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MAJOR ARTICLE

Streptococcus pyogenes Infective Endocarditis—Association With Injection Drug Use: Case Series and Review of the Literature

Melanie T. Rebechi,[1] Emily L. Heil,[2] Paul M. Luethy,[3] and Sarah A. Schmalzle[1,4]

[1]University of Maryland School of Medicine, Baltimore, Maryland, USA, [2]Department of Pharmacy Practice and Science, University of Maryland School of Pharmacy, Baltimore, Maryland, USA, [3]Department of Pathology, University of Maryland School of Medicine, Baltimore, Maryland, USA, and [4]Institute of Human Virology, University of Maryland School of Medicine, Baltimore, Maryland, USA

Background. *Streptococcus pyogenes*, or Group A *Streptococcus* (GAS), is not considered a typical cause of infective endocarditis (IE), but has anecdotally been observed in unexpectedly high rates in people who inject drugs (PWID) at our institution.

Methods. All cases of possible or definite GAS IE per Modified Duke Criteria in adults at an academic hospital between 11/15/2015 and 11/15/2020 were identified. Medical records were reviewed for demographics, comorbidities, treatment, and outcomes related to GAS IE. The literature on cases of GAS IE was reviewed.

Results. Eighteen cases of probable (11) or definite (7) GAS IE were identified; the mean age was 38 years, and the population was predominantly female (56%) and Caucasian (67%), which is inconsistent with local population demographics. Sixteen cases were in people who inject drugs (PWID; 89%); 14 were also homeless, 6 also had HIV (33%), and 2 were also pregnant. Antibiotic regimens were variable due to polymicrobial bacteremia (39%). One patient underwent surgical valve replacement. Four patients (22%) died due to complications of infection. The literature review revealed 42 adult cases of GAS IE, only 17 of which were in PWID (24%).

Conclusions. The 16 cases of possible and definite GAS IE in PWID over a 5-year period in a single institution reported nearly doubles the number of cases in PWID from all previous reports. This suggests a potential increase in GAS IE particularly in PWID and PWH, which warrants further epidemiologic investigation.

Keywords. Group A *Streptococcus*; infective endocarditis; injection drug use; people who inject drugs; *Streptococcus pyogenes*.

Streptococcus pyogenes, or Group A *Streptococcus* (GAS), causes a range of human disease from the more common pharyngitis, cellulitis, and impetigo to rare invasive disease, including necrotizing fasciitis, toxic shock syndrome, pneumonia, bacteremia, meningitis, and endocarditis [1]. While GAS is not typically perceived to be a common cause of infective endocarditis (IE) [2, 3], it has anecdotally been observed in unexpectedly high rates in people who inject drugs (PWID) at our institution. We sought to quantify GAS IE in adult inpatients at our institution, evaluate for risk factors, and compare to the historical literature on GAS IE.

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Correspondence: Sarah A Schmalzle, MD, FIDSA, Institute of Human Virology, University of Maryland School of Medicine, 725 W Lombard Street, N147, Baltimore, MD 21201 (sschmalzle@ihv.umaryland.edu).

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METHODS

Study Design and Data Collection

This was a retrospective review of all cases of GAS bacteremia in adult inpatients at the University of Maryland Medical Center between 11/15/2015 and 11/15/2020. The start date coincided with use of the current electronic medical record system. University of Maryland Medical Center is a 757-bed academic medical center located in Baltimore, Maryland. Medical records of adults with GAS bacteremia were reviewed to identify possible or definite GAS IE cases; records of patients with possible or definite GAS IE by Modified Duke Criteria were reviewed for demographics, comorbidities, treatment, and outcomes related to GAS IE. Data on whether infectious disease was consulted were recorded. This study was approved by the University of Maryland Baltimore Institutional Review Board.

