Epidemiology of Spinal Infection

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Contents

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Abstract

Spinal infection is a serious disease which can result in neurological complications, with potentially high morbidity and mortality. Spondylodiscitis can be due to various pyogenic organisms, granulomatous organisms such as tuberculosis and brucellosis, and rarely, parasitic or fungal organisms. The incidence of spondylodiscitis varies from region to region, with the incidence of pyogenic spondylodiscitis being more frequent in developed countries. Tuberculosis and brucellar infections are more frequent in developing countries. There are also variations in risk factors for the different organisms and locations. The symptoms of spondylodiscitis are typically nonspecific, with a delay between symptom onset and diagnosis usually being long. Rapid and effective diagnosis and management help prevent irreversible neurological and bony complications.

Abbreviations

BSD	Brucellar spondylodiscitis
PSD	Pyogenic spondylodiscitis
SD	Spondylodiscitis
TB	Tuberculosis
TSD	Tuberculous spondylodiscitis

1 Introduction

Spinal infection is an important clinical problem. Spondylodiscitis (SD) can be classified as pyogenic, granulomatous such as tuberculosis (TB) and brucellosis, or rarely, parasitic or fungal. Symptoms of SD may be nonspecific, including fever, back pain, local tenderness, and neurological signs. The disease course may be acute or chronic. The lack of specific symptoms usually results in delayed diagnosis, leading to neurological complications and potentially high morbidity and mortality. In most cases the affected patients have one or more predisposing underlying conditions, such as diabetes mellitus, alcoholism, human immunodeficiency virus (HIV) infection, renal failure, intravenous drug abuse, spinal abnormality or intervention, or a potential local or systemic source of infection (Kapsalaki et al. 2009). TB is the most common cause (around 50% of worldwide cases), followed by pyogenic agents, whereas parasitic and fungal cases are rare (Castilla et al. 2002; Zimmerli 2010; Duarte and Vaccaro 2013; Lee 2014). The incidence of pyogenic spondylodiscitis (PSD) is more frequent in developed countries, while TB and brucellar infections are more frequent and endemic in North Africa, Asia, and the Middle East (Ben Taarit et al. 2002; Menon and Sorour 2016).

2 Epidemiology of Spinal Brucellosis

Brucellosis is one of the most common zoonoses globally (Kursun et al. 2013; Kazak et al. 2016). It is currently still a major public health problem, mainly in the Mediterranean region, the Middle East and parts of Central and South America (Maurin 2005). The disease usually affects young and middle-aged adults, with infants and elderly patients being less vulnerable (Aubry 2017). Brucellosis is a zoonosis caused by *Brucella* spp. that can involve various tissues and systems in humans and leads to different clinical

presentations. The incidence of brucellosis has however shown a mild decrease in some countries in the recent years.

Brucellosis is usually transmitted to humans by direct contact with infected animals, through damaged skin and nasal or conjunctival mucosa. It can also occur through the consumption of unpasteurized milk and milk products from infected animals (Kursun et al. 2013; Kazak et al. 2016) or via airborne transmission from contaminated aerosols in laboratories and meat-packing plants (Aubry 2017). It is more frequently transmitted by occupational exposure in developed countries. Farmers and veterinary surgery operators are the main affected occupational group. Laboratory workers processing specimens are also vulnerable (Aubry 2017). Epidemiological studies conducted in Turkey have demonstrated that 62.6–94.6% of affected patients have a history of consuming unpasteurized dairy products (Kursun et al. 2013).

The disease appears in three forms according to the symptom duration, namely, acute, subacute, and chronic (Kursun et al. 2013; Kazak et al. 2016). In various studies, the acute form is reported to be observed in 25–77% of cases, the subacute form in 12.5–59% of cases, and the chronic form in 5–27.5% of cases (Kursun et al. 2013; Kazak et al. 2016). These differences are attributed to economic and cultural differences among patients, as well as differences in diagnostic approaches.

2.1 **Frequency** (Table 1)

The World Health Organization (WHO) has reported the global incidence of human brucellosis at 500,000 reported cases per year. However, due to the underestimated reporting, which is not yet systematic in some countries, its actual impact remains unknown (Maurin 2005; Ministry of Health Tunisia 2020). The prevalence varies from country to country. As a result, it has practically been eradicated from Japan, Australia, New Zealand, some northern European countries, and North America. However, it remains endemic in the Mediterranean basin, West Asia, the Middle East, South America, Central America, and sub-Saharan Africa (Papadimitriou et al. 2006). Of all the countries reporting their statistics to WHO, Syria has the highest incidence with 1603.4 cases/1,000,000 inhabitants, followed by Mongolia (818.5/1,000,000), Iraq (268.8/1,000,000), Tajikistan (211.9/1,000,000), Saudi Arabia (149.5/1,000,000), and finally Iran (141.6/1,000,000) (Kursun et al. 2013; Kazak et al. 2016; Menon and Sorour 2016). The disease incidence has declined in some countries such as Turkey (49.5/1,000,000) and Kyrgyzstan (88.0/1,000,000) (WHO 2015).

