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CASE REPORT

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Conquering the pneumococcal nemesis with oral antibiotics

Rana Garris [a], Rushdy Abanoub[b], Firas Qaqa[b], Chirag Rana[b], Nirmal Guragai [b], Habib A. Habib[b], Fayez Shamoon[b] and Mahesh Bikkina[b]

aDepartment of Internal Medicine, St. Joseph's University, New York Medical College, Paterson, NJ, USA; bDepartment of Cardiology, St. Joseph's University, New York Medical College, Paterson, NJ, USA

ABSTRACT

Introduction: *Streptococcus pneumoniae* endocarditis (SPE) occurs in <3% of all EI cases due to the evolution of penicillin and vaccination. However, immunocompromised and unvaccinated patients are still at grave risk.

Case: A 58-year-old African American male who used alcohol and intravenous (IV) drugs presented with confusion, fever, and hemoptysis. He had coarse rhonchi with a grade 2/5 holosystolic apical murmur. CT chest showed diffuse bilateral infiltrates. Blood cultures were positive for pansensitive *Streptococcus pneumoniae*. Echocardiogram demonstrated large vegetations on the anterior and posterior leaflets of the mitral valve with flail leaflet and severe eccentric mitral regurgitation. Patient was started on IV ceftriaxone, but after 3 weeks of therapy, he wished to leave against medical advice. He was discharged on combination oral therapy with successful resolution of SPE on follow-up.

Discussion: Invasive pneumococcus is highly virulent causing irreversible valvular destruction or death.

IV beta-lactams are first-line treatment, but there are currently no guideline-recommended alternatives for oral therapy. Recent data suggest partial oral therapy may be noninferior to IV only therapy.

Conclusion: Switching to oral combination antibiotics after at least 2 weeks of IV therapy is an acceptable alternative to treat SPE.

1. Introduction

Streptococcus pneumoniae endocarditis (SPE) is considered a disease of the past with its aggressive and unrelenting destruction nearly forgotten due to the evolution of penicillin and vaccination. In the early 20th century, it was described as an *'almost uniformly fatal'* disease with massive vegetations, necrosis, perforation, and pericardial invasion[1]. SPE currently causes less than 3% of infective endocarditis (IE) cases in the USA (US), but vulnerable populations are still at risk[2]. While intravenous (IV) beta-lactams are first-line therapy, new evidence has suggested that treatment regimens with partial oral combination therapy is noninferior[3]. We present a fulminant case of SPE that was successfully treated with IV, followed by oral combination antibiotics.

