

# Endocarditis, Meningitis, and *Streptococcus agalactiae* Pneumonia: An Unusual Variant of Osler's Triad

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## CASE PRESENTATION

### Initial Presentation and History

A 43-year-old man presented to the emergency department with fever, lethargy, headache, and altered mental status. He had experienced nausea and vomiting the day before presentation. His past medical history indicated that he had diabetes mellitus, which was adequately controlled by diet and an oral hypoglycemic agent; he was a former intravenous drug abuser and was a chronic abuser of alcohol; he was hypertensive, hepatitis C positive, and HIV negative. The patient had been diagnosed with cirrhosis of the liver with secondary splenomegaly and thrombocytopenia. His daily medications were lisinopril, furosemide, cimetidine, and glyburide.

### Physical Examination

On examination, the patient's temperature was 101.4°F. He was tachycardic, with a heart rate of 118 bpm, and tachypneic, with a respiratory rate of 38 breaths/min. His blood pressure was 140/80 mm Hg. The patient was agitated, confused, and disoriented. The oral pharynx appeared to be infected with *Candida* species. Nuchal rigidity was present and signs of meningeal irritation could be elicited with straight leg maneuvers. Crackles were heard over the posterior base of the right lung. Cardiac auscultation was unremarkable except for the tachycardia. The spleen was palpable on examination of the abdomen. He could move all extremities appropriately. Palmar erythema was present. The remainder of the physical examination was unremarkable.

### Laboratory and Imaging Studies

The patient's total white blood cell count was  $12.1 \times 10^3/\mu\text{L}$ , with a platelet count of  $4.6 \times 10^3/\mu\text{L}$ . The peripheral smear demonstrated 21% bands and 68%

neutrophils. Electrolytes were normal. Serum glucose was elevated at 338 mg/dL (normal, 70–110 mg/dL), and serum albumin was below normal at 2.4 g/dL (normal, 3.5–5.0 g/dL). His coagulation profile was unremarkable. A chest radiograph showed a right lower lobe infiltrate consistent with pneumonia. A computed tomography (CT) scan of the head was unremarkable.

### Initial Treatment

The patient received 2 g of ceftriaxone intravenously in the emergency department, and a lumbar puncture was performed. The cerebrospinal fluid (CSF) contained 778 white blood cells. The differential count demonstrated 88% neutrophils and 12% lymphocytes. Both CSF total protein and CSF glucose were elevated at 233 g/dL (normal, 15–45 g/dL) and 93 mg/dL (normal, 50–80 mg/dL), respectively. Ampicillin and vancomycin were prescribed to cover the possibility of meningitis caused by *Listeria* species, meningococcus, or penicillin-resistant pneumococcus. Fluconazole was administered for oral thrush.

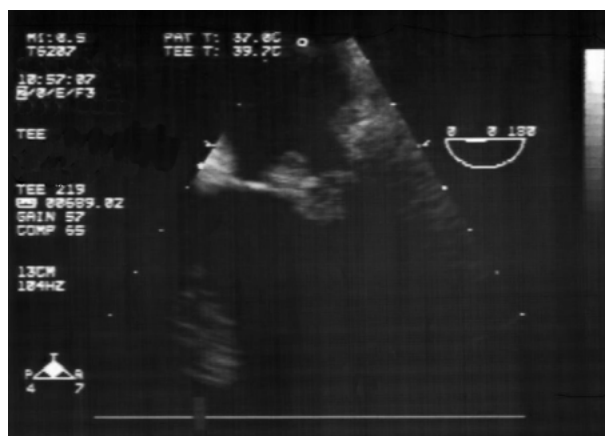
### Hospital Course

Shortly after admission, the patient became more lethargic. Magnetic resonance imaging of his head revealed subacute hemispheric infarcts in the area supplied by the right middle and right anterior cerebral arteries. His oxygen-hemoglobin saturation declined, signaling difficulty with gas exchange. The patient was intubated and placed on positive-pressure mechanical ventilation.

