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Trends in Drug Use–Associated Infective Endocarditis and Heart Valve Surgery, 2007 to 2017

A Study of Statewide Discharge Data

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Background: Drug use–associated infective endocarditis (DUA-IE) is increasing as a result of the opioid epidemic. Infective endocarditis may require valve surgery, but surgical treatment of DUA-IE has invoked controversy, and the extent of its use is unknown.

Objective: To examine hospitalization trends for DUA-IE, the proportion of hospitalizations with surgery, patient characteristics, length of stay, and charges.

Design: 10-year analysis of a statewide hospital discharge database.

Setting: North Carolina hospitals, 2007 to 2017.

Patients: All patients aged 18 years or older hospitalized for IE.

Measurements: Annual trends in all IE admissions and in IE hospitalizations with valve surgery, stratified by patients' drug use status. Characteristics of DUA-IE surgical hospitalizations, including patient demographic characteristics, length of stay, disposition, and charges.

Results: Of 22 825 IE hospitalizations, 2602 (11%) were for DUA-IE. Valve surgery was performed in 1655 IE hospitalizations (7%), including 285 (17%) for DUA-IE. Annual DUA-IE hospitalizations increased from 0.92 to 10.95 and DUA-IE hospitalizations with surgery from 0.10 to 1.38 per 100 000 persons. In the final year, 42% of IE valve surgeries were performed in patients with DUA-IE. Compared with other surgical patients with IE, those with DUA-IE were younger (median age, 33 vs. 56 years), were more commonly female (47% vs. 33%) and white (89% vs. 63%), and were primarily insured by Medicaid (38%) or uninsured (35%). Hospital stays for DUA-IE were longer (median, 27 vs. 17 days), with higher median charges ($250 994 vs. $198 764). Charges for 282 DUA-IE hospitalizations exceeded $78 million.

Limitation: Reliance on administrative data and billing codes.

Conclusion: DUA-IE hospitalizations and valve surgeries increased more than 12-fold, and nearly half of all IE valve surgeries were performed in patients with DUA-IE. The swell of patients with DUA-IE is reshaping the scope, type, and financing of health care resources needed to effectively treat IE.

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Infective endocarditis (IE), an infection of 1 or more heart valves, is a severe complication of injection drug use that may occur through inoculation of bacteria or fungi into the blood or by hematogenous spread from localized infections. Concurrent with the growing number of overdose deaths and rising injection drug use, drug use–associated IE (DUA-IE) has increased markedly in the United States since 2000 (1–4).

The rising incidence of DUA-IE aligns with the rapid growth of the opioid epidemic. During 2000 to 2013, Wurcel and colleagues (1) estimated a greater than 2-fold increase in DUA-IE hospital admissions nationwide, a trend generally seen in other national studies from recent years (2, 5, 6). However, a report from North Carolina for 2010 to 2015 described a 12-fold increase in hospitalizations for DUA-IE, with the sharpest escalation beginning in 2013 (7).

The standard of care for IE is a prolonged course of intravenous antibiotics, often accompanied by surgical valve replacement. However, the use of valve surgery for DUA-IE has invoked controversy because of concern regarding postoperative injection drug use and the associated risk for prosthetic valve infection. Despite the lengthy and expensive course of DUA-IE treatment, drug use disorders and harm reduction often go unaddressed during hospitalization, and the nationwide outpatient infrastructure for treating drug use disorders is often inadequate (8, 9). As a result, clinicians have debated the practical and ethical considerations of valve surgery for DUA-IE (10–13). No large-scale research has been done recently to examine the rate of valve surgery for DUA-IE or to characterize surgical patients with DUA-IE and their hospital stays.

To quantify the impact of rising injection drug use on the application of valve surgery for IE treatment, we examined the case of North Carolina. As of 2016, the state was still seeing an upsurge in overdose deaths, which are increasingly driven by heroin and synthetic narcotics and are disproportionately distributed in certain regions of the state (14, 15). Although our study focuses on 1 state, findings in North Carolina may reflect nationwide trends. Past-year misuse of pain relievers or heroin (16) and the overdose death rate in the state align closely with U.S. averages (17). The health care and political landscape of North Carolina harbors many complexities that have shaped the opioid epidemic, including suboptimal but growing access to opioid treatment and syringe programs as well as a

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Editorial comment 1

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large uninsured population in the wake of Medicaid nonexpansion (14, 18–20).

