

Clinical Characteristics of Community-Acquired Viridans Streptococcal Pneumonia

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Background: Viridans streptococci (VS) are a large group of streptococcal bacteria that are causative agents of community-acquired respiratory tract infection. However, data regarding their clinical characteristics are limited. The purpose of the present study was to investigate the clinical and radiologic features of community-acquired pneumonia (CAP) with or without parapneumonic effusion caused by VS.

Methods: Of 455 consecutive CAP patients with or without parapneumonic effusion, VS were isolated from the blood or pleural fluid in 27 (VS group, 5.9%) patients. *Streptococcus pneumoniae* was identified as a single etiologic agent in 70 (control group) patients. We compared various clinical parameters between the VS group and the control group.

Results: In univariate analysis, the VS group was characterized by more frequent complicated parapneumonic effusion or empyema and bed-ridden status, lower incidences of productive cough, elevated procalcitonin (>0.5 ng/mL), lower age-adjusted Charlson comorbidity index score, and more frequent ground glass opacity (GGO) or consolidation on computed tomography (CT) scans. Multivariate analysis demonstrated that complicated parapneumonic effusion or empyema, productive cough, bed-ridden status, and GGO or consolidation on CT scans were independent predictors of community-acquired respiratory tract infection caused by VS.

Conclusion: CAP caused by VS commonly presents as complicated parapneumonic effusion or empyema. It is characterized by less frequent productive cough, more frequent bed-ridden status, and less common CT pulmonary parenchymal lesions. However, its treatment outcome and clinical course are similar to those of pneumococcal pneumonia.

Keywords: Community-Acquired; Empyema; Respiratory Tract Infections; Viridans Streptococci

Introduction

Viridans streptococci (VS) are a heterogeneous group of streptococci that remain when β -hemolytic streptococci, enterococci, and pneumococci are excluded¹. VS, part of the normal microbial flora of humans, are most prevalent in the oral cavity and upper respiratory tract, followed by the gastrointestinal tract and female genital tract, particularly the vagina^{2,3}. VS are generally considered harmless commensals but their introduction to sterile sites outside of normal habitats can cause severe infections, such as endocarditis⁴. Although VS were previously thought to rarely cause community-acquired pneumonia (CAP)⁵, they have emerged as a causative agent of lung abscess and empyema in several case series^{3,6-8}. In recent studies, VS were reported to be the main etiologic agent of

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empyema^{9,10} and lung abscess¹¹⁻¹³.

Community-acquired respiratory tract infection caused by VS is not as rare as previously believed; VS accounted for 3%–15% of CAP in a few studies^{8,13}. However, data are sparse regarding the clinical and radiologic features of community-acquired VS pneumonia with or without parapneumonic effusion. The aim of the present study was to investigate the clinical characteristics of CAP by comparing the clinical and computed tomography (CT) parameters between patients with CAP caused by VS and those with pneumococcal pneumonia.

Materials and Methods

1. Study design

This study included patients fulfilling the following criteria: (1) a new radiographic infiltrate and two or more of symptoms or signs (cough, sputum, dyspnea, fever, pleuritic chest pain, crackles, or rhonchi); or (2) complicated parapneumonic effusion or empyema.

Complicated parapneumonic effusion or empyema was diagnosed if the parapneumonic effusion fulfilled one of the following criteria: (1) pleural fluid pH <7.2; (2) pleural fluid glucose <60 mg/dL; (3) microorganisms identified by Gram stain or cultured from pleural fluid; and (4) presence of frank pus in the pleural space. Patients with hospital-acquired pneumonia¹⁴, healthcare-associated pneumonia¹⁴, an active thoracic malignancy, or immunosuppression were excluded.