Table 1 Incidence of brucellosis in different countries

Countries	Incidence
Syria	1603.4 cases/1,000,000 inhabitants
Mongolia	818.5 cases/1,000,000 inhabitants
Iraq	268.8 cases/1,000,000 inhabitants
Tajikistan	211.9 cases/1,000,000 inhabitants
Saudi Arabia	149 cases/1,000,000 inhabitants
Iran	141.6 cases/1,000,000 inhabitants
Turkey	49.5 cases/1,000,000 inhabitants
Kyrgyzstan	88.0 cases/1,000,000 inhabitants
Algeria	28 cases/100,000 inhabitants
Libya	22 cases/100,000 inhabitants
Morocco	131 cases/100,000 inhabitants

Eight European countries have been declared free from brucellosis by the European Union. In contrast, Greece, Italy, Portugal, and Spain have the highest incidences, ranging from 0.14 to 0.87 confirmed cases/100,000 persons (Crump et al. 2003; Welburn et al. 2015; Hull and Schumaker 2018). The cases reported were mainly people who had stayed in an endemic country or immigrants from endemic countries (Zhang et al. 2010; Rubach et al. 2013).

In the United States of America, the Institute of Health classifies human brucellosis as a rare disease with 80–120 cases reported per year. Most of the cases are located in the south and southwest and are secondary either to exposure in known endemic regions or to the consumption of cheese illegally imported from Mexico (Bechtol et al. 2011; Ducrotoy et al. 2014; Negrón et al. 2019). Indeed, brucellosis remains endemic in countries of Central and South America such as Mexico (Guzmán et al. 2016), Argentina (Aznar

et al. 2014), and Brazil (Tuon et al. 2017). The incidence of brucellosis remains as high in Asian countries, such as Kyrgyzstan (Mirnejad et al. 2017) and Azerbaijan (Dean et al. 2012) and also in China (European Surveillance System 2020).

Few studies have been done in sub-Saharan Africa. The highest incidences are noted in Niger (European Centre for Disease Prevention and Control 2020), Chad (Pelerito et al. 2017), Ethiopia (Georgi et al. 2017), and Tanzania (Norman et al. 2016). The Maghreb (Northwest Africa) as a whole is still considered an endemic region. In Algeria, the incidence was estimated at 28 cases/100,000 inhabitants in 2010 (Abdullayev et al. 2012). In Libya, the incidence was found to be 22 cases/100,000 inhabitants in 2009 (Lai et al. 2017). In Morocco, this disease is rife with the enzootic state in different regions of the country with varying prevalence. In 2017, an epidemic was notified in the Laayoune region with 131 cases (Abdou 2013).

Brucellosis is a multisystem disease, and patients may present with a broad spectrum of clinical manifestations and develop various complications. Almost every organ can be affected. Musculoskeletal complications are the leading complications of brucellosis, with various prevalence rates reported. Musculoskeletal complications may have a genetic predisposition, as recent data suggest an association with HLA-B39 (Chakroun and Bouzouaia 2007). In brucellosis, any region in the musculoskeletal system may be affected (Zribi et al. 2009; Zhang et al. 2010; WHO 2020). The most important clinical forms of osteoarticular involvement are arthritis, spondylodiscitis (SD), bursitis, tenosynovitis, and osteomyelitis. Arthritis is usually observed in large joints and especially in the sacroiliac joint (Turan et al. 2011). The frequency of osteoarticular complications is in the range of 10–85% in various studies (Turan et al. 2011; Koubaa et al. 2014).

In a Turkish study, musculoskeletal involvement represented 30.6% of subacute brucellosis. SD was the most prevalent complication of musculoskeletal system involvement (19%) in this study (Kursun et al. 2013). In France, brucellar spondylodiscitis (BSD) is very rare, comprising only 0.4% of all cases of SD (Sans et al. 2012). In Turkey, its frequency varied from 19 to 73.6% of all musculoskeletal complications (Sans et al. 2012; Kursun et al. 2013; ErenGok et al. 2014; Kazak et al. 2016). ErenGok et al. (2014) found that out of 214 patients with SD, 96 (45%) had BSD, 63 (29%) had tuberculous spondylodiscitis (TSD), and 55 (26%) had PSD. In a Tunisian study, the frequency of BSD was 19.5% (Koubaa et al. 2014).

2.2 Microbiology

The agent of brucellosis is a small, gram-negative, unencapsulated, and non-sporulating coccobacilli from the *Brucella* genus. This genus is divided into six major animal species based on natural host preference and cultural, metabolic, and antigenic characteristics. Four of these are known to produce disease in humans, namely, *Brucella abortus*, *B. melitensis*, *B. suis*, and *B. canis* (KaragozGuzey et al. 2007). *B. melitensis* accounts for the majority of the human brucellosis (Kazak et al. 2016) and is the most virulent and invasive (Akakpo et al. 2020; WHO 2020). *B. canis* is an infrequent cause of human infection (Maurin 2005). The typical reservoirs of *B. melitensis* are goats and sheep, while *B. abortus* are found principally in cattle, *B. suis* in swine, and *B. canis* in canines. *Brucella* organisms are shed in the excreta (urine, stool, milk, and products of conception) of infected animals (Papadimitriou et al. 2006; Ducrotoy et al. 2014; Ministry of Health Tunisia 2020).

2.3 Age and Gender

BSD is detected in the older age group, while brucellar sacroiliitis affects the young (Sans et al. 2012). In Turkish studies, the mean age varied from 53 to 58.4 years (Sans et al. 2012; Kazak et al. 2016). The mean age was 55 years in a multinational, multicenter study, which included patients from 35 different centers in four countries (Turkey, Egypt, Albania, and Greece) (Erdem et al. 2015). The mean age was 54.8 years

Table 2 Mean ages of patients with spinal brucellosis

Study	Country	Mean age (years)
Kazak et al. (2016)	Turkey	53
Sans et al. (2012)	France	58.4
Erdem et al. (2015)	Multinational and multicenter	55
Lebre et al. (2014)	Greece	54.8
Koubaa et al. (2014)	Tunisia	51

in a Portuguese study (Lebre et al. 2014), 68 years in another Turkish study (Turunc et al. 2007), and 51 (range 19–74) years in a Tunisian study (Koubaa et al. 2014) (Table 2). There was no significant difference between the mean ages of the patients with and without osteoarticular involvement (Turan et al. 2011).

