characteristics associated with both hospital admission and mortality. Variables in this analysis included age (grouped into ≤20, 21–40, 41–60, 61–80, ≥81), sex, household income, primary payer, patient location, hospital region, teaching status of hospital, and the following comorbidities: diabetes mellitus (DM), human immunodeficiency virus (HIV)/immune deficiencies, heart failure, pneumonia, endocarditis, intravenous drug use (IVDU), gastrointestinal infections, renal/urinary tract infections, and cirrhosis/hepatic infections. Weighting was used throughout to identify these variables to account for changes in sampling procedure during this time period. Statistical significance was set at $p < 0.05$.

RESULTS
Demographics and baseline characteristics
In total, there were 29,400 patients with any endophthalmitis diagnosis code (Table 1) identified from 2006 to 2017. This group was further refined to 6400 patients who were identified as having EE using a diagnosis code consistent with septicaemia, of whom 6307 patients were admitted (98.5%) (Table 1). Demographic data are shown in Table 2. Most (55.4%) patients were female, the majority (53.5%) were insured with Medicare, and the median age was 62 years (interquartile range [IQR]: 49–75). The income quartile distribution was evenly distributed with most patients living in the Southern region (40.5%). Most patients presented to non-trauma centre (42.3%), metropolitan teaching hospitals (66.6%).

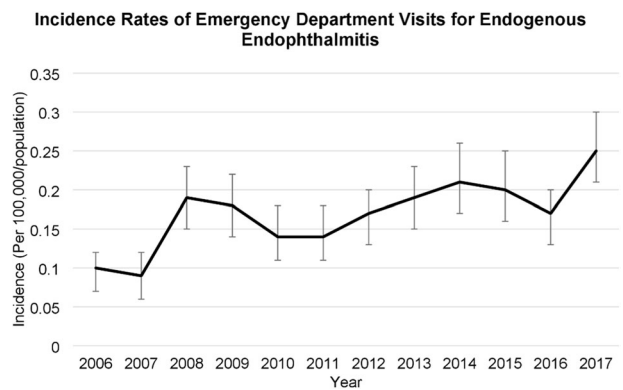#### National trends in incidence, cost and mortality
Incidence of EE increased from 0.10 (95% CI: 0.07–0.12) in 2006 to 0.25 (95% CI: 0.21–0.30) in 2017 ($p < 0.05$, Fig. 1). The median inflation-adjusted cost of ED visits for EE increased from $1229 (IQR: $690-$1563) in 2006 to $2529 (IQR: $1538–4038) in 2017 but was statistically insignificant ($p = 0.23$) (Fig. 2). There was no seasonal variation in the distribution of ED visits for EE ($p = 0.46$).

Table 2. Demographics of Endogenous Endophthalmitis Visits to Emergency Departments in the United States (weighted), 2006–2017.

Sex	
Female	3544 (55.4)
Male	2856 (44.6)
Age	
0–20	123 (1.9)
21–40	492 (7.7)
41–60	2196 (34.3)
61–80	2345 (36.6)
>81	1242 (19.4)
Year	
2006	284 (4.4)
2007	271 (4.2)
2008	570 (8.9)
2009	550 (8.6)
2010	446 (7.0)
2011	451 (7.0)
2012	522 (8.1)
2013	604 (9.4)
2014	685 (10.7)
2015	655 (10.2)
2016	535 (8.3)
2017	827 (12.9)
Insurance	
Medicare	3422 (53.5)
Medicaid	1230 (20.3)
Private	1151 (18.0)
Self-Pay	336 (5.3)
No Charge	41 (0.6)
Other	144 (2.3)
Income Quartile	
First	1830 (29.3)
Second	1589 (25.5)
Third	1444 (23.1)
Fourth	1380 (22.1)
Region	
Northeast	1140 (17.8)
Midwest	1106 (17.3)
South	2589 (40.5)
West	1564 (24.4)
Hospital Teaching Status	
Metropolitan Non-teaching	1815 (28.4)
Metropolitan teaching	4263 (66.6)
Non-Metropolitan	323 (5.0)
Hospital Trauma	
Level	
Non-trauma Centre	2708 (42.3)
Level 1	1670 (26.1)
Level 2	779 (12.2)
Level 3	511 (8.0)
Mortality	822 (12.9)
Admission	6307 (98.5)

Table 2. continued

Comorbidities	
Diabetes	2389 (37.3)
HIV/AIDS/Immune Deficiency	203 (3.2)
Heart Failure	1342 (21.0)
Pneumonia	1695 (26.5)
Endocarditis	1021 (15.9)
IV Drug Use	844 (13.2)
Gastrointestinal Infections	1808 (28.3)
Renal/Urinary Tract Infections	4551 (71.1)
Hepatic Infections/Cirrhosis	1114 (17.4)

