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Unusual *Neisseria* species as a cause of infection in patients taking eculizumab

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Abstract

Background—Non-meningococcal, non-gonococcal *Neisseria* spp. are typically commensal and rarely cause invasive disease. Eculizumab is a terminal complement inhibitor that increases susceptibility to meningococcal disease, but data on disease caused by typically-commensal *Neisseria* spp. are lacking. This series describes postmarketing reports of typically-commensal *Neisseria* spp. disease in patients receiving eculizumab.

Methods—We searched the FDA Adverse Event Reporting System (FAERS) and medical literature for reports of commensal *Neisseria* spp. disease in patients receiving eculizumab, from eculizumab U.S. approval (2007) through January 31, 2018.

Results—We identified seven FAERS reports (including one case also reported in the literature) of non- meningococcal, non-gonococcal *Neisseria* disease, including *N. sicca (mucosa)/subflava* (n=2), *N. cinerea* (n=2), *N. sicca (mucosa)* (n=1), *N. mucosa* (n=1, with concurrent alpha-hemolytic *Streptococcus* bacteremia), and *N. flavescens (subflava)* (n=1). Four cases had sources of patient immunosuppression in addition to eculizumab. Three patients had sepsis (n=2) or septic shock (n=1). Five patients were bacteremic. All patients were hospitalized; the infections resolved with antibiotics.

Conclusions—Our search identified seven cases of disease from typically commensal *Neisseria* spp. In eculizumab recipients. These findings suggest that any *Neisseria* spp. identified from a normally sterile site in an eculizumab recipient could represent true infection warranting prompt treatment.

The views expressed are those of the authors and do not necessarily represent those of, nor imply endorsement from, the U.S. Food and Drug Administration, the Centers for Disease Control and Prevention, or the U.S. government.

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Keywords

Eculizumab; Bacteremia; Nonpathogenic *Neisseria*; *Neisseria mucosa*; *Neisseria cinerea*; *Neisseria subflava*

Background

Non-meningococcal, non-gonococcal *Neisseria* spp., such as *N. mucosa, N. subflava*, and *N. cinerea*, are typically commensal and rarely cause invasive disease in humans[1, 2]. Several *Neisseria* spp. colonize the human upper respiratory tract (e.g., *N. mucosa, N. subflava)* while others colonize the urogenital tract (e.g., *N. subflava*) (Table 1)[3–6]. In contrast to *N. meningitidis* and *N. gonorrhoeae*, these *Neisseria* spp. lack certain virulence factors such as lipopolysaccharide and fimbriae (pili), limiting their pathogenicity[2]. Nevertheless, a range of invasive infections attributed to these organisms, including endocarditis, meningitis, pneumonia, peritonitis, septic arthritis, have been reported in both immune-compromised and otherwise healthy patients[1, 5, 7–12]. Risk factors for developing disease caused by these typically commensal *Neisseria* spp. are not well defined.

Eculizumab is a monoclonal antibody with U.S. Food and Drug Administration (FDA) approval for three indications: paroxysmal nocturnal hemoglobinuria (PNH, 2007), atypical hemolytic uremic syndrome (aHUS, 2011), and anti-acetylcholine receptor positive generalized myasthenia gravis (gMG, 2017)[13, 14]. As a terminal complement inhibitor, eculizumab treats disorders characterized by complement dysregulation; however, terminal complement blockade has suppressive effects on immune system function[13, 15]. Specifically, eculizumab inhibits cleavage of complement protein C5 to C5a and C5b[13]. Without C5b, the membrane attack complex is not formed[15]. Consequently, serum bactericidal activity is impaired, resulting in increased susceptibility to disease caused by *N. meningitidis*[15]. In addition to impaired serum bactericidal activity, C5a upregulation of opsonophagocytosis is lost, disrupting a second critical immune function that defends against *N. meningitidis*[15].

The heightened risk of *N. meningitidis* disease in patients receiving eculizumab has been described previously, with an estimated 1000- to 2000- fold increase in risk relative to the general population[15, 16]. Case reports describing severe disseminated gonococcal infections in eculizumab recipients have also been published[17–19]. However, reports of disease caused by other *Neisseria* spp. in eculizumab recipients are uncommon: the first case report, published in 2018, describes a bloodstream infection caused by *N. cinerea*[20]. Thus, there is a need to characterize the spectrum of disease caused by unusual *Neisseria* spp. in this population. The purpose of this case series is to describe postmarketing reports of disease caused by typically commensal *Neisseria* spp. in patients receiving eculizumab.

