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Retrospective analysis of culture-negative versus culture-positive postoperative spinal infections

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Abstract

Retrospective analysis.

This study aimed to investigate the characteristics, clinical features, and outcomes of culture-negative (CN) and culture-positive (CP) postoperative spinal infections (PSIs).

Causative organism cultures and the use of adequate antibiotics are essential for treating postoperative spinal wound infections. However, managing infected surgical sites with negative wound culture results is a common clinical problem. Although the outcomes of microbiologically confirmed PSIs have been well studied, the outcomes and clinical characteristics of CN PSIs have not been previously published.

Between January 1995 and December 2014, 69 patients diagnosed with PSIs were enrolled. Enrolled patients were classified into 2 groups: CN (28 patients) and CP (41 patients). Baseline data, clinical manifestations, specific treatments, and treatment outcomes were compared with the groups.

The overall rate of CN PSI was 40.6% (28/69). Baseline data and clinical manifestations were similar between the 2 groups. There were no significant differences in the duration of parenteral antibiotic use between the CN and CP groups. Revision surgery was required less often for the CN group (64.3%) than for the CP group (87.8%) ($P = .020$). Revision surgeries were repeated 0.82 times/case in the CN group and 1.34 times/case in the CP group ($P = .014$). Treatment outcomes, such as poor radiologic findings, need for additional anterior surgery, extension of fusion to adjacent segment surgery, and total length of hospital stay, were not different between groups.

Revision surgery was performed less often for the CN group than for the CP group. From the perspective of revision surgery, CN PSIs have better prognosis than CP PSIs. However, clinical presentations and radiologic prognoses were not different between the two groups. We suggest that CN PSIs may be treated in the same way as CP PSIs.

Abbreviations: BMI = body mass index, CDC = centers for disease control, CN = culture-negative, CP = culture-positive, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, PJI = periprosthetic joint infection, PSI = postoperative spinal infection, SSI = surgical site infection.

Keywords: culture negative, organism, postoperative infection, revision surgery, spinal infection, spine, surgical wound

1. Introduction

A postoperative spinal infection (PSI) is a devastating complication that places patients at risk for surgical failure, poor outcomes, adverse neurological deficits, and even death.[1,2] Causative organism cultures and adequate antibiotics are essential for treating PSIs. However, managing infected surgical sites with negative wound culture results is a common clinical problem. Previous reports of the microbiology of surgical site infections (SSIs) suggested that 10% to 30% of all such cultures do not exhibit bacterial growth even when clinical signs of infection are present.[3–5]

Although the outcomes of microbiologically confirmed PSIs have been well studied, the outcomes and clinical characteristics of cases of culture-negative (CN) PSIs have not been previously published.

The identification of microorganisms causing PSI is a critical task for the selection of appropriate treatment options and prognosis prediction; therefore, CN PSIs are considered an important clinical issue.[6] Although the clinical treatment outcomes of PSI with confirmed infectious microorganisms have been well-documented, there are few reports regarding clinical outcomes and demographic characteristics of patients with CN PSIs. Therefore, we aimed to share clinical findings, treatment methods, and outcomes of CN PSIs.

2. Materials and methods

This was a retrospective, case-controlled observational study. The study was approved on December 21, 2017 by the

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Soonchunhyang Institutional Review Board (2017-01-006-001). We used an institution-based electronical registry database to retrieve discharge diagnoses for all cases of "infectious spondylitis," "postoperative wound infection," and "postoperative infection" from January 1995 to December 2014 to identify the PSIs treated by an orthopedic spine department. Each case was manually reviewed. We based our criteria for defining and classifying PSIs on the Centers for Disease Control and Prevention National Health Safety Network criteria, and both superficial and deep SSIs were included.[7] Superficial SSIs included infections that occurred within 30 days after the operative procedure and involved only the skin and the subcutaneous tissue of the incision. Deep SSIs included infections that occurred within 30 days after the operative procedure if no implant was is left in place or within 1 year if the implant was in place and the infection seemed to be related to the operative procedure and involved deep soft tissues (e.g., fascial and muscle layers) of the incision. All cases were confirmed by an infectious diseases physician and the attending surgeon.[7,8] We launched a multidisciplinary approach to PSI in 2001; since then, we have consulted with an available infectious disease specialist about antibiotics, duration of use, reoperation, and other matters. When we could gain access to the wound or treat it with surgery, we performed cultures using samples obtained from the surgical sites. However, there were cases where this was not possible, a blood culture was performed for every case. Specimen identification and antimicrobial susceptibilities were determined using the Microscan Walkaway 96 system (Beckman Coulter Inc., Brea, CA). The determination of complete recovery from PSI was made by a clinician who performed a comprehensive evaluation of clinical features and laboratory tests such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