Definitions

GAS was identified in blood cultures through a combination of Lancefield group latex agglutination testing and matrix-assisted laser desorption/ionization - time of flight mass spectrometry. Patients were categorized as having possible or definite IE according to Modified Duke Criteria, which do not include GAS bacteremia as a major criterion [4]. The presence of vascular

phenomena including septic pulmonary emboli/infarct were based on radiology reports. Trace valvular regurgitation was noted in the data set, but was not used as evidence of valvular regurgitation for Modified Duke Criteria. Valvular regurgitation noted as mild, moderate, or severe was counted toward Modified Duke Criteria. Echocardiogram results were compared with prior if available; otherwise, abnormal findings on echocardiogram at the time of infection were considered to be new. Injection drug use (IDU) was determined by patient-reported history. If available, infectious disease physician consult notes were used to identify the suspected source of infection. Hypotension was defined as systolic blood pressure <90 mmHg. Streptococcal toxic shock syndrome was defined according to 2010 case definition criteria [5]. Both transthoracic echocardiogram (TTE) and transesophageal (TEE) reports were reviewed. The start date used for duration of antibiotic therapy was the date of the first negative blood culture. Time to death was calculated from the date of first positive blood culture.

Data Analysis

Data were compiled and analyzed in Microsoft Excel.

Review of Literature

A review of the medical literature was performed using PubMed (US National Library of Medicine, Bethesda, MD, USA) and the terms "endocarditis" and either "Group A *Streptococcus*" or "*Streptococcus pyogenes*." Only cases of adult patients published from 1970 to 2020 in English were included. All publications were cross-referenced to eliminate redundant cases. References cited in the identified publications were also screened.

Cases were evaluated for the following variables: patient age and sex, presence and location of septic emboli, presence of comorbidities including abnormal heart valves, HIV, IDU, diabetes, and chronic kidney disease, antibiotic therapy (dose, frequency, and duration), surgical intervention, outcome of infection, and year and location of reported cases. Author report of IE diagnosis was used, as categorization of possible or definite IE by Duke Criteria or Modified Duke Criteria was not possible for cases reported before use of either set of criteria.

RESULTS

Blood Culture Data

There were 242 blood cultures with GAS at our institution in the study period, representing 158 episodes in 154 adult patients. Of the 154 adult patients with GAS bacteremia, 18 patients (12%) had probable or definite GAS IE.

Demographics

Of those with GAS IE, average age at diagnosis (range) was 38 (22–66) years, and the majority were female (56%). The predominant race was Caucasian (67%); the remainder were African American (Table 1).

Comorbidities

Seven patients had previously been diagnosed with infective endocarditis (39%), 1 of whom had a bioprosthetic valve. There were 6 people with HIV (PWH; 33%), and none were taking antiretroviral therapy. One patient had unknown HIV status. The average CD4 count for PWH (range) was 244 (12–675) cells/μL; half had a CD4 count <200 cells/μL. Two patients (11%) had chronic kidney disease, both of which were stage IV. Two of the 10 female patients were pregnant (20%) at the time of infection. Sixteen patients reported active IDU at the time of diagnosis (89%; 16 used heroin, 14 also used cocaine) (Table 1). No patients reported use of other stimulants, and urine toxicology for methamphetamine and phenylcyclidine was negative in all who were tested.

Bloodstream Infection and Echocardiogram Data

Fourteen patients had 2 out of 2 sets of initial blood cultures positive for GAS, 3 patients had 1 of 2 sets of initial blood cultures positive for GAS, and 1 patient had only 1 set of blood cultures drawn at admission. Cultures cleared rapidly, typically between 1 and 2 (range, 1–4) days after initial positive blood culture. Seven patients (39%) had polymicrobial bloodstream infections including methicillin-resistant *Staphylococcus aureus* (MRSA; 3), methicillin-sensitive *Staphylococcus aureus* (MSSA; 1), *Bacillus* sp. (1), *Escherichia coli, Staphylococcus hominis* and Group C *Streptococcus* (1), and MRSA and *Streptococcus agalactiae* (1). In 4 cases, GAS and the second bacteria were equal in number of positive blood culture bottles. In 1 case GAS was predominant (6 of 6 GAS, 1 of 6 *S. agalactiae*, 1 of 6 MRSA), in 1 case MRSA was predominant (5 of 6 MRSA, 2 of 6 GAS), and in the last case GAS and Group C *Streptococcus* were both predominant (6 of 6 bottles) and *S. hominis* and *E. coli* grew in 1 of 6 bottles each.