Methods

We searched the FDA Adverse Event Reporting System (FAERS) database and the medical literature for cases of interest. The FAERS database contains postmarketing adverse event

reports mandatorily submitted by sponsors and voluntarily submitted by consumers and healthcare professionals, and has been described in detail elsewhere[21].

The FAERS database and medical literature (i.e., Embase, PubMed) were queried specifically for reports of infection by any non-meningococcal, non-gonococcal *Neisseria* species[1] in patients receiving eculizumab. Both sources were searched to identify reports from any country without limiting the search by a start date, to capture cases starting from eculizumab U.S. approval in 2007[14] through January 31, 2018.

Cases were included if the report noted a diagnosis of disease with any non-meningococcal, non-gonococcal *Neisseria* spp. in a patient receiving eculizumab. Because of the long eculizumab half-life (270 to 375 hours), patients receiving at least one dose of eculizumab within the three months prior to infection onset met criteria for exposure to eculizumab[13]. Documentation of the microbiological evidence of infection (e.g., positive blood culture) was not required for inclusion in the series, as non-healthcare professional reporters often did not provide technical data in FAERS reports; however, microbiological evidence was recorded when available. Blood cultures were assumed to have originated from a peripheral site when a specific site or the presence of a central venous access device was not reported. Cases were excluded if the report did not include diagnosis of an infection by a *Neisseria* spp. of interest, or if the report was a duplicate. All duplicate reports for a given case were reviewed to maximize data capture.

Ribosomal multilocus sequence typing (rMLST) studies of ribosomal protein genes recently demonstrated that *N. sicca, N. macacae*, and *N. mucosa* are the same spp. (named *N. mucosa*)[22]. In addition, rMLST studies confirmed that *N. flavescens* is the same spp. as *N. subflava*[22]. For simplicity, and because testing methods were not reported in all cases, we refer to each *Neisseria* spp. by its reported name and its reclassified name in parentheses.

Results

The FAERS search identified 10 reports of interest, including one FAERS case also reported in the literature (described above, [20]). No additional case reports were identified in the literature. Three of the 10 initially identified reports were excluded: two did not describe an infection by a non-meningococcal, non-gonococcal *Neisseria* spp., and one was a duplicate. A total of seven cases were included in the series, including the FAERS case also reported in the literature.[20]

Among the seven cases in the series, five *Neisseria* spp. were noted as a cause of disease, including *N. sicca/subflava* (cases 1 and 2), *N. sicca* (case 3), *N. cinerea* (cases 4 and 5), *N. mucosa* (case 6), and *N. flavescens* (case 7) (Table 2). For the two reported patients with disease caused by *Neisseria sicca /subflava*, species identification methods for the isolate were not described; presumably the identification methods were unable to distinguish

[1]For this case series, *Neisseria* spp. targeted in the search strategy included *N. animalis, N. animaloris, N. bacilliformis, N. canis, N. cinerea, N. denitrificans, N. dentiae, N. elongata, N. flavescens, N. iguanae, N. lactamica, N. macacae, N. mucosa, N. oralis, N. perflava, N. polysaccharea, N. shayeganii, N. sicca, N. skkuensis, N. subflava, N. tadorna, N. wadsworthii, N. weaveri, N. zoodegmatis*[1]

between *N. sicca* and *N. subflava*[9]. With revised nomenclature, the series includes two cases of *N. mucosa/subflava* (cases 1 and 2), two cases of *N. mucosa* (cases 3 and 6), two cases of *N. cinerea* (cases 4 and 5), and one case of *N. subflava* (case 7).

Ages of the seven patients ranged from 4 to 38 years (median 17 years, mean 21 years). The case series included four females and three males. Five of seven cases were reported in the U.S. Reasons for eculizumab therapy included PNH (cases 1,4,6), aHUS (cases 2,5,7), and catastrophic antiphospholipid antibody syndrome (CAPS, case 3). All patients were receiving eculizumab at the time of infection except the patient in case 1, who had received a 12-week course of eculizumab prior to receiving a hematopoietic stem cell transplant (HSCT) for the treatment of PNH.