The present study was retrospectively performed, and a total of 933 patients with CAP with or without parapneumonic effusion were hospitalized and treated at Kyungpook National University Hospital (KNUH), a tertiary referral center, in Daegu, South Korea, between January 2011 and October 2013. Regardless of the presence or absence of parapneumonic effusion, the VS group included CAP patients with blood culture or pleural fluid positive for VS. We selected CAP patients due to *Streptococcus pneumoniae* as the control group. Pneumococcal pneumonia was diagnosed based on a positive urinary pneumococcal antigen test result or isolation of *S. pneumoniae* from the sputum, blood, or pleural fluid samples. Patients with mixed infections were excluded from the control group. This study was approved by the Institutional Review Board of the KNUH (2013-12-040), which waived the requirement for written informed consent because of the retrospective nature of the study.

2. Data collection

Demographic data including age, gender, smoking history, heavy drinking, and body-mass index (BMI) were reviewed. Heavy drinking was defined as the consumption of seven or

more drinks on one occasion for men and five or more drinks for women¹⁵. Risk factors for aspiration included impaired swallowing due to neurologic disease, mechanical obstruction or esophageal dysfunction, impaired consciousness, and history of vomiting or witnessed aspiration, as previously defined¹⁶. Bed-ridden status and comorbid conditions were checked, and Charlson comorbidity index (CCI) scores were calculated¹⁷. The presence of respiratory symptoms, altered mental status, and vital signs were recorded. The severity of pneumonia at initial presentation was defined according to the pneumonia severity index (PSI)¹⁸ and CURB-65¹⁹ score. Clinical course, measured by hospital stay, treatment success, in-hospital mortality, and use of mechanical ventilation or inotropic support were reviewed. Treatment success was defined as cases with clinically and radiologically improved status. Lastly, complicated pleural effusion or empyema and pleural drainage with percutaneous catheter or chest tube were included in the parameters.

Blood laboratory parameters including white blood cell count, erythrocyte sedimentation rate, and levels of C-reactive protein, procalcitonin, N-terminal-pro-B-type-natriuretic peptide, troponin I, sodium, albumin, and blood urea nitrogen were compared between the two groups.

3. Radiologic evaluation

CT scans were reviewed by one radiologist and one chest physician and a consensus diagnosis was reached. We checked for consolidation, ground glass opacity (GGO), centrilobular nodules, bronchial wall thickening, cavity, and pleural effusion. Similar to previous studies^{20,21}, patients were classified into four levels by measuring the maximum fluid thickness between the visceral and parietal pleurae on a CT scan: no pleural effusion; small pleural effusion, fluid thickness of 5–20 mm; moderate pleural effusion, fluid thickness of 21–50 mm; and large pleural effusion, fluid thickness >50 mm.

4. Statistical analysis

Statistical analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Data were expressed as medians with interquartile ranges (IQR) for continuous variables and as numbers with percentages for categorical variables. The Mann-Whitney U test was used to compare continuous variables between the VS and control groups, and chi-squared test or Fisher exact test was used to compare categorical variables. Multivariate logistic regression analysis was used to identify predictors of CAP caused by VS with or without parapneumonic effusion. The Hosmer-Lemeshow test was used as a test to assess the goodness-of-fit of logistic regression models. p-values of <0.05 were considered statistically significant.

Results

1. Patient characteristics

Causative microbes were identified in 455 from a total of 933 patients diagnosed with CAP with or without parapneumonic effusion. VS were isolated in 27 patients (5.9%), and *S. pneumoniae* were identified in 97 patients, 27 of whom were excluded from analysis owing to the presence of mixed infections. *S. mitis/oralis* were the most common VS species, followed by *S. sanguis* and *S. constellatus* (Figure 1). Only one VS species was isolated from each patient, except one patient in whom *S. mitis/oralis* and *S. parasanguinis* were cultured from the blood samples. We compared various parameters between the VS (n=27) and control groups (n=70).

Age, male gender, smoking history, BMI, and heavy drinking did not significantly differ between the VS and control groups (Table 1). There were no significant differences in CCI between the two groups, but the VS group had a significantly lower age-adjusted CCI score than the control group. The frequency of bed-ridden status was significantly higher in the VS group than in the control group. The incidence of risk factors for aspiration was not significantly different between the two groups.