In a comparative Turkish study, the mean age of the patients with TSD was lower than that of the patients with BSD and PSD: 43 years versus 53 years and 53 years, respectively ($p < 0.001$) (ErenGok et al. 2014). In another comparative study, patients with BSD were younger than patients with TSD or PSD (59 years versus 68 years versus 65.5 years, respectively) (Turunc et al. 2007). A male predominance was noted in the majority of studies. Men represented 52.6% in a multinational and multicenter study (Erdem et al. 2015), 55.6% in a Portuguese study (Lebre et al. 2014), 58–64.3% in Turkish studies (Turgut et al. 2006; Turunc et al. 2007; ErenGok et al. 2014), and 72% in a Tunisian study (Koubaa et al. 2014).

2.4 Risk Factors

The risk factors for BSD are the same for all forms of brucellosis. Brucellosis is transmitted to humans either by direct contact with infected animals or by consumption of unpasteurized milk obtained from infected animals or dairy products produced from such milk (Turan et al. 2011). It is encountered as an "occupational disease" in countries where pasteurized dairy products are consumed; this is especially the case if the infection is found among veterinarians, slaughterhouse workers, farmers, and laboratory workers (Kazak et al. 2016). Even though there are studies showing that occupational brucellosis is more common in men, other studies have reported that men and women are affected equally (Turan et al. 2011).

In a Turkish study including 202 patients, 94 had osteoarticular involvement. A possible source of infection could be identified in 70 cases (74.5%). Fifty-three patients (75.7%) had a history of farming and/or consumption of unpasteurized milk and dairy products (especially fresh cheese). Apart from that, 15 (21.4%) of these patients with osteoarticular involvement had only a history of consumption of unpasteurized milk and dairy products. In addition, two (2.9%) patients were exposed to the disease occupationally (veterinarian, laboratory worker, etc.). Sixty-one percent of patients lived in a rural area (Turan et al. 2011).

In another Turkish study comprising 164 patients, 109 (66.5%) resided in urban areas and 55 (33.5%) in rural areas. Evaluation of patient histories revealed that 83 (50.6%) patients consumed unpasteurized cheese, 61 (37.2%) had animal contact, and 30 (18.3%) both consumed unpasteurized cheese and had animal contact. The transmission route in 48 (29.3%) patients was unknown. Laboratory transmission occurred in one patient (0.6%) (Kazak et al. 2016). In a Tunisian study, 37.5% of patients had occupational exposure, and 87.5% lived in rural areas. The ingestion of unpasteurized milk or milk products of infected cows (96.9%) and contact with infected animals (90.6%) were the main risk factors for human brucellosis (Koubaa et al. 2014).

2.5 Location

The lumbar spine is the most affected (60%), particularly at the L4–L5 level (Turgut et al. 2006; Kursun et al. 2013), followed by thoracic (19%) and cervical spine (12%). More than one level is affected in 6–14% of cases (Papadimitriou et al. 2006; Zribi et al. 2009; Ducrotoy et al. 2014; WHO 2020; Ministry of Health Tunisia 2020). Involvement of the spine may be either focal or

diffuse (Papadimitriou et al. 2006; Zribi et al. 2009; Ducrotoy et al. 2014; WHO 2020; Ministry of Health Tunisia 2020). In a Tunisian study, the lumbar spine was the most frequently involved region with the rate of 78%, particularly at the level of the L4–L5 vertebra, followed by thoracic (21.8%), cervical (6.3%), lumbosacral (6.3%), and thoracolumbar segments (3.1%) (Koubaa et al. 2014).

The focal form is confined to the anterior portion of the vertebral body end plate. This typically occurs in the anterior superior end plate of a lumbar vertebra at the discovertebral junction because of its rich blood supply (Zribi et al. 2009; Ducrotoy et al. 2014). The diffuse form may involve the entire vertebral body and extend to the adjacent disk, vertebrae, and epidural space. Infection diffuses via the ligaments and vascular communications. Posterior elements are rarely involved, but facet joint arthritis may occur (Zribi et al. 2009; Ducrotoy et al. 2014; WHO 2015; Ministry of Health Tunisia 2020). Among the patients with BSD, lumbar involvement is significantly more common than in TSD and PSD ($p < 0.001$) (ErenGok et al. 2014).

2.6 Clinical Signs

Clinical signs and symptoms of brucellosis are usually not specific, with none being characteristic of brucellosis (Kazak et al. 2016). Clinical symptoms of BSD may include moderate fever and spinal pain of variable intensity and of mixed type (Papadimitriou et al. 2006). In a Portuguese study, the most common signs and symptoms of BSD were back pain (98.1%), fever (46.3%), and neurological deficits (25.9%) (Lebre et al. 2014). In a Tunisian study, back or neck pain (100% of patients), fever (78%), and sweats (68.6%) were the most common symptoms (Koubaa et al. 2014). Fever was significantly more frequent in BSD patients than in TSD and PSD ($p < 0.017$) in comparative studies (Turunc et al. 2007; Skaf et al. 2010a, b). Another comparative Turkish study found no statistically difference for the frequency of fever among the three groups; however, sweating was more common (81%) among the patients with BSD ($p < 0.001$), and the history of upper back pain and cervical pain was more common in patients with TSD ($p = 0.016$ and $p = 0.014$, respectively) than in those with BSD and PSD (ErenGok et al. 2014).