2. Case

58-year-old African American male presented with altered mental status, low-grade fever and hemoptysis. Patient was disheveled and smelled of alcohol with urine toxicology positive for opioids. He had bilateral coarse rhonchi with decreased breath sounds over the lung bases. A grade 2/5 holosystolic murmur
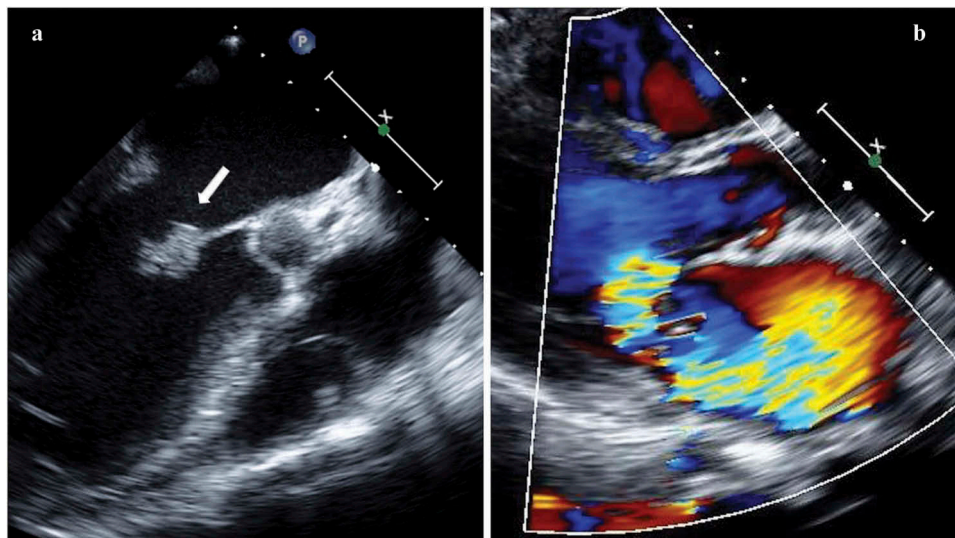
was appreciated along the apex. Labs demonstrated marked leukocytosis with bandemia, normocytic anemia, and thrombocytopenia. Computerized tomography (CT) of chest showed diffuse interstitial infiltrates throughout both lung fields with bilateral pleural effusions and atelectasis of the lower lobes (Figure 1). Blood cultures were positive for pansensitive *Streptococcus pneumoniae*. Urine antigen was also positive for pneumococcus IgG. Transthoracic echocardiogram (TTE) and transesophageal echocardiogram (TEE) demonstrated severe mitral valve regurgitation with eccentric and posteriorly directed jets and 1.34 cm X 1.27 cm vegetation on the anterior mitral leaflet and 0.96 cm X 1.05 cm on the posterior mitral leaflet (Figure 2(a,b)). He was started on IV ceftriaxone 2 g every 24 h and cardiothoracic surgical consult was placed for significant valve destruction and heart failure. After 3 weeks of inpatient treatment, he wished to leave against medical advice, because of family and financial responsibilities. After risk counseling, he opted to leave with oral antibiotics, amoxicillin 1 g every 8 h and levofloxacin 750 mg daily for 4 weeks. On 3-month follow-up visit, he reportedly finished all oral antibiotics, and had abstained from alcohol and heroin use. His

Figure 1. CT chest showing pneumococcal pneumonia.

Figure 2. TEE showing large vegetation on the anterior and posterior mitral leaflet (a) and severe mitral valve regurgitation with eccentric jet with coanda effect seen on doppler (b).

repeat blood cultures were negative and repeat echocardiogram showed a well-organized and calcified mitral valve consistent with healed vegetation and mild mitral regurgitation (Figure 3).

3. Discussion

Historically, SPE was discovered on the autopsy of patients who died of pneumonia[1]. Pneumococcus was once accountable for 15% all IE, but rates drastically declined with the advent of penicillin in 1940 and pneumococcal vaccination in 1977 [2,4,5]. Few cases of SPE are currently reported in developed nations, but unvaccinated and immunocompromised populations are at increased risk with mortality rates reaching 60%[2]. This is due to the rapid and persistent virulence of pneumococcus that results in large vegetations and destruction of endothelial tissue. Pneumococcus has a proclivity for the aortic valve but generally targets left-sided valves. SPE is challenging to eradicate and frequently causes systemic embolization; valvular destruction, abscess, and perforation; and heart failure [4,6]. Understanding the virulence

factors of invasive pneumococcal disease has provided a platform for prevention and treatment strategies [5,7,8].

Streptococcus pneumoniae is a gram-positive, catalase-negative diplococcus facultative anaerobe. Most pneumococcal strains are encapsulated with antigenic polysaccharides coating the capsular surface[6]. Serotyping has utilized these antigens to classify their immunogenicity and virulence, perform antibiotic susceptibility testing, and target vaccination[9]. There are currently 97 known serotypes, but few are associated with invasive disease[10]. Serotypes 12, 1, and 8 are the most common among patients with SPE [5,10]. Serotype negative strains are rare but particularly virulent due to loss of capsule expression, which results in higher hydrophobicity and expression of surface protein K that facilitates adhesion and biofilm formation. Observation of *in vitro* studies has shown that certain strains can induce this capsular loss during the stationary phase to become nontypeable [6,11]. Serotype switching due to capsular gene mutation is another mechanism of disease. This has been demonstrated with invasive serotype 3 and penicillin-resistant serotype 23F[12]. The second line of