In general, the patients in this case series were medically complicated (Table 2). Four cases (cases 1,3,4,7) involved reported sources of patient immunosuppression other than eculizumab. Of these four, two patients (cases 1 and 7) received an HSCT; the timing of the autologous HSCT was not reported in case 7, and the patient in case 1 had an allogeneic HSCT seven days prior to diagnosis of *N. sicca (mucosa)/subflava* disease. Both patients were neutropenic at the time of infection diagnosis. The patient in case 3 (receiving eculizumab for CAPS) had a complicated past medical history that included Common Variable Immunodeficiency, hypogammaglobulinemia, lupus, multiple strokes, previous episodes of bacterial peritonitis and bacteremia associated with vascular access devices; concomitant medications included rituximab, chronic steroid use, and a history of cyclophosphamide therapy. The patient in case 4 had aplastic anemia and a history of “lymphoglobulin therapy” (date of therapy not reported). In three cases (cases 2,5,6) there was no report of any additional source of patient immunosuppression.

Severity of infection and presentation varied substantially among patients in the series, with the most severe presentations reported as sepsis (cases 6 and 7) and septic shock (case 4). In addition to fever of 39.5°C and septic shock, the patient in case 4 presented with abdominal pain, hypotension, and vomiting. An “abdominal ecoscan” result showed “abnormal thickness of the gallbladder”, which the reporter attributed to possible cholecystitis. *N. cinerea* grew from a blood culture. The other two patients with sepsis noted gastroenteritis four days prior to diagnosis of *N. mucosa* disease (case 6) and *N. flavescens* (*subflava*) sepsis in the setting of neutropenic fever without further details on presentation (case 7). The remaining four patients in the series had febrile neutropenia (case 1), fever and cough (case 2), subjective fever with rigors during hemodialysis (HD) (case 5), and bacterial peritonitis (case 3, without further details describing the patient’s symptoms or clinical work-up). There were no reports of meningitis in the case series.

Positive blood cultures were reported for five patients (cases 1,2,4,5, and 6). Of these five patients, three had an indwelling catheter for either vascular access (cases 1 and 2) or hemodialysis (case 5). Blood cultures showing growth of *N. sicca (mucosa)/subflava* were drawn from a central line (case 1) or subcutaneous port (case 2). The patient in case 5 had bacterial growth from peripheral blood cultures (*N. cinerea*) and first noted symptoms suggestive of infection during hemodialysis. Two additional patients also had bacteremia: one had *N. cinerea* septic shock with possible cholecystitis (case 4), and one had *N. mucosa*

sepsis with concurrent alpha-hemolytic *Streptococcus* bacteremia after gastroenteritis (case 6). The remaining two patients in the series included one with a diagnosis of *N. flavescens (subflava)* sepsis (case 7) while neutropenic (specimen source not specified), and *N. sicca (mucosa)* bacterial peritonitis (case 3) associated with a peritoneal dialysis catheter, a positive peritoneal fluid culture, concurrent negative blood cultures, and a reportedly negative transesophageal echocardiogram.

All patients were hospitalized, though one patient (case 1) was an inpatient at the time of diagnosis following an allogeneic HSCT. It was also unclear whether the patient in case 7 was hospitalized prior to, or because of, the *N. flavescens (subflava)* disease, as this patient was neutropenic at the time of the infection with a history of autologous HSCT and chemotherapy. Notably, two patients (cases 2 and 5) were evaluated for complaints of fever but were not hospitalized during initial clinical evaluation. The patient in case 2 had fever and cough, and outpatient evaluation included a normal complete blood count (without differential) and a urinalysis indicating 1+ proteinuria. He received a dose of ceftriaxone and was discharged home. The patient in case 5 noted subjective fever plus rigors during HD. He was evaluated for an infection involving his arteriovenous fistula (AVF); however, the AVF had minimal warmth and tenderness. Thus, the physicians felt there was no active bacterial infection and did not hospitalize the patient at that time. Upon identification of positive blood cultures, both patients (cases 2 and 5) were contacted to return to the hospital for inpatient care.