In this study, we used statewide data to examine the annual trends, characteristics, and charges related to DUA-IE hospitalizations with valve surgery, and we updated overall DUA-IE hospitalization trends through mid-2017. Our findings may frame national discussions about the medical consequences of drug use disorders, contemporary management of IE, and long-term care after valve replacement in young persons.

METHODS

Study Design and Data

We conducted a retrospective study using the North Carolina Hospital Discharge Database, which includes demographic, diagnostic, procedural, and billing data from all short-term, nonfederal, acute care hospitals in the state, covering roughly 1 million hospitalizations yearly. The units of analysis were individual hospitalizations, not unique persons, because personal identifiers were not available for the entire study period.

The study population consisted of all North Carolina residents hospitalized for IE from 1 July 2007 to 30 June 2017 who were aged 18 years or older at the time of admission.

Operationalization of IE, DUA-IE, and Valve Surgery

Hospitalizations for IE were defined by diagnosis codes from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), and 10th Revision, Clinical Modification (ICD-10-CM). Cases due to rare pathogens (such as *Histoplasma* species) were excluded.

Among IE cases, DUA-IE was identified by a diagnosis code indicating recreational drug use, withdrawal, dependence, or poisoning, excluding codes for marijuana or unspecified drug use. Persons born after 1965 with a diagnosis of hepatitis C virus (HCV) infection also were coded for DUA-IE, given the high propensity for HCV to be transmitted through recreational injection and the common method of using HCV infection as a criterion in identifying DUA-IE (1, 21). All IE hospitalizations not meeting these criteria were classified as non–DUA-IE. Drugs were classified as opioids (including opiates), cocaine, amphetamines, or other drugs (benzodiazepines, hallucinogens, or unspecified drugs). For all hospitalizations, we used ICD procedure codes to determine whether valve surgery was performed.

We generated the list of diagnosis and procedure codes used to operationalize IE, DUA-IE, and valve surgery by reviewing published literature and directly examining ICD-9-CM and ICD-10-CM code lists. We used the General Equivalence Mappings from the Centers for Medicare & Medicaid Services, mapping forward from ICD-9-CM to ICD-10-CM codes (22–24). This strategy ensured that we identified all ICD-10-CM codes that correspond ("map") to included ICD-9-CM codes. We assessed the appropriateness of including each code (**Supplement Tables 1** to **3**, available at Annals.org).

Data Analysis

For all IE hospitalizations and for those with surgery, we examined annual trends in the aggregate and stratified by drug use. Yearly rates were calculated for the number of IE hospitalizations per 100 000 North Carolina residents aged 18 years or older by using state population data obtained from the U.S. Census Bureau.

We described the distribution of demographic characteristics (age, race/ethnicity, and sex), insurance payer, valves targeted for surgery, length of stay, disposition location, and hospital charges. Distributions among DUA-IE and non–DUA-IE groups were compared by using Wilcoxon rank-sum tests for continuous variables and χ^2 tests for categorical variables, with statistical significance defined as a P value less than 0.010.

To evaluate the influence of our assumption that HCV-infected patients born after 1965 acquired IE through injection drug use despite having no specific drug-related diagnosis, we conducted a sensitivity analysis restricting our DUA-IE definition to include only hospitalizations with a diagnosis code specific to drug use.

Analyses were performed with SAS, version 9.4 (SAS Institute). The study was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill.

Role of the Funding Source

No agency funding this work had any role in design, data collection, analysis, interpretation, authorship, review, or the decision to submit the findings for publication.

RESULTS

Annual Trends of All IE Hospitalizations and IE Hospitalizations With Valve Surgery

During the 10-year period, 22 825 IE hospitalizations occurred in North Carolina. Of these, 2602 (11%) were for DUA-IE and 20 223 (89%) for non–DUA-IE (**Table 1**). Valve surgery was performed in 1655 (7%) of all IE hospitalizations. Of hospitalizations with surgery, 285 (17%) were for DUA-IE and 1370 (83%) for non–DUA-IE (**Table 2**).

Annual admissions for IE increased during the study period, from 1936 to 2992, corresponding to 27.74 per 100 000 North Carolina residents in the first year and 37.80 per 100 000 in the final year (**Figure 1**). Annual hospitalizations for DUA-IE rose from 64 (0.92 per 100 000) in 2007 to 2008 to 867 (10.95 per 100 000) in 2016 to 2017, an increase of approximately 12-fold. The number of admissions for non–DUA-IE was generally stable across the period (26.84 per 100 000 in the final year), although an upsurge was observed in 2015 to 2016.