Fig. 1 Incidence rates of emergency department visits for endogenous endophthalmitis. Incidence rates (error bars represent 95% confidence interval [CI]) of emergency department visits for endogenous endophthalmitis from 2006 to 2017 have been increasing per 100,000 from 0.10 (95% CI: 0.07–0.12) in 2006 to 0.25 (95% CI: 0.21–0.30) in 2017 ($p < 0.05$).
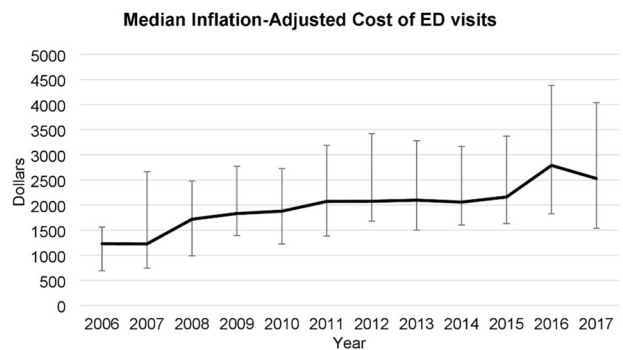
Fig. 2 Median inflation-adjusted cost of ED visits. Median inflation-adjusted cost of ED visits (error bars represent interquartile range [IQR]) for EE has increased from $1229 (IQR: $690–1563) in 2006 to $2529 (IQR: $1538–4038) in 2017 ($p = 0.23$).

Overall mortality rate was 12.9% and increased from 8.6% (95% CI: 3.8–18.3%) in 2006 to 13.8% (95% CI: 9.7–19.2%) in 2017 ($p = 0.94$).

Systemic risk factors

On multivariate analysis, factors associated with hospital admission included older age, specifically ≥81 years (odds ratio [OR] 32.59; [95% confidence interval (CI)]: 2.95–359.78]), and patients with the following comorbidities: pneumonia (OR 9.64 [95% CI: 1.25–74.35]), IVDU (OR 14.90 [95% CI: 1.67–133.16]), and renal/urinary tract infections (OR 4.09 [95% CI: 1.77–9.48]), (Table 3).

Table 3. Predictors of admission and mortality among patients coming to emergency department with Endogenous Endophthalmitis as the primary diagnosis (weighted).

	Admission		Mortality	
	Multivariate, Adjusted (Odds ratio, 95% confidence interval)	*P* value	Multivariate, Adjusted (Odds ratio, 95% confidence interval)	*P* value
Age (reference 0–20 years)				
21–40	1.51 (0.20–11.48)	0.691	2.40 (0.40–14.50)	0.340
41–60	9.25 (1.54–55.43)	0.015	3.56 (0.73–17.32)	0.115
61–80	18.93 (1.64–217.85)	0.018	5.02 (1.08–23.29)	0.039
≥81	32.59 (2.95–359.78)	0.004	2.84 (0.56–14.36)	0.208
Sex (reference men)				
Women	0.46 (0.19–1.14)	0.095	1.17 (0.84–1.62)	0.361
Primary Payer (reference Medicare)				
Medicaid	1.54 (0.28–10.41)	0.658	0.99 (0.60–1.64)	0.980
Private Insurance	1.37 (0.27–6.87)	0.703	0.71 (0.43–1.17)	0.176
Self Pay	0.12 (0.02–0.66)	0.015	0.65 (0.28–1.51)	0.312
No charge	1		1.00	
Other	0.11 (0.02–0.64)	0.014	1.07 (0.33–3.45)	0.905
Comorbidities (reference not having the comorbidity)				
Diabetes	2.10 (0.66–6.62)	0.207	0.49 (0.33–0.73)	<0.001
HIV/AIDS/Immune Deficiency	1		2.58 (1.26–5.28)	0.010
Heart Failure	0.92 (0.21–3.96)	0.909	2.12 (1.47–3.05)	<0.001
Pneumonia	9.64 (1.25–74.35)	0.030	1.64 (1.17–2.29)	0.004
Endocarditis	5.79 (0.96–34.90)	0.055	0.92 (0.58–1.44)	0.704
IV Drug Use	14.90 (1.67–133.16)	0.016	0.74 (0.41–1.32)	0.308
Gastrointestinal Infections	1		1.00 (0.69–1.43)	0.988
Renal/Urinary Tract Infections	4.09 (1.77–9.48)	0.001	1.87 (1.18–2.97)	0.008
Hepatic Infections/Cirrhosis	1.68 (0.19–15.00)	0.641	1.89 (1.28–2.79)	<0.001

Factors associated with mortality included HIV/immune deficiencies (OR 2.58 [95% CI: 1.26–5.28]), heart failure (OR 2.12 [95% CI: 1.47–3.05]), pneumonia (OR 1.64 [95% CI: 1.17–2.29]), renal/urinary tract infections (OR 1.87 [95% CI: 1.18–2.79]), and hepatic infections/cirrhosis (OR 1.89 [95% CI: 1.28–2.79]). DM was associated with a decreased risk for mortality (OR 0.49 [95% CI: 0.33–0.73]), (Table 3).