Infectious diseases was consulted by the primary medical team in all cases of probable or definite endocarditis. The most commonly identified suspected sources of infection were skin and soft tissue infections (6 patients) and direct inoculation by IDU (10 patients). Of the 2 patients who did not use intravenous drugs, 1 patient was thought to have bacteremia from an oral infection, and the other patient was thought to have a central line–associated bloodstream infection from a home infusion pump. Eleven patients (61%) had evidence of metastatic infection upon presentation, most commonly to the lungs (10 of 11) (Table 2).

All 18 patients were evaluated for endocarditis with TTE, and 9 patients (50%) were further evaluated with TEE. A vegetation was visualized on either TTE or TEE in half (Table 1). All 18 patients had some degree of regurgitation identified on echocardiogram, including patients without visualized vegetations. Most (61%) patients had trace regurgitation; 17% of patients had mild regurgitation, 11% moderate, and 11% severe. Only 5 patients had prior TTE or TEE for comparison; however, there were no

Table 1. Patient Characteristics and Echocardiogram Findings

Case	Age, y	Sex	Race	Comorbidities	IDU	Housing	Co-pathogens	Mod. Duke Criteria	TTE or TEE	Vegetation Site, Size, cm	Valve Dysfunction
1	22	M	AA	HIV, CKD, past IE	Cocaine, heroin	Homeless	None	Definite	TTE[a]	AV, 0.7 × 0.6	Mild AR
2	25	F	C	Pregnancy, past IE	Cocaine, heroin	Homeless	*Bacillus* sp.	Definite	TTE & TEE	AV, 1.1 × 0.6 PV, TV	Moderate AR, mild TR
3	26	F	C	Past IE	Cocaine, heroin	Homeless	None	Definite	TTE & TEE	TV	Trace TR
4	27	F	AA	None	Heroin	Homeless	MSSA	Possible	TTE & TEE[a]	MV	Trace MR
5	27	F	C	HIV	Cocaine, heroin	Homeless	MRSA	Possible	TTE[a]	NA	Trace TR
6	28	F	C	None	Cocaine, heroin	Housed	None	Definite	TTE[a]	MV	Severe MR, severe AR
7	32	M	C	HIV, CKD	Cocaine, heroin	Homeless	None	Possible	TTE[a]	NA	Trace TR, trace MR
8	33	M	C	HIV, past IE	Heroin	Homeless	None	Possible	TTE	PV, 0.7 × 0.7	Trace PR
9	35	F	C	Pregnancy	Cocaine, heroin	Homeless	*Escherichia coli*, *Staphylococcus hominis*, GCS	Possible	TTE & TEE[a]	NA	Mild MR
10	36	F	C	Past IE	Cocaine, heroin	Housed	None	Possible	TTE & TEE[a]	NA	Trace MR, trace TR
11	37	M	C	None	Cocaine, heroin	Homeless	MRSA	Possible	TTE[a]	NA	Trace MR
12	40	F	C	HIV, past IE	Cocaine, heroin	Homeless	MRSA	Possible	TTE & TEE	NA	Trace MR, trace TR
13	45	M	C	None	Cocaine, heroin	Homeless	None	Definite	TTE[a]	AV, 1.2 × 1.2	Moderate AR
14	49	M	AA	None	Cocaine, heroin	Homeless	None	Definite	TTE & TEE[a]	NA	Trace TR, trace MR
15	50	F	C	None	Cocaine, heroin	Homeless	GBS, MRSA	Definite	TTE[a]	NA	Trace TR
16	55	M	AA	HIV	Cocaine, heroin	Homeless	None	Possible	TTE & TEE[a]	NA	Mild TR
17	58	F	AA	Past IE	NA	Housed	None	Possible	TTE	TV, 0.5 × 0.5	Severe TR
18	66	M	AA	None	NA	Housed, hoarder	None	Possible	TTE & TEE[a]	AV, 0.5 × 0.5	Trace AR

Abbreviations: AA, African American; AR, aortic regurgitation; AV, aortic valve; C, Caucasian; CKD, chronic kidney disease; GBS, Group B *Streptococcus*; GCS, Group C *Streptococcus*; IDU, injection drug use; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; MV, mitral valve; MR, mitral regurgitation; NA, not applicable; PR, pulmonic regurgitation; PV, pulmonic valve; TEE, transesophogeal echocardiogram; TR, tricuspid regurgitation; TTE, transthoracic echocardiogram; TV, tricuspid valve.