Annual hospitalizations with valve surgery for all IE cases increased from 1.62 per 100 000 residents in 2007 to 2008 to 3.26 per 100 000 in 2016 to 2017 (**Figure 2**). With regard to DUA-IE hospitalizations with surgery, fewer than 10 occurred per year until mid-2013 (representing 0.01 to 0.10 per 100 000). Annual hospitalizations then rose to 109 (1.38 per 100 000) by 2016 to 2017, an overall increase of 13-fold. Non–DUA-IE hospitalizations with surgery increased from 106 (1.52

per 100 000) in the first year to 149 (1.88 per 100 000) in the last year. In the final year, DUA-IE accounted for 42% of all IE hospitalizations in which surgery was performed (109 of 258 hospitalizations) (Supplement Tables 4 and 5, available at Annals.org).

Hospitalizations for DUA-IE increased across the study period for all drug categories, with opioids the most commonly implicated drugs in the last study year for hospitalizations overall (6.71 per 100 000) and for those with surgery (0.80 per 100 000).

Characteristics of All Hospitalizations, by Drug Use Status

Persons hospitalized for DUA-IE were younger than those with non–DUA-IE (median age, 35 years [interquartile range {IQR}, 28 to 45 years] vs. 67 years [IQR, 54 to 79 years]). Female sex was slightly more common among patients with DUA-IE than those with non–DUA-IE (51% vs. 48% female). Race/ethnicity differed by drug use status: 81% of patients with DUA-IE were non-Hispanic white and 10% were non-Hispanic black, whereas 61% of those with non–DUA-IE were non-Hispanic white and 22% were non-Hispanic black. Most patients with DUA-IE were covered by Medicaid (35%) or were self-paying or uninsured (34%), whereas those with non–DUA-IE were more frequently covered by Medicare (67%) or private insurance (16%). The most common drugs observed were opioids, which appeared in 1626 DUA-IE cases (62%) (Table 1).

Characteristics of All Hospitalizations With Valve Surgery, by Drug Use Status

Among IE hospitalizations with valve surgery, the patients with DUA-IE were younger than those with non−DUA-IE (median age, 33 years [IQR, 27 to 42 years]) vs. 56 years [IQR, 44 to 66 years]). Persons with DUA-IE were more likely than those with non–DUA-IE to be female (47% vs. 33%). Of the patients with DUA-IE, 89% were non-Hispanic white and 6% were non-Hispanic black, compared with 63% and 22%, respectively, among those with non–DUA-IE (Table 2).

The distribution of payers between DUA-IE and non–DUA-IE cases differed notably. Hospitalizations for DUA-IE with surgery were predominantly covered by Medicaid (38%) or the patient self-paid or was uninsured (35%), whereas non–DUA-IE hospitalizations with surgery were more commonly paid for by Medicare (42%) or private insurance (31%).

For the 285 hospitalizations with surgery for DUA-IE, opioids were the most commonly identified drug, reported in 176 cases (62%) (Table 2). Fifty-two of the cases (18%) were coded for DUA-IE because the patients had HCV infection without a drug use diagnosis. Overall, 171 (60%) of the patients with DUA-IE had HCV infection.

Target of Valve Surgery

The most common surgical target was the aortic valve (55%), followed by the mitral (47%) and tricuspid (16%) valves. Unlike the aortic and mitral valves, the tricuspid was involved much more often in surgery for DUA-IE than for non–DUA-IE (39% vs. 11%). The pulmo-

Table 1. Characteristics of Hospitalizations for IE in North Carolina, by Drug Use Status: 2007 to 2017*

