JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Risk factors associated with poor clinical outcome in pyogenic spinal infections: 5-years' intensive care experience

Branko Milosevic[1,2]*, Muge Cevik[3,4]*, Aleksandar Urosevic[1,2], Natasa Nikolic[1,2], Jasmina Poluga[1,2], Milica Jovanovic[1], Ivana Milosevic[1,2], Jelena Micic[5], Bianca Paglietti[6], Aleksandra Barac[1,2]

[1] *Clinic for Infectious and Tropical Diseases, Clinical Centre of Serbia, Belgrade, Serbia*
[2] *Faculty of Medicine, University of Belgrade, Belgrade, Serbia*
[3] *School of Medicine, University of St. Andrews, St Andrews, United Kingdom*
[4] *NHS Lothian, Infection Service, Western General Hospital, Edinburgh, United Kingdom*
[5] *Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Belgrade, Serbia*
[6] *Department of Biomedical Sciences, University of Sassari, Sassari, Italy*

* These authors contributed equally

Abstract

Introduction: Management of pyogenic spinal infections (PSI) after the development of neurological deficit has not been specifically addressed in the literature. We aimed to describe real-life clinical outcomes of PSI in patients admitted to an intensive care unit with neurological deficit and identify factors associated with good prognosis.

Methodology: Consecutive patients admitted to ICU with a possible diagnosis of spinal infection over five years' period were included. Descriptive statistics were performed to examine the demographics and clinical parameters.

Results: The majority (71%) of patients were male. The mean age was 57.4 years (27-79), and 71% were > 50 years old. At least one underlying risk factor was identified in 68% of the patients; the most common comorbidity was diabetes mellitus (DM). All patients have presented with fever accompanied by a neurological deficit (86%) and back pain (79%). A complete recovery was achieved in 25% of patients. However, the majority of patients had adverse outcomes with 21.4% mortality, and 43% remaining neurological sequelae. Increased age with a cut-off of 65 years and pre-existing DM were identified as being associated with poor outcome.

Conclusion: Mortality among patients admitted to ICU with PSI was significantly higher than reported in the literature. The residual neurological deficit was common, one-third of patients had remaining neurological sequelae, and only one-fourth had complete recovery. Increased age and background DM were the most important determinants of poor clinical outcome. The impact of DM appears to be much more important than currently recognised in this population.

Key words: pyogenic; spinal infections; spondylodiscitis; discitis; vertebral infections.

J Infect Dev Ctries 2020; 14(1):36-41. doi:10.3855/jidc.12260

(Received 26 November 2019 – Accepted 08 January 2020)

Introduction

Pyogenic spinal infections (PSI) compromises a wide range of clinical entities, including vertebral osteomyelitis, spondylodiscitis, epidural infections, and myelitis-spinal cord abscess [1]. Over the last 30 years, the prevalence of spinal infections have increased as a result of increasing life expectancy and other comorbid factors including diabetes, underlying liver and renal disease as well as increased use of immunosuppression, spinal instrumentation, and advanced imaging techniques [2-4]. Although mortality associated with PSI has dropped due to the broad use of highly bioavailable antimicrobials, there are still significant adverse outcomes associated with PSI. Approximately one-third of patients develop long-term neurological sequela and chronic back pain leading to long-term disability [5-7].

Despite the advances in understanding the pathophysiology and microbiology of PSI, early diagnosis remains challenging due to the insidious onset and non-specific symptoms [8-10,4]. In addition, the current management and treatment strategy is primarily based on expert opinion informed by limited studies [11,12]. Therefore, the optimum management strategy including appropriate duration of antimicrobial treatment, choice of antimicrobials and the role of surgical intervention remains controversial [13]. Management of PSI after the development of

neurological deficit has not been specifically addressed in the literature. In this study, we aimed to describe real-life clinical outcomes of PSI in patients admitted to an intensive care unit with neurological deficit and identify factors associated with good prognosis.

Methodology

Study design and population

A retrospective cross-sectional study was conducted between 1st January 2011 and 31st December 2015. During this period, consecutive patients (over the age of 18) admitted to the intensive care unit (ICU) at the Clinical Centre of Serbia with a possible diagnosis of spinal infection were included. Diagnosis of spinal infection was considered in patients with the following criteria in accordance with the international guidelines [11,12];

(i) Clinical signs of spinal disease (new or acutely worsening chronic back pain) and
(ii) Signs of infection (fever, high leukocyte count and C-reactive protein (CRP)) and
(iii) Imaging findings suggestive of spinal involvement.