Neurological symptoms were more common in patients with TSD (61.5%), followed by pyogenic (50%) and BSD (31.2%), but with no significant differences (Turunc et al. 2007). Physical examination usually shows a "spinal syndrome," with segmental spinal rigidity and paravertebral muscle contracture. Pressure applied to the spinous process of the involved vertebra elicits pain. It is uncommon for BSD to present with spinal cord or nerve root compression. The long latent stage between the onset of symptoms and the appearance of radiological changes (ranging from 2 to 8 weeks) may prevent early diagnosis (Papadimitriou et al. 2006).

3 Epidemiology of Spinal Tuberculosis

Tuberculosis (TB) remains one of the most widespread infectious diseases in the world, mostly found in developing countries. It is still a major health problem globally (Chen et al. 2016). TB infects one-third of the world's population, with 8.7 million new cases annually. Worldwide rates of TB have increased in parallel with acquired immunodeficiency syndrome (AIDS) incidence (Batirel et al. 2015). In addition, TB ranks second, just after HIV infection, among infectious causes of mortality (Batirel et al. 2015). Pulmonary TB is the most frequent manifestation; however, extrapulmonary TB is common among people from TB high-endemic countries (Kristensen et al. 2017). TSD, also known as Pott disease, is a chronic disease that is slowly progressive, and diagnosing it is relatively difficult (Liu et al. 2019). If undiagnosed, it often leads to irreversible neurological injury, including paralysis, with resultant spinal cord compression causing severe and disabling neurological sequelae (Kristensen et al. 2017; Liu et al. 2019; Pu et al. 2019).

Table 3 Frequency of spinal tuberculosis among cases of spinal infection

Study	Country	Frequency (%)
Javed et al. (2018)	Spain	14–45.2
Cebrián Parra et al. (2012)	Spain	19.6
Venugopal Menon and Moawad Sorour (2016)	Oman	17

3.1 Frequency (Table 3)

Worldwide, 80% of patients with TSD are found in developing countries and poverty-stricken areas (Liu et al. 2019). TSD is the most common form of extrapulmonary TB and accounts for less than 5% of all TB cases (Zimmerli 2010; Duarte and Vaccaro 2013; Lee 2014; Kristensen et al. 2017; Javed et al. 2018; Pu et al. 2019) and for half of the bone and joint TB (Kristensen et al. 2017; Tom et al. 2018; Pu et al. 2019). TSD represents 10–35% of the cases of SD (Javed et al. 2018; Tom et al. 2018; Liu et al. 2019).

In Taiwan, TSD accounts for around 2% of all cases of TB and around 15% of extrapulmonary TB (Chen et al. 2016). In a Spanish study, an increase in cases of TSD from 14 to 45.2% among foreign-born residents in Barcelona over a period of 10 years was reported (Javed et al. 2018). In another Spanish study comprising 108 patients, TB was the second most common etiology of SD after *Staphylococcus* spp. (11 cases from 56 positive cultures) (Cebrián Parra et al. 2012). In 2013, TSD represented only 2.3% of all US TB cases (Sans et al. 2012). In a study conducted in Oman, which included 62 cases of SD, the frequency of TSD was 17% (Venugopal Menon and Moawad Sorour 2016).

3.2 Microbiology

Mycobacterium tuberculosis is the most frequent microorganism responsible for TSD. In a multinational, multicenter study consisting of 314 patients, *M. tuberculosis* was identified in 110 cases (Batirel et al. 2015). In France, *M. tuberculosis* is responsible for 21% of all SD in France, with more than 75% of cases of TSD being found in the immigrant population (Sans et al. 2012). In a Tunisian study, among 23 patients with bacteriologically confirmed TSD occurring between January 2014 and May 2018, 19 were caused by *M. tuberculosis* and four by *M. bovis* (Chebbi et al. 2019).

3.3 Age and Gender

This disease is most commonly seen in patients older than 50 years (Batirel et al. 2015). In a multinational, multicenter study (35 centers in Turkey, Egypt, Albania, and Greece) consisting of 314 patients, the mean age was 51 ± 18 years (Batirel et al. 2015). In another retrospective multinational (Turkey, Egypt, Albania, and Greece), and multicenter study (35 centers) of 641 patients (314 TSD and 327 BSD), the median age was similar (53 years versus 55 years, $p = 0.344$) (Erdem et al. 2015). In a comparative study, patients with TSD were older than patients having BSD or PSD (mean ages were 68 years, 59 years, and 65.5 years, respectively), without significant difference (Turunc et al. 2007). In a Chinese study comprising 1378 cases of TSD, patients were younger with a mean age of 43.7 years. A total of 561 patients (40.7%) were aged 18–45 years, followed by those 46–60 years old (27.2%) (Pu et al. 2019). A male predominance has been reported in many studies. In two multinational (Turkey, Egypt, Albania, and Greece), multicenter (35 centers) studies, men represent 51.2% and 51.9%, respectively, of cases (Batirel et al. 2015; Erdem et al. 2015). In a Chinese study comprising 1378 cases of TSD, 805 were men (58.4%) and 573 women (Liu et al. 2019). In a comparative study, there was no significant difference in gender between TSD, BSD, and PSD (Turunc et al. 2007).