We analyzed age, sex, comorbidity, body mass index (BMI), index surgery method, the use of spinal instrumentation and bone graft substitutes, and postoperative albumin levels as baseline data. We analyzed the chronological type, SSI symptoms or signs (increasing or persisting back pain; localized swelling, redness, or feeling of heat; wound dehiscence; and fever $>38\,^{\circ}C$) indicated by the CDC criteria,[9,10] ESR/CRP, antibiotics exposure, layer of infection, and blood/wound culture as clinical characteristics of PSI. Chronologically, PSI was classified as acute onset ($\leq$3 weeks after the index surgery) or delayed onset (>3 weeks after the index surgery). PSI was diagnosed by a surgeon or infectious disease specialist, and ESR/CRP were investigated when the PSI was diagnosed. Antibiotic exposure referred to any use of antibiotics during the 2 weeks before culture samples were obtained. Revision surgery, revision method, antibiotic use, and the duration of antibiotic use were analyzed for specific PSI treatments or outcomes. We defined revision surgery only as surgery that occurred under general anesthesia and excluded irrigation and simple debridement under local anesthesia. We investigated parenteral and oral antibiotic use. We analyzed poor radiologic findings, incidence of additional anterior surgery, extension of fusion to adjacent segment, total length of hospital stay, and death during the treatment course as treatment outcomes of PSI.[11] Poor radiologic findings were defined as disc space collapse, pedicle screw pull-out at the final follow-up, compared with postoperative radiograph findings associated with deterioration of clinical symptoms. Additional anterior surgery and extension of fusion were defined as cases in which a normal anatomic structure was damaged by repeated invasive revision surgery rather than the planned index surgery. If the index surgery had not involved infection, then the virgin anatomical structure of the retroperitoneal space would not have been violated. For a similar reason, additional segments would not have been fixed. Therefore, we considered the additional anterior surgery and extension of fusion for poor treatment outcomes of PSI.

We performed all statistical analyses using SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL). The Chi-square test and Fisher exact test were used to determine the differences in proportions for each variable, and the independent samples *t* test or Mann–Whitney *U* test was used to compare the continuous variables between groups. We considered $P<.05$ as statistically significant.

3. Results

We identified a total of 319 cases of infectious spondylitis. However, 250 were primary spinal infections (104 cases of tuberculous spondylitis, 145 cases of pyogenic spondylitis, 1 case of parasite infection); therefore, they were excluded. Ultimately, 69 patients met our criteria and were included in the study.

3.1. Baseline data and clinical characteristics

We retrospectively analyzed 69 patients in this study (42 men and 27 women). The mean age was 70.6 years (range, 36–94 years). The minimum follow-up was 18 months (mean, 42.7 months; range, 18–140 months) for all except 1 case due to death during the treatment course. Forty-six patients had PSIs from index surgeries that had been performed at our hospital, and 23 patients with PSIs were transferred from other hospitals with their medical information after the index surgeries. We investigated the hospitals that transferred patients to our hospitals. A total of 23 hospitals (17 secondary referral hospitals and 6 tertiary referral hospitals) were identified. Of them, 9 patients were referred from Seoul, 9 from Gyeonggi-do, 2 from Gangwon-do, 2 from Chungcheongnam-do, and 1 from Chungcheongbuk-do. The index surgeries were posterior fusions (40 cases; 58.0%), anterior and posterior fusions (12 cases; 17.3%), and decompressions (17 cases; 24.6%). First-generation cephalosporin was used as prophylactic antibiotics before the index surgery.