Data collection

Patient demographics including background medical history (diabetes mellitus (DM), liver disease, spinal trauma, previous neurosurgery), risk factors (presence of pneumonia, meningitis or other infections), and clinical data including disease onset, presenting symptoms and neurological examination findings were extracted from the medical records. In addition, radiological findings, localization and extent of spinal involvement, management and clinical outcome one year after the presentation were recorded. Patient samples submitted for microbiology evaluation were identified, and detailed microbiological data were retrieved from the laboratory database.

Statistical Analysis

Descriptive statistics were performed to examine the demographics and clinical parameters. Categorical variables were summarized by frequencies and percentages, and continuous data were presented as counts or percentages (%). We compared groups using the Kruskal-Wallis test for continuous variables and Chi-square test for categorical variables. To understand the risk factors associated with adverse outcome, we compared patients who recovered without or with minimal neurological sequelae with those who either died or recovered with significant neurological sequelae. All analyses were performed using SPSS (version 19.0).

Results

Demographic characteristics and clinical presentation

We reviewed 28 consecutive patients who were admitted to the ICU with a possible diagnosis of spinal infection. Of those, the majority (20/28; 71%) were male. The mean age was 57.4 years (range 27-79), and 20 patients (71%) were over the age of 50. At least one underlying risk factor was identified in 19 patients (68%). The most common comorbidity was DM; ten patients (38%) had a background history of DM, nine

Table 1. Demographics, clinical characteristics and clinical outcome.

Variable	N (%) (n = 28)
Age (years)	**54.7 (27 – 79)**
> 50 years of age	20 (71)
Sex	
Female	8 (29)
Male	20 (71)
Risk factors (at least one)	**19 (68)**
Diabetes Mellitus	10 (38)
Spinal trauma	3 (11)
IVDU	2 (7)
Chronic liver disease	2 (7)
Neurosurgery	2 (7)
Clinical presentation	
Fever	28 (100)
Urinary retention	24 (86)
Back pain	22 (79)
Nausea	22 (79)
Unconsciousness	7 (25)
Headache	5 (18)
Acute onset	18 (64)
Positive blood culture	20 (71)
Staphylococcus aureus	19 (95)
Alpha hemolytic Streptococcus	1 (5)
CSF examination (n = 25)	
Staphylococcus aureus	9 (36)
MRI Findings	
Epidural empyema	20 (71)
Lumbar	16 (80)
Cervical	5 (20)
Spondylodiscitis	13 (65)
Spondylitis	11 (39)
Pre-diagnosis antibiotics	13 (65)
Outcome	
Complete recovery	7 (25)
Recovered with neurological sequalae	12 (43)
Died	6 (21.4)
Neurosurgery required	7 (25)
Recovered after neurosurgery	3/7 (49)

IVDU: intravenous drug user; CSF: cerebrospinal fluid; MRI: magnetic resonance imaging.

of those with insulin dependence. Other accompanying health issues seen in patients were pneumonia (n = 7), urinary tract infection (n = 7), *Clostridium difficile* enterocolitis (n = 6) and meningitis (n = 2).

All patients have presented with fever, predominantly accompanied by a neurological deficit (24/28; 86%), back pain (22/28; 79%) and nausea (22/28; 79%). Out of all, 18 (64%) patients had acute onset disease with an average nine days' duration of back pain (range = 0-33 days). With regards to neurological symptoms, 24 (86%) patients had urinary retention, 15 had paraparesis (54%), 5 patients had a headache, and 7 patients were unconscious at the time of admission to the ICU. Demographics, clinical presentation, imaging findings and outcomes are summarised in Table 1.

Microbiology findings

Out of all, 20 (71%) patients had positive blood culture; *Staphylococcus aureus (S. aureus)* was isolated from 19 patients (95%) (all were fully susceptible isolates), and alpha haemolytic *Streptococcus* was isolated from one patient. Twenty-five patients underwent lumbar puncture. The mean cerebrospinal fluid (CSF) white cell count (WCC) was 1063 (0-4200) cells per mm^3 predominantly displaying polymorphic picture (72% polymorphs, 24% lymphocytes), and 3 patients had less than 5 WCC in the CSF. The mean parameters of CSF were as follows; glucose 3 mmol/L (0-10), protein 10 mmol/L (1-44) and CRP 5 mg/L (1-15). CSF culture was positive in 36% (9/25) of patients with *S. aureus* isolated from all samples.