[a]No prior TTE or TEE available. If TTE and TEE results were both available, TEE results are noted above.

cases where Modified Duke Criteria outcomes were affected by valvular regurgitation being new vs previously present. There were no abscesses identified on echocardiogram; however, there was concern for abscess in 2 patients due to new rhythm abnormalities including new junctional rhythm and new bundle branch block. The average left ventricular ejection fraction was 60%, with a range of 35%–70%.

Seven patients (39%) were classified as definite infective endocarditis according to Modified Duke Criteria. The remaining 11 patients (61%) were classified as possible infective endocarditis; of note, 6 of these had new cardiac murmurs (Table 1). IE was only confirmed pathologically in 1 patient who underwent cardiac surgery (patient #2) 85 days after initial positive culture. Surgical valve culture was negative. No autopsies were conducted in any of the deceased patients.

Treatment and Outcomes

Definitive antibiotic regimens were highly variable due to high incidence of polymicrobial infections (39%), preference for ease of administration in subacute rehabilitation facilities after discharge, and concern for allergic reactions. The most commonly selected antibiotics for GAS coverage were ceftriaxone (8), penicillin (5), and ampicillin or ampicillin-sulbactam (4). Four patients also initially received clindamycin for a range of 5–7 days to inhibit toxin production by GAS. Antibiotic therapy was planned for a duration of 4–6 weeks for most patients; however, only 11 patients completed the intended course. Four patients had systolic blood pressure <90 mmHg; 1 met criteria for streptococcal toxic shock syndrome. The most common reasons for incomplete therapy were patient discontinuation (4) and death (3) (Table 2).

Four patients were evaluated by cardiothoracic surgery for potential surgical intervention for IE. Two patients were not considered surgical candidates due to active IDU. Surgical intervention was planned for the other 2 patients; 1 died from ventricular tachycardia before surgery, and the other underwent surgical valve replacement with a bioprosthetic graft, which occurred 85 days after culture positivity. Surgery was delayed in this pregnant patient until fetal viability and delivery (Table 2).

Nine patients underwent additional procedures for the purpose of source control, including incision and drainage of abscesses (7), chest tube insertion (4), septic joint washout (1), and line removal (1) (Table 2).