The overall rate of CN PSIs was 40.6% (28 CN results for 69 cases) in our study; age, sex, comorbidity, BMI, index surgery, the use of instrumentation and bone graft substitutes, and postoperative albumin levels were not different between CN and CP patients (Table 1). Chronological type of PSI and infection symptoms/signs was not significantly different between the 2 groups. Among the 5 SSI signs, increasing or persisting back pain was more frequent among CP patients than among CN patients, although the difference was not significant ($P=.053$). ESR/CRP, antibiotic exposure, antibiotic duration, and layer of infection were similar between the CN and CP groups (Table 2).

3.2. Specific PSI treatment and results

Revision surgery was performed less often for the CN group (64.3%) than for the CP group (87.8%) ($P=.020$) (Table 3), but the detailed revision methods were similar between groups (Table 3). Glycopeptides (vancomycin or teicoplanin) were used most frequently for both groups. The duration of antibiotic use was slightly lower for the CN group (32.6 ± 9.8 days) than for the CP group (39.2 ± 23.7 days), although this difference was not significant ($P=.714$). There were fewer repeated revision

Table 1

Baseline data between culture negative (CN) and culture positive (CP) patients.

Variable	CN patients (n = 28)	CP patients (n = 41)	*P*-value†	OR	95% CI	
					Lower	Upper
Age, mean (SD)$	67.5 ± 13.6	72.6 ± 11.9	.105			
Sex			.983			
Male	17 (60.7%)	25 (61.0%)		0.989	0.370	2.647
Female	11 (39.3%)	16 (39.0%)		Reference		
Comorbidity						
Cigarette smoker	7 (25%)	17 (37%)	.181	0.471	0.163	1.355
Hypertension	13 (46%)	18 (37%)	.836	1.107	0.422	2.908
Diabetes mellitus	4 (14%)	9 (17%)	.982	0.593	0.163	2.155
Liver cirrhosis‡	0 (0%)	2 (5%)	.726	N/A		
Hemodialysis‡	1 (3%)	1 (2%)	1.000	1.481	0.089	24.719
Old age (≥70)	13 (43%)	27 (56%)	.108	0.449	0.168	1.202
No. of comorbidities			.154			
No. <3	23 (82.1%)	31 (75.6%)		1.484	0.446	4.934
No. ≥3	5 (17.9%)	10 (24.4%)		Reference		
BMI, mean (SD)$	23.7 ± 3.2	24.9 ± 3.3	.147			
Index surgery			.939			
Posterior fusion	16 (57.1%)	23 (56.1%)		0.957	0.315	2.908
Anterior and posterior fusion	4 (14.3%)	7 (17.1%)		0.786	0.170	3.626
Decompression	8 (28.6%)	11 (26.8%)		Reference		
Spinal instrumentation			.531			
No	8 (28.6%)	9 (22.0%)		1.422	0.471	4.290
Yes	20 (71.4%)	32 (78.0%)		Reference		
Bone graft substitute	5 (17.9%)	9 (22.0%)	.756			
Postop. albumin level (mg/dL), mean (SD)$	3.2 ± 0.7	3.0 ± 0.6	.122			

CN = culture negative, CP = culture positive, No. = number, Postop. = postoperative.

† *P*-value by Chi-squared test.

$ *P*-value by Student *t* test.

‡ *P*-value by Fisher exact test.

surgeries performed for the CN group (0.82 times/case) than for the CP group (1.34 times/case) ($P = .014$). Poor radiologic findings, need for additional anterior surgery, and extension of fusion to adjacent segment surgery were not different between the CN and CP groups. The total length of hospital stay and the number of deaths during the treatment course were similar between the 2 groups (Table 4).

4. Discussion

The overall rate of CN PSIs was 40.6% in this study. We could not find the rates of CN PSIs in previous reports. However, we were able to calculate the proportions of CN results in other published series in the literature (Table 5).[1,8,12–15] The rate of CN PSIs has been reported to range between 11.1% and 34.5%.[1,12–15] However, another study reported a low rate of 2.9%.[8] CN PSIs have been well-studied by arthroplasty departments, reporting rates between 6.7% and 22.9%.[16–21] Compared with arthroplasty surgery, the rate of CN PSI seems higher. We think that such results may be related to the anatomical characteristics of the spine. First, the spine is located deeper in the body than the knee or hip joints; therefore, it is not easy to detect early highly suggestive infectious symptoms and signs such as localized swelling and heating, redness, wound dehiscence, and pus discharge. Second, a simple examination of wound infections with joint aspiration is difficult in the spine because it is surrounded by important structures such as neural tissues and major vessels. Therefore, spine surgeons may choose to avoid using invasive diagnostic methods for accurate diagnoses. That is, if early postoperative patients report vague or increasing back pain—an unspecific but frequent symptom of spine infection—then the clinicians want that there is no postoperative infection. They may refrain from invasive/expensive diagnostic tests and surgical options with uncertain benefits and instead opt for prolonged use of antibiotics. However, these suggestions should be supported by additional studies.