3.4 Risk Factors (Table 4)

The risk factors of TSD are diabetes mellitus (12%) (Batirel et al. 2015; Liu et al. 2019; Pu et al. 2019), chronic renal failure (5%) (Turunc et al. 2007; Batirel et al. 2015), malignancy (2%) (Batirel et al. 2015), immunosuppression due to

Table 4 Risk factors of spinal tuberculosis (Batirel et al. 2015)

Risk factors	Frequency (%)
Diabetes mellitus	12
Chronic renal failure	5
Malignancy	2
Others (e.g., pulmonary diseases, coronary diseases)	19

treatment with antineoplastic chemotherapy (Batirel et al. 2015; Chen et al. 2016), HIV (Chen et al. 2016), glucocorticoids, TNF-alpha blockers (2%) (Batirel et al. 2015), recent contact with patients with TB (Chen et al. 2016), long-term physical labor (Liu et al. 2019), and others (e.g., hypertension, coronary artery disease, chronic obstructive pulmonary disease, asthma, nephrolithiasis) (19%) (Batirel et al. 2015). The prevalence of TB is three to six times higher in patients with diabetes mellitus, compared to those without diabetes mellitus. Additionally, the incidence of TB is three times higher in patients with poorly controlled diabetes mellitus than in those with ideally controlled diabetes mellitus (Liu et al. 2019). It has been also reported that the incidence of TB increases by 6.9–52.5 times in dialysis patients, compared to the general population (Turunc et al. 2007).

3.5 Location

TSD often affects the thoracic and lumbar spine (Tom et al. 2018). In a multinational, multicenter study, the lumbar spine (56%) was the most commonly involved region of the spinal column, followed by the thoracic spine (49%) (Chen et al. 2016). The same results were found in a Chinese study, where the lumbar segment (38.2%) was the most frequently affected, followed by the thoracic spine (35.7%) (Liu et al. 2019). In another multinational, multicenter study, thoracic and thoracolumbar involvement was the favored site in TSD, while lumbar involvement was more frequent in BSD ($p < 0.001$ for all comparisons) (Erdem et al. 2015). In a Turkish study, the thoracic location was more frequent in TSD (53.8%), while the lumbar spine was more frequent in BSD (65.6%), but the difference was not significant (Turunc et al. 2007).

3.6 Clinical Signs

The clinical pattern of SD is quite nonspecific. Typically, the onset of symptoms is insidious, and disease progression is slow (Chen et al. 2016; Pu et al. 2019). Early clinical manifestations of TSD are also atypical and insidious (Pu et al. 2019). The median duration of symptoms before the diagnosis has been reported to be between 2.5 and 16 months (Batirel et al. 2015; Liu et al. 2019; Varo et al. 2019). Moreover, despite advanced diagnostic methods, diagnosis of TSD is usually delayed. The clinical presentation and physical examination findings depend on the site and stage of the disease, presence of complications, and constitutional symptoms (Chen et al. 2016). The early clinical manifestations of TSD are insidious, usually manifesting first as back pain (83–92.5%) (Batirel et al. 2015; Javed et al. 2018; Liu et al. 2019; Pu et al. 2019) and local tenderness (Batirel et al. 2015; Pu et al. 2019).

The most commonly reported symptoms in a Chinese study were back pain (1438/2040, 70.4%), fever (667/2040, 32.7%), body weight loss (620/2040, 30.3%), neurological abnormalities (315/2040, 15.4%), and night sweats (390/2040, 19.1%) (Chen et al. 2016). In a comparative study, fever (139/314, 44.3%), back pain (176/314, 56%), loss of appetite (154/314, 49%), and weight (132/314, 42%) were more common on TSD than on BSD ($p < 0.001$) (Erdem et al. 2015). In another comparative study, fever was significantly more common in patients with BSD ($p < 0.017$) (KaragozGuzey et al. 2007), and the history of upper back pain and cervical pain were more common in patients with TSD ($p = 0.016$ and $p = 0.014$, respectively) than in those with BSD and PSD (ErenGok et al. 2014). In a comparative Turkish study, neurological symptoms were more common in TSD patients (61.5%), followed by PSD (50%) and BSD patients (31.2%), but there was no significant difference. Likewise, neurological deficit was more common in TSD patients (61.5%), followed by PSD

(46.6%) and BSD patients (25.8%), but with no significant difference (Turunc et al. 2007).

3.7 Complications

In a Chinese study, abscesses were detected by computed tomography (CT) or magnetic resonance imaging (MRI) in 903 of 1378 patients (65.5%), including paravertebral and psoas abscesses (Liu et al. 2019). They were detected in 30% of cases in a Tunisian study (Tarzi Brahem 1983). The incidence of neurological deficit varies from 23 to 76% (Turunc et al. 2007; Chen et al. 2016). In a multinational, multicenter study, 69% of patients had abscesses (with the majority being paravertebral at 39%), 40% had neurologic deficits, 21% had spinal instability, and 16% had spinal deformity (Batirel et al. 2015). Complications were more frequent in patients with an unfavorable outcome: abscesses in 74%, neurological deficits in 56%, spinal instability in 36%, and spinal deformity in 61%, with significant differences ($p < 0.05$). Complications can occur during the course of treatment, namely, neurological deficits (6%) and spinal deformities (4%) (Batirel et al. 2015). In a comparative study, prevertebral, paravertebral, epidural, and psoas abscesses were more frequently observed in TSD than in BSD ($p < 0.01$) (Erdem et al. 2015). Neurological complications ($p < 0.001$), spinal instability ($p < 0.001$), and spinal deformity ($p < 0.002$) were also more frequent with TSD than with BSD ($p < 0.001$) (Erdem et al. 2015).

3.8 Associated Sites

Pulmonary TB is the most commonly associated location. Concomitant pulmonary TB, including a previous history of pulmonary TB, was present in 366/1378 Chinese patients (26.6%) (Liu et al. 2019). In a retrospective multinational (Turkey, Egypt, Albania, and Greece), and multicenter (35 centers) study including 641 patients (314 TSD and 327 BSD), 51 patients who had TSD also had another location of TB (pulmonary 29 and meningitis 13) (Erdem et al. 2015).