Table 2. Treatment and Outcomes

Case	Planned Antibiotic Regimen, Dates Given	Actual Antibiotic Regimen, Dates Given	Source Control	ORT	Additional Comments on Patient Course	Cause of Death, Day
1	Penicillin G IV, 1–42	Unknown	None	Buprenorphine/naloxone	Source = cellulitis; LTFU	NA
2	Vancomycin IV, 1–7 Ceftriaxone IV, 1–28 Clindamycin IV, 1–7	Vancomycin IV 1–7 Ceftriaxone IV, 1–7 Clindamycin IV, 1–7 Penicillin G IV, 8–42	Chest tube, abscess drained, AVR	Methadone	Septic emboli to lungs	NA
3	Penicillin G IV, 1–42	Penicillin G IV, 1–7 Ceftriaxone IV, 8	None	Buprenorphine/naloxone	Antibiotic changed due to AIN; premature discharge	NA
4	Cefazolin IV, 1–42 Clindamycin IV, 1–5	Cefazolin IV, 1–42 Clindamycin IV, 1–5	None	Buprenorphine/naloxone	None	NA
5	Vancomycin IV, 1–42 Clindamycin IV, 1–7	Vancomycin IV, 1–70 Clindamycin IV, 1–7	Abscess drained	Methadone	Hypotension	NA
6	Not determined	Vancomycin IV, 1 Piperacillin/tazobactam IV, 1	None	NA	STSS; septic emboli to lungs, spleen, kidneys, and brain	Cardiogenic shock, 1
7	Ceftaroline IV, 1–42	Ceftaroline IV, 1–42	Chest tube, abscess drained	Methadone	Source = cellulitis; septic emboli to lungs	NA
8	Ceftriaxone IV, 1–14 Gentamycin IV, 1–14	Ceftriaxone IV, 1–5 Gentamycin IV, 1–5 Vancomycin IV, 27–51 Piperacillin/tazobactam IV, 27–51	Abscess drained	Methadone	Source = cellulitis; premature discharge, returned 21 d later	Unknown, 51
9	Ampicillin/sulbactam IV, 1–42	Ampicillin/sulbactam IV, 1–42	Chest tube, joint drained, abscess drained	Methadone	Septic emboli to lungs, joint, kidneys	NA
10	Penicillin G IV, 42	Penicillin G IV, 1–6 Vancomycin IV, 7–10 Piperacillin/tazobactam IV, 7–10 Ampicillin/sulbactam IV, 11–20 Ceftriaxone IV, 21–42	Chest tube	Methadone	Septic emboli to lungs	NA
11	Vancomycin IV, 1–42	Vancomycin IV, 1–42	Chest tube	Buprenorphine/naloxone	Hypotension; septic emboli to lungs; premature discharge	NA
12	Vancomycin IV, 1–42	Vancomycin IV, 1–28	None	Methadone	Septic emboli to lungs; premature discharge	NA
13	Penicillin G IV, 1–42	Penicillin G IV, 1–30	None	Methadone	Hypotension; septic emboli to lungs, spleen, and brain	VTach/cardiogenic shock, 30
14	Ceftriaxone IV, 1–42	Ceftriaxone IV, 1–42	None	Buprenorphine/naloxone	Septic emboli to lungs	NA
15	Vancomycin IV, 1–56 Ceftriaxone IV, 1–56 Rifampin IV, 1–56	Vancomycin IV, 1–56 Ceftriaxone IV, 1–56 Rifampin IV, 1–56	None	Buprenorphine/naloxone	Septic emboli to lungs, joint, spinal abscess, meningitis	NA
16	Ceftriaxone IV, 1–14 Vancomycin IV, 1–14 Cefazolin IV, 15–42	Ceftriaxone IV, 1–42 Vancomycin IV, 1–14	Abscess drained	Methadone	Septic emboli to lungs, spleen, gluteus	NA
17	Ampicillin IV, 1–14	Ampicillin IV, 1–14	Line removed	NA	Source = CLABSI	NA
18	Ceftriaxone IV, 1–5 Clindamycin IV, 1–5 Penicillin G IV, 6–28	Ceftriaxone IV, 1–5 Clindamycin IV, 1–5 Penicillin G IV, 6–28	None	NA	Source = oral mucosal defect	Vtach/cardiogenic shock, 306

Abbreviations: AIN, acute interstitial nephritis; AVR, aortic valve replacement; BSI, bloodstream infection; CLABSI, central-line associated bloodstream infection; IV, intravenous; LTFU, lost to follow-up; NA, not applicable; ORT, opioid replacement therapy; STSS, streptococcal toxic shock syndrome; VTach, ventricular tachycardia.

Of the 16 patients with IE associated with patient-reported IDU, 15 were seen by the substance abuse consult team during their admission. The patient who was not seen had died 1 day after presentation. Six patients (40%) were treated with buprenorphine/naloxone and 9 (60%) with methadone (Table 2).

Four cases included discharges against medical advice, and 1 was lost to follow-up after planned discharge. Four patients (22%) died within 1 year. One died of an unknown cause 4 days after leaving the hospital against medical advice (51 days after initial blood culture). Three patients died from ventricular tachycardia or cardiogenic shock (at 1, 30, and 306 days after initial blood culture) (Table 2).

Review of Literature

A PubMed search of the literature resulted in 69 manuscripts, 16 of which fulfilled inclusion criteria.