Productive cough was significantly less common in the VS group than in the control group. Complicated parapneumonic effusion or empyema occurred more frequently in the VS group than in the control group. The PSI and CURB-65 scores

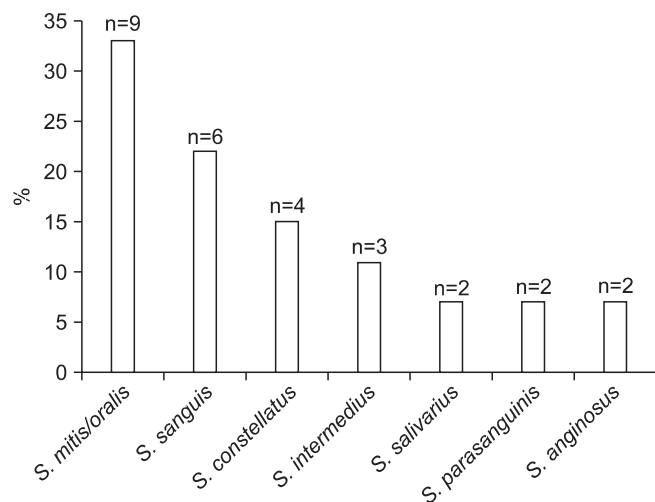


Figure 1. Viridans streptococcal isolates. *Streptococcus mitis/oralis* is the most common pathogen, followed by *S. sanguis* and *S. constellatus* (% the number of each isolate per the number of total viridans streptococcal isolates): *S. mitis/oralis* is isolated from blood (n=8) and pleural fluid (n=2); *S. sanguis* is from blood (n=6); *S. constellatus* is from blood (n=2) and pleural fluid (n=2); *S. intermedius* is from pleural fluid (n=3) and blood (n=1); *S. salivarius*, *S. parasanguinis*, and *S. anginosus* is from blood (n=2, respectively).

did not significantly differ between the two groups. No differences were observed in clinical course parameters between the two groups, including hospital stay, success rate, and in-hospital mortality. Overall, the median duration of follow-up was 46 days (IQR, 12–113 days). The most commonly used antibiotic regimen in the two groups was cefotaxime or ceftriaxone plus macrolide or fluoroquinolone (Figure 2).

2. Blood laboratory findings

Laboratory findings are summarized in Table 2. Procalcitonin level was significantly lower in the VS group than in the control group. The remaining parameters did not significantly differ between the two groups.

3. CT findings

CT findings are presented in Table 3. Pleural effusion was more frequently observed in the VS group than in the control group. In contrast, pulmonary parenchymal lesions including consolidation and GGO were less commonly observed in the VS group.