4 Epidemiology of Spinal Pyogenic Infection

Pyogenic spondylodiscitis (PSD) was first described by Lannelongue in 1879, and the first series of pyogenic cases was published by Kulowski in 1936 (Kulowski 1936). Spontaneous PSD represents 2–7% of all cases of osteomyelitis (Gouliouris et al. 2010). The incidence of PSD appears to be on rise, with the increasing incidence seemingly related to the high number of chronic debilitating diseases, rise of intravenous drug abuse (IVDA), and rising numbers of patients undergoing spinal surgery (Kapsalaki et al. 2009).

4.1 Frequency

The incidence of PSD is more frequent in developed countries. Nevertheless, tuberculous and brucellar infections are more frequent and endemic in North Africa, Asia, and the Middle East (Ben Taarit et al. 2002; Menon and Sorour 2016). The incidence of PSD is estimated to be 5–5.3 per million patients per year. In Europe, the annual incidence of this infection ranges from 0.5 to 2.4 cases per 100,000 inhabitants (Krogsgaard et al. 1998; Hopkinson and Patel 2016). A French study has reported an annual incidence of spinal infection of 2.4 per 100,000 person-years, with the mean age being 59 (1–98) years (Sans et al. 2012). On the other hand, a Danish study has reported an annual incidence of PSD increasing from 2.2 to 5.8/100,000 inhabitants over a 14-year period (Kehrer et al. 2014), while a Japanese study showed an increase in the incidence of approximately 140% from 2007 to 2010 (Akiyama et al. 2013).

4.2 Microbiology

The causative agent of PSD is variable, depending on the initial contamination route. The main microorganism responsible for pyogenic spinal infections is *Staphylococcus aureus* (Chong et al. 2018). According to the series of Koutsoumbelis

et al. (2011), methicillin-resistant *Staphylococcus aureus* (MRSA) was reported in 34% of cases of PSD. Chronic dialysis patients have a higher proportion of MRSA (Kuo et al. 2018). Coagulase-negative staphylococci have been reported in 5–16% of cases. *Staphylococcus epidermidis* is often related to postoperative spinal infection (Fantoni et al. 2012). Staphylococci are followed by gram-negative aerobic bacilli, *Streptococcus pyogenes* and *Enterococcus* spp., in terms of frequency. Gram-negative agents are causative agents in 7–33% of cases of PSD. *Escherichia coli*, *Proteus* spp., *Enterobacter cloacae*, and *Pseudomonas aeruginosa* are are often reported in patients with comorbidities such as diabetes mellitus, IVDA, immunodeficiency, and following procedures or infections involving the genitourinary and gastrointestinal tracts (Skaf et al. 2010a, b; Koutsoumbelis et al. 2011).

There is an increasing proportion of *Streptococcus* spp., coagulase-negative *Staphylococcus*, and other fastidious bacteria compared with gram-negative bacilli. Indeed, coagulase-negative *Staphylococcus* more frequently occurs in postoperative implant-associated spinal infection compared to hematogeneous native PSD (Doutchi et al. 2015). Anaerobic agents are observed in 3% of cases. Among anaerobic bacteria, *Bacteroides* spp., *Peptococcus* spp., and *Propionibacterium acnes* are more common in patients with diabetes mellitus (Bontoux et al. 1992; Hadjipavlou et al. 2000; Kourbeti et al. 2008; Chong et al. 2018). *Bacteroides fragilis* has been reported in patients with diabetes mellitus or intra-abdominal infection. For IVDA patients, *Staphylococcus aureus* was the predominant microorganism detected in 61.7% of cases. *Pseudomonas aeruginosa* were isolated in four cases from the culture of bone biopsy (Ziu et al. 2014).

4.3 Age and Gender

PSD is more frequent in adults older than 50 years of age and in childhood (Petkova et al. 2017). Two peaks of pyogenic spinal infection, in patients under 20 years and in the age range of 50–70 years, have been reported. PSD is more common among men, with a sex ratio of 1.6–2.0:1, which further increases in the elderly population (Skaf et al. 2010a, b).

4.4 Risk Factors

The risk factors known to increase the risk of pyogenic spinal infection include diabetes mellitus, smoking, obesity, distant infection site, advanced age, IVDA, immunosuppression, steroid therapy, HIV infection, chronic kidney disease, alcoholism, malnutrition, malignancy, and liver cirrhosis (Cottle and Riordan 2008; Mylona et al. 2009; Meredith et al. 2012; Chong et al. 2018). The incidence of pyogenic spinal infection is rising, according to an increase in the rate of nosocomial infections associated with vascular devices and other forms of instrumentation and to an increasing prevalence of IVDA (Torda et al. 1995; Skaf et al. 2010a, b).

Pyogenic spinal infection results from hematogeneous infection (60–80% of cases), direct inoculation (15–40% of cases), or contiguous contamination (3% of cases). It is often the result of hematogeneous spread from either the skin, respiratory tract, genitourinary tract, gastrointestinal tract, or the oral cavity giving rise to bacteremia (Govender 2005). The urinary tract has been reported as the predominant source of infection in 17–30% of cases (Mylona et al. 2009; Doutchi et al. 2015). Approximately 37% of PSD does not have an identifiable source (Lestini and Bell 1999).