Figure 3. Post-treatment echocardiogram showing well organized and calcified mitral valve consistent with healed vegetation.

pneumococcal defense is the peptidoglycan cell wall. Deacetylation of the glycan chain aids the escape of phagocytosis via lysozyme resistance. Pneumococcal binding proteins can also inactivate complement and mask cell recognition. Colonization is promoted with IgA binding and protease-induced cleavage, with toll-like receptor signaling pathways and teichoic acids ensuring widespread
inflammation. Tissue destruction is perpetuated upon microbe lysis via a cytoplasmic toxin, pneumolysin, which forms pores within host-cell membranes. Pneumolysin is also implicated in hemolysis, which promotes platelet activation and vegetation formation. Heme transporters sequester the iron, while other lipoproteins confiscate host magnesium, which become microbial antioxidant and energy sources. The now protected pneumococcus secretes hydrogen peroxide inducing chronic oxidative stress in the vulnerable host cell [6,11].

Despite its virulence, pneumococcus is typically a commensal organism that colonizes the oral cavity and nasopharynx. It only becomes opportunistic and causes invasive disease among immunosuppressed patients [4,6,11]. The lung is the most common portal of entry, where it migrates to the valves via direct extension and bacteremia[6]. It can also invade the pericardium, meninges, peritoneum, and joints [13,14]. Alcoholism is the biggest risk factor for pneumococcal IE [7,15]. Alcohol abuse leads to increased oropharyngeal pneumococcal colonization, while aspiration is a conduit for invasion. Acquired hyposplenism with reticuloendothelial system dysfunction limits the clearance of the encapsulated pneumococcus, and bone marrow suppression cause leukopenia and decreases formation of antigen-specific antibodies [6,15].

Beta-lactams are first-line treatment for SPE, but their time dependent, bacteriostatic properties and antimicrobial resistance limit their efficacy [8,10]. The activity of beta-lactams is reduced against highly dense bacterial inoculums, where they require a greater minimum inhibitory concentration or display loss of bactericidal action [8,16]. This is further challenged by multiple vegetation layers of fibrin and platelets, which become a mechanical barrier to penetration [8,14]. Additionally, microbe laden biofilms induce a quiescent stationary phase that shortens the activity of beta-lactams [16,17]. Pneumococcal resistance to beta-lactams is also a growing problem[8]. Recent US rates of penicillin and cephalosporin are estimated at 4% and 2.4%, respectively, while less than 1% of pneumococcus isolates are resistant to quinolones [18,19].

Combination therapy has been suggested to overcome the limitations of beta-lactams via antimicrobial synergy that optimizes pharmacokinetics and pharmacodynamics, and improves rates of susceptibility [14,18,19]. Such regimens may be particularly useful in SPE, which are often polymicrobial due to seeding of both pneumococcal and atypical bacteria from the lungs[6]. Recent data from the POET (*Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis*) demonstrated that switching to combination oral antibiotics after at least 10 days of IV therapy was noninferior to IV only treatment regimens in left-sided endocarditis[3]. All patients in the POET trial had gram-positive IE, of which nearly half consisted of streptococcus. Oral regimens included antibiotics from two different classes with combinations that included penicillin with the addition of fluoroquinolone, rifampin, or clindamycin[3].

4. Conclusion

Invasive pneumococcus is relentlessly virulent, due to its ability to escape and oppress the host immune system, and destruct host cells. SPE is uncommon in developed nations, but immunocompromised and unvaccinated patients are still at significant risk. The consequence of untreated SPE is irreversible valvular destruction or death [4,6]. While IV beta-lactams are the preferred therapy, switching to oral combination antibiotics may be an efficacious alternative[3].

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Rana Garris http://orcid.org/0000-0002-1710-4944
Nirmal Guragai http://orcid.org/0000-0002-6477-7789

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