Although there were no cases in which a history of meningococcal disease was reported prior to the infection by a typically commensal *Neisseria* spp., one (case 2) of seven patients in the series was receiving antibiotic prophylaxis (to prevent meningococcal disease) at the time *N. sicca (mucosa)/subflava* infection was identified. Per the reporter, the patient in case 2 was taking oral penicillin for antibiotic prophylaxis, though duration of and adherence to antibiotic therapy were not reported. Another patient (case 5) initiated antibiotic prophylaxis with oral penicillin following infection with *N. cinerea*.

All patients received antibiotic treatment and all *Neisseria* spp. infections reportedly resolved without sequelae; see Table 2 for treatment details. None of the patients with vascular access devices or dialysis catheters had their devices removed as a result of infection. Five of seven patients reported eculizumab disposition following infection. Four patients (cases 2,3,4,7) continued therapy after recovering from infection, although one of the patients (case 7) died shortly thereafter due to Wilms tumor progression. The remaining patient (case 1) discontinued therapy because the planned 12-week course of eculizumab therapy had concluded.

Conclusions

Our search of postmarketing adverse event reports in FAERS and the medical literature identified seven cases of disease by typically commensal *Neisseria* spp., including *N. sicca (mucosa)/subflava, N. sicca (mucosa), N. cinerea, N. mucosa*, and *N. flavescens (subflava)*. These atypical infections have previously been reported in both immunosuppressed and healthy patients[8, 19], and risk factors remain unclear.

The existing literature on human disease caused by typically commensal *Neisseria* spp. is limited and includes predominantly case reports, as these infections are rare. There is diversity with regard to patient age, site of infection, and co-morbidities in published cases[3–5, 7–11, 20]. The unifying risk factor for infection due to unusual *Neisseria* spp. among patients in this series was eculizumab therapy, which is known to impart high risk for *N. meningitidis* disease due to terminal complement inhibition[13]. In addition, recurrent disseminated gonococcal infection (DGI) is associated with terminal complement deficiency[23], and disseminated *N. gonorrhoeae* infections have been reported in patients receiving eculizumab[17–19]. Our data suggest that eculizumab may also confer increased risk for disease caused by typically commensal *Neisseria* spp. in addition to the known risk of *N. meningitidis* disease. Further, recent data suggest that patients receiving eculizumab are at risk for meningococcal infections caused by nongroupable strains, which do not usually cause invasive disease in healthy people[16, 24]. The patients in this series may be exhibiting a similar susceptibility to severe infection by species that rarely pose a risk for invasive infection in healthy individuals. The full impact of terminal complement inhibition in patients receiving eculizumab needs further characterization, as other non-*Neisseria* bacterial infections (e.g., *Pseudomonas aeruginosa* [25,26]; *Streptococcus pneumoniae* and *Haemophilus influenzae* type B in pediatric patients [13]) and fungal infections (e.g., Aspergillosis [13, 27], disseminated cryptococcosis [28]) have also been reported in patients receiving eculizumab.

In our series, most patients were medically complicated, and more than half of the patients in the series had sources of immunosuppression other than eculizumab. Chronic underlying disease, in addition to the eculizumab therapy, may have contributed to risk of infection. We therefore cannot discern the impact of eculizumab on susceptibility to disease by unusual *Neisseria* spp. relative to other sources of drug- or comorbidity-associated immunosuppression. It is also possible that there is a subgroup of patients receiving eculizumab who may be at even higher risk for disease by typically commensal *Neisseria* spp., such as those with a second immunosuppressive factor (e.g., neutropenia, post-HSCT) or long-term vascular access devices. However, our limited data cannot be used to assess any difference in risk among subgroups of eculizumab recipients.

The *Neisseria* spp. reported in this series are not considered skin flora[1], as these organisms usually colonize either the oropharyngeal or urogenital tracts[3–6]. Thus, it is unlikely that the positive cultures from the vascular access devices seen in cases 1 and 2 were due to skin contamination, but source of infection was unclear.

Of the five patients for whom the antimicrobial agent used in treatment was specified, a beta-lactam was used; four patients received a 3rd or 4th generation cephalosporin and one patient received piperacillin/tazobactam. Unfortunately, our case series cannot provide insight into the efficacy of such agents for treating disease caused by typically commensal *Neisseria* spp. However, because the risk for invasive meningococcal disease is high in patients receiving eculizumab[13, 16], empiric therapy that includes coverage for *N. meningitidis* is of paramount importance in eculizumab-treated patients presenting with signs of any infection until definitive microbiology results are available to guide therapy.