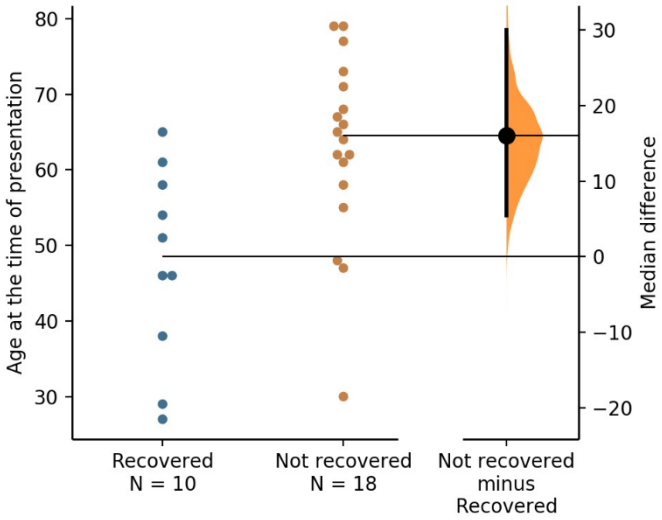
Imaging studies

The initial MRI findings were abnormal in all patients, while the CT scan showed abnormality only in 46.7% of patients. Based on MRI findings, 20 (71%) patients had epidural empyema, 16 of those were located in the lumbar spine. Thirteen patients had imaging suggestive of spondylodiscitis, all of which were accompanied by epidural empyema. Eleven patients had radiological evidence of spondylitis, and 2 patients had subdural empyema. All patients had follow-up MRI 6-8 weeks after the initial imaging. Although 10 patients (38%) had persistent changes on the MRI scan, 50% of those recovered without neurological sequelae.

Antimicrobial management

Thirteen patients had antibiotics before the diagnosis of spinal infection; the majority had received gentamicin (n = 9) and Ceftriaxone (n = 8). The mean time from hospital admission to initiation of antibiotic therapy was 12 days (range 2-34 days), and the meantime from neurological symptoms to the initiation of antibiotics was 8 days (range 2-15 days). Throughout the ICU admission, the average number of antimicrobials prescribed to one patient was 5 (3-10).

Figure 1. Relationship between age at the time of presentation and outcome.



The median age difference between those who recovered and those with poor outcome is shown in the above Gardner-Altman estimation plot. Both groups are plotted on the left axes; the mean difference is plotted on floating axes on the right as a bootstrap sampling distribution. The mean difference is depicted as a dot; the 95% confidence interval is indicated by the ends of the vertical error bar. The unpaired median difference is 16.0 (95.0% CI 5.5, 30.0). The two-sided P value of the Kruskal test is 0.00317.

Follow-up and outcome

One-year follow up was available for all patients. A complete recovery was achieved in 25%(7/28). However, the majority (21/28) patients had adverse outcomes. Out of 21, 8 recovered with neurological sequelae, 87.5% of those with paraparesis. Six patients (21.4%) died, all with *S. aureus* bacteraemia at the time of PSI. Seven patients required neurosurgery, with 3 patients achieving almost complete recovery afterwards with minimal neurological sequelae and the remaining had remaining neurological sequela. In univariate analyses, increased age and the presence of DM were identified as being associated with poor clinical outcome. The median age difference between those who completely recovered and those with poor outcome was 16.0 (95.0% CI 5.5, 30.0) (p = 0.003) with a cut-off of 65 years of age as shown in Figure 1. In addition, the presence of pre-existing diabetes mellitus was associated with poor clinical outcome (p = 0.04). There was no association between outcome and time to

antibiotics from admission, time to antibiotics from neurological symptoms, receipt of prior antimicrobials, number of antibiotics received or other laboratory parameters.

Discussion

The management of PSI remains a controversial and challenging subject. The current study highlights that in real-life clinical practice, PSI is still associated with significant morbidity and mortality. According to earlier studies providing long-term follow-up, the average mortality associated with PSI was 10-15% [7,2,5]. In the current study, the average mortality observed in ICU patients with PSI was higher (20%) than reported in the literature. Additionally, the residual neurological deficit was common, one-third of patients had remaining neurological sequelae, and only one-fourth had complete recovery.

This cohort solely included patients who were admitted to the ICU. Consistent with this, the majority of patients in this cohort had a neurological deficit at the time of presentation to ICU, reflecting the severity of their illness. In this subset of patients managed in ICU, increased age was shown to be a significant risk factor for poor clinical outcome. However, there is contradictory evidence about age as a prognostic factor. The post-hoc analysis of the Duration of Treatment for Spondylodiscitis (DTS) study examining 351 patients showed higher rates of severe adverse events in the ≥ 75-year-old group (45.9% vs 23.3%, $p < 0.001$) regardless of the severity of neurological complications or time to treatment initiation [14]. In this study, older patients were more likely to have neoplasia and chronic inflammatory diseases. In a retrospective observational study of 7118 patients in Japan, increased age was associated with a risk of in-hospital mortality [15] This increased risk was associated with co-infection with infective endocarditis. Another large multicentre study of 253 patients with a 6.5 year follow-up did not find any differences in terms of clinical outcome comparing patients under or over 50 years [5]. Our data add to the available literature and indicates that patients over the age of 65 are at higher risk of poor clinical outcome; higher mortality and neurological complications.