Staining of the CSF revealed gram-positive cocci in chains. Subsequently, cultures of his sputum, blood,

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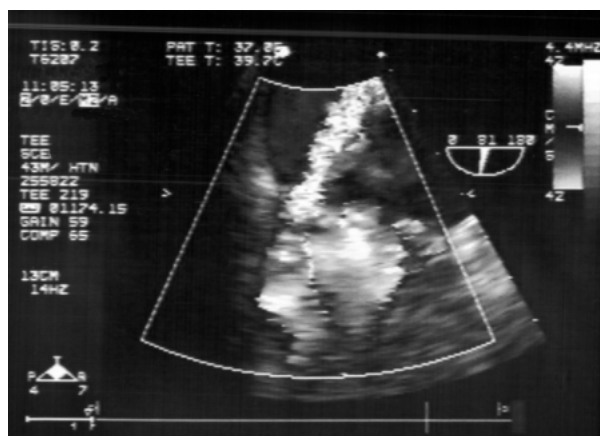


**Figure 1.** Transesophageal echocardiogram showing a mobile echodensity attached to the atrial side of the anterior leaflet measuring 1.14×0.6 cm.

and CSF grew group B streptococci sensitive to ceftriaxone (minimum inhibitory concentration [MIC] < 0.03) and penicillin (MIC < 0.5). Because the MICs were more favorable to ceftriaxone than penicillin, vancomycin and ampicillin were discontinued.

Despite the administration of ceftriaxone and fluconazole, the patient remained febrile. A transthoracic echocardiogram to evaluate for underlying endocarditis (given the positive blood cultures) was performed on hospital day 3, but the study was negative. On hospital day 5, a heart murmur was detected. Transesophageal echocardiography (TEE) was performed, and a 1.14 × 0.6-cm pedunculated mass was identified on the anterior mitral leaflet (**Figure 1**). Gentamicin was added to the patient's regimen, and a cardiothoracic surgeon was consulted. The patient was not sufficiently stable to undergo immediate mitral valve replacement due to hypotension episodes. As antibiotic therapy was continued, blood cultures were rechecked and did not show growth. Gentamicin was discontinued after 5 days of therapy because creatinine levels increased, reaching a peak of 2.7 mg/dL (normal, 0.6–1.2 mg/dL). The patient became more alert and cooperative, although his fever persisted. Surgery still was not an option because the patient experienced intermittent hypotensive episodes requiring pressor support to keep his mean arterial pressure above 65 mm Hg. The intensity of his heart murmur gradually increased. On hospital day 20, he suddenly experienced right extremity weakness and right hemianopia, followed by increasing lethargy.

A CT scan of the head was repeated and confirmed new infarcts in the left basal ganglia, caudate nucleus, and the left occipital lobe. An intracranial bleed was



**Figure 2.** Moderate eccentric jet of the mitral regurgitation across the anterior leaflet, highly suggestive of perforation of the anterior leaflet.

noted. Repeat TEE demonstrated that the vegetation on the anterior mitral valve leaflet had increased in size, and there was now evidence of mitral valve perforation (**Figure 2**). The patient died while being prepared for cardiothoracic surgery.

## DISCUSSION

### Epidemiology

Although group B streptococcus (GBS) remains an important pathogen in neonates and pregnant women, it is now recognized as a cause of bacteremia and locally invasive infection in adults. More than 7600 adults are infected with GBS annually in the United States, reflecting a two- to fourfold increase in the incidence of reported cases in the last 3 decades.<sup>1</sup> In the United States, adult infection now accounts for more than 75% of invasive GBS disease as well as 90% of GBS mortality. Currently, more adults in the United States are infected with invasive GBS each year than with *Neisseria meningitidis*, *Haemophilus influenzae*, and *Listeria monocytogenes* combined.<sup>1</sup> The greatest increase in adult GBS infection has occurred in the population older than 60 years, in whom the incidence may be as high as 18 cases per 100,000 persons.<sup>2</sup> The mean age of nonpregnant adults with invasive GBS disease is 60 years.<sup>3</sup> The reasons for the increase in GBS infections in adults are unclear but are likely related to changes in the prevalence of virulent strains and the larger number of patients living with chronic diseases for longer periods of time.<sup>4</sup>

Pregnant women, elderly patients, and individuals with serious underlying diseases (eg, history of alcohol abuse, liver disease, cardiovascular disease, HIV infection, malignancy, diabetes) are at increased risk of GBS

infection.<sup>5</sup> The patient presented here illustrates this point: he had a history of alcohol abuse and concomitant diabetes and hepatic cirrhosis from chronic hepatitis C infection.