There are multiple limitations to our case series. Adverse event reporting to FDA is voluntary, so our case series likely reflects underreporting for commensal *Neisseria* spp. infections in patients receiving eculizumab. As such, we cannot estimate incidence or calculate absolute risk for these infections in patients receiving eculizumab, or quantify the risk of typically commensal *Neisseria* spp. disease attributable to eculizumab. A further limitation of the case series is incomplete information in FAERS reports. For example, in several cases we had reports of blood culture results from indwelling vascular access devices but no report of peripheral blood culture results. Although a positive blood culture result from an indwelling vascular catheter could yield a false positive result and represent colonization instead of disease[29], we consider the concomitant findings typical of systemic infection to support our conclusion that the *Neisseria* spp. isolated from the blood samples was related to the disease. Finally, reporters often did not describe the species identification method used, so misclassification of *Neisseria* spp. is possible.

In summary, we identified seven postmarketing cases of serious disease caused by typically commensal *Neisseria* spp., including *N. cinerea, N. flavescens (subflava), N. mucosa, N. sicca (mucosa), and N. sicca (mucosa)/subflava*. When gram-negative diplococci are isolated in a patient receiving eculizumab, it is important to distinguish among meningococcal, gonococcal, and typically commensal *Neisseria* spp. for treatment and infection prevention considerations. These findings suggest that identification of any *Neisseria* species from a normally sterile site in a patient receiving eculizumab could represent true infection warranting prompt and appropriate treatment. We encourage healthcare professionals to report suspected adverse events, including all infections in patients receiving eculizumab, to the FDA MedWatch database[30].

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Table 1.

Selected Commensal *Neisseria* spp. and location of colonization

***Neisseria* spp.**	**Location Colonized**
N. mucosa[*]	Oropharynx, nasopharynx[3, 4]
N. subflava[+]	Nasopharynx, genitourinary tract[5]
N. cinerea	Oropharynx, genitourinary tract (rarely)[6]

[*] same species as *N. sicca*

[+] same species as *N. flavescens*

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Table 2.

Case descriptions and clinical course of patients receiving eculizumab who developed disease caused by typically commensal *Neisseria* spp.

Case	*Neisseria* spp.	Age (yrs), Sex	Country	Eculizumab reason for use	Past Medical History	Vascular access devices, dialysis catheters	Clinical course	Microbiology and imaging data	Antibiotics	Outcome
1	*N. sicca (mucosa)/ subflava*	13 M	US	PNH	Type 1 diabetes, bone marrow transplant 7 days prior to infection	Central line	12 weeks of eculizumab prior to bone marrow transplant, febrile neutropenia 7 days after bone marrow transplant, hospitalized for 12 days after infection	"central line culture" positive for *Neisseria sicca/ subflava*, all subsequent cultures negative	Piperacillin/ tazobactam	Resolved
2	*N. sicca (mucosa)/ subflava*	6 M	US	aHUS	Developmental delay, chronic kidney disease, renal hypertension, proteinuria, allergic rhinitis, iron deficiency, cochlear implant, balance problem, muscle weakness, auditory neuropathy, lack of coordination, abnormal involuntary movements, sensorineural hearing loss bilateral, hyperopia, pseudostrabismus, thrombotic thrombocytopenic purpura, prematurity	Subcutaneous port	Fever 100.9 (no units) and cough at presentation in clinic, wbc 4.7 (no units), blood cultures drawn and patient received ceftriaxone; Patient called to go to ED the next day when cultures showed "gram cocci in pairs and clusters", condition reported as "sepsis", hospitalized 4 days	Blood culture from subcutaneous port positive for *Neisseria sicca/ subflava*; Subcutaneous port maintained with plan to draw additional cultures (results not reported)	Ceftriaxone 50mg/kg at presentation; upon return to ER vancomycin and ceftriaxone, definitive treatment ceftriaxone x 7 days	Resolved
3	*N. sicca* (*mucosa*)	38 F	US	Catastrophic antiphospholipid syndrome - compassionate use	End stage renal disease with PD, catastrophic antiphospholipid syndrome, myocarditis, chronic anemia, severe mitral regurgitation, cardiomyopathy, strokes, plasma infusions, heart failure EF 20%, lupus with glomerulonephritis, migraine, midbrain small vessel lesion, chronic steroid use (prednisone, dose not reported), common variable immunodeficiency, hypogammaglobulinemia thrombocytopenia, microangiopathic hemolytic anemia, factor II activity low, device related thrombosis, at least one previous episode of	PD catheter, IV port	Diagnosed as "bacterial peritonitis"	"bacterial peritonitis" with growth of *N. sicca* (peritoneal fluid culture), blood cultures negative and transesophageal echocardiogram "negative"	Yes, but not specified	Resolved, died several years later due to complications of underlying disease