DISCUSSION

There have been few multi-centre investigations examining EE across all regions of the country [15–17]. Previous studies have involved other databases utilizing Medicare insurance billing data for all inpatients (not patients through the emergency department), such as the National Inpatient Sample, but have not evaluated risk factors for mortality or admission [17]. This analysis evaluates risk factors associated with admission and mortality for EE using a large national database evaluating patients presenting to the ED. While the subgroup of IVDU-associated EE has recently been identified as increasing in incidence, our analysis shows that EE at-large has increased regardless of the underlying source [12]. Additionally, multiple comorbidities each demonstrated varying associations with admission or mortality in the setting of EE. These data may be useful in identifying those at higher risk and guiding management early in their clinical presentation.

Incidence rates for EE has been increasing, and the rise in IVDU only explains a subset of this change [12]. We presume a component of this elevation can be attributed to the overall rise of sepsis by 8.7% over the past two decades [18]. Explanations for

growing sepsis rates include the increasing average age of the US population, thereby also increasing susceptibility to more comorbidities and predisposition to systemic infections [19, 20]. Additionally, there has been a greater use of antibiotics resulting in higher rates of antibiotic-resistant infections that also increases the rates of systemic infections [21]. Furthermore, with new advances in medicine, including immunotherapy, chemotherapy, and organ transplantation, there are increasing numbers of patients who are immunocompromised and more susceptible to systemic infections [22]. Finally, recent guidelines have increased surveillance for both sepsis and endophthalmitis, and not necessarily with improved outcomes [5, 6]. Hyperattentive screening paradigms could be contributing to the overdiagnosis of EE in those with non-specific retinal findings (e.g. Roth spots, cotton wool spots, haemorrhages) explained by underlying comorbidities, rather than infection from the bloodstream [6, 23].

The median inflation-adjusted cost of ED visits for EE increased over 11 years, although without statistical significance. A prior study by Friedman et al., evaluated mean inflation-adjusted charge for ED visits for all eye complaints using the NEDS database and found the cost was $1266 for emergent visits and $631 for nonemergent visits; these emergency visit expenses appear comparable to those in our study found with EE [24]. Although the study only compared visits from 2006 to 2011, an increase of $36/visit per year was identified, consistent with the non-significant increase in median cost we noted from 2006 to 2017 in our study [24]. A prior study evaluating EE in the setting of IVDU using the National Inpatient Sample, a large Medicare database, noted the median inflation-adjusted cost per

CONCLUSION

EE, regardless of underlying source, has recently increased in incidence throughout the US. Explanations for this increase include an aging population, advances in medical care increasing the numbers of immunocompromised individuals, and hyperattentive screening paradigms. The two systemic factors that conferred both an increase in mortality and admission were pneumonia, and renal/UTI. These factors predispose to infections with more virulent organisms and have been shown to act as independent markers for worse prognosis in patients with sepsis. Finally, DM was shown to be associated with decreased mortality, which has also been identified in other studies evaluating both sepsis and endophthalmitis. This association warrants further investigation to elucidate how glycaemic regulation affects immune function and has the potential to influence how glucose is managed in patients with sepsis during times of such high metabolic demand. In conclusion, EE will continue to present as an increasing diagnostic and therapeutic challenge; identification of patient demographics, prognostic factors and visit characteristics may serve to improve current management paradigms.

SUMMARY TABLE

What was known before

- Endogenous endophthalmitis (EE) comprises approximately 2–8% of all cases of endophthalmitis.
- The eye becomes a secondary site of inoculation with hematogenous spread of infection from elsewhere.

What this study adds

- EE has increased in incidence throughout US.
- The two systemic factors that conferred both an increase in mortality and admission were pneumonia, and renal/UTI.
- Additional exploration of the potential protective association of DM with decreased mortality in this context is needed.

DATA AVAILABILITY

The data that support the findings of this study are available from the Nationwide Emergency Department Sample (NEDS) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of NEDS.

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COMPETING INTERESTS
The authors declare no competing interests.

ADDITIONAL INFORMATION
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