4. Prediction of community-acquired respiratory tract infection caused by VS

Parameters significant by univariate analysis were selected

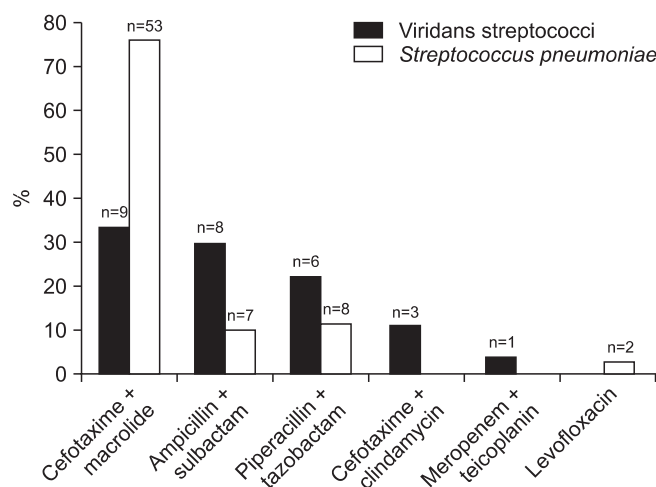


Figure 2. Antibiotic regimens for community-acquired pneumonia. Each regimen includes the following antibiotics: cefotaxime+macrolide: cefotaxime (or ceftriaxone) plus macrolide (or fluoroquinolone); ampicillin+sulbactam: ampicillin+sulbactam with or without macrolide; piperacillin+tazobactam: piperacillin+tazobactam (piperacillin+sulbactam, ticarcillin+clavulanic acid, or maxipime) with or without fluoroquinolone (or macrolide); cefotaxime+clindamycin: cefotaxime plus clindamycin; meropenem+teicoplanin: meropenem plus teicoplanin (or vancomycin); levofloxacin: levofloxacin (or moxifloxacin).

Table 1. Baseline and clinical characteristics of subjects

Characteristic	Viridans streptococci (n=27)	<i>Streptococcus pneumoniae</i> (n=70)	p-value
Age, yr	67 (52–76)	71 (62–79)	0.173
Female gender	10 (37.0)	14 (20.0)	0.114
Smoking history			
Ever-smoker	15 (55.6)	45 (64.3)	0.488
Pack-years	40 (20–80)	30 (25–60)	0.402
Heavy drinking	7 (25.9)	16 (22.9)	0.793
Body mass index, kg/m ²	22.5 (20.0–24.0)	21.0 (19.0–24.0)	0.896
Comorbid conditions			
Chronic pulmonary disease	13 (48.1)	24 (34.3)	0.247
Malignancy	1 (3.7)	7 (10.0)	0.437
Diabetes mellitus	7 (25.9)	15 (21.4)	0.787
Hypertension	9 (33.3)	21 (30.0)	0.808
Ischemic heart disease	2 (7.4)	9 (12.9)	0.722
Chronic liver disease	2 (7.4)	3 (4.3)	0.616
Chronic kidney disease	0	2 (2.9)	>0.999
Stroke	1 (3.7)	1 (1.4)	0.481
Congestive heart failure	2 (7.4)	2 (2.9)	0.309
Atrial fibrillation	0 (0)	5 (7.1)	0.318
Gastrectomy	0 (0)	2 (2.9)	>0.999
Psychiatric disorder	1 (3.7)	4 (5.7)	>0.999
Rheumatoid arthritis	0	1 (1.4)	>0.999
Risk factors for aspiration	8 (29.6)	19 (27.1)	0.805
Bed ridden status	4 (14.8)	2 (2.9)	0.049
Charlson comorbidity index	1 (0–2)	1 (0–2)	0.303
Charlson comorbidity index, age-adjusted	3 (0–5)	4 (2–5)	0.025
Altered mental status	4 (14.8)	8 (11.4)	7.333
Fever	17 (63.0)	40 (57.1)	0.651
Productive cough	8 (29.6)	60 (85.7)	<0.001
Chest pain	11 (40.7)	18 (25.7)	0.215
Dyspnea	14 (51.9)	46 (65.7)	0.247
Hemoptysis	2 (7.4)	4 (5.7)	0.669
Mean blood pressure	89 (81–100)	85 (74–94)	0.075
Pulse rate, /min	103 (89–118)	92 (79–110)	0.050
Respiratory rate, /min	20 (19–22)	20 (19–23)	0.554
CURB-65 ≥2	10 (37.0)	38 (54.3)	0.174
PSI score	82 (63–123)	90 (72–125)	0.449
PSI class IV or V	12 (44.4)	35 (50.0)	0.657
Hospital stay, days	11 (4–18)	8 (4–12)	0.366
Treatment success	22 (81.5)	61 (87.1)	0.525
In-hospital mortality	3 (11.1)	7 (10.0)	>0.999
Mechanical ventilation or inotropic support	3 (11.1)	14 (20.0)	0.383
Pleural drainage	9 (33.3)	3 (4.3)	<0.001
Complicated parapneumonic effusion or empyema	9 (33.3)	1 (1.4)	<0.001

Values are presented as median (interquartile range) or number (%).