Spinal instrumentation influences bacterial adhesion promoted by a polysaccharide biofilm that acts as barrier against host defense mechanisms and antibiotics.[2,22] Furthermore, the biofilm makes it difficult to identify causative infectious organism.[23] Serum albumin has an important role in postoperative infections. Decreased concentrations of serum albumin have been associated with an increased risk of overall postoperative infectious complications.[24] In the present study, serum albumin levels and spinal instrumentation were not different between the CN and CP groups. In addition, there were no differences between the 2 groups regarding baseline data and clinical characteristics. CN wound infections have been actively studied in arthroplasty; however, studies of CN PSIs are few. Although direct comparisons are difficult, the demographics of CN and CP periprosthetic joint infections (PJIs) were similar.[16,17]

Possible causes of CN results are administering antibiotics prior to obtaining tissue samples from wounds, slow-growing organisms; furthermore, common contaminants like *Staphylococcus epidermidis* might be ignored as contaminants but they may actually be the cause of postoperative infection.[25] Of these causes, the most frequent is thought to be culturing the infected site after initiating antibiotics.[25] Trampuz et al[26] demonstrated that any use of antibiotics during the 2 weeks before obtaining culture samples was associated with a lower culture yield. Much literature has described that CN PJI patients had significantly more prior antibiotic use than did the CP PJI group.[16–18,26] In

Table 2

Clinical characteristics between culture negative (CN) and culture positive (CP) patients.

Variable	CN patients (n = 28)	CP patients (n = 41)	*P*-value†	OR	95% CI	
					Lower	Upper
Chronological classification			.861			
Acute onset (≤3 wks)	12 (42.9%)	20 (48.8%)		0.788	0.299	2.071
Delayed onset (>3 wks)	16 (57.1%)	21 (51.2%)		Reference		
Symptoms/signs						
Increasing or persisting back pain	20 (71.4%)	37 (90.2%)	.053	0.270	0.072	1.009
Localized swelling	6 (21.4%)	5 (12.2%)	.304	1.964	0.535	7.205
Redness or feeling of heat	12 (42.9%)	20 (48.6%)	.628	0.788	0.299	2.071
Wound dehiscence	3 (10.7%)	1 (2.4%)	.296	4.800	0.473	48.732
Fever (>38 °C)	4 (14.3%)	8 (19.5%)	.574	0.688	0.185	2.549
ESR level (mm/h), mean (SD) at the time of PSI diagnosis§	70.8 ± 27.6	76.8 ± 29.6	.980			
CRP level (mg/dL), mean (SD) at the time of PSI diagnosis§	8.7 ± 17.0	7.8 ± 8.3	.238			
Antibiotic exposure	20 (71.4%)	26 (63.4%)	.698	1.442	0.511	4.070
Exposure duration (days), mean (SD)§	6.4 ± 6.2	7.3 ± 12.9	.244			
Layer of infection			.078			
Superficial	10 (35.7%)	7 (17.1%)		2.698	0.878	8.289
Deep	18 (64.3%)	34 (82.9%)		Reference		
Microorganism						
MSSA		5 (12.2%)				
MRSA		12 (29.3%)				
MSSE		4 (9.8%)				
MRSE		12 (29.3%)				
Pseudomonas aeruginosa		1 (2.4%)				
E coli		2 (4.9%)				
Enterobacter cloacae		1 (2.4%)				
Polymicrobial		4 (9.8%)				

CRP = C-reactive protein, *E coli* = *Escherichia coli*, ESR = erythrocyte sedimentation rate, MRSA = methicillin-resistant *Staphylococcus aureus*, MRSE = methicillin-resistant *Staphylococcus epidermidis*, MSSA = methicillin-sensitive *Staphylococcus aureus*, MSSE = methicillin-sensitive *Staphylococcus epidermidis*.