The earliest case series, published in 1981, included 85 cases of IE observed at a single hospital over 30 months, including 7 cases of GAS IE [6]. Six of these were in heroin users, all with tricuspid valve (TV) IE. Four of the 7 had polymicrobial bacteremia, 5 were treated with antimicrobials alone, and 1 underwent TV replacement. The next series, including cases from January 1982 through June 1983, identified 40 cases of GAS bacteremia in PWID and 11 with IE [7]. Nine patients had right-sided endocarditis, and only 1 had septic emboli. The authors reported rapid response to antibiotics, low mortality, and few sequelae of infection. Common predisposing factors for IE were absent; these patients were younger and apart from IDU were otherwise healthy. Another case series describing 5 cases of GAS IE over 10 years (1980 through 1989) at a single institution identified no cases in PWID, but 2 had mitral valve prolapse and 1 had a prosthetic valve [8].

A series from France over 6 years (1991–1996) compared 56 cases of beta-hemolytic *Streptococcus* (BHS) IE (7 with GAS) with *Streptococcus milleri* (now *S. anginosus* group) IE [9]. BHS IE was associated with higher mortality, more extracardiac complications, and more underlying medical conditions but less preexisting cardiac disease. Comorbid IDU was not noted. The most recently published case series described 49 cases of BHS IE over 15 years (2000–2014) [10]. There was 1 case associated with IDU and 1 case of GAS IE, but it was not specified whether they were the same case. One-month mortality was 25%.

Several single-case reports were also identified, all published between 2010 and 2020, none of which was associated with IDU [11–21]; 1 case was in a PWH [18]. Overall, 42 cases of GAS IE were identified in the literature between 1970 and 2020, 17 of which were associated with IDU (40%), with 1 in a PWH.

DISCUSSION

The high number of GAS IE cases identified at our institution, both in PWID and in non-PWID, in a short time frame is notable, given that only 42 total cases had previously been reported since 1970. IDU may be under-reported by patients both in our series and in the historical literature due to stigma and criminalization associated with illicit drug use. Possible explanations could include an overall increase in invasive GAS (iGAS) disease, a shift to more invasive circulating strains of GAS, or a link between IDU and this pathogen.

Reports from Australia, Europe, and North America have confirmed shifting epidemiology of cases, with increases in incidence and outbreaks of iGAS [22–28]. Increases in the prevalence of *emm1* strains of GAS, associated with invasive streptococcal disease, have also been identified, both coincident with increases in iGAS infection (increase from 5% to 33% of upper respiratory tract isolates over 2 years) [25] and in periods of stable iGAS incidence [28].Thus, both increased iGAS cases overall and more invasive GAS species are plausible explanations for the high number of GAS IE seen in this series.

Of the 18 cases of definite or probable GAS IE identified at our institution over 5 years, 16 were associated with IDU (89%), nearly doubling the number of cases in PWID combined from previous reports. It is the largest cases series of GAS IE in PWID and is the most recent case series of GAS IE associated with IDU since 1985. Additionally, the number of cases reported here is likely an underestimate given that evaluation for IE was not carried out in many cases and that the Modified Duke Criteria do not include GAS as common IE pathogens. It is notable that 88% of the PWID with GAS IE were also homeless and living in Baltimore City, suggesting potential ties to a shared drug supply or living environment. Although it would be interesting to know if these cases were linked epidemiologically, no external investigation was conducted. The proportion of cases associated with IDU in this case series is significantly higher than seen in the aggregate percentage of previously reported cases (89% vs 40%).

There are several possible explanations for IDU being more commonly associated with GAS IE in our patient population when compared with the above-described published cases. First, there was a higher incidence of IDU-related death in Baltimore in the time of our case series when compared with the other published case series, possibly suggesting a higher burden of IDU. In Maryland, the death rate from drug overdose was 37.2 per 100 000 in 2018 [29], while lower rates per 100 000 were seen in the location and time frame of earlier case series [9, 10] (9.6 in Minnesota in 2014, 4.1 per 100 000 in France in 1997) [29, 30]. One limitation of this comparison is that death rates [31] from IDU are affected by type of drug injected rather than solely IDU rates, and the availability of more potent opioids such as fentanyl has also arisen in this time frame.

The incidence of IE in PWID is known to have increased alongside the opioid epidemic [32]. An association with IDU and iGAS has also been noted in reports from Australia [22], the United States [24, 26], and Canada [27], and GAS IE was found to be 10-fold more frequent in PWID with iGAS than those without IDU in the United States [26]. Among 10 Centers for Disease Control and Prevention Active Bacterial Core surveillance sites, the highest rate of IDU among people with iGAS

infections was in 6 Maryland counties surrounding Baltimore City (range, 1.8%–19.3%) [26].