Characteristic	Total (*n* = 22 825 [100%])	DUA-IE (*n* = 2602 [11%])	Non–DUA-IE (*n* = 20 223 [89%])
Median age (IQR), *y*	65 (49–77)	35 (28–45)	67 (54–79)
Sex			
Male	11 765 (52)	1281 (49)	10 484 (52)
Female	11 060 (48)	1321 (51)	9739 (48)
Race/ethnicity			
Non-Hispanic black	4638 (20)	269 (10)	4369 (22)
Non-Hispanic white	14 411 (63)	2108 (81)	12 303 (61)
Hispanic	743 (3)	32 (1)	711 (4)
Other/unknown	3033 (13)	193 (7)	2840 (14)
Insurance payer			
Private	3648 (16)	317 (12)	3331 (16)
Medicare	14 077 (62)	444 (17)	13 633 (67)
Medicaid	2629 (12)	903 (35)	1726 (9)
Self-pay/uninsured	1880 (8)	873 (34)	1007 (5)
Other/unknown	591 (3)	65 (3)	526 (3)
Drug use–related diagnosis†			
Opioids	–	1626 (62)	–
Cocaine	–	545 (21)	–
Amphetamines	–	294 (11)	–
Benzodiazepines, hallucinogens, or other	–	486 (19)	–
HCV infection and born after 1965	–	1206 (46)	–

DUA-IE = drug use–associated infective endocarditis; HCV = hepatitis C virus; IE = infective endocarditis; IQR = interquartile range; non–DUA-IE = infective endocarditis not associated with drug use.
* Values are numbers (percentages) unless otherwise indicated. Percentages may not sum to 100 due to rounding.
† Each drug was assessed independently, because hospitalizations may have been coded for >1 drug.

Table 2. Characteristics of Hospitalizations for IE Treated With Valve Surgery in North Carolina, by Drug Use Status: 2007 to 2017*

Characteristic	Total (*n* = 1655 [100%])	DUA-IE (*n* = 285 [17%])	Non-DUA-IE (*n* = 1370 [83%])
Median age (IQR), *y*	52 (39–64)	33 (27–42)	56 (44–66)
Sex			
Male	1070 (65)	151 (53)	919 (67)
Female	585 (35)	134 (47)	451 (33)
Race/ethnicity			
Non-Hispanic black	317 (19)	16 (6)	301 (22)
Non-Hispanic white	1124 (68)	255 (89)	869 (63)
Hispanic	30 (2)	0	30 (2)
Other/unknown	184 (11)	14 (5)	170 (12)
Insurance payer			
Private	466 (28)	40 (14)	426 (31)
Medicare	605 (37)	32 (11)	573 (42)
Medicaid	285 (17)	109 (38)	176 (13)
Self-pay/uninsured	242 (15)	99 (35)	143 (10)
Other/unknown	57 (3)	5 (2)	52 (4)
Drug use–related diagnosis†			
Opioids	–	176 (62)	–
Cocaine	–	55 (19)	–
Amphetamines	–	24 (8)	–
Benzodiazepines, hallucinogens, or other	–	48 (17)	–
HCV infection and born after 1965	–	159 (56)	–
Target of valve surgery‡			
Aortic	910 (55)	126 (44)	784 (57)
Mitral	786 (47)	103 (36)	683 (50)
Pulmonic	22 (1)	4 (1)	18 (1)
Tricuspid	260 (16)	110 (39)	150 (11)
Multiple valves	328 (20)	56 (20)	272 (20)

DUA-IE = drug use–associated infective endocarditis; HCV = hepatitis C virus; IE = infective endocarditis; IQR = interquartile range; non–DUA-IE = infective endocarditis not associated with drug use.
* Values are numbers (percentages) unless otherwise indicated. Percentages may not sum to 100 due to rounding.
† Each drug was assessed independently, because hospitalizations may have been coded for >1 drug.
‡ Valves were assessed independently, because patients may have had surgery on >1 valve.

nary valve was involved in 1% of surgeries. For 328 hospitalizations (20%), more than 1 valve was targeted for surgery (Table 2).

Length of Stay and Disposition

For all hospitalizations, stays were longer for DUA-IE than non–DUA-IE cases (median, 11 days [IQR, 5 to 26 days] vs. 7 days [IQR, 4 to 13 days]; $P < 0.001$). Fewer DUA-IE than non–DUA-IE hospitalizations resulted in discharge home (43% vs 49%), and inpatient mortality or hospice discharge rates were lower among patients with DUA-IE (8% vs. 14%). Discharge against medical advice (DAMA) occurred in 13% of DUA-IE hospitalizations, compared with 1% in non–DUA-IE cases (Table 3).