### **Clinical Presentation**

The most common manifestations of GBS infection in the nonpregnant adult are skin and soft-tissue infections, pneumonia, and bacteremia. Pneumonia is thought to be caused by aspiration of GBS. Lung involvement may be unilobar or multilobar, but pleural effusion is uncommon. The mortality rate of GBS bacteremia ranges between 9% and 47% in adults, reflecting the association of GBS bacteremia with significant underlying diseases.<sup>6</sup>

GBS meningitis is rare in nonpregnant adults, with fewer than 70 cases reported in the medical literature.<sup>7</sup> It has a clinical presentation and CSF findings similar to other forms of bacterial meningeal infection. GBS meningitis is characterized by an abrupt onset of symptoms, and bacteremia is present in approximately 80% of cases.<sup>4</sup> A distant focus of infection can be identified in 40% to 50% of affected patients and most commonly involves the endometrium, respiratory tract, and endocardium.<sup>8</sup> The expected mortality rate from adult GBS meningitis without underlying disease ranges from 27% to 34%.<sup>9</sup>

Valvular infection is estimated to occur in 2% to 9% of patients with GBS bacteremia.<sup>10</sup> GBS endocarditis has been reported in patients with and without known valvular disease (mean age, 50 years), and underlying heart disease preexists in more than half of those infected. The vegetations are usually large and friable, leading to frequent embolization. The clinical course may be aggressive, and the case mortality rate ranges from 13% to 50%. Anticipated outcome depends on whether left-sided valves are affected and if timely cardiac surgery is performed. Surgical intervention has been used as a complement to antibiotic therapy, and this approach has improved outcome significantly in some reports.<sup>11</sup>

GBS associated with either meningitis or endocarditis is uncommon, but the occurrence of both conditions simultaneously in the same individual is rare. We identified only 12 published reports of patients with both meningitis and endocarditis caused by *Streptococcus agalactiae* in an English language search of the medical literature (Table).<sup>22</sup> Because our patient had clinical and radiographic evidence of lobar pneumonia on presentation, we presume that GBS pneumonia and bacteremia preceded the development of the meningitis and endocarditis. This combination of infected organ systems with pneumonia, meningitis, and endo-

carditis is called "Osler's triad" or the "Austrian triad," and *S. pneumoniae* is usually the infectious agent rather than *S. agalactiae*.<sup>23</sup>

### **Treatment**

Treatment of most GBS infections in adults is straightforward. The organism is typically susceptible to penicillin, although four- to eightfold less susceptible than group A streptococci.<sup>24</sup> The optimal recommended therapy is penicillin in combination with an aminoglycoside. This combination is thought to provide a synergistic effect in patients with severe disease such as endocarditis. The duration of antimicrobial therapy for meningitis is a minimum of 2 to 3 weeks, and the duration of the therapy for endocarditis is 4 to 6 weeks.<sup>24</sup>

Our case illustrates the difficulties of treating invasive GBS infection in an immunocompromised host. The diagnosis was readily established by growth of the organism in blood and CSF cultures, which allowed for the administration of the appropriate antimicrobial therapy at the onset. Nevertheless, his infection was never totally controlled. In retrospect, some investigations and interventions may have benefited our patient were they performed in a more timely manner. First, the follow-up TEE could have been performed earlier in this patient's course in anticipation of further growth of the valvular vegetation as this organism has a propensity for causing large vegetations, thereby increasing the likelihood of embolization.<sup>25</sup> Documentation of increased size would have been a sign of increased risk given the patient's nonsurgical status but would not have improved his clinical status nor offered any additional therapeutic protection.

Second, although blood cultures remained negative after antibiotic therapy was started, additional blood cultures might have been considered after gentamicin was discontinued. The finding of positive blood cultures in this context would have supported continuing this antibiotic despite the rising creatinine levels as renal dysfunction is not a contraindication for continued use in a patient with a life-threatening situation.