The increase in IVDA has led to the increase of the incidence of PSD. An American study reported 102 cases in patients with a history of IVDA. The mean age was 45.4 years and majority of patients were men. Other comorbidities were associated to IVDA, such as HIV infection, hepatitis C, endocarditis, and alcohol abuse (Ziu et al. 2014). Chronic dialysis patients, particularly those under hemodialysis, may present with PSD as a result of bacteremia which comes from punctures of the water pipeline or from the vascular contamination by intravenous catheters (Cervan et al. 2012). Hemodialysis vascular access is one of the most routes of bacterial entry

(Kuo et al. 2018). In most cases, patients under hemodialysis are elderly, have other underlying diseases, and are immunocompromised. Hence, morbidity and mortality are higher in this population. A Taiwanese study reported 106 cases of PSD in patients under hemodialysis. The average age was 66.7 years, and diabetes mellitus was reported in 48.6% of cases (Kuo et al. 2018).

For iatrogenic PSD, the incidence of postoperative spondylodiscitis (POSD) after lumbar discectomy has been reported to be between 0.7 and 2.8% of operated cases. Spinal instrumentation adds further complicating factors, with infection rates averaging 7% (range 1.3–12%) (Gepstein and Eistmont 1990). POSD is the most common complication following a spinal operation. The incidence of POSD is affected by three types of risk factors, namely, the nature of the spinal pathology, the surgical procedure, and the patient-related risk factors. On the one hand, the incidence of POSD depends on the complexity of the index surgical procedure and its duration. The risk of infection has been found to be higher after arthrodesis with posterior instrumentation (Meredith et al. 2012). In the literature, rates of POSD after thoracic or lumbar spinal arthrodesis range from 1.9 to 4.4% (Meredith et al. 2012). In a systematic review of literature, the rate of POSD was found to be decreased significantly after minimally invasive transforaminal interbody fusion, compared to open transforaminal interbody fusion (0.6% versus 4%) (Parker et al. 2011). Some factors have been cited to increase the rate of infection following a spinal procedure, such as prolonged preoperative hospitalization, suboptimal sterile techniques, prolonged procedures, and increased operating room traffic (Parker et al. 2011).

4.5 Location

The most common level of involvement of PSD is the lumbar spine, followed by the thoracic, cervical, and sacral levels (Wisneski 1991). The literature on cervical PSD is scarce. However, these infections can lead to severe neurological complications compared to other locations (Urrutia et al. 2013). For PSD in patients with a history of IVDA, the most commonly affected level is the lumbar spine (57.8% of cases), followed by the thoracic and cervical spine (Ziu et al. 2014). The lumbar vertebra is also the most affected in patients on chronic dialysis (84.8%) (Cervan et al. 2012; Kuo et al. 2018).

4.6 Clinical Signs

The clinical presentation of PSD is not specific. The delay in diagnosis of PSD varies between 1 and 6 months (Petkova et al. 2017). It is much longer in TSD than in PSD (Batirel et al. 2015; Liu et al. 2019; Varo et al. 2019). In immunocompromised patients, such as patients undergoing hemodialysis, the delay is greater and can range from 5 to 183 days (Cervan et al. 2012). The main symptom is back and/or neck pain, depending on the level of the disease. Unremitting back pain, particularly worsening during the night, is the most common presenting symptom, followed by fever. Fever (>38 °C) is present in about one-half of the cases (Skaf et al. 2010a, b; Fantoni et al. 2012).

For POSD, clinical signs are complex, difficult to interpret, and poorly characterized. The interval between symptom onset and diagnosis is longer for POSD (16 weeks) than for spontaneous PSD (3–4 weeks) (Dufour et al. 2005). Neurological complications, such as spinal cord or nerve root compression, occur more frequently in PSD. They are present in approximately 12% of patients (Skaf et al. 2010a, b). Eismont et al. (1983) found that sensory involvement is rare, whereas motor and long-tract signs are more common because of mainly anterior cord compression. Epidural abscesses are detected in the majority of patients with pronounced neurological symptoms (Petkova et al. 2017).

5 Epidemiology of Spinal Fungal Infection

Fungal SD is uncommon (0.5–1.6%) and is usually due to *Candida albicans*. The immunocompromised population that is susceptible to fungal

infections is ever increasing. Risk factors of fungal infection include prior use of broad-spectrum antibiotics, central venous access devices, immunosuppression, neutropenia, chronic granulomatous disease, and intravenous drug use (Gouliouris et al. 2010; Berbari Elie et al. 2015). A wide variety of fungal organisms can cause spinal infection. The most common fungal organisms causing SD include *Aspergillus* spp., *Candida* spp., and *C. neoformans*. *Candida albicans* is the commonest *Candida* species in the literature (Kim et al. 2006). Whereas *Cryptococcus*, *Candida*, and *Aspergillus* have a worldwide distribution, other fungi such as *Coccidioides immitis* and *Blastomyces dermatitidis* are limited to specific geographical areas. Therefore, residence in or travel to endemic areas should be taken into consideration when evaluating patients with prolonged evolution of SD.

5.1 Candida Spondylodiscitis

Candida spondylitis accounts for approximately 1% of infectious SD (Richaud et al. 2017). It was previously considered a complication of intravenous drug use but is now mostly a healthcare-associated infection, such as most invasive Candida infections. With the increase in invasive Candida infections, the incidence of *Candida* spondylitis is increasing, and this trend will likely continue in the future (Cornely et al. 2012; Pappas et al. 2016). Although there are ten species of Candida that are pathogenic to humans, 62% of cases of vertebral osteomyelitis are caused by *Candida albicans*, 19% by *Candida tropicalis*, and 14% by *Candida glabrata* (Kim et al. 2006). Infection caused by *Candida glabrata* is becoming more common.