In our cohort, there was no association between clinical outcome and time to antibiotics from admission, time to antibiotics from neurological symptoms, receipt of prior antimicrobials or neurological impairment at presentation. In a study of 91 patients, DM, delayed diagnosis, neurological impairment at diagnosis and spinal cord or cauda equina compression were found as strong predictors of poor treatment outcome [16]. The presence of DM, end-stage renal disease and cirrhosis have also been shown to be associated with adverse clinical outcomes [,16,17,18]. This highlights that unfavourable outcome may also be driven by patient-related factors as well as the severity of clinical presentation.

In this study, the presence of pre-existing DM was associated with an unfavourable outcome. DM is one of the major global health threats of the 21st century; it is estimated that by 2045 there will be 693 million persons living with DM [19]. From infectious diseases perspective this is concerning as DM increases the susceptibility to all infections, especially to bone and joint infections [20], and the current study suggests that it may also influence the treatment outcomes in PSI. This highlights the importance of including DM as an important independent variable for future PSI studies to further understand the association between DM control and management of DM-associated complications and PSI incidence as well as treatment outcomes.

The infection in PSI is generally mono-microbial, with *S. aureus* being the leading causative agent accounting for half of the cases [21,1]. Most cases of PSI follow a haematogenous spread but also could follow direct inoculation following surgery or epidural procedures, and although rare could be caused by contiguous spread from a nearby infective focus [22]. The paraspinal or epidural extension is the most frequently reported complications. In this cohort, *S. aureus* was the most commonly isolated organism from the blood culture. CT imaging was abnormal in only half of the patients, whereas simultaneous MRI imaging suggested abnormal findings in all patients. The common finding seen in MRI was epidural empyema with predominantly lumbar spine involvement. In a recent study examining the spinal involvement in PSI, multifocal involvement was found to be common (35%) [23]. This highlights the need to image the entire spine, especially prior to any surgical intervention. In our cohort, the majority of patients had persistent MRI abnormalities 6-8 weeks after the initial imaging, despite half of them recovering without sequelae. This emphasises that imaging could be performed infrequently during the treatment of PSI, as it may not directly inform patient management.

The significance of the present study is that we provide 5-years of real-life clinical experience of managing PSI in an ICU setting. On the other hand, there are some limitations. Due to its retrospective nature, some relevant information might have been missed during data collection. Although our case series is unique to incorporate clinical, microbiological and

treatment information, sample size remains limited. In addition, although 95% of patients with positive blood culture had *S. aureus* bacteraemia, none of the patients had a CT guided biopsy. Previous studies suggest that initial biopsy is only positive in minority of the cases and has an even lower yield in patients with prior antibiotic exposure [24]. Contrary, a few other studies shown that the majority of bone biopsies yield *S. aureus* [22,13]. Therefore, the role of bone biopsy is still debated, especially if the blood culture is positive. In a recent study, diagnosis of PSI with histology has been shown to have better sensitivity compared to microbiology [25], which may be helpful in patients with negative blood culture.

Conclusion

This paper provides valuable information on the management of this challenging condition utilising the real-life clinical data. In patients admitted to ICU with PSI accompanied by neurological deficit, the average mortality observed was higher (20%) than reported in the literature. Additionally, residual neurological deficit was common, one-third of patients had remaining neurological sequelae and only one-fourth had complete recovery. Increased age and background DM were the most important determinants of poor clinical outcome in PSI. The impact of DM appears to be much more important than currently recognised in this population. The impact of DM management on PSI incidence and treatment outcomes should be explored further in this population.

Acknowledgements

Dr. Aleksandra Barac received support for research from the Project of Ministry of Education, Science and Technology of the Republic of Serbia (No. III45005).

Ethical Approval

This work was approved by the local quality improvement team to evaluate the outcomes of patients admitted with pyogenic spinal infections to the intensive care unit (ICU) at the Clinical Centre of Serbia.

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Corresponding author

Aleksandra Barac, MD, PhD, Scientific Associate
Clinic for Infectious and Tropical Diseases, Clinical Centre of Serbia
Faculty of Medicine, University of Belgrade
Bul. Oslobodjenja 16, 11000 Belgrade, Serbia
Phone: +38163/1869502
Fax: +38163/1869502
Email: aleksandrabarac85@gmail.com

Conflict of interests: No conflict of interests is declared.