CURB-65, a six point score, one point for each of confusion, urea >7 mmol/L, respiratory rate ≥30/min, low systolic (<90 mm Hg) or diastolic (≤60 mm Hg) blood pressure, and age ≥65 years.

PSI: pneumonia severity index.

Table 2. Blood laboratory findings of subjects

	No.	Viridans streptococci	No.	<i>Streptococcus pneumoniae</i>	p-value
WBC count, / μ L	27	12,250 (9,170–16,090)	70	12,285 (8,260–17,297)	0.470
Neutrophil, %	27	84 (76–90)	70	87 (81–91)	0.161
ESR, mm/hr	25	50 (29–63)	70	38 (21–63)	0.250
CRP, mg/dL	27	13 (4–19)	70	14 (7–24)	0.230
Procalcitonin, ng/mL	20	0.50 (0.00–1.00)	66	3.00 (0.75–10.25)	0.002
NT-proBNP, pg/mL	23	244 (109–2,640)	66	942 (347–2,748)	0.763
TroponinI, ng/mL	19	0.015 (0.015–0.450)	65	0.015 (0.015–0.080)	0.187
Sodium, mmol/L	27	135 (131–140)	70	137 (134–140)	0.075
Albumin, g/dL	27	3.2 (2.7–3.9)	70	3.2 (2.8–3.8)	0.902
BUN, mg/dL	27	17 (13–26)	70	22 (14–33)	0.531
Creatinine, mg/dL	27	0.8 (0.6–1.1)	70	1.1 (0.8–1.6)	0.464

Values are presented as median (interquartile range).

WBC: white blood cell; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; NT-proBNP: N-terminal-pro-B-type-natriuretic peptide; BUN: blood urea nitrogen.

Table 3. Computed tomographic findings of subjects

	Viridans streptococci (n=25)	<i>Streptococcus pneumoniae</i> (n=70)	p-value
Pleural effusion, mm	17 (68.0)	22 (31.4)	<0.001
No	8 (32.0)	48 (68.6)	
5–20	8 (32.0)	20 (28.6)	
21–50	4 (16.0)	2 (2.9)	
>50	5 (20.0)	0	
Lymphadenopathy	11 (44.0)	24 (34.3)	0.387
Consolidation	18 (72.0)	66 (94.3)	0.003
Ground glass opacity	7 (28.0)	37 (52.9)	0.032
Bronchial wall thickening	18 (72.0)	59 (84.3)	0.178
Centrilobular nodules	2 (8.0)	13 (18.6)	0.213
Cavity	2 (8.0)	0	0.017
Zone			0.266
Upper	2 (8.0)	5 (7.1)	
Lower	21 (84.0)	64 (91.4)	
Random	2 (8.0)	1 (1.4)	

Values are presented as number (%).

Table 4. Multivariate analysis for predictors of viridans streptococcal pneumonia

	Odds ratio	95% Confidence interval	p-value
Complicated parapneumonic effusion/empyema	30.68	2.45–383.41	0.008
Productive cough	0.22	0.05–0.96	0.043
Bed-ridden status	16.80	1.90–148.84	0.011
GGO or consolidation on CT	0.03	0.00–0.43	0.010

GGO: ground glass opacity; CT: computed tomography.

as candidate predictors for multivariate analysis: complicated parapneumonic effusion or empyema, productive cough, elevated procalcitonin (>0.5 ng/mL), bed-ridden status, age-adjusted CCI score, and GGO or consolidation on CT scans. The Hosmer-Lemeshow test indicated that the overall model fit was good ($p=0.699$). Multivariate analysis showed that complicated parapneumonic effusion or empyema, productive cough, bed-ridden status, and GGO or consolidation on CT scans were independent predictors of community-acquired respiratory tract infection caused by VS (Table 4).