For hospitalizations with surgery, the median length of stay was significantly greater in DUA-IE versus non–DUA-IE cases (27 days [IQR, 17 to 44 days] vs. 17 days [IQR, 11 to 26 days]; $P < 0.001$). Distributions of discharge disposition differed significantly by drug use status. Compared with patients with non–DUA-IE, a smaller proportion of those with DUA-IE were discharged home (51% vs. 59%) and a greater proportion were transferred to another facility (38% vs. 31%) (Table 3).

Hospital Charges

Median hospital charges were higher for DUA-IE than non–DUA-IE cases ($60 333 vs. $34 968; $P < 0.001$). For surgical hospitalizations, total charges were greater overall and remained higher for DUA-IE than non–DUA-IE cases (median, $250 994 vs. $198 764; $P < 0.001$). Overall charges for 282 DUA-IE hospitalizations with surgery during the 10 years totaled $78 781 627. Charges for 1361 non–DUA-IE hospitalizations with surgery amounted to $333 536 647 (Table 3).

Sensitivity Analysis for Definition of Drug Use

Restricting the DUA-IE definition to cases involving a drug use diagnosis yielded 2240 hospitalizations (10%) for DUA-IE and 20 585 (90%) for non–DUA-IE. Of hospitalizations with surgery, 233 (14%) were for DUA-IE and 1422 (86%) for non–DUA-IE. Trends and the characteristics of all IE hospitalizations and IE hospitalizations with surgery were similar to those in the main analysis, with total charges of $65 493 939 for the 233 DUA-IE hospitalizations with surgery.

DISCUSSION

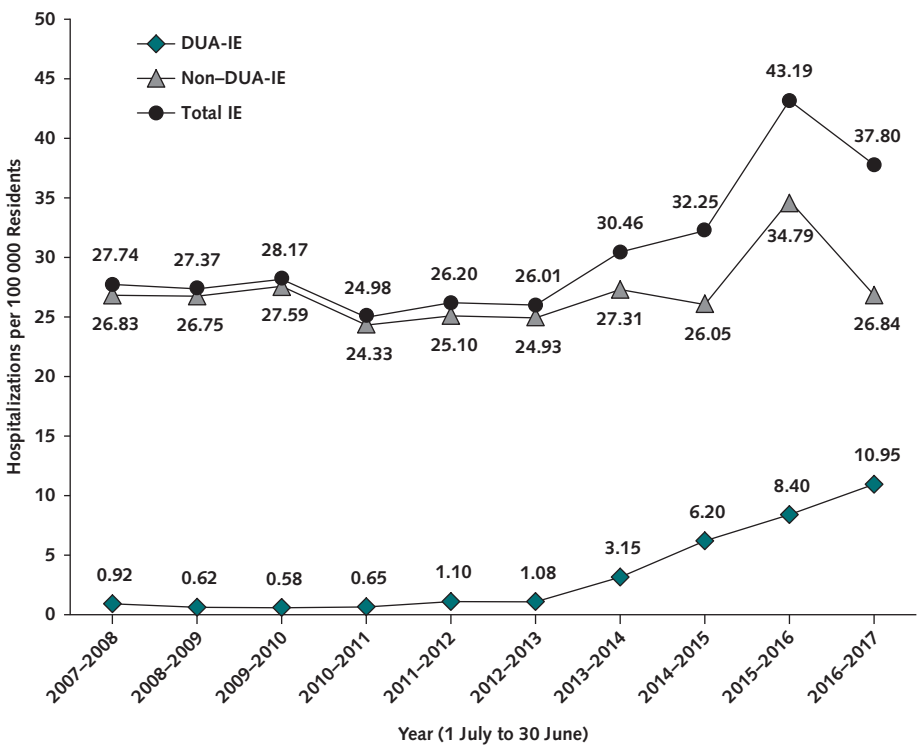
In this large statewide study, we observed a marked increase in overall hospitalizations and valve surgeries among patients with DUA-IE. The rate of DUA-IE hospitalizations with valve surgery rose 13-fold in North Carolina from 2007 to 2017. In the final study year, DUA-IE was associated with 42% of all IE surgeries, indicating a dramatic shift in the demographic and clinical profile of patients undergoing IE surgery.

Our findings are generally consistent with trends reported in earlier studies of hospitalizations and surgeries for IE due to drug use (1, 2, 7, 25). However, in the context of quickly evolving drug epidemics, prior studies did not fully capture the magnitude of the rise in DUA-IE, which increased notably in 2013 to 2014. Our study, which extends through mid-2017, illustrates that the sharply upward trend previously observed in North Carolina is continuing (7). In addition, the observed trend, which is largely attributable to opioids, aligns with the growing number of deaths from heroin and synthetic narcotic use in North Carolina, which began an acute upward trajectory in 2014 (26).