Third, early operation should always be considered in active infectious endocarditis.<sup>26</sup> It is possible that early surgery may have influenced the outcome of the endocarditis and prevented the central nervous system embolic phenomena. This approach has some support in the medical literature,<sup>15,21</sup> and we pursued this option for our patient. Unfortunately, his depressed immune status fostered an increased aggressiveness of the microorganism and also precluded the potentially helpful surgery, first with persistent hypotension and then with catastrophic hemorrhagic cerebral pathology.

**Table.** Reports Published on Nonpregnant Adults with Both Endocarditis and Meningitis Caused by *Streptococcus agalactiae*

Study (year)	Age of Patient (yr)	Sex	Underlying Disease	Complications	Positive GBS Cultures	Antimicrobial Therapy (wk)	Surgery	Outcome
Wolstan <sup>12</sup> (1973)	73	F	DM, gangrenous foot	Heart murmur on the 30th day after BM; BE at autopsy	CSF, blood	Penicillin (N/A)	No	Died
Lerner <sup>13</sup> (1975)	71	F	No	N/A	CSF, blood	Penicillin (4)	N/A	Survived
Bayer et al <sup>14</sup> (1976)	61	M	DM	N/A	CSF, blood, wound	Penicillin (N/A)	No	Survived
John et al <sup>15</sup> (1977)	76	M	No	N/A	CSF	Penicillin + gentamicin (N/A)	Yes	Survived
Lerner et al <sup>16</sup> (1977)	32	M	N/A	N/A	N/A	Penicillin + streptomycin (N/A)	No	Survived
Wilkinson <sup>17</sup> (1978)	59	M	N/A	N/A	N/A	N/A	N/A	Died
Brockman et al <sup>18</sup> (1979)*	45	F	RA, AA, HC	On autopsy: PN, PM, MA, PP, RF	CSF, blood, urine	Ampicillin + vancomycin (5)	No	Died
Dunne et al <sup>19</sup> (1993)	82	F	CAD, SRD, DM, MDS	AV fistula thrombosis	CSF, blood	N/A	No	Died
Colford et al <sup>20</sup> (1995)	89	F	Colon and cervical carcinoma	N/A	N/A	Penicillin + gentamicin (N/A)	N/A	Died
Domingo et al <sup>8</sup> (1997)	63	F	DM	N/A	Blood, urine, synovial fluid	Penicillin + gentamicin (N/A)	N/A	Died
Gupta et al <sup>21</sup> (1998)	60	M	DM, prostate carcinoma	N/A	Blood	Penicillin + gentamicin (2); ampicillin (6)	Yes	Survived
Civiljak et al <sup>22</sup> (2001)*	45	M	HIV, AA, prior CD	HSV, FI, CD, nosocomial PN and furuncle	CSF, blood, urine	Penicillin + gentamicin (9)	No	Survived
Case from this report*	43	M	DM, AA, IVDA, HC, hep C, splenomegaly	Heart murmur 5th day after presentation of BM, PN, CD, FI	CSF, blood, sputum	Ceftriaxone (3); ertapenem (5 d)	No	Died

AA = alcohol abuse; AV = aortic valve; BE = bacterial endocarditis; BM = bacterial meningitis; CAD = coronary artery disease; CD = cardiac decompensation; CSF = cerebrospinal fluid; DM = diabetes mellitus; FI = fungal infection; GBS = group B streptococcus (*Streptococcus agalactiae*); HC = hepatic cirrhosis; HSV = herpes simplex virus; IVDA = intravenous drug abuser; MA = myocardial infection; MDS = myelodysplastic syndrome; MV = mitral valve; N/A = data not available; PM = purulent meningitis; PN = pneumonia; PP = purulent pericarditis; RA = rheumatoid arthritis; RF = renal failure.

\*Presence of pneumonia; only our case's pneumonia was due to GBS as evidenced by sputum culture.

## CONCLUSION

With the aging of the population in the United States and the successful treatment of chronic medical conditions, an increased number of patients are at risk for GBS infection.<sup>24</sup> In the nonpregnant adult, skin and soft-tissue infections, pneumonia, and bacteremia are the most common expressions of GBS infection.<sup>5</sup> **HP**

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