† *P*-value by Chi-squared test.

§ *P*-value by Mann–Whitney *U* test.

the present study, prior exposure to antibiotics was not different between the CN and CP groups. This finding is contrary to that of previous studies.[16–18,26] We suggest that this finding is due to differences in the definition of positive antibiotic exposure. The present study and that by Trampuz et al[26] defined positive antibiotic use as antibiotic administration within 2 weeks before a culture sample was obtained. Berbari et al[18] and Malekzadeh et al[17] used a timeframe of 3 months. Choi et al[16] provided no definition. Moreover, cases involving preoperative prophylactic antibiotics before revision surgery may have been designated as either positive or negative antibiotic exposure in previous studies. We think that these differences influenced our results.

Additionally, in the present study, the CN and CP PSI groups were similar in terms of the type and the duration of antibiotic use. After 2001, the choice of antibiotics was determined in consultation with an infectious disease specialist. These results

Table 3

Specific treatment between culture negative (CN) and culture positive (CP) patients.

Variable	CN patients (n = 28)	CP patients (n = 41)	*P*-value†	OR (95%CI)
Revision surgery			.020*	
Yes	18 (64.3%)	36 (87.8%)		0.25 (0.07–0.84)
No	10 (35.7%)	5 (12.2%)		Reference
Revision method			.213	
I & D	8 (44.4%)	17 (47.2%)		
Instrumentation	8 (44.4%)	13 (36.1%)		
Removal of implant	2 (11.1%)	6 (16.7%)		
No. of revision surgery mean (SD)§	0.82 ± 0.77	1.34 ± 0.94	.014*	
Use of antibiotics			.716	
Glycopeptides	12 (42.9%)	21 (51.2%)		0.71 (0.27–1.89)
Others	16 (57.1%)	20 (48.8%)		Reference
Duration (days) of parenteral antibiotics treatment mean (SD)§	32.6 ± 9.8	39.2 ± 23.7	.714	
Duration (days) of oral antibiotics treatment mean (SD)§	10.8 ± 6.2	12.0 ± 9.3	.721	
Duration (days) of total antibiotics treatment mean (SD)§	39.1 ± 12.4	51.2 ± 22.7	.161	

Analysis by logistic regression.

* Statistically significant, I & D = incision and drainage, No. = number.

† *P*-value by Chi-squared test.

§ *P*-value by Mann–Whitney *U* test.

Table 4

Outcomes of culture negative (CN) and culture positive (CP) patients.

Variable	CN patients (n = 28)	CP patients (n = 41)	*P*-value†	OR	95% CI	
					Lower	Upper
Poor radiologic findings (loosening, collapse, instability)	12 (42.9%)	24 (58.5%)	.200	1.412	0.201	1.405
Need for additional anterior surgery	7 (25.0%)	11 (26.8%)	.865	0.909	0.303	2.730
Extension of fusion to adjacent segment	1 (3.6%)	6 (14.6%)	.698	0.216	0.025	1.903
Total hospital stay (d), mean (SD)§	72.9 ± 48.1	81.2 ± 37.4	.103			
Death	0 (0%)	1 (2.4%)	N/A	N/A		

N/A = not available.

† *P*-value by Chi-squared test.

§ *P*-value by Mann–Whitney *U* test.

are interesting but not surprising. Even though their study did not involve the spine region, Malekzadeh et al[17] reported similar demographics and outcomes for CN and CP patients; therefore, the presumed microbiology of patients with CN PJIs would be similar to that of patients with CP PJIs, and we agree with this opinion. However, revision surgeries were performed less often for the CN group than for the CP group (64.3% vs 87.8%). Because this study was retrospective in design, we were not able to know the precise reasons for the revision surgery decisions.

In our study, CN PSIs tended to require fewer revision surgeries (odds ratio [OR]: 0.25; range, 0.07–0.84; $P = .020$) and fewer repeated revisions (OR: 0.71; range, 0.27–1.89; $P = .716$) than CP PSIs. However, the final outcomes, such as poor radiologic findings, additional anterior surgery, extension of fusion, the total length of hospital stay, and number of deaths, were similar. Therefore, a CN result itself does not necessarily signify well-treated infections or a good prognosis. Clinically, the most important problem with CN results following PSI is that clinicians do not confirm postoperative wound infections. For instance, if a surgeon performs revision surgery based on clinical suspicion and/or based on radiologic and laboratory abnormalities and the expectations are not met (i.e., there was no eruption of pus at the surgical site and no organisms were detected in the culture), then the clinician can become unsure about whether a surgical site infection is actually present.