Discussion

The present study showed that, although uncommon, VS may be a cause of community-acquired respiratory infection. Compared with pneumococcal pneumonia, respiratory tract infection due to VS was characterized by less frequent productive cough and more frequent bed-ridden status. One-third of patients presented with complicated parapneumonic effusion or empyema. However, treatment outcome and prognosis of VS pneumonia did not differ from those of pneumococcal pneumonia.

Similar to previous studies^{8,13}, we found VS to be the causative agent in 5.9% of CAP cases, suggesting that pneumonia caused by VS might not be as rare as previously reported. VS are normal microbial flora of the mouth, upper respiratory tract, gastrointestinal tract, and vagina³. VS can cause respiratory tract infection through the following routes: (1) aspiration of oral secretions; (2) direct implantation due to trauma or surgery; (3) by extension from contiguous foci of infection; and (4) via the bloodstream from distant sites⁷. In contrast to a previous study⁹, no patients in this study had a history of trauma or surgery, which excludes direct implantation as a likely pathogenic route. No contiguous foci of infection were detected on CT scans of 25 patients whose CT scans were available. Although only six patients from the VS group underwent echocardiography, multiple nodules or multifocal infiltrates suggestive of septic pulmonary embolism²² were not observed. Consequently, aspiration of oral secretions is the most plausible access route of VS into the respiratory tract. Furthermore, a previous study reported mixed infections comprising anaerobes and members of *S. milleri* group to be common in thoracic infections, especially lung abscess and empyema⁸. These results suggest that respiratory tract infection caused by VS may commonly present with aspiration pneumonia. However, there was no difference in aspiration risk factors between the VS and *S. pneumoniae* groups in the present study, which corresponds to a previous study where only a half of patients with *S. milleri* pulmonary infections were predisposed to aspiration⁸.

VS are one of the main etiologic agents of empyema. In the same context, we found that two-thirds of patients with VS

infection had pleural effusion and one-third presented with complicated pleural effusion or empyema. This is a major feature that distinguishes VS infection from pneumococcal pneumonia. By contrast, pulmonary parenchymal lesions, such as consolidation and GGO, were less frequently observed in patients with VS infection. Similarly, productive cough occurred less commonly in the VS group than in the *S. pneumoniae* group. Serum procalcitonin elevation reflects severe bacterial infection, in particular pneumonia²³. Serum procalcitonin level was significantly lower in the VS group, although the p -value did not reach a statistical significance in multivariate analysis. This finding was in line with lower PSI and CURB-65 score in the VS group despite no statistical significance, suggesting that VS might cause less severe infection compared with *S. pneumoniae*.

Like pneumococcal pneumonia, most patients with VS pneumonia were successfully treated with antibiotics with or without pleural drainage. In addition, there were no differences in in-hospital mortality, hospital stay, and mechanical ventilation or inotropic support between the two groups. These results can be explained by the fact that all VS isolates were susceptible to commonly used antibiotics, such as cefotaxime (data not shown).

The present study has some limitations. Due to its retrospective nature, the potential for selection bias should be noted. However, to minimize this potential, all consecutive patients were enrolled in the study. Because VS pneumonia was diagnosed only on the basis of positive blood or pleural fluid cultures, the proportion of patients with VS pneumonia might be underestimated and the possibility that more severe form of VS pneumonia was chosen could not be excluded. As VS is also a common pathogen causing infective endocarditis, this diagnosis required exclusion. Of 21 patients from whom VS were cultured only using blood samples, six underwent echocardiography, which showed no evidence of endocarditis. However, the remaining patients had typical CT findings suggestive of lobar pneumonia or bronchopneumonia. Thus, the possibility of endocarditis was considered to be low.

In conclusion, CAP caused by VS commonly presents with complicated parapneumonic effusion or empyema. It is characterized by less frequent productive cough, more frequent bed-ridden status, and less common pulmonary parenchymal lesions on CT scans. However, its clinical course and treatment outcome are similar to those of pneumococcal pneumonia.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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