The young age of patients admitted for DUA-IE surgery raises concerns about their need for subsequent operations, which may be indicated for either recurrent IE or normal valve deterioration. Recent estimates of recurrent endocarditis after surgery for DUA-IE are based on small studies and vary from a low of 13% at a mean of 32 months (27) to a high of 52% at a median of 18 months postoperatively (28). To mitigate the risk for reinfection from injection drug use, the underlying drug use disorder must be addressed as a root cause of IE. In our study, nearly two thirds (62%) of DUA-IE hospitalizations involved opioid use. Although effective pharmacotherapies exist for opioid use disorder, in the absence of treatment, many patients undergo detoxification during their IE hospitalization. Detoxification without pharmacotherapy for opioid use disorder is ineffective, with estimated relapse rates ranging from 60% to 81% within a year or less, suggesting that those who do not receive treatment for opioid use disorder are likely to start using opioids again after discharge, putting them at risk for reinfection if they inject drugs (29–31). Drug use disorders other than opioid use disorder pose additional treatment challenges, because therapeutic options are more limited. Inpatient addiction medicine consultation is a promising tool to address the multifaceted needs of patients with drug use disorders, potentially reducing further infections and overdose by offering patients pharmacotherapy for opioid use disorder and linking them to postdischarge care (32, 33).

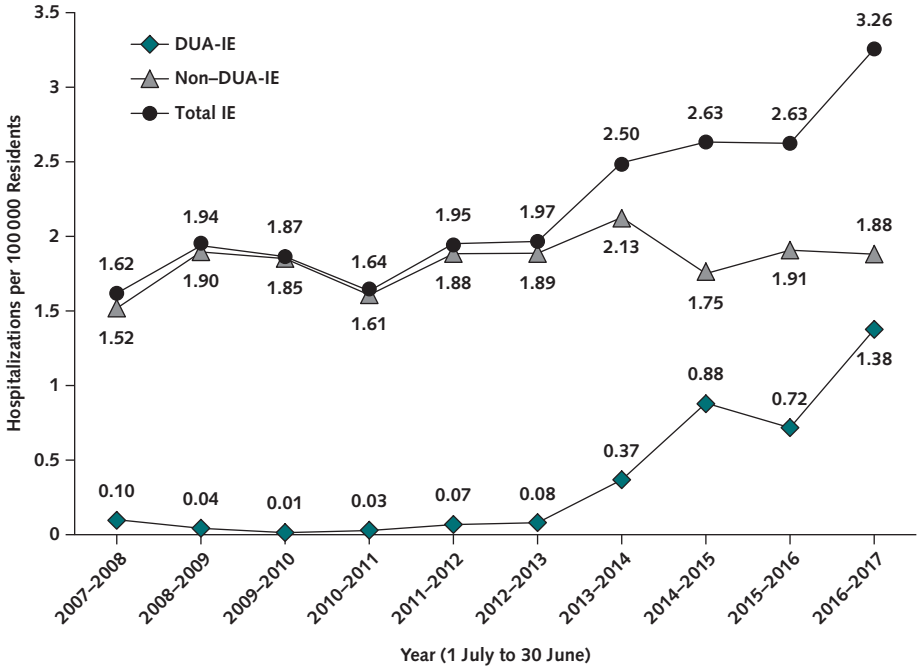
Discharge against medical advice, which occurred in 13% of DUA-IE hospitalizations overall, is a danger-

Figure 1. Rates of hospitalization for IE in North Carolina, by drug use status: 2007 to 2017.



Rates are hospitalizations per 100 000 North Carolina residents aged 18 y or older. North Carolina population is based on U.S. Census Bureau estimates of residents aged 18 y or older on 1 July. Because annual estimates in this study incorporated 2 calendar years (1 July to 30 June), the average of the 2 y was used as the population denominator. DUA-IE = drug use–associated infective endocarditis; IE = infective endocarditis; non-DUA-IE = infective endocarditis not associated with drug use.

Figure 2. Rates of hospitalization for IE in North Carolina treated with valve surgery, by drug use status: 2007 to 2017.