While the higher percentage of cases of IDU is consistent with our local patient population, the racial breakdown was not. In our case series, 67% were Caucasian, while the general population in Baltimore is 30% Caucasian ($P = .0006$). This same trend was noted in a recent study of PWID with IE in North Carolina (89% Caucasian) [33]. In our small series, there was not an appreciable difference noted in drugs used by race to explain this difference, and national reports do not show a higher rate of overdose deaths in African Americans compared with Caucasians [34], making survival bias a less likely explanation as well. This trend warrants further study to determine if biological differences vs systemic societal factors are responsible. It is plausible that Caucasians are more likely to seek care given known differences in health care access and trust of the US medical system [35]. Historically, IE among PWID has been more common in males, but 56% of our cases were female, also consistent with US trends [33, 36].

Thirty-eight percent of GAS IE cases associated with IDU were also associated with HIV in our case series. The incidence of HIV in PWID in 2015 was reported to be 32.7 per 100 000 [37], drastically different than our findings of overlapping HIV, IDU, homelessness, and GAS IE in this case series. IE is known to be more common in HIV-infected PWID than in HIV-uninfected PWID [38–40]; 1 case–control study among PWID in Baltimore noted a 4-fold higher incidence of IE in HIV-infected PWID (13.8 vs 3.3 cases per 1000 person-years) [41]. Lower CD4 counts are also associated with a higher risk of IE in PWID, even after controlling for frequency of drug injection; half of our PWH had CD4 counts <200 cells/μL. Clustering of HIV, hepatitis A, hepatitis C, and iGAS infections in PWID and people experiencing homelessness has been previously reported as an emerging syndemic [27].

Lastly, we report the first 2 published cases of GAS IE in pregnant women, which represented a fifth of our female patients with GAS IE. IE is rare in pregnancy (1 per 100 000 pregnancies) compared with general population rates (3–10 episodes per 100 000 person-years), but both of these cases also had comorbid IDU, likely accounting for their IE [41].

In this case series of 18 patients, 7 (39%) were bacteremic with at least 1 other organism in addition to GAS, making it difficult to definitively state which bacteria were implicated in the endocardial lesions. However, in 6 of 7 cases, the GAS was found in an equal or higher number of positive blood culture bottles compared with the co-pathogens isolated, suggesting a true contribution to the IE. While 3 of these cases with an equal number of positive cultures occurred with *S. aureus,* which is known to carry a high risk of endocarditis, the other 3 had predominant GAS or equal distribution with bacteria that are not considered typical endocarditis pathogens per the Modified Duke Criteria. The Modified Duke Criteria also do not exclude a diagnosis of possible or definitive endocarditis based on the presence of other pathogens. Additionally, the 7 patients with monomicrobial GAS bloodstream infection (BSI) and valvular vegetations plus the 42 cases of GAS IE identified in the literature serve as evidence of GAS's ability to cause IE. Evaluation for IE was not universally pursued in patients with GAS BSI; thus, the 12% rate of IE in GAS BSI reported here may be an underestimate and with full evaluation could approach rates of "typical" endocarditis pathogens.

The review of the literature had several important limitations. Individual case data from case series were often absent due to reporting of aggregate data only; presence or absence of IDU history was not noted in all cases. Additionally, any cases in literature published before the Modified Duke Criteria were considered to be true IE based on authors' report alone. Despite these limitations, the comparison of available historical cases compared with new cases reported here remains quite striking.

CONCLUSIONS

The high number of cases of GAS IE in PWID reported here suggests a potential increase overall in GAS IE, particularly in PWID and PWH. We agree with prior authors that this likely represents an emerging syndemic—the intersection between a worsening opioid epidemic, stimulant use, HIV, homelessness, and iGAS, in addition to an epidemiologic shift in iGAS due to changes in circulating strains, or both. This warrants further epidemiologic investigation and public health measures.

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Availability of data. Data are not publicly available.

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