Case	*Neisseria* spp.	Age (yrs), Sex	Country	Eculizumab reason for use	Past Medical History	Vascular access devices, dialysis catheters	Clinical course	Microbiology and imaging data	Antibiotics	Outcome
					coagulase-negative *Staphylococcus* peritonitis, 2 episodes of coagulase-negative *Staphylococcus* bacteremia with line sepsis, concomitant IV immunoglobulin and rituximab (dates of therapy unclear), history of cyclophosphamide and pulse steroids					
4	*N. cinerea*	17 F	Argentina	PNH	Aplastic anemia, right supra-hepatic vein thrombosis, elevated lactate dehydrogenase levels, history of "lymphoglobulin" therapy, possible immunoglobulin therapy	Not reported	Septic shock, hypotension (70/40), fever 39.5C, abdominal pain, vomiting, anemia (hemoglobin 6.5 mg/dL), renal impairment	1 of 2 blood cultures grew *N. cinerea*, abdominal "ecoscan" showed abnormal thickness of the gallbladder, which could indicate possible cholecystitis"	Ceftriaxone and metronidazole	Resolved
5 [20]	*N. cinerea*	38 F	US	aHUS	ESRD and chronic HD, hepatitis C from remote IVDU	HD arteriovenous fistula	Subjective fever, chills, rigors during HD; left upper extremity arteriovenous fistula had minimal warmth and very mild tenderness to palpation; NO respiratory, cardiovascular, gastrointestinal symptoms and no rashes or ear/nose/pharyngeal complaints; evaluating physicians did not feel patient had "active, systemic, bacterial infection" Hospitalized after cultures showed growth, vital signs stable (HR 57, BP 112/82, RR 18), WBC 7290 cells/mm3	3 sets of peripheral blood cultures grew *N. cinerea* (VITEK 2), cultures redrawn on days 2 and 4 were negative and patient afebrile throughout hospitalization	Cefepime for 14 days	Resolved
6	*N. mucosa*	32 F	US	PNH	Budd-Chiari syndrome with shunt placement, nausea, pain,	Not reported	Gastroenteritis 4 days earlier (hospitalized for 2	Blood cultures showed *Neisseria* spp. not	Ceftriaxone for 14 days then	Resolved

Case	*Neisseria* spp.	Age (yrs), Sex	Country	Eculizumab reason for use	Past Medical History	Vascular access devices, dialysis catheters	Clinical course	Microbiology and imaging data	Antibiotics	Outcome
					recent gastroenteritis 4 days before infection		days), then hospitalized for 6 days with sepsis	*meningitidis* or *gonorrhoeae*, later reported *N. mucosa*, also blood culture with alpha-hemolytic *Streptococcus* was reported; blood cultures drawn one day after hospital discharge showed no growth	amoxicillin for 14 days	
7	*N. flavescens* (*subflava*)	4 M	Taiwan	aHUS	Wilms tumor status post chemotherapy with suspected relapse, autologous peripheral blood stem cell transplant, acute on chronic renal insufficiency, cachexia, anemia, heart failure, bone marrow aspiration, thrombocytopenia, thrombotic microangiopathy, transfusion, upper GIB, blood transfusion, lymph node and tumor excision, laminectomy	Not reported	Febrile neutropenia with sepsis	"neutropenic fever with *Neisseria flavescens* sepsis", micro data not reported	Yes, but not specified	Infection resolved, then death due to Wilms tumor progression according to physician

aHUS = atypical hemolytic uremic syndrome, BP = blood pressure, EF = ejection fraction, ESRD = end-stage renal disease, GIB = gastrointestinal bleed, HD = hemodialysis, HR = heart rate, IVDU = IV drug use, PD = peritoneal dialysis, PNH = paroxysmal nocturnal hemoglobinuria, RR = respiratory rate, WBC = white blood cell count