5.2 Aspergillus Spondylodiscitis

Aspergilli are opportunistic mycelial organisms. They are abundant in the environment. They live as saprophytes, and their concentration in the air undergoes seasonal variation (higher during autumn and winter). Nosocomial aspergillosis is due to infiltration of conidia into ward air from outside. Aspergillus is the most common cause of infection and death in patients with chronic granulomatous disease (Heinrich et al. 1991). Aspergillosis is also the second most common invasive fungal infection in cancer patients and most of them were or had been neutropenic. Bone marrow transplant recipients may be at risk of invasive aspergillosis, especially during profound neutropenia (Govender et al. 1991). Aspergillus is the most common cause of skeletal mycosis, and the vertebrae are the most commonly involved structures in fungal osteomyelitis. The most common causative species is *Aspergillus fumigatus*. In fewer instances, *Aspergillus flavus*, *Aspergillus niger*, *Aspergillus nodulans*, and *Aspergillus terreus* have been isolated (Govender et al. 1991).

5.3 Cryptococcal Spondylodiscitis

Cryptococcosis is a systemic mycosis that often involves the lungs and the central nervous system. It is caused by *Cryptococcus neoformans*, which is found in fruits, milk, soil, and feces of some birds. The disease has a worldwide distribution. Immunosuppression related to altered T-cell function is the most common predisposing factor. In non-HIV-infected patients, predisposing factors for cryptococcosis include malignancy, solid organ transplantation, connective tissue diseases, and immunosuppressive therapy. Estimates of the annual incidence of cryptococcosis in non-HIV individuals are 1.3–8 per 100,000 (Legarth et al. 2014). The disease is generally acquired by the respiratory route through inhalation of aerosolized spores. Pulmonary infection with cryptococcus may be asymptomatic or symptomatic. It may regress, progress, or remain stable for years. Extrapulmonary infection usually results from a hematogeneous spread and can involve any organ. There is a predilection for central nervous system involvement, which is the most common extrapulmonary manifestation (Kim et al. 2006). Osseous involvement is a manifestation of disseminated cryptococcosis in 5–10% of cases.

The most commonly involved skeletal sites are the spine, pelvis, ribs, skull, tibia, and knee (Chhem et al. 2001).

5.4 Coccidioidal Spondylodiscitis

Coccidioidomycosisis endemic in South Africa, South America, and the United States (Dalinka et al. 1971). Coccidioidomycosis results from inhalation of spores of the fungus, which causes a variable pulmonary response in affected individuals. Extrapulmonary dissemination occurs in approximately 0.5% of affected patients. Spinal involvement develops in approximately 25% of patients with disseminated disease (Huntington et al. 1967; Galgiani 1993).

5.5 Blastomycotic Spondylodiscitis

Blastomyces dermatitidis is a dimorphic fungus endemic in the Southeastern and South Central United States of America. *Blastomyces dermatitidis* is considered to be an inhabitant of soil, and infection occurs by inhalation of conidia. For blastomycosis, the hematogeneous dissemination of infection to almost any organ can occur months to years after the initial pulmonary involvement (Kuzo and Goodman 1996). The skin is the most common extrapulmonary site (40–80% incidence). Skeletal blastomycosis is seen in 14–60% of disseminated cases (Riegler et al. 1974; Hadjipavlou et al. 1998). The spine is the most common site of skeletal involvement, followed by the skull, ribs, tibia, and the bones of the foot and wrist.

5.6 Mycetoma Spondylodiscitis

Mycetoma is a neglected tropical disease that is endemic in many tropical and subtropical areas. Mycetoma is a chronic mutilating disease of the skin and the underlying tissues caused by fungi (eumycetomas) or bacteria (actinomycetomas). The most frequent organisms causing actinomycetoma are *Streptomyces somaliensis*, *Actinomadura madurae*, and *A. pelletieri*, while the most common pathogens reported in eumycetoma are *M. mycetomatis*, *M. grisea*, *Pseudallescheria boydii*, and *Leptosphaeria senegalensis*. It follows implantation of infectious organisms into subcutaneous tissue, from where the infection spreads to the skin and bone. The organisms form small microcolonies that are discharged onto the skin surface via sinus tracts or that can burrow into other adjacent tissues including bone (Zijlstra et al. 2016). Mycetoma occurs in all age groups but is rarely seen in children. It commonly occurs in field laborers and cultivators whose occupation involves direct contact with the soil (Lichon and Khachemoune 2006). The foot is the commonest site affected by mycetoma and accounts for 70% of cases, followed by the hand (12%). Spinal cord involvement is rare, and only a few cases have been reported (Fahal 2004, 2011; Cascio et al. 2011).

6 Conclusion

Spinal infection is a serious disease which can induce neurological complications, with potentially high morbidity and mortality. The incidence of PSD is more frequent in developed countries. Many risk factors have been identified for PSD, and it is rising, including an increased rate of nosocomial infections associated with vascular devices and other forms of instrumentation and to an increasing prevalence of IVDA. Tuberculous and brucellar infections are more frequent in developing countries. Worldwide, 80% of patients with TSD are found in developing countries and poverty-stricken areas. TSD accounts for half of the bone and joint TB and is the most common form of extrapulmonary TB. Fungal PSD is uncommon and is usually due to *Candida albicans*, occurring essentially in immunocompromised patients. Early clinical manifestations of spinal infection are usually insidious, leading to a long mean interval between symptom onset and diagnosis; hence complications are frequent. Rapid and effective diagnosis and management help prevent irreversible neurological and bony complications.

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