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ous outcome that puts patients at risk for an inadequately treated, potentially life-threatening infection and is linked to increased mortality and readmissions (34). In addition, DAMA may represent a symptom of the absence or inadequacy of addiction care. Substance and alcohol use disorders are among the conditions most strongly associated with DAMA (34, 35), and untreated drug withdrawal may be a contributing factor (36). Opioid use disorder has been associated with increased odds of DAMA from detoxification admission (37). One study of persons who inject drugs reported that receipt of methadone was associated with reduced odds of DAMA (38), which suggests that for opioid-tolerant patients, opioid substitution may be beneficial in curtailing DAMA. Another study found that among persons who used illicit drugs, unemployment and incarceration were predictors of DAMA (39). Although the reasons for this association are not totally clear, the finding highlights the importance of multidisciplinary efforts in addressing the needs of medical inpatients with drug use disorders.

Beyond the risk for reinfection, structural degeneration of prosthetic valves over time is a common indication for further valve surgery (40). The 15-year reoperation risk due to prosthetic valve degeneration (regardless of indication) is 30% for a person aged 40 years and 50% for a person aged 20 years (41). Among the patients who had surgery for DUA-IE, 186 (65%) were younger than 40 years. Without advances in prosthetic valve longevity, many of these young adults who remain free of reinfection will probably require additional valve replacements. The anticipated need for future surgeries, whether for reinfection or structural degeneration, and long-term cardiac follow-up care is substantial and must be considered in assessing the total downstream costs of DUA-IE.

Persons who inject drugs are frequently not considered candidates for outpatient parenteral antibiotic therapy (OPAT) because of the perception that they might tamper with an intravenous catheter in an unsupervised setting. Therefore, the longer hospital stays for DUA-IE probably stem from the need for prolonged antibiotic therapy (typically 6 weeks) on an inpatient basis (42, 43). Recent injection drug use is not an absolute contraindication to OPAT. Emerging case series have reported favorable outcomes of OPAT for select patients with a history of injection drug use (44–46), and 1 report found that home OPAT was at least as safe as receiving antibiotics in a rehabilitation facility (47). Expanding OPAT eligibility among selected candidates may help offset long hospital stays for drug use–associated infections. Pathophysiology may also explain, in part, the long stays for patients with DUA-IE. Unlike non–DUA-IE, the organism most commonly responsible for DUA-IE is *Staphylococcus aureus*, which is highly virulent and may result in severe and complicated presentations (25, 48, 49).

The surge in DUA-IE cases is driving an overall increase in IE that also affects hospitals and insurance payers. The observed length of stay for patients with DUA-IE, particularly those requiring surgery (median, 27 days), was more than 3 weeks greater than the 4- to 5-day national average for all hospitalizations (50).

Given the high proportion of Medicaid and uninsured patients, care for DUA-IE poses a large financial burden on state and federal budgets, which jointly finance Medicaid, as well as on individual hospitals, which rely in part on Medicaid Disproportionate Share Hospital payments to offset the costs of uninsured patients (51). Our study did not include any admissions that occurred immediately before or after the hospitalization with surgery, underestimating the total charges in treating IE for the one third of patients who were transferred from one institution to another. Given the considerable charges for IE hospitalizations with surgery (median, $250 994) and the costs of downstream care of a prosthetic valve, the expense of caring for patients with DUA-IE almost certainly exceeds that of comprehensive outpatient treatment programs with pharmacotherapy for opioid use disorder (estimated at $5980 to $14 112 per year) (52). A rational public health approach would prioritize funding of inpatient and outpatient drug use disorder treatment, harm reduction, and other activities to prevent IE.

In our study, the proportion of IE hospitalizations resulting in surgery was small (7%) and noticeably below estimates of IE surgery published for other populations (31% to 57%) (53, 54). Our method of examining hospitalizations by using ICD codes is similar to that used in the recent studies describing the increase in DUA-IE (1, 2, 7). We postulate that examining hospital discharge records with IE diagnoses alone, as was done in our analysis and in many previous studies of DUA-IE, is overly sensitive and may capture patients in several hospitalizations across transfers in care for a single IE episode. Adding cardiac surgery procedure codes to IE diagnostic codes, as in our study, may improve detection of incident endocarditis episodes, minimize inclusion of several hospitalizations per episode, and yield more conservative estimates of the number of unique patients with IE.