There are several limitations in the present study. First, because of its retrospective design, we did not examine CN results more specifically. There are advanced methods of detecting infectious organisms, including sonication of implants, molecular techniques, polymerase chain reaction, and others; however, these methods may not be commonly used in clinical practice. Second, because of the aforementioned reasons, for the above mentioned reasons, decisions regarding revision surgeries could not be standardized. In the case of CP results, the clinician tends to diagnose PSI easily. CP results may cause a psychological bias when determining the active treatment of PSI, such as revision surgery. Additionally, we did not consider detailed explanations of antibiotic usage, duration, selection, or adverse effects. Third, we classified 2 PSI groups as CN and CP. If the organism was cultured, then it was included in the CP PSI group. However, with strict classifications, it is more appropriate to create 3 groups, CP, CN, and no obtained tissue culture, because blood culture tests have lower sensitivity and specificity than tissue culture tests when detecting pathogens.[27] Fourth, we could not investigate quantitative clinical prognoses; we investigated only hospital stays and deaths because the patients in our study had a variety of diagnoses and index surgeries. However, the current study is one of the first to focus on characterizing this important issue of CN results and the clinical features of PSIs.

Causative organisms would not be different if the host conditions were not significantly different; therefore, we suggest that PSI data collection is important. The author's hospital has accumulated data regarding orthopedic surgical site infections after 2001. CN infections were treated like a general CP infections, and this helped prevent excessive antibiotic administration and revision surgery. The pattern of antibiotics used and the revision method were not significantly different between the CN from CP groups in the present study. Moreover, if PSI is strongly suspected but the culture result is negative, then we recommend a multidisciplinary approach for all critical decisions and treatment procedures. We think that the most important issue regarding CN PSI is the difficulty confirming the diagnosis

Table 5

The prevalence of CN postoperative infection in previous published literatures.

Author/date/reference	Study design	Subject	No. of cases	Prevalence of CN	Comment
Kuo, 2004[1]	Retrospective	PSI	72	15.3%	
Kowalski, 2007[15]	Retrospective	PSI	81	11.1%	
Gunne, 2010[14]	Retrospective	PSI	121	34.5%	11 cases did not culture
Abdul-Jabbar, 2013[8]	Retrospective	PSI	239	2.9%	
Lee, 2015[12]	Retrospective	PSI	32	27.3%	10 cases did not culture
Kim, 2015[13]	Retrospective	PSI	30	30%	10 cases did not culture
Parvizi, 2006[21]	Prospective	PJI	94	12%	
Berbari, 2007[18]	Retrospective	PJI	897	6.7%	
Ghanem, 2007[20]	Retrospective	PJI	171	12.5%	
Malekzadeh, 2010[17]	Retrospective	PJI	135	10.6%	
Font-Vizcarra, 2010[19]	Retrospective	PJI	87	18.3%	
Choi, 2013[16]	Retrospective	PJI	175	22.9%	

PSI = postoperative spinal infection, PJI = Peri-prosthetic joint infection.

and determining the treatment plan. A prompt decision must be made regarding revision surgery, revision method, and antibiotic type and duration. Therefore, a multidisciplinary approach is needed to make these critical decisions. We think that CN results present more of a challenge for the diagnosis of PSIs than for their treatment.

5. Conclusion

The results of the present study demonstrated that there were no significant differences in clinical characteristics between the CN and CP groups. The need for revision surgery was lower in the CN group than in the CP group, suggesting that CN results may not necessarily be a negative prognostic factor for PSI. From the viewpoint of revision surgery, CN results may indicate a better prognosis than CP results. These findings may help guide the treatment of CN PSIs. We cautiously suggest that CN PSIs do not always result in a bad course. Therefore, clinicians may treat them in the same manner as CP PSIs. However, multicenter, prospective studies should be performed to confirm these results.

Author contributions

Conceptualization: Jae Chul Lee, Sung-Woo Choi, Min Jung Baek.
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