Our study used a statewide discharge database. Nearly all states maintain such databases, which may be a resource for public health practitioners examining DUA-IE locally (55). Each state faces unique challenges in addressing medical complications of drug use, owing to regional variations in drug use practices, the infrastructure for drug use disorder treatment, and the political climate. Studies examining other states and regions may build a more nuanced picture of DUA-IE that looks beyond large-scale national trends.

This study had several limitations. First, it used administrative data lacking granular clinical information and may have been subject to inaccurate coding of drug use or other diagnoses. For that reason, we could not validate IE or drug use diagnoses with other clinical indicators or assess surgical indications. Second, increasing awareness of both HCV and opioid misuse may have enhanced their documentation during the later study years. Third, our use of HCV infection as an indicator of drug use may have artificially increased the number of DUA-IE cases detected, as its inclusion alone accounted for 18% of cases. However, even excluding that population, the increase in DUA-IE hospitalizations remains striking. Fourth, although we were concerned that the 2015 switch from ICD-9-CM to ICD-10-CM might introduce errors into our trend estimates, the relatively steady number of surgeries for non–DUA-IE during the study period suggests that this issue was probably negligible for hospitalizations with surgery. Fifth, certain hospitals, such as Veterans Affairs and military hospitals, are not included in our database, leading to an underestimate of IE prevalence in North Carolina. Young veterans have higher rates of pain reliever misuse and thus may be at greater risk for DUA-IE than the general population (56). Last, our study examined hospitalization events and therefore could not assess the number of unique persons affected.

In summary, rates of overall hospitalizations, as well as hospitalizations with surgery, for DUA-IE increased markedly from 2007 to 2017, and alarmingly, valve replacements for DUA-IE are approaching half of all IE surgeries in North Carolina. Drug use–associated IE is a

Table 3. Length of Stay, Disposition, and Charges for Hospitalizations for IE in North Carolina, by Drug Use Status: 2007 to 2017*

Variable	All Hospitalizations				Hospitalizations With Valve Surgery			
	Total	DUA-IE	Non–DUA-IE	*P* Value†	Total	DUA-IE	Non–DUA-IE	*P* Value†
Median length of stay (IQR), *d*	7 (4–14)	11 (5–26)	7 (4–13)	<0.001	18 (12–29)	27 (17–44)	17 (11–26)	<0.001
Disposition, *n (%)*								
Home	10 983 (48)	1108 (43)	9875 (49)	<0.001	953 (58)	144 (51)	809 (59)	<0.001
Nursing facility, long-term acute care hospital, inpatient rehabilitation, or transfer to another hospital	7748 (34)	861 (33)	6887 (34)		528 (32)	108 (38)	420 (31)	
Discharge against medical advice	502 (2)	333 (13)	169 (1)		11 (1)	8 (3)	3 (<1)	
Died while an inpatient or in hospice	2996 (13)	221 (8)	2775 (14)		133 (8)	17 (6)	116 (8)	
Other/unknown	596 (3)	79 (3)	517 (3)		30 (2)	8 (3)	22 (2)	
Median hospital charges, $‡	36 946	60 333	34 968	<0.001	208 361	250 994	198 764	<0.001
Total charges, $‡	1 667 725 169	266 419 261	1 401 305 908		412 318 275	78 781 627	333 536 647	

DUA-IE = drug use–associated infective endocarditis; IE = infective endocarditis; IQR = interquartile range; non–DUA-IE = infective endocarditis not associated with drug use.
* Percentages may not sum to 100 due to rounding.
† χ^2 tests were performed for categorical variables. Wilcoxon rank-sum tests were used to compare continuous variables.
‡ 32 hospitalizations overall (4 for DUA-IE and 28 for non-DUA-IE), including 12 with valve surgery (3 for DUA-IE and 9 for non-DUA-IE), had incomplete charge data and were excluded from charge analyses.

critical, emerging public health issue that is affecting the lives of young persons, burdening health systems and public insurance payers, and fundamentally reshaping the epidemiology and management of endocarditis. Enhancing the multidisciplinary infrastructure to address treatment and prevention of DUA-IE, including better access to addiction care in the inpatient and outpatient settings, should be an urgent priority (37, 57). Further studies are needed to characterize long-term outcomes for patients with DUA-IE after discharge, including reinfection, reoperation, and mortality, and to understand the role of addiction treatment, harm reduction, and other interventions in improving DUA-IE outcomes.

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